Evaluating quality of life measurement in psoriasis and the development of new solutions to improve the use of patient-reported outcomes

A thesis submitted in accordance with the conditions governing candidates for the

degree of

DOCTOR OF PHILOSOPHY

in

Cardiff University

Presented by

Dr Faraz Mahmood Ali (0332073)

School of Medicine
Cardiff University
Cardiff
UK

March 2021

For God, for His infinite bounties

For my parents, for their unconditional support

For my wife, for her limitless love

For my children, for the countless joy they bring to my life

Table of Contents

Acknowledgements

In the name of God, The Most Merciful, The Most Kind

May peace and blessings be upon Prophet Muhammad, his family and companions

I complete this thesis as the world slowly begins to recover from the COVID-19 pandemic that has affected so many, myself included. When I first embarked upon this journey, I had little to no experience of research and the challenges it can bring, especially having come from a purely clinical background. On the way, there have been numerous trials, difficulties and stumbles and I'm grateful I was able to achieve the little I have during the 7 years of this work. I have had 4 beautiful children, celebrated a decade of my married life, moved homes, started a training position in Dermatology and was redeployed to cover the COVID front lines. It has been eventful to say the least! I have had the opportunity to travel internationally, present my research in different meetings and interact with so many wonderful minds. I have achieved numerous original publications, posters and have also given oral presentations at an international level. This process has been life altering whilst providing me with invaluable lessons and skills along the way.

In a way, this PhD has been central to so many key moments of my life that when I look back at this thesis, it will be inseparable from all my other poignant memories. I will cherish this journey, despite the countless occasions where I felt like giving up. If it weren't for the people around me, their dedication, love and support, I would not have developed the stamina nor the willpower that I have today.

At the very outset I would like to mention Professor Alex Anstey who encouraged me to pursue an academic degree and created opportunities when I needed them most. Thank you for opening the first door!

Most importantly I would like to thank my fantastic supervisors: Professor Andrew Finlay, Professor Sam Salek, Professor Vincent Piguet and Dr John Ingram. Their words of wisdom, guidance and nurture were appreciated in every way possible. They were always approachable day or night and through hundreds of supervisory meetings ensured I was always coping whilst encouraging regular writing and record keeping. I am very grateful for their support towards attending numerous courses and meetings across Europe. Truly very few people are blessed with such supervision, as without it I would have been lost. Indeed,

their zeal for research was inspiring to witness and undoubtedly had a transformative effect on my own approach to learning.

Dr Jui Vyas kindly joined the supervisory team at a later stage but prior to this had always been a trustworthy colleague providing sincere advice and encouragement at all occasions – even if she did sneak coffee from my room at times!

I would like to thank the considerate patients who participated in the various studies of this thesis and for giving their precious time. The research they have helped generate will hopefully contribute to improving the quality of life of psoriasis sufferers globally. Equally, I am grateful to the wonderful Consultants and staff of the Dermatology department at University Hospital of Wales who allowed everything to go smoothly. Further thanks to Helen Falconer, Research Governance Officer for Cardiff University and Carl Phillips, Executive Officer for the South East Wales Research Ethics Committee who were both very helpful towards completing the ethics approval process.

Dr Ausama Atwan was the one person I could always trust and approach for any query that I had. He has since become a very close friend and has continued to counsel me through my professional career. I am truly indebted to him.

I could not have managed without Dr. Andrea Cueva, who was one of the reviewers on the systematic review and supported me heavily and was always a reliable, hard-working colleague. I would also like to thank Clarissa Rizzo and Matthew Manfre, ERASMUS students from Malta, for their contribution and help with the initial stages of the systematic review.

I could not have completed the DLQI mapping study without Professor Richard Kay. He ensured I understood all the difficult statistical concepts and spent several hours at a time discussing complex ideas over Skype and in person. Thank you for helping me complete one of the most challenging aspects of my thesis!

The Cardiff University Dermatology team were all wonderful and assisted me at every step: Joy Hayes, Owen Crawford, Sonia Maurer, Susan Williams, Dr. Flora Kiss, Heather Williams, Paulina Damiecka and Ruth Williams.

Dr. Nutjaree Johns kindly provided a lot of her expertise to the electronic DLQI study and her knowledge of statistics and study design was invaluable. I truly learnt a lot from her.

Several students have helped with data collection and as assessors without whom I would have struggled: Niloufar Campbell, Naomi Spencer, Sue Chong, Natasha Logier, Zhi Lim and Ooi Chung Sen. It was excellent to see enthusiastic researchers of tomorrow!

Whilst thanks are due to everyone in my professional life, those in my personal life deserve my equal gratitude for all that they've done. My parents have always encouraged me to be the best version of myself. They supported me through my academic struggles in every way with their words of wisdom and unparalleled prayers. My father, especially, always encouraged me to aim for the best because he believed in my capabilities. My wife Reja, a full-time homeschooler as well as postgraduate student herself, has always been supportive by giving me the time to rest, work and play. Without her sacrifices and kindness I would not have been able to achieve a fraction of my goals. My children Musa, Maryam, Yusha and Rahma are joyous gifts from God and gave my soul much needed ease during difficult days. I hope they see the sacrifices both parents have made and supersede us in their ambitions.

I want to thank my supportive sister Kiswa for her (brutally!) honest advice whenever I needed it, as well as my brother-in-law, Shehzad. There were always supporting me with their kind words and accompanying me and my family on holidays across the world!

I would like to thank Inaam-ul-Haq, who is like a big brother to me and was someone I could rely on whenever I was stuck or needed some clarity during my thesis and beyond. His mum, may she rest in peace, always treated me like a second son and I will always miss her kindness.

Iltefat Hamzavi, my cousin and also a Dermatologist based in the USA, has always been a voice of reason and guidance and I am grateful for his presence in my life.

To know a man, know who his friends are. I have had the utmost pleasure of being surrounded by the best of them – my Friday night crew. They will never know how a few casual hours every Friday saved me when things were really tough. AA, Emaad, Inaam, Kent, Kidders, Mohs, Putree, Qas and Sha Bhai have been there from the start of my struggles to the end and we've experienced a whole lot as a group of friends. I wouldn't call them anything less than simply marvelous.

This has been an incredible journey, much in part due to the people I have had the pleasure to meet and learn from. These are memories and hard work that I will cherish, forever.

Summary

Psoriasis has considerable impact on the quality of life (QoL) not only of patients but also of their relatives. This impact is as important to consider as clinical parameters in the management of psoriasis. This thesis aims to evaluate current practices in QoL measurement and devise new solutions to improve these processes, to benefit patients, clinicians and policy makers.

The systematic review describing data from 100 psoriasis randomised controlled trials (33 topical, 18 systemic small molecules, 39 biologics and 19 other interventions) in 33,215 subjects highlights that QoL assessment is integral to the assessment of new therapies and to the management of psoriasis. Amongst a variety of generic and disease-specific measures, the Dermatology Life Quality Index (DLQI) is the most commonly utilised QoL tool, though there is heterogeneity in its reporting and analysis. The Minimal Important Clinical Difference (MCID) is an essential baseline in determining treatment efficacy, particularly across measures, but remains grossly under-utilised. This thesis proposes a novel concept of 'multiple-MCID', as well as recommendations on QoL reporting.

In order to address some of these identified recommendations, an electronic version of the DLQI has been validated for the first time using International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines (n=104). The electronic version was scored equivalently to the paper counterpart, was preferred by majority of patients (76%) and provided advantages such as cost-efficiency, quicker completion times and more accurate data analysis. The electronic Psoriasis Area Severity Index (PASI) was also validated demonstrating reduced inter-rater variability. Electronic use of these measures would help standardise QoL measurement and propel psoriasis management into the digital era.

Whilst QoL information is invaluable for clinical decision-making, generic measures are utilised by healthcare policy-makers for resource allocation. This is not always representative of the impact revealed by disease-specific QoL measures. In order to solve this dilemma, the DLQI was mapped to EQ-5D to generate utility values using ordinal logistic regression (OLR) from a dataset of 4,010 patients. This sample size was large enough to allow it to be split in half to perform external and internal validity. Where previous methods have failed, the OLR mapping method successfully allowed the conversion of DLQI scores to utility values for large cohorts of patients, using split half validation and Monte Carlo Simulation. This has the potential to be very useful in economic appraisals of any skin disease, including psoriasis.

By standardising QoL measurement, validating its electronic data capture and translating this information into meaningful healthy utility information, it is hoped this work further consolidates the central role of QoL assessment in psoriasis.

List of Abbreviations

-2LL	-2 Log Likelihood
AA	Ausama Atwan
AAD	American Academy of Dermatology
AC	Andrea Cueva
ACNE-QOL	Acne-specific Quality of Life Questionnaire
AD	Atopic Dermatitis
APP	Application
AYF	Andrew Y Finlay
BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists' Biologic Interventions Register
BD	Betamethasone Diproprionate
BNF	British National Formulary
BSA	Body Surface Area
CADI	Cardiff Acne Disability Index
CADIS	Childhood Atopic Dermatitis Impact Scale
CALC	Calcipotriol
CBA	Computer-Based Assessments
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
CU-Q2OL	Chronic Urticaria Quality of Life Questionnaire
DIF	Differential Item Functioning
DFI	Dermatitis Family Index
DLQI	Dermatology Life Quality Index
DLQI-R	Dermatology Life Quality Index - Relevant
DNA	Deoxyribonucleic acid
DQOLS	Dermatology Quality of Life Scales
DSQL	Dermatology-Specific Quality of Life
EADV	The European Academy of Dermatology and Venereology
EOW	Every Other Week
EPRO	Electronic Patient Reported Outcome
EQ-5D	EuroQol Five-Dimensions
ESDR	European Society for Dermatological Research
FA	Faraz Ali
FACT-M	Functional Assessment of Cancer Therapy – Melanoma
FDLQI	Family Dermatology Life Quality Index
FLQA-d	Freiburg Life Quality Assessment
FROM-16	Family Reported Outcome Measure
GHQ-12	General Health Questionnaire
HLA-C	Human Leukocyte Antigen-C
HOME	Harmonising Outcome Measures in Atopic Eczema
HRQOL	Health-Related Quality Of Life
HTA	Health Technology Assessment
ICC	Intra-class Correlation Coefficient
IDQOL	Infants' Dermatitis Quality of Life Index
IID	International Investigative Dermatology
IL	Interleukin
INTODERMQOL	Infants' and Toddlers' Dermatology Quality of Life
IOF	Impact on Family Scale
IOS	Apple's Operating System
IQR	Interquartile Range

ITT	Intention-To-Treat
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IVR	Interactive Voice Response
LCD	Liquor Carbonis Distillate
LS-PGA	Lattice-System Physician's Global Assessment
MAE	Mean Absolute Error
MCBT	Mindfulness-based Cognitive Therapy
MCID	Minimal Clinically Important Difference
MCS	Mental Component Summary
MHC	Major Histocompatibility Complex
MLCD	Major Life Changing Decisions
MLCDP	Major Life Changing Decisions Profile
MRNA	Messenger Ribonucleic Acid
MSE	Mean Square Error
MTX	Methotrexate
NAPSI	Nail Psoriasis Severity Index
NHP	Nottingham Health Profile
NICE	National Institute for Health and Care Excellence
NRES	National Research Ethics Service
NUVB	Narrowband Ultraviolet Type B
OLR	Ordinal Logistic Regression
QOL	Quality of Life
QOLIAD	Quality of Life Index for Atopic Dermatitis
RCT	Randomised Controlled Trial
PAGA	Patient's Global Assessment
PASI	Psoriasis Area and Severity Index
PASS	Psoriasis Assessment Severity Score
PCS	Physical Component Summary
PDA	Personal Digital Assistant
PDE-4	Phosphodiesterase-4 Inhibitor
PDI	Psoriasis Disability Index
PEASI	Psoriasis Exact Area and Severity Index
PFI-14	Psoriasis Family Index - 14
PGA	Physician's Global Assessment
PIQOLAD	Parents Index of QoL in Atopic Dermatitis
PLASI	Psoriasis Long-based Area and Severity Index
PLSI	Psoriasis Life Stress Inventory
PQOL-12	12-Item Psoriasis Quality of Life Questionnaire
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient-Reported Outcomes
PROM	Patient-Reported Outcome Measure
PROSPERO	The International Prospective Register for Systematic Reviews
PROSPI-S	Simplified Psoriasis Index (severity completed by professionals)
PSA	Psoriatic Arthritis
PSAQOL	Psoriatic Arthritis Quality of Life measure
PSI	Psoriasis Symptom Inventory
PSOREG	Psoriasis Registry
PSORIQOL	Psoriasis Index Quality of Life
PSS	Psoriasis Severity Scale
PUVAsol	Psoralen and Ultraviolet A
QALY	Quality-Adjusted Life Year
QLI	Quality of Life Index
Quimp	Quality of Life Impairment

SAPASI	Self-Administered PASI
SASPI-S	Simplified Psoriasis Index (severity completed by patients)
SCHARR	School of Health and Related Research
SCI	Skin Cancer Index
SD	Standard Deviation
SG	Standard Gamble
SID	Society for Investigative Dermatology
SIGN	Scottish Intercollegiate Guidelines Network
SIP	Sickness Impact Profile
SF-36	Short-Form 36
SPASI	Simplified PASI
sPGA-G	Static Physician's Global Assessment of Genitalia Scale
SPI	Simplified Psoriasis Index
SPI-I	Simplified Psoriasis Index (Interventions)
SPI-P	Simplified Psoriasis Index (Psychosocial Impact)
SPI-S	Simplified Psoriasis Index (Severity Score)
SPSS	Statistical Package for the Social Sciences
SR	Systematic Review
TNF	Tumour Necrosis Factor
T-QOL	Teenager's Quality of Life Index
TTO	Time Trade-Off
UKSIP	United Kingdom Sickness Impact Profile
UVA	Ultraviolet Type A
UVB	Ultraviolet Type B
VAS	Visual Analogue Scale
WHO	World Health Organization
WHOQOL	World Health Organization Quality of Life
WIFI	Wireless Fidelity

List of Tables

List of Figures

Chapter 1: General Introduction

1.1 Background

1.1.1 Brief overview of the three studies

The focus of this PhD thesis is centred around recognising the importance of quality of life (QoL) assessment in psoriasis sufferers and the development of novel strategies in supporting improvements in patient wellbeing and clinical outcome. The thesis is comprised of three separate studies covering key QoL domains that were felt to be central to psoriasis management including: QoL reporting in psoriasis randomised controlled trials (RCTs); validating relevant electronic patient reported outcome measures (PROMs) in a clinical setting and deriving generic economic data from dermatology-specific PROMs.

In brief, a summarised overview of the three parts of this thesis is detailed below:

1) A systematic review to highlight current QoL reporting standards for psoriasis RCTs and recommendations for researchers that may arise from this detailed analysis.
2) Electronic validation of the two most commonly reported outcome measures in psoriasis: Psoriasis Area Severity Index (PASI) (Fredriksson and Pettersson 1978), a clinical outcome measure, and the Dermatology Life Quality Index (DLQI).
3) A mapping study to devise a model to enable the derivation of utility values from the most commonly used PROM in dermatology, the DLQI (Finlay and Khan 1994)

1.1.2 Rationale and 'three-pronged' approach

The focus of this thesis is within the field of dermatology, though attempting to cover all major skin diseases would prove to be a challenge. Therefore, this work will be centred in particular around psoriasis given its recognition as a major global health problem by the World Health Organization (WHO) affecting up to 4% of the worldwide population (Organization 2019). Along with significant impact on QoL (Langley et al. 2005), psoriasis is now considered a systemic disease and has been associated with the metabolic syndrome (Cohen et al. 2008). There is an increased prevalence of metabolic syndrome in psoriasis patients with a higher body surface area involvement (Langan et al. 2012). Patients may also suffer with several other comorbidities such as depression, psoriatic arthritis and other cardiovascular risks (Heydendael et al. 2004; Takeshita et al. 2017) and these are further elaborated on in section 1.2.3.

The disease burden of psoriasis is considerable and far-reaching. For patients, the disease may impact physical, social and emotional well-being (Krueger et al. 2001). However, psoriasis patients do not suffer alone; partners, close family members and relatives inevitably experience QoL impairment. This often results in extra housework, psychological pressures including anxiety, embarrassment and lack of self-confidence, limitations to holiday plans, and strained relationships with the patient and/or other family members (Eghlileb et al. 2007).

There are wider health economic implications: patients with severe disease incur increased medical costs and often become less productive at work (Fowler et al. 2008). The presence of comorbidities may further exacerbate this burden due to increased outpatients visits, emergency visits and potential hospitalisation (Boehncke and Menter 2013).

For many decades, the management of psoriasis was limited to select topical and systemic treatments with variable results (Basra and Hussain 2012). Non-responsive patients often reached a ceiling of care, with no further options available. However, psoriasis management has undergone a revolution with the advent of biologic treatment in the last two decades (Singri et al. 2002). This was preceded a few years earlier by the creation of the DLQI in 1994, the first dermatology-specific quality of life measure (Finlay and Khan 1994). Though many other QoL measures are available and have also been used in psoriasis trials, the DLQI has become the preferential QoL tool (Bhosle et al. 2006). The similar timescale between the introduction of biologics and the development of the DLQI may have contributed towards its status as a key PROM to assess treatment efficacy alongside longer established clinical measures such as the PASI (Fredriksson and Pettersson 1978). Furthermore, several validation studies have shown the DLQI to be sensitive to change in clinical status for psoriasis patients over time, further adding to its usefulness as an outcome measure (Mazzotti et al. 2003; Lewis and Finlay 2004). Despite its limitations (which shall be discussed later), the DLQI has become integral to several registries internationally and is a requirement for assessing disease severity in the British Association of Dermatologists (BAD) guidelines for biologic therapy for psoriasis (Smith et al. 2020), and in guidelines in many other countries (Singh and Finlay 2020). Therefore, the assessment of QoL impairment in psoriasis has become synonymous with the use of the DLQI, which is the most widely used QoL measure in psoriasis worldwide (Feldman and Krueger 2005).

Several challenges remain, however, in the way psoriasis QoL data is captured, reported and consequently utilised in both clinical and research settings.

1.1.2.1 Challenges of implementing quality of life measurement in practice

Given that QoL is central to managing psoriasis and influencing treatment decisions, it is important that it is effectively and routinely captured in a clinical setting. The DLQI is a 10-item questionnaire that takes around two minutes to complete on paper (Loo et al. 2003). Despite this, in one study only 64% of patients completed the DLQI during consultations, and in this study only a quarter of clinicians utilised these scores as part of their overall care (Salek et al. 2007). The frequency with which the DLQI is used in routine dermatology consultations is not known and there is likely to be wide variation within and between different countries. Recent technological advances have somewhat countered these shortfalls by the introduction of electronic PROMs (Deal et al. 2010; Bächinger et al. 2016) to facilitate more efficient QoL data capture. Electronic data capture has several advantages over its paper counterpart, naturally leading to an increase in this format being used over recent years (Leidy and Vernon 2008). However, these versions are not routinely validated, raising questions as to whether the scores are truly comparable to the paper format (Coons et al. 2009). This also holds true with the DLQI as though it has been used electronically for years no formal validation has yet been conducted in this format.
The PASI has become the gold standard for assessing clinical severity, though there are valid criticisms regarding its complexity, lack of sensitivity and poor inter-rater agreement (Ashcroft et al. 1998; Gourraud et al. 2012). The PASI is therefore an important part of any electronic application for monitoring psoriasis treatment and disease progression. It is hoped that a validated electronic application including both the DLQI and PASI would reassure users and further encourage its use amongst clinicians and patients given the format's inherent advantages and acceptance (Saleh et al. 2002; Velikova et al. 2002).

There is a diverse range of QoL tools that are utilised in psoriasis RCTs ranging from generic to disease-specific measures – each with their respective strengths and weaknesses (Bhosle et al. 2006). This may result in confusion on which is the ideal measure to use, whilst creating a heterogeneous dataset that cannot be directly compared. This posits several problems in the standardisation of care to truly discriminate between treatment efficacies. It is therefore crucial to identify current reporting practices in interventional trials for psoriasis to be able to formulate suggestions and criteria by which QoL measurement may be standardised in the future.

Whilst QoL measurement is invaluable for patients and clinicians – its conversion to 'Quality-Adjusted Life Years' (QALYs) is the foundation for deriving meaningful health economic data for decision makers. The QALYs, in turn, may be converted to utility values using a variety of

methods (Szende and Schaefer 2006) allowing governing bodies to determine risk-benefit of interventions across all health specialties. The QALYs are in fact the preferential measure of benefit for health organisations such as the National Institute for Health and Care Excellence (NICE). Generic measures such as the EQ-5D (EuroQol five-dimensions scale) are often used for generating health utility data. However, generic measures are intrinsically designed to be used across all medical conditions for cross-specialty comparison of cost-benefit and therefore their ability to truly capture skin-disease-specific QoL impairment is debatable: dermatology subjects were not considered in the creation of the EQ-5D. In response to this, efforts have been made to 'map' specialty-specific measures (e.g. DLQI) to generic measures (e.g. EQ-5D), though previously without much success (Currie and Conway 2007; Blome et al. 2013). The NICE defines mapping as 'the development and use of a model or algorithm to predict utility values using data on other indicators or measures of health' (Longworth and Rowen 2011). If attainable, such an algorithm would allow more accurate and specialty-specific utility values to be calculated, thereby providing true health status data from optimally designed PROMs with high sensitivity to change.

1.1.2.2 Quality of life as a common thread to improve psoriasis management

The three studies that form this thesis arise after examining the aforementioned challenges in a bid to improve the overall management of psoriasis patients – from patient to healthcare decision makers. The DLQI also becomes a central subject of this thesis given its integral role in psoriasis management, whilst also continuing to be the most utilised PROM across all dermatology diseases worldwide (Basra et al. 2008a).

Firstly, a systematic review will be designed and conducted to identify current QoL measurement and reporting standards in psoriasis RCTs. This would also highlight the most commonly used PROMs in psoriasis trials. Secondly, a study to validate an electronic version of the DLQI and PASI could potentially improve QoL and disease severity reporting in clinical consultations as well as research settings, whilst also alleviating concerns of certain users regarding the format's validity. Lastly, the third study will aim to devise and test a mapping algorithm to generate EQ-5D utility values from the DLQI, given the strong conceptual overlap between the two measures (Longworth and Rowen 2011). This could significantly impact how healthcare authorities allocate resources towards the management of psoriasis as the DLQI is able to generate more meaningful data for economic analysis.

The overall aim of this thesis will thereby be to improve upon current practices within the management of psoriasis, to ultimately generate suggestions and frameworks to guide clinicians and researchers in the future.

1.2 Psoriasis

1.2.1 Background

Psoriasis is a chronic inflammatory relapsing-remitting skin condition that is defined by thick silvery scaly plaques that commonly affect the extensor surfaces of the body, but may affect any region including the scalp, nails and genitalia. The most common type is psoriasis vulgaris contributing to up to 90% of the worldwide psoriasis prevalence (Deng et al. 2016). More recent research has shown that psoriasis may in fact be considered a systemic inflammatory condition and it has been linked to the metabolic syndrome associated with cardiovascular disease, obesity, diabetes and other autoimmune conditions (Cohen et al. 2008). Furthermore, there is an overlap between the genetic loci for psoriasis and inflammatory bowel disease, in particular Crohn's disease (Ellinghaus et al. 2012). This multi-faceted aspect of psoriasis exacerbates the overall impact on QoL for patients, as well as having significant financial implications for healthcare services (Menter et al. 2008a; Chern et al. 2011). The prevalence of psoriasis is still not fully known but has been reported to range from 0.91% (United States) to 8.5% (Norway), with the incidence ranging from 78.9/100,000 (United States) to 230/100,000 (Italy) per annum (Parisi et al. 2020). It also tends to be less common in Asian and African populations compared to Caucasians and Scandinavians (Parisi et al. 2020).

Joints may also be involved as an inflammatory seronegative spondyloarthropathy (psoriatic arthritis, PsA) causing significant disability if left untreated (Ackermann and Kavanaugh 2008). The prevalence of PsA amongst psoriasis patients is not definitively known, but has been reported to be between 6 - 42% (Hukuda et al. 2001; Ruderman and Tambar 2004). A meta-analysis by Alinaghi et al. (2019) assessed nearly a million patients globally and found the prevalence to be around 19.7%.

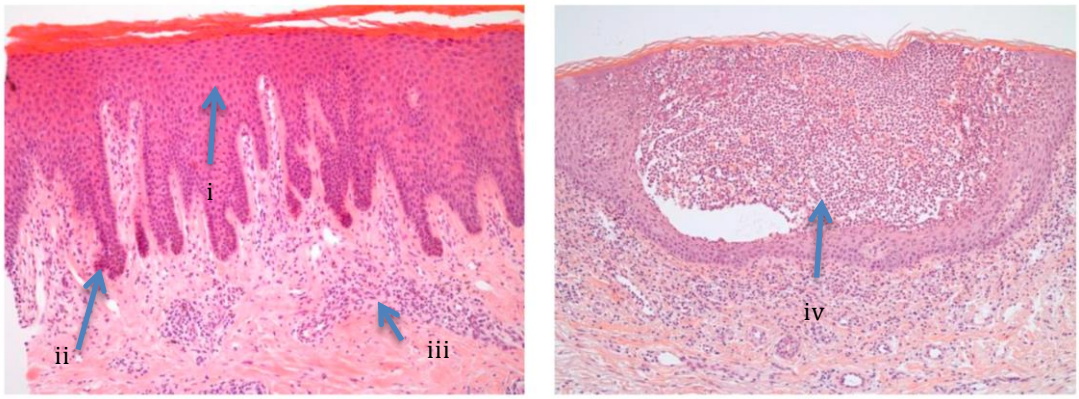
1.2.2 Pathophysiology

Genetics has a significant role in the onset of psoriasis, with many studies conducted on families and twins demonstrating familial predisposition (Allione et al. 2015). Major histocompatibility complex (MHC), human leukocyte antigen (HLA-C) and several genetic loci

have been found to be linked to psoriasis. The HLA-cw6 allele on the PSORS1 gene is perhaps the most important susceptibility locus to be found in psoriasis (Strange et al. 2010).

Histologically, the epidermis demonstrates irregular acanthosis, hyperplastic bloody vessels, parakeratosis and inflammatory infiltrates including T calls, neutrophils, macrophages and dendritic cells (Figure 1.1) (Schцn et al. 2005; Rendon and Schäkel 2019).

Figure 1.1 Histological image of psoriasis demonstrating (A) parakeratosis (i), acanthosis (ii) and dermal inflammation (iii) (B) neutrophilic infiltrates of pustular psoriasis (iv) (adapted from Rendon and Schäkel (2019)). Permission granted for image use as in Appendix XXX.



Psoriasis is a T-cell driven autoimmune disease with abnormal innate and adaptive immune responses (Harden et al. 2015). It is classed as a Th1 disease, where the cutaneous infiltrate consists mainly of memory effector CD45 cells (Vissers et al. 2004). There is usually some form of trigger – trauma, infection, drugs or stress, which is known as the 'initiation phase' whereby T-cells are activated and migrate in to the epidermis, cause hyperplasia due to keratinocyte hyperproliferation (Flatz and Conrad 2013). As the epidermis acts as the body's main defence to the external environment, this hyperplasia is a key component of the innate immune response. Natural killer T Cells and natural killer cells are part of the subsequent inflammation, as well as occasionally neutrophils, especially in pustular disease (Nickoloff 1999; Gaspari 2006). The initiation phase is followed by a 'maintenance phase' which defines the chronicity of the condition (Rendon and Schäkel 2019). Streptococcal infections and the creation of 'superantigens' have also been shown to trigger the T-cell activation seen in psoriasis (Telfer et al. 1992).

Endogenous antimicrobial peptides and dendritic cells (in particular Langerhan cells, XIIIa-positive and plasmacytoid dendritic cells) also have a role in the development of psoriasis.

Langerhan cells survey peripheral antigens and present them to T-cells in local draining lymph nodes. This process is impaired in psoriasis suggesting that Langerhan cells may have a crucial regulatory role in cutaneous immunity. Plasmactyoid dendriti c cells produce interferon-alpha which drive Th1 responses in predisposed individuals leading to the formation of plaques (Griffiths et al. 2005; Griffiths and Barker 2007). This further consolidates the relationship between the innate and adaptive immune processes. A range of cytokines are implicated and this area of expertise is rapidly evolving (Deng et al. 2016). IFN-Ɣ has been shown to play a part earlier on in the development of psoriasis, by inducing the production of antimicrobial peptides, and promoting the release of cytokines such as interleukin (IL)-1 and IL-23. Tumour Necrosis Factor (TNF) alpha (α) has also been identified as a major pro-inflammatory factor regulating the IL-23/Th17 axis, all of which have been targets for biologic treatment (Deng et al. 2016).
Biopsies from psoriasis plaques demonstrate IL-17 mRNA (messenger ribonucleic acid), which is produced by Th17 as well as various other innate immune cells such as mast cells and neutrophils. Suppressing the IL-17 pathway has been shown to improve psoriasis (Krueger et al. 2012).

IL-23 also plays a key role in the proliferation of Th17 cells, and has a strong relationship with the levels of IL-17 (Stockinger and Veldhoen 2007). IL-23 facilitates keratinocyte proliferation and therefore has a major role in the development of psoriatic plaques. IL-23 also shares a sub-unit with IL-12, with both having a strong presence in psoriasis skin (Deng et al. 2016). However, IL-23 levels tend to be higher and therefore IL-23 is believed to be the greater driving force in psoriasis (Yawalkar et al. 2009). Other inflammatory agents are also considered to be important players, including IL-9, IL-2 and CD8+ T-cells (Deng et al. 2016).

Therefore, the site of initiation of plaque psoriasis may be narrowed down to the TNF-a-IL-23-Th17 pathway/axis. A pro-inflammatory feedback loop is then established among keratinocytes, immune cells, and components of the extracellular matrix (e.g., collagen), leading to sustained, active skin inflammation. This cascade is best summarised in Figure 1.2.

Figure 1.2* The psoriasis pathway (Rendon and Schäkel 2019). Permission granted for image use as in Appendix XXX.

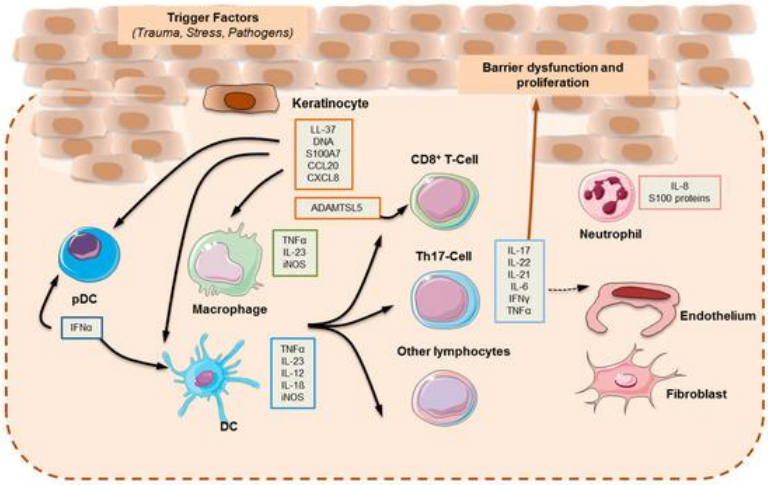
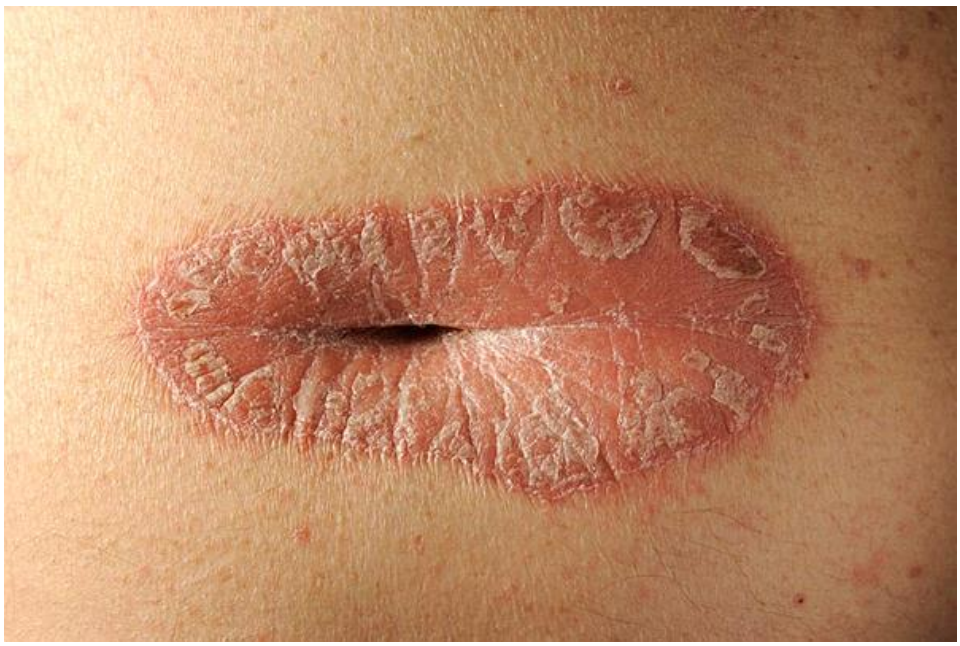


**Diagram demonstrates the trigger factors in psoriasis and the subsequent role of TNFα as a major pro-inflammatory factor regulating the IL-23/Th17 axis. IL-23 facilitates keratinocyte proliferation and therefore has a major role in the development of psoriatic plaques through barrier dysfunction and proliferation. Other inflammatory agents are also considered to be important players, including IL-9, IL-2 and CD8+ T-cells.*
The site of initiation of plaque psoriasis may be narrowed down to the TNF-a-IL-23-Th17 pathway/axis. A pro-inflammatory feedback loop is then established among keratinocytes, immune cells, and components of the extracellular matrix (e.g., collagen), leading to sustained, active skin inflammation.

1.2.3 Clinical presentations & subtypes

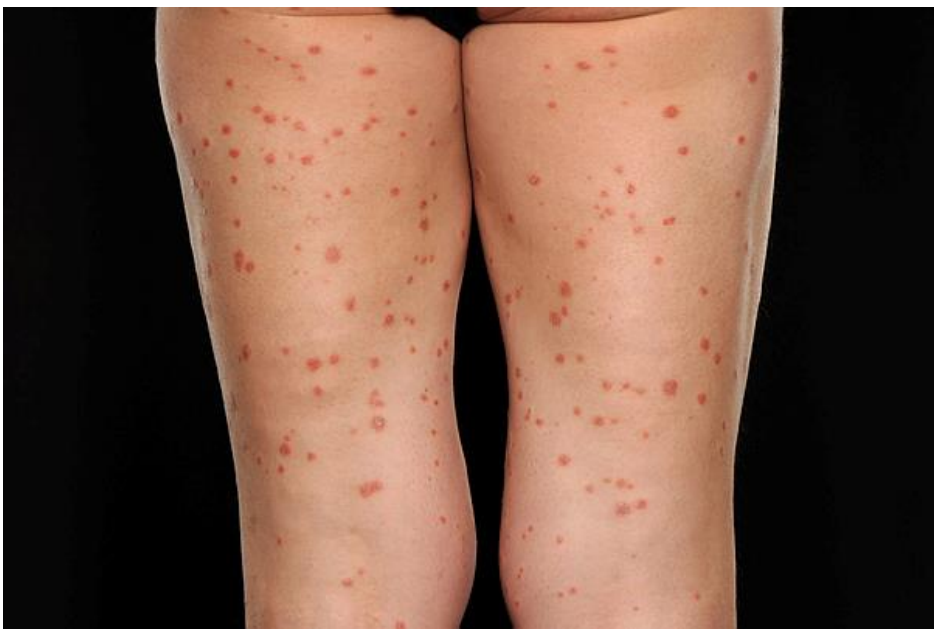
There are various subtypes of psoriasis, with psoriasis vulgaris being the most common (Deng et al. 2016). This presents as the classical plaque type psoriasis (Figure 1.3).

Figure 1.3 Plaque psoriasis (psoriasis vulgaris) (Permission granted by Cardiff and Vale University Health Board. All clinical images used had signed permission from patients to publish the images.)



Inverse psoriasis (also known as flexural psoriasis) usually affects the folds and intertriginous regions of the body. Guttate psoriasis (Figure 1.4) usually has an acute onset, most commonly after group-A streptococcal upper respiratory tract infections (Ko et al. 2010).

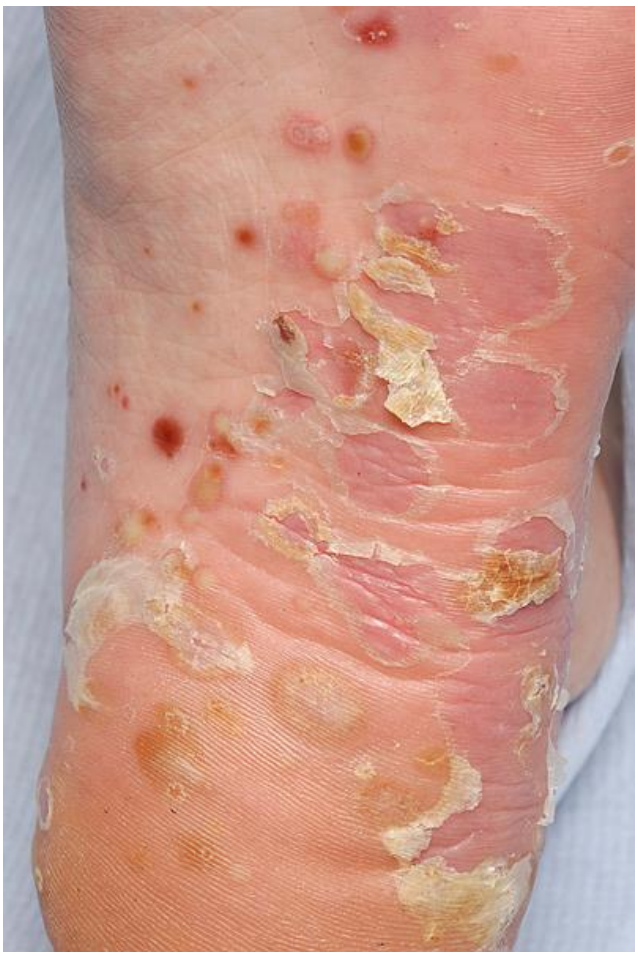
Figure 1.4 Guttate psoriasis (Permission granted by Cardiff and Vale University Health Board. All clinical images used had signed permission from patients to publish the images.)



Pustular psoriasis is identified by the presence of numerous, coalescing sterile pustules and may present in several ways:

a) palmo-plantar pustulosis which affect the hands and feet
b) acrodermatitis of Hallopeau, which affects the distal tips of fingers and toes, including the nails
c) generalised pustular psoriasis (Figure 1.5), which may be acute and is often associated with generalised redness and sub-corneal pustules along with systemic features (Navarini et al. 2017)

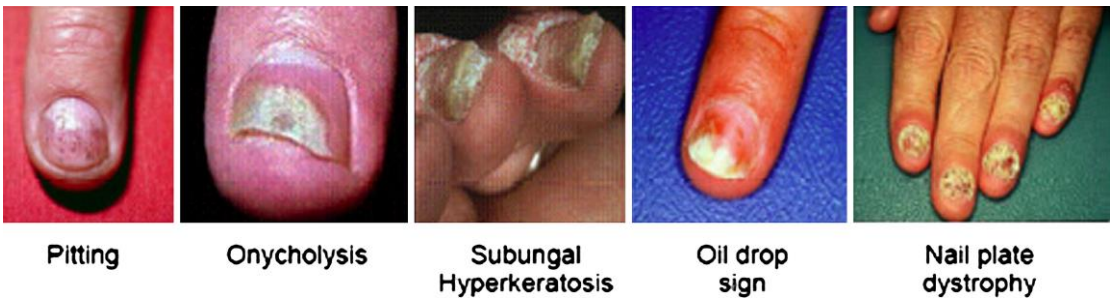
Figure 1.5 Pustular psoriasis (Permission granted by Cardiff and Vale University Health Board. All clinical images used had signed permission from patients to publish the images.)



The final, more severe, subtype is erythrodermic psoriasis, which is a dermatological emergency due to at least 90% of the body surface area being affected by diffuse erythema. This may arise from any other subtype and usually requires admission to hospital (Rendon and Schäkel 2019).

Psoriatic arthritis prevalence is currently unknown, though a diverse range of figures have been reported, and it is often undiagnosed, perhaps in at least 15% of psoriasis patients (Villani et al. 2015). It may be polyarticular or oligoarticular, and is defined by pain, enthesitis and dactylitis. In polyarticular phenotypes, nail involvement is also very common (Stoll et al. 2006). Nail disease may be present in 50% of psoriasis patients, and may be the only presentation of psoriasis in up to 10% of all psoriasis cases (Salomon et al. 2003). It may present as nail plate pitting, onycholysis, oil drop discolouration, splinter haemorrhages or subungual hyperkeratosis (Figure 1.6)

Figure 1.6 Presentations of nail psoriasis (adapted from (Menter et al. 2008a). Permission granted for image use as in Appendix XXXI.



1.2.4 Comorbidities associated with psoriasis

Several comorbidities are associated with psoriasis, including a strong association with the metabolic syndrome (Cohen et al. 2008). Independently, however, several components have been shown to have also shown to have an impact. A 2006 cohort study found that there was an increased risk of myocardial infarction in psoriasis patients, irrespective of other risk factors such as smoking, dyslipidaemia and hypertension (Gelfand et al. 2006). Obesity is considered an independent risk factor with a higher incidence of psoriasis in patients with a higher body mass index (Kumar et al. 2013). Hypertension tends to be more severe and poorly controlled in patients with psoriasis, with poorer control in patients with more severe psoriasis (Takeshita et al. 2015). There is an increased risk of diabetic complications and insulin resistance in psoriasis patients and those with diabetes are more likely to need pharmacological intervention (Azfar et al. 2012).

Studies have also highlighted an overlap in inflammatory and genetic pathways between psoriasis and inflammatory bowel disease (Wolf et al. 2008). However, there are varying degrees of association and prevalence reported in studies, though there seems to be a higher risk of Crohn's disease than ulcerative colitis (Cohen et al. 2009; Li et al. 2013).

Psoriatic arthritis is a chronic musculoskeletal inflammatory disease and though the exact prevalence is not known, it may affect up to 30% of patients usually with plaque-type psoriasis / psoriasis vulgaris (Ritchlin et al. 2017; Ogdie et al. 2020). There are various manifestations of psoriatic arthritis including enthesitis, spondylitis, dactylitis and peripheral arthritis, often resulting in considerable impact on physical functioning as well as social and work life (Orbai et al. 2017).

Psoriasis is also associated with various other comorbidities including hepatic disease (Yeung et al. 2013), nephritic disease (Abuabara et al. 2010) and malignancies (Pouplard et al. 2013; Fuxench et al. 2016). It is clear that patients may experience health-related issues beyond psoriasis and therefore a holistic and complete approach to healthcare is vital.

1.2.5 Clinical Assessment and the PASI

There is a range of clinical assessment tools for physicians and researchers to assess the severity of psoriasis. However, there is no consensus on which of these measures are most suited to be used in clinical trials (Callis et al. 2018). The varying phenotypes of psoriasis means that this is a challenge for both clinicians and patients. Whilst tools such as the PASI may be adequate for assessing plaque psoriasis affecting the body/trunk, most are poor at assessing disease in other areas including the scalp, nails and genitalia. As a result, region specific measures have also been created to assess the impact of localised disease, such as the Nail Psoriasis Severity Index (NAPSI) (Rich and Scher 2003) and the static Physician's Global Assessment of Genitalia (sPGA-G) scale (Merola et al. 2017).

Naldi et al. (2003) have highlighted that at least 44 clinical measures are used in trials, with none of them having been fully validated or standardised. Indeed, there are no 'ideal' measures to be used in psoriasis (Weisman et al. 2003; Feldman and Krueger 2005). In general, the high inter-rater variability and the inability of many tools to discriminate appropriately between disease severities is a telling indictment of the current state of this science.
Spuls et al. (2010) highlighted 11 main psoriasis assessment tools used in clinical trials and these, along with their descriptions, are summarised in Table 1.1.

Table 1.1 Most common psoriasis severity assessment tools, adapted from (Spuls et al. 2010)

Instrument	Description
BSA	Estimation of involved body surface area, several methods are used
Signs	Evaluation of the plaque characteristics erythema, scaling, and induration. Erythema and scaling are easily influenced by external factors
PASI	The affected area and lesion characteristics are entered in a formula that results in a score from 0 to 72. The PASI is most often used in clinical trials
PGA	The PGA is a 5, 6, or 7-point ordinal rating ranging from "clear" to "very severe psoriasis"
PaGA	The PaGA is an ordinal rating ranging from "clear" to "very severe psoriasis" assessed by the patient
SAPASI	The SAPASI is a structured PASI-like instrument designed for patient self-assessments of severity
PASS	The affected area and plaque characteristics are entered in a formula that results in a score from 0 to 140. Infiltration is given more weight than erythema and scaling
LS-PGA	The LS-PGA integrates ranges of involved BSA and the overall plaque morphology in which infiltration is given more weight
SPASI	The SPASI equals the sum of the average redness, thickness, and scaling of all the psoriasis lesions multiplied by the percentage of body surface area involved
PEASI	The PLASI is derived from the PASI but uses actual BSA percentages instead of an area score
PSI	The PSI addresses various symptoms of psoriasis lesions, with a score ranging from 0-32
PLASI	The PLASI is derived from the PASI but uses six BSA groupings with finer partitioning for smaller extents of BSA
SPI	The SPI consists of three elements: a severity score (SPI-s), psychosocial impact (SPI-p) and historical course/interventions (SPI-i).

The body surface area (BSA) is quite a simplistic tool assessing the body percentage affected by psoriasis. This is either calculated by using the "rule of nines" (whereby the head and neck, arms, legs etc, are allocated 9% total each) (Ramsay and Lawrence 1991), or using the method where one hand surface, including fingers, (or "handprint") is equivalent to 1% BSA (Thomas and Finlay 2007). This method generally has excellent inter-rater variability (Yune et al. 2003).

PASI, first used to assess oral retinoid efficacy, is a widely used tool to assess the severity of psoriasis (Fredriksson and Pettersson 1978). The score ranges from 0-72 (72 being most severe), and efficacy of treatments are often described as percentage reduction in PASI i.e. PASI 50, PASI 75 would represent a 50% or 75% reduction in PASI, respectively. The PASI mostly completed by trained health care professionals and study investigators. Although PASI

has been criticised for lacking sensitivity and accuracy, being complex, and its use being resource intensive, in the absence of a "gold standard" it has become an almost universal outcome measure in clinical trials of drugs used for psoriasis (Ashcroft et al. 1999; Harari et al. 2000; Berth‐Jones et al. 2006). It is often used to validate other clinical measures, and indeed correlates well with these physician-based assessments, but less so with HRQoL (Health-related quality of life). However, the PASI has had very few reliability tests conducted and the response distribution is also considered low (Harari et al. 2000; Langley and Ellis 2004; Berth‐Jones et al. 2006). Experienced users produce more reliable PASI results than novice assessors (Langley and Ellis 2004). There are several other criticisms of PASI including concerns around the categorical assignment and weight of each of its components (Weisman et al. 2003), as well as limited inter-rater agreement (Gourraud et al. 2012). Furthermore, there is debate around the interpretation of PASI scores (Van de Kerkhof 1992; Carlin et al. 2004) though descriptors 'mild', 'moderate' and 'severe' have also been commonly used (Schmitt and Wozel 2005). A simplified version also exists, known as Simplified-PASI (SPASI), though its reliability has not been tested and it seems to be less sensitive to change when the BSA is less than 10% (Louden et al. 2004). Two other variants of the PASI, the Psoriasis Long-based Area and Severity Index (PLASI) and Psoriasis Exact Area and Severity Index (PEASI), provide a more accurate evaluation of psoriasis improvement. However, neither measure has been validated or tested for reliability (Jacobson and Kimball 2004).

The Simplified Psoriasis Index (SPI) (Chularojanamontri et al. 2013) is adapted from a holistic measure created in the late 1990s known as the Salford Psoriasis Index (Kirby et al. 2000). The SPI consists of three elements: a severity score (SPI-s), psychosocial impact (SPI-p) and historical course/interventions (SPI-i). The severity score is intended to replace the PASI and is weighted to identify the 'high impact' areas such as the face and genitalia and may be completed by either professionals (proSPI-s) or patients (saSPI-s). The SPI-p was found to have high correlation with the DLQI (r=0.89) and proSPI-s with the PASI (r=0.91). It has been shown to have good intra-rater and inter-rater reliability (Chularojanamontri et al. 2013) and further validation studies have been conducted to demonstrate its interpretability and responsiveness to change (Chularojanamontri et al. 2014).

The Physicians' Global Assessment (PGA), a simpler method of assessing psoriasis severity, has also been used statically (at baseline) or dynamically (change from baseline to follow-up) (Farhi et al. 2008) as a 5-7 point ordinal scoring system ranging from 'clear' to 'very severe'. It

has been shown to correlate well with the PASI as well as with HRQoL assessments (Gottlieb et al. 2003a).

Patients may also self-assess their psoriasis using the Self-Administered PASI (SAPASI) by shading in the affected areas on a body map and using a VAS (visual analogue scale) for the erythema, scaling and induration aspects of the assessment. The total score is then calculated by the assessor, ranging from 0-72 as for the PASI (Fleischer Jr et al. 1994). Overall, the measure has very good reliability (Feldman et al. 1996) with a strong correlation to the PASI in most studies (Feldman et al. 1996; Kirby et al. 2000; Sampogna et al. 2003).

The Psoriasis Symptom Inventory (PSI), though not strictly a clinical outcome measure, is an eight-item PROM designed to assess various psoriasis symptoms including itching, redness, cracking, burning, flaking, stinging and pain (Martin et al. 2013). It is available in 2-hour and 7-day versions which have been shown to be equivalent, sensitive to change as well as possess good construct validity (Bushnell et al. 2013).

There are many other psoriasis assessment tools as seen in Table 1.1, with most having been developed to tackle some of the shortfalls of the PASI. However, they have not superseded the PASI in terms of its clinimetric properties nor its popularity, as it remains the most commonly used clinical severity measure in psoriasis worldwide (Spuls et al. 2010).

1.2.6 An overview of the management of psoriasis

1.2.6.1 Life-style interventions

The management of psoriasis is challenging, particularly for mild and moderate disease where systemic treatment or biologics may not be indicated. Nevertheless, there are conservative measures that may be employed by psoriasis patients to reduce disease burden. For example, in obese/overweight patients, non-surgical and non-medical weight loss may reduce the severity of psoriasis (Upala and Sanguankeo 2015). An RCT by Naldi et al. (2014) demonstrated that this demographic group may also benefit with dietetic control alongside physical exercise.

Smoking cessation and a reduction in alcohol intake have also shown to be important prognostic factors in psoriasis (Higgins 2000). The use of simple measures such as this is known as 'disability prevention' (Farber and Nall 1984), and may go a long way towards reducing prevalence, severity and morbidity.

1.2.6.2 Topical treatments

Topical steroids are very widely used in the treatment of psoriasis, ranging from mild (e.g. 1% hydrocortisone) to very potent strengths (e.g. clobetasol proprionate) (Lebwohl 1995). However, potent topical steroids should not be used long-term due to the risks of numerous side-effects such as epidermal thinning, bruising, ulceration and striae (Coondoo et al. 2014). Other topical treatments include coal tar, tazarotene, salicylic acid, anthralin and vitamin D analogs such as calcipotriol (Lebwohl and Ali 2001). Calcipotriol is more effective than anthralin (Berth‐Jones et al. 1992) and coal tar (Tham et al. 1994) resulting in the latter two to be less commonly used in recent times (Reid and Griffiths 2020). Combination treatment of calcipotriol and betamethasone as a two-compound product has also shown to be efficacious in the treatment of plaque psoriasis (Kragballe et al. 1991) but also scalp psoriasis (Kragballe et al. 2009). Salicylic acid is particularly helpful for thick scales and may have a keratolytic effect (van de Kerkhof and Franssen 2001).

1.2.6.3 Phototherapy

If topical therapies fail to control disease then phototherapy is a safe and widely used alternative. Oral or topical psoralens (photosensitising chemicals) in combination with ultraviolet-A (UVA) phototherapy is a commonly used treatment, but is being increasingly replaced by narrowband ultraviolet-B (UVB) phototherapy (Picot et al. 1992; Reid and Griffiths 2020). Ultraviolet-B in combination with oral retinoids may also produce significant improvement of symptoms (Ruzicka et al. 1990). However, phototherapy may be inconvenient for patients, as the treatment often requires multiple weekly visits for a few months. There is also an increased risk of skin cancers with this mode of treatment (De Rie et al. 2004), with UVA phototherapy in particular linked to squamous cell carcinomas (Ling et al. 2016).

1.2.6.4 Systemic treatments

In about a fifth of psoriasis patients, topical therapies alone are insufficient to adequately control symptoms (De Rie et al. 2004). Therefore, systemic treatments are considered for moderate-severe cases including methotrexate, azathioprine, ciclosporin and retinoids. Some of the common systemic treatments in sufferers of severe psoriasis are listed in Table 1.2 (adapted from Olivier et al. (2010).

Table 1.2 Systemic psoriasis therapy (adapted from Olivier et al. (2010)).

Systemic psoriasis therapy	N (%) of severe psoriasis patients*
Methotrexate	2284 (57.7%)
Psoralen or Phototherapy	680 (17.2%)
Azathioprine	625 (16.5%)
Ciclosporin	412 (10.1%)
Etretinate or Acitretin	351 (8.9%)
Hydroxyurea	222 (5.6%)
Mycophenolate mofetil	12 (0.3%)

**Percentages total up to >100 as some subjects received multiple treatments*

Other important and effective systemic agents include small molecule therapies such as fumaric acid esters (Bovenschen et al. 2010) and phosphodiesterase-4 (PDE-4) inhibitors (Papp et al. 2012a). Systemic treatment is guided by patient needs and requirements. Some treatments are immunosuppressant, hepatotoxic and nephrotoxic (e.g. methotrexate, ciclosporin) whereas others may cause teratogenicity (retinoids), limiting suitable options available to certain patient demographics. Rotational therapy has also been recommended which involves alternating between different treatments to limit the cumulative side effect profile (Weinstein and White 1993).

1.2.6.5 Biological treatments

In the last two decades, the advent of biologic treatment (produced from recombinant deoxyribonucleic acid (DNA) technology) has changed the interventional landscape of psoriasis. Biologics are usually administered subcutaneously and are molecules that target various cytokines in the psoriasis inflammatory cascade. They may also be indicated for use in PsA (Armstrong et al. 2018). Alefacept, a CD2-binding protein, was the first biologic therapy for psoriasis introduced in 2003 (Lebwohl et al. 2003), but was eventually withdrawn due to more efficacious and cost-effective treatments becoming available (Reid and Griffiths 2020). Efalizumab (a monoclonal antibody to CD11a) was another alternative, but was subsequently withdrawn due to cases of progressive multifocal leukoencephalopathy (PML) (Kothary et al. 2011). Later biologics targeted TNF-alpha, though newer biologics have since emerged targeting IL12/23, IL17-A, IL17-A receptors and more recently, IL-23 (Armstrong et al. 2018). However, in the UK, these are only available to patients who have failed (or are contraindicated to) at least two other systemic treatments including methotrexate and ciclosporin, have severe focal disease, and meet the minimum eligibility criteria of PASI 10 and DLQI 10 (Smith et al. 2020). Various factors may influence the choice of biologic: patient

age and weight, patient preference, comorbidities such as PsA, family planning, employment and baseline psoriasis severity, for which criteria may vary from country to country (Davison et al. 2017). Though biologics are generally considered safe with high efficacy (outcomes of PASI 75 ranging from 59-86%), there is a risk of opportunistic infections and reactivation of chronic infections such as hepatitis B or tuberculosis, especially as long-term immunotherapy may alter a patient's immune profile (Davison et al. 2017). Furthermore, there are new treatment modalities on the horizon for psoriasis (Bissonnette et al. 2013; Strober et al. 2019; Todorović et al. 2019).

It is important to consider efficacy end-goals when treating a patient with psoriasis. It has been proposed that a 50% reduction in PASI score (PASI 50) and a DLQI score <5 should be the minimal target, with routine monitoring of long-term treatments at regular intervals (Chernyshov 2019). Although ideally treatment goals should aim for DLQI 0 or 1, and complete PASI resolution, a reduction in PASI score of 75% (PASI 75) has been suggested as the most feasible and practical treatment goal (Pathirana et al. 2009). However, with newer generation biologics achieving PASI 90, there is an argument for this to become the new standard of treatment efficacy (Torii et al. 2012; Elewski et al. 2017).

All things considered, when choosing the appropriate treatment, physicians may be guided by several factors: disease severity, treatment ease, efficacy and side-effect profile, as well as patient QoL (De Rie et al. 2004). However, counseling patients is also an important aspect of managing patients with psoriasis. Issues such as lifestyle adjustments and behavior changes should also be discussed in detail with patients. This enables them to regain control over their lives and their condition by converting their negative thoughts and teaching them distraction techniques. By seeking social support, and learning to express worries and emotions, patients may develop coping mechanisms therefore allowing them to truly improve their psychosocial wellbeing (Lebwohl 1995).

1.3 Heath-Related Quality of Life

1.3.1 What is Health-Related Quality of Life?

The terms 'quality of life' (QoL) and 'health-related quality of life' (HRQoL) are often used interchangeably, though the former has been described in literature since the mid 20th century (Bergner 1985). QoL awareness became particularly important as contention arose around

how interventions balance life span with QoL improvement (Kaplan and Bush 1982). Assessing QoL became as important as assessing physical parameters of well-being, eventually leading to the development of health status measurements (Fanshel and Bush 1970). The term 'HRQoL' was later introduced in order to link health-related issues to QoL and was used alongside QALYs as described in the previous section. The concept of HRQoL has mainly been utilised and developed in three major areas: health economics, clinical research and evaluation of clinical practices (Halioua et al. 2000).

WHO defines health as ''a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity'' (Organization 2014). This definition is incorporated in general health measures such as the EuroQol five-dimensions (EQ-5D) (Group 1990) and short-form 36 (SF-36) (Ware et al. 1978). However, the inclusion of 'social well-being' as a key component in the definition of health is debated (Karimi and Brazier 2016), with the suggestion that an individual's level of function within societal context is more important (Patrick et al. 1973). In some ways, defining QoL has proven to be equally difficult with various definitions having been used over the years including: ''a conscious cognitive judgment of satisfaction with one's life'' (Rejeski and Mihalko 2001) and ''an individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns'' (Kuyken 1995). Though many of these definitions have an element of subjectivity, several authors have stated that factors such as physical, material and social wellbeing are just as important (Felce and Perry 1995; Cummins 2005). Regardless, it is generally agreed that QoL is multidimensional covering five key areas: material wellbeing, physical wellbeing, social wellbeing, emotional wellbeing, and development/activity (Felce and Perry 1995).
The definitions of 'health' and 'QoL' may be combined in various ways to deliver an overall summarised definition of HRQoL. In this context, perhaps the most well-known definition is that by Calman (1984): 'The quality of life can only be described and measured in individual terms, and depends on present lifestyle, past experience, hopes for the future, dreams and ambitions.' The author further postulates that any definition of QoL must consider all the experiences and areas of life, including ill-health and treatment. Good QoL is attained when hopes and expectations tally with experience, whereas poor QoL is the opposite notion of this. Therefore, by reducing the gap between aspirations and reality, one may improve QoL. This may be measured in terms of 'satisfaction, contentment, happiness, fulfillment and ability to cope' (Calman 1984).

At least four other definitions have been reported (Karimi and Brazier 2016):

1. “How well a person functions in their life and his or her perceived wellbeing in physical, mental, and social domains of health.” (Killewo et al. 2010)
2. “Quality of life is an all-inclusive concept incorporating all factors that impact upon an individual’s life. Health-related quality of life includes only those factors that are part of an individual’s health.” (Torrance 1987)
3. “Those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment.” (Ebrahim 1995)
4. “Values assigned to different health states” (Weinstein et al. 1996)

It is interesting to note that these definitions do not always refer to the disease or treatment, and often political and economic considerations are excluded (Torrance 1987). Definition ‘4’ refers to utility values and assigning ‘health states’ to calculate QALYs whereby death is rated ‘0’ and perfect health as ‘1’ (Weinstein et al. 1996). Therefore, whilst the HRQoL definitions are multifaceted, health utility values are a very important aspect of overall patient assessment. A more detailed insight on utility values and their calculation shall be covered in Chapter 4.

Though all four definitions vary in what they consider ‘HRQoL’ to be, health has been considered as only one aspect of wider QoL (Ferrans 1990). However, there is a significant overlap: whilst some QoL definitions only assess wellbeing and functioning rather than biological variables, wider QoL problems are undoubtedly influenced by health. For example, certain conditions may not have a direct impact on domains such as economic status, education or housing – however they may all be indirectly impacted. In practice, a measure covering a narrow range of relevant QoL domains tailored to one type of problem or disease may be more specific. However, in order to be fully encompassing, ‘general’ HRQoL measures need to be able to capture most QoL domains.

The terms ‘health’, ‘QoL’ and ‘HRQoL’ are often confusing and used interchangeably. However, quite simply, they are used to describe the impact of health on QoL (Karimi and Brazier 2016). This thesis will use both acronyms ‘HRQoL’ and ‘QoL’ to describe the impact of skin diseases on patient wellbeing (both physical and psychosocial functional behavior).

1.3.2 The measurement and validation of HRQoL in Dermatology

For many decades, clinical improvement alone was considered sufficient response to treatment. For example, Dahl and Comaish (1972) stated that a reduction in scaling and

lesions corresponded to 'good' treatment outcome, especially if it resulted in a better working and social life. Assessment standards have since evolved and it has now been established that QoL is a vital consideration in any person's life. More recently, the word 'quimp' (i.e. quality of life impairment) was coined in a bid to raise awareness about the importance of this concept in clinical care (Finlay 2017). QoL may be impacted by various non-medical factors: economic status, employment, marital status, career, ambition, personality, religion and expectations (Both et al. 2007). In medicine, HRQoL is the effect a condition has on QoL domains. A number of instruments to measure this impact on patient life have been developed for use in clinical, epidemiological and research settings (Terwee et al. 2007). These instruments will often include psychological, physical and social domains from both subjective (e.g. emotions) and objective (e.g. work impairment) viewpoints (Testa and Simonson 1996). The final questionnaires are often comprised of items/questions that are grouped together under various relevant dimensions (Testa and Simonson 1996). The methodological construction, conceptual validation, mode of administration and target population determine the final quality of these HRQoL measures (Halioua et al. 2000).

Within dermatology, HRQoL is captured by measures of varying scopes and capacities. These include generic measures, dermatology-specific measures, condition specific measures as well as possibly 'crossover measures' which shall be discussed later in this chapter. The former may be used across all medical conditions thereby allowing comparison across specialties; dermatology-specific measures may be used for all skin conditions, whereas condition-specific measures are designed to capture very focused, disease specific QoL impact. Generic measures may be health-profile or preference-based and have the advantage of directly producing utility values (Coons et al. 2000). The disease-specific tools are more responsive with strong conceptual validity and therefore clinically suitable (Wiebe et al. 2003). Measures are designed based on a combination of patient views, evidence from literature and clinical opinion – though the more popular PROMs have been based solely on patient experiences, arguably the most appropriate development method. Therefore, choosing the ideal instrument is dependent on weighing the advantages and disadvantages of each measure within the context of its use, the skin condition and study objectives (Coons et al. 2000).

Evidence of a tool's psychometric properties including its validity and reliability are important considerations in making a decision on whether it is suitable to use. Reliability is the ability of a measure to produce results 'consistently in time and space', whereas the validity of a measure determines whether it captures the information it was designed to do so (Souza et al. 2017). Validation aspects of a measure may further be divided in to: equivalence, content

validity, criterion validity, construct validity and cross-cultural validity. These are summarised in Figure 1.7 (Souza et al. 2017). The reliability of a measure includes testing for stability, internal consistency, reproducibility (e.g. test retest). The more comprehensively a measure is validated, the more likely it will be used widely. However, validation techniques are wide ranging that is from 'basic' to 'advanced' (Prinsen et al. 2013), and there is no absolute definition of how widely a measure should be validated.

Figure 1.7 Types of validity measurement of instruments (Souza et al. 2017)

Types of validity	Definition	Example	Statistical tests
Content validity	It is the degree in which a test includes all the necessary items to represent the concept to be measured.[17]	An instrument that assesses he satisfaction at work must include not only work satisfaction, but other variables related to it, such as, salary, promotions, relationship with co-workers, among others.	- Qualitative approach (experts committee) - Quantitative approach (content validity index [IVC])
Criterion validity	It is assessed when a result can be compared to a 'gold standard'.		
Concurrent validity	It can be evaluated using both the target-test and the 'gold standard', at the same time,	In an investigation on depression, a new tool is used, and with it, a supposedly 'gold standard' question: Do you frequently feel sad or depressed?[38]	Correlation tests
Predictive validity	First the target-test is applied, and then, the 'gold standard'.[38]	Results on blood pressure and cholesterol levels are based on its predictive validity to project the risk of cardiovascular diseases.[38]	Correlation tests
Construct validity	Is is the extent in which a set of variables represent the construct that was projected to be measured.[44]		
Known-groups technique	Different groups of individuals fill in the research instrument and then the groups' results are compared.[38]	A test that assesses quality of life can be applied to a group of patients with chronic diseases and to a group of healthy youngsters. Differences in the scores on quality of life between these groups are expected.[38]	Hypothesis testing
Convergent validity	It is obtained through the correlation between the instrument and another instrument that assesses a similar construct, expecting high correlation results between them.[39]	When administering two instruments that assess satisfaction at work, researchers expect to obtain strong correlation between them.	Correlation tests
Discriminant validity	It tests the hypothesis that the target-measurement is not improperly related to different constructs, that is, with variables from which it should differ.[39]	An instrument that assesses the motivation to work should present low correlation with an instrument that measures self-efficiency.[32]	Correlation tests
Structural or factorial validity	It assesses if one measure captures the hypothetical dimension of a construct.[39]	Researchers intend to assess if some characteristics of the work environment – such as autonomy and feedback – are predictors of professional satisfaction.	Factorial analysis and structural equation modeling
Cross-cultural validity	Measures in which the evidences support the inference that the original instrument and another one, culturally adapted are equivalent.[39]	A tool that assesses the satisfaction at work and that has been translated and adapted into another cultural context, must have a similar performance to the one of the original version.[51]	- Independent translators and back-translators - Experts committee - Pre-test[51]

There have been numerous instruments created ranging from single-item measures to more complex ones with various scoring systems (Chernyshov 2019). Unfortunately, while many questionnaires exist, they have not always been validated or tested appropriately, sometimes having been used in only a single study (Chernyshov 2019). This may raise doubts about the

appropriateness of their use (Bourdel et al. 2019). Choosing the right measure for the disease and population is therefore key towards obtaining optimal and representative results. However, some psychometric properties may be specific to individual situations and may vary depending on the target use, thereby requiring further validation work (Souza et al. 2017). For example, the Children's Dermatology Life Quality Index (CDLQI) (Lewis‐Jones and Finlay 1995) is validated for use in patients aged 4-16, and is not validated to be used for an older population. As a result, there is no real consensus on the "best" QoL measure to use in Dermatology (Both et al. 2007), and indeed the generic concept of "best" may not be meaningful or achievable to define.

Nevertheless, HRQoL assessment is integral to many guidelines within dermatology. This includes the National Institute for Health and Care Excellence (NICE) guidelines for atopic eczema (AD) as well as a Taskforce recommendation (Lewis-Jones and Mugglestone 2007; Vermeulen et al. 2019), vitiligo guidelines (Gawkrodger 2008) and more extensively, psoriasis biologic guidelines (Smith et al. 2020).

1.3.3 Generic HRQoL measures used in Dermatology

These measures, as stated by their description, are broad in nature to capture health-related QoL data even outside the clinical context. The most widely used generic measures in dermatology are the Short-Form 36 (SF-36) and the EQ-5D (Chernyshov 2019). Other commonly used measures include: Sickness Impact Profile (SIP) (Bergner et al. 1981; Patrick and Deyo 1989), World Health Organization Quality of Life (WHOQOL) (Group 1994), the Nottingham Health Profile (NHP), the DUKE Health Profile (Raymond 1996) and the Quality of Well-Being Scale (Hörnquist 1982). All of these measures may be applied to various disease states or the general population therefore allowing impacts of diseases to be compared.

A previous systematic review has recommended that the SF-36 is the preferential generic measure (de Korte et al. 2002). The SF-36 consists of eight scales with varying items, with one item of perceived health change. It is the only instrument which addresses the concept of 'positive health', therefore making it particularly sensitive for better QoL states (Both et al. 2007). Furthermore, the SF-36 has been used as a reference measure in the validation of dermatology-specific measures such as the Skindex (Chren 2012).

The SIP was one of the first self-reported health status tools to be used (Bergner et al. 1981) with 12 scales consisting of 136 items covering physical and psychosocial domains together

with five independent categories. Though it has had formal psychometric validation (Bergner et al. 1981), there are some limitations: patients only select items that are relevant to them, eliciting concerns regarding the interpretation of missing data (systematic versus random omission). Furthermore, it can take up to 30 minutes to complete, and cannot discriminate effectively between healthy subjects (Andresen and Meyers 2000). Nevertheless, the UK version of the SIP, the UKSIP, has also been used in various psoriasis trials over the years, including for one of the first systemic treatments in psoriasis: ciclosporin (Finlay et al. 1990; Salek et al. 1993; Wall et al. 1998; Prins et al. 2005). The UKSIP has also been validated and shown to be reliable in assessing acne handicap (Salek et al. 1996) and the impact of basal cell carcinomas (Blackford et al. 1996).

The EQ-5D (Group 1990) will be covered extensively in Chapters 4 and 5. It is a generic standardised preference-based measure often used for calculating utility values in health economics. Health technology assessment agencies have driven its use for economic comparison between treatments, despite it not being dermatology focussed. The measure consists of two parts, the first comprising five domains namely: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The second part is a visual analogue scale (VAS) on which patients self-assign a score between 0-100 (with '0' being the 'worst imaginable health state' and '100' being the 'best imaginable health state'). While the EQ-5D is broad in nature allowing appraisal between diseases, it may not detect pertinent HRQoL information from dermatology patients (Pereira et al. 2012). It contains items that are not always relevant to dermatological patients resulting in 'background noise' due to responses that are not relevant to the skin disease (Finlay 1997). Some relevant issues may only be addressed by the use of specialty/disease-specific measures. Therefore, generic measures including the EQ-5D may not be entirely sensitive to the QoL impact of skin disease.

1.3.3.1 Dermatology-specific measures

Although many studies use generic measures, there are several 'dermatology-specific' measures that may be used for all skin conditions. The most popular of these is the DLQI (Finlay and Khan 1994) and is described in detail below.

The Dermatology-Specific Quality of Life (DSQL) is a 52-item scale with physical, emotional and social dimensions of QoL (Anderson and Rajagopalan 1997). It is heavily influenced by the SF-36 and the pilot study on item behavior only included contact dermatitis and acne patients. It takes 15 minutes to complete and has been mostly adequately validated.

However, other than a handful of studies on acne/contact dermatitis it has not been used again (Both et al. 2007).

The Skindex-29 is another validated scale that has been found to be reliable and responsive in dermatology patients, with documented categorisation of scores (Nijsten et al. 2009; Rogers et al. 2012). However, additional validation studies have been recommended (Both et al. 2007). There are also shortened versions of the measure in the form of Skindex-16 and Skindex-17 which have both been used in numerous studies (Halioua et al. 2000; Ganemo et al. 2004; Gisondi et al. 2005). However, the presence of numerous versions may be confusing for the end user, resulting in data that are not comparable between the various iterations.

One of the least used scales is the Dermatology Quality of Life Scales (DQOLS) which was developed after 50 outpatients were interviewed (Morgan et al. 1997). It consists of physical, psychosocial and symptom dimensions which yield a score ranging from 0-100. Though it has been validated against the DLQI and was shown to have strong validity, there have been criticisms of the psychometric methods used in its creation (Both et al. 2007). Bar two major studies, use of the DQOLS has rarely been reported (Higaki et al. 2002; Higaki et al. 2004).

Several other dermatology-specific measures are targeted at different age ranges including the CDLQI for ages 4-16 years (Lewis-Jones and Finlay 1995), the Teenager's Quality of Life Index (T-QoL) for ages 12-19 years (Basra et al. 2018) and the Infants' and Toddlers' Dermatology Quality of Life (InToDermQoL) for ages 0-4 years (Chernyshov et al. 2019).

The CDLQI measures the impact of skin conditions on the QoL of children (Lewis-Jones and Finlay 1995). Much like the DLQI, the CDLQI was developed from the answers to an open-ended question asking children how their skin condition affected their life. Based on 169 replies from children aged 3-16 years, a ten-item questionnaire was developed. The CDLQI measures impact of QoL in the domains of symptoms and feelings, leisure, school or holidays, personal relationships, sleep and treatment. Each question has the following four options: not at all (scoring 0), only a little, (1) quite a lot (2), very much (3). The recall period for the CDLQI is one week and as children may have been in school term time or on holiday, one question has a choice of two options dependent on whether or not within the last week the child was in school. A cartoon version has been created to appeal to younger children (Holme et al. 2003). The CDLQI has been translated into over 80 languages and validated extensively (Neri et al. 2012; Salek et al. 2013; Wisuthsarewong et al. 2015). The CDLQI is completed on average in two minutes and has score bands to give meaning to the scores

(Waters et al. 2010): 0-1= 'no effect on child's life', 2-6 'small effect', 7-12 'moderate effect', 13-18 'very large effect', 19-30 'extremely large effect'. The CDLQI has been recommended by the Harmonising Outcome Measures in Atopic Eczema (HOME) initiative as the core QoL instrument for measuring the impact of atopic dermatitis on the QoL of children (Vermeulen et al. 2019).

These dermatology-specific measures may be used across all of dermatology, making it easier to score and compare the impact on QoL of various skin diseases. However, disease-specific measures are also used, which may provide more sensitive and focused QoL information for any particular skin condition.

1.3.3.1.1 The Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) (Finlay and Khan 1994) was the first generic dermatology-specific QoL measure to be introduced and paved the way for QoL assessment alongside clinical severity measures in skin disease trials (Kurwa and Finlay 1995). It is reported to be the most widely used dermatology-specific QoL measure in clinical trials of skin diseases worldwide (Both et al. 2007; Organization 2019). An extensive overview of the measure is detailed in Chapter 4. The DLQI been used in numerous inflammatory and non-inflammatory skin conditions as well as skin cancers and is available in 152 languages as of 9th March 2021, across numerous countries (Basra et al. 2008a; Finlay 2020). It is simple and easy to complete (Bronsard et al. 2010) with an average completion time of around 2 minutes (Loo et al. 2003). It consists of 10 items addressing the impact of skin diseases on different aspects of patient QoL over the last week, as shown in Figure 4.1. The highest total score of 30 represents the worst QoL, whereas 0 would be perfect health. The strong psychometric properties of the DLQI have resulted in the increasing popularity of the DLQI in both clinical research and in clinical practice. Moreover, the content of the DLQI has been shown to include all important and relevant concepts from the perspective of patients with moderate to severe plaque psoriasis supporting its content validity in psoriasis patients (Safikhani et al. 2013). It is not, however, without its share of limitations. Its 'focus on disability, response distribution, and dimensionality and item bias' have been criticised (Both et al. 2007). The criticisms by Nijsten (2012) have been discussed by Finlay et al. (2012). Furthermore, it has been proposed that the 'not relevant' response item of certain DLQI questions may in fact represent higher disease burden (Langenbruch et al. 2019). Eight out of the ten DLQI items have the 'not relevant' option, which usually indicate no impact on QoL when selected. This raises questions over whether patients mark this option due to the considerable impact of their skin disease preventing participation in certain areas of life. It is therefore argued that an

ideal questionnaire would encompass this QoL impairment (Langenbruch et al. 2019). To address these concerns, Rencz et al. (2020) have proposed an alternative scoring system, DLQI-Relevant (DLQI-R), by adjusting for the 'not relevant' responses in to the total score. However, the DLQI-R has yet to be fully validated in the context of score banding (Hongbo et al. 2005) and applicability across different disease populations. Additionally, its comparability to DLQI scores is yet to be proven.

Nevertheless, the DLQI's popularity as a measure has positioned it as an integral PROM in various treatment guidelines, including biologics, for psoriasis (Smith et al. 2020), eczema (Vermeulen et al. 2019) and hidradenitis suppurativa (Ingram et al. 2019).

1.3.3.1.2 Minimal Clinically Important Difference (MCID) of the DLQI

The minimal clinically important difference (MCID) is described as the minimal change in score considered clinically significant by clinicians and patients (Norman et al. 2003). This provides more meaning to QoL score changes than simply assessing absolute values. The DLQI has a MCID value of 4 points (Basra et al. 2015a). A 'multiple-MCID' concept has also been proposed in this thesis to allow a more distinguishing analysis of interventional studies. However, multiple-MCIDs may be a difficult threshold to achieve and the concept requires extensive further validation, beyond the scope of this work.

1.3.3.2 Disease-specific measures in Dermatology

Some may argue that every skin disease would have a specific measure that may be used by clinicians. However, it would be an arduous task to create many hundreds of questionnaires and for the clinician might create confusion by having such vast number of measures that would be virtually impossible to compare. The development of many disease-specific measures could pose further challenges for health economists who would not be able to make meaningful comparisons between this data as part of health technology assessments.

Numerous measures exist with the most popular ones including (Chernyshov 2019): Infants' Dermatitis Quality of Life Index (IDQOL), Quality of Life Index for Atopic Dermatitis (QoLIAD), Childhood Atopic Dermatitis Impact Scale (CADIS), Cardiff Acne Disability Index (CADI), Acne-specific Quality of Life Questionnaire (Acne-QoL), Skin Cancer Index (SCI), The Functional Assessment of Cancer Therapy – Melanoma (FACT-M), Psoriasis Disability Index

(PDI), Scalpdex and Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and many more.

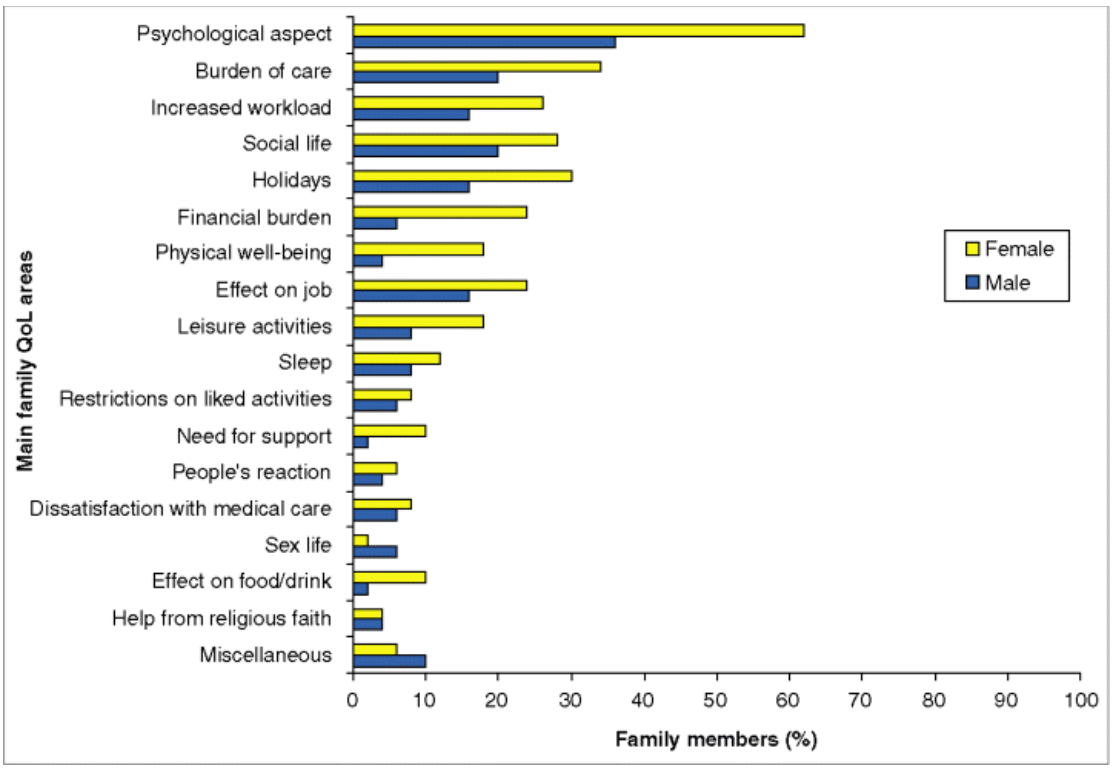
Whilst they may have varying degrees of validity, these questionnaires have all been designed with a specific disease in mind, and therefore patients are more likely to identify with the QoL domains presented. Therefore, disease-specific measures are ideal for monitoring a single condition but may not encompass a holistic approach to HRQoL.

Psoriasis-specific QoL measures in particular will be discussed in the following chapter, given their relevance to the thesis subject.

1.3.3.3 Family measures in Dermatology

Until the last decade, very little attention was given to the impact skin diseases have on the family members of patients with skin diseases (Basra and Finlay 2007). Once patients are diagnosed with skin conditions, partners and family members are almost immediately involved with overall care. Much of this area of research has been conducted in families of children with atopic dermatitis, given the early onset of the disease and heavy impact on parents (Lawson et al. 1998). Parents in particular experience a negative impact on their social life, relationships, finances, lifestyle, family activities and time management (Basra and Finlay 2007). The impact of skin diseases on the lives of family members is as diverse as the impact on the QoL of patients themselves. A summary of the way various family members may be affected is shown in Figure 1.8, with the greatest impact being on psychological health including stress, depression, embarrassment and anxiety. The European Academy of Dermatology and Venereology (EADV) quality of life taskforce has recommended that burden of disease cannot be accurately evaluated without assessing the impact of a skin condition on family and caregivers (Sampogna et al. 2017b).

Figure 1.8 Family quality of life (QoL) areas affected according to gender (Basra and Finlay 2007)



Partners/spouses are similarly affected, but significant problems have also been described with sexual relations, particularly due to the location of lesions or pain (Basra and Finlay 2007), which may further be exacerbated with genital involvement (Wojnarowska et al. 1997). Unsurprisingly, chronic conditions have shown to create problems with intimacy between partners (Larsen 2002). In some cases, partners are unable to cope or deal with their partner's condition expressing this notion as anger or frustration (Kuyper and Wester 1998). Sexual intimacy problems have been reported in up to 23% of patients with various skin diseases, and often these are difficult to discuss in clinical consultations (Sampogna et al. 2017a).

Whilst there are many studies on the QoL of siblings of children affected with other medical conditions, notably cancers (Vermaes et al. 2012; Rana and Mishra 2015; Velleman et al. 2016; Glazner 2017; Long et al. 2018; Chudleigh et al. 2019), there is a lack of information on the impact of QoL on siblings of children affected with skin conditions. It is difficult to compare from the literature the effect on the QoL of siblings of skin disease compared to other diseases, due to the wide variety of instruments that have been used. Siblings of children with chronic conditions may have the same QoL as their peers (Havermans et al. 2015), but it has also been suggested that siblings may have increased levels of distress (Vermaes et al.

2012). The parent child relationship and the sibling bond may also be affected when a child in the family has a chronic condition (Knecht et al. 2015). These negative interactions with family members (Marciniak et al. 2017; Angelhoff et al. 2018) coupled with sleep deprivation can leave patients, and their carers, feeling exhausted, stressed and depressed (Pustišek et al. 2016; Ramirez et al. 2019).

Cultural and religious beliefs no doubt influence the experiences of patients and their families (Seltzer et al. 1995), but certain themes are commonly shared. Furthermore, assessing the entire family's experience as a unit, rather than individuals, may provide a more complete picture of the wider secondary impact of a disease (Basra and Finlay 2007). Nevertheless, the extended implications of skin disease are apparent. It would be prudent to consider the impact on family quality of life alongside patient 'quimp' when discussing patient care, planning research studies and making treatment decisions.

To tackle this very issue, several family QoL measures have been created. Some of the more common ones have been summarised below (Sampogna et al. 2017b).

1.2.3.3.1 Family Dermatology Life Quality Index (FDLQI)

The Family Dermatology Life Quality Index (FDLQI) is a 10 item questionnaire, with a recall period of one month, assessing the impact on the QoL of adult family members of having an adult or child in the family with any skin condition (Basra et al. 2007). The questionnaire includes the domains of emotional and physical wellbeing, relationships, leisure activities, social life, burden of care, impact on job/study, housework and expenditure. Each question is scored on a four-point scale (0-3) with the possible answers 'not at all', 'not applicable', 'a little', 'quite a lot' and 'very much'. The higher the score, the greater the impact on QOL of family members. The FDLQI has been translated into several languages and has been used in various studies involving atopic dermatitis and other dermatological conditions (Martínez-García et al. 2014; Kouris et al. 2015; Wang and Wang 2015; Pustišek et al. 2016; Marciniak et al. 2017; Putterman et al. 2019).

1.3.3.3.2 Dermatitis Family Index (DFI)

The Dermatitis Family Index (DFI) was the first instrument designed to measure the impact of having a child with atopic dermatitis on the QoL of their adult family members (Lawson et al. 1998). Unlike the FDLQI, this is a dermatitis specific questionnaire. It consists of 10 items which measures recall over the past week. The DFI measures the impact of QoL in the domains of housework, food preparation and feeding, sleep of others in the family, family leisure activities, time spent on shopping, expenditure, tiredness, emotional distress,

relationships and impact of child's treatment. Each question is scored from 0-3 points depending on the option chosen between 'Not at all', 'A little', 'A lot' or 'Very much'. The higher the score, the greater the impact on the QoL of the family member. Whilst there are no validated banding descriptors for the DFI, some studies have reported non-validated scoring band descriptors (Al Shobaili 2010; Amaral et al. 2012). This questionnaire has the advantage of being eczema specific rather than generic: a review of its measurement properties is given by Dodington et al. (2013).

1.3.3.3.3 Parents Index of QoL in Atopic Dermatitis (PIQoL-AD)

The Parents Index of QoL in Atopic Dermatitis (PIQoL-AD) is another AD specific measure to assess the impact of the child's AD on the QoL of parents. This can be used for parents of children up to the age of 8 years (McKenna et al. 2005). Developed on the basis of multinational qualitative interviews with parents of children with AD, this is a 28 item unidimensional questionnaire (Meads et al. 2005). The lower the score, the better the QoL, a change of 2-3 PIQoL-AD points over time is considered meaningful.

1.3.3.3.4 Childhood Atopic Dermatitis Impact Scale (CADIS)

Childhood Atopic Dermatitis Impact Scale (CADIS) is a QoL measure for parents of children with atopic dermatitis combined with a proxy measure for children under the age of 6 years (Chamlin et al. 2005). It measures the impact of QoL on the domains of Child Symptoms, Child Activity Limitations and Behaviour, Family and Social Function, Parent Sleep and Parent Emotion. This 45-item questionnaire uses a 5-point Likert Scale with the options of 'never', 'rarely', 'sometimes, 'often' and 'all the time'. The option 'never' scores 0 and 'all the time' scores 4 giving a maximum score of 180. The recall period is the last four weeks and the questionnaire can be completed in approximately 6 minutes (Chamlin et al. 2005). Whilst it does not have score band descriptors, the MCID is considered to be a 12% change from the total score or a 12% change from any of the individual domains (Gabes et al. 2020) .

1.3.3.3.5 Psoriasis Family Index (PFI-14)

The PFI-14 is a 14-item questionnaire that is designed to be completed by adult family members of patients of any age suffering with psoriasis and is completed in two to three minutes (Eghlileb et al. 2009). It is the first disease-specific measure to assess the QoL impairment of family members of psoriasis patients. Each of the 14 questions has four response items: 'Not at all', 'A little', 'A lot', 'Very much', scoring 0-4 respectively. The score ranges from 0 to 42, with the higher values representing worse QoL impairment. Rasch

analysis of its psychometric properties demonstrated optimal functionality (Basra et al. 2015b).

1.3.3.4 Other 'crossover' measures

There are several measures that fall slightly outside the brackets of 'generic', 'dermatology-specific' and 'disease-specific'. These are measures that have had formal validation conducted across various disciplines allowing a true comparison between different diseases.

1.3.3.4.1 Family Reported Outcome Measure (FROM-16)

While speciality specific and condition specific questionnaires exist to measure the QoL of family members, these cannot compare the impact of QoL of family members between different specialties. Golics et al. (2014) developed the Family Reported Outcome Measure (FROM-16), based on a qualitative study involving relatives of patients from 26 medical specialties.

FROM-16 has 16 questions and can be used to assess the QoL of any member of the family of a patient with any disease. The average completion time is two minutes. FROM-16 consists of two domains: the Emotional domain with 6 questions and the Personal and Social Life domain with 10 questions. Each question has an option of three different answers: 'Not at all', 'A little' and 'A lot' scoring 0, 1 and 2 respectively. Validation studies have been completed in Germany and Thailand and further validation characteristics are being studied. The FROM-16, while not being condition specific, has the added advantage that it can be used to compare the QoL of family members across different disciplines in Medicine, thus making it possible to perform meaningful comparisons in QoL trials involving different medical conditions, and to use in widespread epidemiological surveys.

Other measures, such as the Impact on Family Scale (IOF), (Stein and Riessman 1980; Williams et al. 2006) have been validated to measure the impact of QoL on the family members of children suffering with chronic illness or disability. However, unlike the FROM-16, which can be used in the family members of patients of any age, the IOF can only be used for family members of affected children.

1.3.3.4.2 Major Life Changing Decisions Profile

Whilst the majority of HRQoL measures look at the 'current' impact on QoL, there is a dimension that is often overlooked. Bhatti et al. (2013) have proposed the concept of chronic conditions affecting 'Major Life Changing Decisions' (MLCD) such as education, having children, relationships or career. Current HRQoL measures usually assess the current impact of skin disease, and are not designed to capture the long-term impact of conditions on patients' well-being, aspirations and life development (Bhatti et al. 2011).

Following an extensive qualitative study, a 32-item measure, covering five domains, called the Major Life Changing Decisions Profile (MLCDP) was created by Bhatti et al (Bhatti et al. 2013). Patients were recruited from Nephrology, Rheumatology, Cardiology, Dermatology, Diabetes and Respiratory departments to gather a wide range of recurrent themes. Eating habits, smoking, drinking and travelling were the most commonly recorded MLCDs across all specialties.

Though further validation work for the MLCDP is required, it highlights a large area of HRQoL impact that may often be ignored by clinicians and researchers. This raises concerns about unidentified patient needs that should be met in a timely manner to allow patients to fulfill key aspirations and realise their full potential. Additionally, with patients making significant decisions about career, there may be long-term economic impacts for both patients and wider society that are not being fully addressed.

1.3.4 HRQoL in psoriasis

1.3.4.1 The effect of psoriasis on HRQoL

Psoriasis has no effect on life expectancy (though as highlighted, is associated with various co-morbidities), with a significant impact on patient quality of life (Krueger et al. 2001), with up to three-quarters of patients feeling that psoriasis has such a large impact on their life that it interferes with their daily activities (Bhosle et al. 2006). Up to a fifth of patients have even contemplated suicide (Krueger et al. 2001), with many more likely to suffer from depression compared to the general population (Esposito et al. 2006). As a result, the estimated cost attributed to psoriasis may rise as high as billions of dollars every year (Sander and Norris 1993). A large proportion of this cost is due to missed work days for the patient, in some

cases as high as 26 days a year, as well as for their caregivers (De Arruda and De Moraes 2001; Pearce et al. 2006).

The effect of psoriasis on a patient's life is wide-ranging from emotional, psychological, physical, sexual and financial consequences (De Arruda and De Moraes 2001; Choi and Koo 2003). Quality of life impairment may be as severe as or worse than other chronic conditions such as diabetes and heart disease (Møller et al. 2015), especially as patients struggle with perceptions of self-image and feelings of shame and embarrassment (Fortune et al. 2005). This feeling is particularly reinforced in situations where patients have to expose their bodies for example at swimming pools, in intimate relationships, or in public changing rooms (Ginsburg and LINK 1993). In order to cope with this QoL impairment patients often feel the need to cover up their lesions or completely avoid social situations (Finlay and Coles 1995; De Arruda and De Moraes 2001; Pearce et al. 2006). The feelings of hopelessness and lack of control underline the experience of psoriasis patients, given its unpredictability and the lack of a 'cure' (Vardy et al. 2002). Patients feel that society, and in certain cases even their dermatologists, fail to truly understand the extent of the impact psoriasis has on their QoL (Krueger et al. 2001). Furthermore, numerous patients feel physicians are not aggressive enough with the management of their condition (Krueger et al. 2001).

The correlation between PASI and many HRQoL measures is weak, necessitating the need for separate assessment of QoL impairment in psoriasis patients. In fact, it has been argued that as QoL plays such a large part in the lives of patients, it should become the primary assessment criteria in clinical trials (Krueger et al. 2001). Fiteni et al. (2015) argue that HRQoL measurement should be a co-primary endpoint along with clinical parameters such as 'overall survival' in oncological RCTs, as the latter may be limited by sample size and lack of validation. Indeed, several studies in Dermatology (Schuttelaar et al. 2010; Staubach et al. 2018; Oliveira et al. 2020) as well as across different specialties (Tonnel et al. 2008; Farthmann et al. 2016; Marta et al. 2017) have employed HRQoL as a primary endpoint recognising that maintaining patient QoL should be a key treatment goal. There are various arguments as to why QoL scores should also be considered as primary assessments such as: enabling comparison between different diseases, sophisticated development and extensive psychometric testing of QoL tools, better validity and relevance to patients.

As already highlighted in this chapter, there is the concept of 'the greater patient' (Basra and Finlay 2007), recognising the impact of psoriasis on the patient's wider family/social circle. Over a half of family members of psoriasis patients felt the burden of care was great. Furthermore, families felt responsible for taking charge of treatment, often partaking in the

application of creams and reminding patients when to take treatment (Basra and Finlay 2007). Partners of patients with psoriasis experience a large share of the QoL impairment, with increased housework, anxiety about the future and embarrassment (Richards et al. 2004). Having a partner with psoriasis further impacts holidays, leisure activities, shopping and relationships with other family members (Eghlileb et al. 2007). Richards et al. (2004) have demonstrated that divergent beliefs about the emotional and physical impact of psoriasis between patients and their partners are associated with psychological outcomes of worry and depression. Therefore, psoriasis is clearly a condition that has wide-reaching impact that is not limited to the patient. Identifying these issues and discussing them openly with patients and the extended family where possible, may help clinicians optimise their care strategies.

1.3.4.2 HRQoL measurement in psoriasis clinical and research settings

Much of the early recommendations and work in dermatology on QoL has been centred on psoriasis. Finlay (2005) first proposed 'The Rule of Tens', a concept that includes QoL measurement as part of the overall assessment of psoriasis severity. It states: "The Rule of Tens for current severe psoriasis from the clinician's viewpoint is: Current Severe Psoriasis = Body Surface Area involved > 10% or PASI score > 10 or DLQI score > 10."

The British Association of Dermatologists (BAD) suggest the following criteria to qualify for biologic treatment: "Offer biologic therapy to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated and the psoriasis has a large impact on physical, psychological or social functioning (e.g. DLQI or Children's DLQI > 10 or clinically relevant depressive or anxiety symptoms)" (Smith et al. 2020). NICE guidance states failure of at least two systemic therapies and phototherapy are required before biologic treatment may be considered (NICE 2012)

However, there are discussions on whether a high DLQI *or* PASI score alone should be guiding treatment decisions, rather than both PASI *and* DLQI. This is supported by a European consensus whereby only 14% of 'moderate-to-severe' patients had scores of PASI and DLQI > 10, versus 45.3% of either score achieving 10 (Augustin et al. 2018). Therefore, HRQoL is an important consideration as part of any clinical consultation.

Numerous generic and specialty-specific measures exist and have been summarised earlier in this chapter. There are a few psoriasis-specific measures that may be used, and are highly

sensitive, but the scores do not allow comparison of disease burden and QoL impairment between different conditions. Nevertheless, studies such as clinical trials often employ more than one measure as part of their range of outcome measures (Bhosle et al. 2006).

The common psoriasis-specific measures are summarised below.

1.3.4.2.1 Psoriasis Disability Index (PDI)

The PDI (Finlay and Kelly 1987a; Finlay and Coles 1995) is designed for patients over the age of 16, and has a four-week recall period. It consists of 15 questions with a range of 0-45, with higher scores suggestive of worse QoL impairment. It covers domains such as 'daily activities', 'work or school', 'personal relationships', 'leisure' and 'treatment'. It has been extensively translated and validated and has also shown to be sensitive to change (Lewis and Finlay 2005).

1.3.4.2.2 Psoriasis Life Stress Inventory (PLSI)

The PLSI is a 15-item psychosocial measure about the daily struggles of psoriasis, with a four-week recall period (Gupta and Gupta 1995). The score ranges from 0-45 (45 being the worst impairment). A score greater than 10 indicates a significant stress component. However, psychometric evaluation suggests that the internal reliability may be improved (Fortune et al. 1997).

1.3.4.2.3 Psoriasis Index of Quality of Life (PSORIQoL)

The PsoriQoL is based on the proposition that: "life gains its quality from the ability and capacity of individuals to satisfy their needs". Therefore this 25 'dichotomous' item instrument adopts a 'needs-based' approach, which was developed through qualitative interviews in three European countries (UK, Italy and Netherlands). It has good construct validity and reliability with a test re-test coefficient of 0.89 (McKenna et al. 2003). It is interesting to note that the PsoriQoL does not directly assess disability or impairment, but the effect of these on QoL.

1.3.4.2.4 Psoriasis Family Index-14 (PFI-14)

As already described, the PFI-14 is the first disease-specific measure designed for use by adult family members/partners of psoriasis patients of any age (Eghlileb et al. 2009; Basra et al. 2015b). The total score ranges from 0-42, with higher scores signifying worse QoL impairment. Following Rasch analysis, the PFI-14 has been shown to have strong psychometric properties including 'dimensionality, response category functioning, fit statistics, scale reliability and validity, item targeting and differential item functioning (DIF)'.

There is therefore a plethora of QoL instruments, from generic to disease specific, available in the clinician's toolbox. However, there have been proposals to standardise the use of QoL measures only for clinicians – but also for researchers, health technology assessments (HTAs) as well as for the pharmaceutical industry (Schmitt et al. 2015; Chernyshov 2019). With a diverse range of measures used across trials and clinical practice, data comparison, interpretation and application become challenging, especially amongst non-homogenous patient groups. It is unsurprising that efforts are therefore being put into place to identify core outcomes in Dermatology for different disease entities, recommending a core set of outcome measures that should be used in all clinical studies, so that direct comparisons can be made. These core outcomes should include standardised and validated measures in order to provide valuable information for clinicians, researchers, health economists and policy makers (Kottner et al. 2018).

1.4 Aims & Objectives of PhD Thesis

It is apparent that psoriasis has a significant impact on patients' lives worldwide. However, there are certain limitations and deficiencies in the way psoriasis is assessed, and this results in an impact on real world clinical practice.

There are no ideal measures to assess clinical severity or impact on QoL, though the PASI and DLQI are the most commonly used tools for this purpose. Furthermore, QoL plays such an important role in the management of psoriasis, that there is an argument that it may be sufficient alone as a measure of treatment success. As a result, QoL information may further be useful in making clinical decisions for therapy recommendations.

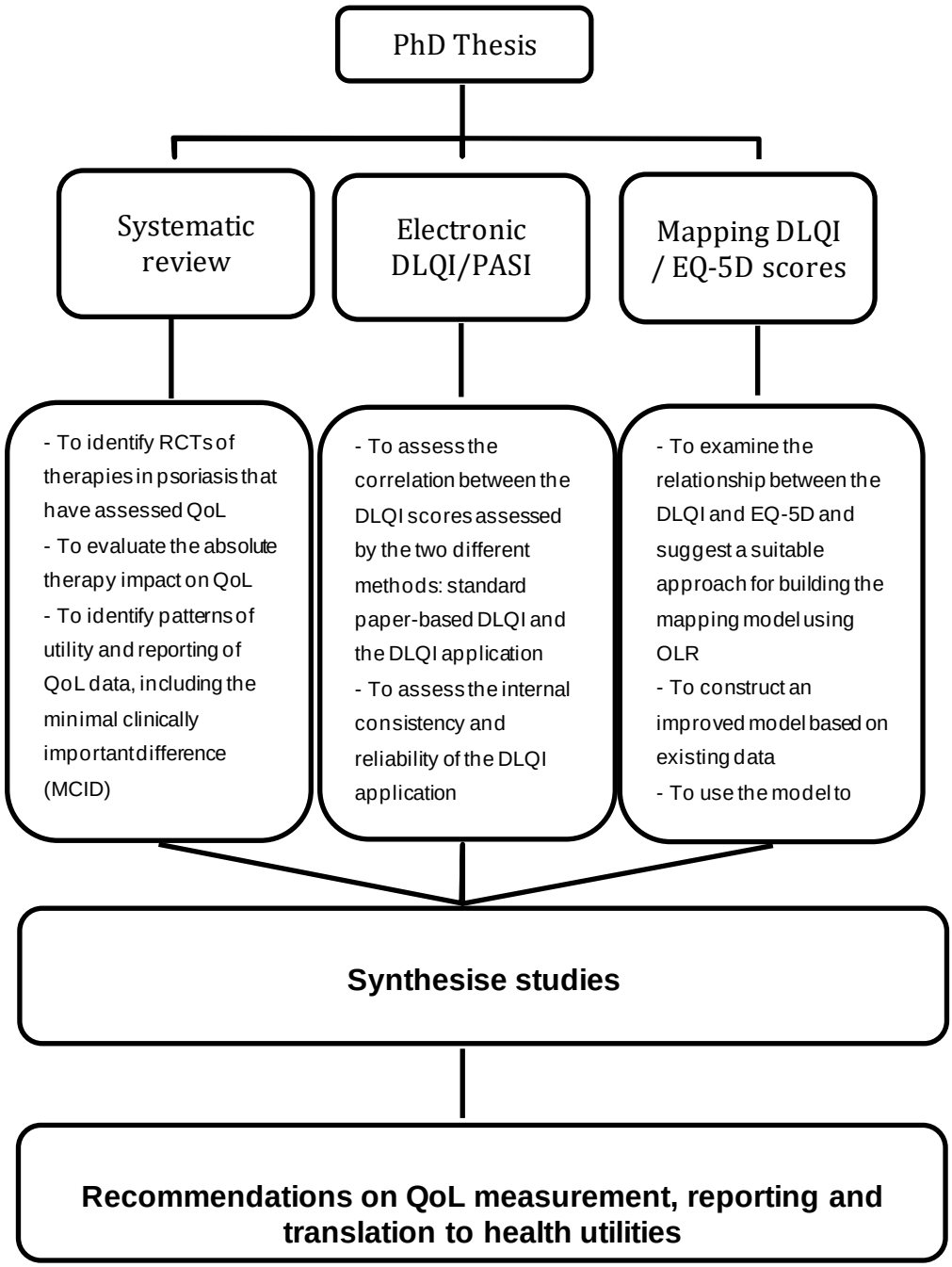
This PhD work aims to conduct three studies to improve our understanding of how QoL plays a role in the assessment and management of psoriasis, and how the data are translated to healthcare policy makers for better allocation of resources on a need by need basis. It is hoped this work will therefore improve the management of psoriasis from the perspective of the patient, the physician and healthcare decision makers.

The three broad aims and objectives are:

1) To conduct a systematic review to identifying patterns of utility and reporting of QoL measures in psoriasis and devise a set of recommendations
2) To compare the conventional paper-based and the novel application versions of the DLQI and PASI
3) To develop a suitable mapping model to predict EQ-5D utility values from DLQI item scores

The structure of the PhD thesis supporting the aims and objectives of the project is summarised in Figure 1.9.

Figure 1.9 Structure of the PhD thesis*



***DLQI - Dermatology Life Quality Index,**

EQ-5D - EuroQoL – Five-Dimensions,

MCID - Minimal Clinically Important Difference,

OLR - Ordinal Logistic Regression,

PASI - Psoriasis Area Severity Index,

QoL - Quality of Life,

RCT - Randomised Controlled Trial

Chapter 2: A systematic review of the impact on health-related quality of life of topical, systemic and biologic therapies for psoriasis

2.1 Introduction

For a patient suffering with psoriasis, quality of life (QoL) improvement is as important as improvement of clinical manifestation (Langley et al. 2005). As a result, health-related QoL (HRQoL) instruments are increasingly being adopted as outcome measures (Finlay and Coles 1995; Gordon et al. 2003; Menter et al. 2009; Thaçi et al. 2014) in clinical and research settings (Finlay 1998; Basra and Shahrukh 2009). Consequently, there have been various types of HRQoL instruments that have been developed and used in medicine including generic, speciality-specific and disease-specific tools. However, patients prefer disease specific tools as these are perceived as more relevant to them and their disease state (de Korte et al. 2002).

Several reviews have been conducted examining the impact of psoriasis interventions on QoL over the last twenty years (De Korte et al. 2004; Katugampola et al. 2007; Reich et al. 2008; Frendl and Ware Jr 2014). De Korte et al. (2004) reviewed QoL data correlating clinical and demographic aspects and found that psoriasis patients suffer from emotional difficulties, physical discomfort and issues surrounding body image as well as experiencing significant limitations to daily social and work life. Kitchen et al. (2015) carried out a systematic review (SR) of patient-reported outcome measures and evidence to demonstrate validation in psoriasis. The authors have reported that existing outcome measures lack an adequate level of feasibility, sensitivity to change and acceptability for both physicians and patients alike, concluding that there is a need for a PRO that is able to assess the 'full impact of psoriasis'. Despite these criticisms, the currently available PROs are widely used with this review highlighting the importance of recording and analysing QoL in psoriasis. However, there is a need to assess how QoL has been reported in previous studies and trials, which instruments have been used by researchers, and what has been the effect of interventions in terms of QoL. There are no formal guidelines for the use of PROs in trials of psoriasis resulting in heterogeneous data that are often difficult to collate and compare (Kitchen et al. 2015). Therefore, a comprehensive review on the use of QoL instruments in randomised controlled trials (RCTs) for interventions in psoriasis would be considerably useful for researchers and clinicians alike. It is hoped that as a result of this review, the groundwork for standardising QoL measurement and reporting may be achieved.

2.2 Aims & Objectives

The main aim of this systematic review is:

- to analyse patterns of utility and reporting of QoL in RCTs of therapies in psoriasis and devise a set of recommendations based on current practices

This overarching aim will be achieved using a series of objectives:

- to evaluate the absolute therapy impact on QoL in psoriasis RCTs
- to identify the most commonly used QoL measures in psoriasis RCTs
- to assess the use of the minimal clinically important difference (MCID) across different QoL measures in psoriasis RCTs

This SR should reveal how QoL instruments have been used across interventional trials of psoriasis, including reporting and consideration of the MCID, frequency of measurement and sensitivity to change. The MCID is the smallest change in outcome that patients consider important thereby justifying a change in patient management. Therefore, this aspect of QoL reporting is particularly important in the interpretation of QoL scores (Wright et al. 2012). The review may be useful for those who wish to understand the types of instruments used, their patterns of use, and the QoL impact of various interventions used for the treatment of psoriasis. The protocol for this SR is provided in Appendix I.

2.3 Methods

2.3.1 Two independent reviewers

Systematic reviews require two independent reviewers for the identification and appraisal of literature, with a third independent adjudicator to reconcile differences of opinion. The detailed methodology is described below. The SR process was started in October 2014 with a colleague at the Department of Dermatology, Cardiff University, Dr. Andrea Cueva (AC) who acted as the second reviewer.

2.3.2 Data sources searched

Six computerised bibliographical databases were searched to include any publications up to November 2014: Cochrane Library CENTRAL, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, WEB OF SCIENCE Core Collection, SCOPUS. Due to the volume of data and restrictions in the ability to perform translations, the search was restricted to publications in English and was conducted using PRISMA (Preferred reporting items for systematic reviews and meta-analyses) guidelines. The systematic review was registered at the inception on The International Prospective Register for Systematic Reviews (PROSPERO) and is available for citing: https://www.crd.york.ac.uk/PROSPERO/, Registration no: CRD42015009193).

In order to identify the most relevant publications for a topic a list of keywords must be devised, alongside search filters. Keywords, for example 'psoriasis', are important essential words pertinent to the topic of interest. These are often very focussed to avoid unnecessary results. Subsequently, search filters utilise these keywords in specific ways to focus the search to more relevant articles. Different databases employ slightly different filters to enhance the search precision and at times tried and tested search strategies may be utilised. For this systematic review, a total of 388 keywords were formulated using Scottish Intercollegiate Guidelines Network (SIGN) and COCHRANE search filters for RCTs and School of Health and Related Research (SCHARR) search filters for QoL. These are an existing list of keyword/search filters that have previously been proven to work for certain concepts and were therefore used as part of this review. Keywords for psoriasis treatments were identified after a pilot search was conducted of other SRs on psoriasis treatments and of the British National Formulary (BNF). The list of keywords, filters and search strategies for each database is provided in the Appendix (Appendices II-VII). Supplementary searches were conducted of trial registers and 'grey literature' including conference abstracts and unpublished results.

The following trials registers were searched:

- The metaRegister of Controlled Trials (http://www.isrctn.com).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
- The EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

Abstracts of proceedings from the following major dermatology conferences that were not already recorded in the Cochrane Skin Group Specialised Register were also searched:

- American Academy of Dermatology (AAD);
- British Association of Dermatologists (BAD);
- European Academy of Dermatology and Venereology (EADV);
- European Society for Dermatological Research (ESDR);
- International Investigative Dermatology (IID); and
- Society for Investigative Dermatology (SID).

Reference lists of all included studies and of recent reviews were also assessed. Emails were sent to authors of conference abstracts, meeting posters and letters to editors to check for unpublished RCTs. If there was no response and if data was inadequate, the citation was discarded. Authors were also contacted where necessary to determine if a study met the criteria for inclusion and to obtain further data if required.

2.3.3 Selection criteria

RCTs regardless of publication status (published, unpublished, in press, or in progress), including cross-over trials with open-label extensions, of any psoriasis treatment were included. It was a requirement that at least one QoL instrument was used in a population comprising of adults (aged 18 and over) suffering with psoriasis, of either sex and of any ethnicity, including all subtypes of psoriasis. Treatments included (but not limited to): systemic therapy, topical therapy, physical therapy (including ultra violet therapy) and psychological therapy with comparisons to placebo or any other active intervention. Psoriatic arthritis trials were only included if a skin-specific QoL instrument was used to differentiate QoL impairment caused by arthritis from that caused by psoriasis. Only papers where the total scores for the QoL tools were provided were included, with the exception when QoL questionnaires are designed with several subsections and are validated to be reported with subtotals (as opposed to a final total score).

2.3.4 Exclusion criteria

The exclusion criteria for the SR were as follows; psoriatic arthritis studies where it was not possible to differentiate data on QoL impact of arthritis from QoL impact of psoriasis, studies

which included any patient less than 18 years of age, and articles where the change in QoL values were not reported or could not be reliably calculated (including where only graphical representation of data was provided). For consistency, QoL data only presented as sub-scales, where total scores are usually calculated, were excluded. Abstracts and posters where further data was not available upon contacting the author were also excluded. For studies with an open label extension, the data was extracted only for the period of the study while it was randomised and controlled. For cross-over trials, the data was only extracted prior to the crossover (i.e. first sequence), as patient baseline data changes after the cross-over occurs with a change in disease severity and the blinding of trials may end introducing bias.

2.3.5 Outcome measures extracted from published articles

2.3.5.1 Primary Outcome

Data recorded in the pre designed 'data extraction template' included QoL instrument (s) used and scores at baseline, treatment and follow-up endpoints and change in QoL attributed to treatment. For studies with an open label extension, the data was only extracted for the period of the study while it was randomised and controlled. For cross-over trials, the data was extracted prior to the crossover.

2.3.5.2 Secondary Outcomes

PASI score or any other psoriasis severity scale (PSS) used for clinical correlation. Therefore, the following were recorded where possible:

1. PASI score OR
2. The proportion of participants attaining PASI 50, 75, and 90, defined as a 50%, 75%, or 90% reduction in PASI score relative to the baseline PASI score immediately prior to treatment initiation OR
3. If 1 or 2 not available, the primary Psoriasis Severity Scale used was recorded

2.3.6 Data extraction and synthesis

Two reviewers (FA and AC) extracted the data independently from all eligible published studies, discussed any disagreements and if necessary involved a third reviewer (Ausama Atwan, AA) for resolution. A form for recording data was adapted (Higgins and Green 2008)

that included study design, details of administration and duration of treatment and follow-up. Parts of the Cochrane Risk of Bias tool were also incorporated into this form (Appendix VIII). The risk of bias was graded as 'low', 'high', or 'unclear' for each of the following domains:

(a) random sequence generation;
(b) allocation concealment;
(c) blinding of participants, personnel, and outcome assessment;
(d) incomplete outcome data;
(e) selective outcome reporting (we checked trial databases to ensure that reported outcomes matched to those prospectively listed); and
(f) other sources of bias, such a selection or attrition bias

Though it was not part of the inclusion criteria, article quality was rated from low to high based on methodological robustness using the Jadad score (Appendix IX)(Jadad et al. 1996). The PASI (or any other PSS) and all QoL data including the baseline, treatment and follow-up endpoint scores were recorded, along with information on whether studies detailed QoL percentage change, full scores, graphs or MCID.

2.4 Results

A total of 3593 records were identified through database searching and 53 through other sources (e.g. trial registries and hand-searching). After the removal of duplicates (n=1630) and initial screening, 99 articles met the inclusion criteria, describing 100 RCTs and 33,215 patients (Figure 2.1).

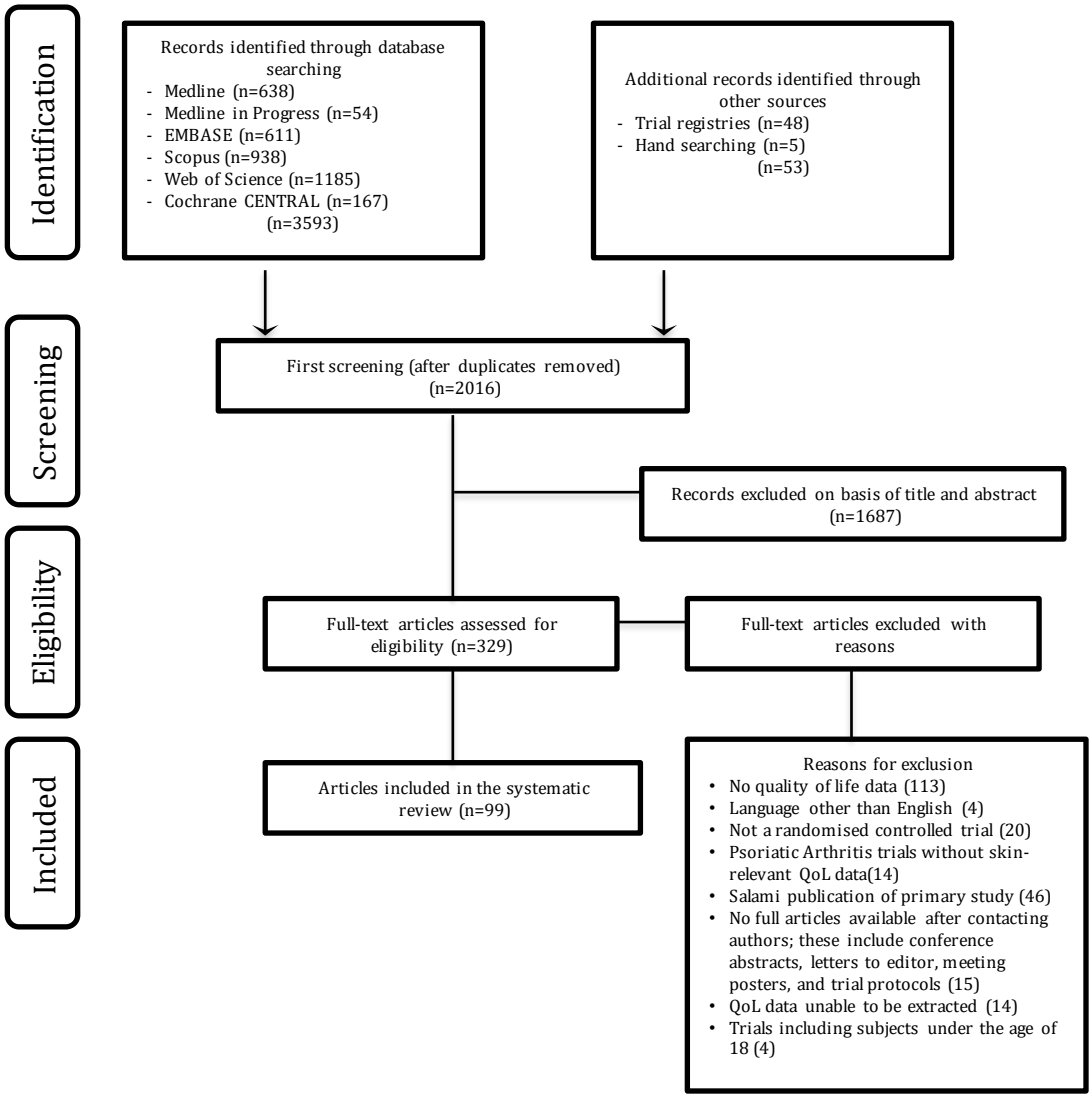


Figure 2.1 Flow diagram of article selection

Some trials were reported in more than one publication: all relevant references are given in Table 2.1. Sixty-three studies were placebo-controlled, 33 head-to-head trials and 36 tested a single drug in different dosage regimens or formulations (the total is greater than 99 as some studies fulfilled more than one criterion). Although Jadad scores (Jadad et al. 1996) were not integral to the inclusion criteria, Table 2.1 ranks interventions from low to high based on their methodological quality per interventional category.

Four articles were sent to the adjudicator (AA) for differences of opinion between the two independent reviewers, of which the study by Leaute-Labreze et al. (2001) was excluded due to an inappropriate QoL measure being utilised. The other three queries pertained to:

- whether intention-to-treat analysis (ITT) was performed in the study by Flytström et al. (2008)
- The blinding risk in the study by Ho et al. (2010)
- Confirmation of treatment duration of the study by Tabolli et al. (2012)

These were all resolved for the final analysis.

Table 2.1 Included studies: Jadad score, treatment duration, sample characteristics, QoL instruments and main psoriasis severity scale used. Where appropriate 'salami' publications also included i.e. data from the same trial that may be published (wholly or in part) in multiple end publications

Main QoL article, Year ('salami' publications used to derive non-QoL data)	**Jadad**	**Interventions** (Grouped per intervention, ranked by increasing Jadad score)	**Treatment End point** (Weeks) Unless specified	**Number of Subjects**	**QoL instruments used**	**Psoriasis severity scale used** (Primary)
BIOLOGICS						
Asahina et al. (2010)	3	Adalimumab vs Placebo	24	169	DLQI*, SF-36*	PASI
Genovese et al. (2007)	4	Adalimumab vs Placebo	12	100	DLQI*, HAQ-DI*, SF-36* (PCS ONLY), FACIT F†	PGA
Mease et al. (2005)	4	Adalimumab vs Placebo	24	313	DLQI*, HAQ-DI*, SF-36* (PCS ONLY)	PASI
Shikiar et al. (2007), Gordon et al. (2006), Menter et al. (2010)	4	Adalimumab vs Placebo	12	148 50	DLQI*, EQ-5D*, SF-36* (EXCEPT FOR PCS IN 40 MG EOW ARM)	PASI

Revicki et al. (2007), Kimball et al. (2011), Menter et al. (2008b), Revicki et al. (2008a), Revicki et al. (2008a)	5	Adalimumab vs Placebo	16	1212	DLQI*, SF-36*	PASI
Revicki et al. (2008b), Saurat et al. (2008), Navarini et al. (2014), Saurat et al. (2011)	5	Adalimumab vs MTX	16	271	DLQI*, EQ-5D*	PASI
Thaci et al. (2010), Paul et al. (2012)	5	Adalimumab + CAL/BD vs Adalimumab + Vehicle	16	730	DLQI†	PASI
Lui et al. (2012)	2	Alefacept vs nUVB	16	98	DLQI†	PASI
Ellis et al. (2003), Ellis and Krueger (2001)	4	Alefacept vs Placebo	12	205	DLQI⁰, SF-36⁰, DQOLS⁰	PASI
Finlay et al. (2003), Lebwohl et al. (2003)	4	Alefacept vs Placebo	12	507	DLQI†, DQOLS* (15 MG ARM ONLY), SF-36* (PCS ONLY)	PASI
Yan et al. (2011)	4	Alefacept vs MTX	12	212	DLQI†, SF-36†	PASI
Papp et al. (2014), Gordon et al. (2012)	5	Briakinumab vs Placebo	12-40	2209	DLQI*, SF-36*	PASI
Gordon et al. (2014), Papp et al.	5	Brodalumab vs Placebo	12	198	DLQI*,	PASI

(2012b)					SF-36* (140 MG ARM ONLY, AND MCS FOR 210 MG ARM)	
Gladman et al. (2014), Mease et al. (2014)	3	Certolizumab vs Placebo	24	409	DLQI*, SF-36*, PSAQOL*, HAQ-DI*	PASI
Reich et al. (2012)	5	Certolizumab vs Placebo	12	176	DLQI[0]	PASI
Dubertret et al. (2006), Ortonne et al. (2005)	4	Efalizumab vs Placebo	12	793	DLQI*, SF-36*	PASI
Gordon et al. (2003), Menter et al. (2005)	5	Efalizumab vs Placebo	12	556	DLQI*, PSA*	PASI
Cassano et al. (2006)	1	Etanercept (Dose-comparison)	12	108	DLQI†	PASI
Dauden et al. (2009), Ortonne et al. (2008), Luger et al. (2009)	1	Etanercept (Continuous vs Intermittent)	54	720	DLQI*, EQ-5D†, SF-36†	PASI
Gelfand et al. (2008), Moore et al. (2007)	2	Etanercept (Continuous vs Intermittent)	24	2546	DLQI[0], EQ-5D[0] (EuroQoL-FT), SF-36[0]	PASI
Gniadecki et al. (2012), Sterry et al. (2010)	3	Etanercept (Dose-comparison)	12	752	DLQI*, EQ-5D†, HAQ-DI†	PASI
Lynde et al. (2012)	3	Etanercept vs Etanercept + nUVB	12	75	DLQI†	PASI

Ortonne et al. (2013)	3	Etanercept (Dose-comparison)	24	72	DLQI[0]	PASI
Thaçi et al. (2014), Strohal et al. (2013)	3	Etanercept (Dose-comparison)	12	273	DLQI[*]	PASI
Zachariae et al. (2008)	3	Etanercept + MTX (Tapered vs Continued)	24	59	DLQI[*], EQ-5D[†]	PASI
Krueger et al. (2005), Papp et al. (2005)	4	Etanercept vs Placebo	12	583	DLQI[*], SF-36[*]	PASI
Feldman et al. (2005b), Leonardi et al. (2003)	5	Etanercept vs Placebo	12	652	DLQI[*]	PASI
Gottlieb et al. (2003b)	5	Etanercept vs Placebo	24	112	DLQI[*]	PASI
Reich et al. (2009), van de Kerkhof et al. (2008)	5	Etanercept vs Placebo	12	142	DLQI[*], SF-36[*]	PASI
Tyring et al. (2007), Tyring et al. (2006)	5	Etanercept vs Placebo	12	618	DLQI[*]	PASI
Reich et al. (2013), extension of trial: Barker et al. (2011)	2	Infliximab (Continuous vs Intermittent)	100	441	DLQI[0], SF-36[0]	PASI
Yang et al. (2012)	2	Infliximab vs Placebo	10	129	DLQI[*]	PASI

Barker et al. (2011)	3	Infliximab vs MTX	16	868	DLQI*, SF-36* (PCS ONLY), EQ-5D*	PASI
Feldman et al. (2008), Menter et al. (2007)	4	Infliximab vs Placebo	10	1430	DLQI*, SF-36*	PASI
Torii and Nakagawa (2010)	4	Infliximab vs Placebo	14	54	DLQI*	PASI
Bissonnette et al. (2011)	5	Infliximab vs Placebo	14	24	DLQI†	m-PPPASI
Feldman et al. (2005a), Gottlieb et al. (2004)	5	Infliximab vs Placebo	10	249	DLQI*	PASI
Reich et al. (2006), Reich et al. (2005)	5	Infliximab vs Placebo	24	378	DLQI*, SF-36*	PASI
Krupashankar et al. (2014)	4	Itolizumab (Loading dose vs. Non-loading dose)	12	225	DLQI0, SF-360	PASI
Leonardi et al. (2012)	5	Ixekizumab vs Placebo	8	142	DLQI*	PASI
Langley et al. (2014)	4	Secukinumab vs Etanercept vs Placebo	12	2044	DLQI* (VS PLACEBO ONLY)	PASI
Mamolo et al. (2014)	4	Tofacitinib vs Placebo	12	197	DLQI*, SF-36*	PASI
Paul et al. (2014), Reich et al. (2014)	2	Ustekinumab + MTX (Gradual vs. Immediate withdrawal)	16	489	DLQI0, EQ-5D0, VAS0	PASI

Nakagawa et al. (2012), Igarashi et al. (2012)	3	Ustekinumab vs Placebo	12	158	DLQI*, SF-36* (PCS ONLY), PDI*	PASI
Kimball et al. (2012), Leonardi et al. (2008), Lebwohl et al. (2010), Kimball et al. (2013)	3	Ustekinumab vs Placebo	12	766	DLQI*, SF-36[0]	PASI
Zhu et al. (2013)	3	Ustekinumab vs Placebo	12	322	DLQI*	PASI
Langley et al. (2010), Papp et al. (2008b)	4	Ustekinumab vs Placebo	12	1230	DLQI*	PASI
McInnes et al. (2013)	4	Ustekinumab vs Placebo	24	615	DLQI*, HAQ-DI*, SF-36* (EXCEPT MCS IN 45 MG ARM)	PASI
Kavanaugh et al. (2010), Gottlieb et al. (2009)	5	Ustekinumab vs Placebo	12	146	DLQI*, HAQ-DI*	PASI
Tsai et al. (2012), Tsai et al. (2011)	5	Ustekinumab vs Placebo	12	121	DLQI*	PASI
SYSTEMICS						
Strand et al. (2013), Papp et al. (2012a)	5	Apremilast vs Placebo	16	352	DLQI* (EXCEPT 10 MG ARM),	PASI

					SF 36* (MCS ONLY)	
Möller et al. (2010)	4	Chondroitin Sulphate vs Placebo	12	116	DLQI†, SF-36†	PASI
Beissert et al. (2009)	3	Ciclosporin vs Mycophenolate Mofetil	12	54	PDI†	PASI
Thaci et al. (2002)	4	Ciclosporin (Body-weight dependent dose vs Independent dose)	12	212	PDI0	PASI
Roberti et al. (2014)	4	Cytokines (low dose)	12	41	DLQI*	PASI
Bagel et al. (1998)	2	DAB389IL02 vs Placebo	4	70	DLQI0	PASI
Greenberger et al. (2012)	3	Dunaliella bardawil (9-cis b-carotene) vs Placebo	12	44	DLQI*	PASI
Salim et al. (2006)	5	MTX + Folic acid vs MTX	12	22	DLQI†	PASI
Kaltwasser et al. (2004), Nash et al. (2006)	5	Leflunomide vs Placebo	24	190	DLQI*, HAQ*	PASI
Faurschou et al. (2015)	4	Liraglutide vs Placebo	8	20	DLQI†	PASI
Flytström et al. (2008)	3	MTX vs Ciclosporin	12	84	DLQI†, SF-36* (PCS ONLY)	PASI
Asawanonda and Nateetongrungsak (2006)	4	MTX + nUVB vs MTX + Placebo	24	24	DLQI†	PASI

Ho et al. (2010)	2	Traditional Chinese Medicine vs MTX	24	61	PDI* (FOR MTX VS PLACEBO)	PASI
Gupta et al. (2008)	3	Voclosporin vs Placebo	12	201	DLQI[0], PDI[0]	PASI
Kunynetz et al. (2011), Papp et al. (2008a)	5	Voclosporin vs Placebo	12	451	DLQI* (FOR 0.3 AND 0.4 MG ARMS), PDI* (FOR 0.3 AND 0.4 MG ARMS)	PASI
Drouin et al. (2008)	5	XP-828L (Dermylex) vs Placebo	8	26	DLQI*	PASI
PHOTOTHERAPY						
Koek et al. (2006)	2	Home UVB (TL-01) vs Outpatient UVB (TL-01)	'46 irradiations'	196	PDI†, SF-36[0], EQ-5D[0]	PASI
Gahalaut et al. (2014)	2	PUVAsol + Isotretinoin vs PUVAsol	12	40	DLQI*	PASI
Klein et al. (2011)	2	Synchronous balneophototherapy vs nUVB monotherapy	'35 sessions'	367	PDI†, SIP*, FLQA-d*(PHYSICAL COMPLAINTS AND GLOBAL HEALTH ONLY)	PASI
TOPICALS						

Choonhakarn et al. (2010)	4	Aloe Vera vs Triamcinolone acetonide	8	75	DLQI†	PASI
Ortonne et al. (2014)	5	Betamethasone valerate dressing vs CAL/BD ointment	4	324	DLQI*	TSS-4
Wall et al. (1998)	1	CAL vs Dithranol	12	306	PDI†, SIP†	IGA
Ortonne et al. (2009), Kragballe et al. (2009)	2	CAL/BD scalp formulation vs CAL scalp solution	8	312	SF-36†, Skindex-16*	TSS
Saraceno et al. (2007)	2	CAL/BD vs CAL	4	150	Skindex-29*	PASI
Zheng et al. (2011)	2	CAL/BD vs CAL	4	320	DLQI*	VAS
De Korte et al. (2008), Van De Kerkhof et al. (2006)	3	CAL vs Dithranol	12	106	Skindex-29†, SF-36†	Modified PASI
Menter et al. (2013)	4	CAL/BD vs BD vs CAL vs Vehicle	8	1152	DLQI* (EXCEPT VS CAL GROUP)	PASI
van de Kerkhof (2004)	4	CAL/BD vs CAL vs Placebo	4	828	EQ-5D*, PDI†	PASI
Woo and McKenna (2003)	5	CAL + nUVB vs CAL vs Vehicle	20 sessions	50	PDI†	PASI
Hutchinson et al. (2000)	1	Calcitriol vs Dithranol	8	114	PDI*	PASI

Bergstrom et al. (2003)	1	Clobetasol (Foam vs Cream/Solution)	2	32	DLQI†, EQ-5D*	PASI
Menter et al. (2009)	1	Clobetasol propionate vs Calcipotriene + Betamethasone dipropionate	4	93	PQOLS†	ODS
Mraz et al. (2008)	1	Clobetasol propionate (Spray vs Foam)	2-4	77	DLQI*	IGS
Sofen et al. (2011)	2	Clobetasol propionate spray vs Vehicle	4	81	Scalpdex*	GSS
Prins et al. (2005)	2	Dithranol (Short contact) + nUVB vs Dithranol (Inpatient)	8-12	238	SIP*, PDI*	PASI
Alora-Palli et al. (2010)	2	Liquor Carbonis Distillate (LCD) Solution vs Calcipotriene cream	12	60	DLQI†	Modified PASI
Bernstein et al. (2006)	2	M. Aquifolium vs Placebo	12	200	QLI*	PASI
Tiplica and Salavastru (2009)	3	Mometasone furoate 0.1% + Salicylic acid 5% vs Mometasone furoate 0.1%	1	359	DLQI0	PASI
Galvez et al. (2012)	3	Sulphurous Mineral Waters Spray vs Distilled Water Spray	2	39	DLQI†	PASI
OTHERS						

Lu et al. (2012)	2	Auricular therapy + Yinxieling formula vs Yinxieling formula	8	84	DLQI†	PASI
Schmitt et al. (2014)	3	Interdisciplinary dermatological and psychiatric care for psoriasis vs Dermatological care for psoriasis	24	47	DLQI†	PASI
Ersser et al. (2012)	2	Educational nursing intervention vs No education intervention	6	64	DLQI†	PASI
Bostoen et al. (2012)	4	Educational programme vs No educational intervention	12	29	DLQI*, PDI*, Skindex-29†	PASI
Vedhara et al. (2007)	2	Emotional disclosure vs Standard control writing intervention	0.5	59	DLQI0	PASI
Guida et al. (2014)	2	Patients on immunosuppressives: Energy-restricted diet vs Usual diet	24	44	DLQI*	PASI
Jensen et al. (2013)	2	Low energy diet vs Standard routine dietary guidance	16	60	DLQI*	PASI
Fordham et al. (2015)	2	MCBT vs Usual treatment	8	29	DLQI*	SAPASI
Chambers et al. (2012)	2	Online Healthcare Delivery vs In-Office Care	16	64	DLQI0, EQ-5D0	PASI
Tabolli et al. (2012)	2	Writing exercise (Pennebaker) vs	0.5	202	Skindex-29†, SF-36†,	PASI

		Educational intervention			GHQ†	

Footnote

* Indicates significant improvement versus comparator(s)

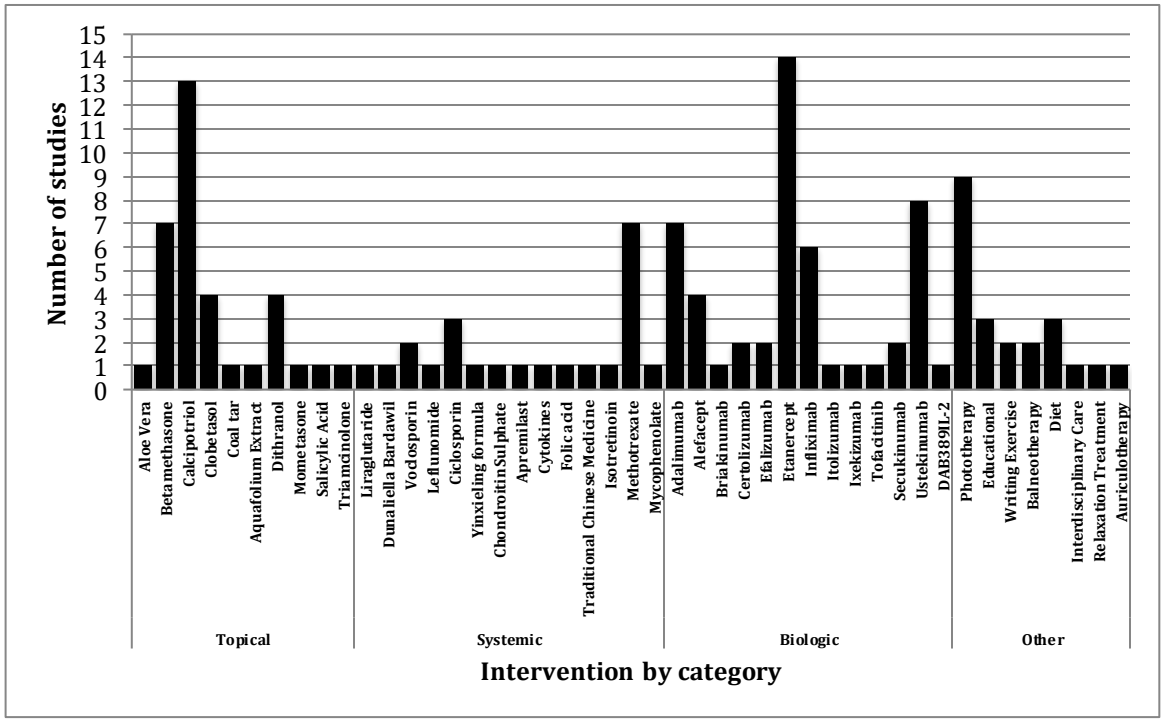
† Indicates no significant improvement versus comparator(s)

0 Indicates no significance data was provided

2.4.1 Interventions assessed

Of the 100 trials that measured QoL, 33 tested topical, 18 systemic, 39 biologics, 9 phototherapy, and 10 tested other interventions including educational treatments, diet, writing exercises, balneotherapy, auriculotherapy, relaxation therapies and interdisciplinary care (Table 2.1, Figure 2.2). The number of studies reporting each topical intervention were: calcipotriol (13 trials), calcipotriol/bethametasone (7), clobetasol (4) and dithranol (4). Systemic medications trials included: methotrexate (7), ciclosporin (3) and voclosporin (2). Biologic trials included etanercept (14), ustekinumab (8), adalimumab (7), infliximab (6) and alefacept (4). Quality of life was evaluated in nine phototherapy trials. In the category of "other interventions" QoL was used most commonly in educational (3) and diet (3) trials.

Figure 2.2 Number of randomised controlled trials of each intervention that measured HRQoL



The mean Jadad score was 3.34 (range 1-5, Table 2.1). QoL was tested a range of 2-6 times for topical, 2-25 times for systemic and 2-12 times for biologic interventions. Sixteen trials lasted more than 12 weeks, 49 from 12 to 24 weeks and 35 under 24 weeks. The subject number ranged from 20 (Faurschou et al. 2015) to 2546 (Gelfand et al. 2008) patients, with a mean male: female ratio of 1.7:1 per study arm. Mean PASI scores at baseline ranged from 1.7 to 33.1.

The range of mean QoL scores at baseline were: DLQI 1.7-20.1 (Minimum-maximum for this measure = 0-30); Short Form 36 (SF-36) physical component summary (PCS) 32.7-56.2 (0-100) and mental component summary (MCS) 35.7-52.4 (0-100); EuroQoL (EQ-5D) Component I 0.48-0.74 (0 to 1), EuroQoL Component II 55.3-76.4 (0-100); and Psoriasis Disability Index (PDI) 7.6-52.6 (0-90).

2.4.2 Types of quality of life instruments

Thirteen instruments were used to measure QoL; some studies used more than one. Five generic instruments were used: the SF-36 (Ware Jr and Sherbourne 1992); EQ-5D (Group 1990); General Health Questionnaire (GHQ-12) (Goldberg and Hillier 1979; Piccinelli et al. 1993); Quality of Life Index (QLI) (Ferrans and Powers 1985); and Sickness Impact Profile (SIP) (Bergner et al. 1981; Finlay et al. 1990). In addition, four dermatology specific instruments, three specific to psoriasis and one for scalp dermatitis were used: DLQI (Finlay and Khan 1994); Skindex (Chren et al. 1996); Dermatology Quality of Life Scales (DQOLS) (Morgan et al. 1997); Freiburg Life Quality Assessment (FLQA-d) (Augustin et al. 2000); PDI (Finlay et al. 1990); 12-Item Psoriasis Quality of Life Questionnaire (PQOL-12) (Koo et al. 2003); Psoriatic Arthritis Quality of Life measure (PsAQoL) (McKenna et al. 2004); and SCALPDEX (Chen et al. 2002). Of these, the DLQI was the most commonly used QoL instrument (number of studies=83, 83%), followed by the SF-36 (31, 31%), EQ-5D (15, 15%), PDI (14, 14%) and Skindex (5, 5%).

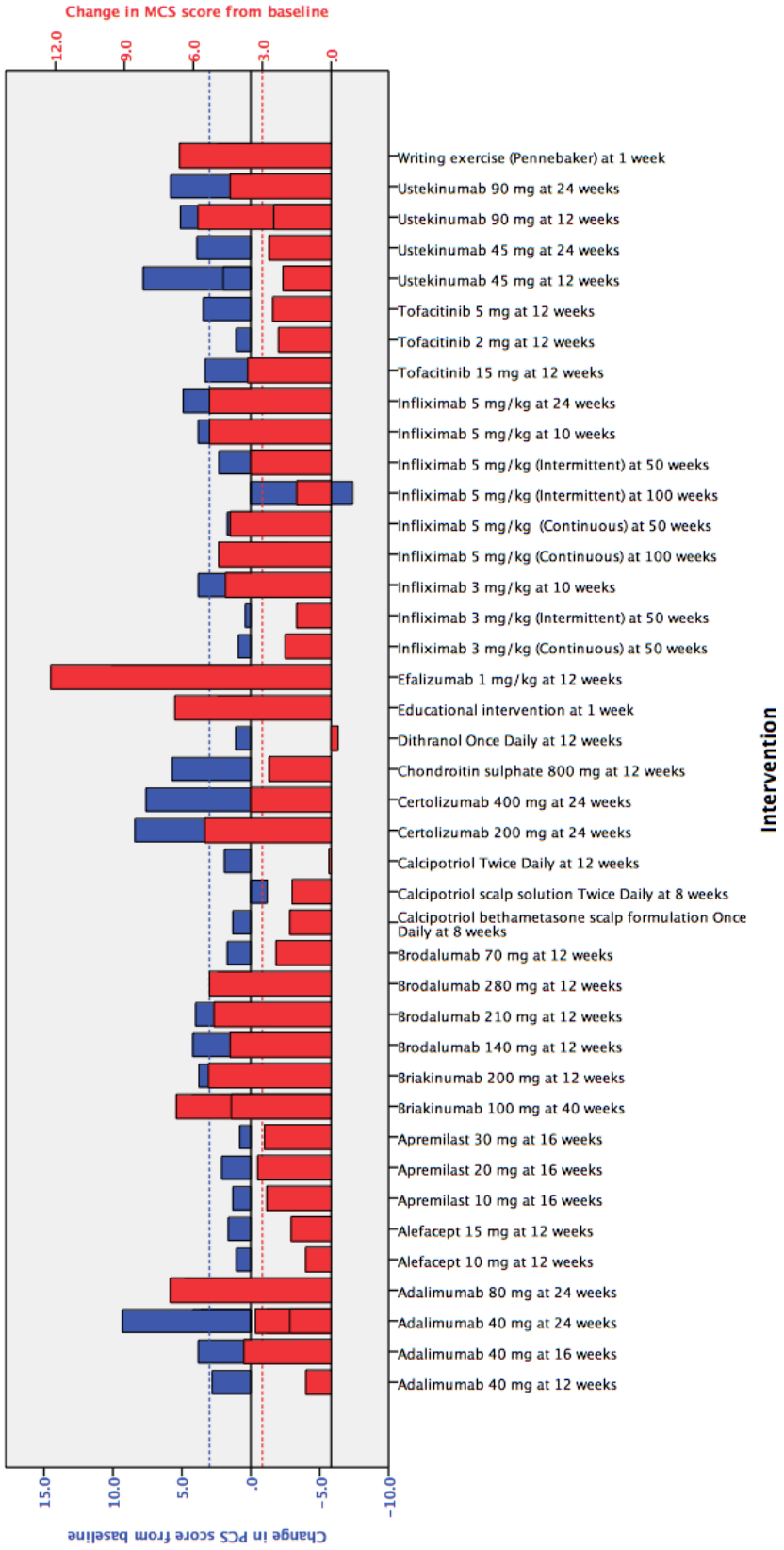
2.4.2.1 Characteristics of the most commonly used quality of life instruments

The DLQI (Finlay and Khan 1994), a dermatology-specific instrument, assesses QoL over the past week. It comprises 10 questions in six categories: symptoms/feelings; daily activities; leisure; work/school; personal relationships; and treatment. Scores range from 0 to 30: higher signifies worse QoL. The MCID was considered to be a score change of five (Khilji 2002) but is now reported as four (Basra et al. 2015c). The DLQI was the most commonly used instrument, in 83 of the RCTs: 32 (39%) trials reported the MCID. Change in mean DLQI scores from baseline to treatment end (Figure 2.5) ranged from -14.4 (Guida et al. 2014) to +3.0 (Reich et al. 2013).

The SF-36 (Ware Jr and Sherbourne 1992) is a general health status questionnaire

evaluating eight daily activity domains: physical function; role limitations due to (i) physical, (ii) emotional and (iii) social role functioning; physical problems; bodily pain; mental health; vitality; and general health perceptions. Scores are separated into physical (PCS) and mental (MCS) component summaries. The scale score ranges from 0 to 100 for each component: higher signifies better QoL. The MCID is a change of three in the total score (Samsa et al. 1999). The SF-36 was used in 31 trials and MCID reported in 10 (32%). The mean SF-36 change from baseline to treatment end (Figure 2.3), ranged from PCS -7.4 (Reich et al. 2013) to +10.1(Ortonne et al. 2005; Dubertret et al. 2006) MCS from -0.3 (De Korte et al. 2008) to +12.2 (Ortonne et al. 2005). The SF-36 score of 50 reflects average QoL of the general population.

Figure 2.3 The absolute change in SF-36 scores (PCS & MCS) for interventions identified in the systematic review



The EQ-5D (Group 1990) is a generic QoL instrument, also used for economic evaluation of therapeutic interventions. It has two components: (I) index score; and (II) visual analogue scale (VAS). Component I has five items rating mobility, self-care, usual activities, pain/discomfort and anxiety/depression using three points (none, some or extreme problems). These scores are assigned a health-state from 0 to 1: higher represents better QoL. In Component II patients choose a number from 0 to 100 representing their current health status: higher means better health status (Group 1990; Revicki et al. 2008b). The EQ-5D was used in 15 trials, 6 reported MCID.
The Psoriasis Disability Index (PDI) has 15 psoriasis-specific QoL items in five categories: daily activities; work or school; personal relationships; leisure; and treatment. Each item is scored from 0 to 6 (total 0 to 90): higher represents worse QoL (Finlay and Kelly 1987b; Finlay et al. 1990). The PDI was used in 14 trials: the MCID is not known.

Skindex (Chren et al. 1996) is a dermatology-specific instrument with four versions: Skindex (61 items); Skindex-29 (29 items); Skindex-17; and Skindex-16. The Skindex-29, used in four trials, consists of physical score (7-35 points), emotional (10-50) and psychosocial sphere (12-60). The total score, indicating the effect on QoL during the past month (past week for Skindex-16) ranges from 29 to 145: higher represents worse QoL (Lambert et al. 2011). Skindex was used in five RCTs, MCIDs for Skindex versions have not been published, though a meaningful score change for dermatomyositis has been recently described (Ahmed et al. 2020).

2.4.3 Minimal Clinically Important Difference

The MCID of QoL measures may be determined using several methodologies, and at least nine approaches have been reported (Crosby et al. 2003). These may be categorised into two main groups: anchor-based and distribution based approaches. Whereas the former incorporates patient perspective, the latter determines MCID using statistical significance. The anchor-based method is the most commonly used for determining the MCID, as used in the case of the DLQI (Basra et al. 2015c).
Each methodology has its limitations, for example, anchor-based methods have often been criticised for unequal changes required for deterioration versus improvement of a condition (Wright et al. 2012). Several factors may influence MCID scores, including patient baseline status, disease group and severity, treatment and patient demographics. Furthermore, it is important to note that MCID values may differ significantly within the same population depending on the methodology chosen (Terwee et al. 2010). Therefore interpreting MCID

scores should be considered in the context of these limitations.

Of the 100 trials identified, 37 reported MCID; 32 were for DLQI, 10 for SF-36 and six for EQ-5D. Where DLQI score changes were reported, 115 of 142 'study arms' met the 4-point MCID (Basra et al. 2015c). Biologic interventions usually attained DLQI MCID: 91.2% (83 of 91 study arms) met the 4-point MCID. The MCID was attained by 77.8% (14 of 18) of topical, and 52.4% (11 of 21) of systemic treatment arms.

One RCT of infliximab measuring QoL at 100 weeks (Reich et al. 2013) reported 3 points worsening of DLQI. However, this study ended prematurely and had a low JADAD score of only 2. Another trial, with a high JADAD score of 5 (Salim et al. 2006) demonstrated mean DLQI score increasing by 0.4 after folic acid was added to methotrexate. The MCID was not met for any study arm.

The SF-36 MCID is a change of three in the total score (Samsa et al. 1999). The SF-36 was used in 31 trials and MCID reported in 10. The mean SF-36 change from baseline to treatment end ranged from PCS -7.4 (Reich et al., 2013) to +10.1 (Dubertret et al, 2006; Ortonnne et al, 2005), MCS from -0.3 (De Korte et al, 2008) to +12.2 (Ortonne et al, 2005). Where extracting change in SF-36 MCS scores was possible, 52.2% (24 of 46) 'study arms' met the 3-point MCID: 58.3% (21 of 36) of biologic interventions met this. For PCS scores, 50% (24 of 48) of 'study arms' met the MCID as did 60.5% (23 of 38) of biologic interventions. Only 25% (1 of 4) of systemic and no topical treatments met the MCID for both MCS and PCS domains.

The EQ-5D was used in 15 trials, 6 reported the MCID, which is 0.05 (O'Brien and Drummond 1994; Dolan 1997). The PDI was used in 14 trials: the MCID is not known. Skindex was used in five RCTs; MCIDs for Skindex versions have not been published.

2.4.3.1 QoL score change interpretation: 2MCID concept

Absolute change or improvement in DLQI score, where available, was derived or calculated per study arm across each interventional category (Figure 2.4a-d). As the DLQI was the most commonly used QoL measure, it was used to assess the absolute score changes across all interventions where possible.

Figure 2.4 The absolute change in DLQI score across the interventions identified in the systematic review divided according to category

Figure 2.4a The absolute change in mean DLQI score across topical interventions at treatment endpoint

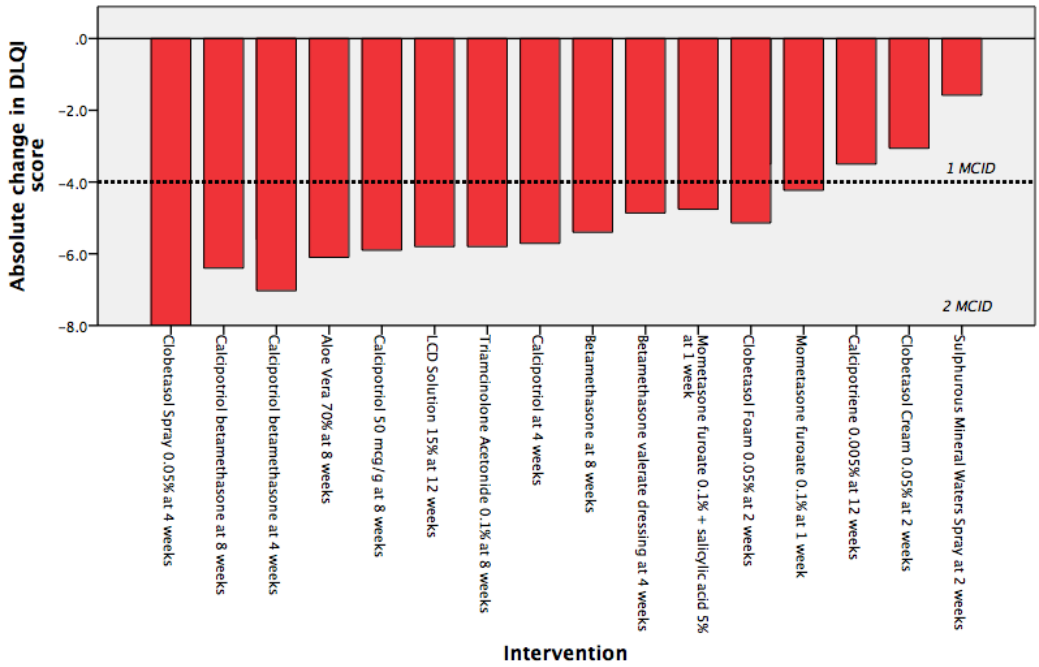


Figure 2.4b The absolute change in mean DLQI score across systemic interventions at treatment endpoint

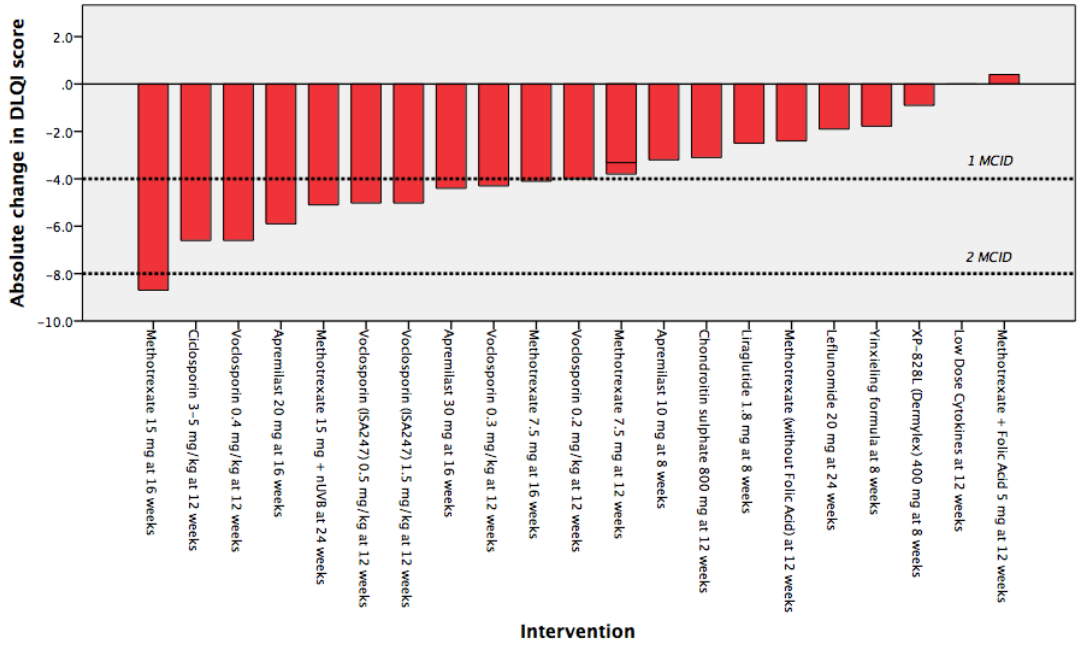


Figure 2.4c The absolute change in mean DLQI score across biologic interventions at treatment endpoint

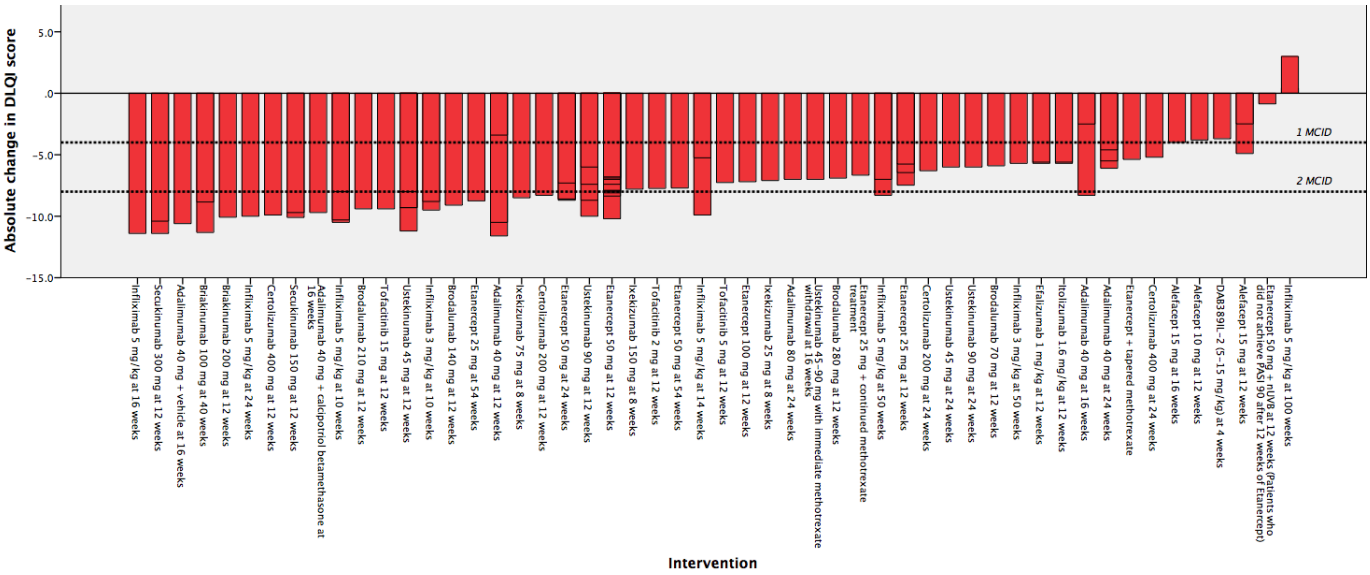
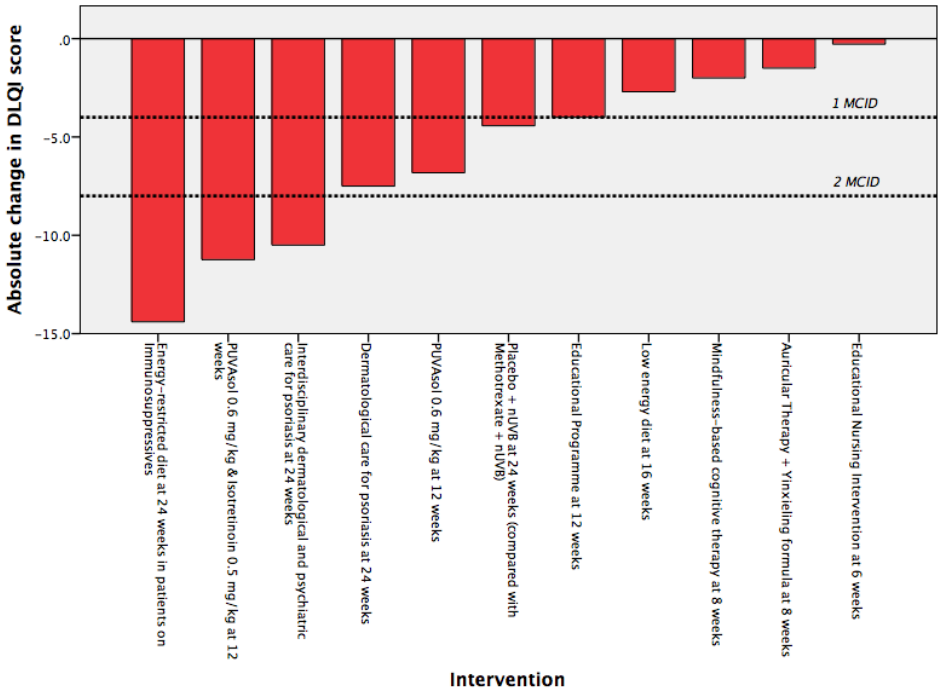


Figure 2.4d The absolute change in mean DLQI score across other interventions at treatment endpoint



In order to give a greater sense of the meaning of score change in the context of this systematic review, the concept of 2MCID was introduced: that is a DLQI score change of at least 8. This approach, novel in dermatology, has been used in other areas (Leaf and

Goldfarb 2008; Paul et al. 2015) and highlights therapies that have reached this higher change threshold.

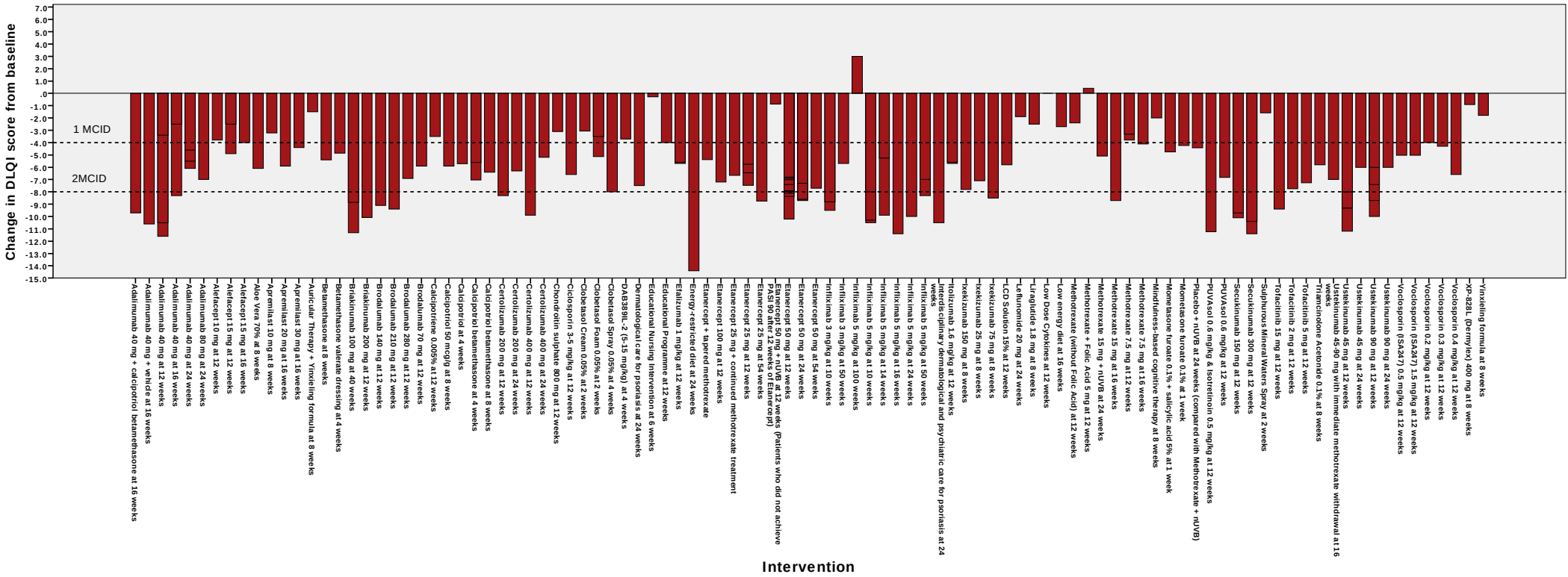
For topical treatments, clobetasol 0.05% spray (Mraz et al. 2008) showed the greatest improvement at 4 weeks (2MCID, 8 point improvement), followed by calcipotriol plus betamethasone (Menter et al. 2013) at 8 weeks (6.4 points). These changes are comparable to ustekinumab 90 mg at 12 weeks (average 2MCID (8 point) improvement, (Kavanaugh et al. 2010; Langley et al. 2010; Igarashi et al. 2012; Kimball et al. 2012)) and ciclosporin 3-5 mg/kg at 12 weeks (6.6 point improvement, (Flytström et al. 2008)). No other topical therapy reached 2MCID. However, it is important to consider these changes in the context of lower baseline psoriasis severity in topical therapy trials, shorter treatment duration and long-term QoL maintenance.

Methotrexate 15 mg at 16 weeks (Barker et al. 2011) was the only systemic intervention over the 2MCID threshold (8.7 points). This was comparable to several biologics, including etanercept 50 mg at 24 weeks (Ortonne et al. 2013) and ustekinumab 90 mg (Kimball et al. 2012) at 12 weeks (8.7points).
Infliximab 5 mg/kg at 16 weeks (Barker et al. 2011) and secukinumab 300 mg at 12 weeks (Langley et al. 2014) on average demonstrated the largest improvement in DLQI score of 11.4 (just short of 3MCID). Amongst other interventions, an energy-restricted diet with immunosuppressive therapy at 24 weeks (Guida et al. 2014) recorded DLQI improvement of 14.4 (>3MCID). DLQI at 12 weeks improved by 11.2 (>2MCID) with PUVAsol 0.6 mg/kg + isotretinoin 0.5 mg/kg: for PUVAsol alone, DLQI improvement was 6.8 (Gahalaut et al. 2014).

For studies with treatment endpoint and assessment at 12 weeks, which is often the endpoint standard, the interventions with the greatest average DLQI impact in each category were secukinumab 300 mg (>2MCID, 11.4 points, (Langley et al. 2014)), ciclosporin 3-5 mg/kg (>1MCID, 6.6 points (Flytström et al. 2008)), PUVAsol 0.6 mg/kg + isotretinoin 0.5 mg/kg (>2MCID, 11.2 points, (Gahalaut et al. 2014)), Liquor Carbonis Distillate solution 15% (>1MCID, 5.8 points, (Alora-Palli et al. 2010)) and educational programme (1MCID, 4 points, (Bostoen et al. 2012)).

Figure 2.5 collates the absolute change in DLQI score across all interventions identified in the systematic review.

Figure 2.5 The absolute change in DLQI scores across the interventions identified in the systematic review*

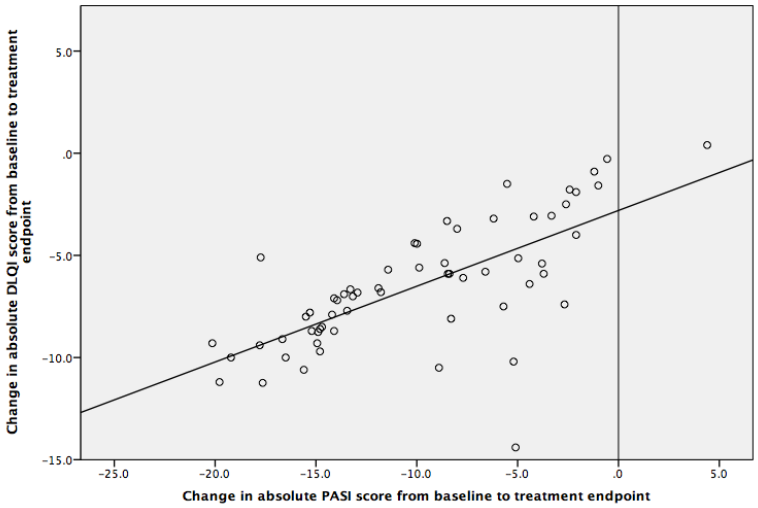


*To associate any of the bars with the published evidence, please refer to Table 2.1

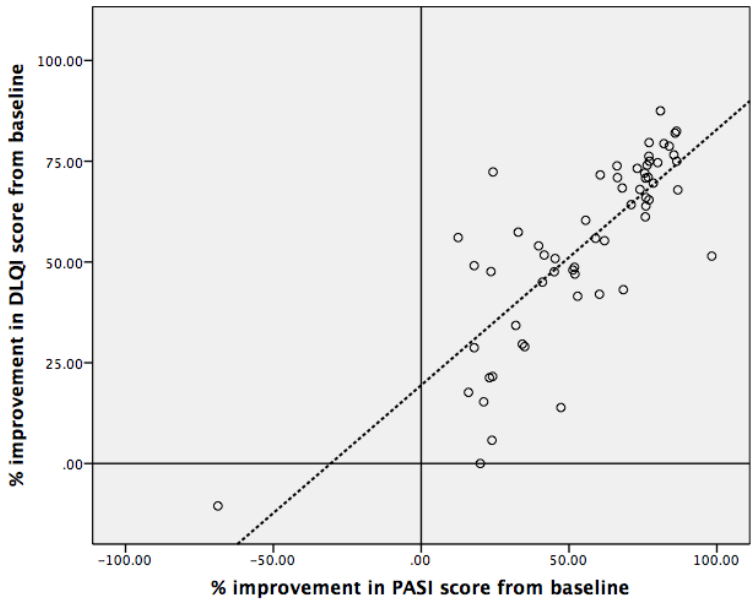
Figure 2.6 shows the correlation between PASI and absolute DLQI (R^2=0.494, y=-2.8+0.37*x) and percentage (R^2=0.641, y=19.43+0.63*x) score changes, where available. In some cases the correlation was weak (Roberti et al. 2014), possibly attributed to non-optimal endpoint measurement for QoL where maximum effect may be missed (Bishop-Bailey et al. 2015). Furthermore some interventions may have a psychological or emotional impact that is often not captured by clinical parameters such as the PASI. Nevertheless, the correlation graphs provide valuable mathematical formulae that may be used as a baseline to interpret and compare data from future studies.

Figure 2.6 Correlation of (a) absolute change in DLQI scores with absolute change in PASI scores (R^2 = 0.494, y=-2.8+0.37*x) (b) percentage improvement in DLQI scores with percentage improvement in PASI scores (R^2 = 0.641, y=19.43+0.63*x)

(a)



(b)

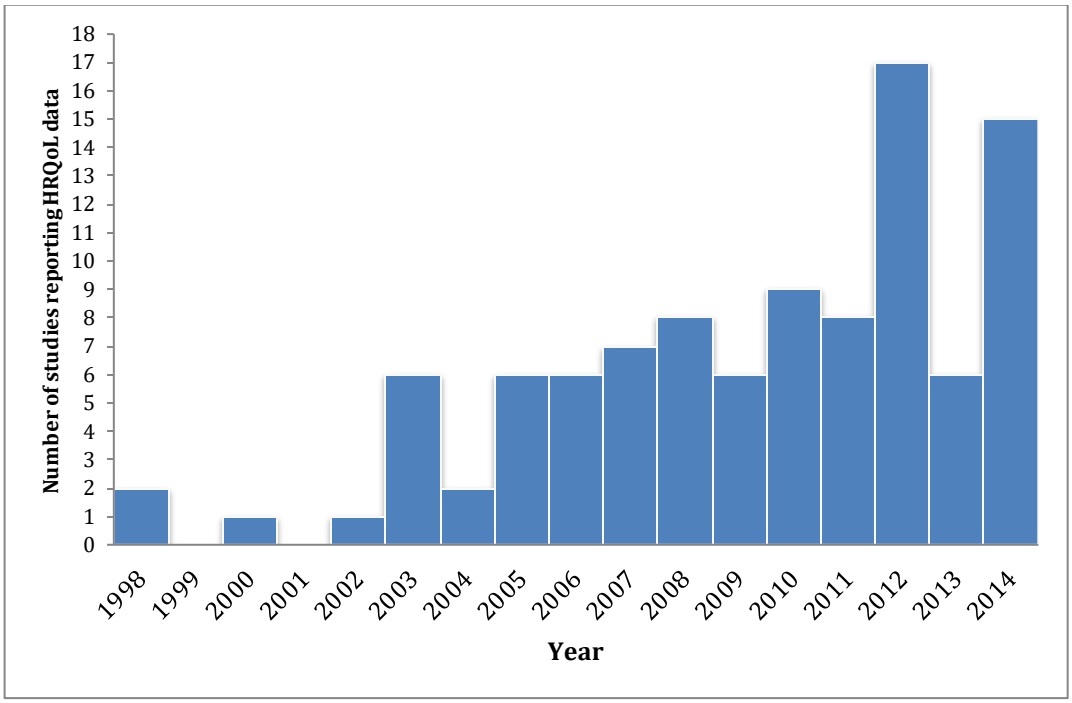


2.4.4 Statistically significant changes

Table 2.1 provides a list of the studies that documented full QoL data and statistical significance for intervention versus comparator. Significant changes (as determined by study researchers, commonly p=<0.05) were reached in 52 trials for the DLQI, 19 for the SF-36, 5 for both the EQ-5D and PDI and 2 for the Skindex. Conversely there was no statistical improvement in 19 trials for the DLQI, 6 for the SF-36, 3 for the EQ-5D, 6 for the PDI and 3 for Skindex. Twelve trials did not report statistical significance for the DLQI, 6 for the SF-36, 4 for the EQ-5D and 2 for the PDI.

Reports of psoriasis interventions that fulfilled inclusion criteria have gradually increased over time: 1998-2004 = 12, 2005-2009 = 33, and 2010-2014 = 55 (Figure 2.7).

Figure 2.7 Prevalence of the use of QoL instruments in the included psoriasis studies since 1998



2.5 Discussion

There have been several challenges in the process of developing this systematic review. Initially it was planned to include any published literature and not limit the search to just RCTs. However, given the sheer number of publications for psoriasis interventions, this would have been an arduous endeavor and the data would be extremely difficult to collate given its heterogeneity. Furthermore, in order to provide the highest level of evidence, RCTs are considered the gold standard in systematic reviews. I had attended a 4 day-course on Systematic Reviews organised by SysNet at Cardiff University (Appendix X) which was a very valuable tool towards planning the review. I was in regular contact with the core team who were extremely helpful throughout the process of developing the protocol and for answering any queries that arose.

This systematic review reaffirms the fact that QoL assessment is a frequent component in assessing psoriasis treatment efficacy in clinical trials as well as in routine clinical practice (Basra et al. 2008b). In the process, it has identified therapeutic RCTs that demonstrated extractable QoL data, inevitably with heterogeneity in design, disease severity and QoL reporting. Many trials were excluded because of inconsistent reporting and analysis of QoL (Le Cleach et al. 2008), despite an initial high search yield. Of the 329 full-text articles

assessed for eligibility, 14 studies reported psoriatic arthritis-only related QoL changes and 14 studies reported QoL data in an inextricable format (i.e. graphical representation with no numerical data, or summarised descriptive QoL information). Baseline and end-of-treatment values were not always provided. Often QoL scores were presented as percentage or value changes without pre or post-intervention scores. Mean values were most commonly reported, though median values are preferable with ordinal data (Basra et al. 2008b). Standard deviation, *p*-values or confidence intervals were sometimes omitted and intention-to-treat (ITT) numbers were sometimes omitted from the QoL data set. This presented challenges for synthesising data in a homogenous fashion.

The MCID is the minimal change in score that is considered of clinical relevance (Norman et al. 2003). Of the 13 QoL instruments used, only the DLQI, SF-36 and EQ-5D have MCID values reported in the literature. Although interventions may result in statistically significant QoL improvement, this does not necessarily correlate with clinically important change. MCID values enhance the clinical meaningfulness of QoL scores, particularly if data are correlated with clinical efficacy. Thirty-seven trials reported consideration of MCID, with the DLQI being the most commonly used instrument with known MCID. The EQ-5D was the only other used instrument with known MCID.

Though it is possible to apply score banding descriptors (Hongbo et al. 2005) which may be used to describe the number of patients within each score band pre and post intervention, there needs to be a method that can discriminate between the extent of the effect of interventions on QoL. The concept of '2MCID' (or multiple-MCID) could add meaning to score change when comparing therapies, and possibly when comparing results across different QoL instruments as a 'unit of change'. However, the establishment of meaningful MCID band descriptors to describe change beyond MCID would require validation and therefore further testing is necessary.

Nevertheless, this systematic review was used as a 'pilot study' for the concept of 'multiple-MCID' to demonstrate the potential benefit of comparing the extent of impact of different categories of interventions on QoL. In the case of this systematic review, it has been demonstrated that certain systemic interventions, for example, may impact QoL as significantly as certain biologic treatments. Similarly, certain topical treatments may be as efficacious as systemic alternatives. These results, however, are not completely ideal in that the dataset is not homogenous and often patients have different baseline severities. Furthermore, whether MCID values change at different ends of a QoL measure is debated and, along with other factors and considerations, would require formal validation to support such extrapolations.

As a ‘proof of concept’ it is believed multiple MCID provides more meaningful information on clinical improvement and may be of value to clinicians, patients and industry alike. For example, medications that meet the ‘2MCID’ minimum threshold may be easier to approve by regulatory authorities for marketing and by health technology assessment (HTA) agencies for reimbursement. This concept may also enable researchers to distinguish more efficiently between interventions and comparators in trials, potentially improving patients’ access to new medicines. Significant further work is imperative before this novel concept is widely adopted in the scientific arena.

The systematic review identified that more generic QoL instruments were used (n=5) than specialty (n=4) or condition specific questionnaires (n=3). The DLQI was the most commonly used instrument; possibly because of its ease of reporting a single summary score, the ease of completion in 2 minutes (Loo et al. 2003) and its widespread use in national psoriasis guidelines (Smith et al. 2020) amongst other reasons (Finlay et al. 2012).

The frequency at which QoL measurement was administered varied across studies depending on intervention type and trial duration. The UK clinical guidelines (NICE 2012), that recommend DLQI measurement at 10 to 16 weeks depending on the biologic, may not capture the best DLQI responses for biologic therapies (Bishop-Bailey et al. 2015). For example, in this systematic review the greatest DLQI score change (14.4) across all interventions was seen with an energy-restricted diet in conjunction with usual immunosuppressive therapy at 24 weeks (Guida et al. 2014). Although, the DLQI is skin-specific, the health benefits of weight loss itself may be reflected in patient DLQI follow-up responses. Psychiatric and interdisciplinary care at 24 weeks (Schmitt et al. 2014) may also significantly impact DLQI (10.5 points), re-enforcing the importance of lifestyle and a holistic approach to the management of psoriasis.

Several reviews have explored the effects of biologic treatment on QoL (Katugampola et al. 2007; Reich et al. 2008; Baker et al. 2012; Mattei et al. 2014), other SRs have explored QoL in psoriasis; the review by De Korte *et al.* (2004) was not limited to RCTs and this provided difficulties in interpreting the dataset. This SR investigates the overall impact of interventions on QoL as well as use patterns. Strict entry criteria were employed to allow for robust comparison across interventions per QoL instrument. Data was only included from the double-blind controlled phases of each trial. Nevertheless, the lack of adequate guidelines on reporting of QoL studies still rendered data analysis problematic.

Kitchen *et al.* (2015) reviewed the ability of psoriasis-specific instruments to adequately capture domains relating to psoriasis: no existing psoriasis specific patient reported outcome (PRO) instrument has sufficient evidence on validity, reliability and sensitivity to change, but

both DLQI (Safikhani et al. 2013) and Skindex demonstrated content validity. However, this SR demonstrates that several generic and disease/specialty-specific instruments were sensitive to change with positive QoL outcomes. In general, disease and specialty-specific instruments tend to be more sensitive to change over time than the generic measures, owing to the involvement of the target population in providing the determinants during the qualitative phase of development.

The DLQI and SF-36 appear to be the most frequently used instruments across psoriasis RCTs. A European S3 guidelines report on psoriasis systemic treatment (Nast et al. 2012) described the DLQI as an 'important' variable in assessment of treatment efficacy. However, the DLQI has limitations, including previous criticisms of its uni-dimensionality and low representation of emotional aspects (Both et al. 2007). There is diverse practice in monitoring therapeutic effect on QoL and questionnaire preference. A total of 113 RCTs were rejected because of inextricable QoL data. The European Academy of Dermatology and Venereology Task Force provides recommendations for use of QoL measures (Prinsen et al. 2013). Currently there is great variation in the quality of reporting of QoL data (Salek et al. 2013; Finlay 2014), creating difficulties in cross-interventional meta-analyses. This SR emphasises the need for guidelines concerning appropriate reporting of QoL data.

2.5.1 Recommendations

As a result of this SR, the recommendations for improvement of QoL reporting are as follows: to

- include baseline data,
- report all assessment visits and follow-up endpoint scores
- report absolute median scores with interquartile range (IQR)
- include patient numbers and their demographic characteristics in table format as well as boxplot showing percentiles
- report percentages together with the actual values
- report whether intention to treat was implemented (Salek et al. 2013; Finlay 2014)
- ensure that graphical representation of QoL is accompanied by numerical data.

Furthermore, authors should not submit only percentage and/or graphical data to represent study outcomes as this data cannot be used in meta-analysis and systematic reviews. Journals should furthermore implement such criteria prior to accepting publications. The MCID and validated band descriptors where available should be used to interpret data as this

holds greater clinical value than statistical significance alone. Researchers should consider the availability of MCID when choosing QoL instruments and be encouraged to publish MCID information. Whilst there are numerous approaches to calculating MCID scores, there is a need for consensus on new or improved methodological approaches towards calculating MCID. Existing methodologies should be cautiously taken into account by clinicians and researchers alike to facilitate the interpretation of results. Though minimal change is clinically important, the question arises of whether intervention endpoints should target perfect quality of life, rather than demonstrating a measurable improvement.

These recommendations in terms of QoL measurement and reporting are summarised below in Table 2.2.

Table 2.2 Summary of QoL measurement and reporting recommendations*

QoL reporting recommendations
Scores should be reported as absolute median scores with IQR at all phases of a study where appropriate. At the very least these should be at baseline, follow-up and treatment endpoint
Patients numbers should be reported alongside intention to treat data if calculated
Graphical QoL data should be accompanied by numerical data
MCID or valid band descriptors should be used to interpret QoL changes
MCID availability should be considered prior to selecting QoL instruments
MCID values should be developed and encouraged
There needs to be consensus on new or improved methodological approaches towards calculating MCID
Journals should consider implementing recommendations for reporting QoL data

* IQR – Inter-quartile range

MCID – Minimal clinically important difference

QoL – Quality of life

Different interventions may impact QoL to a similar extent, though biologic interventions have a very high impact. Psychiatric well-being may play a role in QoL improvement. Several topical treatments, as well as some systemic treatments, may improve QoL at least in the short-term.

Chapter 3: Development and validation of a web-based application of the Dermatology Life Quality Index (DLQI) and Psoriasis Area Severity Index (PASI) scale

3.1 Introduction

The systematic review has highlighted several inconsistencies with the reporting of quality of life (QoL) in psoriasis patients. Though it has been found that the DLQI is the most commonly utilised QoL measure in interventional RCTs for psoriasis, there are significant inconsistencies in how it is utilised across trials. In order to improve the assessment and documentation of DLQI scores in particular, which is the most commonly used dermatology QoL scale world-wide (Basra et al. 2008a), an electronic application (App) was developed in conjunction with Janssen EMEA®. A PASI electronic scoring system was also added to the application, as both clinical and quantitative parameters are vital aspects of assessing psoriasis disease severity (Smith et al. 2005; Katugampola et al. 2007). Therefore, it was deemed prudent and logical to include both aspects in an application designed for the monitoring of psoriasis severity.

It is hoped that this App will be easily accessible by clinicians and patients alike allowing the better monitoring and assessment of psoriasis in home, clinical and research settings. This chapter will separately analyse the validation process for both the DLQI and PASI score calculators built into the application.

3.1.1 The Psoriasis 360 iPad® App

The Psoriasis 360 iPad® app was developed by Janssen EMEA® in order to improve psoriasis monitoring in clinical and research settings. Careful consideration was given to transfer the respective paper versions of the measures to the digital counterparts. This included the BSA, DLQI and PASI score calculators, though only the latter two were validated as part of this study.

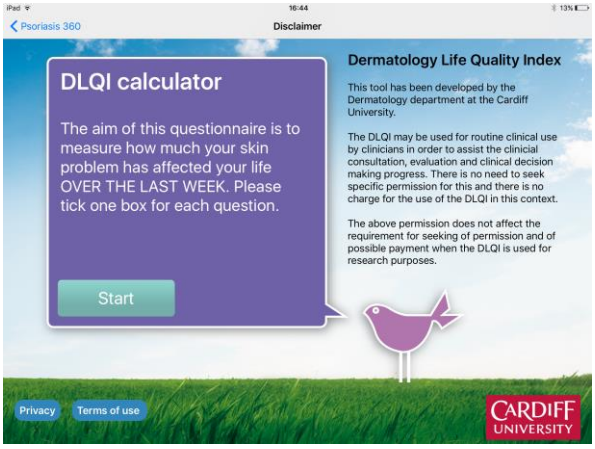
3.1.2 DLQI

The DLQI consists of 10 questions concerning a dermatological patient's perception of the impact of their skin disease on different aspects of their QoL over the last week. The items of the DLQI include symptoms and feelings, daily activities, leisure, work or school, personal relationships and the side effects of treatment. Each item is scored on a 4-point scale: not at all/not relevant, a little, a lot and very much. Scores of individual items (0-3) are added to yield a total score (0-30); higher scores mean greater impairment of patient's QoL. The DLQI has been shown to be a strong instrument with respect to its internal consistency,

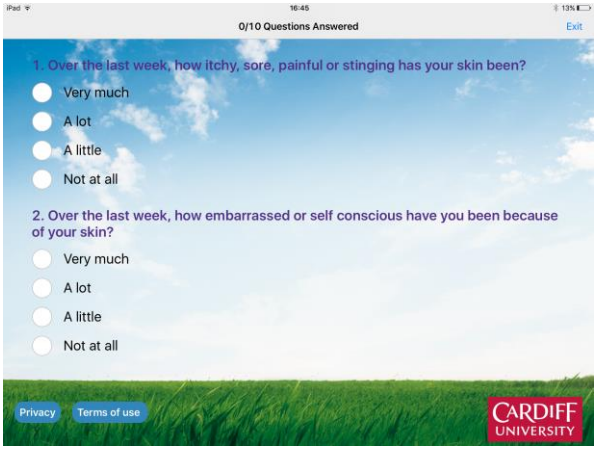
reproducibility, validity and sensitivity to change (Badia et al. 1999; Hahn et al. 2001; Mazzotti et al. 2003; Basra et al. 2008a; Bronsard et al. 2010). It was developed into an electronic application on the iPad® by Janssen EMEA® in conjunction with the original copyright holder (AYF, Cardiff University). The individual items and their responses were unchanged, allowing users to select options using touch. Figure 3.1 demonstrates a series of screenshots of the DLQI section of the App.

Figure 3.1 Screenshots of the DLQI calculator from the Psoriasis 360® App

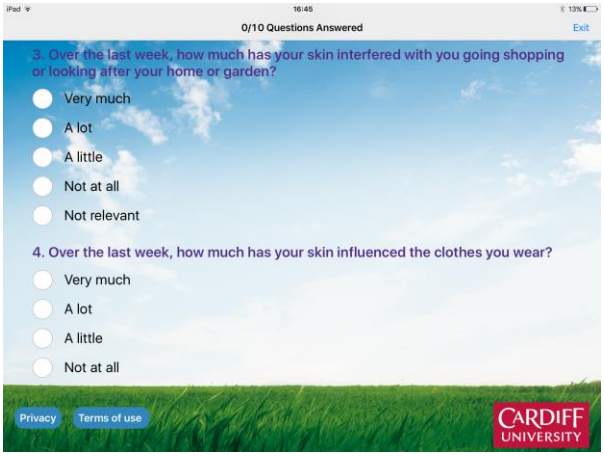
(a) Introduction of DLQI section



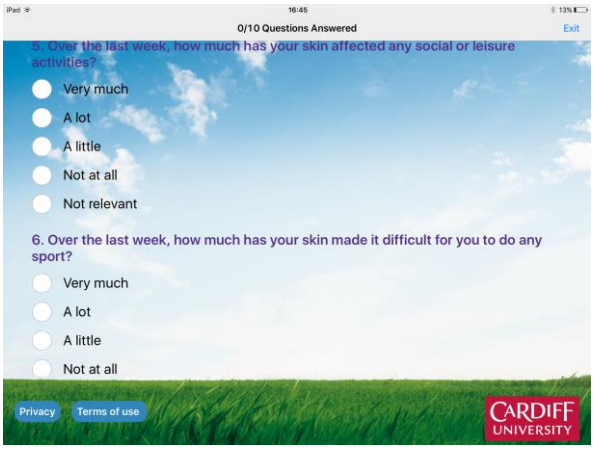
(b) Items 1 and 2 of DLQI



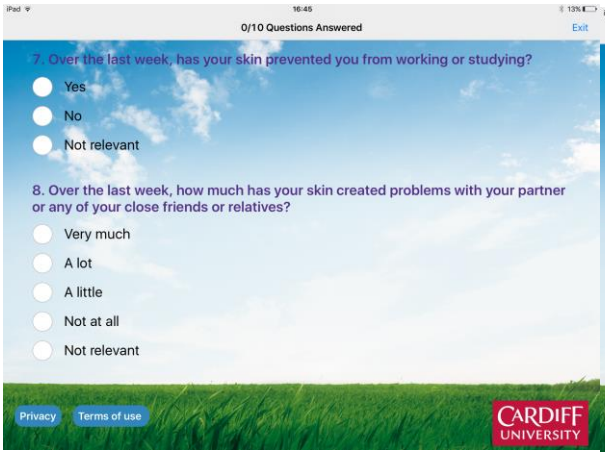
(c) Items 3 and 4 of DLQI



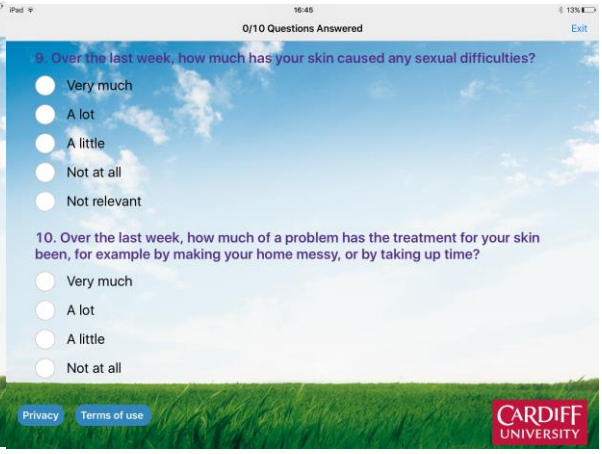
(d) Items 5 and 6 of DLQI



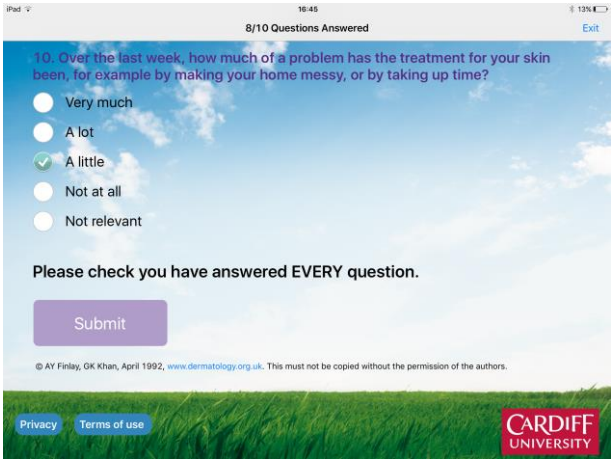
(e) Items 7 and 8 of DLQI



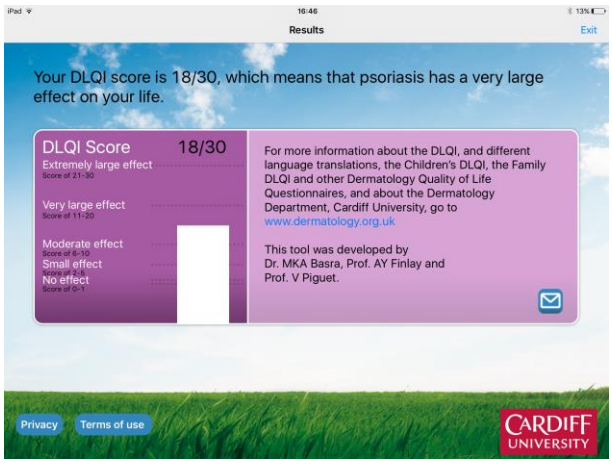
(f) Items 9 and 10 of DLQI



(g) The 'submit' button of DLQI section



(h) Final DLQI score display



3.1.3 PASI

Psoriasis Area and Severity Index (PASI) is a widely used tool to assess the severity of psoriasis (Fredriksson and Pettersson 1978) that is mostly completed by trained health care professionals and study investigators. Although PASI has been criticised for its inter-rater reliability (Bożek and Reich 2017), sensitivity, complexity and being resource intensive, in the absence of a "gold standard" it has become an almost universal outcome measure in clinical trials of drugs used for psoriasis (Ashcroft et al. 1999). The PASI scoring system assesses four body areas: head (corresponding to 10% of total body surface area), upper extremities (20%), trunk (30%) and lower extremities (40%). The area of psoriasis involvement for each of the four body regions is assigned a numerical value of 0-6 corresponding to 0-100% involvement as follows:

0=no involvement; 1= up to 9% involvement; 2= 10-29% involvement; 3=30-49%; 4=50-69%; 5=70-89% and 6=90-100% involvement.

For each body region, erythema, induration and desquamation are rated according to a 5-point scale as follows:

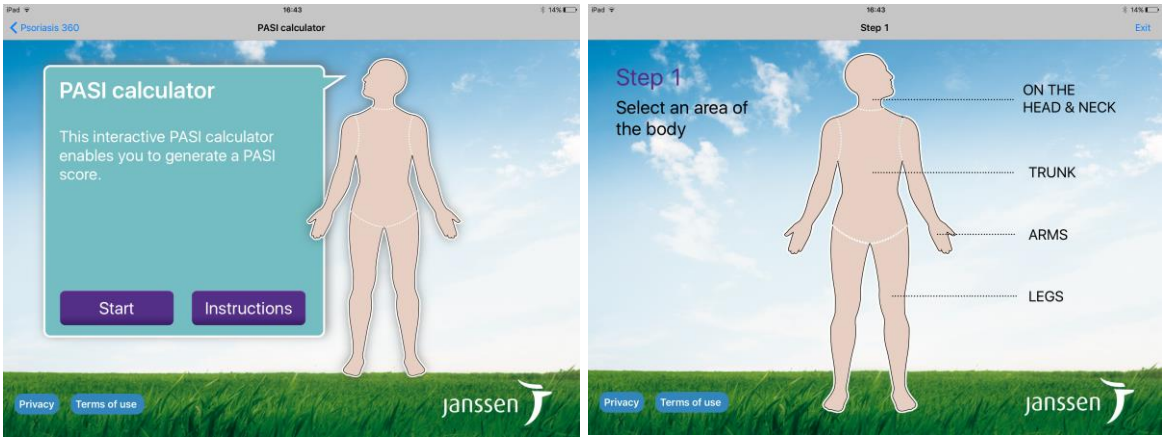
0= no involvement; 1=slight involvement; 2=moderate involvement; 3=marked involvement and 4=very marked involvement

The PASI score is calculated by applying a standard formula. This is achieved by calculating a lesion score sum (A) for one body part (i.e. by adding the scores for erythema, thickness and scaling). This value is then multiplied by the area involvement score (B) for the same body part, providing a subtotal (C). Each of the four body parts (head, upper limbs, trunk and lower limbs) will therefore have an individual subtotal (C). Different body parts are 'weighted' differently according to the total surface area contribution of said body part e.g. head is weighted 0.1, whereas the lower limbs are 0.4. Each subtotal (C) is multiplied by the respective weight to provide the final total (D) for each area. All four totals (D) are summed to provide the final PASI score. The score can vary in increments of 0.1 units and range from 0 to 72; higher score indicates greater degree of severity.

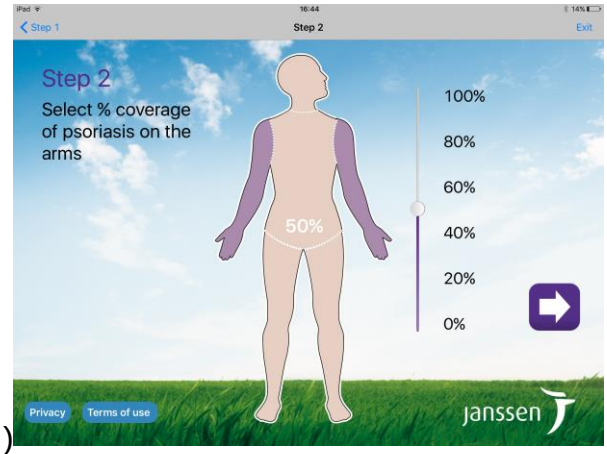
The PASI App was also developed by the team at Janssen EMEA® based on the original paper format, whereby a score is automatically calculated at the end of the form. Each section of the PASI was converted into a graphical representation for easier and more consistent scoring between raters. Raters select the relevant body part and are subsequently guided through the process of scoring the severity of redness, scaling and thickness with the aid of graphical images. The screenshots for the PASI calculator of the Psoriasis 360© application may be seen in Figure 3.2.

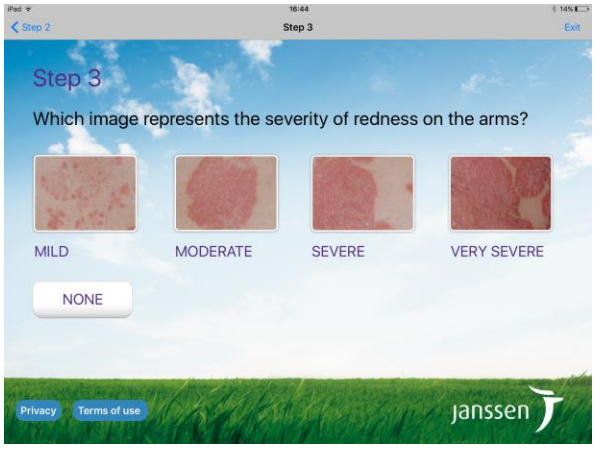
Figure 3.2 Screenshots of the PASI calculator from the Psoriasis 360® App

(a) Introduction of PASI section (b) Step 1: selecting body part



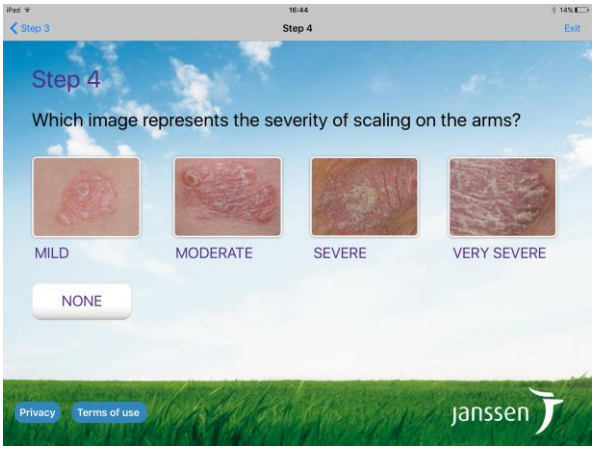
(c) Step 2: selecting percentage affected (d) Step 3: severity of erythema

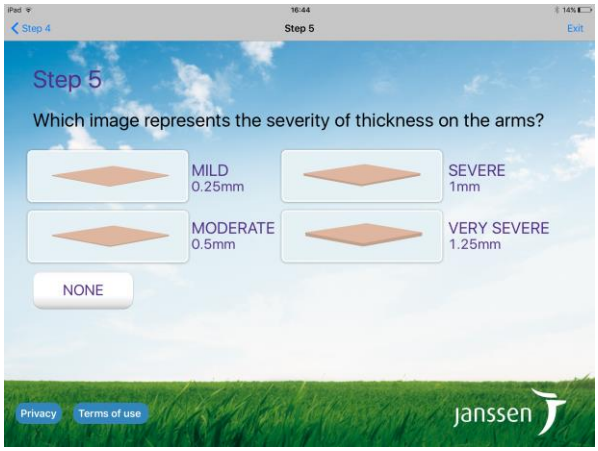




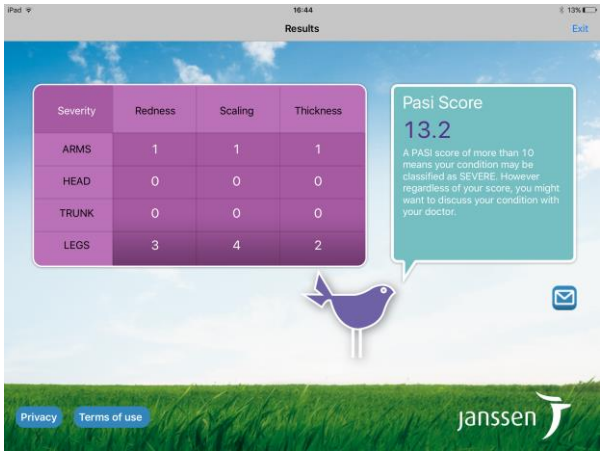
)

(e) Step 4: severity of scaling (f) Step 5: severity of thickness





(g) Final PASI score and breakdown



The application (Psoriasis 360©) is available without charge and may be downloaded from the Apple App Store: https://appsto.re/gb/-JIFw.i. It is also available on the Google (Android) App Store: https://play.google.com/store/apps/details?id=com.sapnagroup.p360&hl=en_GB.

Only this particular iOS version of the App was tested for the purpose of studying equivalence.

3.2 Literature review: equivalence of electronic and paper-based patient reported outcomes

International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidance states that if the psychometric properties of a measure are likely to be impacted during the PRO migration process to a different form of delivery, then 'the measure should be evaluated as if it were a new measure'. The main recommendations include 'tests of agreement' such as Kappa coefficient or Intra-class Correlation Coefficient (ICC), mean score comparisons, distribution and variance of scores and internal consistency reliability where applicable (Coons et al. 2009). Gwaltney et al. (2008) undertook a meta-analysis on the subject, examining literature published before 2007. Forty-six studies were included. They concluded that written assessments were equivalent whether they were paper or computer-based. However, technology has changed greatly since 2007 with the widespread use of smart phones and tablet computers (Arthur 2012; McLellan 2014). This review aims to identify and evaluate publications since 2007 that demonstrate the measurement equivalence of electronic versions of paper-based PRO instruments (ePROs).

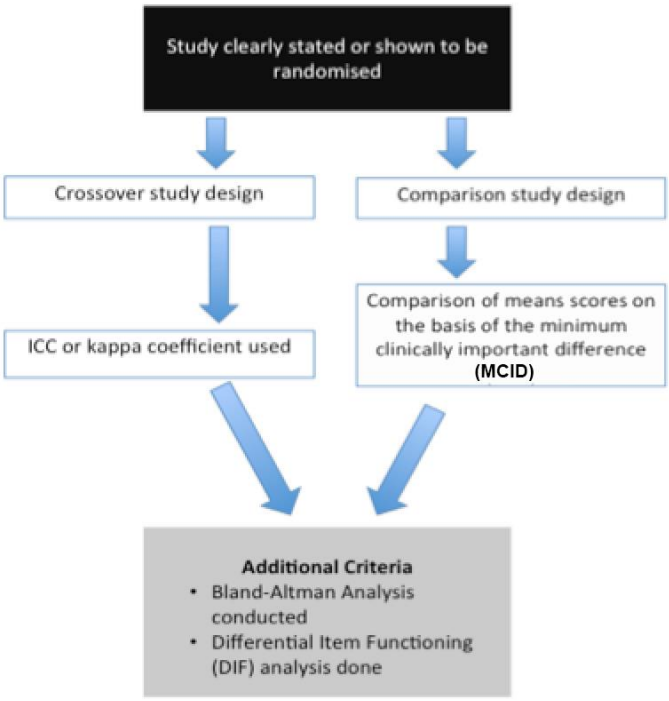
3.2.1 Materials and methods

The following databases were searched during March 2014: OvidSP, including the databases EMBASE, MEDLINE and PsycINFO; Web of Science, including Web of Science Core Collection, BIOSIS Citation Index, SciELO Citation Index and MEDLINE; and PubMed.
An identical set of keywords was used for every database that was searched, refined during two pilot searches. The keywords were: patient report* outcome OR quality of life; AND Internet OR touch screen OR web OR tablet OR computer OR electronic*; AND paper; AND questionnaire; AND compar* or equiv*.
The asterisk (*) represents a search on the stem of these words.
Abstracts of all identified articles were first reviewed. If an abstract indicated that the article might be relevant, the full text article was retrieved and examined. The search was limited to papers published since 2007 to avoid overlap with Gwaltney et al. (2008). Full text articles or abstracts which directly compared a screen-based electronic version of a validated PRO instrument with its paper-based original, with regards to their measurement equivalence, and

publications in English were included. Studies which were published before 2007 or in other languages were excluded. Gwaltney et al. (2008) had also excluded interactive voice response (IVR) formats: this review likewise excluded IVR formats.

The most important factors were suggested by the lead research team member (FA) and joint agreement reached with all other research team members. A template was used to record relevant data from each publication and to record data concerning each instrument that was being validated. Where data for IVR formats were reported as part of a larger study, those data were excluded. It was difficult to identify whether stand-alone visual analogue scales (VAS) had been appropriately validated and it was occasionally clear that they had not (Salaffi et al. 2009). Therefore, data from any VAS presented as a stand-alone measure was excluded. Data from validated instruments where items appeared as a VAS were still included. Extracted data were tabulated in Microsoft Office Excel for Mac 2011. Data were classified according to the study and instrument characteristics and to the statistical measures used to demonstrate equivalence. Data regarding participant preferences, amount of missing data and completion times for each format was extracted. Data were extracted concerning whether the authors believed they had demonstrated equivalence, as described by the main ISPOR recommendations outlined in the Introduction of this review (Coons et al. 2009). As there was very little consistency between the papers reviewed, and original data were not possible to examine, equivalence of the formats under study was based on the papers' authors' own judgments. However, the methods used were not consistent and authors sometimes did not make it clear whether they believed they had found equivalence. Therefore, an informal assessment was made concerning the real outcome of such studies. To assess the quality of equivalence assessment undertaken, studies were compared against the recommendations of Coons et al. (2009) (Figure 3.3).

Figure 3.3 Flow chart demonstrating the criteria used to assess quality of measurement equivalence techniques used in the literature



Different levels of evidence are required depending on the level of modification of the original instrument (Coons et al. 2009). It was not always possible to judge how much of the originals had been adapted, so for simplification all electronic versions were assumed to be 'moderately' adapted, as defined by Coons et al. (2009):

'*A moderate level of modification may change the meaning of the assessment items, but this change might be subtle. Examples of changes to items that could fall in this category include splitting a single item into multiple screens, significantly reducing the font size, and requiring the patient to use a scroll bar to view all item text or responses. Another example might include changing the order of item presentation. When these types of modifications are made to a PRO, it is advisable to formally establish the equivalence of the electronic measure.*'

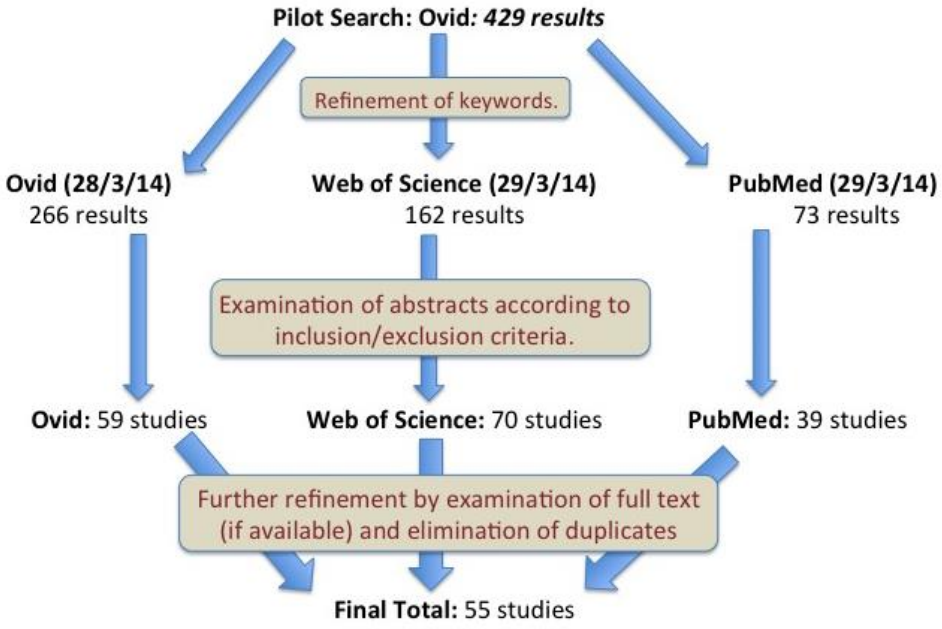
To simplify analysis, as a selection criterion only one relevant statistical method, according to the ISPOR recommendations, was chosen for each study type. However, to provide a wider picture, DIF and Bland-Altman analysis was also always included, if used. If a publication stated that randomisation was undertaken but no details were provided, it was assumed that the method used was appropriate.

Although, the ISPOR guidance (Coons et al. 2009) distinguishes between weighted and un-weighted kappa coefficients, it was not always clear which had been used and so if either one was present this was judged as fitting this criterion.

3.2.2 Results

Database searching identified 501 studies, 55 of which were judged to be relevant according to the inclusion criteria. The way in which 501 abstracts were reduced to 55 is summarised in Figure 3.4. Two papers were excluded due to their use of IVR format. A total of 79 different relevant instruments were described across these publications (Appendix XI).

Figure 3.4 Flow chart demonstrating the search strategy and filtering process



Of the 55 studies, 75% (41) were full-text journal articles, with the remaining 25% consisting of article and conference abstracts. Forty-seven (85%) of the studies used a crossover study design, whereas six studies (11%) used a comparison design. It was not clear which design had been used in two studies. Thirty-three (60%) investigated only one instrument, with the largest number of instruments investigated in one study being 10 (MacKenzie et al. 2011). Eleven (20%) of studies used multiple sample sizes, usually employing a different sample size for each instrument investigated. The use of multiple sample sizes in the same study could lead to results having different statistical validities and reliabilities between questionnaires. However, such use was often unavoidable, for example: sometimes the

number of patients eligible to complete certain surveys differed, and sometimes the number of patients who were lost to follow up differed between questionnaires.

When transposing an instrument from written to an e-delivery format, logically nearly always some changes have to be made, for example instead of saying “Tick one box for each question” one needs to say “Choose one answer for each question”, or perhaps this instruction is completely superfluous because the software will only accept one answer. It is a reasonable assumption to make that only moderate changes were made, though most authors did not give any specific information concerning this and therefore it was not possible to identify whether these moderate changes influenced the degree of equivalence between written and e-delivery.

3.2.2.1 Instrument characteristics

Of the total of 79 PRO instruments identified: 42 (53%) were “condition-specific”; 19 (24%) specialty-specific; and 18 (23%) were generic measures. The most commonly used instrument was the Short Form 36-item Health Survey (SF-36) that was employed in 10 studies: the version of the SF-36 that used was not reported by most authors. However, it would be reasonable to assume that if not mentioned by the authors, the most commonly used version (SF-36) has been employed. The most common format of electronic PROs tested within studies was the ‘Internet’ (36%), followed by ‘touch-screen computers’ (20%).

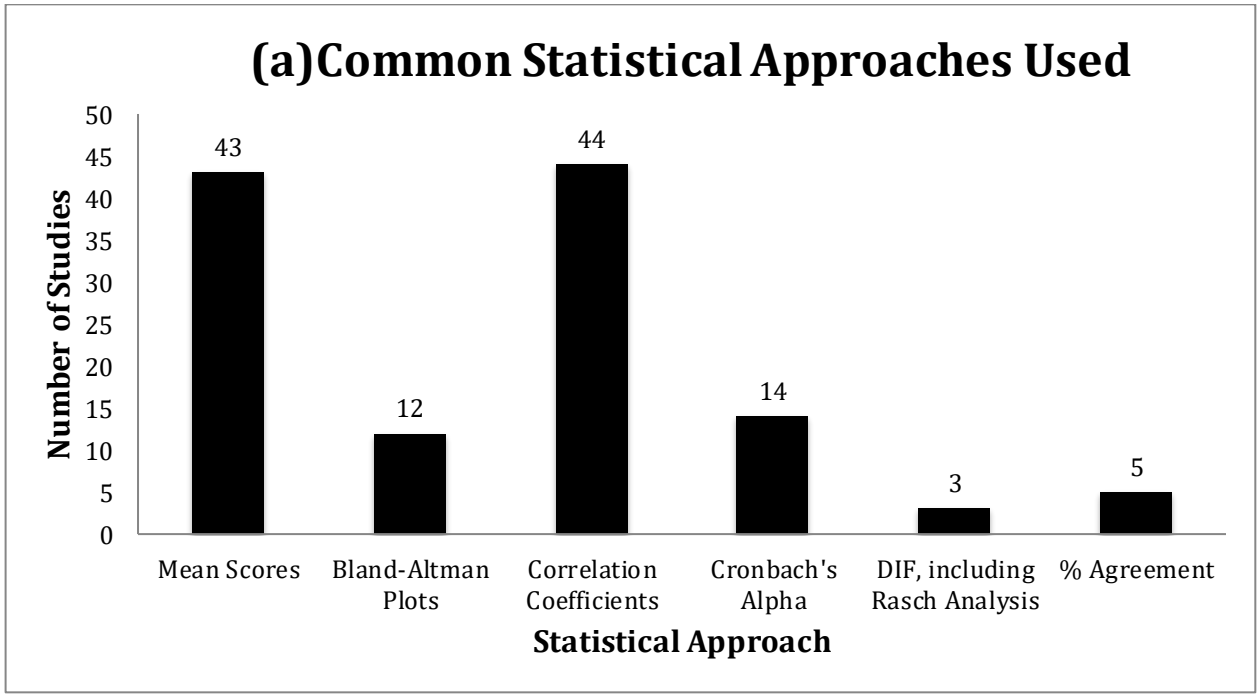
3.2.2.2 Overall conclusions of study authors

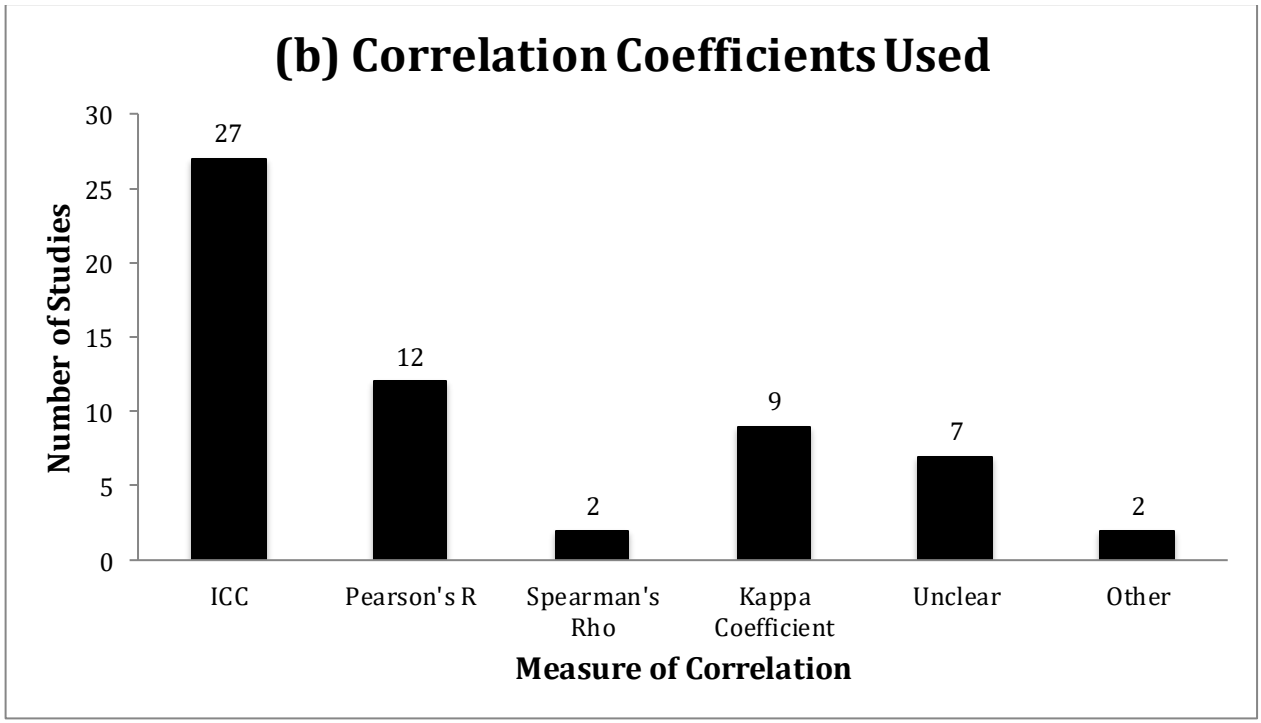
Forty-three studies (78%) found equivalence between the standard paper-based PROs and the ePROs. Two studies (4%) failed to find equivalence. In ten studies (18%) the authors’ conclusions were not clear. For example, in one study, where two out of the three instruments investigated were not comparable, but one instrument showed equivalence (Wu et al. 2009), authors concluded that different versions should not be used in the same trial and individual patient data should not be compared across different formats (Juniper et al. 2007). Though results for each format were similar on a group level, there was high variability at the individual patient level (Ring et al. 2008).

3.2.2.3 Statistical methods used

In examining how often different methods were used to demonstrate equivalence, 80% (44) of studies used a correlation coefficient, with the most common being the Intra-class Correlation Coefficient (ICC) (Figure 3.5).

Figure 3.5 Graphs demonstrating (a) common statistical approaches used (b) correlation coefficients used





3.2.2.4 Comparison with ISPOR recommendations

Twenty-five (47%) publications appeared to fulfil the ISPOR recommended criteria (Coons et al. 2009) (Table 3.1). Of these, 60% (15 studies) were randomised crossover studies that used an ICC or kappa coefficient to measure correlation. Two studies (8%) were randomised comparison studies that analysed mean scores on the basis of the Minimum Clinically Important Difference (MCID). Six (24%) provided Bland-Altman plots, and two of the reports described DIF analysis. Surprisingly, only 30 (55%) of the 55 studies presented data on participant format preferences, 16 (29%) provided comparisons of the amount of missing data and 19 (35%) provided data on completion times. Nine (47%) studies reported longer average completion times for ePROs, and five studies (26%) found that paper-based PROs took longer to complete.

Table 3.1 Number and percentage of studies that fulfilled ISPOR criteria

	Number of Studies	**Percentage of Studies**
Randomised Crossover + ICC/Kappa Coefficient	15	60%
Randomised Comparison + MID	2	8%
Randomised Studies + Bland-Altman Analysis	6	24%
Randomised Studies + DIF	2	8%
Total Number of Studies Fitting Criteria	25	100%

It is important to highlight some of the similarities and differences between this review and that published by Gwaltney et al. (2008) (Table 3.2).

Table 3.2 Key comparisons with Gwaltney et al. (2008)

	Gwaltney at al (5)	**Present Study**
Review year range	Pre-2007	2007-2014
Total studies reviewed	46	55
Most common correlation coefficient used	Intraclass Correlation Coefficient (ICC)	Intraclass Correlation Coefficient (ICC)
Number. of different instruments identified	278	79
Number of different electronic modalities identified	3 (PC/Laptop, PDA, Tablet)	5 (Internet, Tablet, Computer, Touch-screen Computer, PDA)

3.2.3 Literature search update

The initial literature search and subsequent analysis as above was conducted on publications identified up to March 2014. For the purpose of this thesis, the literature search was supplemented by identifying publications from 2014 to 2019 using the same databases and search terms. This identified a further 287 articles, which were further filtered to 72 relevant publications including full articles and conference abstracts. Publications were excluded due to the following reasons: No formal equivalence studies where only one format was tested (n=48), metanalysis/systematic reviews/ literature reviews (n=11), Duplicates/multiple publications (n=59), study protocols (n=11), not-relevant (n=84). Only the abstracts were reviewed and tabulated as seen in Appendix XII. 32/72 (44%) of the included publications used ICC as a measure of equivalence.

3.2.4 Discussion

In the process of demonstrating measurement equivalence, crossover study design was the most commonly used and the commonest electronic format used was the Internet based online version. It is important to note that in some cases the authors did not indicate how or whether the Internet was accessed, in which case it was recorded as a separate 'device'. Most studies used a combination of different statistical tests with correlation coefficients being the most common, however different authors may use different standards. For example, in

one (Juniper et al. 2009) of the two studies that stated no equivalence between formats, the authors used an ICC standard of 0.95 to identify concordance, which is higher than that recommended by ISPOR (0.70 at group level, and 0.85-0.95 at individual level). The authors stated they chose this higher criterion as it was slightly lower than the test-retest reliability value originally calculated for the paper version (Coons et al. 2009).
There may be confusion concerning the interpretation of "equivalence". The strict scientific definition (if a single user were to complete the same instrument by the two methods, the responses and subsequent scores would be the same) may be replaced in practice by a much looser definition, allowing, say, a correlation of 0.8 between two methods of delivery. To clarify this, those reporting equivalence should define their usage of this term.
Less than half of the studies fulfilled the basic ISPOR recommendations (Coons et al. 2009). A reason for the low number of studies identified as fitting these criteria may be that it was not always possible to tell if the criteria had been met, particularly where only an abstract was available. For example, in Naus et al. (2009) and Ribeiro et al. (2010), which were both full-text journal articles, though the correlations between formats were analysed, the measure of correlation used was not specified.

As end-users, patients should have a powerful role to play in influencing the type of assessment that they may be expected to complete. Patients who are already familiar with and comfortable interacting with electronic devices are more likely to prefer this format of delivery, but this should be confirmed by assessing patient preferences. However patient involvement may not be appropriate in the question of "equivalence" as that requires prospective scientific evaluation. The majority of studies indicated that patients prefer the electronic formats, and comments from patients included that "the PDA (personal digital assistant) was efficient and saved paper" (Matthew et al. 2007). Some patients suffering from reduced manual function found the touch-screen computer version easier to use (Schefte and Hetland 2009). The use of electronic formats is less prone to error, such as missing or ambiguous data entry. The ability to program data validation into the electronic software prevents such errors (Handa et al. 2008). This may be considered a disadvantage where a patient deliberately wishes to avoid answering a question. However, it is possible to address this problem (Matthew et al. 2007) by alerting patients if they skip any questions. Patients take a longer time to complete electronic versions. Possible explanations include patients' lack of familiarity with electronic devices and hence their requiring assistance (MacKenzie et al. 2011). As people become more familiar with such devices it is likely that this problem will diminish. A study limitation commonly identified by authors was the generalisability of their results to populations unfamiliar with the Internet. If Internet access was required for

enrolment, participants may have been biased towards the educated and young (Wu et al. 2009).

A major limitation of the studies reviewed here was the lack of detail provided by authors concerning methodology, for example which statistical techniques were utilised (Naus et al. 2009). Though this review doesn't consider patient preference, it would be worthwhile considering in future reviews as the acceptability of electronic formats is essential if they are going to be of practical use. Researchers should also consider capturing this data when planning future studies. As suggested by Gwaltney et al. (2008), a more accurate way to determine whether studies had truly identified equivalence would be to define numerical standards for the statistical methods used (such as using just ICC and cut-off scores for equivalence) and to judge study data directly against these.

Good practice recommendations (Coons et al. 2009) state that every new electronic version should be validated before use. As two studies did not identify equivalence (Swartz et al. 2007; Juniper et al. 2009) and 10 studies had ambiguous findings (Carlbring et al. 2007; Juniper et al. 2007; Saunders et al. 2007; Ring et al. 2008; Naus et al. 2009; Wu et al. 2009; Frennered et al. 2010; Clayer and Davis 2011; Oliveira et al. 2011; Silveira et al. 2011), validation of electronic versions should still be carried out, even though this review indicated that electronic versions are usually judged to be equivalent to the original version. Interactive voice response (IVR) formats were excluded in both reviews as auditory transference of ePROs from a written format presents lower probabilities of equivalence.

Intra-class Correlation Coefficient ICC) was identified as the most commonly used correlation technique in both reviews, with a majority of the studies demonstrating equivalence. Similar to the findings by Gwaltney et al. (2008), this review highlights that details of how items were altered to be presented in an electronic format were not elucidated within the individual studies. Therefore, where formats of instruments are drastically changed it may not be appropriate to assess equivalence. Further studies which employ cognitive interviews may be useful to determine whether such changes influence the way in which instruments are completed by the target population. This review also identified several studies that employed 'tablets' and 'touch screen' devices, which were not mentioned in the review by Gwaltney et al. (2008). The use of tablets and touch screen formats has seen a rise mostly in the last few years, accounting for this disparity. However, whether this innovation in delivery format of PRO instruments provides an additional advantage to that of standard electronic data entry methods needs to be further examined. Both reviews, however, suggest that most studies

demonstrate equivalence between electronic and paper-based versions of patient reported outcomes.

Electronic PRO instruments have an expanding role in the provision of patient-centred care, both in clinical practice and by providing a way to gather information from patients during clinical trials. The advantages of computerising paper-based PRO instruments are extensive: such instrument formats have benefits to patients, including convenience, and benefits to clinicians and researchers, as they can save time, manpower and other resources. They can also remove sources of error created when data from paper-and-pencil formats is manually transferred to computer databases (this has been partially remedied in recent years with the advent of electronic scanners). As the public become more experienced in the use of e-technology, electronic PRO instruments gain greater acceptability, and are commonly preferred by patients over paper-based versions of the same instrument. There are now PRO instruments originally developed in electronic formats (Wright et al. 2005), thereby not requiring equivalence testing.

There may be disadvantages to computerising PRO instruments, though it appears that fears of computer aversion may be overestimated. The transfer of a PRO instrument to an electronic format may require new psychometric assessment, in order to prove that measurement properties such as reliability and validity are equal or improved from those of the original version. The degree of assessment required depends on the amount of change that is made to the instrument, but major change may require full psychometric evaluation. However, the evidence suggests that where changes appear to have been relatively minor or moderate, equivalency in psychometric values is retained. Gwaltney et al. (2008) and this review provide evidence that paper-based and electronic versions of the same measure are comparable and that therefore computerising paper-based PRO instruments is a successful and worthwhile step.

3.3 Validation of the electronic DLQI

Patient reported outcome questionnaires (PROs) are typically instruments completed by patients or sometimes by others (i.e. proxy or significant others) on their behalf (Marshall et al. 2006) and are traditionally paper-based. However, there is increasing interest in utilising technology within clinical medicine: innovations include computerised data entry (Bates et al. 1998; Gill et al. 2001), communication initiatives (Guo et al. 2016) and virtual reality (Ershow et al. 2011). Dermatology has witnessed several technological initiatives, for example

handheld multi-modal imaging (Sancho-Durá et al. 2018), potential applications of blockchain technology (Tung and Nambudiri 2018) and remote scribing using face-mounted technology in outpatient consultations (Odenheimer et al. 2018), with several other innovations using electronics and information technology (Shaw and de Berker 2007; DeLouise 2012; Hattori et al. 2014). The use of PROs in electronic format has also kept pace with such other digital technologies in medicine (Leidy and Vernon 2008; Muehlhausen et al. 2015). Electronic PRO instruments can be more convenient to patients, particularly where portable, and can provide real-time data recording and immediate scoring. Automated data entry makes them more convenient to clinicians, and improves accuracy by removing human error (Lee et al. 2007). Disadvantages, albeit increasingly less common, include patients being less comfortable or having difficulties with the use of electronic devices (Leidy and Vernon 2008) or lack of availability of Wi-Fi (wireless fidelity). However, these formats are usually not validated or compared to their original paper-based versions. This may have several connotations, as it is possible that the mode of delivery of questions may possibly influence the way in which they are answered. If this were so, then the scores and interpretation of the scores might differ depending on mode of delivery, resulting in unreliability of the measurement method. This may result in data that are either invalid or incomparable between the two formats due to the lack of equivalence. "Equivalence" of two methods of delivering instruments is defined as follows: if a single user were to complete the same instrument by the two methods, the responses and subsequent scores would be the same. The level of evidence required depends on the amount of modification made to the original (Coons et al. 2009). Coons et al. (2009) have also proposed guidelines detailing the level of evidence required to demonstrate equivalence, depending on the amount of modification to the original PRO. This will be covered in more depth in the methodology section.

The DLQI (Finlay and Khan 1994) is the most commonly used dermatology-specific quality of life (QoL) measure in clinical trials (Both et al. 2007; Basra et al. 2008a; Le Cleach et al. 2008). The DLQI is easy to use in clinical practice due to its brevity and simplicity (Bronsard et al. 2010) with an average completion time of two minutes (Loo et al. 2003). In the current era of widespread use of digital devices such as Tablets and smartphones, clinicians, researchers and patients often substitute non-validated electronic versions in place of the original paper version. However, there is an underlying concern whether such data are comparable to the two decades of data gathered via the validated paper DLQI (Finlay and Khan 1994; Basra et al. 2008a) potentially posing several challenges in data analysis and interpretation. The availability of a DLQI application that had been validated as equivalent to the original paper-based would alleviate such concerns and contribute to better management of patients with skin conditions by making available an easy tool for regular monitoring of

disease severity from the patient's own perspective. Moreover, this tool could potentially be used by general practitioners to assist decisions over which patients need to be referred, as well as providing reassurance for users of electronic QoL measures across dermatology and other medical fields.

3.3.1 Aims & objectives

This study aimed at comparing the conventional paper-based and a novel application version of the DLQI, following ISPOR guidelines (Coons et al. 2009), concerning patient acceptability and preference and in terms of consistency of scores. The presence of a carryover effect depending on which format patients completed first (paper versus iPad) was also assessed.

Therefore, the primary objective of this study was:

- To compare the conventional paper-based and the novel application versions of the DLQI in terms of patient acceptability and preference and in terms of consistency of their scores, respectively.

Secondary objectives:

- To assess the correlation between the DLQI scores assessed by the two different methods: standard paper-based DLQI and the DLQI application
- To assess the internal consistency and reliability of the DLQI application
- To assess the feasibility of the DLQI application in the dermatology outpatient clinic
- To compare the response burden between the two formats in terms of time spent on completion
- To compare patients' preferences for the use of the DLQI application versus conventional versions of these tools in terms of ease of use, comfort of use and perceived time to completion.

3.3.2 Methodology

3.3.2.1 Study participants

The study employed a randomised cross-over design using a within-subjects comparison of the two formats of the questionnaire. The study was conducted at the Dermatology outpatient department, University Hospital of Wales, Cardiff, UK.

3.3.2.2 Inclusion / exclusion criteria

The inclusion criteria were thus:

- Aged 18 years and older
- Confirmed diagnosis of any skin condition
- Able to read, write and understand English

The exclusion criteria were thus:

- Aged under 18 years
- Having a co-existing non-dermatological medical condition of considerable severity, as determined by the investigator
- Having a co-existing dermatological condition of considerable severity, as determined by the investigator
- Not able to read and/or understand written English
- Physical disability which would prevent writing or use of an iPad.

3.3.2.3 Ethical considerations

The study protocol underwent one major amendment (see below). The original protocol (Version 7, dated 21.5.14, Appendix XIII) and a major amendment (Version 8, dated 22.10.14, Appendix XIV) were approved by a local Ethics Committee (Ref: 14/SW/0085, National Research Ethics Service (NRES) Committee, South West-Central Bristol, UK, Appendices XV & XVI). The local Cardiff and Vale University Health Board Research & Development Department also approved the study. Written informed consent (Appendix XVII) was completed by each study participant prior to entering the study.

3.3.2.4 Recruitment

The initial protocol (Appendix XV) was approved to approach patients on the waiting list several weeks prior to their outpatient appointments. All patients were sent invitation letters with prepaid envelopes should they wish to participate (Appendix XIX). This involved a short inclusion criteria checklist and a reply slip to be returned prior to their next appointment. Once

the investigator received the replies, patients would be consented on the day of their appointment and enrolled in to the study if appropriate.

However, this process presented significant administrative difficulties in the initial stages as very few replies were being received. A total of 396 patients were approached via mail prior to the appointment of which only 53 accepted to participate. Given the high non-participation rate, an alternative approach to recruitment was drafted and this was submitted to the Ethics Committee as a major amendment and was subsequently approved (Appendix XVI). The new protocol allowed investigators to approach patients as they attended their scheduled dermatology outpatient appointments. Thus, according to the new protocol, the following method of recruitment was employed:

'*Patients will be given the information sheet (Version 5, dated 22.10.14, Appendix XX): they will be given the option to take the information sheet home and will be given a reply slip with a prepaid envelope should they wish to have more time to think about it. They may then decide in their own time if they would like to participate at their next appointment and can return the reply slip.*

However, patients will also be given the opportunity, should they wish, to participate immediately after they have had their appointment. Most patients arrive up to half an hour prior to their appointment which should provide ample opportunity to consider participation, eligibility and to present any questions to the researchers.

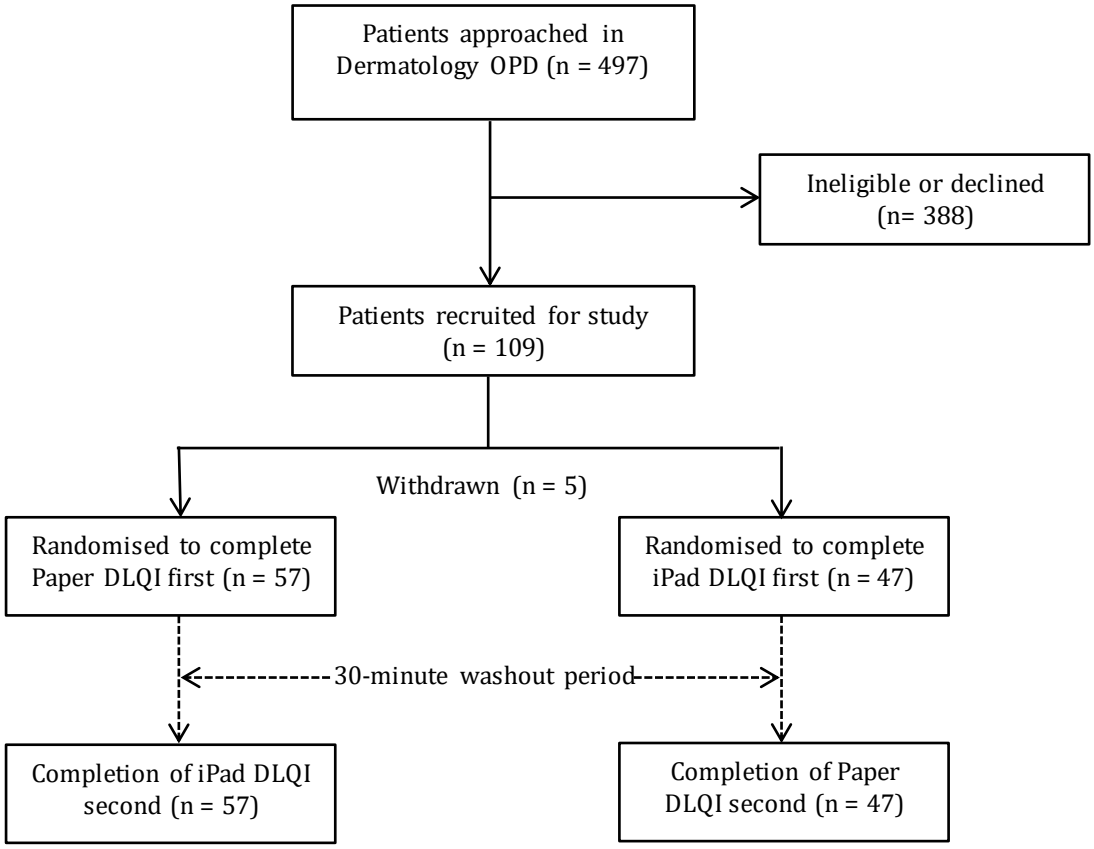
Should the patient agree to participate on the same day and if they are assessed to be eligible, the study will be conducted immediately after their appointment and will not take longer than an hour. This will include study briefing, consenting and administering the questionnaires. The study will not have an impact on the patient's clinic appointment itself.' This alteration in protocol significantly improved recruitment rates: a further 101 patients were approached with 56 participants agreeing to take part.

3.3.2.5 Study procedure

Eligible patients were asked to complete the DLQI (both paper and electronic versions). The order of completing of the questionnaires (paper version first versus an iPad® version first) was randomised using a random number generator. After 30 minutes patients were asked to complete the other format (Figure 3.6). Thirty minutes interval was used to minimise the carryover effect and bias. However, a shorter duration also helps reduce patient waiting time and burden, as following up patients to complete the study at a later date would result in a higher cost and increase the chances of change in disease severity (Coons et al. 2009). The

research team ensured that patients read a magazine, talked to staff or used their phones to browse in-between testing, as forms of distraction to reduce potential bias from carryover effect.

Figure 3.6 Flow diagram of the study procedure



Training to operate the electronic application was given in person to every subject by a member of the research team, who remained with the patient throughout the duration of completion in case the subject needed assistance. The electronic application also has basic instructions on the home screen and all patients were given time to read this prior to completion. Prior to completing either format of the DLQI, patients also completed a short demographic questionnaire on age, gender, literacy levels, visual and tactile impairments, diagnosis, and previous use of tablet computers or the DLQI. Completion of both versions were conducted in a similar environment, both completions for the same subject were either before or after their visit with the doctor, in order to reduce the effect of the doctor's consultation upon patient reported QoL. The time taken by participants to complete the DLQI using the paper version and the application was recorded. Patients were asked to also complete a short questionnaire asking about their perception, attitude and experience with

the paper-based and electronic methods, concerning ease or difficulty of administration, acceptability, time requirement, feasibility and being comfortable with disclosing personal information using the novel application-based method.

3.3.2.6 Sample size

Sample size was calculated in accordance with ISPOR guidelines (Coons et al. 2009). The study power was set at 95%, with an expected intra-class correlation coefficient (ICC) of 0.9 ($\alpha = 0.05$), resulting in a target sample size of 104 patients.

3.3.2.7 Data analysis

Data analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 20®. The concordance of DLQI scores between paper-based and the application-based data was analysed using a two way fixed effects ICC model, which is the most commonly utilised statistical measure in equivalence studies of this nature (Gwaltney et al. 2008). Wilcoxon signed rank test was used to compare DLQI scores and completion times between the two formats; both variables were found to be non-normally distributed using the Shapiro-Wilk test. A more stringent score difference of 1 point (3%) between the two versions was considered equivalent, though a majority of studies target a maximum of 5% difference (Coons et al. 2009). Sub-analysis was conducted to identify any carryover effect depending on which format of the DLQI patients completed first.

Bland-Altman plots were drawn to measure the limits of agreement between the two formats. Equivalence was considered with limits of agreement <= 4, which is the minimal clinically important difference (MCID) for the DLQI (Basra et al. 2015a).

Descriptive analysis was used to present demographic data of the patients and their feedback on the preference and experience of using the tools. Linear regression techniques were used to identify correlation of iPad completion times with age.

3.3.3 Results

3.3.3.1 Socio-demographic characteristics of the study participants

A total of 104 patients were recruited, mean age 52 years (SD ± 18.7, 43% male): demographic details are given in Table 3.3. The most common diagnoses were psoriasis (39%), 'skin lesion' (19%) and eczema (13%). The majority of patients (61%) had their highest level of education at school. Seventeen percent of patients had never used a Tablet before and 46% stated that they were "a little" or "not" comfortable with a Tablet (Table 3.3) prior to participating in this study.

Table 3.3 Demographic characteristic of the study participants (DLQI study)

	All (n=104)		**Paper First (n=57)**		**iPad First (n=47)**	
Age	Mean ± sd Median ± IQR Range *(n=96)*	51.5 ± 18.7 53.5 ± 31 20 - 89	Mean ± sd Median ± IQR Range *(n=53)*	51.5 ± 19.3 54 ± 35 20 - 89	Mean ± sd Median ± IQR Range *(n=43)*	51.4 ± 18.2 50 ± 29 20 - 85
Sex	Male Female	43.3% (45) 56.7% (59)	Male Female	50.9% (29) 49.1% (28)	Male Female	34.0% (16) 66.0% (31)
Nationality	British Other	91.3% (95) 8.7% (9)	British Other	91.2% (52) 8.8% (5)	British Other	91.5% (43) 8.5% (4)
First Language	English Welsh Other	90.4% (94) 1.9% (2) 7.7% (8)	English Welsh Other	87.7% (50) 3.5% (2) 8.8% (5)	English Welsh Other	93.6% (44) - 6.4% (3)
Education	Secondary School University	60.6% (63) 37.6% (41)	Secondary School University	57.9% (33) 42.1% (24)	Secondary School University	63.8% (30) 36.2% (17)
Visual Impairment	None Glasses Other condition Unspecified Missing data	59.6% (62) 29.8% (31) 5.8% (6) 1.9% (2) *2.9% (3)*	None Glasses Other condition Unspecified Missing data	64.9% (37) 24.6% (14) 5.3% (3) 3.5% (2) *1.8% (1)*	None Glasses Other condition Unspecified Missing data	53.2% (25) 36.2% (17) 6.4% (3) - 4.3% (2)
Tactile Impairment	Yes No	9.6% (10) 90.4% (94)	Yes No	8.8% (5) 91.2% (52)	Yes No	10.6% (5) 89.4% (42)
Diagnosis	Skin Lesion Psoriasis Eczema/Dermatitis Alopecia Vitiligo Infection Acne/Folliculitis Cyst Non-skin cancer Allergy Hidradenitis Autoimmune/inflammatory condition Unknown diagnosis *Missing data*	19.2% (20) 38.5% (40) 13.5% (14) 1.0% (1) 1.9% (2) 3.8% (4) 6.7% (7) 2.9% (3) 1.9% (2) 1.0% (1) 1.9% (2) 1.9% (2) … 2.9% (3) *2.9% (3)*	Skin Lesion Psoriasis Eczema/Dermatitis Alopecia Vitiligo Infection Acne/Folliculitis Cyst Non-skin cancer Allergy Hidradenitis Autoimmune/inflammatory condition Unknown diagnosis *Missing data*	 22.8% (13) 33.3% (19) 14.0% (8) - 1.8% (1) 3.5% (2) 5.3% (3) 3.5% (2) 1.8% (1) 1.8% (1) 3.5% (2) 1.8% (1) … 5.3% (3) *1.8% (1)*	Skin Lesion Psoriasis Eczema/Dermatitis Alopecia Vitiligo Infection Acne/Folliculitis Cyst Non-skin cancer Allergy Hidradenitis Autoimmune/inflammatory condition Unknown diagnosis *Missing data*	14.9% (7) 44.7% (21) 12.8% (6) 2.1% (1) 2.1% (1) 4.3% (2) 8.5% (4) 2.1% (1) 2.1% (1) - - 2.1% (1) … - -
Tablet Use	Daily Less Often	49.0% (51) 32.7% (34)	Daily Less Often	40.4% (23) 43.9% (25)	Daily Less Often	59.6% (28) 19.1% (9)

	Never *Missing data*	17.3% (18) *1.0% (1)*	Never *Missing data*	14.0% (8) *1.8% (1)*	Never *Missing data*	21.3% (10) -
Tablet Comfort	Very Comfortable A Little Comfortable Not Comfortable *Missing data*	52.9% (55) 30.8% (32) 15.4% (16) *1.0% (1)*	Very Comfortable A Little Comfortable Not Comfortable *Missing data*	54.4% (31) 29.8% (17) 14.0% (8) *1.8% (1)*	Very Comfortable A Little Comfortable Not Comfortable *Missing data*	51.1% (24) 31.9% (15) 17.0% (8) -
Used DLQI before?	Yes No *Missing data*	9.6% (10) 89.4% (93) *1.0% (1)*	Yes No *Missing data*	7.0% (4) 93.0% (53) -	Yes No *Missing data*	12.8% (6) 85.1% (40) *2.1% (1)*

3.3.3.2 Comparisons of validity and reliability

The ICC showed high concordance between the total DLQI scores from paper and iPad® versions (ICC = 0.98; 95% CI 0.97-0.99) (Table 3.4a).

Table 3.4a Equivalence analysis of paper and electronic DLQI overall mean scores and mean completion time

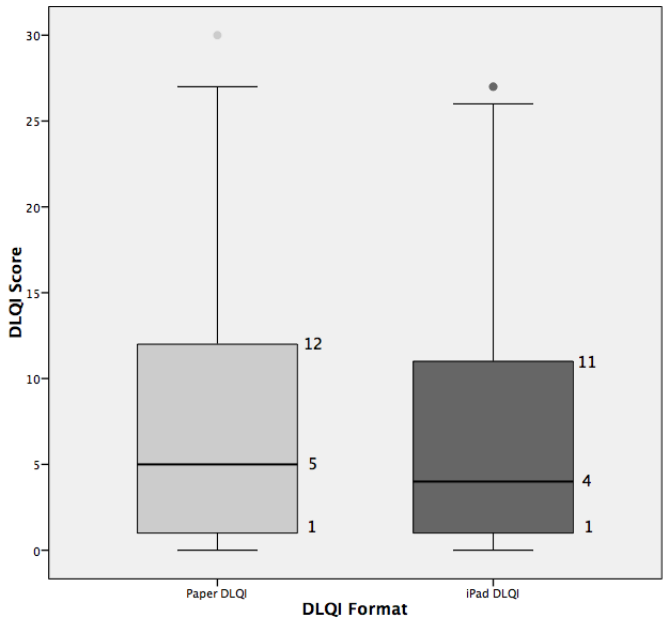
				Difference (P – iP)	Limits of agreement‡	
	Paper	iPad®	ICC* (95% CI)	mean ± SD	lower	upper
DLQI scores (n=104)						
Mean ± SD	7.5 ± 8.0	6.9 ± 7.6	0.98 (0.97 – 0.99)	0.5 ± 1.8†	0.17	0.87
Median ± IQR	5.0 ± 11.0	4.0 ± 10.0		0.0 ± 1.0		
DLQI times (mins:seconds)						
Mean ± SD	1:19 ± 0:03	1:32 ± 0:57	0.59 (0.39 – 0.72)	-0:12 ± 0:5††	-0:22	-0:02
Median ± IQR	1:13 ± 0:40	1:18 ± 0:36		-0:09 ± 0:38		

Footnote:

P-iP = Paper - iPad®
* Hypothesising coefficient of ≥ 0.9
† p value < 0.05 calculated by Wilcoxon Signed Rank test
†† p value < 0.05 calculated by paired t-test
‡ Limit of agreement are 95% confidence interval around the difference of ± 1

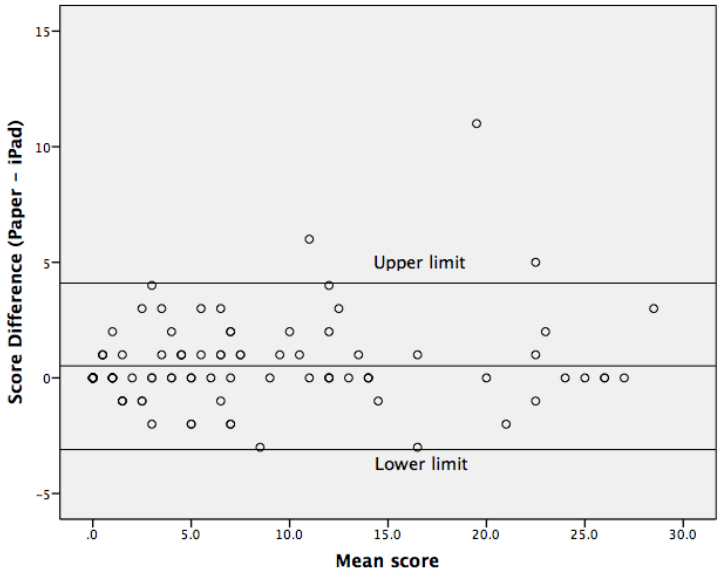
The median difference of scores was also within the hypothesised difference of ±1 point (p=0.006, Figure 3.7). The lower and higher limits of agreement were -3.1 and 4.1, respectively (Figure 3.8).

Figure 3.7 Box plot demonstrating the score distribution of both paper and iPad DLQI formats



The bottom whisker represents the lowest value, and the upper whisker represents the highest value. The dot represents 'one outlier'. The upper level of the box represents the 75th percentile and the lower level of the box represents the 25th percentile. The broad horizontal line in the middle of the box represents the median.

Figure 3.8 Bland-Altman plot demonstrating Paper and iPad DLQI score agreement



Patients took a slightly longer time to complete the DLQI on the iPad® than on paper. The median of the individual time differences was 9 seconds (IQR=-25-13 seconds, p=0.008). However, as shown in Table 3.4b, there was no carryover effect on scores (p=0.56) or completion times (p=0.76) regardless of which format of the DLQI was used first. Linear regression demonstrated that the time taken to complete the iPad version was weakly

correlated in a positive manner with age, with older patients taking slightly longer (R^2=0.257, p=0.012). The estimated increase was 7.99 seconds for each 10-year increase in age.

Table 3.4b Equivalence analysis of paper and electronic DLQI as per first modality used

	All (n=104)	Paper First (n=57)	iPad® First (n=47)
Paper Score:*Mean ± sd* *Median ± IQR* *Range*	7.5 ± 8.0 5 ± 11 0 – 30	7.3 ± 7.9 5 ± 12 0 - 26	7.6 ± 8.1 6 ± 11 0 – 30
iPad® Score: *Mean ± sd* *Median ± IQR* *Range*	6.9 ± 7.6 4 ± 10 0 - 27	6.4 ± 7.5 4 ± 10 0 - 26	7.6 ± 7.8 6 ± 11 0 – 30
Paper Time: *Mean ± sd* *Median ± IQR* *Range*	01:19 ± 00:03 01:13 ± 00:40 00:28 – 04:15	01:27 ± 00:36 01:24 ± 00:33 00:28 – 04:15	01:10 ± 00:30 01:03 ± 00:39 00:30 – 02:49
iPad® Time: *Mean ± sd* *Median ± IQR* *Range*	01:32 ± 00:57 01:18 ± 00:36 00:35 – 08:24	01:26 ± 01:07 01:13 ± 00:29 00:35 – 08:24	01:39 ± 00:43 01:25 ± 00:44 00:49 – 02:49
Score difference:*Mean ± sd* *Median ± IQR* *Range* *Confidence Intervals* *p value* *Carryover effect*	0.5 ± 1.8 0 ± 1 (-3) – 11 0.17 – 0.87 0.006†	1.0 ± 2.0 0 ± 2 (-2) -11 0.43 -1.47	0.0 ± 1.4 0 ± 0 (-3) – 5 (-0.42) – 0.42 0.56†
Time difference: *Mean ± sd* *Median ± IQR* *Range* *Confidence Intervals* *p value* *Carryover effect*	(-00:12) ± 00:50 (-00:09) ± 00:38 (-06:45) – 00:58 (-00:22) – (-00:02) 0.008†	00:00 ± 01:01 00:09 ± 00:32 (-06:45) – 00:58 (-00:16) – 00:16	(-00:28) ± 00:26 (-00:26) ± 00:35 (-01:53) – 00:16 (-00:36) – (-00:20) 0.76†

† p-value calculated by Wilcoxon Signed Rank test (matched pairs)

3.3.3.3 Comparisons of applicability and practicality

Patients were asked: 'On a scale of 1 to 10, where 1 is very uncomfortable and 10 is very comfortable, how comfortable were you using the iPad application version of the DLQI?'. In addition, patients were also asked: 'On a scale of 1 to 10, where 1 is very difficult and 10 is very easy, how easy did you find it to use the iPad application version of the DLQI?'. Both questions were also asked about the paper version of the DLQI. Patients found both paper and iPad® versions were easy (mean 9.4 ± 1.3 for paper and 9.6 ± 1.3 for iPad®) and comfortable to use (mean 9.4 ± 1.1 for paper and 9.6 ± 1.4 for iPad®) (Table 3.5). Overall, 57% of patients reported perceived time to complete the iPad® version as shorter than that of the paper version. The format of the questionnaire used first has an effect on the perceived time of iPad® completion; more patients perceived shorter time with iPad® when paper was used first than when iPad® used first (70% vs. 43%; p=0.023). The feedback results in other

areas were the same whether paper or iPad® was completed first. The majority of patients (76%) preferred iPad® over the paper version. The patients' demographics or previous experience with Tablets did not have any effect on the choice of preference and completion of the questionnaire.

Table 3.5 Comparisons of applicability and practicality of paper and electronic versions of the DLQI

	All (n=104)		**Paper First (n=57)**		**iPad® First (n=47)**	
	Paper	iPad®	Paper	iPad®	Paper	iPad®
***Ease of use**: Mean ± SD*	9.4 ± 1.3	9.6 ± 1.3	9.6 ± 0.8	9.8 ± 0.7	9.1 ± 1.6	9.4 ± 1.8
Median ± IQR	10 ± 1	10 ± 0	10 ± 0	10 ± 0	10 ± 1	10 ± 1
***Comfort**: Mean ± SD*	9.4 ± 1.1	9.6 ± 1.4	9.5 ± 0.9	9.8 ± 0.4	9.3 ± 1.4	9.4 ± 2.0
Median ± IQR	10 ± 1	10 ± 0	10 ± 1	10 ± 0	10 ± 1	10 ± 0
Perceived time to complete iPad®						
Shorter than paper	57.7% (60)		70.2% (40)		42.6% (20)	
The same as paper	35.6% (37)		26.3% (15)		46.8% (22)	
Longer than paper	5.8% (6)		3.5% (2)		8.5% (4)	
Missing data	*1.0% (1)*		-		*2.1% (1)*	
Preference						
Paper	13.5% (14)		15.8% (9)		10.6% (5)	
iPad®	76.0% (79)		75.4% (43)		76.6% (36)	
No preference	10.6% (11)		8.8% (5)		12.8% (6)	

Score: 10 = very easy or very comfortable, 1 = very difficult or very uncomfortable

3.4 Validation of the electronic PASI

Despite its many shortcomings, the PASI remains the standard method worldwide for psoriasis assessment (Fredriksson and Pettersson 1978; Ashcroft et al. 1999). As with the DLQI, the use of new electronic methods of recording PASI scores raises further concerns about whether the method of administration may affect sign recording and score calculation. This issue is of importance to all users of PASI applications in the clinic and in clinical studies.

The aim of this study was to determine whether it is appropriate to continue to assume that scores remain equivalent, whatever the administration method.

Though there is no ideal measure of assessing clinical severity, the PASI has become the most widely used tool and is often utilised for validating new psoriasis severity measures (Jensen et al. 2011). There are several criticisms of PASI including debates around the categorical assignment and weight of each of its components (Weisman et al. 2003), as well as limited inter-rater agreement (Gourraud et al. 2012). Although traditionally the PASI is completed on paper (BAD 2019) and the total score is calculated manually, several studies (Kreft et al. 2006; Schmitt-Egenolf 2007) have implemented electronic versions. However, there is no obvious evidence that these formats are validated or have been compared to the original paper-based version, raising the prospect of incomparable data between the two formats due to a lack of equivalence. As detailed previously, Coons et al. (2009) have proposed guidelines detailing the level of evidence required to demonstrate equivalence for patient-reported outcomes (PRO), depending on the amount of modification to the original PRO. This methodology may be applicable to clinical severity measures.

There is widespread use of hand-held and portable devices such as smartphones and Tablets amongst clinicians, researchers and patients. Thus, there is potential to streamline the doctor-patient consultation enabling healthcare systems to become more efficient (Batista and Gaglani 2013). Nevertheless, as with ePROs, these devices are often used for clinical severity assessment without formal validity testing raising concerns of appropriateness of use. The availability of a validated PASI application would alleviate such concerns and contribute to better management of patients with psoriasis by having an easy tool for regular monitoring of disease severity by utilising an illustrated step-by-step application for scoring by both patients and clinicians alike. Moreover, this tool could potentially reduce inter-rater variability due to the visual nature of electronic scoring, and reduce error by automatic final score calculation, as well as encouraging the conversion of other clinical measures across dermatology and other medical fields. In the research setting, the availability of an application would facilitate more efficient data collection.

3.4.1 Aims & objectives

This study aimed at comparing the conventional paper-based and a novel application version of the PASI, following ISPOR guidelines (Coons et al. 2009), concerning rater preference and

in terms of consistency of scores. An assessment was also conducted of carryover effect depending on which format raters completed first (paper versus iPad).

3.4.2 Methodology

The study also employed a randomised cross-over design using a within-subjects comparison of the two formats of the PASI. The study was conducted at the Dermatology outpatient department, University Hospital of Wales, Cardiff, UK.

3.4.2.1 Ethical considerations

The ethics committee that approved the study protocol (Appendices XIII & XIV) was the National Research Ethics Service (NRES) Committee, South West-Central Bristol, UK (Ref: 14/SW/0085, Appendices XV & XVI), and the Cardiff and Vale University Health Board Research & Development Department also approved the study. Written informed consent (Appendix XVII) was completed by each patient prior to entering the study.

3.4.2.2 Study participants

3.4.2.2.1 Inclusion / exclusion criteria

Inclusion criteria were:

- Patients aged 18 years or older
- Clinical diagnosis of chronic plaque psoriasis
- The ability to read and understand English

The exclusion criteria included:

- Aged under 18 years
- Having a co-existing non-dermatological medical condition of considerable severity, as determined by the investigator
- Having a co-existing dermatological condition of considerable severity, as determined by the investigator
- Not able to read and/or understand written English
- Physical disabilities which would prevent writing or use of an iPad

3.4.2.2.2 Raters

Not all raters had experience in using the PASI measure. Therefore, they received standardised clinical training for using the PASI assessment template prior to enrolment of patients with psoriasis to ensure uniformity of assessment. Formal inter-rater testing was also conducted.

3.4.2.3 The Psoriasis Area Severity Index iPad® App

The PASI was developed into an electronic application on the iPad® by Janssen EMEA®. Only this particular iOS (Apple's Operating System) version was tested for the purpose of studying equivalence. The individual items and their response categories/scale were unchanged, allowing the raters to select options using touch. The application (Psoriasis 360©) is available without charge and may be downloaded from the Apple App Store: https://appsto.re/gb/-JIFw.i. It is also available on the Google (Android) App Store: https://play.google.com/store/apps/details?id=com.sapnagroup.p360&hl=en_GB. The screenshots of the electronic App are displayed in Figure 3.2, the paper version may be seen in Figure 3.9.

Figure 3.9 The PASI assessment template (BAD 2019)

PSORIASIS AREA AND SEVERITY INDEX (PASI) WORKSHEET

HOSPITAL NO.: .
PATIENT NAME: .
DATE OF VISIT: .

The Psoriasis Area and Severity Index (PASI) is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance.

Plaque characteristic	Lesion score	Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Induration/Thickness					
Scaling					
Add together each of the 3 scores for each body region to give 4 separate sums (A).					
Lesion Score Sum (A)					

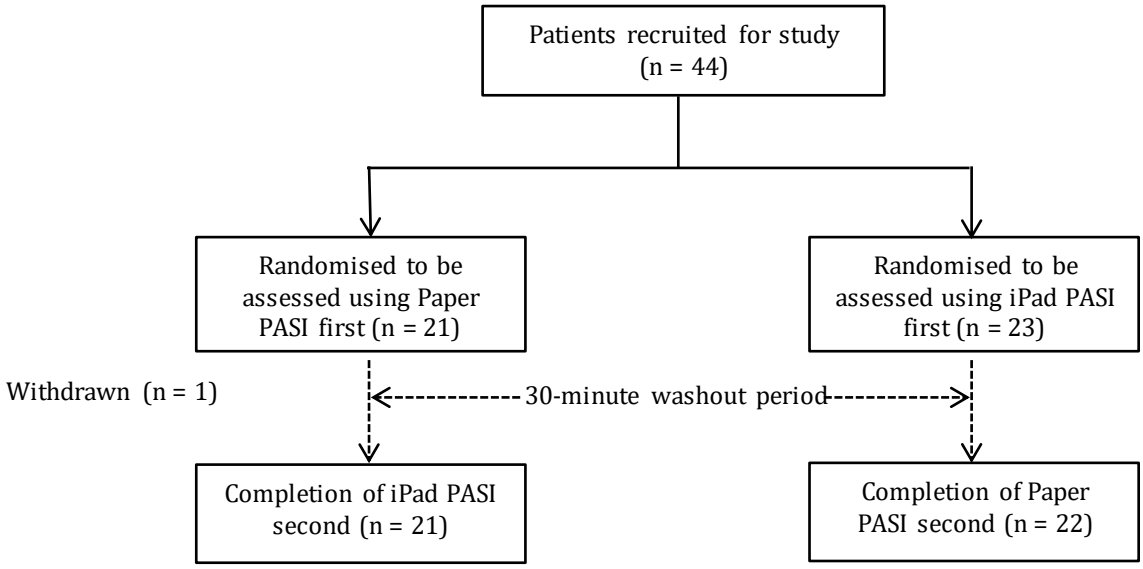
Percentage area affected	Area score	Head	Upper Limbs	Trunk	Lower Limbs
Area Score (B) *Degree of involvement as a percentage for each body region affected (score each region with score between 0-6)*	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%				
Multiply Lesion Score Sum (A) by Area Score (B), for each body region, to give 4 individual subtotals (C).					
Subtotals (C)					
Multiply each of the Subtotals (C) by amount of body surface area represented by that region, i.e. x 0.1 for head, x 0.2 for upper body, x 0.3 for trunk, and x 0.4 for lower limbs.					
Body Surface Area		**x 0.1**	**x 0.2**	**x 0.3**	**x 0.4**
Totals (D)					
Add together each of the scores for each body region to give the final PASI Score.					

PASI Score = ☐

3.4.2.4 Study procedure

Eligible patients were recruited into the study whereby individual raters completed the PASI (both paper and electronic versions). The order of completion of the PASI (paper version first versus an iPad® version first) was randomised using a random number generator. There was a 30-minute interval between completing the two formats (Figure 3.10).

Figure 3.10 Flow diagram of the study procedure



As with the DLQI, a thirty-minute interval was introduced in order to minimise patient burden and waiting time: asking patients to complete the study at a later date would have affected the validity of the results because of the fluctuating nature of psoriasis severity, as well as increasing the total study cost (Coons et al. 2009). Furthermore, several patients completed both the DLQI and PASI study at the same time (n=10) making similar interval times more convenient. The research team ensured that the raters completed other clinical tasks or administrative work in-between testing as forms of distraction in order to reduce training effect and hence minimising bias.

Raters had varying experience with the PASI and consisted of a medical student, a post-graduate doctor with a master's degree in dermatology and a senior research fellow in dermatology. In order to minimise differences between raters, training to operate the electronic application was given in person to each rater by a member of the research team who was available on site in case the raters needed assistance. The electronic application also has basic instructions on the home screen and all three raters were given time to practice its use prior to starting patient assessment. Initially five patients were chosen, using purposive sampling, to ensure that there were no significant differences (i.e. inter-rater bias) in how raters completed the PASI. Each rater assessed the same patient with both paper and electronic versions and then the PASI components were compared. This pilot was carried out at the outset to ensure there were no major discrepancies (bias) between how raters scored the PASI.

The patients completed a short demographic questionnaire on age, gender and diagnosis. Completion of both PASI formats were conducted in a similar environment, both completions for the same subject were either before or after any treatment application, in order to reduce the effect of intervention on disease severity. The time taken by the raters to complete the PASI using the paper version and the application was recorded by the raters themselves. The time taken for calculating the scores on the paper version was not recorded, though the electronic application provides this automatically. The raters were interviewed regarding their experience of using the electronic application compared to the paper-based version.

3.4.2.5 Sample size

Sample size was calculated in accordance to ISPOR guidelines (Coons et al. 2009). The study power was set at 80%, with an expected intra-class correlation coefficient (ICC) of 0.9 ($\alpha = 0.05$), resulting in a target sample size of 44 patients.

3.4.2.6 Data analysis

Data analysis was conducted using SPSS version 20®. The concordance of PASI scores between paper-based and the application-based data were analysed using a two-way fixed effects ICC model (Gwaltney et al. 2008), as per the electronic DLQI study. Wilcoxon signed rank test was used to compare PASI scores and completion times between the two formats. A more stringent score difference of 1.5 points (2%) between the two versions was considered equivalent, though a majority of studies target a maximum of 5% difference (Gwaltney et al. 2008). Bland-Altman plots were drawn to measure the limits of agreement between the two formats. Equivalence was considered with limits of agreement <=3.2, which is the minimal clinically important difference (MCID) for the PASI (Mattei et al. 2014). Sub-analysis was conducted to identify any carryover effect depending on which format of the PASI raters completed first. Descriptive analysis was used to present demographic data of the patients.

3.4.3 Results

3.4.3.1 Performance of raters

All three raters had high correlation in test scores (Pearson correlation 0.95, $p<0.05$, n=5 (number of patients)) ensuring that the assessment criteria were standardised.

3.4.3.2 Socio-demographic characteristics of the study participants

Forty-four patients were recruited, mean age 45 years (SD ± 16, 59.1% male) (Table 3.6). The mean duration of chronic plaque psoriasis diagnosis was 19.2 years (SD ± 14.8, IQR 8-30), with PASI severity ranging from 0.7 to 28.5. Most patients did not have other medical conditions, though a minority suffered from diseases such as diabetes (2%) and hypertension (2%).

Table 3.6 Demographic characteristics of the study participants (PASI study)

	All (n=44)		**Paper First (n=21)**		**iPad First (n=23)**	
Age	Mean ± sd Median (IQR) Range	45.4 ± 16 41 (31.5-57.5) 20 - 78	Mean ± sd Median (IQR) Range	47.1 ± 17.4 41 (30-61) 23 - 77	Mean ± sd Median (IQR) Range	44 ± 15 43 (31.8-51.5) 20 - 78
Sex	Male Female	59.1% (26) 40.9% (18)	Male Female	42.9% (9) 57.1% (12	Male Female	73.9% (17) 26.1% (6)
Nationality	British Other	95.5% (42) 4.5% (2)	British Other	95.2% (20) 4.8% (1)	British Other	95.7% (22) 4.3% (1)
Duration of Psoriasis (years)	Mean ± sd Median (IQR) Range	19.2 ± 14.8 15 (8-30) 0-7	Mean ± sd Median (IQR) Range	21.4 ± 17.4 18 (8-32.5) 0 - 70	Mean ± sd Median (IQR) Range	17.1 ± 11.7 13 (8.75-30) 1 - 40
Concomitant Diagnoses	None PTSD/Anxiety Coeliac disease Adenomyosis Psoriatic arthritis Hypertension Diabetes Contact allergy Bipolar disorder Eczema	82% (36) 2.3% (1) 2.3% (1) 2.3% (1) 2.3% (1) 2.3% (1) 2.3% (1) 2.3% (1) 2.3% (1) 2.3% (1)	None PTSD/Anxiety Eczema	90.5% (19) 4.8% (1) 4.8% (1)	None Coeliac disease Adenomyosis Psoriatic arthritis Hypertension Diabetes Contact allergy Bipolar disorder	73.9% (17) 4.3% (1) 4.3% (1) 4.3% (1) 4.3% (1) 4.3% (1) 4.3% (1) 4.3% (1)

3.4.3.3 Comparisons of validity and reliability

The ICC showed high concordance between the total PASI scores from paper and iPad® versions (ICC = 0.993; 95% CI = 0.988-0.996) (Table 3.7a).

Table 3.7a Equivalence analysis of paper and electronic PASI: overall mean scores and mean completion time

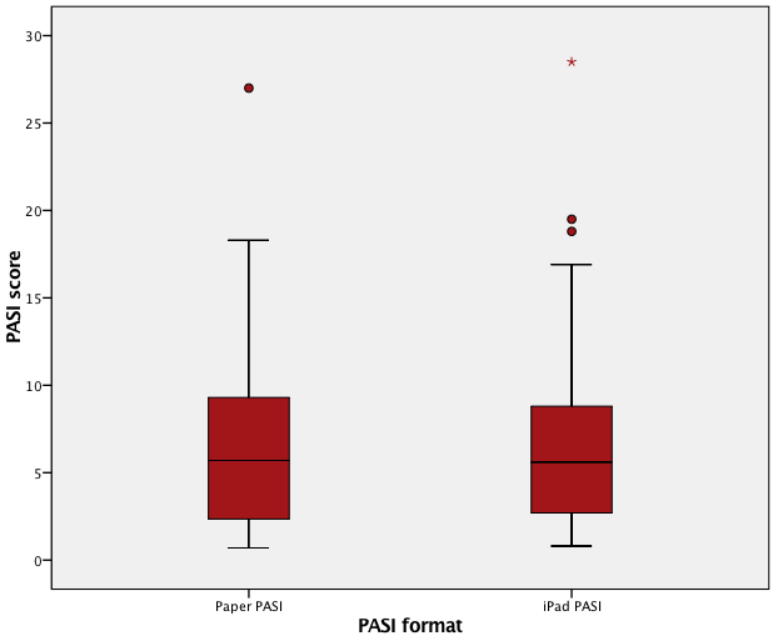
	Paper	iPad®	ICC* (95% CI)	Difference (P – iP)	Limits of agreement‡	
PASI scores (n=104)					lower	upper
Median (IQR)	5.7 (2.1-10.7)	5.8 (2.7-9.3)	0.993 (0.988 – 0.996)	0.0 (-0.3 – 0.4)†	-1.4	1.4
PASI times (mins:seconds)						
Median (IQR)	2:32 (01:55-03:07)	2:27 (01:54-03:00)	0.444 (0.148 – 0.665)	-00:10 (-00:31-00:40)†		

Footnote:

P-iP = Paper - iPad®
* Hypothesising coefficient of ≥ 0.9
† p value > 0.05 calculated by Wilcoxon Signed Rank test (matched pair)
‡ Limits of agreement calculated from Bland-Altman plots (Figure 3.12)

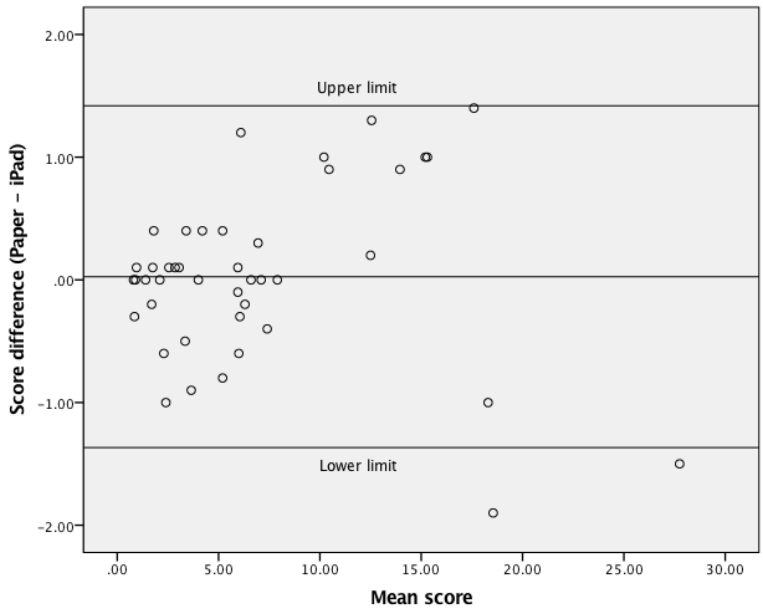
The median difference in PASI scores was also within the hypothesised difference of ±1.5 points (p=0.72, Figure 3.11). The lower and higher limits of agreement were -1.4 and +1.4, respectively (Figure 3.12).

Figure 3.11 Box plot demonstrating the score distribution of both paper and iPad PASI formats



The bottom whisker represents the lowest value, and the upper whisker represents the highest value. The dots represent 'outliers'. The upper level of the box represents the 75th percentile and the lower level of the box represents the 25th percentile. The broad horizontal line in the middle of the box represents the median.

Figure 3.12 Bland-Altman plot demonstrating Paper and iPad PASI score agreement



The PASI iPad® version demonstrated reduced inter-rater variability compared to the paper version (Pearson correlation = 0.982 vs 0.949, number of patients assessed=5). As shown in

Table 3.7b, there was no carryover effect demonstrated with scores (p=0.82) or time to completion (p=0.16) regardless of which format of the PASI was used first.

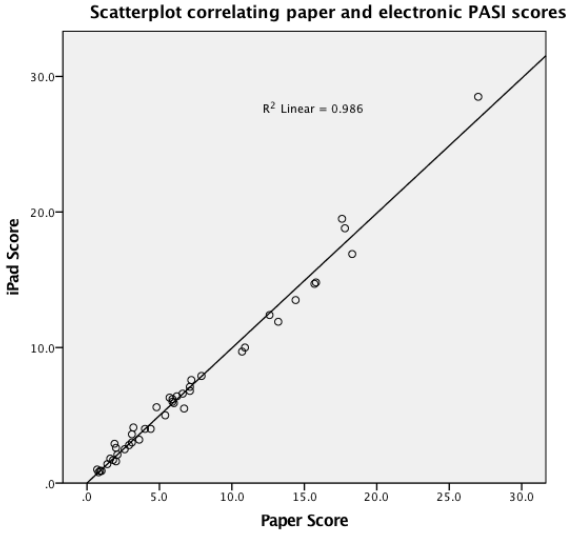
Table 3.7b Equivalence and carryover analysis of paper and electronic PASI

	All	**Paper First (n=21)**	**iPad® First (n=23)**
Paper Score (n=43):			
Median (IQR)	5.7 (2.1-10.7)	6.8 (1.8-10.8)	4.4 (2.5-8.9)
Range	0.7 – 27	0.7 – 17.6	1 – 27
iPad® Score (n=44):			
Median (IQR)	5.8 (2.7-9.3)	6.3 (2.2-9.9)	5 (2.8-7.7)
Range	0.8 – 28.5	0.8 – 19.5	0.9 – 28.5
Paper Time* (mins:seconds)*:			
Median (IQR)	02:32 (01:55-03:07)	03:01 (02:26-03:31)	02:08 (01:37-02:36)
Range	00:51 – 04:30	00:51 – 04:30	01:22 – 04:30
iPad® Time* (mins:seconds)*:			
Median (IQR)	02:27 (01:54-03:00)	02:15 (01:45-02:56)	02:37 (02:08-03:05)
Range	00:41 – 05:58	00:41 – 05:58	01:27 – 04:37
Score difference:			
Median (IQR)	0 (-0.3-0.4)	0 (-0.3-0.7)	0 (-0.6-0.4)
Range	(-1.9) – 1.4	(-1.9) -1.3	(-1.5) – 1.4
p value	0.72†		
Carryover effect			0.82†
Time difference (*mins:seconds)*:			
Median (IQR)	-00:10 (-00:31-00:40)	00:38 (00:12-01:07)	-00:24 (-00:57--00:12)
Min and max	(-02:41) – 01:57	(-02:41) – 01:57	(-02:04) – 00:14
p value	0.81†		
Carryover effect			0.16†

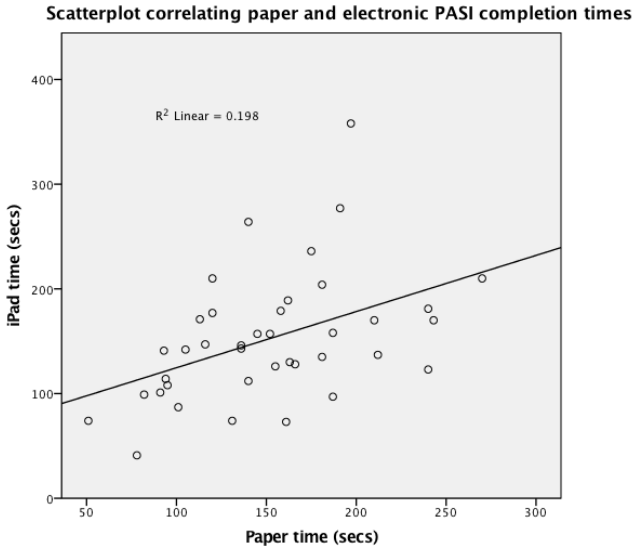
† p-value calculated by Wilcoxon Signed Rank test (matched pair)

Scatterplots (Figure 3.13) demonstrated a strong correlation between iPad and paper scores ($R^2 = 0.986$), though a weaker correlation between time taken for completion ($R^2 = 0.198$).

Figure 3.13 Scatterplots demonstrating Paper and iPad PASI score and completion time correlations
(a)



(b)



3.4.3.4 PASI completion time

The raters took a median of 147 seconds (iPad®) versus 152 seconds (paper), not including calculation time (p=0.81, Table 3.7a).

3.4.3.5 PASI applicability and practicality

The raters documented their experience of utilising the iPad version of the PASI with respect to its applicability and practicality. They reported that the iPad version was easier to use

compared to the paper version due to the visual nature of the App allowing accurate assessment and calculation of severity scores. However, suggestions were made to improve the user interface, in particular the body area percentage which had to be selected on a scale as opposed to set categories. Concerns regarding infection control were also mentioned. Nevertheless, there was unanimous preference of the iPad version in a clinical context.

3.5 Discussion

Computer-based assessments (CBAs), measures of clinical severity and PROs have been increasingly used in preference over their paper and pencil versions. This trend is attributed to the inherent benefits of digital formats of administration including increased reliability of data, improved error rates and patient compliance (Hanscom et al. 2002; Gwaltney et al. 2008), as well as being, on balance, more environmentally friendly (Faulds et al. 2016). Disadvantages of traditional paper-based completion include issues such as missing values and storage space and costs for large volumes of data. Research data were often manually transferred from paper to static computers or terminals which is not only time consuming, but has the capacity to introduce transcription errors (Saleh et al. 2002; Lee et al. 2007), thereby reducing the reliability of captured data. These issues can be avoided by the use of CBAs of QoL questionnaires. Researchers are now making a concerted effort to validate their measures electronically from the outset, or alongside their paper counterparts in order to benefit from better data analysis and reduced administrative costs (Deal et al. 2010; Bächinger et al. 2016). Nevertheless, CBAs have limitations (Bezjak et al. 2001; Carlson et al. 2001). There is often a learning curve associated with electronic applications alongside considerable investment of resources, with consistent internet connectivity often as a requirement (Tung and Nambudiri 2018). Data confidentiality and protection require much thought, as patient information needs regular back up, with a digital infrastructure in place to prevent cyber-attacks or exposure to computer viruses (Faulds et al. 2016).

This discussion will aim to summarise and discuss the findings of each study pertaining to the DLQI and PASI and synthesise conclusions accordingly.

3.5.1 DLQI

Computer-based administrations of QoL measures such as in the form of electronic applications using touchscreen computers, including Tablets (e.g. iPad®), is one of the ways that more frequent assessments can be conducted with minimal burden on patients and

clinical staff, in addition to meeting the requirements outlined above. This method, that includes not only CBA, but also scoring and presentation of QoL results, eliminates the need for a test (interviewer) administrator, as usually needed for traditional paper and pencil formats, while providing immediate "real-time" feedback. Information from assessments can be displayed in graphic reports as visual aids that help guide discussions about treatment options and care planning. The availability of electronic versions of QoL instruments on various computer-based devices has the potential to reduce both the respondent burden and administrative time required to transfer the results of these patient-reported outcomes e.g. QoL scores to the clinician's desk enhancing the feasibility and logistics of integrating real-time QoL assessment data for immediate use into routine clinical care to aid decision-making. A further benefit of electronic data capture is the ability to record time and date stamps, in contrast to paper capture whereby completion may occur at a different time to that recorded or intended; a feature particularly useful for diary data. The computer-based measurement of QoL was well accepted by patients who felt that this method was a useful tool to inform the clinician about their problems (Velikova et al. 2002). Data are more complete on the electronic questionnaires compared with paper questionnaires, data handling is greatly simplified and the majority of patients prefer electronic completion (Drummond et al. 1995). The availability of an electronic format of the DLQI could potentially streamline referral systems from primary care, allowing more appropriate allocation of appointments and resources. For example, the DLQI is integral to guidelines assessing the severity of psoriasis (Finlay 2005) and chronic hand eczema (Paulden et al. 2010) and referrals could potentially be triaged according to DLQI severity (Atwan et al. 2017). In the research setting the availability of an electronic application would facilitate more efficient data collection in multicentre clinical trials and for longitudinal assessments of disease severity.

In response to the increasing interest, an electronic application of the DLQI has been developed to encourage its further uptake in the current modernised clinical and research settings in many countries. Although, computerised administration of QoL tools in other specialities has been shown to have numerous advantages over traditional paper-based tools (Hanscom et al. 2002), this method of QoL assessment to encapsulate an overall disease severity concept has not yet been widely used in dermatology.

Level of education and literacy are important to consider when conducting PRO studies (Bushnell et al. 2003): this study is representative of the general population with the study subjects' education ranging from secondary school (22.9%) to university level (37.6%). Previous experience with use of a Tablet device did not affect results, with 17.3% of patients having never used one before and 46.2% stating that they were 'a little comfortable' or 'not

comfortable' with using a Tablet. Overall, 76% of patients preferred the iPad version to the paper version and found it easier to use and more comfortable. Furthermore, 93% of patients perceived that the iPad was quicker to complete or took at least the same time as the paper version, though the iPad completion was actually slower by a median of 9 seconds ($p=<0.008$). Similar findings have been reported in many studies comparing the electronic and paper PROs (Kleinman et al. 2001; Gwaltney et al. 2008; Campbell et al. 2015). However, patients were aware they were being timed when completing both versions of the DLQI, which could be a potential source of bias. Slower completion times could be attributed to the lack of familiarity of navigating on the iPad and occasional non-responsiveness of the touch screen. Investigators reported that various patients did not know how to 'touch' the screen appropriately and often searched for a 'next' button rather than scrolling down, despite instructions provided to the user on every occasion. This may be attributed to a simple design flaw in the application itself whereby navigation may be updated to become more intuitive. This study indicates that patients enjoy using the iPad more and the extra time spent had a negligible impact on patient experience. One concern exhibited by a few patients included potential cross-infection risk with shared iPads, though this may be less of an issue where personal electronic devices are used to monitor QoL changes over a period of time.

There are some limitations to the study. For example, a 30 minutes washout period may be considered too short and result in a carryover, or 'training', effect, though there was no statistical evidence of this (Table 3.4b). Theoretically, this only may have occurred when the iPad was administered first, as patients spent longer on average completing it, therefore possibly having more time to remember the questions and answers. This effect however was counteracted by the cross-over study design, and reading material was provided to patients as a 'distraction'. Nevertheless, there is no consensus on the ideal interval period between PRO administrations: interval times between administrations have ranged from one minute to seven years (sic) (Quadri et al. 2013). Other studies have also used 30 minutes as a washout period (Sun et al. 2015). In order to reduce patient time and travel burden, as well as to ensure that disease severity did not fluctuate in-between administrations, the shorter washout period of 30 minutes was used. Touch screen surfaces are also prone to accidental touches, which may result in recording unintentional item responses, contributing to final score differences. The electronic version of the DLQI utilised in this study does not allow completion until all items are answered, which may impact validity if patients are coerced into answering questions they may have otherwise skipped on a paper format. This could have ethical implications from not giving patients the choice of not responding to a question if they do not wish to do so. In the DLQI, this issue is partly addressed by having a 'not relevant' option in eight of the ten questions. The median score difference of '0' provides reassurance that there

are no clinically significant differences in completion and the strong correlation suggests that the two formats may be used interchangeably. Though the significant p-value of 0.006 for median total score difference is statistically significant, this is likely due to the large sample size (Doll and Carney 2005) as well as other biases such as unfamiliarity of the patients with the device/application. Furthermore, the MCID for the DLQI is four (Basra et al. 2015a) and therefore the difference in scores is negligible in a clinical context. The limits of agreement from the Bland-Altman plots (-3.4 to +4.1) are also similarly reassuring.

Touchscreen devices offer many advantages including portability and real-time assessment of QoL status (Dale and Hagen 2007). Though this study did not involve full psychometric evaluation of the DLQI, there is evidence to suggest that where minimal modifications have been made, psychometric properties remain intact and need not be tested again (Gwaltney et al. 2008; Coons et al. 2009; Muehlhausen et al. 2015). Whilst cognitive debriefing is suggested for equivalence studies of electronic PROs where only minor modifications are made (Coons et al. 2009), this requirement was circumvented by using a higher threshold for testing equivalence (i.e. by comparing scores). It is hoped this will provide further reassurance for users who may have had concerns regarding the validity of scores from the use of the DLQI in the previously non-validated electronic formats that have been used for many years. Formally testing such measures in this novel format provides confidence for end users who might otherwise have been reluctant to consider use of such formats because of concerns about validity or applicability. Thus, such studies may have wider and reassuring implications not just for the DLQI, but also for PROs within dermatology and across other medical specialties, encouraging the validation of electronic versions simultaneously with the paper format. Several challenges remain, including interface design decisions, data collection (Zbrozek et al. 2013) and adapting electronic PROs to target populations, particularly in patients with physical disabilities or other impairments (Hahn and Cella 2003). However, patients with hand arthritis or eczema for whom paper completion would not be possible may find touch screen or voice controlled completion easier. This study has demonstrated that when the DLQI is migrated to an electronic format, the scores are equivalent, despite an overall slower completion time, which should become negligible with increased use and improvements to the application interface. This study provides evidence of equivalence for this electronic application in particular (Psoriasis 360©), and future/other iterations of the electronic DLQI may not necessarily be equivalent. However, in most cases the changes to font size and layout are minor and thus repeated equivalence studies may be deemed unnecessary (Coons et al. 2009).

The majority of patients preferred the electronic DLQI over the paper format, reflecting the findings of many similar studies (Velikova et al. 1999; Ryan et al. 2002; Bushnell et al. 2003).

This study demonstrates equivalence in the measurement properties of paper and electronic formats, providing confidence for the use of electronic format of the DLQI in both clinical and research settings, thereby paving the way for current practice to enter the digital era. This digital era in medicine will continue to be fuelled by a new generation of healthcare professionals who will have been trained in the context of accepting as normal the central role of electronic devices in healthcare. Patients and healthcare professionals are becoming more comfortable communicating and delivering their experience (non-medical expertise) and clinical expertise, respectively, within a digital environment. In this context the electronic DLQI should be a valuable instrument in a professional's digital healthcare toolbox.

3.5.2 PASI

The same electronic application (Psoriasis 360©) was also utilised for the purpose of validating the electronic PASI using an iPad®. In most clinical settings, the PASI is completed using a printed paper version such as that downloadable from the British Association of Dermatologists (BAD) website (BAD 2019) (Figure 3.9). Though psoriasis photo guides are available from third party organisations, there are often no images accompanying the PASI form and therefore scoring of the domains is dependent on the level of training of individual assessors. The total score is awkward to calculate, using a two-step formula that introduces the possibility of user-dependent error. As a result, the PASI has been criticised due to its subjectivity and high inter-rater variability despite becoming a 'gold standard' mostly due to the lack of a suitable alternative, its 'validation by extensive use' and its acceptance by various national licensing authorities. The application used in this study not only includes the CBA alongside a visual representation of the domains (erythema, scaling, thickness and body surface area), but similarly to the DLQI version, also provides an instantaneous 'real-time' total score upon completion with the sub-scale breakdown. The inclusion of a universal scoring guide utilised by every assessor contributed to a reduced inter-rater variability of the electronic PASI compared to the paper version (Pearson correlation 0.982 vs 0.949, respectively, no. of patients=5).

The PASI and DLQI are often used in conjunction when assessing disease severity in psoriasis patients and are an integral part of the assessment criteria for biologic therapy (Finlay 2005) . This application will enable more frequent assessments allowing real-time measurement of disease and QoL severity in a clinical setting to aid decision-making. There is no requirement for manual date and time entry as these are automatically registered and are often accidentally omitted or incorrectly recorded when entered manually. Written

feedback from the raters in this study demonstrated a preference for electronic clinical severity assessment due to the visual nature of the application and simplified data handling. The availability of a fully validated PASI/DLQI application has the potential to streamline clinical sessions as well as triage psoriasis referrals from primary care, particularly when they are already requested electronically (Atwan et al. 2017). The application would further facilitate more efficient data collection in multicentre research trials and for longitudinal assessments of psoriasis severity. There is also the potential to increase participation in electronic/web-based psoriasis registries, such as the British Association of Dermatologists' Biologic Interventions Register (BADBIR) (Burden et al. 2012).

The iPad PASI version was completed in a median of 147 seconds versus 152 seconds for the paper version (p=0.81). These times do not include calculation time for the paper version, whereas the iPad® provides an instant score. The calculation timing was deliberately omitted in order to provide a more direct comparison of time to completion between both versions. In real-life scenarios, PASI scoring time is prolonged by individual arithmetic ability and human error, therefore the time to completion in reality is likely to be much longer for the paper version than identified in this study. Conversely, despite formal training, the lack of familiarity of the PASI application and occasional non-responsiveness of the touch screen may result in slower completion times. The raters suggested changes to the user interface which may improve score assignment: for example, the body surface area requires users to input a specific percentage along a visual analogue scale, whereas the paper PASI allows users to select between groups of percentages. Implementing this change on the electronic PASI would intuitively streamline the scoring process by providing to assessors seven categories to choose between as per the paper version (Figure 3.9). It is important to note that for both modalities, assessors timed themselves, introducing a potential source of bias. One concern mentioned by a few patients from the DLQI study, and re-iterated by raters here, was the potential of an infection risk with shared iPads between patients. Infection control may be a prudent consideration with repeated use in a clinical setting.

As with the DLQI study, there are some shared limitations of this study. For example, a 30 minutes washout period may again be considered too short and result in a carryover, or 'training', effect, though there was no statistical evidence of this (Table 3.7b). Theoretically, raters may have recall bias given the short duration between assessments; this effect was counteracted by the cross-over study design, and the raters completed other clinical and administrative work including seeing other patients in-between scoring as a 'distraction'. As demonstrated already, previous studies have reported intervals ranging from one minute to seven years (sic) (Quadri et al. 2013), albeit for PRO measures (Sun et al. 2015). A shorter

duration was also used for the PASI study to ensure that the clinical severity of psoriasis was consistent between assessments and to reduce patient burden and travel costs (particularly if they enrolled for the DLQI study simultaneously, n=10). The PASI application contains more steps than the DLQI version, and in the absence of tactile feedback, accidental touches are more likely, resulting in unintentional score allocation. Only three raters were enrolled in the study to ensure uniformity in measuring the 'effect' of the PASI application on scores including one undergraduate student, one postgraduate student and a dermatologist trainee with ~6 years' experience. Though this reflects various levels of experience, the influence of this variation is difficult to quantify for the purpose of this study. In clinical practice the inter-rater difference is likely to be wide given the varying backgrounds of assessors as well as the pre-existing issues with PASI score reliability (Gourraud et al. 2012).
There was strong correlation between both PASI modalities with a median score difference of '0' (p=0.72) suggesting each format may be used interchangeably. Furthermore, the MCID for the PASI is 3.2 (Mattei et al. 2014) and therefore the difference in scores is likely to be negligible in a clinical context. The limits of agreement from the Bland-Altman plots (-1.4 to 1.4) are within the hypothesised difference of ±1.5 points and add further credence to the validity of the electronic PASI. Unlike PROs, clinical assessment measures such as the PASI are often not subjected to full psychometric evaluation, although ideally this should be done. In a clinical context, variation of the sub-category scores are often irrelevant in assessing global severity, which is where the PASI is particularly useful. In certain cases, knowing the extent of scaling, for example, may help guide treatment – though this would be evident from clinical examination alone. Electronic versions of the PASI have been used for many years, though without formal testing for validity. Conducting formal validity testing provides reassurance for end users and clinicians who have perhaps been hesitant to utilise formats that have not been adequately validated.

It is hoped that studies such as this provide wider reassurance for dermatologists and for the wider medical community by providing confidence from the validation of clinical assessment tools, such as the PASI, in electronic formats. There are of course several hurdles to overcome, including training needs, resource allocation, data protection (Zbrozek et al. 2013) and user interface design challenges. This study has shown the electronic PASI to be equivalent to the paper version, with reduced inter-rater variability and a quicker time to final score completion. The user experience will only improve with further formal testing and user feedback to developers on ways to enhance its usability. It is important to note that this study provides evidence of equivalence limited to this application in particular (Psoriasis 360©). Other versions of the electronic PASI may not necessarily be equivalent and may require further testing, though as with the DLQI, repeated validation studies are not always indicated

(Coons et al. 2009). Although, the PASI is a familiar tool to dermatologists for assessing psoriasis severity, the graphical layout may differ quite considerably between digital formats and thus need further evaluation.

3.6 Conclusions

There have been no previous formal validation studies of electronic versions of the DLQI or PASI. This study has demonstrated that not only is there equivalence between paper and electronic versions for both measures, but the user experience is enhanced through digital and graphical representation of the respective measures. There is more uniformity between measurements by different assessors for the same patient in the case of the PASI.

The future of medical practice is intricately anchored within the evolution of digital technology; more and more people are using smartphones in their day-to-day lives (Higgins 2016). The current coronavirus pandemic has further accelerated the introduction and acceptance of electronic changes in healthcare (Das et al. 2020; Marandino et al. 2020). There is also a large movement for user-controlled monitoring of health, for example innovations such as 'wearable technology' are becoming increasingly popular to improve overall quality of life for patients (Park and Jayaraman 2003). There have been advanced developments within dermatology too: computer-guided PASI measurements have been shown to have similar precision and higher reproducibility compared to trained physicians (Fink et al. 2019). Although, healthcare services always face increasing demands on resources and consequently have to grapple with the challenges of financial constraints (i.e. purchasing ten iPads versus 1000 printouts), the potential of such technology to improve healthcare in the near future remains considerable. The adoption of electronic applications such as the 'Psoriasis 360' App validated in this study contributes to this process and is very much relevant for the growing 'digitally reliant' population. Although the degree of smartphone technology use amongst the elderly population remains unclear, it is likely that even this age group may embrace the new technology in the near future (Berenguer et al. 2017). However, younger patients and medical practitioners are more likely to be accustomed to using electronic devices from primary school years and therefore may prefer using this format.

Clinicians, researchers and patients are becoming more accustomed to the role of their smart devices in day-to-day life – and the workplace is no exception. Despite its inherent challenges, the recording and dissemination of digital healthcare information is becoming increasingly common and promises to improve the way in which health is assessed and

managed. Patients may access and monitor health-related information in one single device that has the potential to develop into an integrated health system accessible by healthcare professionals. As a result, the validated Psoriasis 360 application©, bringing together the two most commonly used assessment tools in dermatology in the form of the DLQI and PASI, has the potential to be of significant practical value to both clinicians and patients in the future.

Chapter 4: Development of the conceptual framework for mapping of the DLQI scores to utility values

4.1 Introduction & rationale

The 'Health-related Quality of Life' (HRQoL) instruments are used to measure the impact of an individual's health state on their life quality thereby guiding their treatment. Rather than focusing on illness severity, they capture a multi-dimensional concept including physical, psychological and emotional factors that may affect a patient's quality of life. 'Quality-Adjusted Life Years' (QALYs) may be derived from this data, which in turn are implemented in economic analyses to aid healthcare decision makers.

The DLQI and the EQ-5D are examples of measures that may be used to gather HRQoL information from patients. The DLQI (Finlay and Khan 1994) is a specialty-specific measure and is the most commonly utilised HRQoL instrument for patients with skin diseases (Basra et al. 2008a): the items (i.e. questions) are specific to the impact of skin diseases. In contrast, the EQ-5D (Group 1990) is a generic utility measure and provides a utility value, or a single summary index, which may be used for comparison of burden of disease. The items of the EQ-5D are designed to be of relevance across all diseases, not just for one specialty (Klassen et al. 2000). Often in trials only the DLQI is used and no formal utility assessment is conducted. Although both measures may be used in tandem, integrating data from multiple measures presents several challenges (Feeny 2002) and there is a debate on whether it is appropriate to use both types of measures to inform the same decision (Dowie 2002). Furthermore, requesting patients to fill out numerous questionnaires may be considered burdensome.

In response to such difficulties, several 'mapping techniques' have been developed (Mortimer and Segal 2008) involving algorithms to derive utility values from disease-specific measures, such as the DLQI. Where EQ-5D values have been unavailable or not recorded, researchers have attempted to predict scores using DLQI scores, though non-validated and on limited sample sizes (Woolacott et al. 2006). A linear model derived by Currie and Conway (2007) has been previously used to predict utility values from the DLQI (Lloyd et al. 2009; Blank et al. 2010; Rodgers et al. 2010). However, the methodology had several limitations including a small sample size and a psoriasis-only population. Subsequent mapping models were derived using multiple linear regression (Norlin et al. 2012) and bivariate/multivariate analysis (Blome et al. 2013), though the authors did not conduct formal validation to predict utility values and only went as far as predicting EQ-5D VAS or total scores. Blome et al. (2013) further postulated that 'any prediction of utilities with the DLQI and other variables regularly assessed in psoriasis studies will be vague and not of clinical relevance'.

Gray et al. (2006) have succeeded in mapping the Short-Form 12 to categorical EQ-5D responses using Ordinal Logistic Regression (OLR). The aim of this study was to provide a mapping model using OLR to reliably predict EQ-5D domain values, and thus subsequently allow the prediction of utility values from DLQI scores. The model will be tested on a second patient dataset as a form of external validation, comparing predicted and actual values. Therefore, the hypothesis is that EQ-5D domain scores, and subsequently utility values, can be reliably estimated from a given set of DLQI scores for a group of subjects. A key difference between this approach and the previous unsatisfactory or failed attempts to map DLQI data to EQ-5D is that previous attempts have used total DLQI scores, whereas the OLR methodology uses data from responses to individual items.

4.2 Aims & objectives

The aim of this study was to provide a suitable mapping model to predict EQ-5D utility values from DLQI item scores. The hypothesis is that EQ-5D utilities can be reliably estimated from DLQI scores for a group of subjects.

The objectives may be divided in to three primary points:

1) To examine the relationship between the DLQI and EQ-5D and suggest a suitable approach for building the mapping model using OLR

2) To construct an improved model based on existing data

3) To use the model to predict EQ-5D utility values, testing for accuracy and validity by comparing predicted and actual values. In turn this will be compared to the previous model by Currie and Conway (2007)

4.3 Study instruments

4.3.1 Brief overview of the DLQI

The DLQI (Finlay and Khan 1994) is currently the most commonly used dermatology-specific QoL measure in clinical trials of skin diseases (Both et al. 2007). It has been used in more than 36 skin diseases (inflammatory, non-inflammatory and skin cancers), in more than 32 countries and is available in 152 international language versions (Basra et al. 2008a; Singh

and Finlay 2020). The DLQI has been shown to be easy to use in clinical practice due to its simplicity and brevity (Bronsard et al. 2010) with an average completion time of around 2 minutes (Loo et al. 2003). It consists of 10 questions concerning dermatological patients' perception of the impact of skin diseases on different aspects of their QoL over the last week (Figure 4.1). The items of the DLQI encompass aspects such as symptoms and feelings, daily activities, leisure, work or school, personal relationships and the side effects of treatment. Each item is scored on a 4-point scale: not at all/not relevant, a little, a lot and very much. Scores of individual items (0-3) are added to yield a total score (0-30); higher scores mean greater impairment of patient's QoL. Hongbo et al. (2005) introduced the much needed banding of the DLQI scores to facilitate the clinical interpretation of scores. According to this banding system a DLQI score of 0 and 1 means no impact on patient's QoL while a score of 2-5, 6-10, 11-20 and 21-30 indicate a small, moderate, large and extremely large effect on patient's QoL respectively. Psychometrically, the DLQI has been shown to be a strong instrument with respect to its internal consistency, reproducibility, validity and sensitivity to change (Hahn et al. 2001; Mazzotti et al. 2003; Bronsard et al. 2010). The strong psychometric properties of the DLQI have resulted in the increasing popularity of the DLQI in both clinical research and in clinical practice. Moreover, the content of the DLQI has been shown to include all important and relevant concepts from the perspective of patients with moderate to severe plaque psoriasis supporting its content validity in psoriasis patients (Safikhani et al. 2013).

Figure 4.1 The Dermatology Quality of Life Index (from: http://www.cardiff.ac.uk/dermatology/) (Finlay 2020)

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

4.3.2 Brief overview of the European Quality of Life Index – 5 Dimensions (EQ-5D)

The EQ-5D consists of two pages. The first of which is the 'descriptive' system and the second a visual analogue scale (VAS). The descriptive system is composed of five dimensions (or domains): mobility, self-care, usual activities, pain and depression, each of which are assessed with 3 possible answers: no problems, some problems or extreme problems (Figure 4.2). The information from this part may be useful for the following reasons:

1) The scores may be used to attribute a health profile to an individual or a group of subjects at single or multiple points in time. Health outcomes may therefore be described based on the differences in these profiles.
2) Using the 5-dimensional scale in the first part of the EQ5D health states may be defined and be converted to health utility scores. This is done using 'value sets' which are derived from various population samples.

The latter is achieved by scoring each of the dimensional outcomes '1', '2' and '3' respectively, allowing the descriptive system to be represented using these number descriptors to define health states. The number descriptors range from '11111' to '33333', resulting in 243 possible numerical combinations, or health states. For example, the health state 11223 would signify 'no problems with mobility', 'no problems with self-care', 'some problems with performing usual activities', 'moderate pain or discomfort' and 'extremely anxious or depressed'. There are a total of 245 health states defined by the EQ5D, including the additions of 'unconscious' and 'death'. This instrument is widely used among health economists for comparison of disease burden between diseases (Group 1990).

Figure 4.2 The EQ-5D 3L (a) part one (b) part two

(a)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

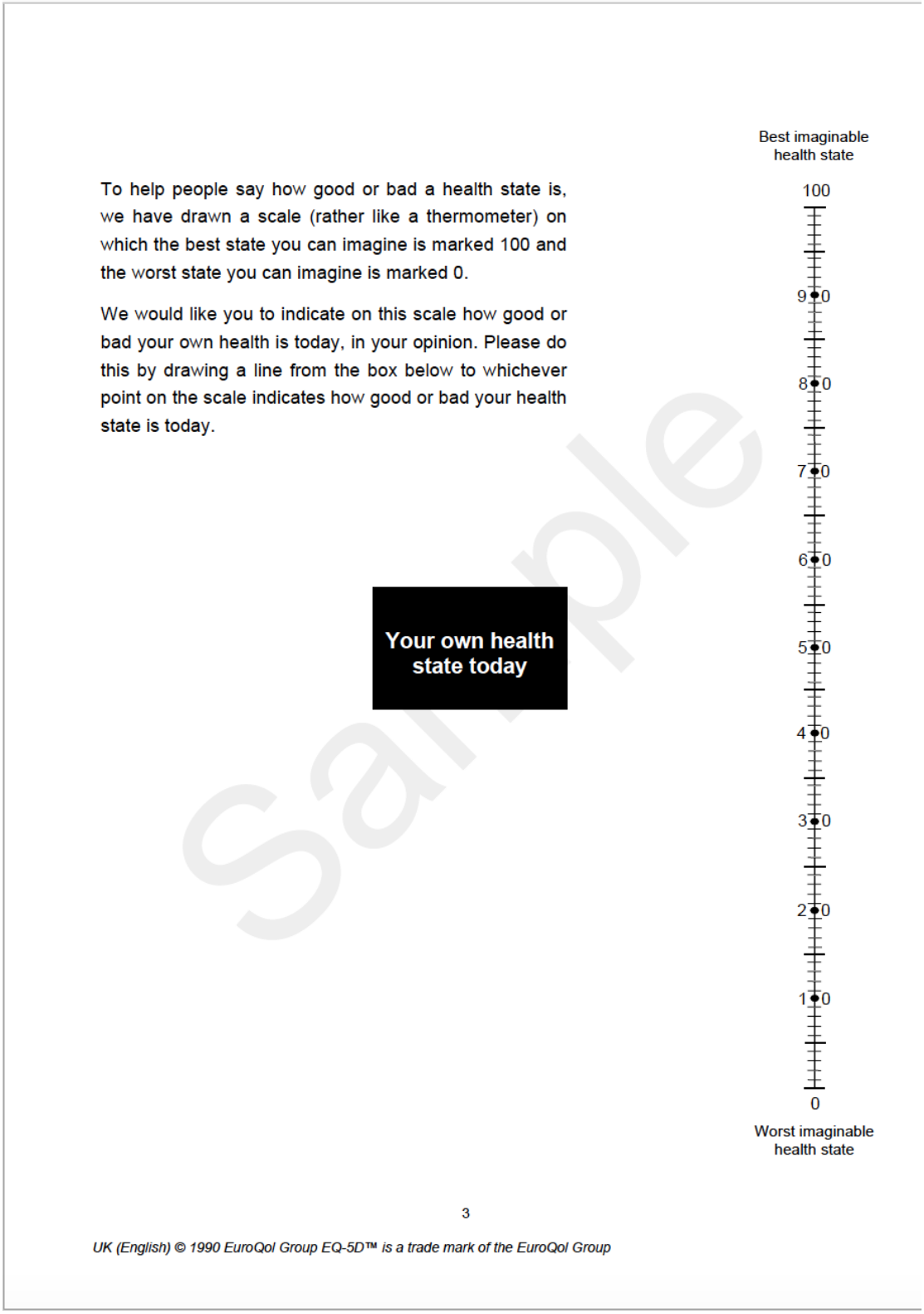
Anxiety / Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

(b)



A key advantage of the EQ-5D is its ability to yield both a detailed health profile and a single summary utility value.

4.4 Brief overview of health-related quality of life

4.4.1 Quality of life adjusted years

Health organisations such as the National Institute for Health and Care Excellence (NICE) lists the following as the number one principle on their charter: "to help health, public health and social care professionals deliver the best possible care within the resources available". In order to achieve this and consequently standardise healthcare, NICE utilises the health technology assessment (HTA) programme to identify treatments that should be made available across England and Wales. These evidence-based recommendations provide the most cost and clinically effective options for clinicians, across a multitude of diseases and conditions from relatively benign to life-threatening, across all specialties. Apart from clinical parameters, health-related quality of life (HRQoL) is a key measure of the level of well-being and is associated with current health state. This usually incorporates a multidimensional concept which includes physical, emotional & psychological aspects of illness. Therefore, these factors must also be considered before any intervention is assessed to provide holistic therapeutic effect, though it may be argued that these are very difficult to objectively and appropriately assess. Hence numerous HTA bodies are tasked with the challenge of translating medical interventions, health strategies and drug costs against life expectancy and health benefits. As a result, the use of quality-adjusted life years (QALYs) has become an indispensable tool and integral to this process of cost-benefit analysis.

Health-related quality of life collected from patients is used to calculated quality-adjusted life years (QALYs), which are in turn used to assess and compare the effectiveness and value of any given medical intervention. This involves assessing how long patients are expected to live and the impact on quality of life with a certain treatment. Life has two dimensions: quantity and quality, therefore QALY include both of these dimensions – one QALY equates to one year in perfect health. Thus, by combining these factors into a single measure, health economists may identify how much a certain intervention will prolong a patient's life and its contribution towards improving quality of life. As a result QALYs are considered particularly useful for health economists and are recommended by organisations such as NICE as a standard measure of benefit (Ogden 2017) of new treatments against existing baselines. This allows us to compare cost-benefit across diseases of different specialties where interventions with a lower cost per QALY are preferred and given more economic health distribution.

In theory, one year of perfect health (physical, mental and social well-being and not the absence of disease alone) is equal to one QALY (Ogden 2017). If health is impaired for a year the utility value (or quality of life) has a value between 0-1, where 0 = death. Utility values below 0, though uncommon, are also possible i.e. subjects experience quality of life that is worse than death through either a terminal illness or severe distress. By multiplying years of life with utility value (or QoL) QALYs may be calculated.

Quality of life is often measured across numerous clinical trials, which is important from an efficacy standpoint. However, few are able to generate the relevant information for economists as cost-utility analysis can only be deducted from utility measures, which are able to produce the index values needed to generate QALYs. The NICE prefers simple generic questionnaires such as the EQ-5D as it has five dimensions of health and may be used across different diseases. Nevertheless, due to the broad nature of generic measures, including the EQ-5D, there is less relevance to patients with a specific illness. Conversely, disease-specific measures are more responsive to change and user-friendly for patients (Krahn et al. 2007). As a result, occasionally both generic and disease-specific measures are used in tandem.

4.4.2 Utility measures and utility values

There are two main components of utility measurement, namely:

a) Establishing and defining a set of health states of interest
b) Assigning value to said health states (i.e. measuring how strongly each health state is preferred)

These components may be applied using two methods (Szende and Schaefer 2006): (i) direct measurement; which is commonly used for disease-specific health states (ii) indirect measurement; which may be performed by conducting algorithms for disease-specific preference-based or generic measures, or by mapping a disease or specialty-specific questionnaire (e.g. the DLQI) on to a generic measure (e.g. EQ-5D).

Several factors must be considered with direct measurement: most notably health dimensions or attributes (of which may often be up to nine (Miller 1956) such as physical/social functionality, symptomology and psychological well-being. It is important that these correspond to patient outcomes as together they form 'health state' descriptions for specific diseases. Though in an ideal scenario these must originate directly from patient experience,

often clinicians or expert opinions are used in order to save time and cost. These health states must be assigned a 'utility valuation' of which there are several methods: time trade-off (TTO), standard gamble (SG), rating scales, ratio scaling, equivalence technique and person trade-off.

Standard Gamble (Neumann et al. 1953) is an oft-used method whereby patients are asked to choose between two outcomes: one worse and one better than their existing health-state. Patients are asked to choose at what probability of a better outcome would they choose to go for the 'risky' option as opposed to remaining in their existing health-state. One of the criticisms of this approach is that it is often dependent on the risk behaviour of respondents, where patients with less of a risk-seeking behaviour would produce higher utilities compared to those with risk-seeking tendencies (Torrance et al. 1995). The TTO method elicits how much (often in years) of their life subjects are willing to sacrifice in order to avoid their existing health-state. For example, if a patient suffering with atopic dermatitis were to be given the option of living 10 years in their existing poor health-state or the maximum reduced number of years where the said health state may be avoided, an answer of 7 years would result in a utility score of 0.7. Though there is discussion and differences of opinion on the lifetime duration utilised for TTO studies (Arnesen and Trommald 2005), the element of risk is less of an issue compared to SG. Rating scales use a visual analogue scale (VAS) wherein subjects rate various health states across a single line with death and best possible health at either end, the intervals reflecting the perceived differences between health states. Though this process generates values rather than utilities and is devoid of aspects of choice under uncertainty, it has been argued its empirical performance is superior to both SG and TTO (Parkin and Devlin 2006).

Health economists prefer the use of choice-based methods such as SG or TTO over VAS given their grounding in economic theory (Tolley 2009). However, the SG method may be more time-consuming and the concept of probabilities is often challenging for subjects to comprehend. For this reason, the TTO option is the most commonly utilised method by economists, though the concept of 'trade-off' still proves to be difficult for users.

There are four main methods of obtaining utility values using HRQoL profile scores (Mortimer and Segal 2008): (i) transfer to utility, where regression is performed on the summary scores of the base measure on to the end target measure, (ii) direct revaluation, where weights are assigned to set health states in the base measure, (iii) response mapping, where subject responses to questions in the end measure are predicted using logistic regression, and (iv) effect size translation, where the standard deviation (SD) for the start measure is estimated,

allowing the calculation of a 'QALY-weights per SD' conversion factor. Method (i), transfer to utility, is the most commonly used approach in the literature (Mortimer and Segal 2008). It is also worth noting that mapping is considered less ideal than using a utility measure in the first instance as the accuracy of estimates is unpredictable (Brazier et al. 2010). However, mapping is still considered to be the most practical solution due to its ease and economical superiority ensuring that mapping research remains extremely pertinent, particularly amongst health economists.

4.5 Mapping methodology

4.5.1 What is mapping?

National Institute for Health and Care Excellence (NICE) defines mapping as 'the development and use of a model or algorithm to predict utility values using data on other indicators or measures of health' (Longworth and Rowen 2011). Regression is used to 'map' utility values of the target measure from the scores on the base measure, which have been obtained from a group of subjects. This technique may be particularly useful in studies where descriptive HRQoL scores have been collected and researchers need to derive utility values. Mapping is more likely to be successful where there is a conceptual overlap between the two measures (Longworth and Rowen 2011). This is the case for the DLQI and EQ-5D, for which many studies have reported a strong association (Shikiar et al. 2003; Scalone et al. 2006; Radtke et al. 2009; Matusiak et al. 2010; Cortesi et al. 2011; Hjortsberg et al. 2011).

4.5.2 Previous work & the ideal model

Currie and Conway (2007) derived a mapping model to convert DLQI summary scores into EQ-5D utility values. The following equation was derived from their work:

EQ-5D utility score = 0.956 – [0.02548 x (DLQI total score)]

However, several limitations have been identified with this equation (Woolacott et al. 2006). It was derived solely from psoriasis patients (n=96), therefore limiting its use in other skin diseases, as the impact on HRQoL can vary across different skin diseases (Rodgers et al. 2010). A maximum predicted value of 0.956 is below the actual maximum value of 1, which can have a significant impact on cost-utility data comparisons, given the small scale of the

EQ-5D. Furthermore, this equation was derived using the UK population scoring tariff, and may not be as suitable for non-UK based populations. Norlin et al. (2012) performed a simple bivariate regression with a larger psoriasis-only population of 2450 from a Swedish registry 'PsoReg', though the derived equation had a lower maximum predicted value of 0.8777 (EQ-5D = 0·8777 – 0·0196 DLQI). The modelling work also demonstrated strong correlations between DLQI and EQ-5D domains e.g. shopping/looking after the home correlated strongly with 'usual activities', respectively. Age and gender were significant factors in the multiple linear regression where EQ-5D was regressed against various DLQI items as well as age and gender. Finally, Blome et al. (2013) hypothesised that including more predictors for psoriasis patients would improve the model fit and address the unexplained variance identified by the two aforementioned studies. Bivariate and multivariate approaches were explored. For the bivariate method the DLQI was the only independent variable and univariate linear regression of EQ-5D VAS and global score was conducted on DLQI total score. The results showed the DLQI and EQ-5D VAS to be significantly linearly associated and the authors derived the following equation: EQ-5D VAS (predicted) = 77.367 + DLQI global score x -1.493. However, upon cross-validation this equation produced an average difference of 15.21 +/- 11.76 VAS units (n=1844). In 56.72% of the patients the model over or under-predicted the VAS score by 15 units at most. The multivariate approach included the use of up to sixteen independent variables which were assumed to be associated to HRQoL, including the DLQI. Thirteen of these variables significantly correlated with EQ-5D VAS and global scores. PASI scores correlated the highest with EQ-5D VAS (r=0.24) and 'active arthritis' correlated highest with EQ-5D global score (r=0.20). Only four of the thirteen predictors were included in both EQ-5D VAS and global score models: DLQI, age, active arthritis and concomitant diseases, whereby age was the highest correlating regression coefficient after the DLQI. Prediction of VAS values were found to be more accurate than global scores: overall the model performed significantly better compared to the bivariate method ($p<0.001$). Using the coefficients identified by the multivariate linear regression of the EQ-5D VAS scores, the following algorithm was defined for the prediction of utility values:

EQ-5D VAS (predicted) = 93.002 + DLQI global score x -1.418 + PASI x -0.153 + active arthritis x -4.728 + concomitant disease x -3:563 + light/laser therapy x 2.252 + age x -0.256 + number of hospitalisations due to psoriasis x -1.104

Cross-validation of the multivariate algorithm demonstrated an average difference of 14.4 +/- 11.5 VAS units (n=1578) and the predicted vs. actual EQ-5D VAS correlation was r=0.518. In 39.2% of the patients the equation over or under-predicted by at least 15 VAS points. Due to the significant differences between actual and predicted utility scores using both methods, the

authors concluded that 'mapping of DLQI on EQ-5D in psoriasis patients will have substantial limitations in validity and clinical relevance'. The methodology employed by Blome et al. (2013) was more robust than the approaches by Currie and Conway (2007) and Norlin et al. (2012) given the larger sample size, multivariate regression, external sample cross-validation and multiple predictor variables. However, the selection of variables could arguably be considered arbitrary and the final algorithm, like the previous mapping endeavours, only examined global EQ-5D and DLQI scores. Furthermore, the suggested equation is quite complex and often these variables are not immediately available to researchers.

As such, it was imperative an improved model was developed with a larger and wide-reaching population base using a different mapping approach. Previous modelling work has been limited by sample size, mapping methodology, skin conditions studied or geographic location, indicating that the ideal algorithm for deriving utility values from HRQoL data must overcome these challenges. Therefore, a pan-European dataset of considerable size with EQ-5D, DLQI and socio-demographic data of patients suffering from various dermatological conditions would be an ideal starting point for deriving an efficient model with high predictive ability.

4.5.3 Patient database used to derive models

The patient dataset (n = 4010) was accessed from an international multicentre observational cross-sectional study examining the association between depressive symptoms and dermatological conditions ranging from benign and malignant skin lesions to chronic inflammatory diseases such as psoriasis and lupus erythematous (Dalgard et al. 2015). These patients attended the outpatient dermatology clinics at various Dermatology Outpatient Clinics across Europe between 2011 and 2013. Each participant was examined clinically and the main diagnosis (and if necessary a secondary one) was recorded. Patients completed several questionnaires, amongst which were the DLQI, EQ-5D and socio-demographic information. Though a majority of the recruitment was completed prior to the commencement of this modelling study, further recruitment was necessary as part of the original study, and is explained in detail in the subsequent section.

4.5.4 Scoring the DLQI

If any question for the DLQI was left unanswered, it would be scored zero as per the questionnaire's instructions for use (Finlay 2020) and would be added to the remaining scores of the questionnaire expressed out of 30. Question 7 of the DLQI has two parts, though for ease of analysis these were combined in to one score.

The process for developing models underwent several refinements and adaptations, which shall be highlighted in the proceeding sections. An overview of the sociodemographic data is shown in Table 4.1 below.

Table 4.1 Sociodemographic data for the complete dataset

		No. of patients		
Country	Belgium	222		
	Denmark	247		
	France	116		
	Germany	254		
	Hungary	171		
	Italy	517		
	Netherlands	209		
	Norway	468		
	Poland	247		
	Russia	269		
	Spain	274		
	Turkey	280		
	UK	268		
Most common diagnoses	Psoriasis	484		
	Eczema	239		
	Acne	185		
		No. of patients	*Average age (years, range)*	
	All subjects	3542	46.29 (18-95)	
Sex	Male (n)	1558	47.76 (18-92)	
	Female (n)	1984	45.14 (18-95)	
		Average score across study population		
Average DLQI score*		6.69		
EQ-5D Domain (no. of patients)		No problems	Some problems	Extreme problems
Mobility		2692	839	11
Self-care		3162	372	8
Usual activities		2615	874	53
Pain or discomfort		1604	1739	199
Anxiety or depressed		1954	1431	157

Footnote: *DLQI total score range is 0-30, 0 indicating no impairment and 30 indicating maximum impairment of quality of life.

4.5.5 Ethical considerations

Data from subjects from a previously conducted study (Dalgard et al. 2015) was utilised for the mapping process. This was a European Multicentre study on depression, anxiety, quality of life and attachment among adult patients with common skin disorders, which utilised both the DLQI and EQ5D measures.

However, the European centres failed to provide Dalgard et al. (2015) with withdrawal numbers. As a result, every centre was required to recruit 25 extra patients to allow withdrawal and dropout rates to be extrapolated. Unfortunately, the previous sub-investigator at Cardiff had declared the study closed, and therefore I had to apply for ethical permission as a brand new study (Ref: 13/WA/0363, Appendix XXI), which was extremely challenging and time-consuming. The South Wales Research Ethics Committee. had to be convinced that this extra recruitment was necessary, which created a significant delay in commencement, as the modelling database would not be available until the central study was completed and in the process of publication. The recruitment was completed within a few months allowing the modelling work to proceed.

Ethics for the purpose of the mapping project was not deemed necessary, as retrospective data were utilised.

Chapter 5: Development of the final ordinal logistic regression model for mapping of the DLQI scores to utility values

5.1 Introduction

Due to the complex evolution of the methodology of this project, the various steps towards developing the final model will be described as a narrative in this chapter. Given the nature of the modelling, adjustments often had to be made to the way data were approached and analysed. Thus, several changes to the methodology were implemented throughout the process to achieve optimal results.

5.2 Method one: the forward stepwise variable selection method and predicted response categories

The patient dataset (n= 4010) (Dalgard et al. 2015) was randomly split into separate estimation (2003 patients) and validation (2007 patients) sets using the random number generator within SPSS version 22. Cases with data missing in any of the DLQI or EQ5D variables were removed. The estimation set was used to derive the mapping model and conduct 'internal validation', whilst the 'out-of-sample' validation set was utilised for 'external validation' of the fitted model. Following validation, the model was fitted to the complete dataset (4010 patients minus deleted cases with missing data) to improve its overall accuracy. The process of 'internal' and 'external' validation was repeated several times as the mapping methodology was refined to obtain the final model.

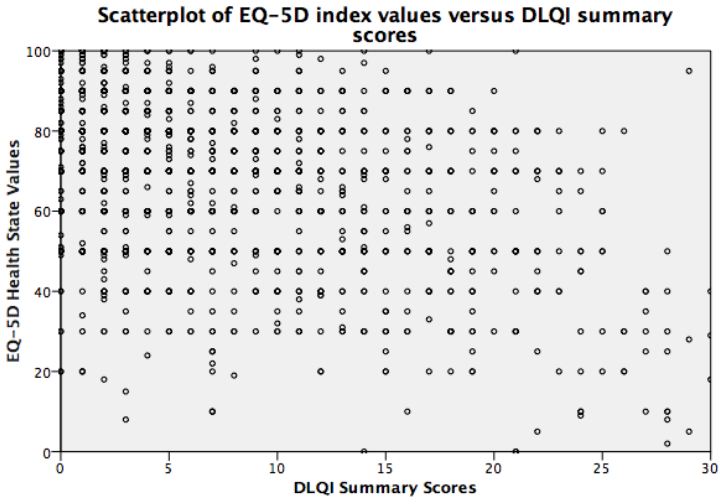
5.2.1 Forward stepwise variable selection

A series of ordinal logistic regressions were fitted for each of the five EQ-5D dimensions against the ten individual items of the DLQI using SPSS version 22. Forward stepwise variable selection was employed to select the most significant DLQI predictors for each EQ-5D dimension. Selection was based on twice the change in the log likelihood, comparing this to the chi-squared distribution on 3 degrees of freedom (since there are 4 levels for each of the DLQI items) and obtaining the associated p-values. Forward selection was continued until there were no further significant predictors identified; a value of 0.05 was chosen as the criterion for non-significance.

5.2.2 Results of forward variable selection

There was no correlation between the DLQI and EQ-5D total scores (Figure 5.1) – as demonstrated in previous studies where results have not been ideal (Currie and Conway 2007). In contrast, ordinal logistic regression is ideal as it includes the ordinal nature of DLQI data, thereby allowing 'weight' to be applied to each DLQI item.

Figure 5.1 Scatterplot of total DLQI summary scores and EQ-5D health state values



Ten series of OLR were conducted to determine the most significant DLQI predictors (Tables 5.1-5.10). This would allow the identification of the DLQI items with the heaviest influence on the final mapping data.

Table 5.1a -2 Log Likelihood (-2LL) Model Fitting Information from Series One of ordinal regressions (single-predictor), using EQ-5D dimensions as dependent variables and individual DLQI items as predictors.

EQ-5D Dimension	Model fitting information: Chi-squared value (p-value)									
	DLQI 1	**DLQI 2**	**DLQI 3**	**DLQI 4**	**DLQI 5**	**DLQI 6**	**DLQI 7**	**DLQI 8**	**DLQI 9**	**DLQI 10**
Mobility	51.985 (0.000)	11.342 (0.010)	68.894 (0.000)	33.442 (0.000)	61.777 (0.000)	41.263 (0.000)	61.752 (0.000)	29.467 (0.000)	13.199 (0.004)	57.242 (0.000)
Self-care	78.540 (0.000)	45.072 (0.000)	107.996 (0.000)	56.160 (0.000)	89.510 (0.000)	48.033 (0.000)	80.866 (0.000)	61.062 (0.000)	32.817 (0.000)	127.298 (0.000)
Usual Activities	139.014 (0.000)	65.720 (0.000)	191.228 (0.000)	94.396 (0.000)	168.300 (0.000)	124.371 (0.000)	143.155 (0.000)	94.699 (0.000)	74.751 (0.000)	169.168 (0.000)
Pain/Discomfort	363.103 (0.000)	140.328 (0.000)	202.038 (0.000)	153.986 (0.000)	184.383 (0.000)	168.390 (0.000)	80.723 (0.000)	154.615 (0.000)	110.852 (0.000)	174.400 (0.000)
Anxiety/Depression	122.984 (0.000)	211.523 (0.000)	161.156 (0.000)	91.885 (0.000)	169.913 (0.000)	59.388 (0.000)	127.625 (0.000)	151.745 (0.000)	95.348 (0.000)	103.146 (0.000)

Table 5.1b The most significant DLQI item, x, for each EQ-5D dimension as obtained from Series One regressions (single- predictor).

EQ-5D Dimension	Most Significant DLQI Item, *x* (P-value <0.010 considered significant)
Mobility	3
Self-care	10
Usual activities	3
Pain/discomfort	1
Anxiety/depression	2

Table 5.2a -2 Log Likelihood (-2LL) Model Fitting Information from Series Two regressions (two-predictor), using EQ-5D dimensions as dependent variables and a combination of two DLQI items, x + a second item of the DLQI, as predictors. x is the most significant DLQI predictor for that dimension from the Series One models.

EQ-5D Dimension	Model fitting information: Chi-squared value (p-value)									
	***x* + DLQI 1**	***x* + DLQI 2**	***x* + DLQI 3**	***x* + DLQI 4**	***x* + DLQI 5**	***x* + DLQI 6**	***x* + DLQI 7**	***x* + DLQI 8**	***x* + DLQI 9**	***x* + DLQI 10**
Mobility	83.161 (0.000)	74.724 (0.000)	-	72.479 (0.000)	81.380 (0.000)	81.700 (0.000)	93.683 (0.000)	73.169 (0.000)	68.778 (0.000)	86.531 (0.000)
Self-care	148.616 (0.000)	136.340 (0.000)	158.500 (0.000)	136.235 (0.000)	147.749 (0.000)	132.930 (0.000)	149.547 (0.000)	137.791 (0.000)	129.016 (0.000)	-
Usual	221.	199.	-	201.	216.	222.	223.	203.	210.	247.

Activities	595 (0.000)	459 (0.000)		084 (0.000)	985 (0.000)	856 (0.000)	137 (0.000)	099 (0.000)	249 (0.000)	580 (0.000)
Pain/Discomfort	-	367.474 (0.000)	394.526 (0.000)	398.780 (0.000)	395.443 (0.000)	410.022 (0.000)	365.912 (0.000)	387.822 (0.000)	380.509 (0.000)	406.617 (0.000)
Anxiety/Depression	237.752 (0.000)	-	251.955 (0.000)	220.889 (0.000)	243.919 (0.000)	220.255 (0.000)	252.862 (0.000)	247.234 (0.000)	246.396 (0.000)	245.193 (0.000)

Table 5.2b Two-predictor combinations of DLQI items showing the most significant combination within that group.

EQ-5D Dimension	Most Significant combinations of DLQI Items (Series Two)	Chi-square difference from the most significant item addition in current regression series, from the most significant item combination in previous regression series (P-value <0.010 considered significant)
Mobility	3 + 7	93.682896 - 68.894390 = 24.788506 (< 0.00001)
Self-care	10 + 3	158.499712 - 127.298293 = 31.201419 (< 0.00001)
Usual activities	3 + 10	247.579638 - 191.227997 = 56.351641 (< 0.00001)
Pain/discomfort	1 + 6	410.021858 - 363.102725 = 46.919133 (< 0.00001)
Anxiety/depression	2 + 7	252.862407 - 211.523043 = 41.339364 (< 0.00001)

Table 5.3a -2 Log Likelihood (-2LL) Model Fitting Information from Series Three regressions (three-predictor), using EQ-5D dimensions as dependent variables and a combination of three DLQI items, ***x* + x2** and a third item of the DLQI, as predictors. **x2** is the most significant DLQI predictor for that dimension from the Series Two models.

EQ-5D Dimension	**Model fitting information: Chi-squared value (p-value)**									
	***x* + x2 + DLQI 1**	***x* + x2 + DLQI 2**	***x* + x2 + DLQI 3**	***x* + x2 + DLQI 4**	***x* + x2 + DLQI 5**	***x* + x2 + DLQI 6**	***x* + x2 + DLQI 7**	***x* + x2 + DLQI 8**	***x* + x2 + DLQI 9**	***x* + x2 + DLQI 10**
Mobility	105.077 (0.000)	101.380 (0.000)	-	97.444 (0.000)	105.343 (0.000)	105.327 (0.000)	-	95.860 (0.000)	95.849 (0.000)	108.668 (0.000)
Self-care	165.665 (0.000)	163.997 (0.000)	-	165.010 (0.000)	163.634 (0.000)	159.979 (0.000)	169.047 (0.000)	164.817 (0.000)	160.201 (0.000)	-
Usual Activities	265.796 (0.000)	251.084 (0.000)	-	251.281 (0.000)	260.045 (0.000)	268.227 (0.000)	268.724 (0.000)	249.195 (0.000)	253.870 (0.000)	-
Pain/Discomfort	-	408.707 (0.000)	421.758 (0.000)	430.402 (0.000)	417.967 (0.000)	-	407.498 (0.000)	418.104 (0.000)	412.633 (0.000)	431.432 (0.000)
Anxiety/Depression	267.406 (0.000)	-	269.533 (0.000)	256.629 (0.000)	266.686 (0.000)	251.424 (0.000)	-	270.880 (0.000)	276.911 (0.000)	269.592 (0.000)

Table 5.3b Three-predictor combinations of DLQI items showing the most significant combination within that group.

EQ-5D Dimension	Most Significant combinations of DLQI Items (Series Three)	Chi-square difference from the most significant item addition in current regression series, from the most significant item combination in previous regression series (P-value <0.010 considered significant)
Mobility	3 + 7 + 10	108.667867 - 93.682896 = 14.984971 (0.000108)
Self-care	10 + 3 + 7	169.047368 - 158.499712 = 10.547656 (0.001164)
Usual activities	3 + 10 + 7	268.723910 - 247.579638 = 21.144272 (< 0.00001)
Pain/discomfort	1 + 6 + 10	431.432198 - 410.021858 = 21.41034 (< 0.00001)
Anxiety/depression	2 + 7 + 9	276.910533 - 252.862407 = 24.048126 (< 0.00001)

Table 5.4a -2 Log Likelihood (-2LL) Model Fitting Information from Series Four regressions (four-predictor), using EQ-5D dimensions as dependent variables and a combination of four DLQI items, ***x* + x2+ x3** and a fourth item of the DLQI, as predictors. **x3** is the most significant DLQI predictor for that dimension from the Series Three models.

EQ-5D Dimension	**Model fitting information: Chi-squared value (p-value)**									
	***x* + x2+ x3 + DLQI 1**	***x* + x2+ x3 + DLQI 2**	***x* + x2+ x3 + DLQI 3**	***x* + x2+ x3 + DLQI 4**	***x* + x2+ x3 + DLQI 5**	***x* + x2+ x3 + DLQI 6**	***x* + x2+ x3 + DLQI 7**	***x* + x2+ x3 + DLQI 8**	***x* + x2+ x3 + DLQI 9**	***x* + x2+ x3 + DLQI 10**
Mobility	116.940 (0.000)	119.461 (0.000)	-	110.476 (0.000)	118.687 (0.000)	118.636 (0.000)	-	110.610 (0.000)	109.371 (0.000)	-
Self-care	175.248 (0.000)	174.738 (0.000)	-	175.167 (0.000)	173.963 (0.000)	171.328 (0.000)	-	175.086 (0.000)	172.648 (0.000)	-
Usual Activities	280.610 (0.000)	268.579 (0.000)	-	272.289 (0.000)	279.378 (0.000)	286.554 (0.000)	-	269.409 (0.000)	276.838 (0.000)	-
Pain/Discomfort	-	428.673 (0.000)	436.514 (0.000)	441.965 (0.000)	435.606 (0.000)	-	432.662 (0.000)	433.450 (0.000)	429.074 (0.000)	-

Anxiety/Depression	286.093 (0.000)	-	288.998 (0.000)	279.892 (0.000)	284.468 (0.000)	272.260 (0.000)	-	282.675 (0.000)	-	286.879 (0.000)

Table 5.4b Four-predictor combinations of DLQI items showing the most significant combination within that group.

EQ-5D Dimension	Most Significant combinations of DLQI Items (Series Four)	Chi-square difference from the most significant item addition in current regression series, from the most significant item combination in previous regression series (P-value <0.010 considered significant)
Mobility	3 + 7 + 10 + 2	119.460603 - 108.667867 = 10.792736 (0.001)
Self-care	10 + 3 + 7 + 1	175.248251 - 169.047368 = 6.200883 (0.013)
Usual activities	3 + 10 + 7 + 6	286.553692 - 268.723910 = 17.829782 (0.000024)
Pain/discomfort	1 + 6 + 10 + 4	441.964904 - 431.432198 = 10.532706 (0.0012)
Anxiety/depression	2 + 7 + 9 + 3	288.998351 - 276.910533 = 12.087818 (0.00051)

Table 5.5a -2 Log Likelihood (-2LL) Model Fitting Information from Series Five regressions (five-predictor), using EQ-5D dimensions as dependent variables and a combination of five DLQI items, ***x* + x2+ x3 +x4** and a fifth item of the DLQI, as predictors. **x4** is the most significant DLQI predictor for that dimension from the Series Four models.

EQ-5D Dimension	**Model fitting information: Chi-squared value (p-value)**									
	***x* + *x2*+ *x3* + *x4* + DLQI 1**	***x* + *x2*+ *x3* + *x4* + DLQI 2**	***x* + *x2*+ *x3* + *x4* + DLQI 3**	***x* + *x2*+ *x3* + *x4* + DLQI 4**	***x* + *x2*+ *x3* + *x4* + DLQI 5**	***x* + *x2*+ *x3* + *x4* + DLQI 6**	***x* + *x2*+ *x3* + *x4* + DLQI 7**	***x* + *x2*+ *x3* + *x4* + DLQI 8**	***x* + *x2*+ *x3* + *x4* + DLQI 9**	***x* + *x2*+ *x3* + *x4* + DLQI 10**
Mobility	133.193 (0.000)	-	-	121.651 (0.000)	136.376 (0.000)	129.259 (0.000)	-	121.452 (0.000)	119.606 (0.000)	-
Self-care	-	182.455 (0.000)	-	182.002 (0.000)	179.770 (0.000)	177.028 (0.000)	-	182.824 (0.000)	179.971 (0.000)	-
Usual Activities	294.701 (0.000)	287.829 (0.000)	-	291.580 (0.000)	290.738 (0.000)	-	-	286.714 (0.000)	290.205 (0.000)	-
Pain/Discomfort	-	439.182 (0.000)	444.281 (0.000)	-	442.557 (0.000)	-	445.942 (0.000)	442.440 (0.000)	438.882 (0.000)	-

Anxiety/Depression	295.098 (0.000)	-	-	291.128 (0.000)	290.796 (0.000)	284.491 (0.000)	-	294.013 (0.000)	-	294.930 (0.000)

Table 5.5b Five-predictor combinations of DLQI items showing the most significant combination within that group.

EQ-5D Dimension	Most Significant combinations of DLQI Items (Series Five)	Chi-square difference from the most significant item addition in current regression series, from the most significant item combination in previous regression series (P-value <0.010 considered significant)
Mobility	3 + 7 + 10 + 2 + 5	136.376031 - 119.460603 = 16.915428 (0.000039)
Self-care	10 + 3 + 7 + 1 + 8	182.823801 - 175.248251 = 7.57555 (0.006)
Usual activities	3 + 10 + 7 + 6 + 1	294.700869 - 286.553692 = 8.147177 (0.0043)
Pain/discomfort	1 + 6 + 10 + 4 + 7	445.941542 - 441.964904 = 3.976638 (0.046)
Anxiety/depression	2 + 7 + 9 + 3 + 1	295.098288 - 288.998351 = 6.099937 (0.014)

Table 5.6a -2 Log Likelihood (-2LL) Model Fitting Information from Series Six regressions (six-predictor), using EQ-5D dimensions as dependent variables and a combination of five DLQI items, ***x + x2+ x3 + x4 + x5*** and a sixth item of the DLQI, as predictors. **x5** is the most significant DLQI predictor for that dimension from the Series Five models.

EQ-5D Dimension	**Model fitting information: Chi-squared value (p-value)**									
	x + x2+ x3 + x4 + x5 + DLQI 1	***x + x2+ x3 + x4 + x5 + DLQI 2***	***x + x2+ x3 + x4 + x5 + DLQI 3***	***x + x2+ x3 + x4 + x5 + DLQI 4***	***x + x2+ x3 + x4 + x5 + DLQI 5***	***x + x2+ x3 + x4 + x5 + DLQI 6***	***x + x2 + x3 + x4 + x5 + DLQI 7***	***x + x2+ x3 + x4 + x5 + DLQI 8***	***x + x2+ x3 + x4 + x5 + DLQI 9***	***x + x2+ x3 + x4 + x5 + DLQI 10***
Mobility	147.634 (0.000)	-	-	137.714 (0.000)	-	141.335 (0.000)	-	136.724 (0.000)	133.309 (0.000)	-
Self-care	-	189.605 (0.000)	-	187.070 (0.000)	186.785 (0.000)	183.797 (0.000)	-	-	189.832 (0.000)	-
Usual Activities	-	301.084	-	300.076	298.064	-	-	295.567	298.021	-

		(0.000)		(0.000)	(0.000)			(0.000)	(0.000)	
Pain/Discomfort	-	443.749 (0.000)	450.409 (0.000)	-	447.130 (0.000)	-	-	446.496 (0.000)	442.771 (0.000)	-
Anxiety/Depression	-	-	-	297.850 (0.000)	296.551 (0.000)	291.037 (0.000)	-	299.806 (0.000)	-	300.211 (0.000)

Table 5.6b Six-predictor combinations of DLQI items showing the most significant combination within that group.

EQ-5D Dimension	Most Significant combinations of DLQI Items (Series Six)	Chi-square difference from the most significant item addition in current regression series, from the most significant item combination in previous regression series (P-value <0.010 considered significant)
Mobility	3 + 7 + 10 + 2 + 5 + 1	147.633784 - 136.376031 = 11.257753 (0.0008)
Self-care	10 + 3 + 7 + 1 + 8 + 9	189.832414 - 182.823801 = 7.008613 (0.008)
Usual activities	3 + 10 + 7 + 6 + 1 + 2	301.084163 - 294.700869 = 6.383294 (0.012)
Pain/discomfort	1 + 6 + 10 + 4 + 7 + 3	450.409205 - 445.941542 = 4.467663 (0.035)
Anxiety/depression	2 + 7 + 9 + 3 + 1 + 10	300.211357 - 295.098288 = 5.113069 (0.024)

Table 5.7a -2 Log Likelihood (-2LL) Model Fitting Information from Series Seven regressions (seven-predictor), using EQ-5D dimensions as dependent variables and a combination of six DLQI items, ***x + x2+ x3 + x4 + x5 + x6*** and a seventh item of the DLQI, as predictors. **x6** is the most significant DLQI predictor for that dimension from the Series Six models.

EQ-5D Dimension	**Model fitting information: Chi-squared value (p-value)**									
	x + x2 + x3 + x4 + x5 + x6 + DLQI 1	***x + x2+ x3 + x4 + x5 + x6 + DLQI 2***	***x + x2 + x3 + x4 + x5 + x6 + DLQI 3***	***x + x2+ x3 + x4 + x5 + x6 + DLQI 4***	***x + x2+ x3 + x4 + x5 + x6 + DLQI 5***	***x + x2+ x3 + x4 + x5 + x6 + DLQI 6***	***x + x2 + x3 + x4 + x5 + x6 + DLQI 7***	***x + x2+ x3 + x4 + x5 + x6 + DLQI 8***	***x + x2+ x3 + x4 + x5 + x6 + DLQI 9***	***x + x2 + x3 + x4 + x5 + x6 + DLQI 10***
Mobility	-	-	-	148.758 (0.000)	-	151.080 (0.000)	-	146.974 (0.000)	144.170 (0.000)	-
Self-care	-	196.821 (0.000)	-	194.442 (0.000)	192.899 (0.000)	192.006 (0.000)	-	-	-	-
Usual Activities	-	-	-	306.553	307.199	-	-	301.621	304.132	-

				(0.000)	(0.000)			(0.000)	(0.000)		
Pain/Discomfort	-	448.688 (0.000)	-	-	450.622 (0.000)	-	-	449.485 (0.000)	447.290 (0.000)	-	
Anxiety/Depression	-	-	-	304.350 (0.000)	301.395 (0.000)	296.439 (0.000)	-	305.431 (0.000)	-	-	

Table 5.7b Seven-predictor combinations of DLQI items showing the most significant combination within that group.

EQ-5D Dimension	Most Significant combinations of DLQI Items (Series Seven)	Chi-square difference from the most significant item addition in current regression series, from the most significant item combination in previous regression series (P-value <0.10 considered significant)
Mobility	3 + 7 + 10 + 2 + 5 + 1 + 6	151.079931 - 147.633784 = 3.446147 (0.063)
Self-care	10 + 3 + 7 + 1 + 8 + 9 + 2	196.820925- 189.832414 = 6.988511 (0.0082)
Usual activities	3 + 10 + 7 + 6 + 1 + 2 + 5	307.198539 - 301.084163 = 6.114376 (0.013)
Pain/discomfort	1 + 6 + 10 + 4 + 7 + 3 + 5	450.621994 - 450.409205 = 0.212789 (0.64)
Anxiety/depression	2 + 7 + 9 + 3 + 1 + 10 + 8	305.431355 - 300.211357 = 5.219998 (0.022)

Table 5.8a -2 Log Likelihood (-2LL) Model Fitting Information from Series Eight regressions (eight-predictor), using EQ-5D dimensions as dependent variables and a combination of seven DLQI items, ***x + x2+ x3 + x4 + x5 + x6 + x7*** and an eighth item of the DLQI, as predictors. **x7** is the most significant DLQI predictor for that dimension (where applicable) from the Series Seven models.

EQ-5D Dimension	**Model fitting information: Chi-squared value (p-value)**									
	x + x2 + x3 + x4 + x5 + x6 + x7 + DLQI 1	***x + x2 + x3 + x4 + x5 + x6 + x7 + DLQI 2***	***x + x2 + x3 + x4 + x5 + x6 + x7 + DLQI 3***	***x + x2+ x3 + x4 + x5 + x6 + x7 + DLQI 4***	***x + x2+ x3 + x4 + x5 + x6 + x7 + DLQI 5***	***x + x2+ x3 + x4 + x5 + x6 + x7 + DLQI 6***	***x + x2 + x3 + x4 + x5 + x6 + x7 + DLQI 7***	***x + x2+ x3 + x4 + x5 + x6 + x7 + DLQI 8***	***x + x2+ x3 + x4 + x5 + x6 + x7 + DLQI 9***	***x + x2 + x3 + x4 + x5 + x6 + x7 + DLQI 10***
Mobility	-	-	-	152.072 (0.000)	-	-	-	150.360 (0.000)	147.341 (0.000)	-
Self-care	-	-	-	201.247 (0.00	201.322 (0.00	199.168 (0.00	-	-	-	-

				0)	0)	0)					
Usual Activities	-	-	-	313.988 (0.000)	-	-	-	310.328 (0.000)	309.126 (0.000)	-	
Anxiety/Depression	-	-	-	309.175 (0.000)	305.509 (0.000)	301.414 (0.000)	-	-	-	-	

Table 5.8b Seven-predictor combinations of DLQI items showing the most significant combination within that group.

EQ-5D Dimension	Most Significant combinations of DLQI Items (Series Eight)	Chi-square difference from the most significant item addition in current regression series, from the most significant item combination in previous regression series (P-value <0.010 considered significant)
Mobility	3 + 7 + 10 + 2 + 5 + 1 + 6 + 4	152.071540 - 151.079931 = 0.991609 (0.319)
Self-care	10 + 3 + 7 + 1 + 8 + 9 + 2 + 5	201.322209 - 196.820925 = 4.501284 (0.034)
Usual activities	3 + 10 + 7 + 6 + 1 + 2 + 5 + 4	313.988167 - 307.198539 = 6.789628 (0.0092)
Anxiety/depression	2 + 7 + 9 + 3 + 1 + 10 + 8 + 4	309.174576 - 305.431355 = 3.743221 (0.053)

Table 5.9a -2 Log Likelihood (-2LL) Model Fitting Information from Series Nine regressions (nine-predictor), using EQ-5D dimensions as dependent variables and a combination of eight DLQI items, ***x + x2+ x3 + x4 + x5 + x6 + x7 + x8*** and a ninth item of the DLQI, as predictors. **x8** is the most significant DLQI predictor for that dimension (where applicable) from the Series Eight models.

EQ-5D Dimension	**Model fitting information: Chi-squared value (p-value)**									
	x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + DLQI 1	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + DLQI 2***	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + DLQI 3***	***x + x2+ x3 + x4 + x5 + x6 + x7 + x8 + DLQI 4***	***x + x2+ x3 + x4 + x5 + x6 + x7 + x8 + DLQI 5***	***x + x2+ x3 + x4 + x5 + x6 + x7 + x8 + DLQI 6***	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + DLQI 7***	***x + x2+ x3 + x4 + x5 + x6 + x7 + x8 + DLQI 8***	***x + x2+ x3 + x4 + x5 + x6 + x7 + x8 + DLQI 9***	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + DLQI 10***
Self-care	-	-	-	206.559 (0.000)	-	204.050 (0.000)	-	-	-	-
Usual Activities	-	-	-	-	-	-	-	316.216	315.332	-

								(0.000)	(0.000)		
Anxiety/Depression	-	-	-	-	309.657 (0.000)	304.898 (0.000)	-	-	-	-	

Table 5.9b Nine-predictor combinations of DLQI items showing the most significant combination within that group.

EQ-5D Dimension	Most Significant combinations of DLQI Items (Series Nine)	Chi-square difference from the most significant item addition in current regression series, from the most significant item combination in previous regression series (P-value <0.010 considered significant)
Self-care	10 + 3 + 7 + 1 + 8 + 9 + 2 + 5 + 4	206.559277 - 201.322209 = 5.237068 (0.022)
Usual activities	3 + 10 + 7 + 6 + 1 + 2 + 5 + 4 + 8	316.215997 - 313.988167 = 2.22783 (0.136)
Anxiety/depression	2 + 7 + 9 + 3 + 1 + 10 + 8 + 4 + 5	309.657434 - 309.174576 = 0.482858 (0.487)

Table 5.10a -2 Log Likelihood (-2LL) Model Fitting Information from Series Ten regressions (ten-predictor), using EQ-5D dimensions as dependent variables and a combination of nine DLQI items, ***x + x2+ x3 + x4 + x5 + x6 + x7 + x8 + x9*** and a tenth item of the DLQI, as predictors. **x9** is the most significant DLQI predictor for that dimension (where applicable) from the Series Nine models.

EQ-5D Dimension	**Model fitting information: Chi-squared value (p-value)**									
	x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + x9 + DLQI 1	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + x9 + DLQI 2***	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + x9 + DLQI 3***	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + x9 + DLQI 4***	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + x9 + DLQI 5***	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + x9 + DLQI 6***	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + x9 + DLQI 7***	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + x9 + DLQI 8***	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + x9 + DLQI 9***	***x + x2 + x3 + x4 + x5 + x6 + x7 + x8 + x9 + DLQI 10***
Self-care	-	-	-	-	-	209.315 (0.	-	-	-	-

	00 0)

Table 5.10b Ten-predictor combinations of DLQI items showing the most significant combination within that group.

EQ-5D Dimension	Most Significant combinations of DLQI Items (Series Ten)	Chi-square difference from the most significant item addition in current regression series, from the most significant item combination in previous regression series (P-value <0.010 considered significant)
Self-care	10 + 3 + 7 + 1 + 8 + 9 + 2 + 5 + 4 + 6	209.315475 - 206.559277 = 2.756198 (0.0969)

5.2.3 Conceptual correlations

There are strong conceptual correlations between the DLQI and EQ-5D and several key themes were significantly associated (i.e. $p<0.05$). The key concepts that apply to each DLQI item are thus: 'Symptoms and feelings' (Items 1 and 2), 'Daily activities' (Items 3 and 4), 'Leisure' (5 and 6), 'Work and school' (Item 7), 'Personal relationships' (Item 8 and 9), 'Treatment' (Item 10) (Finlay and Khan 1994).

For the 'Mobility' EQ-5D domain, DLQI items 3, 7 and 10 were most strongly correlated, which cover the concepts of 'daily activities', 'work and school' and 'treatment'. The 'Pain' domain was strongly correlated with almost all key concepts of the DLQI including items 1, 3, 6, 8, 9 and 10. It correlated most with Item 1 of the DLQI, in particular, which asks about pain and soreness of the patient's skin condition. The 'Self-care' domain correlated most strongly with item 10 (treatment), as well as items 1, 3 and 7. 'Usual activities' correlated strongly with item 3 (daily activities) as expected, as well as items 1, 5, 6, 7 and 10. Finally, the 'Anxiety' domain was most strongly correlated to item 2, which enquires about 'embarrassment' and whether patients feel 'self-conscious' due to their skin condition, as well as items 4, 5, 7, 9, 10. Overall, all ten DLQI items correlated strongly with the EQ-5D domains, re-emphasising the strong conceptual correlation between the two questionnaires.

Now that the most significant predictor combinations of the DLQI items (Table 5.11) were identified, they may be used in the ordinal models to predict EQ5D domain scores.

Table 5.11 All the significant predictor combinations of the DLQI items against each EQ-5D modality as derived from Tables 5.1-5.10.

EQ-5D Dimension	Most Significant combination of DLQI Items until no further significant items identified on regression models
Mobility	3 + 7 + 10 + 2 + 5 + 1 + 6
Self-care	10 + 3 + 7 + 1 + 8 + 9 + 2 + 5 + 4 + 6
Usual activities	3 + 10 + 7 + 6 + 1 + 2 + 5 + 4
Pain/discomfort	1 + 6 + 10 + 4 + 7 + 3
Anxiety/depression	2 + 7 + 9 + 3 + 1 + 10 + 8 + 4

5.2.4 Interpreting the ordinal model equations

Ordinal models may be utilised to produce a set of probabilities for each of the five possible outcome categories of the EQ-5D, as given by the following equations (Figure 5.2):

Figure 5.2 The ordinal logistic regression formulae to predict domain outcomes

$$P(Y=1) = \frac{1}{1+e^{(-a_1+b_1x_1+b_2x_2+\cdots+b_mx_m)}}$$

$$P(Y=2) = \frac{1}{1+e^{(-a_2+b_1x_1+b_2x_2+\cdots+b_mx_m)}} - P(Y=1)$$

$$P(Y=3) = 1 - P(Y=2) - P(Y=1)$$

In the above equation, 'Y' represents the outcome of any given EQ-5D domain ("mobility", "self-care", "usual activities", "pain/discomfort" or "anxiety/depression"). The outcome categories Y = 1, 2 and 3 represent the three possible responses for a given EQ-5D domain i.e. "no problems", "some problems" or "extreme problems" respectively. The x-variables are indicator variables derived from the scores on the selected DLQI items while the b's are the regression coefficients. The b's are essentially 'weights' attached to each indicator of each of the DLQI item scores and they are then used to calculate the estimated probabilities of each EQ-5D response. The model is based on the assumption that for each EQ-5D dimension there is an under-lying continuous 'latent' variable, for example measuring 'mobility'. The value of the linear combination $b_1x_1 + b_2x_2 + \cdots + b_mx_m$ provides a predicted score, Z, on this continuum. If we are to assume that these scores Z follow a logistic distribution then the OLR model follows from assuming that if $Z < a_1$, the subjects would record an outcome $Y = 1$, if $a_1 < Z < a_2$, they would record an outcome of $Y = 2$ and if $Z > a_2$ they would record an outcome $Y = 3$.

The SPSS v22 was used to automatically produce the three probabilities for any given EQ-5D domain and the relevant DLQI items. The model was initially tested on the derivation dataset as part of 'internal validation' as described below, followed by 'external validation' on the validation dataset.

5.2.5 Internal validation of the forward variable selection method: predicted response frequency

Following the series of OLR and stepwise selection, all the significant predictor DLQI items were fitted back in to the derivation set (internal validation) in SPSS v22. The model calculated a 'predicted response' for each EQ-5D domain response. In other words, for every domain, the response category (Y = 1, 2 or 3) with the highest probability was taken to be the predicted answer. The model calculated predicted probabilities from the actual DLQI item scores of individual patients. The total frequency of each predicted EQ-5D domain response was then summated and compared with the actual DLQI responses within the population.

For predicting response frequency, in the first instance patients' data with missing values were included (Tables 5.12 – 5.16) and then cases with missing EQ-5D and DLQI values were excluded (Tables 5.17 – 5.21), thereby providing more reliable results.

5.2.6 Internal validation before deleting cases with missing data from DLQI and EQ-5D variables

Table 5.12 Fitting the model for 'Mobility' in to the derivation data set: predicted category frequencies versus actual category frequencies

Mobility Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	1456 (72.5 %)	1755 (87.4 %)
'Some'	474 (23.6 %)	112 (5.6%)
'Extreme'	8 (0.4%)	0 (0%)
Missing Data	69 (3.4%)	140 (7%)

Table 5.13 Fitting the model for 'Self-care' in to the derivation data set: predicted category frequencies versus actual category frequencies

Self-care Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	1740 (86.7 %)	1805 (89.9 %)
'Some'	190 (9.5 %)	37 (1.8%)
'Extreme'	9 (0.4%)	0 (0%)
Missing Data	68 (3.4%)	8.2 (7%)

Table 5.14 Fitting the model for 'Usual Activities' into the derivation data set: predicted category frequencies versus actual category frequencies

Usual Activities Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	1422 (70.9 %)	1622 (89.9 %)
'Some'	493 (24.6 %)	239 (11.9%)
'Extreme'	25 (1.2%)	0 (0%)
Missing Data	67 (3.3%)	146 (7.3%)

Table 5.15 Fitting the model for 'Pain/discomfort' into the derivation data set: predicted category frequencies versus actual category frequencies

Pain/Discomfort Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	858 (42.8 %)	917 (45.7 %)
'Some'	969 (48.3 %)	957 (47.7%)
'Extreme'	110 (5.5%)	0 (0%)
Missing Data	70 (3.5%)	133 (6.6%)

Table 5.16 Fitting the model for 'Anxiety/Depression' into the derivation data set: predicted category frequencies versus actual category frequencies

Anxiety Depression Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	1060 (52.8 %)	1276 (63.6 %)
'Some'	793(39.5 %)	583 (29 %)
'Extreme'	79 (3.9%)	0 (0%)
Missing Data	75 (3.7%)	148 (7.4%)

5.2.7 Internal validation after deleting cases with missing data from DLQI and EQ-5D variables

Table 5.17 Fitting the model for 'Mobility' into the derivation data set: predicted category frequencies versus actual category frequencies

Mobility Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	1374 (75.8 %)	1705 (94 %)
'Some'	433 (23.9 %)	108 (6%)
'Extreme'	6 (0.3%)	0 (0%)

Table 5.18 Fitting the model for 'Self-care' into the derivation data set: predicted category frequencies versus actual category frequencies

Self-care Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	1627 (89.7 %)	1778 (98 %)
'Some'	180 (9.9 %)	36 (2%)
'Extreme'	7 (0.4%)	0 (0%)

Table 5.19 Fitting the model for 'Usual Activities' into the derivation data set: predicted category frequencies versus actual category frequencies

Usual Activities Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	1343 (74.0 %)	1579 (86.9 %)
'Some'	450 (24.8 %)	237 (13.1%)
'Extreme'	23 (1.3%)	0 (0%)

Table 5.20 Fitting the model for 'Pain/Discomfort' into the derivation data set: predicted category frequencies versus actual category frequencies

Pain/Discomfort Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	817 (45.0 %)	925 (51 %)
'Some'	899 (49.6 %)	889 (49%)
'Extreme'	98 (5.4%)	0 (0%)

Table 5.21 Fitting the model for 'Anxiety/Depression' into the derivation data set: predicted category frequencies versus actual category frequencies

Anxiety Depression Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	997 (55.1 %)	1246 (68.9 %)
'Some'	735(40.6 %)	561 (31 %)
'Extreme'	77 (4.3%)	2 (0.1%)

The internal validation method exploring the 'predicted response frequency' demonstrated promising results (Tables 5.17- 5.21) – particularly for the 'no' and 'some' EQ-5D responses, but showed very poor predictive power for all 'extreme' categories. For example, in the 'anxiety/depression' domain (Table 5.21) the actual number of subjects who answered 'extreme' was 77, compared to the predicted 2. The model was under-predicting the

frequency of 'extreme' responses across all EQ-5D domains. This could be due to the very low number of patients selecting that option in the actual patient dataset and the fact that this method of incorporating 'predicted response frequency' only isolates the 'most probable' outcome. Therefore, whilst the model provides a predicted probability for the 'extreme' category, the numerical value was of no significance in the model when calculating the final predictions, as inevitably Y = 1 or 2 always had the higher probabilities.

To overcome this problem, a different analysis method was therefore used: 'total sum of probabilities'. This method considers the individual predicted probability for each EQ-5D domain response, with the total column sum of these probabilities providing the predicted number of patients within that category. Therefore, the predicted probabilities for each possible EQ-5D domain response were summed over all subjects allowing us to predict, within a cohort of patients, how many in total would answer "no problems", "some problems" or "extreme problems" for each of the five EQ-5D domains. These results were then compared at a group level with the actual number of responses within the 'internal' derivation set, followed by the 'external' validation set. As a final step, the model was re-fitted on the entire patient dataset to produce a model with increased accuracy.

5.3 Method two: the forward stepwise variable selection method and total sum of probabilities

As the 'predicted response category' methodology yielded non-optimal results (in particular for respondents who answered 'extreme' for the respective categories), the next step involved total sum of probabilities providing predicted frequency of responses for subjects in the derivation set. The results of this 'internal validation' process are shown in tables 5.22-5.26;

5.3.1 Internal validation of the forward variable selection method: total sum of probabilities

Table 5.22 Fitting the model for 'Mobility' into the derivation data set: predicted category frequencies versus actual category frequencies

Mobility Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	1374 (75.8 %)	1373.52 (75.8 %)
'Some'	433 (23.9 %)	433.58 (23.9 %)
Extreme'	6 (0.3%)	5.91 (0.3 %)

Table 5.23 Fitting the model for 'Self-care' into the derivation data set: predicted category frequencies versus actual category frequencies

Self-care Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	1627 (89.7 %)	1627.95 (89.7 %)
'Some'	180 (9.9 %)	179.06 (9.9 %)
Extreme'	7 (0.4%)	6.99 (0.39 %)

Table 5.24 Fitting the model for 'Usual Activities' into the derivation data set: predicted category frequencies versus actual category frequencies

Usual Activities Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	1343 (74.0 %)	1345.95 (74.1 %)
'Some'	450 (24.8 %)	447.63 (24.7 %)
Extreme'	23 (1.3%)	22.42 (1.2 %)

Table 5.25 Fitting the model for 'Pain/Discomfort' into the derivation data set: predicted category frequencies versus actual category frequencies

Pain/Discomfort Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	817 (45.0 %)	815.96 (45.0 %)
'Some'	899 (49.6 %)	899.35 (49.6 %)
Extreme'	98 (5.4%)	98.69 (5.4 %)

Table 5.26 Fitting the model for 'Anxiety/Depression' into the derivation data set: predicted category frequencies versus actual category frequencies

Anxiety Depression Response	Actual Response Frequency (% of total)	Predicted Response Frequency (% of total)
'No'	997 (55.1 %)	996.53 (55.1 %)
'Some'	735(40.6 %)	735.31 (40.6 %)
Extreme'	77 (4.3%)	77.15 (4.3 %)

As may be noted from Tables 5.22-5.26, the predicted response frequency from the internal validation process was very close to the actual response frequency, with almost identical results. As the model was being fitted back into the same set it was derived from, this was to be expected. However, the next step would involve fitting the model into the 'external' (validation) set to assess how well mapping with OLR predicts EQ-5D domain responses.

5.3.2 External validation of the forward variable selection method: total sum of probabilities

5.3.2.1 Building the models

In order to build the model for external validation, 'estimates' from the most significant DLQI items were utilised as identified in Table 5.11. These estimates are displayed below in tables 5.27-5.31. Each formula was based on the OLR formulae as shown in Figure 5.2.

5.3.2.1.1 Mobility

Table 5.27 Estimates for the 'Mobility' EQ-5D domain using the most significant DLQI predictor items. The relevant DLQI question is represented in numerical order by DLQI 1, DLQI 2 etc up to DLQI 10

		Estimate	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Threshold	[EQ5D Mobility a_1 = 1]	-.514	.302	-1.106	.079
	[EQ5D Mobility a_2 = 2]	4.256	.497	3.281	5.231
DLQI Item	[dlqi3=0]	.089	.325	-.549	.727
	[dlqi3=1]	.609	.318	-.015	1.232

	[dlqi3=2]	.543	.300	-.046	1.132
	[dlqi3=3]	0[a]	.	.	.
	[dlqi7=0]	-.632	.204	-1.031	-.233
	[dlqi7=1]	-1.019	.222	-1.454	-.584
	[dlqi7=2]	-.942	.317	-1.564	-.320
	[dlqi7=3]	0[a]	.	.	.
	[dlqi10=0]	-.507	.280	-1.055	.042
	[dlqi10=1]	-.194	.292	-.766	.378
	[dlqi10=2]	.191	.299	-.395	.777
	[dlqi10=3]	0[a]	.	.	.
	[dlqi2=0]	.841	.259	.335	1.348
	[dlqi2=1]	.765	.244	.287	1.244
	[dlqi2=2]	.204	.244	-.275	.683
	[dlqi2=3]	0[a]	.	.	.
	[dlqi5=0]	-.930	.318	-1.553	-.307
	[dlqi5=1]	-.674	.300	-1.262	-.085
	[dlqi5=2]	-.709	.299	-1.294	-.124
	[dlqi5=3]	0[a]	.	.	.
	[dlqi1=0]	-.543	.231	-.996	-.090
	[dlqi1=1]	-.652	.211	-1.067	-.238
	[dlqi1=2]	-.311	.204	-.710	.088
	[dlqi1=3]	0[a]	.	.	.
	[dlqi6=0]	-.311	.258	-.817	.196
	[dlqi6=1]	-.486	.286	-1.046	.074
	[dlqi6=2]	-.436	.304	-1.033	.161
	[dlqi6=3]	0[a]	.	.	.

Figure 5.3 The ordinal logistic regression formulae to predict EQ-5D 'mobility' domain outcomes

$$P(Mobility = 1) = \frac{1}{1 + e^{(-Mobiity\,1 + DLQI3 + DLQI7 + DLQI10 + DLQI2 + DLQI5 + DLQI1 + DLQI6)}}$$

$$P(Mobiity = 2) = \frac{1}{1 + e^{(-Mobiity\,2 + DLQI3 + DLQI7 + DLQI10 + DLQI2 + DLQI5 + DLQI1 + DLQI6)}} - P(Y = 1)$$

$$P(Mobility = 3) = 1 - P(Y = 2) - P(Y = 1)$$

The following formulae were inputted into Excel to produce three probabilities per patient using the estimates from Table 5.27 in the equation shown in Figure 5.3:

P (Mobility = 1)

=1/(1+EXP(0.514+((IF(AB2=0,0.089,0))+(IF(AB2=1,0.609,0))+(IF(AB2=2,0.543,0))+(IF(AB2=3,0,0))+(IF(AH2=0,-0.632,0))+(IF(AH2=1,-1.019,0))+(IF(AH2=2,-0.942,0))+(IF(AH2=3,0,0))+(IF(AK2=0,-0.507,0))+(IF(AK2=1,-0.194,0))+(IF(AK2=2,0.191,0))+(IF(AK2=3,0,0))+(IF(AA2=0,0.841,0))+(IF(AA2=1,0.765,0))+(IF(AA2=2,0.204,0))+(IF(AA2=3,0,0))+(IF(AD2=0,-0.93,0))+(IF(AD2=1,-0.674,0))+(IF(AD2=2,-0.709,0))+(IF(AD2=3,0,0))+(IF(Z2=0,-0.543,0))+(IF(Z2=1,-0.652,0))+(IF(Z2=2,-0.311,0))+(IF(Z2=3,0,0))+(IF(AE2=0,-0.311,0))+(IF(AE2=1,-0.486,0))+(IF(AE2=2,-0.436,0))+(IF(AE2=3,0,0)))))

P (Mobility = 2)

=(1/(1+EXP(-4.256+(IF(AB2=0, 0.089,0)) + (IF(AB2=1, 0.609,0)) + (IF(AB2=2, 0.543,0)) + (IF(AB2=3, 0,0))+(IF(AH2=0, -0.632,0)) + (IF(AH2=1, -1.019,0)) + (IF(AH2=2, -0.942,0)) + (IF(AH2=3, 0,0))+(IF(AK2=0, -0.507,0)) + (IF(AK2=1, -0.194,0)) + (IF(AK2=2, 0.191,0)) + (IF(AK2=3, 0,0))+(IF(AA2=0, 0.841,0)) + (IF(AA2=1, 0.765,0)) + (IF(AA2=2, 0.204,0)) + (IF(AA2=3, 0,0))+(IF(AD2=0, -0.93,0)) + (IF(AD2=1, -0.674,0)) + (IF(AD2=2, -0.709,0)) + (IF(AD2=3, 0,0))+(IF(Z2=0, -0.543,0)) + (IF(Z2=1, -0.652,0)) + (IF(Z2=2, -0.311,0)) + (IF(Z2=3, 0,0)) + (IF(AE2=0, -0.311,0)) + (IF(AE2=1, -0.486,0)) + (IF(AE2=2, -0.436,0)) + (IF(AE2=3, 0,0))))) - BC2

P (Mobility = 3) = 1 - P (Mobility = 2) - P (Mobility = 1)

5.3.2.1.2 Self-care

Table 5.28 Estimates for the 'Self-care' EQ-5D domain using the most significant DLQI predictor items. The relevant DLQI question is represented in numerical order by DLQI 1, DLQI 2 etc up to DLQI 10

		Estimate	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Threshold	[EQ5D Self-care a_1 = 1]	.393	.397	-.384	1.171
	[EQ5D Self-care a_2 = 2]	4.022	.538	2.969	5.076
DLQI item	[dlqi10=0]	-1.437	.330	-2.083	-.791
	[dlqi10=1]	-1.285	.351	-1.972	-.598
	[dlqi10=2]	-.295	.323	-.929	.339

	[dlqi10=3]	0[a]	.	.	.
	[dlqi3=0]	-.630	.403	-1.420	.160
	[dlqi3=1]	-.083	.380	-.829	.662
	[dlqi3=2]	.083	.343	-.590	.755
	[dlqi3=3]	0[a]	.	.	.
	[dlqi7=0]	-.469	.262	-.984	.045
	[dlqi7=1]	-.692	.284	-1.249	-.135
	[dlqi7=2]	-.410	.371	-1.137	.316
	[dlqi7=3]	0[a]	.	.	.
	[dlqi1=0]	-.639	.331	-1.289	.010
	[dlqi1=1]	-.777	.278	-1.322	-.232
	[dlqi1=2]	-.310	.250	-.800	.180
	[dlqi1=3]	0[a]	.	.	.
	[dlqi8=0]	.784	.481	-.159	1.727
	[dlqi8=1]	.984	.461	.080	1.887
	[dlqi8=2]	.998	.424	.167	1.829
	[dlqi8=3]	0[a]	.	.	.
	[dlqi9=0]	-.546	.344	-1.221	.128
	[dlqi9=1]	-.607	.382	-1.355	.141
	[dlqi9=2]	-1.448	.467	-2.363	-.534
	[dlqi9=3]	0[a]	.	.	.
	[dlqi2=0]	.215	.349	-.469	.900
	[dlqi2=1]	.325	.305	-.273	.923
	[dlqi2=2]	-.062	.298	-.647	.522
	[dlqi2=3]	0[a]	.	.	.
	[dlqi5=0]	-.839	.431	-1.685	.007
	[dlqi5=1]	-.319	.388	-1.079	.441
	[dlqi5=2]	-.390	.369	-1.113	.333
	[dlqi5=3]	0[a]	.	.	.
	[dlqi4=0]	.534	.340	-.133	1.201
	[dlqi4=1]	.494	.335	-.163	1.151
	[dlqi4=2]	.760	.323	.128	1.392
	[dlqi4=3]	0[a]	.	.	.
	[dlqi6=0]	.148	.337	-.513	.809
	[dlqi6=1]	.054	.376	-.682	.791
	[dlqi6=2]	.467	.383	-.283	1.218
	[dlqi6=3]	0[a]	.	.	.

Figure 5.4 The ordinal logistic regression formulae to predict EQ-5D 'self-care' domain outcomes

$$P(Selfcare = 1) = \frac{1}{1 + e^{(-Selfcare\,1 + DLQI10 + DLQI3 + DLQI7 + DLQI1 + DLQI8 + DLQI9 + DLQI2 + DLQI5 + DLQI4 + DLQI6)}}$$

$$P(Selfcare = 2) = \frac{1}{1 + e^{(-Selfcare\,2 + DLQI10 + DLQI3 + DLQI7 + DLQI1 + DLQI8 + DLQI19 + DLQI2 + DLQI5 + DLQI4 + DLQI6)}} - P(Y = 1)$$

$$P(Selfcare = 3) = 1 - P(Y = 2) - P(Y = 1)$$

The following formulae were inputted into Excel to produce three probabilities per patient using the estimates from Table 5.28 in the equation shown in Figure 5.4:

P (Self-care = 1)

=1/(1+EXP(-0.393+((IF(AK2=0,-1.437,0))+(IF(AK2=1,-1.285,0))+(IF(AK2=2,-0.295,0))+(IF(AK2=3,0,0))+(IF(AB2=0,-0.630,0))+(IF(AB2=1,-0.083,0))+(IF(AB2=2,0.083,0))+(IF(AB2=3,0,0))+(IF(AH2=0,-0.469,0))+(IF(AH2=1,-0.692,0))+(IF(AH2=2,-0.410,0))+(IF(AH2=3,0,0))+(IF(Z2=0,-0.639,0))+(IF(Z2=1,-0.777,0))+(IF(Z2=2,-0.310,0))+(IF(Z2=3,0,0))+(IF(AI2=0,0.784,0))+(IF(AI2=1,0.984,0))+(IF(AI2=2,0.998,0))+(IF(AI2=3,0,0))+(IF(AJ2=0,-0.546,0))+(IF(AJ2=1,-0.607,0))+(IF(AJ2=2,-1.448,0))+(IF(AJ2=3,0,0))+(IF(AA2=0,0.215,0))+(IF(AA2=1,0.325,0))+(IF(AA2=2,-0.062,0))+(IF(AA2=3,0,0)) +(IF(AD2=0,-0.839,0))+(IF(AD2=1,-0.319,0))+(IF(AD2=2,-0.390,0))+(IF(AD2=3,0,0))
+(IF(AC2=0,0.534,0))+(IF(AC2=1,0.494,0))+(IF(AC2=2,0.760,0))+(IF(AC2=3,0,0))
+(IF(AE2=0,0.148,0))+(IF(AE2=1,0.054,0))+(IF(AE2=2,0.467,0))+(IF(AE2=3,0,0)))))

P (Self-care = 2)

=1/(1+EXP(-4.022+((IF(AK2=0,-1.437,0))+(IF(AK2=1,-1.285,0))+(IF(AK2=2,-0.295,0))+(IF(AK2=3,0,0))+(IF(AB2=0,-0.630,0))+(IF(AB2=1,-0.083,0))+(IF(AB2=2,0.083,0))+(IF(AB2=3,0,0))+(IF(AH2=0,-0.469,0))+(IF(AH2=1,-0.692,0))+(IF(AH2=2,-0.410,0))+(IF(AH2=3,0,0))+(IF(Z2=0,-0.639,0))+(IF(Z2=1,-0.777,0))+(IF(Z2=2,-0.310,0))+(IF(Z2=3,0,0))+(IF(AI2=0,0.784,0))+(IF(AI2=1,0.984,0))+(IF(AI2=2,0.998,0))+(IF(AI2=3,0,0))+(IF(AJ2=0,-0.546,0))+(IF(AJ2=1,-0.607,0))+(IF(AJ2=2,-

1.448,0))+(IF(AJ2=3,0,0))+(IF(AA2=0,0.215,0))+(IF(AA2=1,0.325,0))+(IF(AA2=2,-0.062,0))+(IF(AA2=3,0,0)) +(IF(AD2=0,-0.839,0))+(IF(AD2=1,-0.319,0))+(IF(AD2=2,-0.390,0))+(IF(AD2=3,0,0))
+(IF(AC2=0,0.534,0))+(IF(AC2=1,0.494,0))+(IF(AC2=2,0.760,0))+(IF(AC2=3,0,0))
+(IF(AE2=0,0.148,0))+(IF(AE2=1,0.054,0))+(IF(AE2=2,0.467,0))+(IF(AE2=3,0,0)))))
- BC2

P (Self-care = 3) = 1 - P (Self-care = 2) - P (Self-care = 1)

5.3.2.1.3 Usual activities

Table 5.29 Estimates for the 'Usual activities' EQ-5D domain using the most significant DLQI predictor items. The relevant DLQI question is represented in numerical order by DLQI 1, DLQI 2 etc up to DLQI 10

		Estimate	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Threshold	[EQ5D Usual Activities a_1 = 1]	-1.064	.308	-1.668	-.460
	[EQ5D Usual Activities a_2 = 2]	2.696	.353	2.004	3.389
DLQI Item	[dlqi3=0]	-.394	.311	-1.004	.216
	[dlqi3=1]	.085	.303	-.509	.679
	[dlqi3=2]	.467	.289	-.099	1.033
	[dlqi3=3]	0[a]	.	.	.
	[dlqi10=0]	-.727	.277	-1.270	-.185
	[dlqi10=1]	-.513	.288	-1.078	.053
	[dlqi10=2]	.295	.294	-.281	.871
	[dlqi10=3]	0[a]	.	.	.
	[dlqi7=0]	-.533	.202	-.929	-.138
	[dlqi7=1]	-.754	.217	-1.179	-.330
	[dlqi7=2]	-.403	.295	-.981	.174
	[dlqi7=3]	0[a]	.	.	.
	[dlqi6=0]	-.774	.257	-1.279	-.270
	[dlqi6=1]	-.783	.282	-1.336	-.230
	[dlqi6=2]	-.601	.298	-1.185	-.018
	[dlqi6=3]	0[a]	.	.	.
	[dlqi1=0]	-.804	.233	-1.262	-.347
	[dlqi1=1]	-.621	.207	-1.026	-.216
	[dlqi1=2]	-.276	.199	-.667	.114

	[dlqi1=3]	0[a]	.	.	.
	[dlqi2=0]	.623	.256	.121	1.125
	[dlqi2=1]	.621	.238	.155	1.086
	[dlqi2=2]	.131	.235	-.329	.591
	[dlqi2=3]	0[a]	.	.	.
	[dlqi5=0]	-.837	.320	-1.465	-.209
	[dlqi5=1]	-.447	.299	-1.032	.139
	[dlqi5=2]	-.337	.292	-.910	.235
	[dlqi5=3]	0[a]	.	.	.
	[dlqi4=0]	.475	.251	-.016	.966
	[dlqi4=1]	.312	.251	-.181	.804
	[dlqi4=2]	.571	.252	.077	1.066
	[dlqi4=3]	0[a]	.	.	.

Figure 5.5 The ordinal logistic regression formulae to predict EQ-5D 'Usual activities' domain outcomes

$$P(Usual\ Activities = 1) = \frac{1}{1 + e^{(-Usual\ Activities\ 1 + DLQI3 + DLQI10 + DLQI7 + DLQI6 + DLQI1 + DLQI2 + DLQI5 + DLQI4)}}$$

$$P(Usual\ Activities = 2) = \frac{1}{1 + e^{(-Usual\ Activities\ 2 + DLQI3 + DLQI10 + DLQI7 + DLQI6 + DLQI1 + DLQI2 + DLQI5 + DLQI4)}} - P(Y = 1)$$

$$P(Usual\ Activities = 3) = 1 - P(Y = 2) - P(Y = 1)$$

The following formulae were inputted into Excel to produce three probabilities per patient using the estimates from Table 5.29 in the equation shown in Figure 5.5:

P (Usual Activities = 1)

=1/(1+EXP(1.064+((IF(AB2=0,-0.394,0))+(IF(AB2=1,0.085,0))+(IF(AB2=2,0.467,0))+(IF(AB2=3,0,0))+(IF(AK2=0,-0.727,0))+(IF(AK2=1,-0.513,0))+(IF(AK2=2,0.295,0))+(IF(AK2=3,0,0))+(IF(AH2=0,-0.533,0))+(IF(AH2=1,-0.754,0))+(IF(AH2=2,-0.403,0))+(IF(AH2=3,0,0))+(IF(AE2=0,-0.774,0))+(IF(AE2=1,-0.783,0))+(IF(AE2=2,-0.601,0))+(IF(AE2=3,0,0))+(IF(Z2=0,-0.804,0))+(IF(Z2=1,-0.621,0))+(IF(Z2=2,-0.276,0))+(IF(Z2=3,0,0))+(IF(AA2=0,0.623,0))+(IF(AA2=1,0.621,0))+(IF(AA2=2,0.131,0))+(IF(AA2=3,0,0))+(IF(AD2=0,-0.837,0))+(IF(AD2=1,-0.447,0))+(IF(AD2=2,-0.337,0))+(IF(AD2=3,0,0))+(IF(AC2=0,0.475,0))+(IF(AC2=1,0.312,0))+(IF(AC2=2,0.571,0))+(I

F(AC2=3,0,0)))))

P (Usual Activities = 2)

=1/(1+EXP(-2.696+((IF(AB2=0,-0.394,0))+(IF(AB2=1,0.085,0))+(IF(AB2=2,0.467,0))+(IF(AB2=3,0,0))+(IF(AK2=0,-0.727,0))+(IF(AK2=1,-0.513,0))+(IF(AK2=2,0.295,0))+(IF(AK2=3,0,0))+(IF(AH2=0,-0.533,0))+(IF(AH2=1,-0.754,0))+(IF(AH2=2,-0.403,0))+(IF(AH2=3,0,0))+(IF(AE2=0,-0.774,0))+(IF(AE2=1,-0.783,0))+(IF(AE2=2,-0.601,0))+(IF(AE2=3,0,0))+(IF(Z2=0,-0.804,0))+(IF(Z2=1,-0.621,0))+(IF(Z2=2,-0.276,0))+(IF(Z2=3,0,0))+(IF(AA2=0,0.623,0))+(IF(AA2=1,0.621,0))+(IF(AA2=2,0.131,0))+(IF(AA2=3,0,0))+(IF(AD2=0,-0.837,0))+(IF(AD2=1,-0.447,0))+(IF(AD2=2,-0.337,0))+(IF(AD2=3,0,0))+(IF(AC2=0,0.475,0))+(IF(AC2=1,0.312,0))+(IF(AC2=2,0.571,0))+(IF(AC2=3,0,0))))) - BC2

P (Usual activities = 3) = 1 - P (Usual activities = 2) - P (Usual activities = 1)

5.3.2.1.4 Pain / discomfort

Table 5.30 Estimates for the 'Pain/discomfort' EQ-5D domain using the most significant DLQI predictor items. The relevant DLQI question is represented in numerical order by DLQI 1, DLQI 2 etc up to DLQI 10

		Estimate	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Threshold	[EQ5D Pain / Discomfort a_1 = 1]	-2.732	.316	-3.352	-2.112
	[EQ5D Pain / Discomfort a_2 = 2]	.987	.302	.395	1.579
DLQI Item	[dlqi1=0]	-2.050	.211	-2.464	-1.637
	[dlqi1=1]	-1.345	.198	-1.732	-.957
	[dlqi1=2]	-.480	.195	-.863	-.097
	[dlqi1=3]	0[a]	.	.	.
	[dlqi6=0]	-.986	.244	-1.465	-.507
	[dlqi6=1]	-.758	.265	-1.277	-.238
	[dlqi6=2]	-.559	.282	-1.113	-.006
	[dlqi6=3]	0[a]	.	.	.
	[dlqi10=0]	-.407	.268	-.932	.119

	[dlqi10=1]	-.073	.280	-.621	.475
	[dlqi10=2]	.270	.291	-.301	.841
	[dlqi10=3]	0[a]	.	.	.
	[dlqi4=0]	-.076	.215	-.497	.345
	[dlqi4=1]	.171	.222	-.263	.605
	[dlqi4=2]	.455	.237	-.009	.918
	[dlqi4=3]	0[a]	.	.	.
	[dlqi7=0]	.350	.193	-.029	.729
	[dlqi7=1]	.028	.205	-.373	.429
	[dlqi7=2]	.256	.290	-.312	.824
	[dlqi7=3]	0[a]	.	.	.
	[dlqi3=0]	-.464	.279	-1.011	.083
	[dlqi3=1]	-.197	.277	-.741	.347
	[dlqi3=2]	-.131	.272	-.665	.403
	[dlqi3=3]	0[a]	.	.	.

Figure 5.6 The ordinal logistic regression formulae to predict EQ5D 'Pain/discomfort' domain outcomes

$$P(Pain/Discomfort = 1) = \frac{1}{1 + e^{(-Pain/discomfort\ 1 + DLQI1 + DLQI6 + DLQI10 + DLQI4 + DLQI7 + DLQI3)}}$$

$$P(Pain/Discomfort = 2) = \frac{1}{1 + e^{(-Pain/discomfort\ 2 + DLQI1 + DLQI6 + DLQI10 + DLQI4 + DLQI7 + DLQI3)}} - P(Y = 1)$$

$$P(Pain/Discomfort = 3) = 1 - P(Y = 2) - P(Y = 1)$$

The following formulae were inputted into Excel to produce three probabilities per patient using the estimates from Table 5.30 in the equation shown in Figure 5.6:

P (Pain = 1)

=1/(1+EXP(2.732+((IF(Z2=0,-0.2050,0))+(IF(Z2=1,-1.345,0))+(IF(Z2=2,-0.480,0))+(IF(Z2=3,0,0))+(IF(AE2=0,-0.986,0))+(IF(AE2=1,-0.758,0))+(IF(AE2=2,-0.559,0))+(IF(AE2=3,0,0))+(IF(AK2=0,-0.407,0))+(IF(AK2=1,-0.073,0))+(IF(AK2=2,0.270,0))+(IF(AK2=3,0,0))+(IF(AC2=0,-0.076,0))+(IF(AC2=1,0.171,0))+(IF(AC2=2,0.455,0))+(IF(AC2=3,0,0))+(IF(AH2=0,0.350,0))+(IF(AH2=1,0.028,0))+(IF(AH2=2,0.256,0))+(IF(AH2=3,0,0))+(IF(AB2=0,-0.464,0))+(IF(AB2=1,-0.197,0))+(IF(AB2=2,-0.131,0))+(IF(AB2=3,0,0)))))

P (Pain = 2)

=1/(1+EXP(-0.987+((IF(Z2=0,-0.2050,0))+(IF(Z2=1,-1.345,0))+(IF(Z2=2,-0.480,0))+(IF(Z2=3,0,0))+(IF(AE2=0,-0.986,0))+(IF(AE2=1,-0.758,0))+(IF(AE2=2,-0.559,0))+(IF(AE2=3,0,0))+(IF(AK2=0,-0.407,0))+(IF(AK2=1,-0.073,0))+(IF(AK2=2,0.270,0))+(IF(AK2=3,0,0))+(IF(AC2=0,-0.076,0))+(IF(AC2=1,0.171,0))+(IF(AC2=2,0.455,0))+(IF(AC2=3,0,0))+(IF(AH2=0,0.350,0))+(IF(AH2=1,0.028,0))+(IF(AH2=2,0.256,0))+(IF(AH2=3,0,0))+(IF(AB2=0,-0.464,0))+(IF(AB2=1,-0.197,0))+(IF(AB2=2,-0.131,0))+(IF(AB2=3,0,0))))) - BC2

P (Pain = 3) = 1 - P (Pain = 2) - P (Pain = 1)

5.3.2.1.5 Anxiety / depression

Table 5.31 Estimates for the 'Anxiety/Depression' EQ-5D domain using the most significant DLQI predictor items. The relevant DLQI question is represented in numerical order by DLQI 1, DLQI 2 etc up to DLQI 10

		Estimate	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Threshold	[EQ5D Anxiety/ Depression a_1 = 1]	-2.848	.342	-3.519	-2.177
	[EQ5D Anxiety/ Depression a_2 = 2]	.489	.328	-.153	1.131
DLQI Item	[dlqi2=0]	-1.296	.208	-1.704	-.887
	[dlqi2=1]	-.881	.197	-1.268	-.495
	[dlqi2=2]	-.495	.201	-.888	-.101
	[dlqi2=3]	0[a]	.	.	.
	[dlqi7=0]	-.638	.190	-1.010	-.266
	[dlqi7=1]	-.474	.199	-.864	-.084
	[dlqi7=2]	-.409	.286	-.970	.152
	[dlqi7=3]	0[a]	.	.	.
	[dlqi9=0]	-.624	.262	-1.137	-.110
	[dlqi9=1]	-.627	.284	-1.184	-.069
	[dlqi9=2]	-.157	.319	-.783	.468
	[dlqi9=3]	0[a]	.	.	.
	[dlqi3=0]	-.228	.282	-.780	.324
	[dlqi3=1]	.095	.282	-.458	.647

	[dlqi3=2]	.021	.273	-.515	.556
	[dlqi3=3]	0[a]	.	.	.
	[dlqi1=0]	-.429	.206	-.832	-.025
	[dlqi1=1]	-.493	.191	-.868	-.118
	[dlqi1=2]	-.471	.190	-.844	-.098
	[dlqi1=3]	0[a]	.	.	.
	[dlqi10=0]	-.741	.269	-1.267	-.215
	[dlqi10=1]	-.757	.280	-1.305	-.209
	[dlqi10=2]	-.478	.287	-1.040	.084
	[dlqi10=3]	0[a]	.	.	.
	[dlqi8=0]	-.300	.327	-.941	.341
	[dlqi8=1]	-.085	.319	-.711	.541
	[dlqi8=2]	-.172	.311	-.782	.437
	[dlqi8=3]	0[a]	.	.	.
	[dlqi4=0]	.402	.217	-.024	.828
	[dlqi4=1]	.427	.221	-.007	.861
	[dlqi4=2]	.453	.232	-.002	.909
	[dlqi4=3]	0[a]	.	.	.

Figure 5.7 The ordinal logistic regression formulae to predict EQ-5D 'Anxiety/depression' domain outcomes

$$P(Anxiety/Depression = 1) = \frac{1}{1 + e^{(-Anxiety/Depression\ 1 + DLQI2 + DLQI7 + DLQI9 + DLQI3 + DLQI1 + DLQ10 + DLQI8 + DLQI4)}}$$

$$P(Anxiety/Depression = 2) = \frac{1}{1 + e^{(-Anxiety/Depression\ 2 + DLQI2 + DLQI7 + DLQI9 + DLQI3 + DLQI1 + DLQ10 + DLQI8 + DLQI4)}} - P(Y = 1)$$

$$P(Anxiety/Depression = 3) = 1 - P(Y = 2) - P(Y = 1)$$

The following formulae were inputted into Excel to produce three probabilities per patient using the estimates from Table 5.31 in the equation shown in Figure 5.7:

P (Anxiety = 1)

=1/(1+EXP(2.848+((IF(AA2=0,-1.296,0))+(IF(AA2=1,-0.881,0))+(IF(AA2=2,-0.495,0))+(IF(AA2=3,0,0))+(IF(AH2=0,-0.638,0))+(IF(AH2=1,-0.474,0))+(IF(AH2=2,-0.409,0))+(IF(AH2=3,0,0))+(IF(AJ2=0,-0.624,0))+(IF(AJ2=1,-0.627,0))+(IF(AJ2=2,-0.157,0))+(IF(AJ2=3,0,0))+(IF(AB2=0,-0.228,0))+(IF(AB2=1,0.095,0))+(IF(AB2=2,0.021,0))+(IF(AB2=3,0,0))+(IF(Z2=0,-0.429,0))+(IF(Z2=1,-0.493,0))+(IF(Z2=2,-0.471,0))+(IF(Z2=3,0,0))+(IF(AK2=0,-

0.741,0))+(IF(AK2=1,-0.757,0))+(IF(AK2=2,-0.478,0))+(IF(AK2=3,0,0))+(IF(AI2=0,-0.300,0))+(IF(AI2=1,-0.085,0))+(IF(AI2=2,-0.172,0))+(IF(AI2=3,0,0))+(IF(AC2=0,0.402,0))+(IF(AC2=1,0.427,0))+(IF(AC2=2,0.453,0))+(IF(AC2=3,0,0)))))

P (Anxiety = 2)

=1/(1+EXP(-0.489 +((IF(AA2=0,-1.296,0))+(IF(AA2=1,-0.881,0))+(IF(AA2=2,-0.495,0))+(IF(AA2=3,0,0))+(IF(AH2=0,-0.638,0))+(IF(AH2=1,-0.474,0))+(IF(AH2=2,-0.409,0))+(IF(AH2=3,0,0))+(IF(AJ2=0,-0.624,0))+(IF(AJ2=1,-0.627,0))+(IF(AJ2=2,-0.157,0))+(IF(AJ2=3,0,0))+(IF(AB2=0,-0.228,0))+(IF(AB2=1,0.095,0))+(IF(AB2=2,0.021,0))+(IF(AB2=3,0,0))+(IF(Z2=0,-0.429,0))+(IF(Z2=1,-0.493,0))+(IF(Z2=2,-0.471,0))+(IF(Z2=3,0,0))+(IF(AK2=0,-0.741,0))+(IF(AK2=1,-0.757,0))+(IF(AK2=2,-0.478,0))+(IF(AK2=3,0,0))+(IF(AI2=0,-0.300,0))+(IF(AI2=1,-0.085,0))+(IF(AI2=2,-0.172,0))+(IF(AI2=3,0,0))+(IF(AC2=0,0.402,0))+(IF(AC2=1,0.427,0))+(IF(AC2=2,0.453,0))+(IF(AC2=3,0,0))))) - BC2

P (Anxiety = 3) = 1 - P (Anxiety = 2) - P (Anxiety = 1)

5.3.3 Results

Having derived five ordinal models, one for each EQ-5D dimension, the models were used to predict the probability of each EQ-5D response for each subject in the validation set. The total sums of probabilities were then calculated to predict the number of responses for each domain across the entire validation cohort and these were then compared with the actual frequencies recorded, as shown in Table 5.32. These frequencies are also displayed as bar charts in Figure 5.8 (a and b), which demonstrate the predictive capability of the models across each domain. The models were shown to be highly predictive except for the pain/discomfort domain where some minor differences were noted (Table 5.32).

Table 5.32 Table summarising the ordinal regression model predictions against actual population responses following forwards stepwise variable method

		EQ-5D Response within each domain		
EQ5D Domain		**No**	**Some**	**Extreme**
Mobility	*Actual*	1389.00	435.00	5.00
	Predicted	1392.21	430.97	5.82
Self-care	*Actual*	1611.00	196.00	5.00
	Predicted	1628.25	176.93	6.83
Usual Activities	*Actual*	1342.00	447.00	34.00
	Predicted	1346.66	453.95	22.39
Pain/Discomfort	*Actual*	823.00	901.00	111.00
	Predicted	565.39	1132.65	136.96
Anxiety/Depression	*Actual*	1001.00	730.00	82.00
	Predicted	983.41	746.31	83.28

Figure 5.8a Actual versus predicted EQ-5D outcome per domain using the ordinal regression model

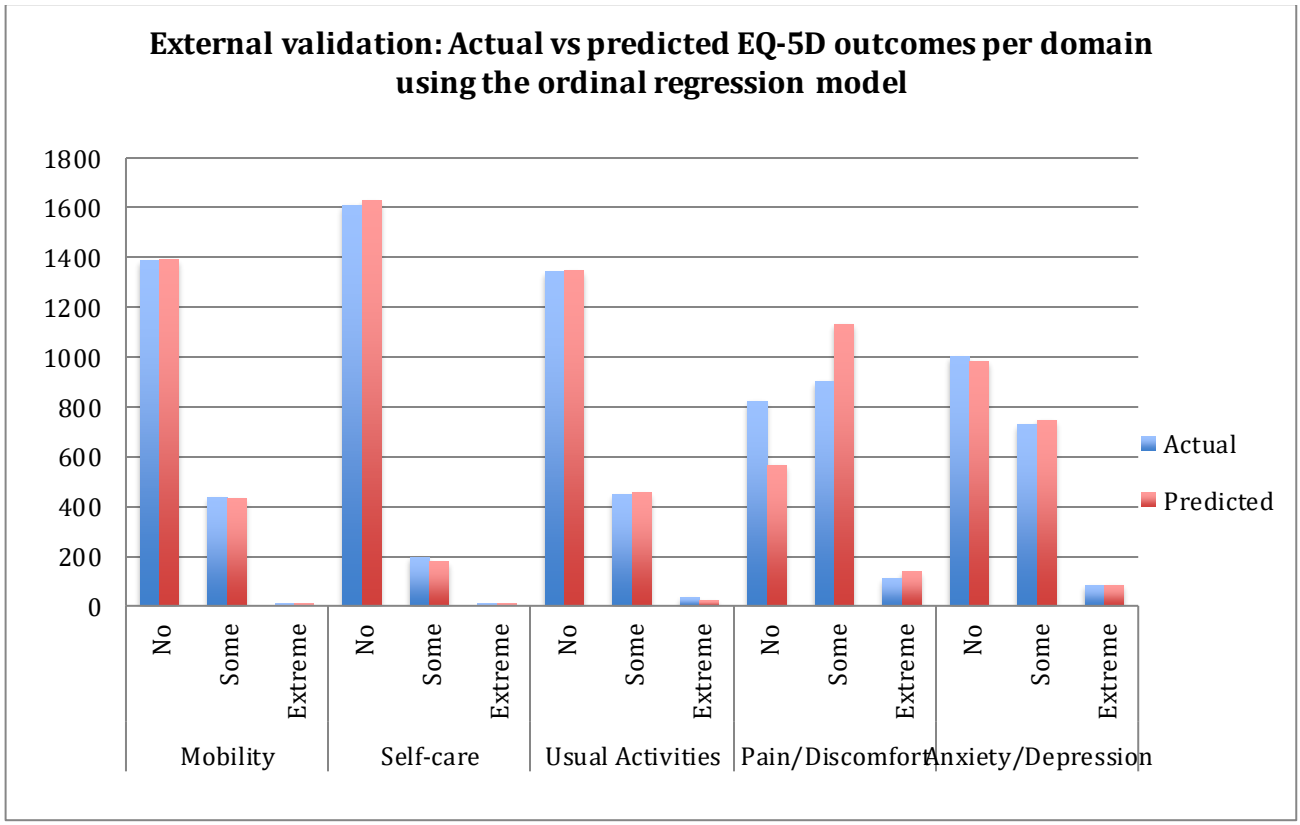
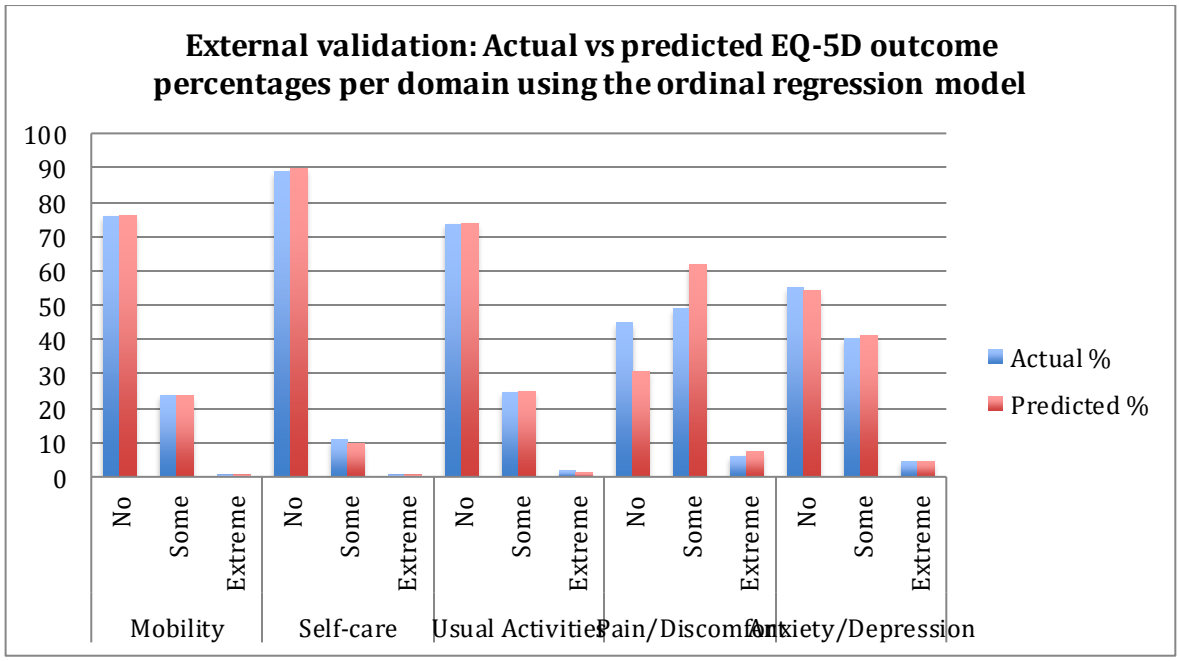


Figure 5.8b Actual versus predicted EQ-5D outcome percentages per domain using the ordinal regression model



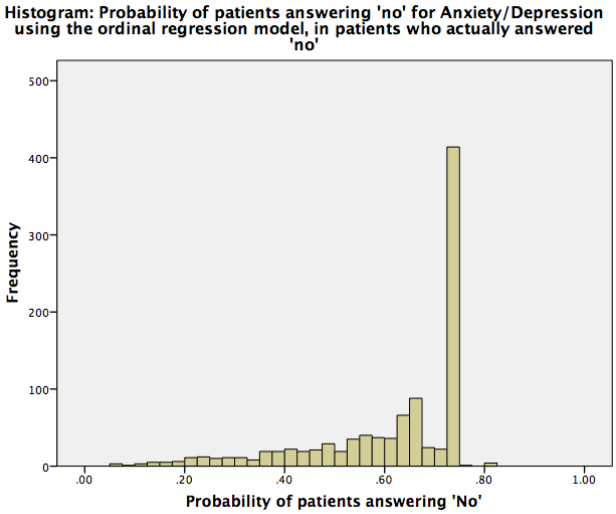
5.3.3.1 Is the model predictive at an individual level?

5.3.3.1.1 Histograms

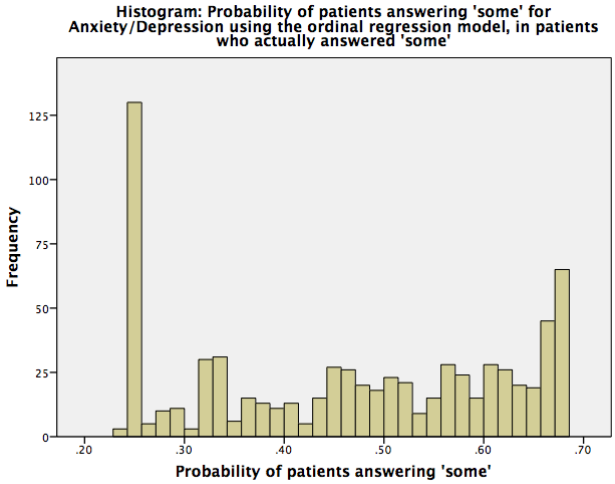
The model's discriminatory power was initially explored using histograms (Figures 5.9-5.13) for each response of each domain of the EQ-5D. For example, when assessing the 'no' response of the 'Anxiety/depression' domain, the probability of patients answering 'no' in patients who actually answered 'no' was plotted. This was one method of assessing the model's predictive power at an individual level.

Figure 5.9 Anxiety & Depression histogram

a) 'No'



b) 'Some'



c) ‘Extreme’

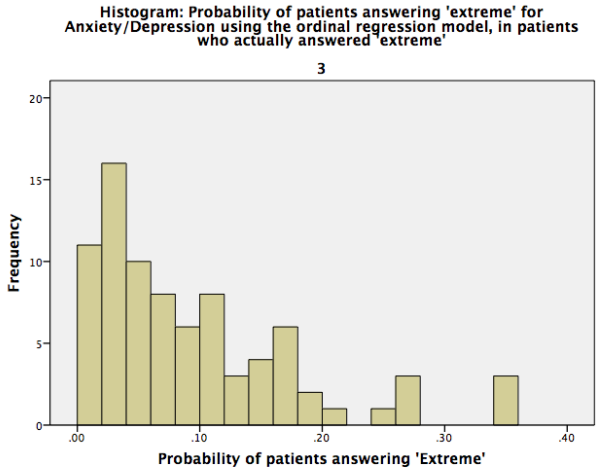
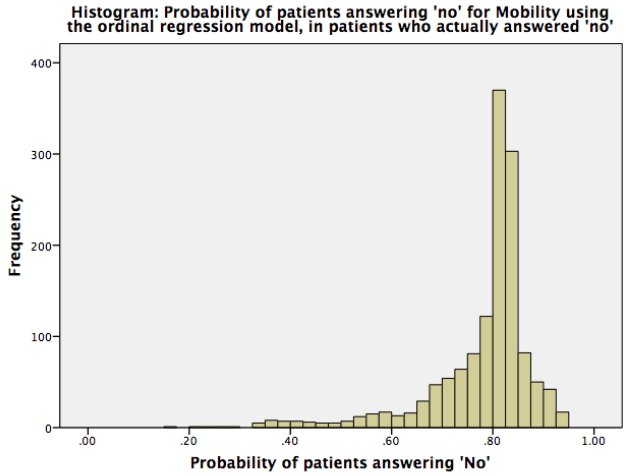
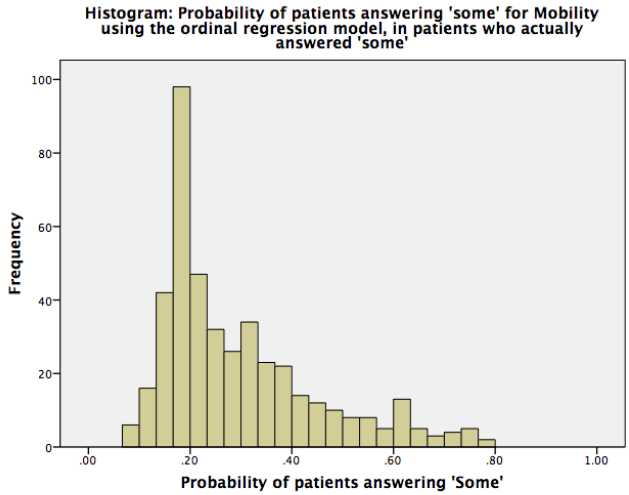


Figure 5.10 Mobility histogram

a) ‘No’



b) ‘Some’



c) ‘Extreme’

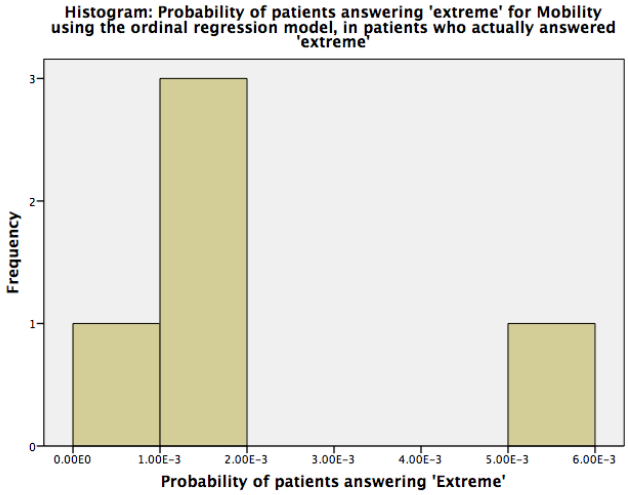
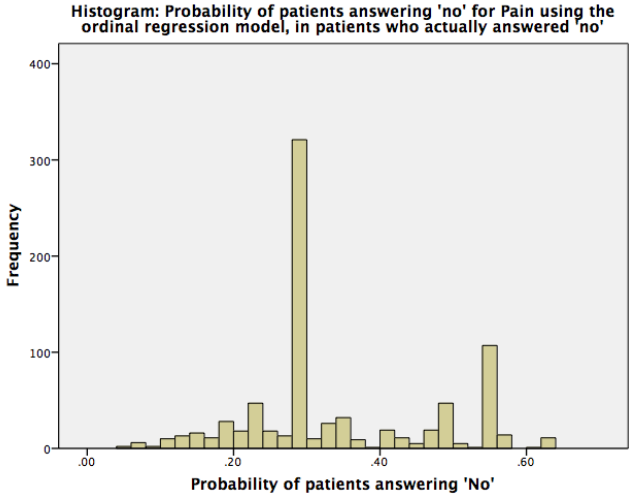
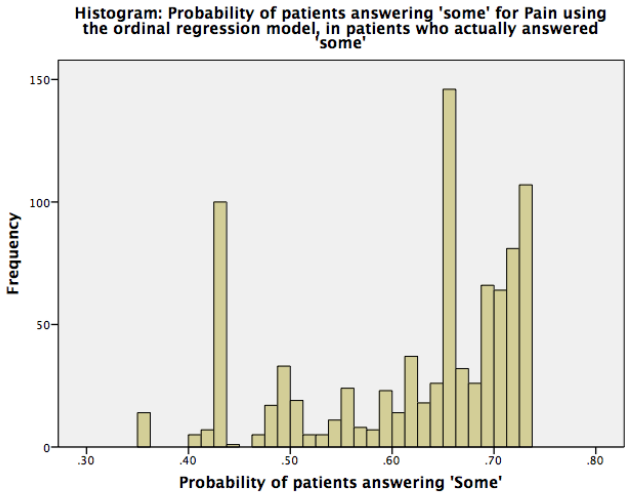


Figure 5.11 Pain histogram

a) ‘No’



b) ‘Some’



c) ‘Extreme’

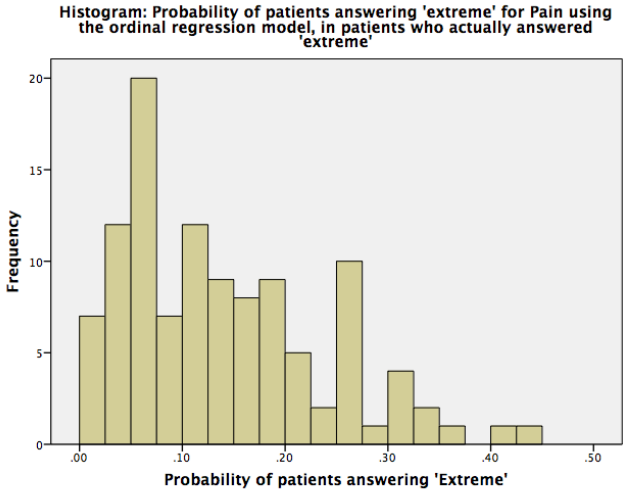
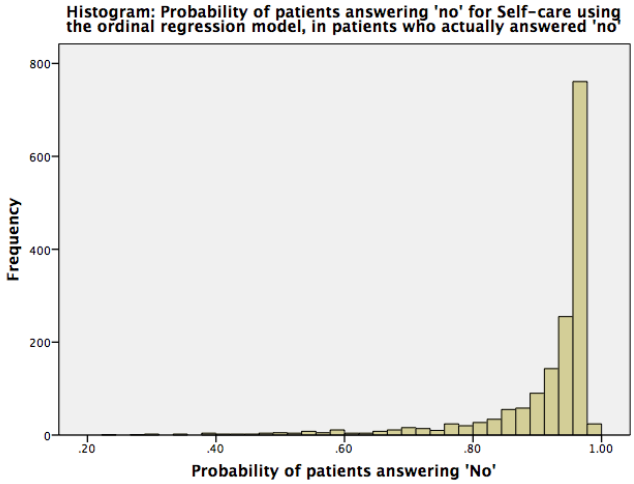
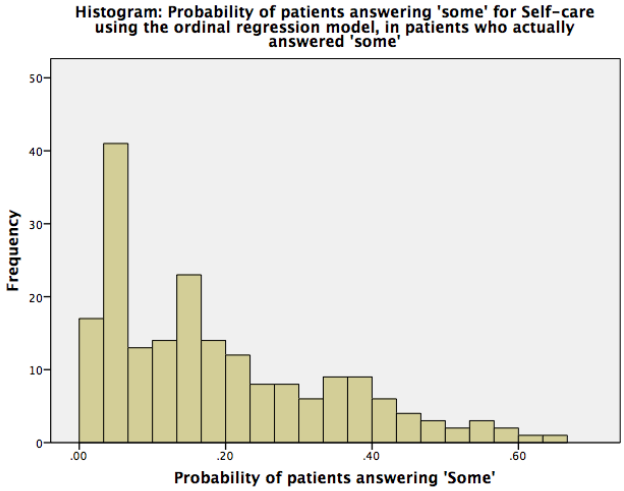


Figure 5.12 Self-care histogram

a) ‘No’



b) ‘Some’



c) ‘Extreme’

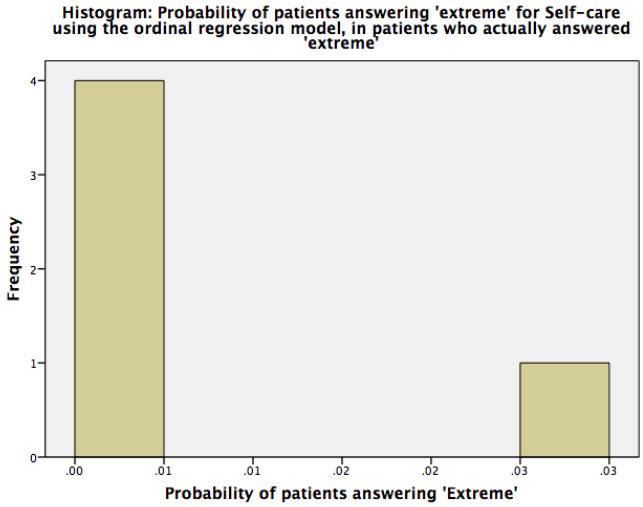
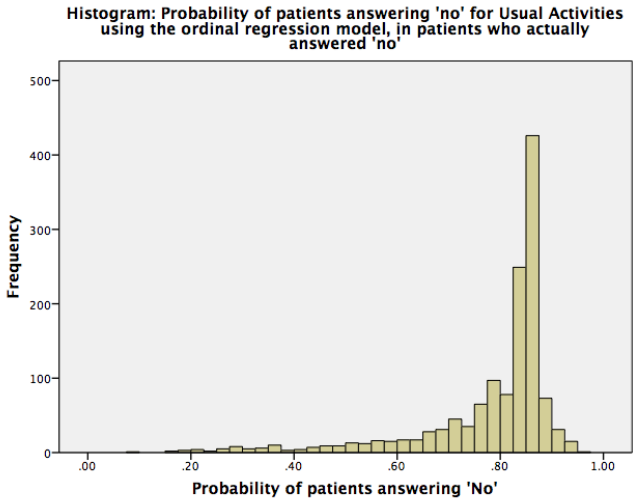
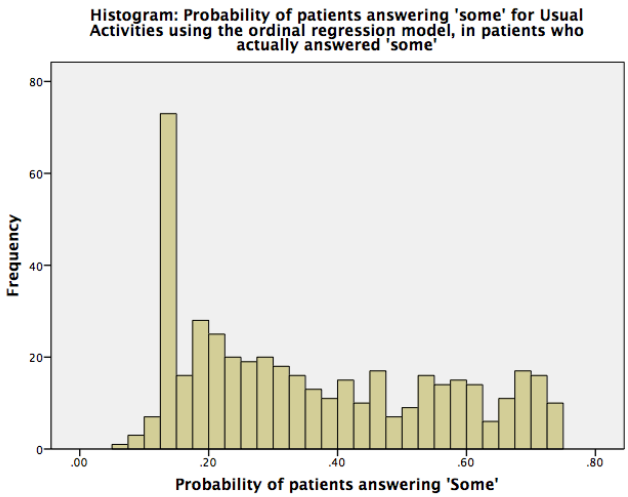


Figure 5.13 Usual Activities histogram

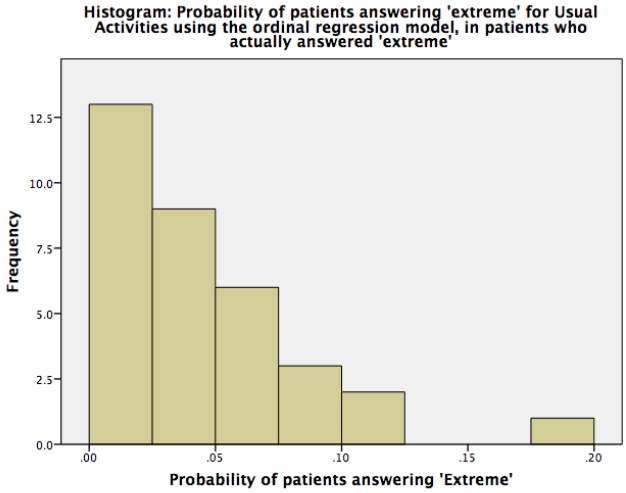
a) ‘No’



b) ‘Some’



c) 'Extreme'



The histograms shown above demonstrate an expected shift from right to left as the graphs progress within each domain, with the 'peak' of the histograms appropriately representative of the population. For example, the 'Anxiety/depression' domain had more actual responses in the 'no' category, compared to 'some' and 'extreme', resulting in the tendency for higher probabilities for this response. However, given the lower number of patients in the 'extreme' category the final graphs were not always ideal (Figures 5.10c and 5.12c).

5.3.3.1.2 Exploring latent variables

The second method of assessing the predictive ability of the model at an individual level involved charting the predicted values for the 'latent variables' (Figure 5.14). The 'latent variable' is the summation of the DLQI and threshold estimates (as seen in the formula of Figure 5.2) that allows the conversion of the ordinal data in to a 'continuum'. For example, suppose we were able to measure pain on a continuous scale y^* - this is an unobserved 'latent' variable. With the EQ-5D we observe y where:

$$y = 0\ (no\ anxiety)\ if\ y^* < \mu_1$$
$$y = 1\ (some\ anxiety)\ if\ \mu_1 \leq y^* < \mu_2$$
$$y = 2\ (extreme\ anxiety)\ if\ y^* \geq \mu_2$$

The ordinal logistic model for y gives an estimated value on the y^*scale for each subject as a function of their scores with the DLQI domains (these are the x values) as follows:

$$y^* = \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p$$

Therefore, subjects recording 'No' with the 'Anxiety/depression' domain of the EQ-5D should give low values on the 'y∗' latent variable scale while subjects recording 'Extreme' with this domain should give high values on that same latent variable scale. Subjects recording 'Some' should give values somewhere in the middle providing the model is predicting outcome at the individual subject level. Once the predicted latent variables were plotted against the number of actual respondents within each category, this was indeed the case as can be seen from Figure 5.14e. For subjects recording 'No' the bulk of the distribution of the latent variable values is towards the left-hand side, while for those recording 'Some' the distribution is shifted to the right and finally for those recording 'Extreme', the distribution is shifted yet further to the right. Figures 5.14a – 5.14d provide corresponding distributions for the remaining domains of the EQ-5D and each of the figures demonstrates that the model was able to reliably achieve a suitable distribution of latent variable values for each domain, therefore providing discrimination at the subject level.

Figure 5.14(a)-(e) Percentage of actual responses against predicated latent variable scores for each domain of the EQ-5D. *Note that the extreme values have been removed for the 'mobility' and 'self-care' domains due to low sample sizes (n=5)

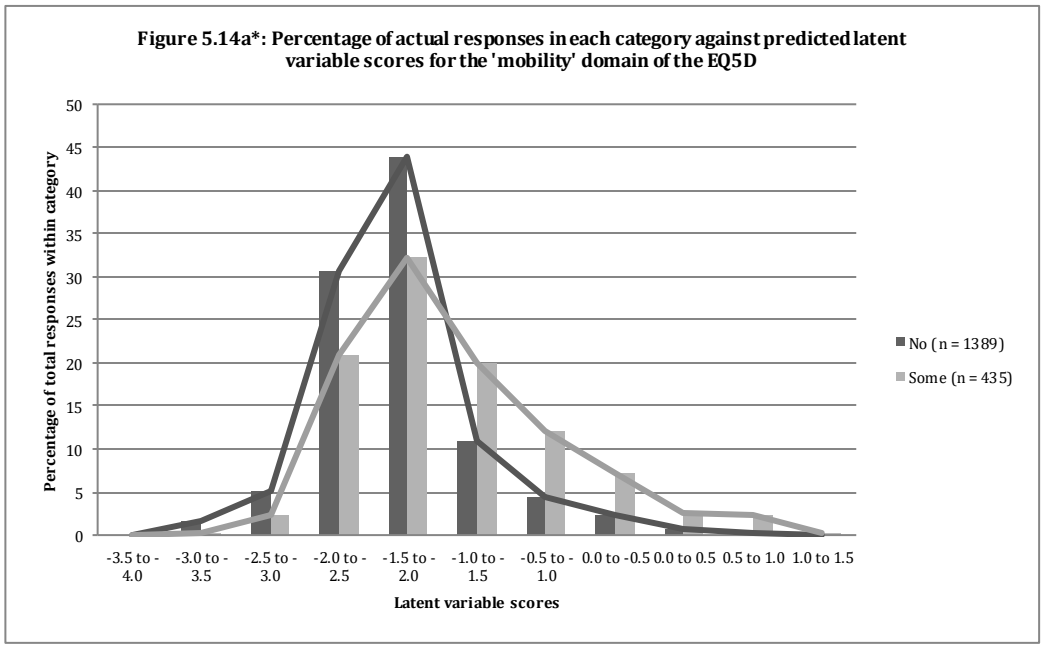


Figure 5.14b*: Percentage of actual responses in each category against predicted latent variable scores for the 'self-care' domain of the EQ5D

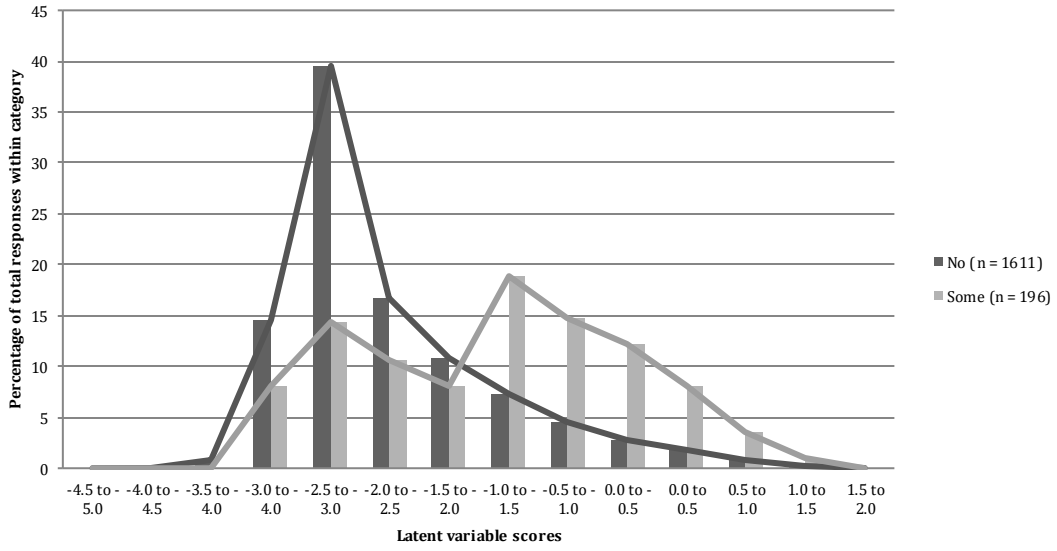
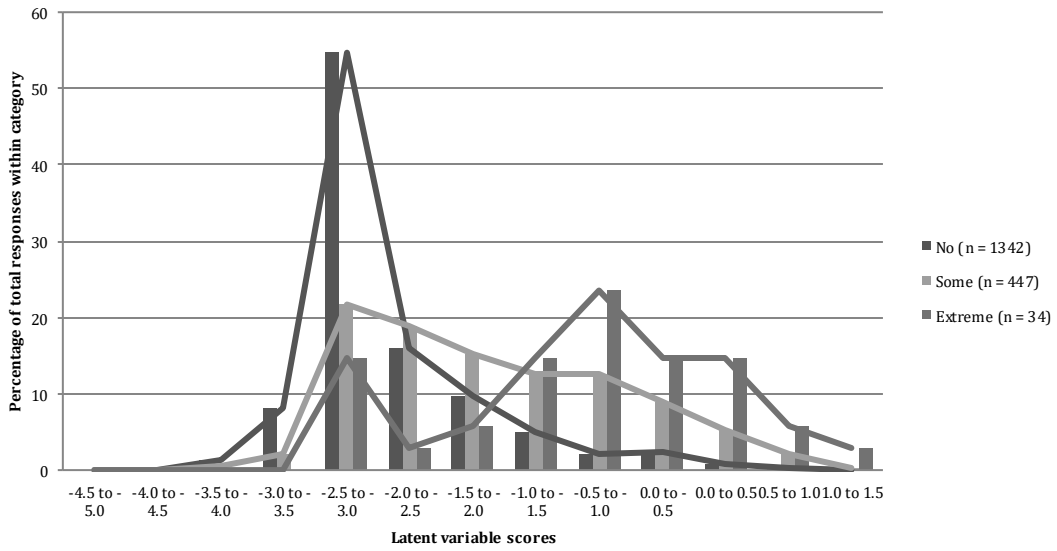
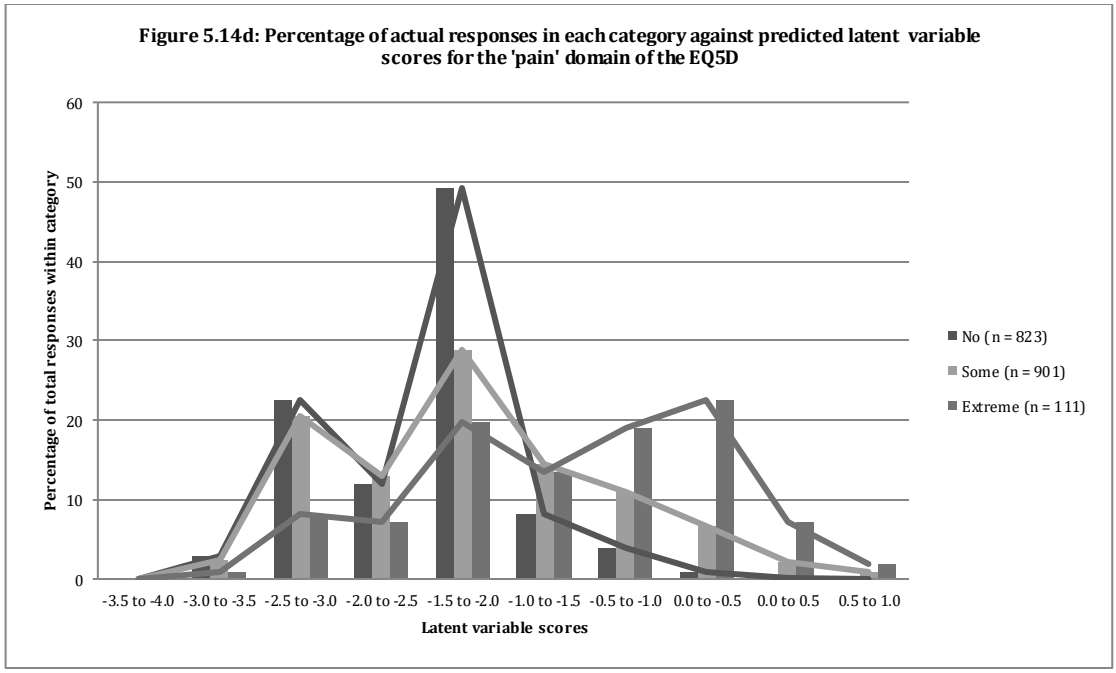
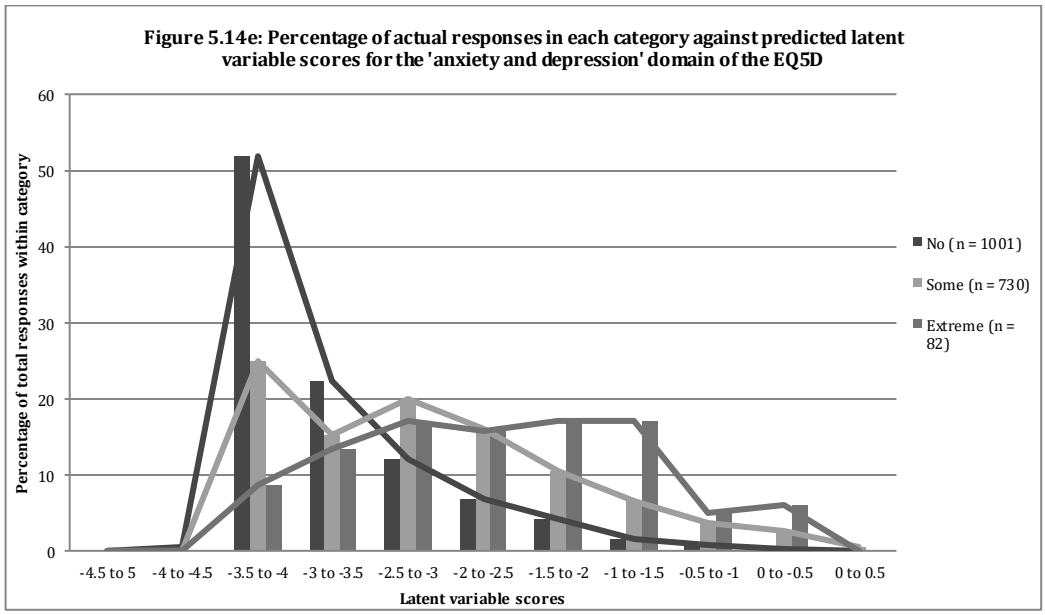


Figure 5.14c: Percentage of actual responses in each category against predicted latent variable scores for the 'usual activities' domain of the EQ5D







5.3.3.2 Final Model

The results for the five models for the five EQ-5D domains are shown in Table 5.33, including estimated coefficients and standard errors from the entire population of 4010 subjects. The complete SPSS output for this work may be found in Appendix XXII. The updated Excel formulae utilising the estimates from the complete dataset may be found in Appendix XXIII.

Table 5.33 Final model coefficients (standard errors) for each EQ-5D domain (Method Two)

	Mobility	Self-Care	Usual activities	Pain/Discomfort	Anxiety/Depression
Threshold a_1	-0.761 (0.211)	0.077 (0.257)	-1.632 (0.222)	-3.148 (0.225)	-2.576 (0.235)
Threshold a_2	4.081 (0.359)	3.859 (0.378)	1.939 (0.236)	0.524 (0.210)	0.711 (0.226)
DLQI1=0	-0.469 (0.160)	-0.636 (0.228)	-0.879 (0.164)	-1.981 (0.145)	-0.224 (0.142)
DLQI1=1	-0.329 (0.145)	-0.386 (0.187)	-0.436 (0.143)	-1.133 (0.136)	-0.254 (0.132)
DLQI1=2	-0.181 (0.141)	-0.233 (0.173)	-0.097 (0.138)	-0.490 (0.490)	-0.246 (0.132)
DLQI2=0	0.448 (0.172)	0.101 (0.237)	0.606 (0.177)	-	-1.215 (0.144)
DLQI2=1	0.381 (0.159)	0.182 (0.203)	0.531 (0.160)	-	-0.829 (0.135)
DLQI2=2	0.024 (0.156)	-0.156 (0.193)	0.135 (0.155)	-	-0.388 (0.136)
DLQI3=0	-0.632 (0.211)	-0.884 (0.263)	-1.034 (0.206)	-0.656 (0.192)	-0.351 (0.192)
DLQI3=1	-0.080 (0.204)	-0.524 (0.247)	-0.557 (0.199)	-0.312 (0.191)	-0.111 (0.190)
DLQI3=2	0.250 (0.192)	0.018 (0.219)	-0.030 (0.190)	-0.150 (0.186)	0.028 (0.185)
DLQI4=0	-	0.154 (0.230)	0.070 (0.173)	-0.140 (0.154)	0.142 (0.153)
DLQI4=1	-	0.339 (0.225)	0.088 (0.173)	0.024 (0.158)	0.050 (0.157)
DLQI4=2	-	0.556 (0.214)	0.330 (0.172)	0.214 (0.165)	0.191 (0.162)
DLQI5=0	-0.396 (0.216)	-0.254 (0.297)	-0.620 (0.219)	-	-
DLQI5=1	-0.201 (0.205)	0.077 (0.268)	-0.336 (0.206)	-	-
DLQI5=2	-0.149 (0.193)	0.012 (0.242)	-0.207 (0.194)	-	-
DLQI6=0	-0.392 (0.183)	-0.063 (0.230)	-0.766 (0.182)	-0.936 (0.173)	-
DLQI6=1	-0.642 (0.203)	-0.253 (0.257)	-0.684 (0.198)	-0.676 (0.187)	-
DLQI6=2	-0.298 (0.205)	0.104 (0.248)	-0.490 (0.203)	-0.422 (0.195)	-
DLQI7=0	-0.268 (0.142)	-0.355 (0.179)	-0.552 (0.140)	0.431 (0.135)	-0.510 (0.131)
DLQI7=1	-0.722 (0.154)	-0.676 (0.196)	-0.741 (0.149)	0.171 (0.143)	-0.281 (0.138)
DLQI7=2	-0.690 (0.204)	-0.537 (0.243)	-0.422 (0.193)	0.353 (0.190)	-0.114 (0.185)
DLQI8=0	-	0.262 (0.303)	-	-	-0.426 (0.224)
DLQI8=1	-	0.307 (0.293)	-	-	-0.263 (0.220)
DLQI8=2	-	0.428 (0.268)	-	-	-0.124 (0.214)
DLQI9=0	-	-0.172 (0.236)	-	-	-0.442 (0.183)

DLQI9=1	-	-0.153 (0.263)	-	-	-0.395 (0.198)
DLQI9=2	-	-0.590 (0.282)	-	-	-0.073 (0.214)
DLQI10=0	-0.728 (0.195)	-1.404 (0.230)	-0.616 (0.197)	-0.843 (0.193)	-0.571 (0.192)
DLQI10=1	-0.357 (0.200)	-0.935 (0.231)	-0.302 (0.202)	-0.481 (0.198)	-0.540 (0.197)
DLQI10=2	-0.155 (0.207)	-0.365 (0.225)	-0.069 (0.208)	-0.241 (0.206)	-0.337 (0.204)

Footnotes

***** In Column 1, the first figure after 'DLQI' is the item number of the DLQI and the last figure is the score of the response to that item, as per author's instructions (http://www.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/dlqi-instructions-for-use-and-scoring/) (Finlay 2020)

**For each DLQI item the coefficients corresponding to DLQIx=3 equate to zero in all cases as this category was used as the reference category to which each of the other categories was compared

5.3.3.3 Summary of the forward variable selection method

The process of selecting the most significant DLQI items and implementing these in the ordinal regression formula demonstrates that the model works. However, this process results in the total predicted number of respondents in each category for an entire population. As described in the previous chapter, this provides some difficulties in calculating utility values, as it is important to affirm individual responses according to the EQ-5D-3L scoring tariff, not just the number of each of the responses. Furthermore, though the predicted numbers are reassuring, the histograms (Figures 5.9 – 5.13) and latent variable graphs (Figure 5.14) demonstrate that the model could yet be strengthened, particularly at the extreme ends of the scale, with closer predicted values.

5.4 Method three: Monte Carlo simulation without forward variable selection and added age & sex variables

Results using the forward variable selection method, though highly predictive at the group level (Figure 5.8), needed further development to avoid systematic bias and reduce the discrepancies between actual and predicted utility values.

To calculate utility values one needs a SPSS syntax, which are available upon request from EuroQol (http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-3l-value-sets.html). This syntax calculates individual utility values depending on subject EQ-5D domain scores. To manually calculate these values is possible, but given the large sample size utility value calculations would be prone to significant time consumption as well as human error. Therefore, it was prudent to develop a model that would allow the accurate prediction of domain scores per patient. Another consideration for improving the model fit was to add extra variables, which in this case were 'age' and 'sex'. The same dataset from 4010 patients with skin diseases (Dalgard et al. 2015) was used.

The dataset was once again randomly split into separate estimation and validation sets using the SPSS version 22 random number generator. Subjects with missing data in the DLQI, EQ-5D and age/sex fields were removed from both datasets to enable model fitting and evaluation. As previously, the estimation set was used to derive the mapping models, whilst the out-of-sample validation set was utilised for validating the fitted models (Results Appendix XXIV). Following validation, the models were fitted to the complete dataset to improve their overall accuracy.

A series of ordinal logistic regressions were fitted for each of the five EQ-5D dimensions against the ten individual items of the DLQI using SPSS version 22. All ten DLQI items were included this time for each domain model in order to capture all the correlations induced by each DLQI item. Monte Carlo simulations were run using these variables only. Subsequently, regressions were run with age and sex alone, DLQI items alone, as well as age and sex combined with DLQI items in order to evaluate the contribution of age and sex, and collectively the ten DLQI items. For each domain the combination of ten DLQI items with age and sex significantly improved the fit of the models, which included just age and sex, or just the ten DLQI items (Table 5.34). It should be noted that age and sex are invariably recorded, and therefore accessible and have been shown to significantly impact on QoL (Sampogna et al. 2006). For the purpose of modelling, males were encoded as '0' and females as '1'; age was inputted in years.

Table 5.34 The significance of the DLQI items and age and sex compared to the model containing age, sex and the DLQI items for each EQ-5D domain

EQ-5D Domain	Covariates: Age / Sex			Covariates: DLQI			Covariates: Age / Sex / DLQI
	-2 log likelihood	Chi-square comparing to full model	Degrees of freedom (df)	-2 log likelihood	Chi-square comparing to full model	Degrees of freedom (df)	-2 log likelihood
Mobility	507.39	171.87	2	1311.04	107.01	10	1565.91
Self-care	430.84	18.67	2	862.51	172.87	10	988.67
Usual activities	610.24	36.59	2	1388.09	269.24	10	1754.06
Pain	783.75	37.54	2	1737.99	424.87	10	2373.31
Anxiety/ depression	772.55	18.91	2	1787.89	284.41	10	2451.74

Due to the improved fit, it was hypothesised that these extra variables may improve the predictive ability of the models. The estimates from the final five models were fitted into the OLR equations. These ordinal models produced a set of probabilities for each possible outcome category, as given by the equations in Figure 5.2.

However, the summation of probabilities was not used in this instance as this process was previously used to calculate the total predicted number of respondents within each EQ-5D domain. This was not required for method three: the model was tested on the validation dataset to produce three predicted probabilities per subject per EQ-5D domain (Y = 1, 2 or 3). Using these predicted probabilities, a series of Monte Carlo simulations were run for each subject resulting in predicted domain responses and consequently utility scores. Each Monte Carlo simulation involved randomly generating a number between 0 and 1 for each EQ-5D domain, which was then assigned a score depending on where it stood between the domain probabilities. This was repeated ten times to ensure the model output was stable. The average predicted utility scores for each Monte Carlo simulation were then compared with the actual average utility score within the validation set across the entire patient population. As a final step, the model was re-fitted on the entire patient dataset to produce a model with increased accuracy.

5.4.1 Calculating utility values

For each subject, an actual utility value (based on actual patient responses) and a predicted utility value (derived from models) were calculated. For the purpose of this work, utility value is defined as 'the cardinal value that reflects an individual's preference for different health outcomes' (Tolley 2009). In this thesis, these will be defined by the pre-existing EQ-5D health states (i.e. between 'perfect health' and 'death'). Permission was sought from EuroQol (http://www.euroqol.org) to utilise the standardised UK time-trade-off (TTO) values, as European values did not exist at the time of the request. A pre-existing syntax was provided by EuroQol, which was used to calculate utility values within SPSS version 22, as seen below:

```
*****************************************************************
*        SPSS syntax code for the computation of     *
*        index values with the UK MVH-A1 TTO value set     *
*****************************************************************

compute UK_TTO = 1.0.

if (mobility eq 2) UK_TTO = UK_TTO - 0.069.
If (mobility eq 3) UK_TTO = UK_TTO - 0.314.

if (selfcare eq 2) UK_TTO = UK_TTO - 0.104.
if (selfcare eq 3) UK_TTO = UK_TTO - 0.214.

if (activity eq 2) UK_TTO = UK_TTO - 0.036.
if (activity eq 3) UK_TTO = UK_TTO - 0.094.

if (pain eq 2) UK_TTO = UK_TTO - 0.123.
if (pain eq 3) UK_TTO = UK_TTO - 0.386.

if (anxiety eq 2) UK_TTO = UK_TTO - 0.071.
if (anxiety eq 3) UK_TTO = UK_TTO - 0.236.

if (mobility ne 1 or activity ne 1 or selfcare ne 1 or pain ne 1 or anxiety ne 1)
 UK_TTO = UK_TTO - 0.081.
```

```
if (mobility eq 3 or selfcare eq 3 or activity eq 3 or anxiety eq 3 or pain eq 3)
 UK_TTO = UK_TTO - 0.269.

if (missing(mobility) or missing(activity) or missing(selfcare) or missing(pain) or
missing(anxiety))
UK_TTO = 9.

missing values UK_TTO (9).

execute.
```

Syntax key

eq = 'equal to', ne = 'not equal to'

Utility values were adjusted for whether individual subjects scored 'all ones' (i.e. 'no problems' in every EQ-5D domain) or 'at least one three' (i.e. the patient scored 'extreme problems' in at least one EQ-5D domain). Binary logistic regression models were created to counteract any systematic bias in the overall utility values (Appendix XXV). However, this would eventually become an unnecessary step in the process as these shifts in utility values are already considered in the SPSS syntax, as seen above.

5.4.2 Results of Monte Carlo simulation without forward variable selection and added age & sex variables

The patient dataset (n=4010) was randomly split into estimation (n=2007) and validation (n=2003) data sets. After excluding subjects with missing Age, Sex, DLQI, and EQ-5D data there were 1769 patients in the estimation set (11.9% excluded), and 1773 in the validation set (11.5% excluded). The socio-demographic characteristics of the original dataset are shown in Table 5.1.

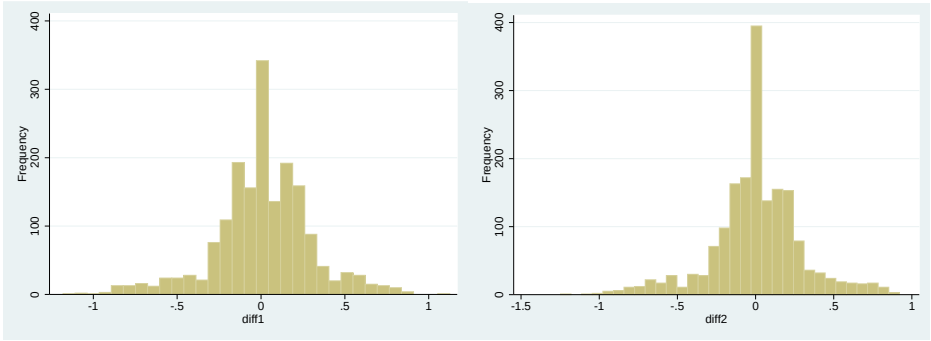
5.4.2.1 External validation

Five ordinal models were derived, for each EQ-5D domain, and used to predict the probability of each EQ-5D response for each subject in the validation set, and subsequently the utility scores using Monte Carlo simulations. The model was shown to be highly predictive and repeated simulations demonstrated a stable model (Figure 5.15, Appendix XXVI). The

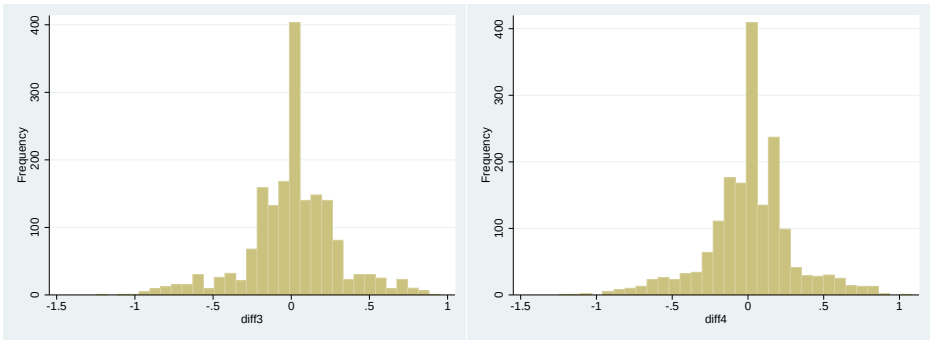
average predicted utility value for the entire validation set ranged from 0.742 to 0.753 across the 10 Monte Carlo simulations compared to the actual average utility value of 0.754.

The predictive ability of the model at an individual subject level was also examined using histograms to display the difference between predicted utility score and the actual utility score for each Monte Carlo simulation. Figure 5.15 depicts a centrality around '0' which indicates the strong predictive collective capability of the OLR models. Of all ten Monte Carlo simulations shown, on average, 38% of the individual utility values were predicted to lie within 0.1 of the actual values, while 66% were predicted to lie within 0.2 and 80% within 0.3.

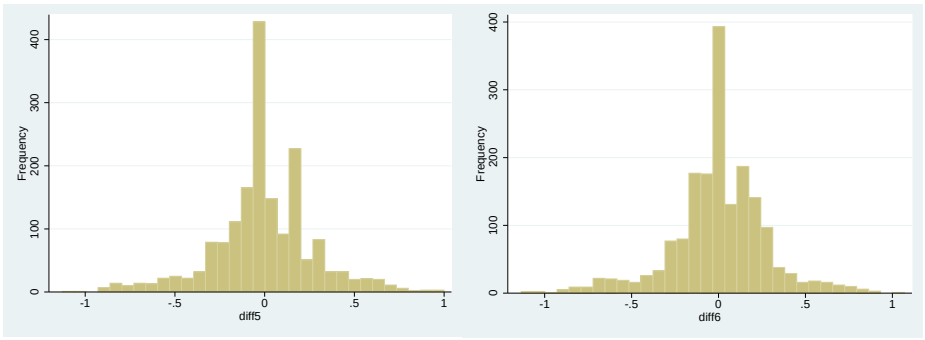
Figure 5.15 (a)-(j) Histograms demonstrating the average difference between predicted and actual utility scores for each Monte Carlo simulation



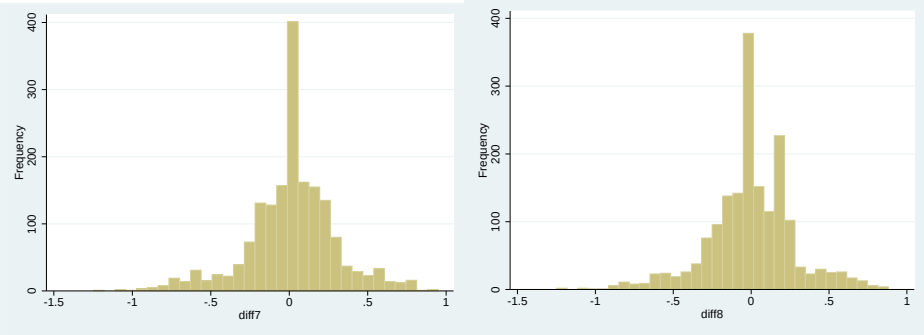
(a) (b)



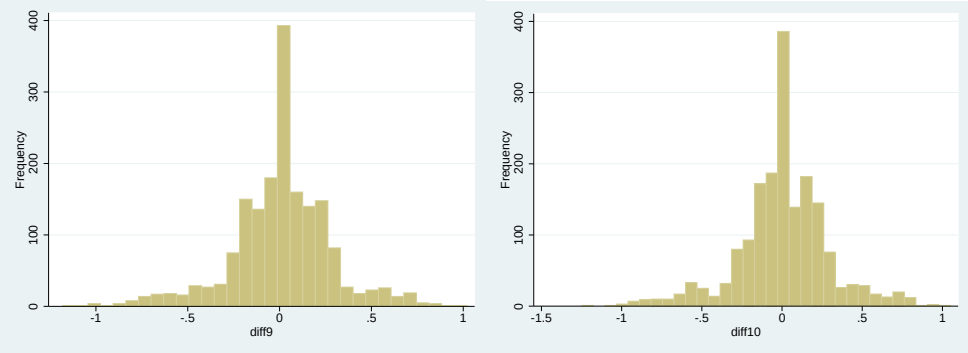
(c) (d)



(e) (f)



(g) (h)



(i) (j)

5.4.2 2 Final model coefficients

Table 5.35 shows results for the five models for the five EQ-5D domains, including estimated coefficients and standard errors from all subjects. These coefficients are the 'weights' that influence the final ordinal model equation whereby higher figures indicate a stronger correlation between the relevant items. For example, DLQI item 1 asks: 'Over the last week, how itchy, sore, painful or stinging has your skin been?' and this correlated most highly with the 'pain/discomfort' domain (0.685). Similarly, DLQI item 10 asks: 'Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?'. The highest coefficient for this question was 0.478 for the 'self-care' EQ-5D domain, reaffirming the strong conceptual correlation between the two questionnaires as described previously.

Table 5.35 Final model coefficients (standard errors) for each EQ-5D domain (Method Three)

	Mobility	Self-Care	Usual activities	Pain/Discomfort	Anxiety/Depression
Threshold a_1	4.546 (0.232)	4.640 (0.306)	3.680 (0.216)	2.381 (0.173)	1.934 (0.170)
Threshold a_2	9.552 (0.392)	8.861 (0.471)	7.364 (0.272)	6.229 (0.211)	5.240 (0.199)
Age	0.051 (0.003)	0.033 (0.004)	0.027 (0.003)	0.025 (0.002)	0.003 (0.002)
Sex	0.046 (0.089)	-0.213 (0.120)	0.133 (0.087)	0.177 (0.073)	0.465 (0.073)
DLQI 1	0.087 (0.055)	0.176 (0.074)	0.270 (0.052)	0.685 (0.047)	0.035 (0.044)
DLQI 2	0.013 (0.061)	0.052 (0.079)	-0.114 (0.059)	0.014 (0.049)	0.378 (0.048)
DLQI 3	0.209 (0.068)	0.278 (0.085)	0.351 (0.063)	0.199 (0.060)	0.107 (0.057)
DLQI 4	0.071 (0.058)	0.053 (0.072)	0.051 (0.055)	0.097 (0.050)	-0.099 (0.048)
DLQI 5	0.113 (0.075)	0.064 (0.095)	0.209 (0.070)	-0.122 (0.064)	0.205 (0.062)
DLQI 6	0.116 (0.060)	0.014 (0.071)	0.215 (0.055)	0.310 (0.054)	-0.075 (0.052)
DLQI 7	0.251 (0.053)	0.236 (0.063)	0.283 (0.049)	-0.048 (0.046)	0.186 (0.044)
DLQI 8	-0.008 (0.076)	-0.013 (0.091)	-0.081 (0.071)	0.163 (0.066)	0.121 (0.064)
DLQI 9	-0.094 (0.065)	0.002 (0.075)	0.068 (0.060)	0.132 (0.057)	0.194 (0.054)
DLQI 10	0.233 (0.061)	0.478 (0.071)	0.210 (0.057)	0.245 (0.054)	0.155 (0.052)

5.5 Method four: split-half cross validation

All the methods employed thus far have involved randomly splitting the original database of 4010 patients only once, resulting in one derivation and one validation set with unequally sized populations. This process does not result in true randomisation and the results were therefore subject to possible statistical bias. Therefore, to truly test the OLR model, the entire process was repeated with numerous random splits. This was done in order to help improve the overall accuracy of the model and also to prove that the accuracy of the predicted utility values was not due to chance.

The database was filtered after deleting cases with missing data in variables for DLQI, EQ-5D, age and sex. This differed from the previous methods where missing data were only removed following the modelling. This resulted in 'pure' base data that may be used to derive estimates, as previously it was assumed SPSS v22 would automatically ignore missing data, though perhaps this was not the case, resulting in aberrant data. There was no clear indication on the software used as to whether data from incomplete cases would be considered in the final analysis and therefore it was safer to filter the data prior to any further detailed work. The core database was then randomly split into two groups, one for the derivation of the models, and one for the validation, as before. This process was repeated five times resulting in five random pairs of derivation/validation datasets. The process of ordinal logistic regression as described above was conducted again for each pair of datasets using DLQI, age and sex as variables. Therefore, a total of 25 models (5 x 5 domains) were created to test the validity of the OLR method. As described in the previous section, using the

three predicted probabilities for each domain, one Monte Carlo simulation was run on each validation set, following which predicted utility values were calculated, averaged and compared with the actual population average. Once this entire process had occurred five times, the derivation and validation datasets were switched around to further consolidate the split-half validation method for calculating utility values (see results in Appendix XXVI). This resulted in a total of ten Monte Carlo simulations.

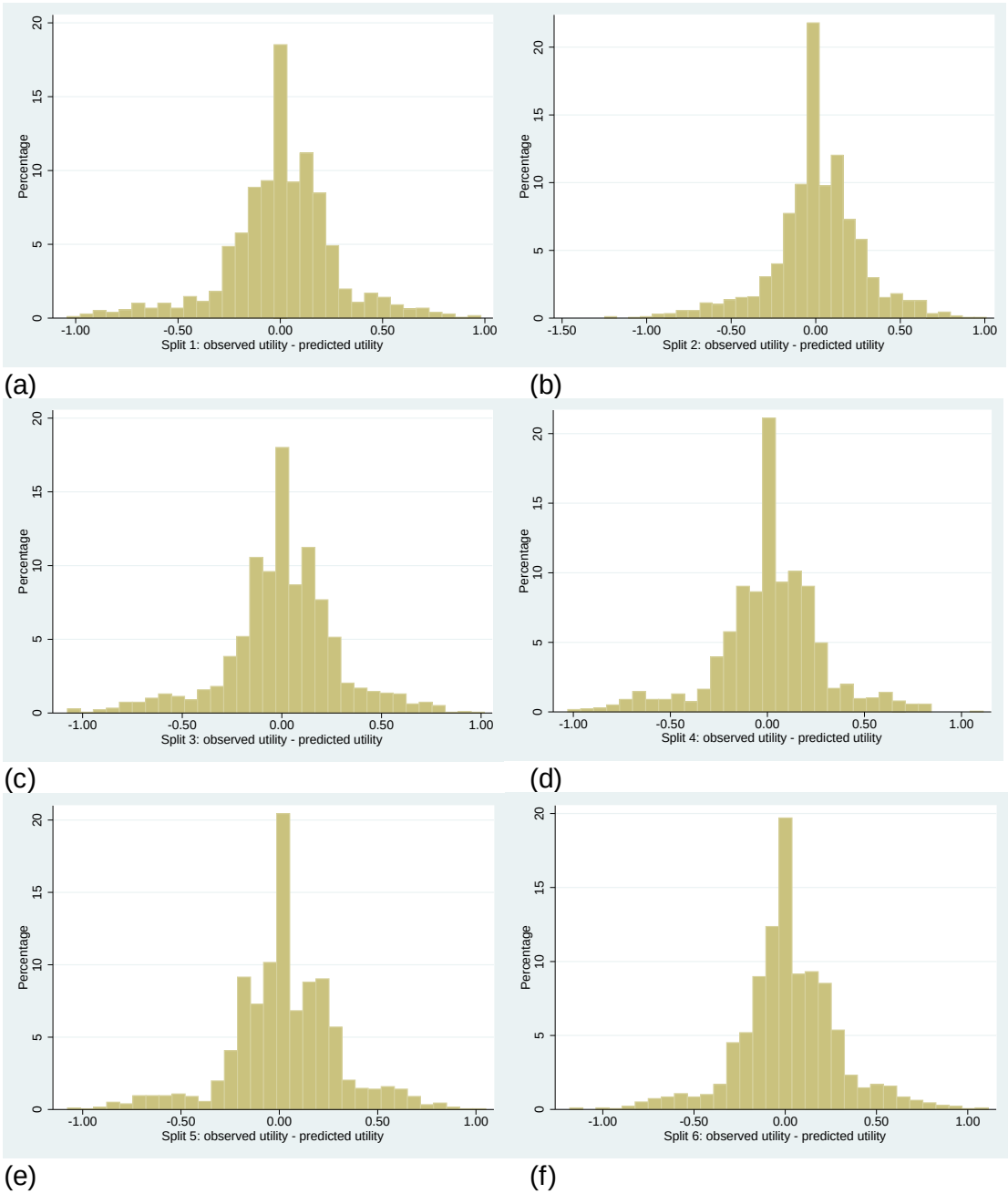
The proportional odds assumption was assessed using the test for parallelism within SPSS. For each domain, except mobility, this test gave a non-significant result supporting the assumption for proportional odds. For mobility the p-value of 0.01 did indicate some departure from this assumption but this can be explained by the small number of subjects (n=11) in the dataset who have a mobility outcome category of 3. As a consequence, the sub-model that compares categories 1 and 2 combined with category 3 is unstable and the results for the test for parallelism unreliable. However, as the results demonstrate, this was not the case with the other domains and the overall results demonstrate that the methodology is reliable.

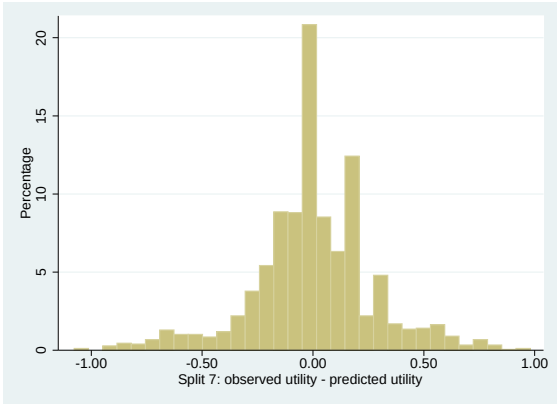
5.5.1 Results of the split-half cross validation

The dataset (n=4010) was filtered to exclude subjects with missing age, sex, DLQI, and EQ-5D data. This resulted in a total of 3542 subjects. Each random derivation and validation set therefore had exactly 1771 patients.

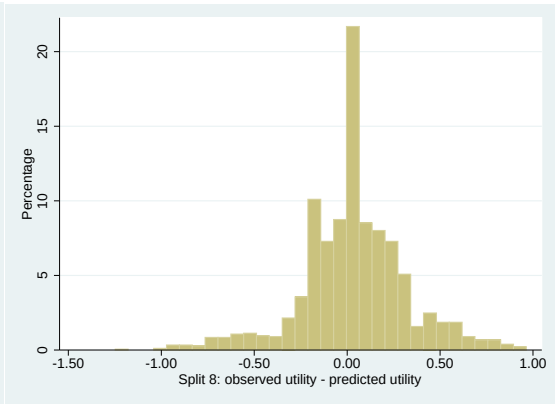
For each EQ-5D domain, five ordinal models were derived and used to predict the probability of each EQ-5D response for each subject in each validation set, and subsequently the utility scores using Monte Carlo simulation. The model was shown to be highly predictive and repeated data splits demonstrated a stable model (Figure 5.16).

Figure 5.16 (a)-(j) Histograms demonstrating the mean difference between predicted and actual utility scores for each Monte Carlo simulation

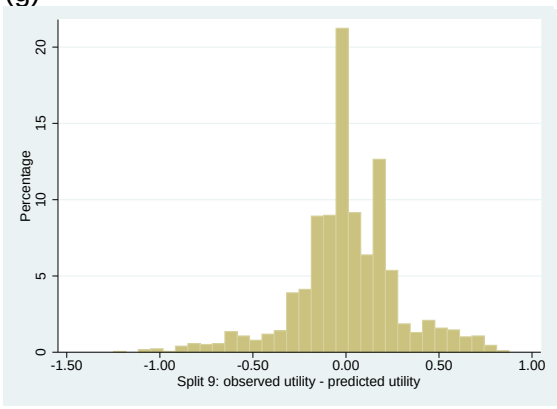




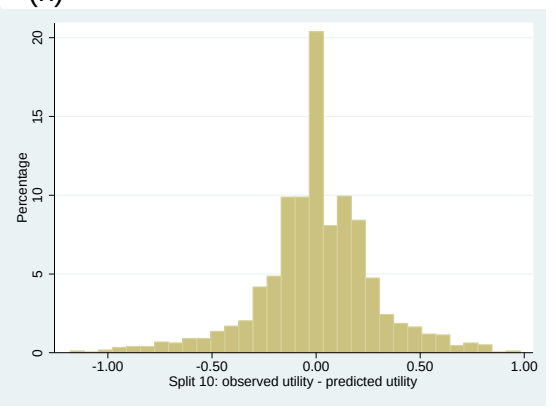
(g)



(h)



(i)



(j)

In each case the predicted mean utility value was a slight underestimate of the actual mean utility and across the ten validation sets (Table 5.36), the difference between these values ranged from -0.0024 to -0.0239, with a mean overall difference of -0.0120. This 1.59% underestimate represents a clinically unimportant effect (Coretti et al. 2014). The mean square error (MSE) across all ten splits ranged from 0.0728 to 0.0818 with an average of 0.0766. The mean absolute error (MAE) across all ten splits ranged from 0.1873 to 0.2009 with an average of 0.1934.

Table 5.36 Summary of the average predicted utility values across all ten splits

	Split 1	Split 2	Split 3	Split 4	Split 5	Split 6	Split 7	Split 8	Split 9	Split 10	AVERAGE
Average Utility Value Difference	0.0024	0.0121	0.0040	0.0127	0.0214	0.0211	0.0044	0.0239	0.0131	0.0046	**0.0120**
% Utility Values Within 0.1 of Actual UV	37.0977	38.6787	36.3071	36.6460	36.4201	38.1141	37.3800	35.4037	38.0576	38.1705	**37.2275**
% Utility Values Within 0.2	62.2247	63.8622	62.0553	62.5071	60.7002	61.6036	62.1118	60.7566	62.1118	61.3213	**61.9255**

of Actual UV											
% Utility Values Within 0.3 of Actual UV	81.6488	80.6889	80.1807	81.5359	80.8583	81.0841	80.5195	79.1079	80.2372	80.2936	**80.6155**

The predictive ability of the model at an individual subject level was also examined using histograms to display the difference between predicted utility score and the actual utility score for each simulation at the individual subject level. The results from these splits are displayed in Figure 5.16. All the plots depict a centrality around '0' which indicates the strong predictive collective capability of the OLR models. On average, 37% of the individual utility values were predicted to lie within 0.1 of the actual values, while 62% were predicted to lie within 0.2 and 81% within 0.3 over all ten validation exercises (Table 5.36).

5.5.2 The final model and spread-sheet template

Details of the final fitted models using data from the 3542 subjects are provided in Table 5.37. These are the final estimates that will be available to researchers should they wish to map DLQI scores to utility values, and has been included in the final publication of this study (Ali et al. 2017c).

Table 5.37 Final model coefficients (standard errors) for each EQ-5D domain (Method Four). The 10 DLQI questions are represented in order by DLQI 1, DLQI 2 etc

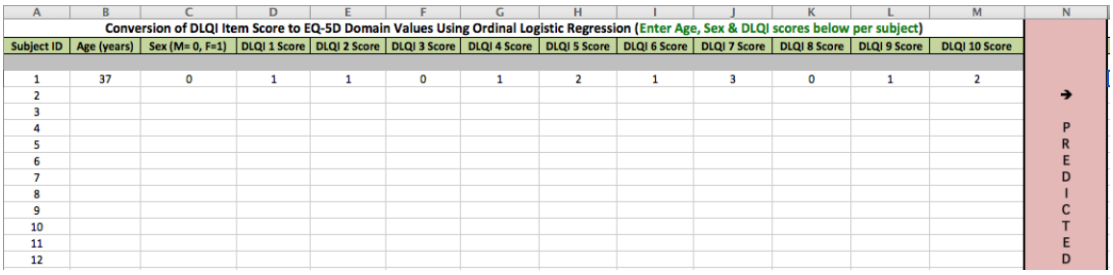
	Mobility	Self-Care	Usual activities	Pain/Discomfort	Anxiety/Depression
Threshold a_1	4.500 (0.190)	4.854 (0.251)	3.574 (0.171)	2.204 (0.133)	1.469 (0.128)
Threshold a_2	9.506 (0.368)	9.074 (0.438)	7.231 (0.237)	6.052 (0.178)	4.775 (0.162)
Age	0.051 (0.003)	0.033 (0.004)	0.027 (0.003)	0.025 (0.002)	0.003 (0.002)
Sex	0.046 (0.089)	-0.213 (0.120)	0.133 (0.087)	0.177 (0.073)	0.465 (0.073)
DLQI 1	0.087 (0.055)	0.176 (0.074)	0.270 (0.052)	0.685 (0.047)	0.035 (0.044)
DLQI 2	0.013 (0.061)	0.052 (0.079)	-0.114 (0.059)	0.014 (0.049)	0.378 (0.048)
DLQI 3	0.209 (0.068)	0.278 (0.085)	0.351 (0.063)	0.199 (0.060)	0.107 (0.057)
DLQI 4	0.071 (0.058)	0.053 (0.072)	0.051 (0.055)	0.097 (0.050)	-0.099 (0.048)
DLQI 5	0.113 (0.075)	0.064 (0.095)	0.209 (0.070)	-0.122 (0.064)	0.205 (0.062)
DLQI 6	0.116 (0.060)	0.014 (0.071)	0.215 (0.055)	0.310 (0.054)	-0.075 (0.052)
DLQI 7	0.251 (0.053)	0.236 (0.063)	0.283 (0.049)	-0.048 (0.046)	0.186 (0.044)
DLQI 8	-0.008 (0.076)	-0.013 (0.091)	-0.081 (0.071)	0.163 (0.066)	0.121 (0.064)
DLQI 9	-0.094 (0.065)	0.002 (0.075)	0.068 (0.060)	0.132 (0.057)	0.194 (0.054)
DLQI 10	0.233 (0.061)	0.478 (0.071)	0.210 (0.057)	0.245 (0.054)	0.155 (0.052)

In order to further make this process more accessible and easy to use, a spreadsheet was designed with the relevant estimates and formulae already inputted (Figure 5.17). Following simple instructions, researchers shall therefore be able to calculate utility values for a cohort

of patients with given DLQI values. A step-by-step 'recipe' is also available (Appendix XXVII) should researchers wish to recreate the model.

Figure 5.17 (a)-(d) Lateral sequential screenshots of the spread-sheet available to researchers upon request

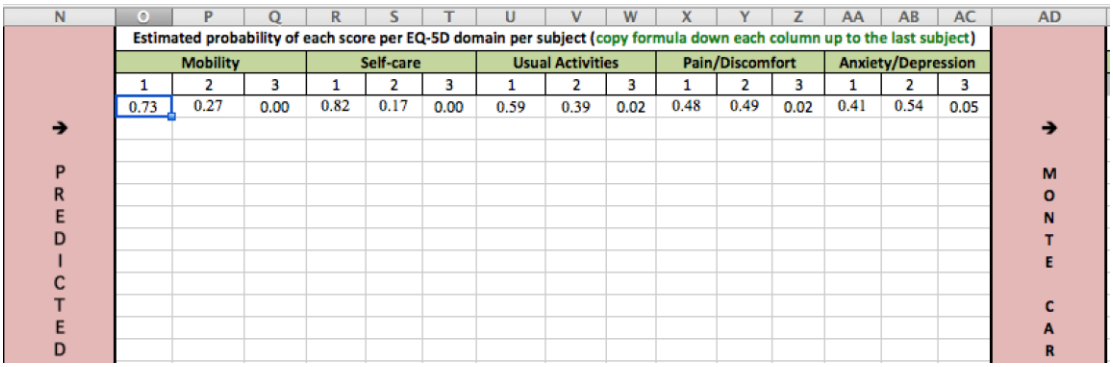
a)



Conversion of DLQI Item Score to EQ-5D Domain Values Using Ordinal Logistic Regression (Enter Age, Sex & DLQI scores below per subject)												
Subject ID	Age (years)	Sex (M= 0, F=1)	DLQI 1 Score	DLQI 2 Score	DLQI 3 Score	DLQI 4 Score	DLQI 5 Score	DLQI 6 Score	DLQI 7 Score	DLQI 8 Score	DLQI 9 Score	DLQI 10 Score
1	37	0	1	1	0	1	2	1	3	0	1	2

→ PREDICTED

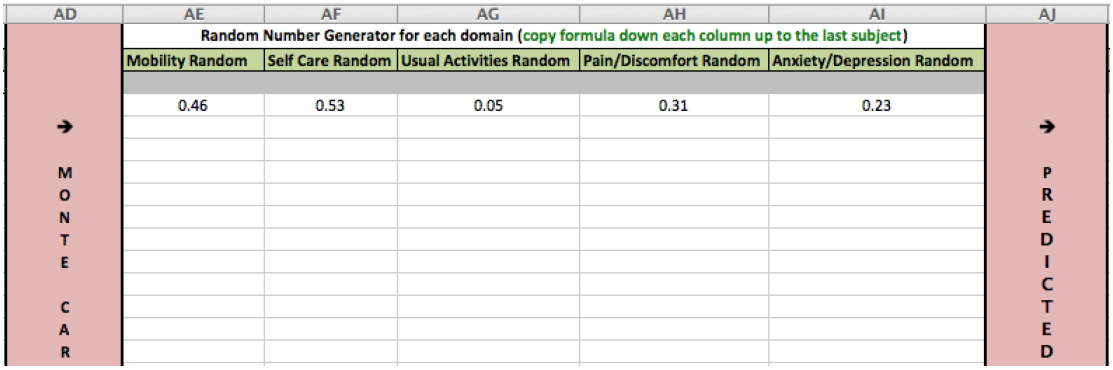
b)



Estimated probability of each score per EQ-5D domain per subject (copy formula down each column up to the last subject)															
	Mobility			Self-care			Usual Activities			Pain/Discomfort			Anxiety/Depression		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
	0.73	0.27	0.00	0.82	0.17	0.00	0.59	0.39	0.02	0.48	0.49	0.02	0.41	0.54	0.05

→ PREDICTED → MONTE CAR

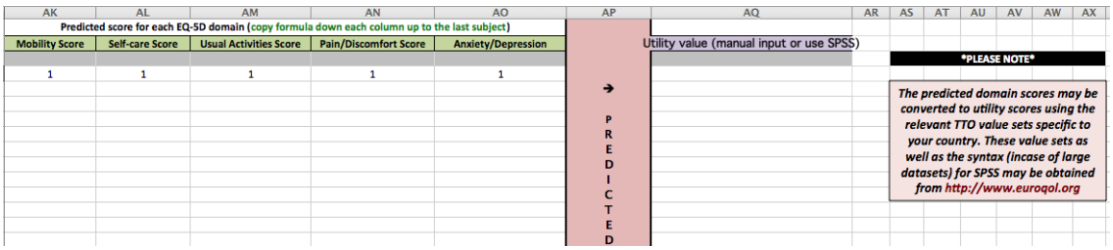
c)



Random Number Generator for each domain (copy formula down each column up to the last subject)				
Mobility Random	Self Care Random	Usual Activities Random	Pain/Discomfort Random	Anxiety/Depression Random
0.46	0.53	0.05	0.31	0.23

→ MONTE CAR → PREDICTED

d)



Predicted score for each EQ-5D domain (copy formula down each column up to the last subject)				
Mobility Score	Self-care Score	Usual Activities Score	Pain/Discomfort Score	Anxiety/Depression
1	1	1	1	1

→ PREDICTED

Utility value (manual input or use SPSS)

PLEASE NOTE

The predicted domain scores may be converted to utility scores using the relevant TTO value sets specific to your country. These value sets as well as the syntax (incase of large datasets) for SPSS may be obtained from http://www.euroqol.org

5.5.3 Further validation: analysis on subsets of patient population

To further evaluate the model's reliability, the OLR mapping method was also applied to different subsets of the study population.

A model was derived from psoriasis-only patients (n=484) and tested on patients with all other skin conditions (n=3058) (Appendix XXVIII). The mean difference between the observed and predicted health utility estimates was 0.05 (MSE 0.08, MAE 0.20). Thirty six percent of the individual health utility estimates were predicted to lie within 0.1 of the observed values, while 61% were predicted to lie within 0.2 and 78% within 0.3.

Similarly, the model performance was tested on different geographical groups of patients. As a test exercise, a model derived from patients in Italy (n=517) was tested on patients from Norway (n=468) (Appendix XXIX). The mean health utility estimate difference for the Norway patients was 0.06 (MSE 0.09. MAE 0.21). Thirty six percent of the individual health utility estimates were predicted to lie within 0.1 of the observed values, while 59% were predicted to lie within 0.2 and 78% within 0.3.

Despite the small sample sizes for the model building exercise in these two cases, their evaluations support the reliability and robustness of the modelling framework.

5.5.4 Comparison with the Currie and Conway linear regression model

The final step was to compare the performance of the OLR method to a previously used model. Thus, using split-half cross validation and Monte Carlo simulation, the modelling framework was repeated to test the linear regression algorithm utilised by (Currie and Conway 2007) on this dataset, which is larger and more diverse, to compare the accuracy of the two distinct mapping techniques. This method uses the total DLQI scores and correlates it directly with the final health utility estimates resulting in a linear regression formula in the format: Utility = a – (b x DLQI total score).

For this Currie and Conway (2007) linear regression model the mean difference between the observed and predicted estimates was -0.0007. The MSE across all ten splits ranged from 0.04 to 0.05 with a mean MSE of 0.05. The mean absolute error (MAE) across all ten splits ranged from 0.15 to 0.16 with an average MAE of 0.16. On average, 38% of the individual health utility estimates were predicted to lie within 0.1 of the observed estimates, while 78% were predicted to lie within 0.2 and 89% within 0.3 over all 10 validation exercises.

5.6 Discussion

This mapping exercise presented many challenges resulting in numerous refinements over three years. Repeated submissions to journals and peer reviews was a valuable experience resulting in improved modelling strategies and methods, ultimately providing evidence that OLR is a valid mapping tool in calculating utility values from DLQI scores.

There is increasing interest in correlating and mapping specialty and disease-specific scores into generic measures, such as the EQ-5D, for cost-effective analysis and to provide more accurate disease-specific data which generic measures are unable to capture. Schmitt and Küster (2015) correlated the Work Limitations Questionnaire with the DLQI ($r = 0.47$, $p < 0.0001$) to derive a model to calculate work productivity in psoriasis. Møller et al. (2015) state that "disutility among psoriasis patients is within the ranges of other chronic diseases". There is therefore a need to accurately represent and compare data from dermatology, as well as specialty- or disease-specific instruments with utility values from other conditions. Furthermore, there are several inherent disadvantages with generic measures such as the EQ-5D or Short-Form 36 (SF-36) e.g. they contain irrelevant questions for patients with severe inflammatory conditions requiring imputation due to systematically missing answers in the questionnaires. Patients may also develop 'questionnaire fatigue' from repeated completions. Focusing on one specialty- or disease-specific questionnaire, from which utility values may be derived, provides a perception of relevance encouraging thorough careful completion by patients whilst also reducing study time and costs for researchers.

Several approaches were employed to map the DLQI on to EQ-5D values using OLR. Over a long process of trial and error, the final methodology of split-half validation and Monte Carlo simulation truly demonstrated the strength of this model: this study has succeeded in mapping DLQI scores to EQ-5D utility data. The model reliably predicts EQ-5D scores, in particular at a group level, demonstrated through an external validation process resulting in very close utility score predictions. The model is shown also to provide close prediction of utility scores at an individual subject level. On average, 38% of the individual utility values were predicted to lie within 0.1 of the actual values, while 66% were predicted to lie within 0.2 and 80% within 0.3. As these are still fairly significant differences on a scale of 0-1, the model's group-level performance demonstrates better predictive ability.

There are strong conceptual associations between the DLQI and EQ-5D items. Mapping is more likely to be successful where conceptual overlap between two measures exists (Longworth and Rowen 2011). This is so for the DLQI and EQ-5D; many studies have

reported a strong association (Scalone et al. 2006; Shikiar et al. 2007; Radtke et al. 2009; Matusiak et al. 2010; Cortesi et al. 2011; Hjortsberg et al. 2011), which is reaffirmed by this study. Although overall predictions were strongly correlated to the actual scores at a group level, the individual predicting power of the model requires further testing, perhaps on a separate patient database.

The linear regression model utilised by Currie and Conway (2007) provided better predictive accuracy when fitted on this study's dataset (average difference between predicted and observed health utility estimates = 0.00065, compared to OLR = 0.0120). This was also reflected in the respective MAE (linear regression = 0.16, OLR = 0.19) and MSE (linear regression = 0.05, OLR = 0.08) values. It is therefore plausible that this mapping method performs better when fitted on a larger and dermatologically diverse dataset, compared to its previous validation study which was limited to a small sample size and to psoriasis patients in the UK (Currie and Conway 2007). However, there is one structural advantage in the use of the ordinal model over the linear model (Currie and Conway 2007). Since the DLQI total score always takes a positive value, the maximum utility value derived from the linear regression equation has an upper bound of 'a'. In a typical application the value of the constant 'a' will approach 1 but will never be equal to 1 and a predicted health utility estimate of '1' ('perfect health') cannot be obtained. In the OLR model and the associated Monte Carlo simulation such an outcome can be achieved. Both models' estimates are derived from a European dataset of over 3,500 patients (after deleting missing data) with various dermatological conditions and the predicted responses may be used to calculate country-specific health utility estimates (Rivero-Arias et al. 2010). This was not possible using the previous linear model (Currie and Conway 2007), derived from a UK dataset, because of differing health utility estimate tariffs between countries (Tsuchiya et al. 2002; Rutten-van Mölken et al. 2006). Thus, the proposed ordinal model, as well as the revised linear regression model, may be used as mapping tools in other European countries.

Nevertheless, there are some limitations of the OLR model. The actual scores for the DLQI and the EQ-5D were sometimes inconsistent within the same subject e.g. one subject answered 1 on every EQ-5D domain ('perfect health') but 29 on the DLQI (very poor health). This could be due to poor understanding of the items, the reliability or validity of the instruments or due to random errors. Though these data were included to avoid bias, Van Hout et al. (2012) argue analysis should be restricted to logically consistent responses. Perhaps including more socio-demographic variables in the model, other than age and sex, may improve its predictive performance, though this may result in only marginal improvements that would not outweigh the complexity of running the model (Gray et al.

2006).

The UK time trade-off (TTO) values were used in the derivation of this model; it is worth considering that these health states were elicited in 1993 and therefore may not be up to date with current health valuations. Furthermore, no official European TTO values exist for EQ-5D health states and therefore the UK TTO values were applied throughout the validation process. Further, sensitivity analysis may be conducted using preference value-sets from different countries. However, these were not accessible for this study, but would be a useful consideration for future studies.

Though there may be cultural variation influencing HRQoL and utility responses, it has not been possible to test this specific question. Experience suggests that within the European context there is some uniformity of attitudes, cultural norms and responses, as the DLQI has undergone over one hundred validated translations, with a significant number in European countries (Basra et al. 2008a). However, the methodology remains intact and consistent, regardless of the TTO values utilised. Though bootstrapping may indeed be the best approach for testing such models, this would require some additional theoretical considerations to extend existing methodology for the binary logistic model to the ordinal setting. This approach was bypassed by using 'split-half cross validation', which is a valid technique for large sample sizes (Steyerberg et al. 2001). Nevertheless, this study presents the opportunity for further statistical research.

There may be concerns regarding the use of these models in different diseases and whether single disease models would provide more accurate utility data. This study includes a wide range of the most common different skin diseases from a wide range of different European countries, giving the models additional strength in terms of universality. However, a model was successfully derived from psoriasis-only patients and was tested on patients with all other conditions, with the predicted results reassuringly similar to the original OLR model validation exercise. Two limitations of this exercise were the sample size of psoriasis patients, which was relatively small (n=484) and that none of the patients had answered 'extreme' for the self-care domain of the EQ-5D. Given the overall sample size from which the OLR model was created, it is therefore plausible that the model may be implemented successfully across different conditions, limiting the need for condition-specific modelling, which may be practically difficult to create. Furthermore, numerous models may result in confusion for researchers, whereas a single tool for utility prediction may prove to be more pragmatic, user-friendly and accessible.

This thorough modelling process has identified a template that may be used as a road map across other medical disciplines in instances where similar needs exist. The current methodology based on the OLR model will therefore be useful for researchers interested in deriving generic HRQoL data, including descriptive information, from disease-specific populations without having to implement numerous questionnaires. Though OLR has previously been used for converting measures (Gray et al. 2006), this is the first time it has been used to convert a specialty-specific instrument into a generic measure. A step-by-step guide is provided to implement the OLR model (Appendix XXVII 'Supplementary material') in the particular setting of mapping the DLQI scores to EQ-5D utility values. An Excel spread-sheet is also available upon request with pre-programmed formulae to enable EQ-5D domain probability calculations for a cohort of patients, from which utility values may be predicted using Monte Carlo simulation. The DLQI is the most commonly reported outcome measure in dermatology (Basra et al. 2008a; Ali et al. 2017a), and therefore there are many datasets from which generic EQ-5D and utility data can now be derived.

Chapter 6: General Discussion

Psoriasis has been recognised by WHO as a 'serious non-communicable disease' highlighting its global impact on public health as well as the need for united efforts in raising awareness and tackling the stigma surrounding it (Michalek et al. 2017). The consequential effect on a patient's quality of life (QoL), as well as on the wider social group, has also been extensively detailed (Krueger et al. 2001; Basra and Finlay 2007). Inevitably, this has a 'knock-on' effect on the economy as the burden of disease often results in loss of work productivity and increased medical costs (Fowler et al. 2008). Therefore, to truly assess the impact of this chronic skin disease it is not only important to capture accurate QoL information representative of patient burden, but to report it in a concise and standardised manner and to derive worthwhile data for clinicians, researchers and health authorities alike. This thesis brings together three original studies with the aim to improve the methodologies employed by clinicians, researchers and health economists in the management of psoriasis. These include:

1. A systematic review that highlights commonly used QoL tools, the current QoL reporting standards for psoriasis RCTs and the inherent limitations of current practices.
2. A mapping study that devised a model to enable the derivation of EQ-5D utility values from the most commonly used PROM in dermatology, the DLQI (Finlay and Khan 1994).
3. Validation of the electronic version of the two most commonly reported outcome measures in psoriasis: PASI, a clinical outcome measure, and the DLQI (Fredriksson and Pettersson 1978).

It is hoped this work contributes to major stages in the psoriasis management cascade: how it is assessed in a clinical setting, how it is reported and assessed in the development of new therapies and at a macroscopic level how all of this data may be used by health economists in a way that truly reflects the disease burden thereby enabling better resource allocation.

The systematic review is the first to highlight the range of QoL measures implemented and the way the data are reported in psoriasis RCTs. A combination of generic, specialty- and disease-specific measures (n=13) were used, indicating the heterogeneity in the type of QoL tools that are employed. However, it also highlighted a significant variation in the quality of reporting of this QoL data including: the frequency at which measures are administered, utility of the minimal clinically important difference (MCID) value as a clinical parameter or endpoint, presentation of results (e.g. graphical, percentage change) and use of statistics (median or mean values, ITT, standard deviation etc). Some studies did not provide extractable QoL data, making cross-study comparison considerably challenging. The SR further demonstrated

that the majority of QoL measures implemented do not have MCIDs described in the literature. The measures which have attributable MCID values possess the ability to discriminate between intervention efficacy and may also be useful in the planning of new trials (Jaeschke et al. 1989; Embry and Piccirillo 2020). This idea may be further explored with the novel concept of "multiple MCID" that has been introduced in this thesis (Ali et al. 2018). This concept potentially adds further meaning to QoL data interpretation as well as being able to more effectively distinguish between the impact of therapies. However, the concept of multiple MCID requires extensive further validation: in addition, it is not clear if MCID remains constant across a measure's score range. Nevertheless, the concept of MCID continues to be studied, is still being established across other measures in dermatology, and continues to have practical value in interpreting score change (Ofenloch et al. 2015; Kulthanan et al. 2016; Wu et al. 2019).

Quite importantly, however, the DLQI stood out as the most commonly utilised QoL measure across all psoriasis RCTs (83% of studies), which is also supported by evidence from another major European study (Obradors et al. 2016). Despite the DLQI's limitations (Both et al. 2007; Langenbruch et al. 2019), its simplicity, psychometric properties and strong content validity have contributed to it being the most commonly used QoL measure in dermatology worldwide (Basra et al. 2008a; Safikhani et al. 2013). The high percentage use of a single measure allowed the QoL data extracted from this SR to be easily compared across all the identified RCTs in a standardised manner.

The systematic review conducted for this thesis focused on the adult population. A review of QoL impact of psoriasis on the paediatric and adolescent population demonstrated that the DLQI was also one of the most used measures, alongside the children's version (CDLQI) (Randa et al. 2017). Another systematic review assessed PROMs used in the paediatric psoriasis population and identified 29 measures including the CDLQI, SPI and Children's Scalpdex in Psoriasis (Salame et al. 2018), reiterating the diverse practices that exist. The authors further highlight the dearth of evidence of PROM validation as well as the heterogeneity in the domains these instruments capture. Similar to the work of this thesis, Salame et al. (2018) conclude that there is a need for standardised use of PROMs in research as well as clinical practice. Further systematic reviews of PROMs used in nail psoriasis (Busard et al. 2018) and psoriatic arthritis (Højgaard et al. 2018) demonstrate similar results with a diverse range of instruments of varying validity being administered across studies.

The SR of this thesis nevertheless confirms that the DLQI is central to the assessment of psoriasis, further underpinning the planned focus for the electronic application and mapping studies that comprise the other elements of this PhD thesis.

Computer-based assessments are on the rise and preferred over their paper and pencil counterparts, especially given their relevance in the current 'smartphone generation'. Though efforts are made to validate measures electronically from the outset (Deal et al. 2010; Bächinger et al. 2016), electronic equivalence studies are frequently being conducted for older traditional paper-based PROMs as demonstrated by the literature review (Chapter 3, section 3.2). This transition to electronic formats is bolstered by inherent disadvantages of paper-based data including high costs, increased risk of missing values and practical issues with the storage of large amounts of data (Faulds et al. 2016). Neither the DLQI nor the PASI have been formally validated in the electronic format prior to the original study described in this thesis. The electronic DLQI version has not only been shown to be equivalent to the paper-based version, but patients have demonstrated preference for the digital medium. The electronic PASI version is also equivalent to the paper version and is preferred by raters. The validation study further demonstrates reduced inter-rater variability and quicker completion times compared to the paper-based version. The calculation of the PASI score is cumbersome and with the introduction of a novel visually-aided application, the scoring process can be standardised whilst reducing human errors that may influence treatment decisions, such as incorrect score calculation. Accidental input errors are also a possibility with the digital format, though compared to the paper format there are far fewer steps involved. For example, paper based measures may also inherently have input errors (patients may accidentally misread, or mis-record a response to an item) or errors as a result of electronic transcription of data (Saleh et al. 2002). The lower number of required steps, along with the ability to efficiently back up data, provides the electronic format a superior edge over other mediums.

When examining the results of the SR, it is evident that there is significant discrepancy between how QoL is measured across studies. Whilst the SR identifies some of the problems in QoL measurement and reporting, by introducing electronic data capture researchers and clinicians will be able to produce detailed and in-depth analyses alongside graphical representation, saving on time and resources. Psoriasis severity assessment for consideration of biologic therapies and for the British Association of Dermatology (BAD) psoriasis registry (BADBIR) requires documentation of both the DLQI and PASI scores (Finlay 2005; Burden et al. 2012; Smith et al. 2020). Therefore, both measures are vital inclusions for any electronic application assessing psoriasis severity. The subsequent production and validation of a novel electronic psoriasis application sets the framework to

capture clinical and QoL data across various settings in an efficient and standardised manner. Whilst this information is vital for assessing interventional efficacy and monitoring patient wellbeing, there is an argument that QoL data are not always adequately translated into meaningful outcomes when considering health utilities resulting in economic inequalities of resource allocation.

Utility values and the use of QALYs are integral to healthcare resource allocation and are considered by health economists as the standard measure of benefit (Ogden 2017). Utility values may be derived from easy-to-use generic measures such as the EQ-5D, which is a preference-based measure of health status, and may be used to compare the HRQoL impact of all diseases across different specialties (Klassen et al. 2000). However, for more disease-specific HRQoL data, measures such as the DLQI are necessary to truly represent the disease burden that generic measures often fail to capture (Krahn et al. 2007). Therefore, researchers often employ numerous measures in tandem, which not only increases patient burden, but study costs. As a result, mapping studies are conducted to generate utility values from disease-specific QoL data, which would thereby aid health economists advise on the allocation of resources more efficiently. Various specialties within the field of medicine such as bariatric surgery (Sauerland et al. 2009), endocrinology (Badia et al. 2018) and psychiatry (Gamst-Klaussen et al. 2018) have conducted mapping studies to overcome this challenge.

While the SR identified problems with QoL data collection and reporting, the electronic psoriasis assessment application offers a simple day-to-day solution for reducing this variability. Both of these studies contribute towards improving the process of assessing QoL impairment at the ground level for the patient, clinician and researcher. The mapping study presented in this thesis has the potential to translate this QoL information at a national, decision-making level for the benefit of reimbursement agencies (payers), health authorities and HTAs. Whilst previous mapping attempts have been unsuccessful or have concluded that the process is not possible (Currie and Conway 2007; Norlin et al. 2012; Blome et al. 2013), this original and novel mapping exercise utilising OLR has shown that utility values may accurately be predicted from DLQI scores at a group level. The database utilised for this study contained QoL information from numerous dermatological conditions, including psoriasis. A decision was therefore made to devise a model that would be applicable to psoriasis as well as the wider dermatological patient demographic, given the unique opportunity available with the dataset. However, the model works just as well by utilising the psoriasis-only data. Davison et al. (2018) have also employed various regression techniques in successfully mapping DLQI scores to EQ-5D-3L utility values by focusing solely on a much larger psoriasis patient population (n=22,305). Similar to the mapping study of this thesis, the Davison et al. (2018) model did not perform as well at the lower (or extreme) ends of the EQ-

5D scale due to fewer patients within that scoring bracket. This is a common problem with mapping studies whereby models perform worse at the tail-ends of the EQ-5D score distribution (Longworth and Rowen 2011). However, this may have negligible effects on cost-effectiveness prediction when mapping cohorts contain data mostly from the middle of the score distribution (Wailoo et al. 2017). Overall, the mapping algorithm and resultant spreadsheet could be a valuable tool in translating psoriasis QoL information for cohorts of patients into tangible utility value data.

There are several reasons why being able to convert DLQI population scores to utility values would be of value to the scientific community. The first relates to the vast wealth of data concerning DLQI values in many hundreds of studies, not only in psoriasis but across over forty different skin diseases. It would be now possible for researchers to 'mine' this published information to calculate utility values from these populations using the conversion formula created in this thesis. Secondly, utility values are frequently calculated directly from EQ-5D data. However, the EQ-5D was not originally validated in Dermatology and other sub-specialties. By sourcing utility data directly from a specialty-specific measure it can be argued that the utility data are more relevant. A third major possible benefit of this mapping method is that there is the potential to reduce responder burden if the DLQI is being completed anyway for different purpose(s).

Though there are several positive outcomes from the aforementioned studies adding value to the existing body of knowledge, as summarised above, they have several limitations which are detailed below.

6.1 Limitations

The SR has several limitations. Only English language literature was examined due to constraints in translation facilities and only studies with extractable QoL data were included. It was only possible to compare DLQI results in detail because of its predominant usage (83% of studies). There was too little data from other QoL instruments for them to be included in some comparisons and several studies were excluded due to inadequate QoL data reporting. Collating data across studies other than RCTs was not possible due to the wide variation in methodologies and the heterogeneity would pose comparative challenges. However, by focusing the systematic review solely on RCTs, one may argue the analysis and conclusions were derived from the best available evidence, with lower level evidence such as case reports and series being excluded. The search bias was countered by having two

independent principal reviewers conducting data search, extraction and synthesis, with a third independent adjudicator reviewer.

The electronic DLQI/PASI validation studies also had a few limitations. For example, a 30 minutes washout period may be considered too short and result in a carryover, or 'training', effect, though there was no statistical evidence of this (Table 3.4b). Theoretically, this only may have occurred when the iPad was administered first, as patients spent longer on average completing it, therefore possibly having more time to remember the questions and answers. This effect however was counteracted by the cross-over study design, and reading material was provided to patients as a 'distraction'. Nevertheless, there is no consensus on the ideal interval period between PRO administrations (Quadri et al. 2013). Other studies have also used 30 minutes as a washout period (Sun et al. 2015), which can reduce patient burden and ensures that disease severity does not fluctuate in-between administrations. Touch screen surfaces are also prone to accidental touches, which may result in recording unintentional item responses, contributing to final score differences. The electronic version of the DLQI utilised in this study does not allow completion until all items are answered, which may impact validity if patients are coerced into answering questions they may have otherwise skipped on a paper format. This could have ethical implications from not giving patients the choice of not responding to a question if they do not wish to do so. In the DLQI, this issue is partly addressed by having a 'not relevant' option in eight of the ten questions. The median score difference of '0' provides reassurance that there are no clinically significant differences in completion and the strong correlation suggests that the two formats may be used interchangeably. Though the p-value of 0.006 for median total score difference is statistically significant, this is likely due to the large sample size (Doll and Carney 2005). Furthermore, the MCID for the DLQI is four (Basra et al. 2015a) and therefore the difference in scores is negligible in a clinical context. The limits of agreement from the Bland-Altman plots (-3.4 to +4.1) are also similarly reassuring.

For the PASI, the short washout period was countered by raters completing other clinical and administrative work including seeing other patients in-between scoring as a 'distraction'. Only three raters were enrolled in the study to ensure uniformity in measuring the 'effect' of the PASI application on scores including one undergraduate student, one postgraduate student and a dermatologist trainee with ~6 years' experience. Though this reflects various levels of experience, the influence of this variation is difficult to quantify for the purpose of this study. In clinical practice the inter-rater difference is likely to be wide given the varying backgrounds of assessors as well as the pre-existing issues with PASI score reliability (Gourraud et al. 2012).

There are some limitations of the OLR model. The actual scores for the DLQI and the EQ-5D were sometimes inconsistent within the same subject e.g. one subject answered 1 on every EQ-5D domain ('perfect health') but 29 on the DLQI (very poor health). This could be due to poor understanding of the items, the reliability or validity of the instruments or due to random errors. Though these data were included to avoid bias, Van Hout et al. (2012) argue analysis should be restricted to logically consistent responses. Perhaps including more socio-demographic variables in the model, other than age and sex, may improve its predictive performance, though this may result in only marginal improvements that would not outweigh the complexity of running the model (Gray et al. 2006).

The UK time trade-off (TTO) values were used in the derivation of this model; it is worth considering that these health states were elicited in 1993 and, therefore, may not be up to date with current health valuations. Furthermore, no official European TTO values exist for EQ-5D health states and therefore the UK TTO values were applied throughout the validation process. Further, sensitivity analysis may be conducted using preference value-sets from different countries. However, these were not accessible for this study, but would be a useful consideration for future studies.

Though there may be cultural variation influencing HRQoL and utility responses, it has not been possible to test this specific question. Experience suggests that within the European context there is some uniformity of attitudes, cultural norms and responses, as the DLQI has undergone over one hundred validated translations, with a large number in European countries (Basra et al. 2008a). However, the methodology remains intact and consistent, regardless of the TTO values utilised. Though bootstrapping may indeed be the best approach for testing such models, this would require some additional theoretical considerations to extend existing methodology for the binary logistic model to the ordinal setting. This approach was bypassed by using 'split-half cross validation', which is a valid technique for large sample sizes (Steyerberg et al. 2001). Nevertheless, this study presents the opportunity for further statistical research.

There may be concerns regarding the use of these models in different diseases and whether single disease models would provide more accurate utility data. This study includes a wide range of the most common different skin diseases from a wide range of different European countries, giving the models additional strength in terms of universality. However, a model was successfully derived from the psoriasis-only patients within the larger data set and was tested on patients with all other conditions, with the predicted results reassuringly similar to

the original OLR model validation exercise. Two limitations of this exercise were the sample size of psoriasis patients, which was relatively small (n=484) and that none of the patients had answered 'extreme' for the self-care domain of the EQ-5D. Given the overall sample size from which the OLR model was created, it is therefore plausible that the model may be implemented successfully across different conditions, limiting the need for condition-specific modelling, which may be practically difficult to create. Furthermore, numerous models may result in confusion for researchers, whereas a single tool for utility prediction may prove to be more pragmatic, user-friendly and accessible. This raises a dilemma frequently encountered when balancing practicality of a clinical measure against strictly scientific considerations. There is no point in having a technique that is extremely accurate but which will never be used in the clinical setting because of the burden that its use involves.

6.2 Future work

The management landscape of skin diseases has been evolving rapidly with the introduction of biologics over the last two decades (Smith et al. 2020), with patients achieving PASI 75, PASI 90 and even PASI 100 in some cases (Sawyer et al. 2019). However, these advancements in clinical outcomes must be matched by improvements in humanistic outcomes assessment such as QoL to encourage utilisation in the day-to-day care of patients at a ground level as well as by health authorities. This also would demonstrate a proactive shift towards successful delivery of a patient-centred care.

It is prudent to have formal guidelines for QoL measurement and reporting to ensure interventional studies are designed within a framework allowing for efficient comparison of efficacy leading to generation of sound evidence to aid treatment decision-making. These guidelines should include suggestions on appropriate QoL measures, frequency of measurement, MCID consideration as well as reporting standards. Further systematic reviews would be useful to compare how practices have changed as a result of increased awareness of QoL measurement variation across studies. The novel 'multiple MCID' concept was introduced in this thesis, though further work would be required to explore the validation of this proposal. The concept of MCID has been scrutinised as it may vary due to context (or condition), baseline severity, whether there is improvement versus deterioration or the anchoring method with which the MCID was calculated (Beaton et al. 2002). These limitations would need to be considered when conducting further validation work with the multiple MCID as perhaps 'multiples' may be variable in value and therefore clinical meaning.

Whilst electronic implementation continues to be adopted widely, the devices and methodologies used will inevitably evolve. For example, Reolid et al. (2020) have developed a method of automatically estimating body surface area affected by psoriasis using an optical pencil whereby assessors simply draw the affected areas on a touchscreen. This novel method was shown to be reliable and comparable to the paper-based version of PASI and may become a natural and more intuitive update to the application described in this thesis. Digital photography alongside current computing capabilities may allow full body images to be automatically assessed by a software. Indeed, there is an argument on whether physical input would be required at all in the near future: the rise of artificial intelligence may potentially replace traditional formats with PROMs being completed simply by voice command with the assistance of devices such as Amazon Echo or Google Home (O'Brien et al. 2020). Such major advancements, or change in format, may necessitate the need for up-to-date validation and re-testing of PROMs to not only improve upon user-experience, but to ensure QoL measurement remains as relevant and central to all future clinical decisions. More likely, entirely novel methods of assessing diseases and their impacts on patients may evolve, rather than current methods being transferred to a different medium.

The mapping study resulted in the creation of a spreadsheet, which may be utilised by health economists and HTAs. At the time of writing this thesis, the spreadsheet has been requested at least ten times by researchers and industry representatives across the world. However, it would be interesting to compare the actual and estimated values on a completely different patient dataset (such as BADBIR) as well as individual skin conditions to further validate its reliability. The final model maps DLQI scores into EQ-5D domain scores with gender and age as extra variables. The inclusion of additional variables may further increase reliability of the model. Further refinement of the model software would make it more intuitive to use and derive utility estimates with fewer required steps. Nevertheless, whilst mapping is not ideal, it may be the ideal option to derive disease-specific health economic data. The next challenge will be to develop mapping techniques that can be applied to scores from individual subjects rather than simply to population cohorts.

6.3 Conclusions

Despite the aforementioned limitations, all three studies of this thesis are intended to improve and advance the role of QoL assessment in people with psoriasis. There is no doubt that psoriasis is a severely debilitating and chronic condition that patients often live with life-long. However, assessment of clinical parameters solely is not enough for appropriate long-term

control of psoriasis or for understanding its impact on patients' lives. As a result, it is not only prudent to raise awareness of QoL impairment as a consequence of suffering from psoriasis, but to be able to capture this impairment in an efficient manner and translate the results into meaningful information for clinicians and health authorities with an ultimate goal of improving patients' physical and psychosocial functionality.

This thesis is the culmination of three extensive studies that have worked in harmony to address existing deficiencies in QoL assessment across the care pathway. More importantly, it offers valid solutions for those shortfalls by improving upon the understanding and implementation of QoL measurement in the management of psoriasis. It is hoped this work will form the foundation for future research to develop the field of quality of life sciences thereby ensuring patients continue to remain at the centre of clinical care decisions.

References

Abuabara, K. et al. 2010. Cause‐specific mortality in patients with severe psoriasis: a population‐based cohort study in the UK. *British Journal of Dermatology* 163(3), pp. 586-592.

Acaster, S. et al. 2015. Measurement equivalence of the 'allergy diary by MACVIA ARIA' app touch screen visual analogue scale versus pen and paper: 1032. *Allergy: European Journal of Allergy and Clinical Immunology* 70, pp. 414-415.

Ackermann, C. and Kavanaugh, A. 2008. Economic burden of psoriatic arthritis. *Pharmacoeconomics* 26(2), pp. 121-129.

Ahmed, S. et al. 2020. Evaluating important change in cutaneous disease activity as an efficacy measure for clinical trials in dermatomyositis. *British Journal of Dermatology* 182(4), pp. 949-954.

Al Shobaili, H. A. 2010. The impact of childhood atopic dermatitis on the patients' family. *Pediatric dermatology* 27(6), pp. 618-623.

Ali, F. et al. 2017a. A systematic review of the use of quality‐of‐life instruments in randomized controlled trials for psoriasis. *British Journal of Dermatology* 176(3), pp. 577-593.

Ali, F. et al. 2017b. Comparison of the paper‐based and electronic versions of the Dermatology Life Quality Index: evidence of equivalence. *British Journal of Dermatology* 177(5), pp. 1306-1315.

Ali, F. M. et al. 2017c. Mapping of the DLQI scores to EQ-5D utility values using ordinal logistic regression. *Quality of Life Research*, pp. 1-10.

Ali, F. M. et al. 2018. Two Minimal Clinically Important Difference (2MCID): A New Twist on an Old Concept. *Acta dermato-venereologica* 98(7-8), pp. 715-717.

Alinaghi, F. et al. 2019. Prevalence of psoriatic arthritis in patients with psoriasis: A systematic review and meta-analysis of observational and clinical studies. *Journal of the American Academy of Dermatology* 80(1), pp. 251-265. e219.

Allione, A. et al. 2015. Novel epigenetic changes unveiled by monozygotic twins discordant for smoking habits. *PloS one* 10(6), p. e0128265.

Alora-Palli, M. B. et al. 2010. Efficacy and Tolerability of a Cosmetically Acceptable Coal Tar Solution in the Treatment of Moderate Plaque Psoriasis A Controlled Comparison with Calcipotriene (Calcipotriol) Cream. *American Journal of Clinical Dermatology* 11(4), pp. 275-283.

Amaral, C. S. F. d. et al. 2012. Quality of life in children and teenagers with atopic dermatitis. *Anais brasileiros de dermatologia* 87(5), pp. 717-723.

Anderson, R. T. and Rajagopalan, R. 1997. Development and validation of a quality of life instrument for cutaneous diseases. *Journal of the American Academy of Dermatology* 37(1), pp. 41-50.

Andresen, E. M. and Meyers, A. R. 2000. Health-related quality of life outcomes measures. *Archives of physical medicine and rehabilitation* 81, pp. S30-S45.

Angelhoff, C. et al. 2018. “To Cope with Everyday Life, I Need to Sleep”–A Phenomenographic Study Exploring Sleep Loss in Parents of Children with Atopic Dermatitis. *Journal of pediatric nursing* 43, pp. e59-e65.

Armstrong, A. W. et al. 2018. The evolving landscape of psoriasis treatment. *Semin Cutan Med Surg* 37(2S), p. S39.

Arnesen, T. and Trommald, M. 2005. Are QALYs based on time trade‐off comparable?–A systematic review of TTO methodologies. *Health economics* 14(1), pp. 39-53.

Arthur, C. 2012. *The history of smartphones: timeline* [Online]. The Guardian. Available at: http://www.theguardian.com/technology/2012/jan/24/smartphones-timeline [Accessed: 27th May].

Asahina, A. et al. 2010. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: Efficacy and safety results from a Phase II/III randomized controlled study. *Journal of Dermatology* 37(4), pp. 299-310.

Asawanonda, P. and Nateetongrungsak, Y. 2006. Methotrexate plus narrowband UVB phototherapy versus narrowband UVB phototherapy alone in the treatment of plaque-type psoriasis: A randomized, placebo-controlled study. *Journal of the American Academy of Dermatology* 54(6), pp. 1013-1018.

Ashcroft, D. M. et al. 1998. Quality of life measures in psoriasis: a critical appraisal of their quality. *Journal of Clinical Pharmacy & Therapeutics* 23(5), pp. 391-398.

Ashcroft, D. M. et al. 1999. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. *British Journal of Dermatology* 141(2), pp. 185-191.

Atwan, A. et al. 2017. Dermatology Life Quality Index (DLQI) as a psoriasis referral triage tool. *British Journal of Dermatology* 177(4), pp. e136-e137.

Augustin, M. et al. 2018. Definition of psoriasis severity in routine clinical care: current guidelines fail to capture the complexity of long‐term psoriasis management. *British Journal of Dermatology* 179(6), pp. 1385-1391.

Augustin, M. et al. 2000. Validation and clinical results of the FLQA-d, a quality of life questionnaire for patients with chronic skin disease. *Dermatology and Psychosomatics/Dermatologie und Psychosomatik* 1(1), pp. 12-17.

Azfar, R. S. et al. 2012. Increased risk of diabetes mellitus and likelihood of receiving diabetes mellitus treatment in patients with psoriasis. *Archives of dermatology* 148(9), pp. 995-1000.

Bächinger, D. et al. 2016. Development and validation of the Zurich chronic middle ear inventory (ZCMEI-21): an electronic questionnaire for assessing quality of life in patients with chronic otitis media. *European Archives of Oto-Rhino-Laryngology* 273(10), pp. 3073-3081.

BAD. 2019. *Psoriasis Area and Severity Index (PASI) Worksheet* [Online]. British Association of Dermatologists. Available at: http://www.bad.org.uk/shared/get-file.ashx?id=1654&itemtype=document [Accessed: 27th January].

Badia, X. et al. 1999. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQI. The Cavide Research Group. *British Journal of Dermatology* 141(4), pp. 698-702.

Badia, X. et al. 2018. Mapping AcroQoL scores to EQ-5D to obtain utility values for patients with acromegaly. *Journal of medical economics* 21(4), pp. 382-389.

Bagattini, Â. M. et al. 2018. Electronic version of the EQ-5D quality-of-life questionnaire: Adaptation to a Brazilian population sample. *Value in health regional issues* 17, pp. 88-93.

Bagel, J. et al. 1998. Administration of DAB389IL-2 to patients with recalcitrant psoriasis: a double-blind, phase II multicenter trial. *Journal of the American Academy of Dermatology* 38(6 Pt 1), pp. 938-944.

Baker, E. et al. 2012. Effect of Biologic Agents on Non-PASI Outcomes in Moderate-to-Severe Plaque Psoriasis: Systematic Review and Meta-Analyses. *Dermatol Ther* 2(1), pp. 1-20.

Bandarian‐Balooch, S. et al. 2017. Electronic‐Diary for Recording Headaches, Triggers, and Medication Use: Development and Evaluation. *Headache: The Journal of Head and Face Pain* 57(10), pp. 1551-1569.

Barker, J. et al. 2011. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). *British journal of dermatology* 165(5), pp. 1109-1117.

Basra, M. et al. 2008a. The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *British Journal of Dermatology* 159(5), pp. 997-1035.

Basra, M. and Finlay, A. Y. 2007. The family impact of skin diseases: the Greater Patient concept. *British Journal of Dermatology* 156(5), pp. 929-937.

Basra, M. et al. 2015a. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology* 230(1), pp. 27-33.

Basra, M. et al. 2018. Conceptualization, development and validation of T‐QoL©(Teenagers' Quality of Life): a patient‐focused measure to assess quality of life of adolescents with skin diseases. *British Journal of Dermatology* 178(1), pp. 161-175.

Basra, M. et al. 2007. The Family Dermatology Life Quality Index: measuring the secondary impact of skin disease. *British Journal of Dermatology* 156(3), pp. 528-538.

Basra, M. K. et al. 2015b. PFI-14©: A Rasch Analysis Refinement of the Psoriasis Family Index. *Dermatology* 231(1), pp. 15-23.

Basra, M. K. A. et al. 2008b. The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *British Journal of Dermatology* 159(5), pp. 997-1035.

Basra, M. K. A. and Hussain, S. 2012. Application of the dermatology life quality index in clinical trials of biologics for psoriasis. *Chinese Journal of Integrative Medicine* 18(3), pp. 179-185.

Basra, M. K. A. et al. 2015c. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology* 230(1), pp. 27-33.

Basra, M. K. A. and Shahrukh, M. 2009. Burden of skin diseases. *Expert Rev Pharmacoecon Outcomes Res* 9(3), pp. 271-283.

Bates, D. W. et al. 1998. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *Jama* 280(15), pp. 1311-1316.

Batista, M. A. and Gaglani, S. M. 2013. The future of smartphones in health care. *AMA Journal of Ethics* 15(11), pp. 947-950.

Beaton, D. E. et al. 2002. Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. *Current opinion in rheumatology* 14(2), pp. 109-114.

Beissert, S. et al. 2009. A comparison of mycophenolate mofetil with ciclosporine for the treatment of chronic plaque-type psoriasis. *Dermatology* 219(2), pp. 126-132.

Bennett, A. V. et al. 2016a. Mode equivalence and acceptability of tablet computer-, interactive voice response system-, and paper-based administration of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Health and quality of life outcomes* 14(1), p. 24.

Bennett, A. V. et al. 2016b. Evaluation of mode equivalence of the MSKCC Bowel Function Instrument, LASA Quality of Life, and Subjective Significance Questionnaire items administered by Web, interactive voice response system (IVRS), and paper. *Quality of Life Research* 25(5), pp. 1123-1130.

Berenguer, A. et al. 2017. Are Smartphones Ubiquitous?: An in-depth survey of smartphone adoption by seniors. *IEEE Consumer Electronics Magazine* 6(1), pp. 104-110.

Bergner, M. 1985. Measurement of health status. *Medical care* 23(5), pp. 696-704.

Bergner, M. et al. 1981. The Sickness Impact Profile: development and final revision of a health status measure. *Medical care*, pp. 787-805.

Bergstrom, K. G. et al. 2003. Medication Formulation Affects Quality of Life: A Randomized Single-Blind Study of Clobetasol Propionate Foam 0.05% Compared With a Combined Program of Clobetasol Cream 0.05% and Solution 0.05% for the Treatment of Psoriasis. *Cutis* 72(5), pp. 407-411.

Bernstein, S. et al. 2006. Treatment of mild to moderate psoriasis with Relieva, a Mahonia aquifolium extract - A double-blind, placebo-controlled study. *American Journal of Therapeutics* 13(2), pp. 121-126.

Berth‐Jones, J. et al. 1992. A multicentre, parallel‐group comparison of calcipotriol ointment and short‐contact dithranol therapy in chronic plaque psoriasis. *British Journal of Dermatology* 127(3), pp. 266-271.

Berth‐Jones, J. et al. 2006. A study examining inter‐and intrarater reliability of three scales for measuring severity of psoriasis: Psoriasis Area and Severity Index, Physician's Global

Assessment and Lattice System Physician's Global Assessment. *British Journal of Dermatology* 155(4), pp. 707-713.

Bezjak, A. et al. 2001. Oncologists' use of quality of life information: results of a survey of Eastern Cooperative Oncology Group physicians. *Quality of Life Research* 10(1), pp. 1-14.

Bhatti, Z. U. et al. 2011. Chronic diseases influence major life changing decisions: a new domain in quality of life research. *Journal of the Royal Society of Medicine* 104(6), pp. 241-250.

Bhatti, Z. U. et al. 2013. The development and validation of the major life changing decision profile (MLCDP). *Health and quality of life outcomes* 11(1), p. 78.

Bhosle, M. J. et al. 2006. Quality of life in patients with psoriasis. *Health and quality of life outcomes* 4(1), p. 35.

Bishop-Bailey, A. et al. 2015. Dermatology Quality Life Index (DLQI) responses to biological therapy for psoriasis during standard U.K. clinical care: NICE assessment timelines may not capture the best DLQI response. *British Journal of Dermatology* 108, 173 (Suppl. S1), p. 70 (Abstr.).

Bissonnette, R. et al. 2013. Tofacitinib for moderate to severe chronic plaque psoriasis: 24-week preliminary analysis from the 56-week phase 3 opt re-treatment study. *Journal of the European Academy of Dermatology and Venereology* 27, p. 23.

Bissonnette, R. et al. 2011. Treatment of palmoplantar psoriasis with infliximab: A randomized, double-blind placebo-controlled study. *Journal of the European Academy of Dermatology and Venereology* 25(12), pp. 1402-1408.

Bjorner, J. B. et al. 2014. Method of administration of PROMIS scales did not significantly impact score level, reliability, or validity. *Journal of clinical epidemiology* 67(1), pp. 108-113.

Blackford, S. et al. 1996. Basal cell carcinomas cause little handicap. *Quality of Life Research* 5(2), pp. 191-194.

Blank, P. R. et al. 2010. Cost-effectiveness of oral alitretinoin in patients with severe chronic hand eczema - a long-term analysis from a Swiss perspective. *BMC Dermatology* 10.

Blome, C. et al. 2013. Mapping DLQI on EQ-5D in psoriasis: Transformation of skin-specific health-related quality of life into utilities. *Archives of Dermatological Research* 305(3), pp. 197-204.

Boehncke, W.-H. and Menter, A. 2013. Burden of disease: psoriasis and psoriatic arthritis. *American journal of clinical dermatology* 14(5), pp. 377-388.

Bostoen, J. et al. 2012. An educational programme for patients with psoriasis and atopic dermatitis: a prospective randomized controlled trial. *British journal of dermatology* 167(5), pp. 1025-1031.

Both, H. et al. 2007. Critical review of generic and dermatology-specific health-related quality of life instruments. *Journal of Investigative Dermatology* 127(12), pp. 2726-2739.

Bourdel, N. et al. 2019. Systematic review of quality of life measures in patients with endometriosis. *PloS one* 14(1), p. e0208464.

Bovenschen, H. J. et al. 2010. Dimethylfumarate for psoriasis. *American journal of clinical dermatology* 11(5), pp. 343-350.

Bożek, A. and Reich, A. 2017. The reliability of three psoriasis assessment tools: Psoriasis area and severity index, body surface area and physician global assessment. *Adv Clin Exp Med* 26(5), pp. 851-856.

Brazier, J. E. et al. 2010. A review of studies mapping (or cross walking) non-preference based measures of health to generic preference-based measures. *The European journal of health economics* 11(2), pp. 215-225.

Broering, J. M. et al. 2014. Measurement equivalence using a mixed-mode approach to administer health-related quality of life instruments. *Quality of Life Research* 23(2), pp. 495-508.

Bronsard, V. et al. 2010. What are the best outcome measures for assessing quality of life in plaque type psoriasis? A systematic review of the literature. *Journal of the European Academy of Dermatology and Venereology* 24(s2), pp. 17-22.

Burden, A. et al. 2012. The British Association of Dermatologists' Biologic Interventions Register (BADBIR): design, methodology and objectives. *British Journal of Dermatology* 166(3), pp. 545-554.

Busard, C. et al. 2018. Reporting of outcomes in randomized controlled trials on nail psoriasis: a systematic review. *British Journal of Dermatology* 178(3), pp. 640-649.

Bushnell, D. et al. 2003. Electronic versus paper questionnaires: a further comparison in persons with asthma. *Journal of Asthma* 40(7), pp. 751-762.

Bushnell, D. M. et al. 2018. Mixed-methods development of a new patient-reported outcome instrument for chronic low back pain: part 2—The Patient Assessment for Low Back Pain–Impacts (PAL-I). *Pain* 159(10), p. 2066.

Bushnell, D. M. et al. 2013. Validation of the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure to assess psoriasis symptom severity. *Journal of dermatological treatment* 24(5), pp. 356-360.

Byrom, B. et al. 2018. Measurement equivalence of patient-reported outcome measures migrated to electronic formats: a review of evidence and recommendations for clinical trials and bring your own device. *Therapeutic innovation & regulatory science*, p. 2168479018793369.

Caetano, T. A. et al. 2016. Comparing a tablet computer and paper forms for assessing patient-reported outcomes in edentulous patients. *The journal of advanced prosthodontics* 8(6), pp. 457-464.

Callis, K. D. et al. 2018. Identifying a Core Domain Set to Assess Psoriasis in Clinical Trials. *JAMA dermatology* 154(10), pp. 1137-1144.

Calman, K. C. 1984. Quality of life in cancer patients--an hypothesis. *Journal of medical ethics* 10(3), pp. 124-127.

Campbell, N. et al. 2015. Equivalence of electronic and paper-based patient-reported outcome measures. *Quality of Life Research* 24(8), pp. 1949-1961.

Carlbring, P. et al. 2007. Internet vs. paper and pencil administration of questionnaires commonly used in panic/agoraphobia research. *Computers in Human Behavior* 23(3), pp. 1421-1434.

Carlin, C. S. et al. 2004. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. *Journal of the American Academy of Dermatology* 50(6), pp. 859-866.

Carlson, L. E. et al. 2001. Computerized quality-of-life screening in a cancer pain clinic. *Journal of Palliative Care* 17(1), p. 46.

Cassano, N. et al. 2006. Once-weekly administration of high-dosage Etanercept in patients with plaque psoriasis: results of a pilot experience (power study). *International journal of immunopathology and pharmacology* 19(1), pp. 225-229.

Chai‐Adisaksopha, C. et al. 2019. Test‐retest properties of the Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire and its constituent domains. *Haemophilia* 25(1), pp. 75-83.

Chambers, C. et al. 2012. Patient-centered online management of psoriasis: a randomized controlled equivalency trial. *Journal of the American Academy of Dermatology* 66(6), pp. 948-953.

Chamlin, S. L. et al. 2005. Development of the Childhood Atopic Dermatitis Impact Scale: initial validation of a quality-of-life measure for young children with atopic dermatitis and their families. *Journal of investigative dermatology* 125(6), pp. 1106-1111.

Chang, Y.-J. et al. 2014. Measurement equivalence and feasibility of the EORTC QLQ-PR25: paper-and-pencil versus touch-screen administration. *Health and quality of life outcomes* 12(1), p. 23.

Chen, S. C. et al. 2002. Scalpdex: a quality-of-life instrument for scalp dermatitis. *Archives of dermatology* 138(6), pp. 803-807.

Chern, E. et al. 2011. Positive effect of modified goeckerman regimen on quality of life and psychosocial distress in moderate and severe psoriasis. *Acta Dermato-Venereologica* 91(4), pp. 447-451.

Chernyshov, P. et al. 2019. Validation of the dermatology‐specific proxy instrument the Infants and Toddlers Dermatology Quality of Life. *Journal of the European Academy of Dermatology and Venereology*.

Chernyshov, P. V. 2019. The evolution of quality of life assessment and use in dermatology. *Dermatology* 235(3), pp. 167-174.

Choi, J. and Koo, J. Y. 2003. Quality of life issues in psoriasis. *Journal of the American Academy of Dermatology* 49(2), pp. 57-61.

Choonhakarn, C. et al. 2010. A prospective, randomized clinical trial comparing topical aloe vera with 0.1% triamcinolone acetonide in mild to moderate plaque psoriasis. *Journal of the European Academy of Dermatology and Venereology* 24(2), pp. 168-172.

Chren, M.-M. et al. 1996. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. *Journal of investigative Dermatology* 107(5), pp. 707-713.

Chren, M. M. 2012. The Skindex Instruments to Measure the Effects of Skin Disease on Quality of Life. *Dermatologic Clinics* 30(2), pp. 231-236.

Chudleigh, J. et al. 2019. Impact of Cystic Fibrosis on Unaffected Siblings: A Systematic Review. *The Journal of Pediatrics* 210, pp. 112-117. e119.

Chularojanamontri, L. et al. 2013. The Simplified Psoriasis Index (SPI): a practical tool for assessing psoriasis. *Journal of Investigative Dermatology* 133(8), pp. 1956-1962.

Chularojanamontri, L. et al. 2014. Responsiveness to change and interpretability of the simplified psoriasis index. *Journal of Investigative Dermatology* 134(2), pp. 351-358.

Clayer, M. and Davis, A. 2011. Can the Toronto Extremity Salvage Score produce reliable results when used online? *Clinical Orthopaedics and Related Research*® 469(6), pp. 1750-1756.

Cohen, A. et al. 2009. Psoriasis associated with ulcerative colitis and Crohn's disease. *Journal of the European Academy of Dermatology and Venereology* 23(5), pp. 561-565.

Cohen, A. et al. 2008. Association between psoriasis and the metabolic syndrome. *Dermatology* 216(2), pp. 152-155.

Coondoo, A. et al. 2014. Side-effects of topical steroids: A long overdue revisit. *Indian dermatology online journal* 5(4), p. 416.

Coons, S. J. et al. 2009. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force report. *Value in Health* 12(4), pp. 419-429.

Coons, S. J. et al. 2000. A comparative review of generic quality-of-life instruments. *Pharmacoeconomics* 17(1), pp. 13-35.

Coretti, S. et al. 2014. The minimum clinically important difference for EQ-5D index: a critical review. *Expert review of pharmacoeconomics & outcomes research* 14(2), pp. 221-233.

Cortesi, P. et al. 2011. PSS31 Association between Eq-5D and Dermatology Life Quality Index (Dlqi) in patients with chronic hand eczema. *Value in Health* 14(7), p. A507.

Crist, B. D. and Pashuck, T. D. 2018. Reliability of a Condensed Computer-Based Patient Outcomes Scoring Tool in Orthopaedic Trauma Patients. *Journal of orthopaedic trauma* 32(6), pp. e226-e228.

Crosby, R. D. et al. 2003. Defining clinically meaningful change in health-related quality of life. *Journal of clinical epidemiology* 56(5), pp. 395-407.

Cummins, R. A. 2005. Moving from the quality of life concept to a theory. *Journal of Intellectual disability research* 49(10), pp. 699-706.

Cunha-Miranda, L. et al. 2015. Validation of Portuguese-translated computer touch-screen questionnaires in patients with rheumatoid arthritis and spondyloarthritis, compared with paper formats. *Rheumatology international* 35(12), pp. 2029-2035.

Currie, C. J. and Conway, P. 2007. PSK11 evaluation of the association between EQ5D utility and dermatology life quality index (DLQI) score in patients with psoriasis. *Value in Health* 10(6), pp. A470-A471.

Dahl, M. G. and Comaish, J. S. 1972. Long-term effects of hydroxyurea in psoriases. *Br Med J* 4(5840), pp. 585-587.

Dale, O. and Hagen, K. B. 2007. Despite technical problems personal digital assistants outperform pen and paper when collecting patient diary data. *Journal of clinical epidemiology* 60(1), pp. 8-17.

Dalgard, F. J. et al. 2015. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *Journal of Investigative Dermatology* 135(4), pp. 984-991.

Dang, J. et al. 2016. Development and Validation of the Eyelash Satisfaction Questionnaire. *Aesthetic surgery journal* 36(2), pp. 221-228.

Dang, P. et al. 2018. A single center experience of an electronic implementation of patient reported outcome measures in daily clinical practice. *European Spine Journal* 27(11), pp. 2975-2976.

Das, A. V. et al. 2020. Tele-consultations and electronic medical records driven remote patient care: Responding to the COVID-19 lockdown in India. *Indian Journal of Ophthalmology* 68(6), p. 1007.

Dauden, E. et al. 2009. Improvements in patient‐reported outcomes in moderate‐to‐severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. *Journal of the European Academy of Dermatology and Venereology* 23(12), pp. 1374-1382.

Davison, N. et al. 2017. Identification of factors that may influence the selection of first‐line biological therapy for people with psoriasis: a prospective, multicentre cohort study. *British Journal of Dermatology* 177(3), pp. 828-836.

Davison, N. J. et al. 2018. Generating EQ-5D-3L utility scores from the dermatology life quality index: a mapping study in patients with psoriasis. *Value in Health* 21(8), pp. 1010-1018.

De Arruda, L. and De Moraes, A. 2001. The impact of psoriasis on quality of life. *British Journal of Dermatology* 144, pp. 33-36.

de Korte, J. et al. 2002. The suitability of quality-of-life questionnaires for psoriasis research: a systematic literature review. *Archives of dermatology* 138(9), pp. 1221-1227.

De Korte, J. et al. 2004. Quality of life in patients with psoriasis: a systematic literature review. *J Investig Dermatol Symp Proc* 9(2), pp. 140-147.

De Korte, J. et al. 2008. A comparison of twice-daily calcipotriol ointment with once-daily short-contact dithranol cream therapy: quality-of-life outcomes of a randomized controlled trial

of supervised treatment of psoriasis in a day-care setting. *British journal of dermatology* 158(2), pp. 375-381.

De Rie, M. A. et al. 2004. Overview of psoriasis. *Dermatologic therapy* 17(5), pp. 341-349.

Deal, L. S. et al. 2010. The development and validation of the daily electronic Endometriosis Pain and Bleeding Diary. *Health and quality of life outcomes* 8(1), p. 64.

Delgado-Herrera, L. et al. 2017. Diarrhea-predominant irritable bowel syndrome: creation of an electronic version of a patient-reported outcome instrument by conversion from a pen-and-paper version and evaluation of their equivalence. *Patient related outcome measures* 8, p. 83.

DeLouise, L. A. 2012. Applications of nanotechnology in dermatology. *Journal of Investigative Dermatology* 132(3), pp. 964-975.

Deng, Y. et al. 2016. The inflammatory response in psoriasis: a comprehensive review. *Clinical reviews in allergy & immunology* 50(3), pp. 377-389.

Dodington, S. R. et al. 2013. The Dermatitis Family Impact questionnaire: a review of its measurement properties and clinical application. *British Journal of Dermatology* 169(1), pp. 31-46.

Dolan, P. 1997. Modeling valuations for EuroQol health states. *Medical care* 35(11), pp. 1095-1108.

Doll, H. and Carney, S. 2005. Statistical approaches to uncertainty: p values and confidence intervals unpacked. *Evidence-Based Medicine* 10(5), pp. 133-134.

Dowie, J. 2002. Decision validity should determine whether a generic or condition‐specific HRQOL measure is used in health care decisions. *Health economics* 11(1), pp. 1-8.

Drouin, R. et al. 2008. A double-blind, placebo-controlled, randomized trial of XP-828L (800 mg) on the quality of life and clinical symptoms of patients with mild-to-moderate psoriasis. *Alternative medicine review* 13(2), pp. 145-152.

Drummond, H. et al. 1995. Electronic quality of life questionnaires: a comparison of pen-based electronic questionnaires with conventional paper in a gastrointestinal study. *Quality of life research* 4(1), pp. 21-26.

Dubertret, L. et al. 2006. CLinical experience acquired with the efalizumab (Raptiva®)(CLEAR) trial in patients with moderate‐to‐severe plaque psoriasis: results from a phase III international randomized, placebo‐controlled trial. *British journal of dermatology* 155(1), pp. 170-181.

Duracinsky, M. et al. 2014. Electronic versus paper-based assessment of health-related quality of life specific to HIV disease: reliability study of the PROQOL-HIV questionnaire. *Journal of medical Internet research* 16(4), p. e115.

Ebrahim, S. 1995. Clinical and public health perspectives and applications of health-related quality of life measurement. *Social science & medicine* 41(10), pp. 1383-1394.

Eghlileb, A. et al. 2007. Psoriasis has a major secondary impact on the lives of family members and partners. *British Journal of Dermatology* 156(6), pp. 1245-1250.

Eghlileb, A. M. et al. 2009. The psoriasis family index: preliminary results of validation of a quality of life instrument for family members of patients with psoriasis. *Dermatology* 219(1), pp. 63-70.

El Miedany, Y. et al. 2016. Toward electronic health recording: evaluation of electronic patient-reported outcome measures system for remote monitoring of early rheumatoid arthritis. *The Journal of rheumatology* 43(12), pp. 2106-2112.

Elash, C. C. et al. 2015. Equivalence of paper and electronic administration of patient reported outcomes: a comparison in psoriatic arthritis. *Value in Health* 18(7), p. A342.

Elewski, B. E. et al. 2017. Psoriasis patients with psoriasis Area and Severity Index (PASI) 90 response achieve greater health-related quality-of-life improvements than those with PASI 75–89 response: results from two phase 3 studies of secukinumab. *Journal of Dermatological Treatment* 28(6), pp. 492-499.

Ellinghaus, D. et al. 2012. Combined analysis of genome-wide association studies for Crohn disease and psoriasis identifies seven shared susceptibility loci. *The American Journal of Human Genetics* 90(4), pp. 636-647.

Ellis, C. N. and Krueger, G. G. 2001. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *New England Journal of Medicine* 345(4), pp. 248-255.

Ellis, C. N. et al. 2003. Effects of alefacept on health-related quality of life in patients with psoriasis: Results from a randomized, placebo-controlled phase II trial. *American Journal of Clinical Dermatology* 4(2), pp. 131-139.

Embry, T. W. and Piccirillo, J. F. 2020. Minimal Clinically Important Difference Reporting in Randomized Clinical Trials. *JAMA Otolaryngology–Head & Neck Surgery*.

Eremenco, S. et al. 2014. Qualitative Equivalence Between A Paper and Electronic Tablet Version of the Womac® Nrs3. 1 and Patient Global Assessment. *Value in Health* 17(7), p. A386.

Eremenco, S. et al. 2015a. Migration of the Fatigue Symptoms and Impacts Questionnaire–Relapsing Multiple Sclerosis (Fsiq-Rmstm) from Paper to an Electronic Diary Format. *Value in Health* 18(7), p. A717.

Eremenco, S. et al. 2015b. Qualitative Equivalence Between Paper and Ediary Versions and Usability of 4 Pro Questionnaires for Uterine Fibroids. *Value in Health* 18(7), p. A711.

Eremenco, S. et al. 2015c. Qualitative Equivalence Between Paper and Ediary Versions and Usability of 6 Pro Questionnaires for Endometriosis. *Value in Health* 18(7), p. A716.

Ershow, A. G. et al. 2011. Virtual reality technologies for research and education in obesity and diabetes: research needs and opportunities. SAGE Publications.

Ersser, S. et al. 2012. A pilot randomized controlled trial to examine the feasibility and efficacy of an educational nursing intervention to improve self-management practices in patients with mild-moderate psoriasis. *Journal of the European Academy of Dermatology and Venereology* 26(6), pp. 738-745.

Eshoj, H. et al. 2017. Translation, adaptation and measurement properties of an electronic version of the Danish Western Ontario Shoulder Instability Index (WOSI). *BMJ open* 7(7), p. e014053.

Esposito, M. et al. 2006. An Italian study on psoriasis and depression. *Dermatology* 212(2), pp. 123-127.

Fanshel, S. and Bush, J. W. 1970. A health-status index and its application to health-services outcomes. *Operations research* 18(6), pp. 1021-1066.

Farber, E. M. and Nall, L. 1984. An appraisal of measures to prevent and control psoriasis. *Journal of the American Academy of Dermatology* 10(3), pp. 511-517.

Farhi, D. et al. 2008. Global assessment of psoriasis severity and change from photographs: a valid and consistent method. *Journal of Investigative Dermatology* 128(9), pp. 2198-2203.

Farthmann, J. et al. 2016. Improvement of pelvic floor-related quality of life and sexual function after vaginal mesh implantation for cystocele: primary endpoint of a prospective multicentre trial. *Archives of gynecology and obstetrics* 294(1), pp. 115-121.

Faulds, M. et al. 2016. The feasibility of using 'bring your own device'(BYOD) technology for electronic data capture in multicentre medical audit and research. *Anaesthesia* 71(1), pp. 58-66.

Faurschou, A. et al. 2015. Lack of effect of the glucagon-like peptide-1 receptor agonist liraglutide on psoriasis in glucose-tolerant patients - a randomized placebo-controlled trial. . *Journal of the European Academy of Dermatology and Venereology* 29(3), pp. 555-559.

Feeny, D. 2002. Commentary on Jack Dowie,"Decision validity should determine whether a generic or condition‐specific HRQOL measure is used in health care decisions" . *Health economics* 11(1), pp. 13-16.

Felce, D. and Perry, J. 1995. Quality of life: Its definition and measurement. *Research in developmental disabilities* 16(1), pp. 51-74.

Feldman, S. et al. 2005a. Infliximab treatment results in significant improvement in the quality of life of patients with severe psoriasis: a double-blind placebo-controlled trial. *British journal of dermatology* 152(5), pp. 954-960.

Feldman, S. et al. 2008. Infliximab improves health-related quality of life in the presence of comorbidities among patients with moderate-to-severe psoriasis. *British journal of dermatology* 159(3), pp. 704-710.

Feldman, S. R. et al. 1996. The self-administered psoriasis area and severity index is valid and reliable. *Journal of Investigative Dermatology* 106(1), pp. 183-186.

Feldman, S. R. et al. 2005b. Etanercept improves the health-related quality of life of patients with psoriasis: Results of a phase III randomized clinical trial. *Journal of the American Academy of Dermatology* 53(5), pp. 887-889.

Feldman, S. R. and Krueger, G. G. 2005. Psoriasis assessment tools in clinical trials. *Annals of the Rheumatic Diseases* 64 (Suppl 2), pp. ii65-ii68.

Ferrans, C. E. ed. 1990. *Quality of life: conceptual issues*. Seminars in oncology nursing.

Ferrans, C. E. and Powers, M. J. 1985. Quality of life index: development and psychometric properties. *Advances in nursing science* 8(1), pp. 15-24.

Fink, C. et al. 2019. Precision and reproducibility of automated computer‐guided Psoriasis Area and Severity Index measurements in comparison with trained physicians. *British Journal of Dermatology* 180(2), pp. 390-396.

Finlay, A. 2020. *Dermatology Life Quality Index* [Online]. Cardiff University. Available at: https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index [Accessed: 9th September 2020].

Finlay, A. and Kelly, S. 1987a. Psoriasis‐an index of disability. *Clinical and experimental dermatology* 12(1), pp. 8-11.

Finlay, A. Y. 1997. Quality of life measurement in dermatology: a practical guide. *British Journal of Dermatology* 136(3), pp. 305-314.

Finlay, A. Y. 1998. Quality of life assessments in dermatology. *Seminars in cutaneous medicine and surgery* 17, pp. 291-296.

Finlay, A. Y. 2005. Current severe psoriasis and the rule of tens. *British Journal of Dermatology* 152(5), pp. 861-867.

Finlay, A. Y. 2014. Quality of life in dermatology: after 125 years, time for more rigorous reporting. *British Journal of Dermatology* 170(1), pp. 4-6.

Finlay, A. Y. 2017. Quimp: A Word Meaning. *Acta dermato-venereologica* 97(4), pp. 546-547.

Finlay, A. Y. et al. 2012. Dermatology Life Quality Index (DLQI): A Paradigm Shift to Patient-Centered Outcomes. *J Invest Dermatol* 132(10), pp. 2464-2465.

Finlay, A. Y. and Coles, E. 1995. The effect of severe psoriasis on the quality of life of 369 patients. *British Journal of Dermatology* 132(2), pp. 236-244.

Finlay, A. Y. and Kelly, S. E. 1987b. Psoriasis‐an index of disability. *Clinical and experimental dermatology* 12(1), pp. 8-11.

Finlay, A. Y. and Khan, G. 1994. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clinical and experimental dermatology* 19(3), pp. 210-216.

Finlay, A. Y. et al. 1990. Validation of sickness impact profile and psoriasis disability index in psoriasis. *British Journal of Dermatology* 123(6), pp. 751-756.

Finlay, A. Y. et al. 2003. Intramuscular alefacept improves health-related quality of life in patients with chronic plaque psoriasis. *Dermatology* 206(4), pp. 307-315.

Fiteni, F. et al. 2015. Health-related quality-of-life as co-primary endpoint in randomized clinical trials in oncology. *Expert review of anticancer therapy* 15(8), pp. 885-891.

Flatz, L. and Conrad, C. 2013. Role of T-cell-mediated inflammation in psoriasis: pathogenesis and targeted therapy. *Psoriasis: Targets and Therapy* 3, pp. 1-10.

Fleischer Jr, A. B. et al. 1994. Patient measurement of psoriasis disease severity with a structured instrument. *Journal of investigative dermatology* 102(6), pp. 967-969.

Flytström, I. et al. 2008. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. *British journal of dermatology* 158(1), pp. 116-121.

Fordham, B. et al. 2015. A pilot study examining mindfulness-based cognitive therapy in psoriasis. *Psychology, Health and Medicine* 20(1), pp. 121-127.

Fortune, D. G. et al. 1997. Assessing illness-related stress in psoriasis: the psychometric properties of the Psoriasis Life Stress Inventory. *Journal of Psychosomatic Research* 42(5), pp. 467-475.

Fortune, D. G. et al. 2005. Psychologic factors in psoriasis: consequences, mechanisms, and interventions. *Dermatologic clinics* 23(4), pp. 681-694.

Fowler, J. F. et al. 2008. The impact of psoriasis on health care costs and patient work loss. *Journal of the American Academy of Dermatology* 59(5), pp. 772-780.

Fredriksson, T. and Pettersson, U. 1978. Severe psoriasis–oral therapy with a new retinoid. *Dermatology* 157(4), pp. 238-244.

Frendl, D. M. and Ware Jr, J. E. 2014. Patient-reported functional health and well-being outcomes with drug therapy: a systematic review of randomized trials using the SF-36 health survey. *Medical care* 52(5), pp. 439-445.

Frennered, K. et al. 2010. Validity of a computer touch-screen questionnaire system in back patients. *Spine* 35(6), pp. 697-703.

Fuxench, Z. C. C. et al. 2016. The risk of cancer in patients with psoriasis: a population-based cohort study in the health improvement network. *JAMA dermatology* 152(3), pp. 282-290.

Gabes, M. et al. 2020. Evaluation of responsiveness and estimation of smallest detectable change and minimal important change scores for the Childhood Atopic Dermatitis Impact Scale. *British Journal of Dermatology* 182(2), pp. 348-354.

Gahalaut, P. et al. 2014. Clinical efficacy of psoralen+sunlight vs. combination of isotretinoin and psoralen+sunlight for the treatment of chronic plaque-type psoriasis vulgaris: A randomized hospital-based study. *Photodermatology Photoimmunology and Photomedicine* 30(6), pp. 294-301.

Galvez, G. J. et al. 2012. Quality of life and assessment after local application of sulphurous water in the home environment in patients with psoriasis vulgaris: A randomised placebo-controlled pilot study. *European Journal of Integrative Medicine* 4(2), pp. e213-e218.

Gamst-Klaussen, T. et al. 2018. Assessment of outcome measures for cost–utility analysis in depression: mapping depression scales onto the EQ-5D-5L. *BJPsych open* 4(4), pp. 160-166.

Ganemo, A. et al. 2004. Health-related quality of life among patients with ichthyosis. *European Journal of Dermatology* 14(1), pp. 61-66.

Gaspari, A. A. 2006. Innate and adaptive immunity and the pathophysiology of psoriasis. *Journal of the American Academy of Dermatology* 54(3), pp. S67-S80.

Gawkrodger, D. 2008. Therapy Guidelines and Audit Subcommittee, British Association of Dermatologists; Clinical Standards Department, Royal College of Physicians of London;

Cochrane Skin Group; Vitiligo Society. Guideline for the diagnosis and management of vitiligo. *Br J Dermatol* 159, pp. 1051-1076.

Gelfand, J. M. et al. 2008. Patient‐Reported Outcomes and Health‐Care Resource Utilization in Patients with Psoriasis Treated with Etanercept: Continuous versus Interrupted Treatment. *Value in Health* 11(3), pp. 400-407.

Gelfand, J. M. et al. 2006. Risk of myocardial infarction in patients with psoriasis. *Journal of the American Medical Association* 296(14), pp. 1735-1741.

Genovese, M. et al. 2007. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *Journal of rheumatology* 34(5), pp. 1040-1050.

Gill, J. et al. 2001. Impact of an electronic medical record on quality of care in a primary care office. *Delaware medical journal* 73(5), pp. 187-194.

Ginsburg, I. H. and LINK, B. G. 1993. Psychosocial consequences of rejection and stigma feelings in psoriasis patients. *International Journal of Dermatology* 32(8), pp. 587-591.

Gisondi, P. et al. 2005. Severe Impairment of Quality of Life in Hailey‐Hailey Disease. *Acta dermato-venereologica* 85(2), pp. 132-135.

Gladman, D. et al. 2014. Effect of certolizumab pegol on multiple facets of psoriatic arthritis as reported by patients: 24-week patient-reported outcome results of a phase III, multicenter study. *Arthritis care & research* 66(7), pp. 1085-1092.

Glazner, J. A. 2017. *"What about me?": The impact of cystic fibrosis on parental differential treatment, sibling relationships and adjustment.* Doctoral dissertation,

Gniadecki, R. et al. 2012. Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. *Journal of the European Academy of Dermatology and Venereology* 26(11), pp. 1436-1443.

Goldberg, D. P. and Hillier, V. F. 1979. A scaled version of the General Health Questionnaire. *Psychological medicine* 9(01), pp. 139-145.

Golics, C. J. et al. 2014. The development and validation of the Family Reported Outcome Measure (FROM-16)© to assess the impact of disease on the partner or family member. *Quality of Life Research* 23(1), pp. 317-326.

Gordon, K. et al. 2014. Impact of brodalumab treatment on psoriasis symptoms and health-related quality of life: Use of a novel patient-reported outcome measure, the Psoriasis Symptom Inventory. *British journal of dermatology* 170(3), pp. 705-715.

Gordon, K. et al. 2003. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *Jama* 290(23), pp. 3073-3080.

Gordon, K. B. et al. 2012. A phase III, randomized, controlled trial of the fully human IL-12/23 mAb briakinumab in moderate-to-severe psoriasis. *Journal of Investigative Dermatology* 132(2), pp. 304-314.

Gordon, K. B. et al. 2006. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *Journal of the American Academy of Dermatology* 55(4), pp. 598-606.

Goswami, P. et al. 2019. Paper and electronic versions of HM-PRO, a novel patient-reported outcome measure for hematology: an equivalence study. *Journal of comparative effectiveness research* 8(7), pp. 523-533.

Gottlieb, A. et al. 2004. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *Journal of the American Academy of Dermatology* 51(4), pp. 534-542.

Gottlieb, A. et al. 2009. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *The Lancet* 373(9664), pp. 633-640.

Gottlieb, A. B. et al. 2003a. The National Psoriasis Foundation Psoriasis Score (NPF-PS) system versus the Psoriasis Area Severity Index (PASI) and Physician's Global Assessment (PGA): a comparison. *Journal of Drugs in Dermatology: JDD* 2(3), pp. 260-266.

Gottlieb, A. B. et al. 2003b. A Randomized Trial of Etanercept as Monotherapy for Psoriasis. *Archives of Dermatology* 139(12), pp. 1627-1632.

Gourraud, P.-A. et al. 2012. Why statistics matter: limited inter-rater agreement prevents using the psoriasis area and severity index as a unique determinant of therapeutic decision in psoriasis. *Journal of Investigative Dermatology* 132(9), pp. 2171-2175.

Gray, A. M. et al. 2006. Estimating the association between SF-12 responses and EQ-5D utility values by response mapping. *Medical Decision Making* 26(1), pp. 18-29.

Greenberger, S. et al. 2012. 9-cis-rich β-carotene powder of the alga dunaliella reduces the severity of chronic plaque psoriasis: A randomized, double-blind, placebo-controlled clinical trial. *Journal of the American College of Nutrition* 31(5), pp. 320-326.

Griffiths, C. et al. 2005. Cytokines and Langerhans cell mobilisation in mouse and man. *Cytokine* 32(2), pp. 67-70.

Griffiths, C. E. and Barker, J. N. 2007. Pathogenesis and clinical features of psoriasis. *The Lancet* 370(9583), pp. 263-271.

Groff, G. D. et al. 1983. Low dose oral methotrexate in rheumatoid arthritis: an uncontrolled trial and review of the literature. *Seminars in Arthritis & Rheumatism* 12(4), pp. 333-347.

Group, T. E. 1990. EuroQol-a new facility for the measurement of health-related quality of life. *Health policy* 16(3), pp. 199-208.

Group, W. 1994. Development of the WHOQOL: Rationale and current status. *International Journal of Mental Health* 23(3), pp. 24-56.

Guida, B. et al. 2014. Energy-restricted, n-3 polyunsaturated fatty acids-rich diet improves the clinical response to immuno-modulating drugs in obese patients with plaque-type psoriasis: A randomized control clinical trial. *Clinical Nutrition* 33(3), pp. 399-405.

Guo, Q. et al. 2016. Keep in touch (KIT): perspectives on introducing internet-based communication and information technologies in palliative care. *BMC palliative care* 15(1), p. 66.

Gupta, A. et al. 2008. ISA247: quality of life results from a phase II, randomized, placebo-controlled study. *Journal of cutaneous medicine and surgery* 12(6), pp. 268-275.

Gupta, M. and Gupta, A. 1995. The Psoriasis Life Stress Inventory: a preliminary index of psoriasis-related stress. *Acta dermato-venereologica* 75(3), pp. 240-243.

Gwaltney, C. J. et al. 2008. Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. *Value in Health* 11(2), pp. 322-333.

Hafner, B. J. et al. 2016. Psychometric evaluation of self-report outcome measures for prosthetic applications. *Journal of rehabilitation research and development* 53(6), p. 797.

Hahn, E. A. and Cella, D. 2003. Health outcomes assessment in vulnerable populations: measurement challenges and recommendations. *Archives of physical medicine and rehabilitation* 84, pp. S35-S42.

Hahn, H. B. et al. 2001. Use of the Dermatology Life Quality Index (DLQI) in a midwestern US urban clinic. *Journal of the American Academy of Dermatology* 45(1), pp. 44-48.

Halioua, B. et al. 2000. Quality of life in dermatology. *International journal of dermatology* 39(11), pp. 801-806.

Handa, V. L. et al. 2008. Paper versus web-based administration of the pelvic floor distress inventory 20 and pelvic floor impact questionnaire 7. *International Urogynecology Journal* 19(10), pp. 1331-1335.

Hanscom, B. et al. 2002. Computerized questionnaires and the quality of survey data. *Spine* 27(16), pp. 1797-1801.

Harari, M. et al. 2000. Clinical evaluation of a more rapid and sensitive Psoriasis Assessment Severity Score (PASS), and its comparison with the classic method of Psoriasis Area and Severity Index (PASI), before and after climatotherapy at the Dead‐Sea. *International journal of dermatology* 39(12), pp. 913-918.

Harden, J. L. et al. 2015. The immunogenetics of psoriasis: a comprehensive review. *Journal of autoimmunity* 64, pp. 66-73.

Hattori, Y. et al. 2014. Multifunctional skin‐like electronics for quantitative, clinical monitoring of cutaneous wound healing. *Advanced healthcare materials* 3(10), pp. 1597-1607.

Havermans, T. et al. 2015. Belgian siblings of children with a chronic illness: Is their quality of life different from their peers? *Journal of Child Health Care* 19(2), pp. 154-166.

Heydendael, V. M. et al. 2004. The burden of psoriasis is not determined by disease severity only. *Journal of Investigative Dermatology Symposium Proceedings* 9(2), pp. 131-135.

Higaki, Y. et al. 2002. The Japanese version of Skindex‐16: a brief quality‐of‐life measure for patients with skin diseases. *The Journal of dermatology* 29(11), pp. 693-698.

Higaki, Y. et al. 2004. Measurement of the Impact of Atopic Dermatitis on Patients' Quality of Life: A Cross‐Sectional and Longitudinal Questionnaire Study Using the Japanese Version of Skindex‐16. *The Journal of dermatology* 31(12), pp. 977-982.

Higgins, E. 2000. Alcohol, smoking and psoriasis. *Clinical and experimental dermatology* 25(2), pp. 107-110.

Higgins, J. P. 2016. Smartphone applications for patients' health and fitness. *The American journal of medicine* 129(1), pp. 11-19.

Higgins, J. P. T. and Green, S. 2008. *Cochrane handbook for systematic reviews of interventions*. Wiley Online Library.

Hjortsberg, C. et al. 2011. Are treatment satisfaction, quality of life, and self-assessed disease severity relevant parameters for patient registries? Experiences from Finnish and Swedish patients with psoriasis. *Acta Dermato-Venereologica* 91(4), pp. 409-414.

Ho, S. et al. 2010. Methotrexate versus traditional Chinese medicine in psoriasis: a randomized, placebo-controlled trial to determine efficacy, safety and quality of life. *Clinical and experimental dermatology* 35(7), pp. 717-722.

Hofstedt, O. et al. 2019. Comparison of agreement between internet-based registration of patient-reported outcomes and clinic-based paper forms within the Swedish Rheumatology Quality Register. *Scandinavian journal of rheumatology*, pp. 1-5.

Højgaard, P. et al. 2018. A systematic review of measurement properties of patient reported outcome measures in psoriatic arthritis: A GRAPPA-OMERACT initiative. *Seminars in arthritis and rheumatism* 47(5), pp. 654-665.

Holme, S. et al. 2003. The Children's Dermatology Life Quality Index: validation of the cartoon version. *British Journal of Dermatology* 148(2), pp. 285-290.

Hongbo, Y. et al. 2005. Translating the science of quality of life into practice: what do dermatology life quality index scores mean? *Journal of Investigative Dermatology* 125(4), pp. 659-664.

Hörnquist, J. O. 1982. The concept of quality of life. *Scandinavian journal of social medicine* 10(2), pp. 57-61.

Hudgens, S. et al. 2019. Development and Validation of the FSIQ-RMS: A New Patient-Reported Questionnaire to Assess Symptoms and Impacts of Fatigue in Relapsing Multiple Sclerosis. *Value in Health* 22(4), pp. 453-466.

Hukuda, S. et al. 2001. Spondyloarthropathies in Japan: nationwide questionnaire survey performed by the Japan Ankylosing Spondylitis Society. *The Journal of rheumatology* 28(3), pp. 554-559.

Hutchinson, P. E. et al. 2000. The efficacy, safety and tolerance of calcitriol 3 μg/g ointment in the treatment of plaque psoriasis: A comparison with short-contact dithranol. *Dermatology* 201(2), pp. 139-145.

Igarashi, A. et al. 2012. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: Long-term results from a phase 2/3 clinical trial. *Journal of Dermatology* 39(3), pp. 242-252.

Inderjeeth, C. et al. 2017. Comparing the Electronic Patient Reported Outcome (ePro) Tool Versus the Paper Reported Outcome (pPro) Tool in Rheumatoid Arthritis Patients Treated with Certolizumab Pegol. *Internal Medicine Journal (Print)* 47, pp. 12-12.

Ingram, J. et al. 2019. British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018. *British Journal of Dermatology* 180(5), pp. 1009-1017.

Jacobson, C. and Kimball, A. 2004. Rethinking the Psoriasis Area and Severity Index: the impact of area should be increased. *British Journal of Dermatology* 151(2), pp. 381-387.

Jadad, A. R. et al. 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled clinical trials* 17(1), pp. 1-12.

Jaeschke, R. et al. 1989. Measurement of health status: ascertaining the minimal clinically important difference. *Controlled clinical trials* 10(4), pp. 407-415.

Jensen, J. D. et al. 2011. Validation of psoriasis clinical severity and outcome measures: searching for a gold standard. *Archives of dermatology* 147(1), pp. 95-98.

Jensen, P. et al. 2013. Effect of weight loss on the severity of psoriasis: a randomized clinical study. *JAMA dermatology* 149(7), pp. 795-801.

Juniper, E. et al. 2007. Development and validation of an electronic version of the Rhinoconjunctivitis Quality of Life Questionnaire. *Allergy* 62(9), pp. 1091-1093.

Juniper, E. F. et al. 2009. Patients may respond differently to paper and electronic versions of the same questionnaires. *Respiratory medicine* 103(6), pp. 932-934.

Kaltwasser, J. et al. 2004. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis and rheumatism* 50(6), pp. 1939-1950.

Kaplan, R. M. and Bush, J. W. 1982. Health-related quality of life measurement for evaluation research and policy analysis. *Health psychology* 1(1), p. 61.

Karimi, M. and Brazier, J. 2016. Health, health-related quality of life, and quality of life: what is the difference? *Pharmacoeconomics* 34(7), pp. 645-649.

Katugampola, R. P. et al. 2007. The Dermatology Life Quality Index: assessing the efficacy of biological therapies for psoriasis. *British Journal of Dermatology* 156(5), pp. 945-950.

Katusiime, B. et al. 2015. Experiences of using prescription medicines among the general public in the UK: A comparison of paper-and online-reported experiences. *International Journal of Clinical Pharmacy* 37(2), p. 403.

Kavanaugh, A. et al. 2010. Effect of ustekinumab on physical function and health-related quality of life in patients with psoriatic arthritis: a randomized, placebo-controlled, phase II trial. *Current Medical Research & Opinion* 26(10), pp. 2385-2392.

Keilmann, L. et al. 2019. Quality of life measurement in breast cancer patients: Reliability of an ePRO tool using EORTC QLQ-C30. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 234, pp. e148-e149.

Kesterke, N. et al. 2015. Patient-reported outcome assessment after total joint replacement: comparison of questionnaire completion times on paper and tablet computer. *Archives of orthopaedic and trauma surgery* 135(7), pp. 935-941.

Khilji, F. 2002. Clinical meaning of change in Dermatology Life Quality Index scores. *Br J Dermatol* 147(62), p. 50.

Killewo, J. et al. 2010. *Epidemiology and demography in public health*. Academic Press.

Kim, H. et al. 2016. Evaluation of quality of life using a tablet PC-based survey in cancer patients treated with radiotherapy: a multi-institutional prospective randomized crossover comparison of paper and tablet PC-based questionnaires (KROG 12–01). *Supportive Care in Cancer* 24(10), pp. 4399-4406.

Kimball, A. et al. 2012. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial through up to 3 years. *British journal of dermatology* 166(4), pp. 861-872.

Kimball, A. B. et al. 2011. Efficacy and Safety of Adalimumab among Patients with Moderate to Severe Psoriasis with Co-Morbidities Subanalysis of Results from a Randomized, Double-Blind, Placebo-Controlled, Phase III Trial. *American Journal of Clinical Dermatology* 12(1), pp. 51-62.

Kimball, A. B. et al. 2013. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study. *Journal of the European Academy of Dermatology and Venereology* 27(12), pp. 1535-1545.

Kirby, B. et al. 2000. The Salford Psoriasis Index: an holistic measure of psoriasis severity. *British Journal of Dermatology* 142(4), pp. 728-732.

Kitchen, H. et al. 2015. Patient‐reported outcome measures in psoriasis: the good, the bad and the missing! *British Journal of Dermatology* 172(5), pp. 1210-1221.

Klassen, A. F. et al. 2000. Measuring quality of life in people referred for specialist care of acne: comparing generic and disease-specific measures. *Journal of the American Academy of Dermatology* 43(2), pp. 229-233.

Klein, A. et al. 2011. A randomized clinical trial in psoriasis: synchronous balneophototherapy with bathing in Dead Sea salt solution plus narrowband UVB vs. narrowband UVB alone (TOMESA-study group). *Journal of the European Academy of Dermatology and Venereology* 25(5), pp. 570-578.

Kleinman, L. et al. 2001. A comparative trial of paper-and-pencil versus computer administration of the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire. *Medical care* 39(2), pp. 181-189.

Knecht, C. et al. 2015. The perspective of siblings of children with chronic illness: a literature review. *Journal of pediatric nursing* 30(1), pp. 102-116.

Knoerl, R. et al. 2017. Electronic versus paper-pencil methods for assessing chemotherapy-induced peripheral neuropathy. *Supportive Care in Cancer* 25(11), pp. 3437-3446.

Ko, H. C. et al. 2010. Clinical course of guttate psoriasis: Long‐term follow‐up study. *The Journal of dermatology* 37(10), pp. 894-899.

Koek, M. B. G. et al. 2006. UVB phototherapy in an outpatient setting or at home: a pragmatic randomised single-blind trial designed to settle the discussion. The PLUTO study. *BMC Medical Research Methodology* 6, p. 39.

Koo, J. et al. 2003. Development of a disease specific quality of life questionnaire: the 12-item Psoriasis Quality of Life Questionnaire (PQOL-12). *61st Annual Meeting of the American Academy of Dermatology. San Francisco, CA* abstract number: P606.

Kothary, N. et al. 2011. Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients. *Journal of the American Academy of Dermatology* 65(3), pp. 546-551.

Kottner, J. et al. 2018. Core outcome sets in dermatology: report from the second meeting of the International Cochrane Skin Group Core Outcome Set Initiative. *British Journal of Dermatology* 178(4), pp. e279-e285.

Kouris, A. et al. 2015. Quality of life in G reek family members living with leg ulcer patients. *Wound Repair and Regeneration* 23(5), pp. 778-780.

Kragballe, K. et al. 1991. Double-blind, right left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis-vulgaris. *Lancet* 337(8735), pp. 193-196.

Kragballe, K. et al. 2009. Efficacy and safety of calcipotriol plus betamethasone dipropionate scalp formulation compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized controlled trial. *British Journal of Dermatology* 161(1), pp. 159-166.

Krahn, M. et al. 2007. Responsiveness of disease-specific and generic utility instruments in prostate cancer patients. *Quality of life research* 16(3), p. 509.

Kreft, S. et al. 2006. Computer-aided measurement of psoriatic lesion area in a multicenter clinical trial-Comparison to physician's estimations. *Journal of Dermatological Science* 44(1), pp. 21-27.

Krueger, G. et al. 2001. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. *Archives of dermatology* 137(3), pp. 280-284.

Krueger, G. et al. 2005. Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial. *British journal of dermatology* 153(6), pp. 1192-1199.

Krueger, J. G. et al. 2012. IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. *Journal of Allergy and Clinical Immunology* 130(1), pp. 145-154. e149.

Krupashankar, D. et al. 2014. Efficacy and safety of itolizumab, a novel anti-CD6 monoclonal antibody, in patients with moderate to severe chronic plaque psoriasis: Results of a double-blind, randomized, placebo-controlled, phase-III study. *Journal of the American Academy of Dermatology* 71(3), pp. 484-492.

Kulthanan, K. et al. 2016. Minimal clinical important difference (MCID) of the Thai chronic urticaria quality of life questionnaire (CU-Q2oL). *Asian Pacific Journal of Allergy and Immunology* 34(2), pp. 137-145.

Kumar, S. et al. 2013. Obesity, waist circumference, weight change and the risk of psoriasis in US women. *Journal of the European Academy of Dermatology and Venereology* 27(10), pp. 1293-1298.

Kunynetz, R. et al. 2011. Quality of life in plaque psoriasis patients treated with voclosporin: a Canadian phase III, randomized, multicenter, double-blind, placebo-controlled study. *European journal of dermatology* 21(1), pp. 89-94.

Kurwa, H. and Finlay, A. Y. 1995. Dermatology in‐patient management greatly improves life quality. *British Journal of Dermatology* 133(4), pp. 575-578.

Kuyken, W. 1995. The World Health Organisation quality of life assessment (WHOQOL): position paper from the World Health Organisation. *Soc Sci Med* 41, pp. 1409-1409.

Kuyper, M. B. and Wester, F. 1998. In the shadow: the impact of chronic illness on the patient's partner. *Qualitative health research* 8(2), pp. 237-253.

Lambert, J. et al. 2011. A novel multidisciplinary educational programme for patients with chronic skin diseases: Ghent pilot project and first results. *Archives of dermatological research* 303(1), pp. 57-63.

Langan, S. M. et al. 2012. Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. *Journal of Investigative Dermatology* 132(3), pp. 556-562.

Langenbruch, A. et al. 2019. Does the Dermatology Life Quality Index (DLQI) underestimate the disease‐specific burden of psoriasis patients? *Journal of the European Academy of Dermatology and Venereology* 33(1), pp. 123-127.

Langley, R. et al. 2010. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebo-controlled phase III trial. *Journal of the American Academy of Dermatology* 63(3), pp. 457-465.

Langley, R. et al. 2005. Psoriasis: epidemiology, clinical features, and quality of life. *Annals of the rheumatic diseases* 64(suppl 2), pp. ii18-ii23.

Langley, R. G. et al. 2014. Secukinumab in plaque psoriasis - Results of two phase 3 trials. *New England Journal of Medicine* 371(4), pp. 326-338.

Langley, R. G. and Ellis, C. N. 2004. Evaluating psoriasis with psoriasis area and severity index, psoriasis global assessment, and lattice system physician's global assessment. *Journal of the American Academy of Dermatology* 51(4), pp. 563-569.

Larsen, P. D. 2002. *Chronic illness: Impact and interventions*. Boston: Jones & Bartlett Learning.

Lawson, V. et al. 1998. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire. *The British journal of dermatology* 138(1), pp. 107-113.

Le Cleach, L. et al. 2008. Poor reporting of quality of life outcomes in dermatology randomized controlled clinical trials. *Dermatology* 216(1), pp. 46-55.

Leaf, D. E. and Goldfarb, D. S. 2008. Interpretation and review of health-related quality of life data in CKD patients receiving treatment for anemia. *Kidney Int* 75(1), pp. 15-24.

Leaute-Labreze, C. et al. 2001. Saline spa water or combined water and UV-B for psoriasis vs conventional UV-B: lessons from the Salies de Bearn randomized study. *Archives of Dermatology* 137(8), pp. 1035-1039.

Lebwohl, M. 1995. Future psoriasis therapy. *Dermatol Clin* 13(4), pp. 915-923.

Lebwohl, M. and Ali, S. 2001. Treatment of psoriasis. Part 1. Topical therapy and phototherapy. *Journal of the American Academy of Dermatology* 45(4), pp. 487-502.

Lebwohl, M. et al. 2003. An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. *Archives of dermatology* 139(6), pp. 719-727.

Lebwohl, M. et al. 2010. Ustekinumab improves health-related quality of life in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial. *British journal of dermatology* 162(1), pp. 137-146.

Lee, E. H. et al. 2014. Measurement equivalence of touch‐screen computerized and paper‐based diabetes‐specific quality‐of‐life questionnaires. *International journal of nursing practice* 20(4), pp. 382-389.

Lee, S. J. et al. 2007. Electronic and computer-generated patient questionnaires in standard care. *Best Practice & Research Clinical Rheumatology* 21(4), pp. 637-647.

Leidy, N. K. and Vernon, M. 2008. Perspectives on patient-reported outcomes. *Pharmacoeconomics* 26(5), pp. 363-370.

Leonardi, C. et al. 2012. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *New England Journal of Medicine* 366(13), pp. 1190-1191.

Leonardi, C. L. et al. 2008. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *The Lancet* 371(9625), pp. 1665-1674.

Leonardi, C. L. et al. 2003. Etanercept as Monotherapy in Patients with Psoriasis. *New England Journal of Medicine* 349(21), pp. 2014-2022.

Lewis, V. and Finlay, A. Y. 2004. 10 years experience of the Dermatology Life Quality Index (DLQI). *Journal of Investigative Dermatology Symposium Proceedings* 9(2), pp. 169-180.

Lewis, V. J. and Finlay, A. Y. 2005. Two decades experience of the Psoriasis Disability Index. *Dermatology* 210(4), pp. 261-268.

Lewis-Jones, S. and Mugglestone, M. A. 2007. Management of atopic eczema in children aged up to 12 years: summary of NICE guidance. *Bmj* 335(7632), pp. 1263-1264.

Lewis‐Jones, M. and Finlay, A. 1995. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *British Journal of Dermatology* 132(6), pp. 942-949.

Li, W.-Q. et al. 2013. Psoriasis, psoriatic arthritis and increased risk of incident Crohn's disease in US women. *Annals of the rheumatic diseases* 72(7), pp. 1200-1205.

Linehan, L. A. et al. 2014. Assessing quality of life questionnaires in urogynaecology–tick or type? *Australian and New Zealand Journal of Obstetrics and Gynaecology* 54(4), pp. 390-392.

Ling, T. et al. 2016. British Association of Dermatologists and British Photodermatology Group guidelines for the safe and effective use of psoralen–ultraviolet A therapy 2015. *British Journal of Dermatology* 174(1), pp. 24-55.

Lloyd, A. et al. 2009. Economic evaluation of etanercept in the management of chronic plaque psoriasis. *British Journal of Dermatology* 160(2), pp. 380-386.

Long, K. A. et al. 2018. Psychosocial functioning and risk factors among siblings of children with cancer: An updated systematic review. *Psycho ‐ oncology* 27(6), pp. 1467-1479.

Longworth, L. and Rowen, D. 2011. NICE DSU technical support document 10: the use of mapping methods to estimate health state utility values. *Sheffield: Decision Support Unit, ScHARR, University of Sheffield*.

Loo, W. et al. 2003. Dermatology Life Quality Index: influence of an illustrated version. *British Journal of Dermatology* 148(2), pp. 279-284.

Louden, B. A. et al. 2004. A Simplified Psoriasis Area Severity Index (SPASI) for rating psoriasis severity in clinic patients. *Dermatology online journal* 10(2), p. 7.

Lu, C. et al. 2012. A randomized controlled single-blind clinical trial on 84 outpatients with psoriasis vulgaris by auricular therapy combined with optimized Yinxieling Formula. *Chinese journal of integrative medicine* 18(3), pp. 186-191.

Luger, T. et al. 2009. Sustained improvement in joint pain and nail symptoms with etanercept therapy in patients with moderate-to-severe psoriasis. *Journal of the European Academy of Dermatology and Venereology* 23(8), pp. 896-904.

Lui, H. et al. 2012. A randomized controlled study of combination therapy with alefacept and narrow band UVB phototherapy (UVB) for moderate to severe psoriasis: efficacy, onset, and duration of response. *J. Drugs Dermatol.* 11(8), pp. 929-937.

Lynde, C. W. et al. 2012. A randomized study comparing the combination of nbUVB and etanercept to etanercept monotherapy in patients with psoriasis who do not exhibit an excellent response after 12 weeks of etanercept. *Journal of Dermatological Treatment* 23(4), pp. 261-267.

MacKenzie, H. et al. 2011. Patient-reported outcome in psoriatic arthritis: a comparison of Web-based versus paper-completed questionnaires. *The Journal of rheumatology* 38(12), pp. 2619-2624.

Mahil, S. K. et al. 2016. Update on psoriasis immunopathogenesis and targeted immunotherapy. *Seminars in immunopathology* 38(1), pp. 11-27.

Mamolo, C. et al. 2014. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, improves patient-reported outcomes in a phase 2b, randomized, double-blind, placebo-controlled study in patients with moderate-to-severe psoriasis. *Journal of the European Academy of Dermatology and Venereology* 28(2), pp. 192-203.

Marandino, L. et al. 2020. COVID-19 emergency and the need to speed up the adoption of electronic patient-reported outcomes in cancer clinical practice. *JCO oncology practice* 16(6), p. 295.

Marciniak, J. et al. 2017. Quality of life of parents of children with atopic dermatitis. *Acta dermato-venereologica* 97(6-7), pp. 711-714.

Marshall, S. et al. 2006. Impact of patient‐reported outcome measures on routine practice: a structured review. *Journal of evaluation in clinical practice* 12(5), pp. 559-568.

Marta, G. N. et al. 2017. A critical evaluation of quality of life in clinical trials of breast cancer patients treated with radiation therapy. *Annals of palliative medicine* 6(Suppl 2), pp. S223-S232.

Martin, M. L. et al. 2018. Mixed-methods development of a new patient-reported outcome instrument for chronic low back pain: Part 1—the Patient Assessment for Low Back Pain-Symptoms (PAL-S). *Pain* 159(6), p. 1045.

Martin, M. L. et al. 2013. Early development and qualitative evidence of content validity for the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure of psoriasis symptom severity. *Journal of Dermatological Treatment* 24(4), pp. 255-260.

Martínez-García, E. et al. 2014. Quality of life in persons living with psoriasis patients. *Journal of the American Academy of Dermatology* 71(2), pp. 302-307.

Mattei, P. L. et al. 2014. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. *Journal of the European Academy of Dermatology & Venereology* 28(3), pp. 333-337.

Matthew, A. G. et al. 2007. Serial personal digital assistant data capture of health-related quality of life: a randomized controlled trial in a prostate cancer clinic. *Health and quality of life outcomes* 5(1), p. 38.

Matusiak, L. et al. 2010. Psychophysical Aspects of Hidradenitis Suppurativa. *Acta Dermato-Venereologica* 90(3), pp. 264-268.

Mazzotti, E. et al. 2003. Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis. *British Journal of Dermatology* 149(2), pp. 318-322.

McInnes, I. B. et al. 2013. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *The Lancet* 382(9894), pp. 780-789.

McKenna, S. P. et al. 2003. Development of the PSORIQoL, a psoriasis-specific measure of quality of life designed for use in clinical practice and trials. *British Journal of Dermatology* 149(2), pp. 323-331.

McKenna, S. P. et al. 2004. Development of the PsAQoL: A quality of life instrument specific to psoriatic arthritis. *Annals of the Rheumatic Diseases* 63(2), pp. 162-169.

McKenna, S. P. et al. 2005. International development of the parents' index of quality of life in atopic dermatitis (PIQoL-AD). *Quality of Life Research* 14(1), pp. 231-241.

McLellan, C. 2014. *The History of Tablet Computers: A timeline* [Online]. ZDNet. Available at: http://www.zdnet.com/the-history-of-tablet-computers-a-timeline-7000026555/ [Accessed: 27th May].

Meads, D. et al. 2005. The quality of life of parents of children with atopic dermatitis: interpretation of PIQoL-AD scores. *Quality of life research* 14(10), p. 2235.

Mease, P. et al. 2014. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Annals of the rheumatic diseases* 73(1), pp. 48-55.

Mease, P. et al. 2005. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis and rheumatism* 52(10), pp. 3279-3289.

Menter, A. et al. 2009. Comparing clobetasol propionate 0.05% spray to calcipotriene 0.005% betamethasone dipropionate 0.064% ointment for the treatment of moderate to severe plaque psoriasis. *J. Drugs Dermatol.* 8(1), pp. 52-57.

Menter, A. et al. 2010. The effect of adalimumab on reducing depression symptoms in patients with moderate to severe psoriasis: a randomized clinical trial. *Journal of the American Academy of Dermatology* 62(5), pp. 812-818.

Menter, A. et al. 2007. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *Journal of the American Academy of Dermatology* 56(1), pp. 31.e31-15.

Menter, A. et al. 2013. Calcipotriene plus betamethasone dipropionate topical suspension for the treatment of mild to moderate psoriasis vulgaris on the body: A randomized, double-blind, vehicle-controlled trial. *J. Drugs Dermatol.* 12(1), pp. 92-98.

Menter, A. et al. 2005. Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis. *Archives of dermatology* 141(1), pp. 31-38.

Menter, A. et al. 2008a. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *Journal of the American Academy of Dermatology* 58(5), pp. 826-850.

Menter, A. et al. 2008b. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *Journal of the American Academy of Dermatology* 58(1), pp. 106-115.

Merola, J. F. et al. 2017. The Static Physician's Global Assessment of Genitalia: A Clinical Outcome Measure for the Severity of Genital Psoriasis. *Journal of Drugs in Dermatology: JDD* 16(8), pp. 793-799.

Michalek, I. et al. 2017. A systematic review of worldwide epidemiology of psoriasis. *Journal of the European Academy of Dermatology and Venereology* 31(2), pp. 205-212.

Miller, G. A. 1956. The magical number seven, plus or minus two: some limits on our capacity for processing information. *Psychological review* 63(2), p. 81.

Minard, J. P. et al. 2016. Assessing the burden of childhood asthma: validation of electronic versions of the Mini Pediatric and Pediatric Asthma Caregiver's Quality of Life Questionnaires. *Quality of Life Research* 25(1), pp. 63-69.

Møller, A. H. et al. 2015. A systematic literature review to compare quality of life in psoriasis with other chronic diseases using EQ-5D-derived utility values. *Patient related outcome measures* 6, p. 167.

Möller, I. et al. 2010. Effectiveness of chondroitin sulphate in patients with concomitant knee osteoarthritis and psoriasis: a randomized, double-blind, placebo-controlled study. *Osteoarthritis and cartilage* 18 Suppl 1, pp. S32-40.

Moore, A. et al. 2007. A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis. *Journal of the American Academy of Dermatology* 56(4), pp. 598-603.

Morgan, M. et al. 1997. Dermatology quality of life scales–a measure of the impact of skin diseases. *British journal of dermatology* 136(2), pp. 202-206.

Morley, D. et al. 2015. comparing the psychometric properties of the paper and e-based versions of the 39-item Parkinson's disease questionnaire (pdq-39): 1084. *Movement Disorders* 30, p. S419.

Mortimer, D. and Segal, L. 2008. Comparing the incomparable? A systematic review of competing techniques for converting descriptive measures of health status into QALY-weights. *Medical decision making* 28(1), pp. 66-89.

Mraz, S. et al. 2008. Different treatment outcomes with different formulations of clobetasol propionate 0.05% for the treatment of plaque psoriasis. *Journal of Dermatological Treatment* 19(6), pp. 354-359.

Muehlhausen, W. et al. 2015. Equivalence of electronic and paper administration of patient-reported outcome measures: a systematic review and meta-analysis of studies conducted between 2007 and 2013. *Health and quality of life outcomes* 13(1), p. 167.

Nakagawa, H. et al. 2012. Impact of ustekinumab on health-related quality of life in Japanese patients with moderate-to-severe plaque psoriasis: Results from a randomized, double-blind, placebo-controlled phase 2/3 trial. *Journal of dermatology* 39(9), pp. 761-769.

Naldi, L. et al. 2014. Diet and physical exercise in psoriasis: A randomized controlled trial. *British Journal of Dermatology* 170(3), pp. 634-642.

Naldi, L. et al. 2003. Randomized clinical trials for psoriasis 1977–2000: the EDEN survey. *Journal of investigative dermatology* 120(5), pp. 738-741.

Nash, P. et al. 2006. Leflunomide improves psoriasis in patients with psoriatic arthritis: An in-depth analysis of data from the TOPAS study. *Dermatology* 212(3), pp. 238-249.

Nast, A. et al. 2012. S3 – Guidelines on the treatment of psoriasis vulgaris (English version). Update. *J Dtsch Dermatol Ges* 10, pp. S1-s95.

Naus, M. J. et al. 2009. From paper to pixels: A comparison of paper and computer formats in psychological assessment. *Computers in Human Behavior* 25(1), pp. 1-7.

Navarini, A. A. et al. 2017. European consensus statement on phenotypes of pustular psoriasis. *Journal of the European Academy of Dermatology and Venereology* 31(11), pp. 1792-1799.

Navarini, A. A. et al. 2014. Analysis of Body Regions and Components of PASI Scores During Adalimurnab or Methotrexate Treatment for Patients With Moderate-to-Severe Psoriasis. *J. Drugs Dermatol.* 13(5), pp. 554-562.

Neri, E. et al. 2012. Italian validation of the Childhood Atopic Dermatitis Impact Scale: a contribution to its clinical application. *Journal of Investigative Dermatology* 132(11), pp. 2534-2543.

Neumann, J. et al. 1953. *Theory of games and economic behavior*. Princeton University Press, Commemorative Ed edition (1 May 2007).

NICE. 2012. *Psoriasis: assessment and management* [Online]. Available at: https://www.nice.org.uk/guidance/cg153/chapter/1-Guidance - ftn.footnote_14 [Accessed.

Nickoloff, B. J. 1999. Skin innate immune system in psoriasis: friend or foe? *The Journal of clinical investigation* 104(9), pp. 1161-1164.

Nijsten, T. 2012. Dermatology life quality index: time to move forward. *Journal of Investigative Dermatology* 132(1), pp. 11-13.

Nijsten, T. et al. 2009. Categorization of Skindex-29 scores using mixture analysis. *Dermatology* 218(2), pp. 151-154.

Nishimura, K. et al. 2017. Comparison between electronic and paper versions of the Evaluating Respiratory Symptoms in COPD (E-RS) and the COPD Assessment Test (CAT). *European Respiratory Journal* 50(suppl 61), p. PA3630.

Nitikman, M. et al. 2017. Internet-administered health-related quality of life questionnaires compared with pen and paper in an adolescent scoliosis population: a randomized crossover study. *Journal of Pediatric Orthopaedics* 37(2), pp. e75-e79.

Norlin, J. M. et al. 2012. Analysis of three outcome measures in moderate to severe psoriasis: a registry-based study of 2450 patients. *British Journal of Dermatology* 166(4), pp. 797-802.

Norman, G. R. et al. 2003. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Medical care*, pp. 582-592.

Norquist, J. et al. 2017. Assessing the comparability of paper and electronic versions of the EORTC QOL module for head and neck cancer: a qualitative study. *JMIR cancer* 3(1), p. e7.

O'Brien, K. et al. 2020. Voice‐Controlled Intelligent Personal Assistants to Support Aging in Place. *Journal of the American Geriatrics Society* 68(1), pp. 176-179.

O'Donohoe, P. et al. 2015. COPD symptom data-usability and validation of electronic, tablet-based implementations of the SGRQ-C and CAT questionnaires. *Quality of LIfe Research* 24, pp. 82-82.

O'Gorman, H. et al. 2014. Comparing the equivalence of EQ-5D-5L across different modes of administration. *Value in Health* 17(7), p. A517.

O'Brien, B. J. and Drummond, M. F. 1994. Statistical versus quantitative significance in the socioeconomic evaluation of medicines. *PharmacoEconomics* 5(5), pp. 389-398.

Obradors, M. et al. 2016. Health-related quality of life in patients with psoriasis: a systematic review of the European literature. *Quality of Life Research* 25(11), pp. 2739-2754.

Odenheimer, S. et al. 2018. Patient Acceptance of Remote Scribing Powered by Google Glass in Outpatient Dermatology: Cross-Sectional Study. *Journal of medical Internet research* 20(6), p. e10762.

Ofenloch, R. F. et al. 2015. Severity and functional disability of patients with occupational contact dermatitis: validation of the German version of the Occupational Contact Dermatitis Disease Severity Index. *Contact dermatitis* 72(2), pp. 84-89.

Ogden, J. 2017. QALYs and their role in the NICE decision‐making process. *Prescriber* 28(4), pp. 41-43.

Ogdie, A. et al. 2020. Treatment guidelines in psoriatic arthritis. *Rheumatology* 59(Supplement_1), pp. i37-i46.

Oliveira, A. et al. 2011. OnQol: Electronic device to capture QoL data in oncology: Difference between patients 65 years or older and patients younger than 65 years of age. *Journal of Geriatric Oncology* 2(4), pp. 253-258.

Oliveira, F. A. P. d. et al. 2020. Cosmetic camouflage improves health-related quality of life in women with systemic lupus erythematosus and permanent skin damage: A controlled intervention study. *Lupus* 0(0), pp. 1-11.

Olivier, C. et al. 2010. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. *Archives of dermatology* 146(8), pp. 891-895.

Orbai, A.-M. et al. 2017. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. *Annals of the rheumatic diseases* 76(4), pp. 673-680.

Organization, W. H. 2014. Constitution of the World Health Organization. *Geneva: Basic documents of the World Health Organization* 48th ed.

Organization, W. H. 2019. *Global report on psoriasis* [Online]. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/204417 [Accessed: 29th October].

Ortonne, J. et al. 2009. Quality of life in patients with scalp psoriasis treated with calcipotriol/betamethasone dipropionate scalp formulation: a randomized controlled trial. *Journal of the European Academy of Dermatology and Venereology* 23(8), pp. 919-926.

Ortonne, J. et al. 2005. Impact of efalizumab on patient-reported outcomes in high-need psoriasis patients: results of the international, randomized, placebo-controlled Phase III Clinical Experience Acquired with Raptiva (CLEAR) trial. *BMC dermatology* 5, p. 13.

Ortonne, J.-P. et al. 2008. Efficacy and safety of continuous versus paused etanercept treatment in patients with moderate-to-severe psoriasis over 54 weeks: the CRYSTEL study. *Expert Review of Dermatology* 3(6), pp. 657-665.

Ortonne, J. P. et al. 2014. Betamethasone valerate dressing is non-inferior to calcipotriol-betamethasone dipropionate ointment in the treatment of patients with mild-to-moderate chronic plaque psoriasis: Results of a randomized assessor-blinded multicentre trial. *Journal of the European Academy of Dermatology and Venereology* 28(9), pp. 1226-1234.

Ortonne, J. P. et al. 2013. A 24-week randomized clinical trial investigating the efficacy and safety of two doses of etanercept in nail psoriasis. *British Journal of Dermatology* 168(5), pp. 1080-1087.

Palmer, C. et al. 2018. Are Electronic and Paper Questionnaires Equivalent to Assess Patients with Overactive Bladder? *The Journal of urology* 200(2), pp. 369-374.

Papp, K. et al. 2008a. Efficacy of ISA247 in plaque psoriasis: a randomised, multicentre, double-blind, placebo-controlled phase III study. *The Lancet* 371(9621), pp. 1337-1342.

Papp, K. et al. 2012a. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *Lancet* 380(9843), pp. 738-746.

Papp, K. et al. 2014. Effects of briakinumab treatment for moderate to severe psoriasis on health-related quality of life and work productivity and activity impairment: Results from a randomized phase III study. *Journal of the European Academy of Dermatology and Venereology* 28(6), pp. 790-798.

Papp, K. A. et al. 2008b. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 371(9625), pp. 1675-1684.

Papp, K. A. et al. 2012b. Brodalumab, an Anti-Interleukin-17-Receptor Antibody for Psoriasis. *New England Journal of Medicine* 366(13), pp. 1181-1189.

Papp, K. A. et al. 2005. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *British Journal of Dermatology* 152(6), pp. 1304-1312.

Parisi, R. et al. 2020. National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. *BMJ* 369.

Park, S. and Jayaraman, S. 2003. Enhancing the quality of life through wearable technology. *IEEE Engineering in medicine and biology magazine* 22(3), pp. 41-48.

Parkin, D. and Devlin, N. 2006. Is there a case for using visual analogue scale valuations in cost‐utility analysis? *Health economics* 15(7), pp. 653-664.

Pathirana, D. et al. 2009. European S3-guidelines on the systemic treatment of psoriasis vulgaris. *Journal of the European Academy of Dermatology and Venereology* 23(SUPPL. 2), pp. 5-70.

Patrick, D. L. et al. 1973. Toward an operational definition of health. *Journal of health and social behavior*, pp. 6-23.

Patrick, D. L. and Deyo, R. A. 1989. Generic and disease-specific measures in assessing health status and quality of life. *Medical care*, pp. S217-S232.

Paul, C. et al. 2012. Influence of psoriatic arthritis on the efficacy of adalimumab and on the treatment response of other markers of psoriasis burden: Subanalysis of the BELIEVE study. *European Journal of Dermatology* 22(6), pp. 762-769.

Paul, C. et al. 2014. Transition to ustekinumab in patients with moderate-to-severe psoriasis and inadequate response to methotrexate: A randomized clinical trial (TRANSIT). *British journal of dermatology* 170(2), pp. 425-434.

Paul, W. J. et al. 2015. Responder Analyses for Treatment Effects in COPD Using the SGRQ Appear to be Largely Independent of the Value Used to Determine a Clinically Significant Response.*C45. ACROSS THE UNIVERSE OF COPD EPIDEMIOLOGY*. American Thoracic Society, pp. A4454-A4454.

Paulden, M. et al. 2010. Alitretinoin for the treatment of severe chronic hand eczema. *Health Technol Assess* 14(Suppl 1), pp. 39-46.

Pearce, D. J. et al. 2006. The negative impact of psoriasis on the workplace. *Journal of Dermatological Treatment* 17(1), pp. 24-28.

Pereira, F. et al. 2012. The role of the EQ-5D in the economic evaluation of dermatological conditions and therapies. *Dermatology* 225(1), pp. 45-53.

Peters, M. et al. 2016. The coeliac disease assessment questionnaire (CDAQ): comparison of the paper and electronic versions. *Quality of Life Research* 25, pp. 180-181.

Petersen, M. A. et al. 2016. An initial international validation of the EORTC computer adaptive test (CAT) confirmed feasibility. *Quality of Life Research* 25, p. 80.

Piccinelli, M. et al. 1993. Validity and test-retest reliability of the Italian version of the 12-item General Health Questionnaire in general practice: a comparison between three scoring methods. *Comprehensive psychiatry* 34(3), pp. 198-205.

Picot, E. et al. 1992. Treatment of psoriasis with a 311‐nm UVB lamp. *British Journal of Dermatology* 127(5), pp. 509-512.

Pompili, C. et al. 2018. The role of sociodemographic factors in determining the uptake of electronic PROM completion in lung cancer patients: early indicators from the Life after lung cancer (LILAC) study. *Quality of LIfe Research* 27, pp. S83-S84.

Pouplard, C. et al. 2013. Risk of cancer in psoriasis: a systematic review and meta‐analysis of epidemiological studies. *Journal of the European Academy of Dermatology and Venereology* 27, pp. 36-46.

Prins, M. et al. 2005. The effect of treatment on quality of life in psoriasis patients. *Acta Dermato-Venereologica* 85(4), pp. 304-310.

Prinsen, C. et al. 2013. Measurement of health‐related quality of life in dermatological research and practice: outcome of the EADV Taskforce on Quality of Life. *Journal of the European Academy of Dermatology and Venereology* 27(10), pp. 1195-1203.

Prinz, J. C. 2004. Disease mimicry—a pathogenetic concept for T cell-mediated autoimmune disorders triggered by molecular mimicry? *Autoimmunity reviews* 3(1), pp. 10-15.

Pustišek, N. et al. 2016. Quality of life in families with children with atopic dermatitis. *Pediatric dermatology* 33(1), pp. 28-32.

Putterman, E. et al. 2019. Severity of disease and quality of life in parents of children with alopecia areata, totalis, and universalis: A prospective, cross-sectional study. *Journal of the American Academy of Dermatology* 80(5), pp. 1389-1394.

Quadri, N. et al. 2013. A literature review of the variance in interval length between administrations for assessment of test retest reliability and equivalence of pro measures. *Value in Health* 16(3), pp. A40-A41.

Radtke, M. A. et al. 2009. Willingness-to-pay and quality of life in patients with vitiligo. *British Journal of Dermatology* 161(1), pp. 134-139.

Rajmil, L. et al. 2014. Comparison of the Web-Based and Digital Questionnaires of the Spanish and Catalan Versions of the KIDSCREEN-52. *PloS one* 9(12), p. e114527.

Ramirez, F. D. et al. 2019. Assessment of Sleep Disturbances and Exhaustion in Mothers of Children With Atopic Dermatitis. *JAMA dermatology* 155(5), pp. 556-563.

Ramsay, B. and Lawrence, C. 1991. Measurement of involved surface area in patients with psoriasis. *British Journal of Dermatology* 124(6), pp. 565-570.

Rana, P. and Mishra, D. 2015. Quality of life of unaffected siblings of children with chronic neurological disorders. *The Indian Journal of Pediatrics* 82(6), pp. 545-548.

Randa, H. et al. 2017. Health-related quality of life in children and adolescents with psoriasis: a systematic review and meta-analysis. *Acta dermato-venereologica* 97(5), pp. 555-563.

Rasmussen, S. L. et al. 2016. High level of agreement between electronic and paper mode of administration of a thyroid-specific patient-reported outcome, ThyPRO. *European thyroid journal* 5(1), pp. 65-72.

Raymond, J. 1996. Pourquoi et comment mener des études de qualité de vie en gastroentérologie? *Gastroentérologie clinique et biologique* 20(12), pp. 1067-1070.

Reich, K. et al. 2006. Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. *British journal of dermatology* 154(6), pp. 1161-1168.

Reich, K. et al. 2005. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *The Lancet* 366(9494), pp. 1367-1374.

Reich, K. et al. 2012. Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab certolizumab pegol: Results of a phase II randomized, placebo-controlled trial with a re-treatment extension. *British Journal of Dermatology* 167(1), pp. 180-190.

Reich, K. et al. 2014. One-year safety and efficacy of ustekinumab and results of dose adjustment after switching from inadequate methotrexate treatment: the TRANSIT randomized trial in moderate-to-severe plaque psoriasis. *British Journal of Dermatology* 170(2), pp. 435-444.

Reich, K. et al. 2009. Once-weekly administration of etanercept 50 mg improves patient-reported outcomes in patients with moderate-to-severe plaque psoriasis. *Dermatology* 219(3), pp. 239-249.

Reich, K. et al. 2008. Comparative effects of biological therapies on the severity of skin symptoms and health-related quality of life in patients with plaque-type psoriasis: a meta-analysis. *Current Medical Research and Opinion*® 24(5), pp. 1237-1254.

Reich, K. et al. 2013. Efficacy and safety of infliximab as continuous or intermittent therapy in patients with moderate-to-severe plaque psoriasis: Results of a randomized, long-term extension trial (RESTORE2). *British Journal of Dermatology* 168(6), pp. 1325-1334.

Reid, C. and Griffiths, C. E. 2020. Psoriasis and Treatment: Past, Present and Future Aspects. *Acta dermato-venereologica* 100.

Rejeski, W. J. and Mihalko, S. L. 2001. Physical activity and quality of life in older adults. *The Journals of Gerontology Series A: Biological sciences and medical sciences* 56(suppl_2), pp. 23-35.

Rencz, F. et al. 2020. DLQI‐R scoring improves the discriminatory power of the Dermatology Life Quality Index in patients with psoriasis, pemphigus and morphea. *British Journal of Dermatology* 182(5), pp. 1167-1175.

Rendon, A. and Schäkel, K. 2019. Psoriasis pathogenesis and treatment. *International journal of molecular sciences* 20(6), p. 1475.

Reolid, A. et al. 2020. Validation of an Optical Pencil Method to Estimate the Affected Body Surface Area in Psoriasis. *Actas Dermo-Sifiliográficas (English Edition)* 111(2), pp. 143-148.

Revicki, D. et al. 2008a. Adalimumab improves health-related quality of life in patients with moderate to severe plaque psoriasis compared with the United States general population norms: results from a randomized, controlled Phase III study. *Health and quality of life outcomes* 6, p. 75.

Revicki, D. et al. 2008b. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *British journal of dermatology* 158(3), pp. 549-557.

Revicki, D. A. et al. 2007. Impact of adalimumab treatment on patient-reported outcomes: Results from a Phase III clinical trial in patients with moderate to severe plaque psoriasis. *Journal of Dermatological Treatment* 18(6), pp. 341-350.

Ribeiro, C. et al. 2010. Development and use of touch-screen computer-assisted self interviewing in Portuguese patients with chronic immune diseases: evaluation of an electronic version of sf-36v2. *Acta reumatologica portuguesa* (35), pp. 208-214.

Rich, P. and Scher, R. K. 2003. Nail Psoriasis Severity Index: A useful tool for evaluation of nail psoriasis. *Journal of the American Academy of Dermatology* 49(2), pp. 206-212.

Richards, H. L. et al. 2004. Divergent beliefs about psoriasis are associated with increased psychological distress. *Journal of Investigative Dermatology* 123(1), pp. 49-56.

Richter, J. G. et al. 2015. mobile Medical Documentation of Patient-reported-outcome: abstract Number: 2319. *Arthritis & Rheumatology* 67, pp. 2796-2798.

Ring, A. E. et al. 2008. A randomized study of electronic diary versus paper and pencil collection of patient-reported outcomes in patients with non-small cell lung cancer. *The Patient: Patient-Centered Outcomes Research* 1(2), pp. 105-113.

Ritchlin, C. T. et al. 2017. Psoriatic arthritis. *New England Journal of Medicine* 376(10), pp. 957-970.

Rivero-Arias, O. et al. 2010. Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. *Medical decision making* 30(3), pp. 341-354.

Roberti, M. L. et al. 2014. Immunomodulating treatment with low dose interleukin-4, interleukin-10 and interleukin-11 in psoriasis vulgaris. *Journal of biological regulators and homeostatic agents* 28(1), pp. 133-139.

Robles, N. et al. 2015. Development of the web-based Spanish and Catalan versions of the Euroqol 5D-Y (EQ-5D-Y) and comparison of results with the paper version. *Health and quality of life outcomes* 13(1), p. 72.

Robson, J. C. et al. 2016. Scale Structure and Measurement Properties of a Disease Specific Patient-Reported Outcome for Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis. *Arthritis Rheumatology* 68(suppl 10).

Rodgers, M. et al. 2010. Alitretinoin for severe chronic hand eczema. *Pharmacoeconomics* 28(5), pp. 351-362.

Rogers, A. et al. 2012. Clinical Meaning in Skin-specific Quality of Life Instruments: A Comparison of the Dermatology Life Quality Index and Skindex Banding Systems. *Dermatologic Clinics* 30(2), pp. 333-342.

Rosato, R. et al. 2017. Equivalence of the electronic versus paper-based short version of the MSQOL-54 (MSQOL-29). *Multiple Sclerosis Journal* 23, pp. 422-423.

Ruderman, E. M. and Tambar, S. 2004. Psoriatic arthritis: prevalence, diagnosis, and review of therapy for the dermatologist. *Dermatologic Clinics* 22(4), pp. 477-486.

Rutten-van Mölken, M. P. et al. 2006. Does quality of life of COPD patients as measured by the generic EuroQol five-dimension questionnaire differentiate between COPD severity stages? *Chest* 130(4), pp. 1117-1128.

Ruzicka, T. et al. 1990. Efficiency of acitretin in combination with UV-B in the treatment of severe psoriasis. *Archives of dermatology* 126(4), pp. 482-486.

Ryan, J. M. et al. 2002. A comparison of an electronic version of the SF-36 General Health Questionnaire to the standard paper version. *Quality of life research* 11(1), pp. 19-26.

Safikhani, S. et al. 2013. Qualitative assessment of the content validity of the Dermatology Life Quality Index in patients with moderate to severe psoriasis. *Journal of Dermatological Treatment* 24(1), pp. 50-59.

Salaffi, F. et al. 2014. AB1049 Collection of Patient-Reported Outcomes in RA: A Comparison between an Innovative and Interactive Touch-Screen Computer-Based System and the Traditional, Paper-Administered Format in the Multicentre, Observational Action Study. *Annals of the Rheumatic Diseases* 73(Suppl 2), pp. 1147-1147.

Salaffi, F. et al. 2009. The use of computer touch-screen technology for the collection of patient-reported outcome data in rheumatoid arthritis: comparison with standardized paper questionnaires. *Clinical & Experimental Rheumatology* 27(3), p. 459.

Salame, N. et al. 2018. Patient-Reported Outcome Measures for Pediatric Psoriasis: A Systematic Review and Critical Appraisal from International Dermatology Outcome Measures (IDEOM). *Dermatology* 234(3-4), pp. 112-119.

Saleh, K. J. et al. 2002. Comparison of commonly used orthopaedic outcome measures using palm‐top computers and paper surveys. *Journal of Orthopaedic Research* 20(6), pp. 1146-1151.

Salek, M. et al. 2013. Clinical experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995–2012. *British Journal of Dermatology* 169(4), pp. 734-759.

Salek, M. et al. 1996. Questionnaire techniques in assessing acne handicap: reliability and validity study. *Quality of life research* 5(1), pp. 131-138.

Salek, M. S. et al. 1993. Cyclosporine greatly improves the quality-of-life of adults with severe atopic-dermatitis - a randomized, double-blind, placebo-controlled trial. *British Journal of Dermatology* 129(4), pp. 422-430.

Salek, S. et al. 2007. The practical reality of using a patient-reported outcome measure in a routine dermatology clinic. *Dermatology* 215(4), pp. 315-319.

Salim, A. et al. 2006. Folic acid supplementation during treatment of psoriasis with methotrexate: a randomized, double-blind, placebo-controlled trial. *British journal of dermatology* 154(6), pp. 1169-1174.

Salomon, J. et al. 2003. Psoriatic nails: a prospective clinical study. *Journal of Cutaneous Medicine and Surgery: Incorporating Medical and Surgical Dermatology* 7(4), pp. 317-321.

Sampogna, F. et al. 2017a. Impairment of sexual life in 3,485 dermatological outpatients from a multicentre study in 13 European countries. *Acta dermato-venereologica* 97(4), pp. 478-482.

Sampogna, F. et al. 2006. Age, gender, quality of life and psychological distress in patients hospitalized with psoriasis. *British journal of dermatology* 154(2), pp. 325-331.

Sampogna, F. et al. 2017b. Measuring the impact of dermatological conditions on family and caregivers: a review of dermatology‐specific instruments. *Journal of the European Academy of Dermatology and Venereology* 31(9), pp. 1429-1439.

Sampogna, F. et al. 2003. Performance of the self-administered psoriasis area and severity index in evaluating clinical and sociodemographic subgroups of patients with psoriasis. *Archives of dermatology* 139(3), pp. 353-358.

Samsa, G. et al. 1999. Determining clinically important differences in health status measures. *Pharmacoeconomics* 15(2), pp. 141-155.

Sancho‐Durá, J. et al. 2018. Handheld multi‐modal imaging for point‐of‐care skin diagnosis based on akinetic integrated optics optical coherence tomography. *Journal of biophotonics* 11(10), p. e201800193.

Sander, H. and Norris, L. 1993. Phillips PE Menter A'The annual cost of psoriasis. *Journal of American Academy of Dermatology* 28, pp. 422-425.

Saraceno, R. et al. 2007. Efficacy, safety and quality of life of calcipotriol/betamethasone dipropionate (Dovobet®) versus calcipotriol (Daivonex®) in the treatment of psoriasis vulgaris: A randomized, multicentre, clinical trial. *Journal of Dermatological Treatment* 18(6), pp. 361-365.

Sauerland, S. et al. 2009. Mapping utility scores from a disease-specific quality-of-life measure in bariatric surgery patients. *Value in Health* 12(2), pp. 364-370.

Saunders, G. et al. 2007. The Attitudes towards Loss of Hearing Questionnaire (ALHQ): a comparison of paper and electronic formats. *Journal of the American Academy of Audiology* 18(1), pp. 66-77.

Saurat, J. et al. 2011. Relationship between methotrexate dosing and clinical response in patients with moderate to severe psoriasis: subanalysis of the CHAMPION study. *British journal of dermatology* 165(2), pp. 399-406.

Saurat, J. H. et al. 2008. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *British Journal of Dermatology* 158(3), pp. 558-566.

Sawyer, L. et al. 2019. Long‐term efficacy of novel therapies in moderate‐to‐severe plaque psoriasis: a systematic review and network meta‐analysis of PASI response. *Journal of the European Academy of Dermatology and Venereology* 33(2), pp. 355-366.

Scalone, L. et al. 2006. PSK8 Convergent validity and sensitivity to change of the generic instrument EQ-5S and the disease specific DLQI in atopic dermatitis. *Value in Health* 9(6), pp. A268-A269.

Schefte, D. B. and Hetland, M. L. 2009. An open-source, self-explanatory touch screen in routine care. Validity of filling in the Bath measures on Ankylosing Spondylitis Disease Activity Index, Function Index, the Health Assessment Questionnaire and Visual Analogue Scales in comparison with paper versions. *Rheumatology* 49(1), pp. 99-104.

Schmitt, J. et al. 2015. The Harmonizing Outcome Measures for Eczema (HOME) roadmap: a methodological framework to develop core sets of outcome measurements in dermatology. *Journal of Investigative Dermatology* 135(1), pp. 24-30.

Schmitt, J. and Küster, D. 2015. Correlation between Dermatology Life Quality Index (DLQI) scores and Work Limitations Questionnaire (WLQ) allows the calculation of percent work productivity loss in patients with psoriasis. *Archives of dermatological research* 307(5), pp. 451-453.

Schmitt, J. and Wozel, G. 2005. The Psoriasis Area and Severity Index is the adequate criterion to define severity in chronic plaque-type psoriasis. *Dermatology* 210(3), pp. 194-199.

Schmitt, J. et al. 2014. Effectiveness of Interdisciplinary vs. Dermatological care of moderate-to-severe psoriasis: A pragmatic randomised controlled trial. *Acta Dermato-Venereologica* 94(2), pp. 192-197.

Schmitt-Egenolf, M. 2007. PsoReg - The Swedish registry for systemic psoriasis treatment. *Dermatology* 214(2), pp. 112-117.

Schougaard, L. M. V. et al. 2018. Patient-reported outcome (PRO) measure-based algorithm for clinical decision support in epilepsy outpatient follow-up: a test–retest reliability study. *BMJ open* 8(7), p. e021337.

Schuttelaar, M. et al. 2010. A randomized controlled trial in children with eczema: nurse practitioner vs. dermatologist. *British Journal of Dermatology* 162(1), pp. 162-170.

Schцn, M. et al. 2005. Medical progress. Psoriasis. *N Engl J Med* 352, pp. 1899-1912.

Seltzer, M. M. et al. 1995. Cross‐national comparisons of ageing mothers of adults with intellectual disabilities. *Journal of Intellectual Disability Research* 39(5), pp. 408-418.

Sharma, P. et al. 2016. Evaluation of point-of-care PRO assessment in clinic settings: integration, parallel-forms reliability, and patient acceptability of electronic QOL measures during clinic visits. *Quality of Life Research* 25(3), pp. 575-583.

Shaw, L. J. and de Berker, D. A. 2007. Strengths and weaknesses of electronic referral: comparison of data content and clinical value of electronic and paper referrals in dermatology. *Br J Gen Pract* 57(536), pp. 223-224.

Shikiar, R. et al. 2003. Validity and reliability of patient reported outcomes used in psoriasis: results from two randomized clinical trials. *Health & Quality of Life Outcomes* 1, p. 53.

Shikiar, R. et al. 2007. Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a phase II randomized controlled trial. *Journal of Dermatological Treatment* 18(1), pp. 25-31.

Silveira, A. et al. 2011. Computer-based quality-of-life monitoring in head and neck cancer patients: a validation model using the EORTC-QLQ C30 and EORTC-H&N35 Portuguese PC-software version. *Acta medica portuguesa* 24, pp. 347-354.

Simpson, H. et al. 2016. A Study of the Successful Adaptation of the Quality of Life Questionnaire-Bronchiectasis From Paper To Electronic Format. *Value in Health* 19(7), pp. A388-A389.

Singh, R. and Finlay, A. 2020. DLQI use in skin disease guidelines and registries worldwide. *Journal of the European Academy of Dermatology and Venereology*.

Singri, P. et al. 2002. Biologic therapy for psoriasis: the new therapeutic frontier. *Archives of dermatology* 138(5), pp. 657-663.

Skerritt, B. et al. 2015. Cognitive Debriefing And Usability Assessment Of The Eortc Qlq-C30 And Qlq-Br23 As Presented On Tablet And Handheld Devices. *Value in Health* 18(7), pp. A466-A467.

Smith, C. et al. 2020. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020–a rapid update. *British Journal of Dermatology*.

Smith, C. H. et al. 2005. British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. *British Journal of Dermatology* 153(3), pp. 486-497.

Sofen, H. et al. 2011. Clobetasol propionate 0.05% spray for the management of moderate-to-severe plaque psoriasis of the scalp: results from a randomized controlled trial. *J. Drugs Dermatol.* 10(8), pp. 885-892.

Solé, A. et al. 2018. Development and electronic validation of the revised Cystic Fibrosis Questionnaire (CFQ-R Teen/Adult): New tool for monitoring psychosocial health in CF. *Journal of Cystic Fibrosis* 17(5), pp. 672-679.

Sorenson, S. C. et al. 2015. The Trojan Lifetime Champions health survey: development, validity, and reliability. *Journal of athletic training* 50(4), pp. 407-418.

Souza, A. C. d. et al. 2017. Psychometric properties in instruments evaluation of reliability and validity. *Epidemiologia e Serviços de Saúde* 26(3), pp. 649-659.

Spangenberg, L. et al. 2015. Differences in Patient Health Questionnaire and Aachen Depression Item Bank scores between tablet versus paper-and-pencil administration. *Quality of Life Research* 24(12), pp. 3023-3032.

Spuls, P. I. et al. 2010. How good are clinical severity and outcome measures for psoriasis?: quantitative evaluation in a systematic review. *Journal of Investigative Dermatology* 130(4), pp. 933-943.

Staubach, P. et al. 2018. Omalizumab rapidly improves angioedema‐related quality of life in adult patients with chronic spontaneous urticaria: X‐ACT study data. *Allergy* 73(3), pp. 576-584.

Stein, R. E. and Riessman, C. K. 1980. The development of an impact-on-family scale: preliminary findings. *Medical care* 18(4), pp. 465-472.

Sterry, W. et al. 2010. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. *British medical journal* 340, p. c147.

Steyerberg, E. W. et al. 2001. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *Journal of clinical epidemiology* 54(8), pp. 774-781.

Stockinger, B. and Veldhoen, M. 2007. Differentiation and function of Th17 T cells. *Current opinion in immunology* 19(3), pp. 281-286.

Stoll, M. L. et al. 2006. Patients with juvenile psoriatic arthritis comprise two distinct populations. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology* 54(11), pp. 3564-3572.

Storck, M. et al. 2018. Validation of pruritus measures gathered with the electronic patient-reported outcome system MoPat. *Acta dermato-venereologica* 98(1-2), pp. 38-43.

Strand, V. et al. 2013. Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: results from a phase IIb randomized, controlled study. *Health and quality of life outcomes* 11, p. 82.

Strange, A. et al. 2010. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nature genetics* 42(11), p. 985.

Strober, B. et al. 2019. Tofacitinib benefit‐risk profile in chronic plaque psoriasis. *British Journal of Dermatology* 180(1), pp. e19-e19.

Strohal, R. et al. 2013. The efficacy and safety of etanercept when used with as-needed adjunctive topical therapy in a randomised, double-blind study in subjects with moderate-to-severe psoriasis (the PRISTINE trial). *Journal of Dermatological Treatment* 24(3), pp. 169-178.

Sun, T. et al. 2015. A smartphone version of the Faces Pain Scale‐Revised and the Color Analog Scale for postoperative pain assessment in children. *Pediatric Anesthesia* 25(12), pp. 1264-1273.

Sun, Z.-J. et al. 2016. The usability of a WeChat-based electronic questionnaire for collecting participant-reported data in female pelvic floor disorders: a comparison with the traditional paper-administered format. *Menopause* 23(8), pp. 856-862.

Swartz, R. J. et al. 2007. Mode effects in the center for epidemiologic studies depression (CES-D) scale: personal digital assistant vs. paper and pencil administration. *Quality of Life Research* 16(5), p. 803.

Sydor, B. and Spertus, J. 2016. Linguistic validation and electronic migration of the Kansas City cardiomyopathy questionnaire (KCCQ). *Value in Health* 19(7), p. A391.

Szende, A. and Schaefer, C. 2006. A taxonomy of health utility assessment methods and the role for uncertainty analysis. *The European Journal of Health Economics* 7(2), pp. 147-151.

Tabolli, S. et al. 2012. Evaluation of the impact of writing exercises interventions on quality of life in patients with psoriasis undergoing systemic treatments. *British journal of dermatology* 167(6), pp. 1254-1264.

Takegami, Y. et al. 2019. Measurement of equivalence between the web and paper versions of the Japanese Orthopaedic Association Hip Disease Evaluation Questionnaire. *Modern Rheumatology*, pp. 1-5.

Takeshita, J. et al. 2017. Psoriasis and comorbid diseases: epidemiology. *Journal of the American Academy of Dermatology* 76(3), pp. 377-390.

Takeshita, J. et al. 2015. Effect of psoriasis severity on hypertension control: a population-based study in the United Kingdom. *JAMA dermatology* 151(2), pp. 161-169.

Tan, J. and Caird, J. 2016. Will electronic integrated text, visual and audio questionnaire be a better tool to evaluate the health status of paediatric hydrocephalus patients? *European Journal of Pediatrics* 175(11), pp. 1689-1689.

Telfer, N. R. et al. 1992. The role of streptococcal infection in the initiation of guttate psoriasis. *Archives of dermatology* 128(1), pp. 39-42.

Terwee, C. B. et al. 2007. Quality criteria were proposed for measurement properties of health status questionnaires. *Journal of clinical epidemiology* 60(1), pp. 34-42.

Terwee, C. B. et al. 2010. Mind the MIC: large variation among populations and methods. *Journal of clinical epidemiology* 63(5), pp. 524-534.

Testa, M. A. and Simonson, D. C. 1996. Assessment of quality-of-life outcomes. *New England journal of medicine* 334(13), pp. 835-840.

Thaci, D. et al. 2002. Body-weight-independent dosing of cyclosporine micro-emulsion and three times weekly maintenance regimen in severe psoriasis. A randomised study. *Dermatology* 205(4), pp. 383-388.

Thaçi, D. et al. 2014. Improvement in aspects of sleep with etanercept and optional adjunctive topical therapy in patients with moderate-to-severe psoriasis: Results from the PRISTINE trial. *Journal of the European Academy of Dermatology and Venereology* 28(7), pp. 900-906.

Thaci, D. et al. 2010. A phase IIIb, multicentre, randomized, double‐blind, vehicle‐controlled study of the efficacy and safety of adalimumab with and without calcipotriol/betamethasone topical treatment in patients with moderate to severe psoriasis: the BELIEVE study. *British Journal of Dermatology* 163(2), pp. 402-411.

Tham, S. et al. 1994. A comparative study of calcipotriol ointment and tar in chronic plaque psoriasis. *British Journal of Dermatology* 131(5), pp. 673-677.

Thomas, C. and Finlay, A. 2007. The 'handprint'approximates to 1% of the total body surface area whereas the 'palm minus the fingers' does not. *British Journal of Dermatology* 157(5), pp. 1080-1081.

Tiplica, G. and Salavastru, C. 2009. Mometasone furoate 0.1% and salicylic acid 5% vs. mometasone furoate 0.1% as sequential local therapy in psoriasis vulgaris. *Journal of the European Academy of Dermatology and Venereology* 23(8), pp. 905-912.

Todorović, V. et al. 2019. Small Molecule IL-36γ Antagonist as a Novel Therapeutic Approach for Plaque Psoriasis. *Scientific Reports* 9(1), p. 9089.

Tolley, K. 2009. What are health utilities. *Hayward Medical Communications, London*.

Tonnel, A. et al. 2008. Effect of tiotropium on health-related quality of life as a primary efficacy endpoint in COPD. *International journal of chronic obstructive pulmonary disease* 3(2), p. 301.

Torii, H. and Nakagawa, H. 2010. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. *Journal of dermatological science* 59(1), pp. 40-49.

Torii, H. et al. 2012. Dramatic impact of a Psoriasis Area and Severity Index 90 response on the quality of life in patients with psoriasis: an analysis of Japanese clinical trials of infliximab. *Journal of Dermatology* 39(3), pp. 253-259.

Torrance, G. W. 1987. Utility approach to measuring health-related quality of life. *Journal of chronic diseases* 40(6), pp. 593-600.

Torrance, G. W. et al. 1995. Multi-attribute preference functions. *Pharmacoeconomics* 7(6), pp. 503-520.

Touchèque, M. et al. 2016. A comparison of a tablet version of the Quality of Life Systemic Inventory for Children (QLSI-C) to the standard paper version. *Psychological assessment* 28(6), p. 780.

Tsai, T. et al. 2011. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *Journal of dermatological science* 63(3), pp. 154-163.

Tsai, T. et al. 2012. Ustekinumab improves health-related quality of life in Korean and Taiwanese patients with moderate to severe psoriasis: results from the PEARL trial. *J. Drugs Dermatol.* 11(8), pp. 943-949.

Tsuchiya, A. et al. 2002. Estimating an EQ‐5D population value set: the case of Japan. *Health economics* 11(4), pp. 341-353.

Tung, J. and Nambudiri, V. 2018. Beyond Bitcoin: potential applications of blockchain technology in dermatology. *British Journal of Dermatology* 179(4), pp. 1013-1014.

Tyring, S. et al. 2007. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Archives of dermatology* 143(6), pp. 719-726.

Tyring, S. et al. 2006. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 367(9504), pp. 29-35.

Upala, S. and Sanguankeo, A. 2015. Effect of lifestyle weight loss intervention on disease severity in patients with psoriasis: a systematic review and meta-analysis. *International Journal of obesity* 39(8), p. 1197.

Van de Kerkhof, P. 1992. On the limitations of the psoriasis area and severity index (PASI). *British Journal of Dermatology* 126(2), pp. 205-206.

van de Kerkhof, P. C. and Franssen, M. E. 2001. Psoriasis of the scalp. Diagnosis and management. *American Journal of Clinical Dermatology* 2(3), pp. 159-165.

van de Kerkhof, P. C. M. 2004. The impact of a two-compound product containing calcipotriol and betamethasone dipropionate (Daivobet/ Dovobet) on the quality of life in patients with psoriasis vulgaris: a randomized controlled trial. *British Journal of Dermatology* 151(3), pp. 663-668.

van de Kerkhof, P. C. M. et al. 2008. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. *British Journal of Dermatology* 159(5), pp. 1177-1185.

Van De Kerkhof, P. C. M. et al. 2006. A comparison of twice‐daily calcipotriol ointment with once‐daily short‐contact dithranol cream therapy: a randomized controlled trial of supervised treatment of psoriasis vulgaris in a day‐care setting. *British journal of dermatology* 155(4), pp. 800-807.

Van Hout, B. et al. 2012. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in Health* 15(5), pp. 708-715.

Vardy, D. et al. 2002. Experiences of stigmatization play a role in mediating the impact of disease severity on quality of life in psoriasis patients. *British Journal of Dermatology* 147(4), pp. 736-742.

Vedhara, K. et al. 2007. Changes in mood predict disease activity and quality of life in patients with psoriasis following emotional disclosure. *Journal of psychosomatic research* 62(6), pp. 611-619.

Velikova, G. et al. 2002. Computer-based quality of life questionnaires may contribute to doctor–patient interactions in oncology. *British journal of cancer* 86(1), p. 51.

Velikova, G. et al. 1999. Automated collection of quality-of-life data: a comparison of paper and computer touch-screen questionnaires. *Journal of clinical oncology* 17(3), pp. 998-998.

Velleman, S. et al. 2016. Psychological wellbeing and quality-of-life among siblings of paediatric CFS/ME patients: a mixed-methods study. *Clinical child psychology and psychiatry* 21(4), pp. 618-633.

Vermaes, I. P. et al. 2012. Psychological functioning of siblings in families of children with chronic health conditions: A meta-analysis. *Journal of Pediatric Psychology* 37(2), pp. 166-184.

Vermeulen, F. et al. 2019. TRE atment of AT opic eczema (TREAT) Registry Taskforce: consensus on how and when to measure the core dataset for atopic eczema treatment research registries. *British Journal of Dermatology* 181(3), pp. 492-504.

Villani, A. P. et al. 2015. Prevalence of undiagnosed psoriatic arthritis among psoriasis patients: systematic review and meta-analysis. *Journal of the American Academy of Dermatology* 73(2), pp. 242-248.

Vissers, W. et al. 2004. Memory effector (CD45RO+) and cytotoxic (CD8+) T cells appear early in the margin zone of spreading psoriatic lesions in contrast to cells expressing natural killer receptors, which appear late. *British Journal of Dermatology* 150(5), pp. 852-859.

Wæhrens, E. et al. 2015. Agreement between touch-screen and paper-based patient-reported outcomes for patients with fibromyalgia: a randomized cross-over reproducibility study. *Scandinavian journal of rheumatology* 44(6), pp. 503-510.

Wailoo, A. J. et al. 2017. Mapping to estimate health-state utility from non–preference-based outcome measures: an ISPOR good practices for outcomes research task force report. *Value in Health* 20(1), pp. 18-27.

Wall, A. R. J. et al. 1998. A comparison of treatment with dithranol and calcipotriol on the clinical severity and quality of life in patients with psoriasis. *British Journal of Dermatology* 139(6), pp. 1005-1011.

Wang, I. J. and Wang, J. Y. 2015. Children with atopic dermatitis show clinical improvement after Lactobacillus exposure. *Clinical & Experimental Allergy* 45(4), pp. 779-787.

Ware, J. E. et al. 1978. *Conceptualization and measurement of health for adults in the health insurance study: Vol. V, general health perceptions*. Rand Corporation.

Ware Jr, J. E. and Sherbourne, C. D. 1992. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Medical care* 30(6), pp. 473-483.

Waters, A. et al. 2010. Severity stratification of Children's Dermatology Life Quality Index (CDLQI) scores. *British Journal of Dermatology* 163.

Weinstein, G. D. and White, G. M. 1993. An approach to the treatment of moderate to severe psoriasis with rotational therapy. *Journal of the American Academy of Dermatology* 28(3), pp. 454-459.

Weinstein, M. C. et al. 1996. *Cost-effectiveness in health and medicine*. Oxford university press.

Weisman, S. et al. 2003. Psoriasis disease severity measures: comparing efficacy of treatments for severe psoriasis. *Journal of Dermatological Treatment* 14(3), pp. 158-165.

Wiebe, S. et al. 2003. Comparative responsiveness of generic and specific quality-of-life instruments. *Journal of clinical epidemiology* 56(1), pp. 52-60.

Williams, A. R. et al. 2006. Validity of the revised Impact on Family (IOF) scale. *The Journal of pediatrics* 149(2), pp. 257-261.

Wisuthsarewong, W. et al. 2015. The validity and reliability of the Thai version of children's dermatology life quality index (CDLQI). *J Med Assoc Thai* 98(10), pp. 968-973.

Wojnarowska, F. et al. 1997. Psychological characteristics and outcome of patients attending a clinic for vulval disease. *Journal of the European Academy of Dermatology and Venereology* 8(2), pp. 121-129.

Wolf, N. et al. 2008. Psoriasis is associated with pleiotropic susceptibility loci identified in type II diabetes and Crohn disease. *Journal of medical genetics* 45(2), pp. 114-116.

Woo, W. K. and McKenna, K. E. 2003. Combination TL01 ultraviolet B phototherapy and topical calcipotriol for psoriasis: a prospective randomized placebo-controlled clinical trial. *British Journal of Dermatology* 149(1), pp. 146-150.

Woolacott, N. et al. 2006. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. *Health Technology Assessment (Winchester, England)* 10(46), p. 48.

Wright, A. et al. 2012. Clinimetrics corner: a closer look at the minimal clinically important difference (MCID). *Journal of Manual & Manipulative Therapy* 20(3), pp. 160-166.

Wright, E. et al. 2005. Development and evaluation of an instrument to assess social difficulties in routine oncology practice. *Quality of Life Research* 14(2), pp. 373-386.

Wu, J. et al. 2019. Minimal clinically important difference (MCID) for work productivity and activity impairment (WPAI) questionnaire in psoriasis patients. *Journal of the European Academy of Dermatology and Venereology* 33(2), pp. 318-324.

Wu, R. et al. 2009. Comparing administration of questionnaires via the internet to pen-and-paper in patients with heart failure: randomized controlled trial. *Journal of medical Internet research* 11(1), p. e3.

Yan, H. et al. 2011. Treatment of psoriasis with recombinant human LFA3-antibody fusion protein: A multi-center, randomized, double-blind trial in a Chinese population. *European Journal of Dermatology* 21(5), pp. 737-743.

Yang, H. et al. 2012. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. *Chinese medical journal* 125(11), pp. 1845-1851.

Yawalkar, N. et al. 2009. Increased expression of IL-12p70 and IL-23 by multiple dendritic cell and macrophage subsets in plaque psoriasis. *Journal of dermatological science* 54(2), pp. 99-105.

Yeung, H. et al. 2013. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA dermatology* 149(10), pp. 1173-1179.

Yune, Y. M. et al. 2003. Objective assessment of involved surface area in patients with psoriasis. *Skin Research and Technology* 9(4), pp. 339-342.

Zachariae, C. et al. 2008. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. *Acta Dermato-Venereologica* 88(5), pp. 495-501.

Zbrozek, A. et al. 2013. Validation of electronic systems to collect patient-reported outcome (PRO) data—recommendations for clinical trial teams: report of the ISPOR ePRO Systems Validation Good Research Practices Task Force. *Value in Health* 16(4), pp. 480-489.

Zheng, Z. et al. 2011. Effect of daivobet® on the quality of life in chinese patients with stable psoriasis vulgaris: A multicenter, randomized, double-blind, positive controlled and parallel group study. *World Applied Sciences Journal* 13(5), pp. 1240-1247.

Zhu, X. et al. 2013. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). *J. Drugs Dermatol.* 12(2), pp. 166-174.

Publications

Abstracts & Conference Presentations

1) Ali FM, Salek MS, Piguet V, Finlay AY. Development of a novel electronic application of the Psoriasis Area Severity Index (PASI). Presented at the AAD Meeting, 1-5th March 2019, Washington DC, USA

2) Ali FM, Salek MS, Piguet V, Finlay AY . Development of a novel electronic application of the Psoriasis Area Severity Index (PASI). I&I Meeting, Cardiff University, 22nd November 2018, Cardiff, UK.

3) Ali F, Finlay AY, Salek S. 2MCID: a novel approach to strengthening the utility of the concept of MCID. Qual Life Res. 2018. 27:S162-S163. Presented at ISOQOL 2018 24-27th October 2018, Dublin, Ireland.

4) Ali F, Salek S, Piguet V, Finlay, AY. Validation of an electronic application of the Psoriasis Area Severity Index (PASI). British Journal of Dermatology. Jul 2018;179 (Suppl. 1):pp. 31-31. Presented at BAD 2018 3-5th July 2018, Edinburgh, UK.

5) Salek MS, Ali FM, Piguet V, Kay R, Kupfer J, Dalgard F, Finlay AY. PEC002: Mapping of the DLQI scores to EQ-5D utility values using ordinal logistic regression and Monte Carlo simulations: is it plausible? Int J Clin Pharm. 2017. 39:221.

6) Salek SS, Ali FM, Cueva AC, Vyas J, Piguet V, Finlay AY. PE007: The value of quality of life assessment in monitoring the efficacy of interventions in psoriasis and the role of minimal clinically important difference in interpretation of scores: a systematic review. Int J Clin Pharm. 2017. 39:238.

7) Ali, F.M., Johns, N., Salek, S., Finlay, A. and Piguet, V., 2017. 044 Validation of the electronic version of the Dermatology Life Quality Index (DLQI). *Journal of Investigative Dermatology*, *137*(10), p.S200. Presented at ESDR 2017 27-30th September 2017, Salzburg, Austria.

8) Ali F, Johns N, Finlay AY, Salek SS, Piguet V. P.24 Equivalence of the paper-based and electronic versions of the Dermatology Life Quality Index. British Journal of Dermatology. 2017 Jul 3;177(Suppl. 1):35. Presented at BAD 2017 4-6th July 2017, Liverpool, UK.

9) Ali F, Johns N, Piguet V, Finlay AY, Salek SS. Demonstrating equivalence of the electronic and paper-based versions of the Dermatology Life Quality Index (DLQI). Poster at ISOQOL 2017 18-21st October 2017, Philadelphia, USA.

10) Ali FM, Johns N, Salek S, Piguet V, Finlay AY. The development of a novel Dermatology Quality of Life Index (DLQI) iPad application. Presented at APAM 2017 6-7th April 2017, UCL, London, UK.

11) Ali FM, Kay R, Piguet V, Salek MS, Finlay AY. Mapping of DLQI scores to EQ-5D Utility Values. Presented at Postgraduate Research Day 12th January 2017, Cardiff University, UK.

12) Ali FM, Kay R, Piguet V, Kupfer J, Dalgard F, Finlay AY, Salek MS. Mapping and correlating individual DLQI items to EQ-5D domain scores using ordinal logistic regression. Quality of Life Research Journal. 2016. 25(1):39. Presented at ISOQOL Meeting 2016, Copenhagen.

13) Ali FM, Cueva AC, Atwan AA, Vyas J, Piguet V, Salek SS, Finlay AY. Systematic review: do treatments for psoriasis meet the minimal clinically important difference for PRO measures? Quality of Life Research Journal. 2016. 25(1):70-1. Presented at ISOQOL Meeting 2016, Copenhagen.

14) Ali F, Cueva A, Vyas J, Piguet V, Salek S, Finlay A. A systematic review of the impact on quality of life of interventions for psoriasis. British Journal of Dermatology. 2016 Jul 1;175:54. Presented at BAD 2016, Birmingham, UK.

15) Ali F, Kay R, Finlay A, Piguet V, Kupfer J, Dalgard F, Salek S. How to map the Dermatology Life Quality Index to Eq-5d domain scores for cost-effective analysis: an ordinal logistic regression model. British Journal of Dermatology. 2016 Jul 1;175:39-40. Presented at BAD 2016, Birmingham, UK.

16) Ali FM, Cueva A, Vyas J, Atwan AA, Piguet V, Salek S, Finlay A. 031 The impact of interventions on quality of life in psoriasis and the concept of multiple minimal clinically important difference (MCID): a systematic review. Journal of Investigative Dermatology. 2016 Sep 30;136(9):S166. Presented at ESDR 2016, Munich, Germany

17) Ali FM, Kay R, Finlay A, Piguet V, Kupfer J, Dalgard F, Salek S. 016 Ordinal logistic regression and Monte Carlo simulation in the mapping of DLQI scores to EQ-5D utility values. Journal of Investigative Dermatology. 2016 Sep 30;136(9):S163. Presented at ESDR 2016, Munich, Germany.

18) Ali FM, Kay R, Finlay AY, Salek SS. PEC012 Can health-related quality of life scores be converted to utility values? - A paradigm shift. Int J Clin Pharm. 2016. 38:569.

19) Ali FM, Cueva A, Atwan AA, Vyas J, Piguet V, Finlay A, Salek S. PE012 Can systematic reviews help with choosing a suitable health-related quality of life measure in interventional studies of psoriasis? Int J Clin Pharm. 2016. 38:565.

20) Ali FM, Kay R, Finlay A, Piguet V, Kupfer J, Dalgard F, Salek S. An Ordinal Logistic Regression Model To Reliably Map The Dermatology Life Quality Index (DLQI) To EQ-5D Domain Scores. Presented at Association of Physicians Meeting 2016, London.

21) Ali FM, Kay R, Finlay AY, Salek SS. Challenges in the conversion of quality of life data to utility values. Quality of Life Research Journal. 2015. 24(1):82

22) Ali FM, Cueva AC, Atwan AA, Vyas J, Piguet V, Salek SS, Finlay AY. A systematic review of Quality of Life measurement in studies investigating treatments of psoriasis. Quality of Life Research Journal. 2015. 24(1):117-8

23) Ali FM, R Kay, AY Finlay, Salek SS. Ordinal regression in the mapping of DLQI scores to EQ-5D utility values: is it plausible? Journal of Investigative Dermatology. 2015. 135 (S2), S39. Presented at ESDR Meeting 2015, Rotterdam, Netherlands.

24) Ali FM, Cueva AC, Vyas J, Piguet V, Salek SS, Finlay AY. Quality of life measurement in therapeutic trials of psoriasis: a systematic review, Journal of Investigative Dermatology. 2015. 135 (S2), S37. Presented at ESDR Meeting 2015, Rotterdam, Netherlands.

25) Ali FM, Cueva A, Vyas J, Atwan AA, Piguet V, Salek S, Finlay A. Systematic Review: Quality of life measurement in psoriasis therapeutic trials. Presented at Infection &

Immunity Meeting 2015, Cardiff UK.

26) Campbell N, Ali FM, Finlay AY, Salek MS. An Evaluation of the measurement equivalence of electronic paper-based patient-reported outcome measures. Qual Life Res. 2014. 23:136.

Journal Full Articles

1) Ali, F.M., Cueva, A.C., Vyas, J., Atwan, A.A., Salek, M.S., Finlay, A.Y. and Piguet, V., 2017. A systematic review of the use of quality-of-life instruments in randomised controlled trials for psoriasis. *British Journal of Dermatology*, *176*(3), pp.577-593.

SYSTEMATIC REVIEW

BJD
British Journal of Dermatology

A systematic review of the use of quality-of-life instruments in randomized controlled trials for psoriasis

F.M. Ali,[1] A.C. Cueva,[1,2] J. Vyas,[1] A.A. Atwan,[1] M.S. Salek,[3,4] A.Y. Finlay[1] and V. Piguet[1]

[1]Department of Dermatology and Academic Wound Healing, Division of Infection and Immunity, School of Medicine, Cardiff University, 3rd Floor Glamorgan House, Heath Park, Cardiff CF14 4XN, U.K.
[2]Centro de la Piel, Quito, Ecuador
[3]School of Life and Medical Sciences, University of Hertfordshire, Hatfield, U.K.
[4]Institute for Medicines Development, Cardiff, U.K.

Linked Comment: Kivelevitch *et al. Br J Dermatol* 2017; **176**:563.

Summary

Planners of interventional studies in psoriasis face the dilemma of selecting suitable quality-of-life (QoL) measures. Systematic reviews have the potential of identifying psychometrically sound measures in a given therapeutic area, while guiding the development of practice guidelines. The aim of this systematic review was to generate evidence of the use of QoL instruments in randomized controlled trials (RCTs) for interventions in psoriasis. The methodology followed the PRISMA guidelines. Six databases were searched with 388 search terms. Abstracts of articles were reviewed independently by two assessors, and a third adjudicator resolved any opinion differences. Risk of bias was assessed using the Jadad scale. Of 3646 screened publications, 99 articles (100 trials) met the eligibility criteria for inclusion, describing research on 33 215 patients. Thirty-three trials tested topical therapy, 18 systemic, 39 biologics, nine phototherapy and 10 other interventions. The Dermatology Life Quality Index (DLQI) was the most commonly used QoL instrument (83 studies, 83%), followed by the 36-Item Short Form Survey (SF-36) (31, 31%), EuroQoL-5D (EQ-5D) (15, 15%), Psoriasis Disability Index (14, 14%) and Skindex (five, 5%). There was widespread inconsistency in the way that QoL data were reported. Of the 100 trials identified, 37 reported minimal clinically important difference (MCID): 32 for DLQI, 10 for SF-36 and six for EQ-5D. QoL measurement is increasingly being reported in RCTs of psoriasis. Formal guidelines are needed for assessment and publishing of QoL data. Researchers should consider whether MCID information is available, and development of MCID data should be encouraged.

What's already known about this topic?

- Psoriasis significantly impacts quality of life (QoL) in patients.
- Generic, skin-specific and disease-specific instruments are used in psoriasis interventional studies.
- In psoriasis randomized controlled trials (RCTs), biologics are the most researched interventions for which QoL is reported.

What does this study add?

- The most commonly used QoL instruments in psoriasis RCTs are the Dermatology Life Quality Index, 36-Item Short Form Survey and EuroQol-5D.
- There is an increasing use of QoL instruments in RCTs in psoriasis.

Correspondence

Vincent Piguet and Andrew Finlay.
E-mails: piguetv@cardiff.ac.uk; FinlayAY@cardiff.ac.uk
http://orcid.org/0000-0002-4184-2023 (F.M.A.)
http://orcid.org/0000-0002-6260-370X (A.C.C.)
http://orcid.org/0000-0003-2839-2651 (J.V.)
http://orcid.org/0000-0003-2104-6350 (A.A.A.)
http://orcid.org/0000-0002-4612-5699 (M.S.S.)
http://orcid.org/0000-0003-2143-1646 (A.Y.F.)
http://orcid.org/0000-0001-6079-4517 (V.P.)

Accepted for publication

23 May 2016

Funding sources

None.

Conflicts of interest

A.Y.F. is joint copyright owner of the DLQI; Cardiff University and A.Y.F. receive royalties. A.Y.F. has had paid consultancies or advisory boards with Novartis, Napp Pharmaceuticals, Pfizer, Sanofi and Galderma. V.P. has received educational and/or research grants from AbbVie, Celgene, Novartis and Johnson & Johnson. M.S.S. has received educational and/or research grants from Sanofi, Novartis, BMS, Pfizer and Sevier. The other authors declare no conflicts of interest.

DOI 10.1111/bjd.14788

- The minimal clinically important difference of QoL measure scores is underreported.
- There is inconsistent reporting of QoL data and a need for guidelines when reporting.

From the perspective of the patient with psoriasis, quality-of-life (QoL) improvement is as important as improvement in clinical signs.[1] Health-related QoL instruments are increasingly used as outcome measures[2–5] in assessing interventions.[6,7] Types of health-related QoL instruments used include generic, specialty-specific and disease-specific measures; specific tools are perceived as more relevant and thus preferred by patients.[8]

Previous reviews have examined the impact of psoriasis interventions on QoL.[9–12] De Korte *et al.*[9] reviewed QoL data with clinical and demographic correlations. Kitchen *et al.*[13] carried out a systematic review of patient-reported outcome measures and evidence of their validation in psoriasis. These reviews underscored the value of QoL measurement in psoriasis. However, we need to understand how QoL has been reported in previous trials; a comprehensive review is needed of the use of QoL instruments in randomized controlled trials (RCTs) for interventions in psoriasis.

The aims of this systematic review were to identify RCTs of therapies in psoriasis that have assessed QoL, and to evaluate patterns of utility and reporting of QoL data. This systematic review should reveal how QoL instruments have been used across therapeutic trials, including consideration of the minimal clinically important difference (MCID), frequency of measurement and sensitivity to change. The review may be useful for those who wish to understand the patterns of use of QoL measures in interventional trials for psoriasis.

Materials and methods

Data sources

We searched six computerized bibliographical databases up to November 2014: Cochrane Library CENTRAL, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, Web of Science Core Collection and Scopus. The search was restricted to publications in English and was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Prospero registration no. CRD42015009193).

Keywords were formulated using Scottish Intercollegiate Guidelines Network and Cochrane search filters for RCTs, and ScHARR search filters for QoL. Keywords for psoriasis treatments were developed through a pilot search of other systematic reviews on psoriasis treatments and of the British National Formulary. The search filters used are given in Appendix S1 (see Supporting Information). We ran supplementary searches and reviewed trial registers and grey literature. Reference lists of all included studies and of recent reviews were also assessed. Electronic publications in advance of print were also included.

Selection criteria

We included RCTs of any psoriasis treatment using at least one QoL instrument in adults (aged $\geq$ 18 years) with psoriasis, of either sex and of any ethnicity, including all subtypes of psoriasis. Psoriatic arthritis trials were included only if a skin-specific QoL instrument was used to differentiate QoL impairment for arthritis from that of psoriasis.

Exclusion criteria

The exclusion criteria for the systematic review were as follows: psoriatic arthritis studies where it was not possible to differentiate data on QoL impact of arthritis from QoL impact of psoriasis, studies that included any patient aged < 18 years, and articles where the change in QoL values could not be reliably calculated (including graphical representation). For consistency, QoL data presented only as subscales, where total scores are usually calculated, were excluded. Abstracts and posters where further data were not available upon contacting the author were also excluded.

Outcome measures extracted

Primary outcomes recorded included the QoL instrument used; scores at baseline, treatment and follow-up end points; and change in QoL attributed to treatment. For studies with an open-label extension, the data were extracted only for the period of the study while it was randomized and controlled. For crossover trials, the data were extracted prior to the crossover.

Secondary outcomes were Psoriasis Area and Severity Index (PASI) score or any other psoriasis severity scale used.

Data extraction and synthesis

Two reviewers (F.M.A. and A.C.C.) extracted data independently from all eligible published studies, discussed any disagreements and, if necessary involved a third reviewer (A.A.A.) for resolution. We adapted a form, which included the Cochrane Risk of Bias tool, for recording data[14] that included study design, details of administration, methodological quality and duration of treatment and follow-up. Article quality was quantitatively rated using the Jadad score.[15]

We recorded PASI or any other psoriasis severity scale and all QoL data including the baseline, treatment and follow-up

end-point scores and whether the studies detailed QoL percentage change, full scores, graphs or MCID.

Results

Of 3646 screened records, 99 articles met the inclusion criteria, describing 100 RCTs and 33 215 patients (Fig. 1). Some trials were reported in more than one publication; all relevant references are given in Table 1. Sixty-three studies were placebo controlled, 33 were head to head and 36 tested a single drug in different dosage regimens or formulations (some studies fulfilled more than one criterion). Although Jadad scores[15] were not integral to the inclusion criteria, Table 1 ranks interventions from low to high methodological quality for each intervention.

Of the 100 trials that measured QoL, 33 tested topical, 18 systemic, 39 biologics, nine phototherapy and 10 other interventions, including educational treatments, diet, writing exercises, balneotherapy, auriculotherapy, relaxation therapies and interdisciplinary care (Table 1; Fig. 2). The numbers of studies reporting each topical intervention were calcipotriol (13 trials), calcipotriol/betamethasone (seven), clobetasol (four) and dithranol (four). Systemic medications included methotrexate (seven), ciclosporin (three) and voclosporin (two). Biological trials included etanercept (14), ustekinumab (eight), adalimumab (seven), infliximab (six) and alefacept (four). QoL was evaluated in nine phototherapy trials. In the category of 'other interventions', QoL was used most commonly in educational (three) and diet (three) studies.

The mean Jadad score was 3·34 (range 1–5; Table 1). QoL was tested a range of two to six times for topical, two to 25 times for systemic and two to 12 times for biological interventions. Sixteen trials lasted > 12 weeks, 49 lasted 12–24 weeks and 35 lasted > 24 weeks. The number of patients ranged from 20[16] to 2546,[17] with a mean male-to-female ratio of 1·7 : 1 per study arm. The mean PASI at baseline ranged from 1·7 to 33·1.

The ranges of mean QoL scores at baseline were Dermatology Life Quality Index (DLQI) 1·7–20·1 (range for this measure = 0–30); 36-Item Short Form Survey (SF-36) physical component summary (PCS) 32·7–56·2 (0–100) and mental component summary (MCS) 35·7–52·4 (0–100); EuroQoL-5D (EQ-5D) component I 0·48–0·74 (0–1) and component II 55·3–76·4 (0–100); and Psoriasis Disability Index (PDI) 7·6–52·6 (0–90).

Instruments used

Thirteen instruments were used to measure QoL; some studies used more than one. Five generic instruments used were the SF-36,[18] EQ-5D,[19] General Health Questionnaire,[20,21] Quality of Life Index[22] and Sickness Impact Profile.[23,24] In addition, four dermatology-specific instruments were used, three specific to psoriasis and one for scalp dermatitis: DLQI,[25] Skindex,[26] Dermatology Quality of Life Scales,[27] Freiburg Life Quality Assessment,[28] PDI,[24] 12-Item Psoriasis Quality of Life Questionnaire,[29] Psoriatic Arthritis Quality of Life measure[30] and Scalpdex.[31] Of these, the DLQI was the most commonly used QoL instrument (83 studies, 83%), followed by the SF-36 (31, 31%), EQ-5D (15, 15%), PDI (14, 14%) and Skindex (five, 5%).

Minimal clinically important difference and statistical reporting

Of the 100 trials identified, 37 reported MCID; 32 were for DLQI, 10 for SF-36 and six for EQ-5D. The DLQI MCID was considered to be a score change of five,[32] but is now reported as four.[33] Of the 83 RCTs that utilized the DLQI, 32 trials reported the MCID. Changes in mean DLQI scores from baseline to treatment end ranged from −14·4[34] to +3·0.[35] Where DLQI score changes were reported, 115 of 142 'study arms' met the four-point MCID.[33] Biological interventions usually attained the DLQI MCID: 91% (83 of 91 study arms) met the four-point MCID. The MCID was attained by 78% (14 of 18) of topical and 52% (11 of 21) of systemic treatment arms. One RCT of infliximab measuring QoL at 100 weeks[35] reported a three-point worsening of DLQI. However, this study ended prematurely and had a low Jadad score of only 2. Another trial, with a high Jadad score of 5,[36] demonstrated the mean DLQI score increasing by 0·4 after folic acid was added to methotrexate. The MCID was not met for any study arm.

The SF-36 MCID is a change of three in the total score.[37] The SF-36 was used in 31 trials and MCID was reported in 10. The mean SF-36 change from baseline to treatment end ranged from −7·4[35] to +10·1[38,39] in the PCS and from −0·3[40] to +12·2[39] in the MCS. Where extracting change in SF-36 MCS scores was possible, 52% (24 of 46) study arms met the three-point MCID; 58% (21 of 36) of biological interventions met this. For PCS scores, 50% (24 of 48) of study arms met the MCID, as did 61% (23 of 38) of biological interventions. Only 25% (one of four) of systemic and no topical treatments met the MCID for both the MCS and PCS domains.

EQ-5D was used in 15 trials; six reported the MCID, which is 0·05.[41,42] The PDI was used in 14 trials, but the MCID is not known. Skindex was used in five RCTs; MCIDs for Skindex versions have not been published.

Figure 3 shows the correlations between PASI and absolute DLQI (R^2 = 0·49) and percentage (R^2 = 0·64) score changes, where available. In some cases the correlation was weak,[43] possibly attributed to nonoptimal end-point measurement for QoL, where the maximum effect may be missed.[44] Furthermore, some interventions may have a psychological impact not captured by clinical parameters.

Table 1 gives the studies included that documented full QoL data and statistical significance for intervention vs. comparator. Significant changes were reached in 52 trials for the DLQI, 19 for the SF-36, five for both EQ-5D and the PDI and two for Skindex. Conversely there was no statistical improvement in 19 trials for the DLQI, six for the SF-36, three for

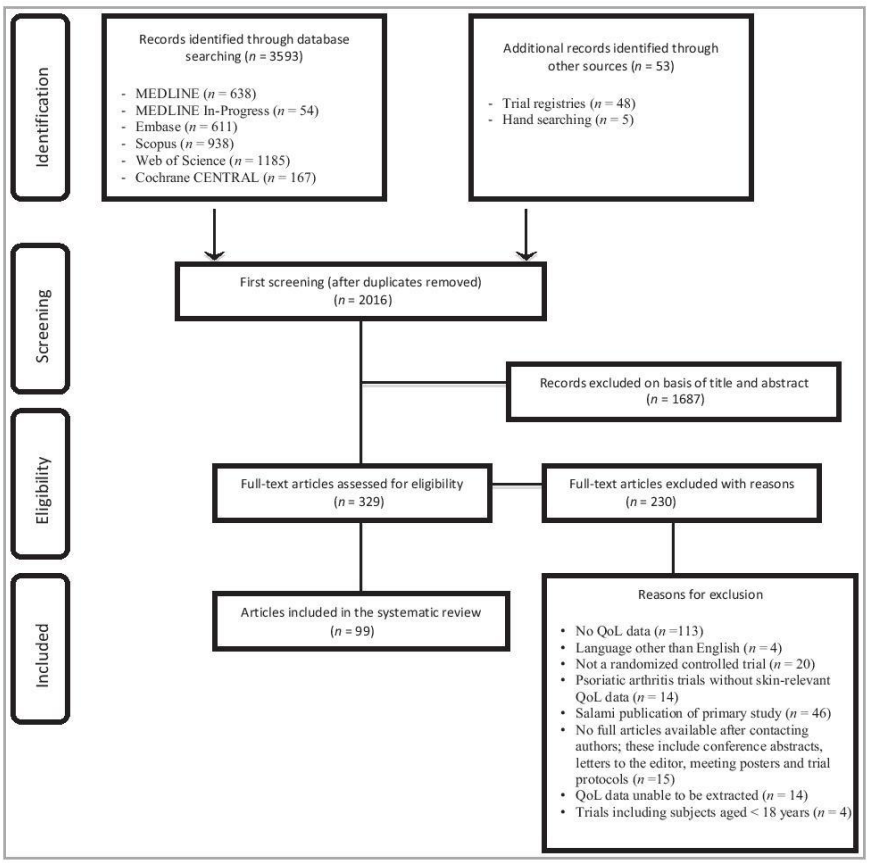


Fig 1. Flow diagram of article selection. QoL, quality of life.

EQ-5D, six for the PDI and three for Skindex. Twelve trials did not report statistical significance for the DLQI, six for the SF-36, four for EQ-5D and two for the PDI.

The first two studies identified that fulfilled the inclusion criteria were published in 1998.[45,46] Since then, reports of psoriasis interventions that fulfilled the inclusion criteria have gradually increased over time: 12 in 1998–2004, 33 in 2005–2009 and 55 in 2010–2014 (Fig. 4).

Discussion

QoL assessment is a frequent component in assessing psoriasis treatment efficacy.[47] This systematic review has identified therapeutic RCTs that demonstrated extractable QoL data, inevitably with heterogeneity in design, disease severity and QoL reporting. Many trials were excluded because of inconsistent reporting and analysis of QoL (Fig. 1).[48] Baseline and end-of-treatment values were not always provided. Often QoL scores were presented as percentage or value changes without pre- or postintervention scores. Mean values were most commonly reported, although median values are preferable with ordinal data.[47] Standard deviations, *P*-values or confidence intervals were sometimes omitted, and intention-to-treat numbers were sometimes omitted from the QoL dataset. This presented challenges for synthesizing data.

The MCID is the minimal change in score that is considered of clinical relevance.[49] Of the 13 QoL instruments used, only the DLQI, SF-36 and EQ-5D have MCID values reported in the

Table 1 Included studies: Jadad score, treatment duration, sample characteristics, quality-of-life (QoL) instruments and main psoriasis severity scale used

Main QoL article (salami publications used to derive non-QoL data)	Jadad	Interventions (grouped per intervention, ranked by increasing Jadad score)	Treatment end point[a]	No. of Patients	QoL instruments used	Psoriasis severity scale used (primary)
Biologics						
Asahina 2010[64]	3	Adalimumab vs. placebo	24	169	DLQI,[b] SF-36[b]	PASI
Genovese 2007[65]	4	Adalimumab vs. placebo	12	100	DLQI,[b] HAQ-DI,[b] SF-36[b] (PCS only), FACIT F[c]	PGA
Mease 2005[66]	4	Adalimumab vs. placebo	24	313	DLQI,[b] HAQ-DI,[b] SF-36[b] (PCS only)	PASI
Shikiar 2007[67] (Gordon 2006,[68] Menter 2010[69])	4	Adalimumab vs. placebo	12	148	DLQI,[b] EQ-5D,[b] SF-36[b] (except for PCS in 40-mg EOW arm)	PASI
Revicki 2007[70] (Kimball 2011,[71] Menter 2008,[72] Revicki 2008[73])	5	Adalimumab vs. placebo	16	1212	DLQI,[b] SF-36[b]	PASI
Revicki 2008[74] (Saurat 2008,[75] Navarini 2014,[76] Saurat 2011[77])	5	Adalimumab vs. MTX	16	271	DLQI,[b] EQ-5D[b]	PASI
Thaçi 2010,[78] Paul 2012[79]	5	Adalimumab + CAL/BD vs. adalimumab + vehicle	16	730	DLQI[c]	PASI
Lui 2012[80]	2	Alefacept vs. nUVB	16	98	DLQI[c]	PASI
Ellis 2003[81] (Ellis 2001[82])	4	Alefacept vs. placebo	12	205	DLQI,[d] SF-36,[d] DQOLS[d]	PASI
Finlay 2003[83] (Lebwohl 2003[84])	4	Alefacept vs. placebo	12	507	DLQI,[c] DQOLS[b] (15-mg arm only), SF-36[b] (PCS only)	PASI
Yan 2011[85]	4	Alefacept vs. MTX	12	212	DLQI,[c] SF-36[c]	PASI
Papp 2014[86] (Gordon 2012[87])	5	Briakinumab vs. placebo	12–40	2209	DLQI,[b] SF-36[b]	PASI
Gordon 2014[88] (Papp 2012[89])	5	Brodalumab vs. placebo	12	198	DLQI,[b] SF-36[b] (140-mg arm only, and MCS for 210-mg arm)	PASI
Gladman 2014[90] (Mease 2014[91])	3	Certolizumab vs. placebo	24	409	DLQI,[b] SF-36,[b] PsAQoL,[b] HAQ-DI[b]	PASI
Reich 2012[92]	5	Certolizumab vs. placebo	12	176	DLQI[d]	PASI
Dubertret 2006[38] (Ortonne 2005[39])	4	Efalizumab vs. placebo	12	793	DLQI,[b] SF-36[b]	PASI
Gordon 2003[3] (Menter 2005[93])	5	Efalizumab vs. placebo	12	556	DLQI,[b] PSA[b]	PASI
Cassano 2006[94]	1	Etanercept (dose comparison)	12	108	DLQI[c]	PASI
Dauden 2009[95] (Ortonne 2008,[96] Luger 2009[97])	1	Etanercept (continuous vs. intermittent)	54	720	DLQI,[b] EQ-5D,[c] SF-36[c]	PASI
Gelfand 2008[17] (Moore 2007[98])	2	Etanercept (continuous vs. intermittent)	24	2546	DLQI,[d] EQ-5D[d] (EuroQoL-FT), SF-36[d]	PASI
Gniadecki 2012[99] (Sterry 2010[100])	3	Etanercept (dose comparison)	12	752	DLQI,[b] EQ-5D,[c] HAQ-DI[c]	PASI
Lynde 2012[101]	3	Etanercept vs. etanercept + nUVB	12	75	DLQI[c]	PASI
Ortonne 2013[102]	3	Etanercept (dose comparison)	24	72	DLQI[d]	PASI
Thaçi 2014[5] (Strohal 2013[103])	3	Etanercept (dose comparison)	12	273	DLQI[b]	PASI

(continued)

Table 1 (continued)

Main QoL article (salami publications used to derive non-QoL data)	Jadad	Interventions (grouped per intervention, ranked by increasing Jadad score)	Treatment end point[a]	No. of Patients	QoL instruments used	Psoriasis severity scale used (primary)
Zachariae 2008[104]	3	Etanercept + MTX (tapered vs. continued)	24	59	DLQI,[b] EQ-5D[c]	PASI
Krueger 2005[105] (Papp 2005[106])	4	Etanercept vs. placebo	12	583	DLQI,[b] SF-36[b]	PASI
Feldman 2005[107] (Leonardi 2003[108])	5	Etanercept vs. placebo	12	652	DLQI[b]	PASI
Gottlieb 2003[109]	5	Etanercept vs. placebo	24	112	DLQI[b]	PASI
Reich 2009[110] (van de Kerkhof 2008[111])	5	Etanercept vs. placebo	12	142	DLQI,[b] SF-36[b]	PASI
Tyring 2007[112] (Tyring 2006[113])	5	Etanercept vs. placebo	12	618	DLQI[b]	PASI
Reich 2013,[35] extension of trial Barker 2011[114]	2	Infliximab (continuous vs. intermittent)	100	441	DLQI,[d] SF-36[d]	PASI
Yang 2012[115]	2	Infliximab vs. placebo	10	129	DLQI[b]	PASI
Barker 2011[114]	3	Infliximab vs. MTX	16	868	DLQI,[b] SF-36[b] (PCS only), EQ-5D[b]	PASI
Feldman 2008[116] (Menter 2007[117])	4	Infliximab vs. placebo	10	1430	DLQI,[b] SF-36[b]	PASI
Torii 2010[118]	4	Infliximab vs. placebo	14	54	DLQI[b]	PASI
Bissonnette 2011[119]	5	Infliximab vs. placebo	14	24	DLQI[c]	m-PPPASI
Feldman 2005[120] (Gottlieb 2004[121])	5	Infliximab vs. placebo	10	249	DLQI[b]	PASI
Reich 2006[122] (Reich 2005[123])	5	Infliximab vs. placebo	24	378	DLQI,[b] SF-36[b]	PASI
Krupashankar 2014[124]	4	Itolizumab (loading dose vs. nonloading dose)	12	225	DLQI,[d] SF-36[d]	PASI
Leonardi 2012[125]	5	Ixekizumab vs. placebo	8	142	DLQI[b]	PASI
Langley 2014[126]	4	Secukinumab vs. etanercept vs. placebo	12	2044	DLQI[b] (vs. placebo only)	PASI
Mamolo 2014[127]	4	Tofacitinib vs. placebo	12	197	DLQI,[b] SF-36[b]	PASI
Paul 2014[128] (Reich 2014[129])	2	Ustekinumab + MTX (gradual vs. immediate withdrawal)	16	489	DLQI,[d] EQ-5D,[d] VAS[d]	PASI
Nakagawa 2012[130] (Igarashi 2012[131])	3	Ustekinumab vs. placebo	12	158	DLQI,[b] SF-36[b] (PCS only), PDI[b]	PASI
Kimball 2012[132] (Leonardi 2008,[133] Lebwohl 2010,[134] Kimball 2013[135])	3	Ustekinumab vs. placebo	12	766	DLQI,[b] SF-36[d]	PASI
Zhu 2013[136]	3	Ustekinumab vs. placebo	12	322	DLQI[b]	PASI
Langley 2010[137] (Papp 2008[138,139])	4	Ustekinumab vs. placebo	12	1230	DLQI[b]	PASI
McInnes 2013[140]	4	Ustekinumab vs. placebo	24	615	DLQI,[b] HAQ-DI,[b] SF-36[b] (except MCS in 45-mg arm)	PASI
Kavanaugh 2010[141] (Gottlieb 2009[142])	5	Ustekinumab vs. placebo	12	146	DLQI,[b] HAQ-DI[b]	PASI
Tsai 2012[143] (Tsai 2011[144])	5	Ustekinumab vs. placebo	12	121	DLQI[b]	PASI
Systemics						
Strand 2013[145] (Papp 2012[146])	5	Apremilast vs. placebo	16	352	DLQI[b] (except 10-mg arm), SF 36[b] (MCS only)	PASI
Möller 2010[147]	4	Chondroitin sulfate vs. placebo	12	116	DLQI,[c] SF-36[c]	PASI
Beissert 2009[148]	3	Ciclosporin vs. mycophenolate mofetil	12	54	PDI[c]	PASI

(continued)

Table 1 (continued)

Main QoL article (salami publications used to derive non-QoL data)	Jadad	Interventions (grouped per intervention, ranked by increasing Jadad score)	Treatment end point[a]	No. of Patients	QoL instruments used	Psoriasis severity scale used (primary)
Thaçi 2002[149]	4	Ciclosporin (body-weight-dependent dose vs. independent dose)	12	212	PDI[d]	PASI
Roberti 2014[43]	4	Cytokines (low dose)	12	41	DLQI[b]	PASI
Bagel 1998[46]	2	DAB389IL02 vs. placebo	4	70	DLQI[d]	PASI
Greenberger 2012[150]	3	*Dunaliella bardawil* (9-cis β-carotene) vs. placebo	12	44	DLQI[b]	PASI
Salim 2006[36]	5	MTX + folic acid vs. MTX	12	22	DLQI[c]	PASI
Kaltwasser 2004[151] (Nash 2006[152])	5	Leflunomide vs. placebo	24	190	DLQI,[b] HAQ[b]	PASI
Faurschou 2015[16]	4	Liraglutide vs. placebo	8	20	DLQI[c]	PASI
Flytström 2008[153]	3	MTX vs. ciclosporin	12	84	DLQI,[c] SF-36[b] (PCS only)	PASI
Asawanonda 2006[154]	4	MTX + nUVB vs. MTX + placebo	24	24	DLQI[c]	PASI
Ho 2010[155]	2	Traditional Chinese medicine vs. MTX	24	61	PDI[b] (for MTX vs. placebo)	PASI
Gupta 2008[156]	3	Voclosporin vs. placebo	12	201	DLQI,[d] PDI[d]	PASI
Kunynetz 2011[157] (Papp 2008[139])	5	Voclosporin vs. placebo	12	451	DLQI[b] (for 0·3 and 0·4-mg arms), PDI[b] (for 0·3 and 0·4-mg arms)	PASI
Drouin 2008[158]	5	XP-828L (Dermylex) vs. placebo	8	26	DLQI[b]	PASI
Phototherapy						
Koek 2009[159] (Koek 2006[160])	2	Home UVB (TL-01) vs. outpatient UVB (TL-01)	46 irradiations	196	PDI,[c] SF-36,[d] EQ-5D[d]	PASI
Gahalaut 2014[161]	2	PUVAsol + isotretinoin vs. PUVAsol	12	40	DLQI[b]	PASI
Klein 2011[162]	2	Synchronous balneophototherapy vs. nUVB monotherapy	35 sessions	367	PDI,[c] SIP,[b] FLQA-d[b] (physical complaints and global health only)	PASI
Topicals						
Choonhakarn 2010[163]	4	Aloe vera vs. triamcinolone acetonide	8	75	DLQI[c]	PASI
Ortonne 2014[164]	5	Betamethasone valerate dressing vs. CAL/BD ointment	4	324	DLQI[b]	TSS-4
Wall 1998[45]	1	CAL vs. dithranol	12	306	PDI,[c] SIP[c]	IGA
Ortonne 2009[165] (Kragballe 2009[166])	2	CAL/BD scalp formulation vs. CAL scalp solution	8	312	SF-36,[c] Skindex-16[b]	TSS
Saraceno 2007[167]	2	CAL/BD vs. CAL	4	150	Skindex-29[b]	PASI
Zheng 2011[168]	2	CAL/BD vs. CAL	4	320	DLQI[b]	VAS
De Korte 2008[40] (van de Kerkhof 2006[169])	3	CAL vs. dithranol	12	106	Skindex-29,[c] SF-36[c]	Modified PASI
Menter 2013[170]	4	CAL/BD vs. BD vs. CAL vs. vehicle	8	1152	DLQI[b] (except vs. CAL group)	PASI
van de Kerkhof 2004[171]	4	CAL/BD vs. CAL vs. placebo	4	828	EQ-5D,[b] PDI[c]	PASI
Woo 2003[172]	5	CAL + nUVB vs. CAL vs. vehicle	20 sessions	50	PDI[c]	PASI
Hutchinson 2000[173]	1	Calcitriol vs. dithranol	8	114	PDI[b]	PASI
Bergstrom 2003[174]	1	Clobetasol (foam vs. cream/solution)	2	32	DLQI,[c] EQ-5D[b]	PASI
Menter 2009[4]	1	Clobetasol propionate vs. calcipotriene + betamethasone dipropionate	4	93	PQOLS[c]	ODS
Mraz 2008[175]	1	Clobetasol propionate (spray vs. foam)	2–4	77	DLQI[b]	IGS
Sofen 2011[176]	2	Clobetasol propionate spray vs. vehicle	4	81	Scalpdex[b]	GSS

(continued)

Table 1 (continued)

Main QoL article (salami publications used to derive non-QoL data)	Jadad	Interventions (grouped per intervention, ranked by increasing Jadad score)	Treatment end point[a]	No. of Patients	QoL instruments used	Psoriasis severity scale used (primary)
Prins 2005[177]	2	Dithranol (short contact) + nUVB vs. dithranol (inpatient)	8–12	238	SIP,[b] PDI[b]	PASI
Alora-Palli 2010[178]	2	Liquor carbonis distillate solution vs. calcipotriene cream	12	60	DLQI[c]	Modified PASI
Bernstein 2006[179]	2	*Mahonia aquifolium* vs. placebo	12	200	QLI[b]	PASI
Tiplica 2009[180]	3	Mometasone furoate 0·1% + salicylic acid 5% vs. mometasone furoate 0·1%	1	359	DLQI[d]	PASI
Galvez 2012[181]	3	Sulfurous mineral waters spray vs. distilled water spray	2	39	DLQI[c]	PASI
Others						
Lu 2012[182]	2	Auricular therapy + yinxieling formula vs. yinxieling formula	8	84	DLQI[c]	PASI
Schmitt 2014[183]	3	Interdisciplinary dermatological and psychiatric care for psoriasis vs. dermatological care for psoriasis	24	47	DLQI[c]	PASI
Ersser 2012[184]	2	Educational nursing intervention vs. no educational intervention	6	64	DLQI[c]	PASI
Bostoen 2012[185]	4	Educational programme vs. no educational intervention	12	29	DLQI,[b] PDI,[b] Skindex-29[c]	PASI
Vedhara 2007[186]	2	Emotional disclosure vs. standard control writing intervention	0·5	59	DLQI[d]	PASI
Guida 2014[34]	2	Patients on immunosuppressives: energy-restricted diet vs. usual diet	24	44	DLQI[b]	PASI
Jensen 2013[187]	2	Low-energy diet vs. standard routine dietary guidance	16	60	DLQI[b]	PASI
Fordham 2015[188]	2	MCBT vs. usual treatment	8	29	DLQI[b]	SAPASI
Chambers 2012[189]	2	Online healthcare delivery vs. in-office care	16	64	DLQI,[d] EQ-5D[d]	PASI
Tabolli 2012[190]	2	Writing exercise (Pennebaker) vs. educational intervention	0·5	202	Skindex-29,[c] SF-36,[c] GHQ[c]	PASI

BD, betamethasone dipropionate; CAL, calcipotriol; DLQI, Dermatology Life Quality Index; DQOLS, Dermatology Quality of Life Scales; EOW, every other week; EQ-5D, EuroQol 5-D; EuroQol-FT, EuroQol Feeling Thermometer; FACIT-F, Functional Assessment of Chronic Illness Therapy, Fatigue scale; FLQA-d, Freiburg Life Quality Assessment; GHQ, General Health Questionnaire; GSS, Global Severity Score; HAQ-DI, Health Assessment Questionnaire Disability Index; MCBT, mindfulness-based cognitive therapy; MCS, mental component summary; m-PPPASI, modified Palmo-plantar Pustular Psoriasis Area Severity Index; MTX, methotrexate; nUVB, narrowband ultraviolet B; ODS, Overall Disease Severity; PASI, Psoriasis Area and Severity Index; PCS, physical component summary; PDI, Psoriasis Disability Index; PGA, Physician's Global Assessment; PQOLS, 12-Item Psoriasis Quality of Life Questionnaire; PsAQoL, Psoriatic Arthritis Quality of Life measure; PUVAsol, psoralen plus natural sunlight; QLI, Quality of Life Index; SF-36, 36-Item Short Form Survey; SIP, Sickness Impact Profile; TSS, total skin score; UVB, ultraviolet B. [a]Weeks unless specified otherwise. [b]Significant improvement vs. comparator(s). [c]No significant improvement vs. comparator(s). [d]No significance data provided.

literature. Although interventions may result in statistically significant QoL improvement, this does not necessarily correlate with clinically important change. MCID values enhance the clinical meaningfulness of QoL scores, particularly if data are correlated with clinical efficacy. Thirty-seven trials reported consideration of MCID, with the DLQI and SF-36 being the most commonly used instruments with known MCID. EQ-5D was the only other used instrument with known MCID; these data are not reported as the numbers were so low.

The MCID of QoL measures may be determined using several methodologies, and at least nine approaches have been reported.[50] These may be categorized into two main groups: anchor-based and distribution-based approaches. Whereas the former incorporates the patient perspective, the latter determines MCID using statistical significance. The anchor-based method is the most commonly used for determining the MCID, as used in the case of the DLQI.[33]

Each methodology has its limitations. For example, anchor-based methods have often been criticized for unequal changes required for deterioration vs. improvement of a condition.[51] Several factors may influence MCID scores, including patient baseline status, disease group and severity, treatment, and

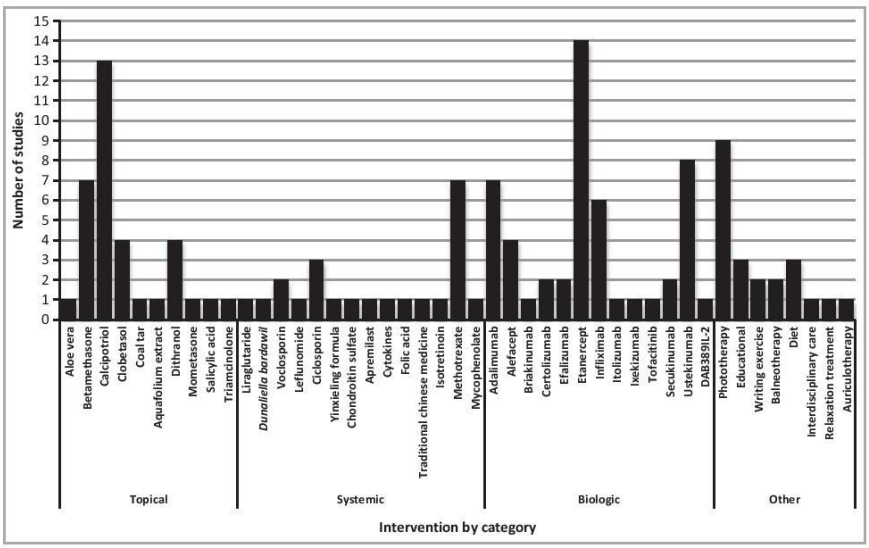


Fig 2. Number of randomized controlled trials of each intervention that measured health-related quality of life.

patient demographics. Furthermore, it is important to note that MCID values may differ significantly within the same population depending on the methodology chosen.[52] Therefore, interpreting MCID scores should be considered in the context of these limitations.

More generic QoL instruments were used (n = 5) than specialty- (n = 4) or condition-specific questionnaires (n = 3). The DLQI was the most commonly used instrument, possibly because of the simplicity of reporting a single summary score, the ease of completion in 2 min,[53] its widespread use in national psoriasis guidelines,[54] and other reasons.[55] The frequency of QoL measurement varied across studies depending on intervention type and trial duration. The U.K. guidelines, which recommend DLQI measurement at 10–16 weeks depending on the biologic, may not capture the best DLQI responses for biological therapies.[44]

Several reviews have explored the effects of biological treatment on QoL.[10,11,56,57] Other systematic reviews have explored QoL in psoriasis; the review by De Korte *et al.*[9] was not limited to RCTs and this provided difficulties in interpreting the dataset. The current systematic review investigates the patterns of use of QoL instruments, as well as the reporting of the outcomes. We employed strict entry criteria, allowing for robust comparison across interventions per QoL instrument. We included only data from the double-blind controlled phases of each trial. Nevertheless, the lack of adequate guidelines on QoL data reporting still rendered data analysis problematic.

Kitchen *et al.*[13] reviewed the ability of psoriasis-specific instruments to capture adequately domains relating to psoriasis: no existing psoriasis-specific patient-reported outcome instrument has sufficient evidence on validity, reliability and sensitivity to change, but both DLQI[58] and Skindex demonstrated content validity. However, this systematic review demonstrates that several generic and disease/specialty-specific instruments were sensitive to change with positive QoL outcomes.

The DLQI and SF-36 are the most frequently used instruments across psoriasis RCTs. A European S3 guidelines report on psoriasis systemic treatment[59] described the DLQI as an 'important' variable in assessment of treatment efficacy. However, the DLQI has limitations, including previous criticisms of its unidimensionality and low representation of emotional aspects.[60] There is diverse practice in monitoring therapeutic effect on QoL and questionnaire preference. We rejected 113 RCTs because of inextricable QoL data. The European Academy of Dermatology and Venereology Task Force provides recommendations for use of QoL measures.[61] Currently there is great variation in the quality of reporting of QoL data,[62,63] creating difficulties in cross-interventional meta-analyses. This systematic review emphasizes the need for guidelines concerning appropriate reporting of QoL data.

This review has several limitations. Only English-language literature was examined and only studies with extractable QoL data were included. There was too little comparative information from other QoL instruments to be included. Several studies were excluded due to inadequate QoL data reporting.

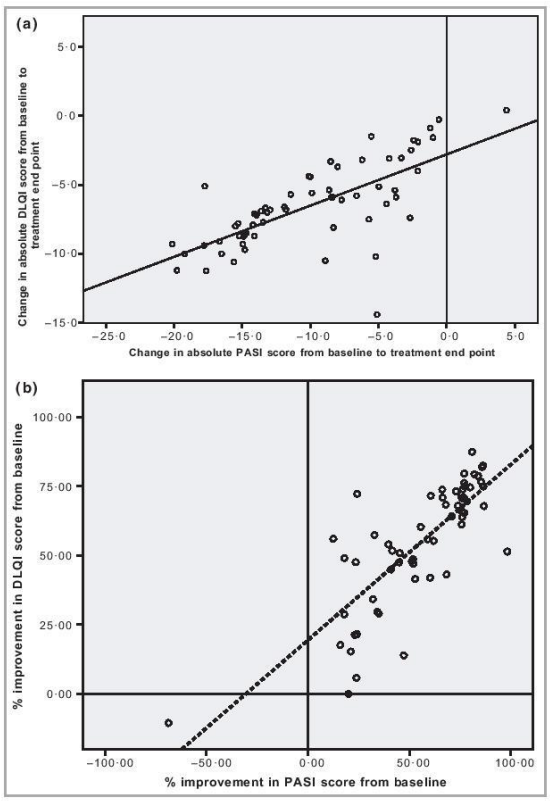


Fig 3. (a) Correlation of absolute change in Dermatology Life Quality Index (DLQI) scores with absolute change in Psoriasis Area and Severity Index (PASI) scores (R^2 = 0·49). (b) Correlation of percentage improvement in DLQI scores with percentage improvement in PASI scores (R^2 = 0·64).

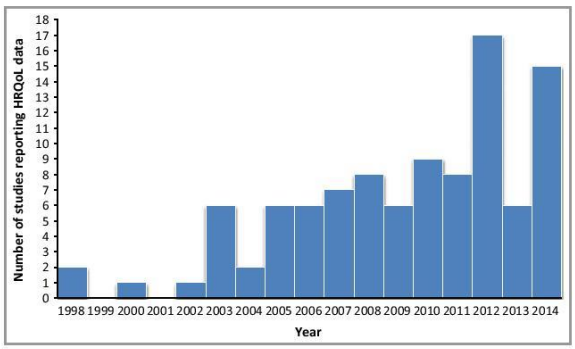


Fig 4. Increasing use of health-related quality-of-life (HRQoL) instruments in the included psoriasis studies since 1998 (n = 100).

Collating data across studies other than RCTs was not possible due to the wide variation in methodologies. Although an author (A.Y.F.) is joint DLQI copyright holder, bias was countered by two independent principal reviewers conducting the data search, extraction and synthesis, with a third independent adjudicator reviewer.

We recommend improvement of QoL reporting to include baseline, treatment and follow-up end-point absolute median scores with interquartile ranges. Patient numbers should always be reported, as well as whether intention to treat was implemented, as previously suggested.[62,63] If a graphical representation of QoL is published, it should be accompanied by numerical data. Authors should not submit only percentage and/or graphical data to represent study outcomes, as these data cannot be used in meta-analysis and systematic reviews. Journals should furthermore implement such criteria prior to accepting publications.

The MCID and validated band descriptors where available should be used to interpret data, as this holds greater clinical value than statistical significance alone. Researchers should consider the availability of MCID when choosing QoL instruments, and be encouraged to publish MCID information. While there are numerous approaches for calculating MCID scores, there is a need for consensus on new or improved methodological approaches towards calculating MCID. Existing methodologies should be cautiously taken into account by clinicians and researchers alike to facilitate the interpretation of results. Although minimal change is clinically important, the question arises of whether intervention end points should target perfect QoL, rather than demonstrating a measurable improvement.

Acknowledgments

We would like to thank Matthew Manfre and Clarissa Rizzo from Malta University Medical School, who aided with preliminary research for this study. We would also like to thank Dr John Ingram (Cardiff University) for his invaluable support and guidance throughout the study. Finally we acknowledge the National Institution of Higher Education, Science, Technology and Innovation-SENESCYT, who made it possible for Dr Andrea Cueva to contribute to this review.

References

1 Langley RGB, Krueger GG, Griffiths CEM. Psoriasis: epidemiology, clinical features, and quality of life. *Ann Rheum Dis* 2005; **64** (Suppl. 2):ii18–23.
2 Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. *Br J Dermatol* 1995; **132**:236–44.
3 Gordon K, Papp K, Hamilton T *et al.* Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA* 2003; **290**:3073–80.
4 Menter A, Abramovits W, Colón LE *et al.* Comparing clobetasol propionate 0.05% spray to calcipotriene 0.005% betamethasone dipropionate 0.064% ointment for the treatment of moderate to severe plaque psoriasis. *J Drugs Dermatol* 2009; **8**:52–7.
5 Thaçi D, Galimberti R, Amaya-Guerra M *et al.* Improvement in aspects of sleep with etanercept and optional adjunctive topical therapy in patients with moderate-to-severe psoriasis: results from the PRISTINE trial. *J Eur Acad Dermatol Venereol* 2014; **28**:900–6.
6 Finlay AY. Quality of life assessments in dermatology. *Semin Cutan Med Surg* 1998; **17**:291–6.
7 Basra MKA, Shahrukh M. Burden of skin diseases. *Expert Rev Pharmacoecon Outcomes Res* 2009; **9**:271–83.
8 de Korte J, Mombers FMC, Sprangers MAG *et al.* The suitability of quality-of-life questionnaires for psoriasis research: a systematic literature review. *Arch Dermatol* 2002; **138**:1221–7.
9 de Korte J, Sprangers MAG, Mombers FMC *et al.* Quality of life in patients with psoriasis: a systematic literature review. *J Investig Dermatol Symp Proc* 2004; **9**:140–7.
10 Katugampola RP, Lewis VJ, Finlay AY. The Dermatology Life Quality Index: assessing the efficacy of biological therapies for psoriasis. *Br J Dermatol* 2007; **156**:945–50.
11 Reich K, Sinclair R, Roberts G *et al.* Comparative effects of biological therapies on the severity of skin symptoms and health-related quality of life in patients with plaque-type psoriasis: a meta-analysis. *Curr Med Res Opin* 2008; **24**:1237–54.
12 Frendl DM, Ware JE Jr. Patient-reported functional health and well-being outcomes with drug therapy: a systematic review of randomized trials using the SF-36 health survey. *Med Care* 2014; **52**:439–45.
13 Kitchen H, Cordingley L, Young H *et al.* Patient-reported outcome measures in psoriasis: the good, the bad and the missing!. *Br J Dermatol* 2015; **172**:1210–21.
14 Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*, vol. 5. Hoboken, NJ: Wiley, 2008.
15 Jadad AR, Moore RA, Carroll D *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**:1–12.
16 Faurschou A, Gyldenløve M, Rohde U *et al.* Lack of effect of the glucagon-like peptide-1 receptor agonist liraglutide on psoriasis in glucose-tolerant patients – a randomized placebo-controlled trial. *J Eur Acad Dermatol Venereol* 2015; **29**:555–9.
17 Gelfand JM, Kimball AB, Mostow EN *et al.* Patient-reported outcomes and health-care resource utilization in patients with psoriasis treated with etanercept: continuous versus interrupted treatment. *Value Health* 2008; **11**:400–7.
18 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care* 1992; **30**:473–83.
19 The EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**:199–208.
20 Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. *Psychol Med* 1979; **9**:139–45.
21 Piccinelli M, Bisoffi G, Bon MG *et al.* Validity and test–retest reliability of the Italian version of the 12-item General Health Questionnaire in general practice: a comparison between three scoring methods. *Compr Psychiatry* 1993; **34**:198–205.
22 Ferrans CE, Powers MJ. Quality of life index: development and psychometric properties. *Adv Nurs Sci* 1985; **8**:15–24.
23 Bergner M, Bobbitt RA, Carter WB *et al.* The Sickness Impact Profile: development and final revision of a health status measure. *Med Care* 1981; **19**:787–805.
24 Finlay AY, Khan GK, Luscombe DK *et al.* Validation of sickness impact profile and psoriasis disability index in psoriasis. *Br J Dermatol* 1990; **123**:751–6.
25 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**:210–16.
26 Chren M-M, Lasek RJ, Quinn LM *et al.* Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. *J Invest Dermatol* 1996; **107**:707–13.
27 Morgan M, McCreedy R, Simpson J *et al.* Dermatology quality of life scales – a measure of the impact of skin diseases. *Br J Dermatol* 1997; **136**:202–6.

28 Augustin M, Zschocke I, Seidenglanz K *et al.* Validation and clinical results of the FLQA-d, a quality of life questionnaire for patients with chronic skin disease. *Dermatol Psychosom* 2000; **1**:12–17.
29 Koo J, Kozma CM, Menter A *et al.* Development of a disease specific quality of life questionnaire: the 12-item Psoriasis Quality of Life Questionnaire (PQOL-12). Presented at the *61st Annual Meeting of the American Academy of Dermatology*, San Francisco, CA, 21–26 March 2003; abstr. P606.
30 McKenna SP, Doward LC, Whalley D *et al.* Development of the PsAQoL: a quality of life instrument specific to psoriatic arthritis. *Ann Rheum Dis* 2004; **63**:162–9.
31 Chen SC, Yeung J, Chren M-M. Scalpdex: a quality-of-life instrument for scalp dermatitis. *Arch Dermatol* 2002; **138**:803–7.
32 Khilji FA, Gonzalez M, Finlay AY. Clinical meaning of change in Dermatology Life Quality Index scores. *Br J Dermatol* 2002; **147** (Suppl. 62):50–1.
33 Basra MKA, Salek MS, Camilleri L *et al.* Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology* 2015; **230**:27–33.
34 Guida B, Napoleone A, Trio R *et al.* Energy-restricted, n-3 polyunsaturated fatty acids-rich diet improves the clinical response to immuno-modulating drugs in obese patients with plaque-type psoriasis: a randomized control clinical trial. *Clin Nutr* 2014; **33**:399–405.
35 Reich K, Wozel G, Zheng H *et al.* Efficacy and safety of infliximab as continuous or intermittent therapy in patients with moderate-to-severe plaque psoriasis: results of a randomized, long-term extension trial (RESTORE2). *Br J Dermatol* 2013; **168**:1325–34.
36 Salim A, Tan E, Ilchyshyn A *et al.* Folic acid supplementation during treatment of psoriasis with methotrexate: a randomized, double-blind, placebo-controlled trial. *Br J Dermatol* 2006; **154**:1169–74.
37 Samsa G, Edelman D, Rothman ML *et al.* Determining clinically important differences in health status measures. *Pharmacoeconomics* 1999; **15**:141–55.
38 Dubertret L, Sterry W, Bos JD *et al.* Clinical experience acquired with the efalizumab (Raptiva®) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from a phase III international randomized, placebo-controlled trial. *Br J Dermatol* 2006; **155**:170–81.
39 Ortonne J, Shear N, Shumack S *et al.* Impact of efalizumab on patient-reported outcomes in high-need psoriasis patients: results of the international, randomized, placebo-controlled phase III Clinical Experience Acquired with Raptiva (CLEAR) trial. *BMC Dermatol* 2005; **5**:13.
40 de Korte J, Valk P, Sprangers M *et al.* A comparison of twice-daily calcipotriol ointment with once-daily short-contact dithranol cream therapy: quality-of-life outcomes of a randomized controlled trial of supervised treatment of psoriasis in a day-care setting. *Br J Dermatol* 2008; **158**:375–81.
41 O'Brien BJ, Drummond MF. Statistical versus quantitative significance in the socioeconomic evaluation of medicines. *Pharmacoeconomics* 1994; **5**:389–98.
42 Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997; **35**:1095–108.
43 Roberti ML, Ricottini L, Capponi A *et al.* Immunomodulating treatment with low dose interleukin-4, interleukin-10 and interleukin-11 in psoriasis vulgaris. *J Biol Regul Homeost Agents* 2014; **28**:133–9.
44 Bishop-Bailey A, Finlay AY, Hatchard C *et al.* Dermatology Quality Life Index (DLQI) responses to biological therapy for psoriasis during standard U.K. clinical care: NICE assessment timelines may not capture the best DLQI response. *Br J Dermatol* 2015; **173** (Suppl. S1):70.
45 Wall ARJ, Poyner TF, Menday AP. A comparison of treatment with dithranol and calcipotriol on the clinical severity and quality of life in patients with psoriasis. *Br J Dermatol* 1998; **139**:1005–11.
46 Bagel J, Garland W, Breneman D *et al.* Administration of DAB389IL-2 to patients with recalcitrant psoriasis: a double-blind, phase II multicenter trial. *J Am Acad Dermatol* 1998; **38**:938–44.
47 Basra MKA, Fenech R, Gatt RM *et al.* The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159**:997–1035.
48 Le Cleach L, Chassany O, Levy A *et al.* Poor reporting of quality of life outcomes in dermatology randomized controlled clinical trials. *Dermatology* 2008; **216**:46–55.
49 Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003; **41**:582–92.
50 Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol* 2003; **56**:395–407.
51 Wright A, Hannon J, Hegedus EJ *et al.* Clinimetrics corner: a closer look at the minimal clinically important difference (MCID). *J Man Manip Ther* 2012; **20**:160–6.
52 Terwee CB, Roorda LD, Dekker J *et al.* Mind the MIC: large variation among populations and methods. *J Clin Epidemiol* 2010; **63**:524–34.
53 Loo WJ, Diba V, Chawla M *et al.* Dermatology Life Quality Index: influence of an illustrated version. *Br J Dermatol* 2003; **148**:279–84.
54 Smith CH, Anstey AV, Barker JNWN *et al.* British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *Br J Dermatol* 2009; **161**:987–1019.
55 Finlay AY, Basra MKA, Piguet V *et al.* Dermatology Life Quality Index (DLQI): a paradigm shift to patient-centered outcomes. *J Invest Dermatol* 2012; **132**:2464–5.
56 Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. *J Eur Acad Dermatol Venereol* 2014; **28**:333–7.
57 Baker E, Coleman C, Reinhart K *et al.* Effect of biologic agents on non-PASI outcomes in moderate-to-severe plaque psoriasis: systematic review and meta-analyses. *Dermatol Ther (Heidelb)* 2012; **2**:9.
58 Safikhani S, Sundaram M, Bao Y *et al.* Qualitative assessment of the content validity of the Dermatology Life Quality Index in patients with moderate to severe psoriasis. *J Dermatolog Treat* 2011; **24**:50–9.
59 Nast A, Boehncke W-H, Mrowietz U *et al.* S3 – Guidelines on the treatment of psoriasis vulgaris (English version). Update. *J Dtsch Dermatol Ges* 2012; **10**:S1–95.
60 Both H, Essink-Bot M-L, Busschbach J *et al.* Critical review of generic and dermatology-specific health-related quality of life instruments. *J Invest Dermatol* 2007; **127**:2726–39.
61 Prinsen CAC, Korte J, Augustin M *et al.* Measurement of health-related quality of life in dermatological research and practice: outcome of the EADV Taskforce on Quality of Life. *J Eur Acad Dermatol Venereol* 2013; **27**:1195–203.
62 Finlay AY. Quality of life in dermatology: after 125 years, time for more rigorous reporting. *Br J Dermatol* 2014; **170**:4–6.

63 Salek MS, Jung S, Brincat-Ruffini LA *et al.* Clinical experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995–2012. *Br J Dermatol* 2013; **169**:734–59.

64 Asahina A, Nakagawa H, Etoh T *et al.* Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a phase II/III randomized controlled study. *J Dermatol* 2010; **37**:299–310.

65 Genovese M, Mease P, Thomson G *et al.* Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *J Rheumatol* 2007; **34**:1040–50.

66 Mease P, Gladman D, Ritchlin C *et al.* Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; **52**:3279–89.

67 Shikiar R, Heffernan M, Langley RG *et al.* Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a phase II randomized controlled trial. *J Dermatolog Treat* 2007; **18**:25–31.

68 Gordon KB, Langley RG, Leonardi C *et al.* Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006; **55**:598–606.

69 Menter A, Augustin M, Signorovitch J *et al.* The effect of adalimumab on reducing depression symptoms in patients with moderate to severe psoriasis: a randomized clinical trial. *J Am Acad Dermatol* 2010; **62**:812–18.

70 Revicki DA, Willian MK, Menter A *et al.* Impact of adalimumab treatment on patient-reported outcomes: results from a phase III clinical trial in patients with moderate to severe plaque psoriasis. *J Dermatolog Treat* 2007; **18**:341–50.

71 Kimball AB, Bensimon AG, Guerin A *et al.* Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with co-morbidities: subanalysis of results from a randomized, double-blind, placebo-controlled, phase III trial. *Am J Clin Dermatol* 2011; **12**:51–62.

72 Menter A, Tyring SK, Gordon K *et al.* Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol* 2008; **58**:106–15.

73 Revicki D, Menter A, Feldman S *et al.* Adalimumab improves health-related quality of life in patients with moderate to severe plaque psoriasis compared with the United States general population norms: results from a randomized, controlled phase III study. *Health Qual Life Outcomes* 2008; **6**:75.

74 Revicki D, Willian M, Saurat J *et al.* Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *Br J Dermatol* 2008; **158**:549–57.

75 Saurat JH, Stingl G, Dubertret L *et al.* Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol* 2008; **158**:558–66.

76 Navarini AA, Poulin Y, Menter A *et al.* Analysis of body regions and components of PASI scores during adalimumab or methotrexate treatment for patients with moderate-to-severe psoriasis. *J Drugs Dermatol* 2014; **13**:554–62.

77 Saurat J, Langley R, Reich K *et al.* Relationship between methotrexate dosing and clinical response in patients with moderate to severe psoriasis: subanalysis of the CHAMPION study. *Br J Dermatol* 2011; **165**:399–406.

78 Thaçi D, Ortonne JP, Chimenti S *et al.* A phase IIIb, multicentre, randomized, double-blind, vehicle-controlled study of the efficacy and safety of adalimumab with and without calcipotriol/betamethasone topical treatment in patients with moderate to severe psoriasis: the BELIEVE study. *Br J Dermatol* 2010; **163**:402–11.

79 Paul C, van de Kerkhof P, Puig L *et al.* Influence of psoriatic arthritis on the efficacy of adalimumab and on the treatment response of other markers of psoriasis burden: subanalysis of the BELIEVE study. *Eur J Dermatol* 2012; **22**:762–9.

80 Lui H, Gulliver W, Tan J *et al.* A randomized controlled study of combination therapy with alefacept and narrow band UVB phototherapy (UVB) for moderate to severe psoriasis: efficacy, onset, and duration of response. *J Drugs Dermatol* 2012; **11**:929–37.

81 Ellis CN, Mordin MM, Adler EY. Effects of alefacept on health-related quality of life in patients with psoriasis: results from a randomized, placebo-controlled phase II trial. *Am J Clin Dermatol* 2003; **4**:131–9.

82 Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Engl J Med* 2001; **345**:248–55.

83 Finlay AY, Salek MS, Haney J. Intramuscular alefacept improves health-related quality of life in patients with chronic plaque psoriasis. *Dermatology* 2003; **206**:307–15.

84 Lebwohl M, Christophers E, Langley R *et al.* An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. *Arch Dermatol* 2003; **139**:719–27.

85 Yan H, Tang M, You Y *et al.* Treatment of psoriasis with recombinant human LFA3-antibody fusion protein: a multi-center, randomized, double-blind trial in a Chinese population. *Eur J Dermatol* 2011; **21**:737–43.

86 Papp K, Sundaram M, Bao Y *et al.* Effects of briakinumab treatment for moderate to severe psoriasis on health-related quality of life and work productivity and activity impairment: results from a randomized phase III study. *J Eur Acad Dermatol Venereol* 2014; **28**:790–8.

87 Gordon KB, Langley RG, Gottlieb AB *et al.* A phase III, randomized, controlled trial of the fully human IL-12/23 mAb briakinumab in moderate-to-severe psoriasis. *J Invest Dermatol* 2012; **132**:304–14.

88 Gordon K, Kimball A, Chau D *et al.* Impact of brodalumab treatment on psoriasis symptoms and health-related quality of life: use of a novel patient-reported outcome measure, the Psoriasis Symptom Inventory. *Br J Dermatol* 2014; **170**:705–15.

89 Papp KA, Leonardi C, Menter A *et al.* Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med* 2012; **366**:1181–9.

90 Gladman D, Fleischmann R, Coteur G *et al.* Effect of certolizumab pegol on multiple facets of psoriatic arthritis as reported by patients: 24-week patient-reported outcome results of a phase III, multicenter study. *Arthritis Care Res* 2014; **66**:1085–92.

91 Mease PJ, Fleischmann R, Deodhar AA *et al.* Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014; **73**:48–55.

92 Reich K, Ortonne JP, Gottlieb AB *et al.* Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab certolizumab pegol: results of a phase II randomized, placebo-controlled trial with a re-treatment extension. *Br J Dermatol* 2012; **167**:180–90.

93 Menter A, Gordon K, Carey W *et al.* Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis. *Arch Dermatol* 2005; **141**:31–8.

94 Cassano N, Loconsole F, Galluccio A *et al.* Once-weekly administration of high-dosage etanercept in patients with plaque psoriasis: results of a pilot experience (power study). *Int J Immunopathol Pharmacol* 2006; **19**:225–9.
95 Daudén E, Griffiths CEM, Ortonne JP *et al.* Improvements in patient-reported outcomes in moderate-to-severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. *J Eur Acad Dermatol Venereol* 2009; **23**:1374–82.
96 Ortonne J-P, Griffiths CEM, Daudén E *et al.* Efficacy and safety of continuous versus paused etanercept treatment in patients with moderate-to-severe psoriasis over 54 weeks: the CRYSTEL study. *Expert Rev Dermatol* 2008; **3**:657–65.
97 Luger T, Barker J, Lambert J *et al.* Sustained improvement in joint pain and nail symptoms with etanercept therapy in patients with moderate-to-severe psoriasis. *J Eur Acad Dermatol Venereol* 2009; **23**:896–904.
98 Moore A, Gordon K, Kang S *et al.* A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis. *J Am Acad Dermatol* 2007; **56**:598–603.
99 Gniadecki R, Robertson D, Molta C *et al.* Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. *J Eur Acad Dermatol Venereol* 2012; **26**:1436–43.
100 Sterry W, Ortonne J-P, Kirkham B *et al.* Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. *Br Med J* 2010; **340**:c147.
101 Lynde CW, Gupta AK, Guenther L *et al.* A randomized study comparing the combination of nbUVB and etanercept to etanercept monotherapy in patients with psoriasis who do not exhibit an excellent response after 12 weeks of etanercept. *J Dermatolog Treat* 2012; **23**:261–7.
102 Ortonne JP, Paul C, Berardesca E *et al.* A 24-week randomized clinical trial investigating the efficacy and safety of two doses of etanercept in nail psoriasis. *Br J Dermatol* 2013; **168**:1080–7.
103 Strohal R, Puig L, Chouela E *et al.* The efficacy and safety of etanercept when used with as-needed adjunctive topical therapy in a randomised, double-blind study in subjects with moderate-to-severe psoriasis (the PRISTINE trial). *J Dermatolog Treat* 2013; **24**:169–78.
104 Zachariae C, Mork N-J, Reunala T *et al.* The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. *Acta Derm Venereol* 2008; **88**:495–501.
105 Krueger G, Langley R, Finlay A *et al.* Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial. *Br J Dermatol* 2005; **153**:1192–9.
106 Papp KA, Tyring S, Lahfa M *et al.* A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005; **152**:1304–12.
107 Feldman SR, Kimball AB, Krueger GG *et al.* Etanercept improves the health-related quality of life of patients with psoriasis: results of a phase III randomized clinical trial. *J Am Acad Dermatol* 2005; **53**:887–9.
108 Leonardi CL, Powers JL, Matheson RT *et al.* Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003; **349**:2014–22.
109 Gottlieb AB, Matheson RT, Lowe N *et al.* A randomized trial of etanercept as monotherapy for psoriasis. *Arch Dermatol* 2003; **139**:1627–32.
110 Reich K, Segaert S, van de Kerkhof P *et al.* Once-weekly administration of etanercept 50 mg improves patient-reported outcomes in patients with moderate-to-severe plaque psoriasis. *Dermatology* 2009; **219**:239–49.
111 van de Kerkhof PCM, Segaert S, Lahfa M *et al.* Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. *Br J Dermatol* 2008; **159**:1177–85.
112 Tyring S, Gordon K, Poulin Y *et al.* Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol* 2007; **143**:719–26.
113 Tyring S, Gottlieb A, Papp K *et al.* Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 2006; **367**:29–35.
114 Barker J, Hoffmann M, Wozel G *et al.* Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). *Br J Dermatol* 2011; **165**:1109–17.
115 Yang H, Wang K, Jin H *et al.* Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. *Chin Med J* 2012; **125**:1845–51.
116 Feldman S, Gottlieb A, Bala M *et al.* Infliximab improves health-related quality of life in the presence of comorbidities among patients with moderate-to-severe psoriasis. *Br J Dermatol* 2008; **159**:704–10.
117 Menter A, Feldman S, Weinstein G *et al.* A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2007; **56**:31.e1–15.
118 Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. *J Dermatol Sci* 2010; **59**:40–9.
119 Bissonnette R, Poulin Y, Guenther L *et al.* Treatment of palmoplantar psoriasis with infliximab: a randomized, double-blind placebo-controlled study. *J Eur Acad Dermatol Venereol* 2011; **25**:1402–8.
120 Feldman S, Gordon K, Bala M *et al.* Infliximab treatment results in significant improvement in the quality of life of patients with severe psoriasis: a double-blind placebo-controlled trial. *Br J Dermatol* 2005; **152**:954–60.
121 Gottlieb A, Evans R, Li S *et al.* Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004; **51**:534–42.
122 Reich K, Nestle F, Papp K *et al.* Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2006; **154**:1161–8.
123 Reich K, Nestle FO, Papp K *et al.* Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366**:1367–74.
124 Krupashankar D, Dogra S, Kura M *et al.* Efficacy and safety of itolizumab, a novel anti-CD6 monoclonal antibody, in patients with moderate to severe chronic plaque psoriasis: results of a double-blind, randomized, placebo-controlled, phase-III study. *J Am Acad Dermatol* 2014; **71**:484–92.
125 Leonardi C, Matheson R, Zachariae C *et al.* Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med* 2012; **366**:1190–1.
126 Langley RG, Elewski BE, Lebwohl M *et al.* Secukinumab in plaque psoriasis – results of two phase 3 trials. *N Engl J Med* 2014; **371**:326–38.

127 Mamolo C, Harness J, Tan H *et al.* Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, improves patient-reported outcomes in a phase 2b, randomized, double-blind, placebo-controlled study in patients with moderate-to-severe psoriasis. *J Eur Acad Dermatol Venereol* 2014; **28**:192–203.

128 Paul C, Puig L, Kragballe K *et al.* Transition to ustekinumab in patients with moderate-to-severe psoriasis and inadequate response to methotrexate: a randomized clinical trial (TRANSIT). *Br J Dermatol* 2014; **170**:425–34.

129 Reich K, Puig L, Paul C *et al.* One-year safety and efficacy of ustekinumab and results of dose adjustment after switching from inadequate methotrexate treatment: the TRANSIT randomized trial in moderate-to-severe plaque psoriasis. *Br J Dermatol* 2014; **170**:435–44.

130 Nakagawa H, Schenkel B, Kato M *et al.* Impact of ustekinumab on health-related quality of life in Japanese patients with moderate-to-severe plaque psoriasis: results from a randomized, double-blind, placebo-controlled phase 2/3 trial. *J Dermatol* 2012; **39**:761–9.

131 Igarashi A, Kato T, Kato M *et al.* Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. *J Dermatol* 2012; **39**:242–52.

132 Kimball A, Gordon K, Fakharzadeh S *et al.* Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial through up to 3 years. *Br J Dermatol* 2012; **166**:861–72.

133 Leonardi CL, Kimball AB, Papp KA *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; **371**:1665–74.

134 Lebwohl M, Papp K, Han C *et al.* Ustekinumab improves health-related quality of life in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial. *Br J Dermatol* 2010; **162**:137–46.

135 Kimball AB, Papp KA, Wasfi Y *et al.* Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study. *J Eur Acad Dermatol Venereol* 2013; **27**:1535–45.

136 Zhu X, Zheng M, Song M *et al.* Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). *J Drugs Dermatol* 2013; **12**:166–74.

137 Langley R, Feldman S, Han C *et al.* Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: results from a randomized, double-blind, placebo-controlled phase III trial. *J Am Acad Dermatol* 2010; **63**:457–65.

138 Papp KA, Langley RG, Lebwohl M *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; **371**:1675–84.

139 Papp K, Bissonnette R, Rosoph L *et al.* Efficacy of ISA247 in plaque psoriasis: a randomised, multicentre, double-blind, placebo-controlled phase III study. *Lancet* 2008; **371**:1337–42.

140 McInnes IB, Kavanaugh A, Gottlieb AB *et al.* Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 2013; **382**:780–9.

141 Kavanaugh A, Menter A, Mendelsohn A *et al.* Effect of ustekinumab on physical function and health-related quality of life in patients with psoriatic arthritis: a randomized, placebo-controlled, phase II trial. *Curr Med Res Opin* 2010; **26**:2385–92.

142 Gottlieb A, Menter A, Mendelsohn A *et al.* Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet* 2009; **373**:633–40.

143 Tsai T, Song M, Shen Y *et al.* Ustekinumab improves health-related quality of life in Korean and Taiwanese patients with moderate to severe psoriasis: results from the PEARL trial. *J Drugs Dermatol* 2012; **11**:943–9.

144 Tsai T, Ho J, Song M *et al.* Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *J Dermatol Sci* 2011; **63**:154–63.

145 Strand V, Fiorentino D, Hu C *et al.* Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: results from a phase IIb randomized, controlled study. *Health Qual Life Outcomes* 2013; **11**:82.

146 Papp K, Cather J, Rosoph L *et al.* Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *Lancet* 2012; **380**:738–46.

147 Möller I, Pérez M, Monfort J *et al.* Effectiveness of chondroitin sulphate in patients with concomitant knee osteoarthritis and psoriasis: a randomized, double-blind, placebo-controlled study. *Osteoarthritis Cartilage* 2010; **18** (Suppl. 1):S32–40.

148 Beissert S, Pauser S, Sticherling M *et al.* A comparison of mycophenolate mofetil with ciclosporine for the treatment of chronic plaque-type psoriasis. *Dermatology* 2009; **219**:126–32.

149 Thaçi D, Brautigam M, Kaufmann R *et al.* Body-weight-independent dosing of cyclosporine micro-emulsion and three times weekly maintenance regimen in severe psoriasis. A randomised study. *Dermatology* 2002; **205**:383–8.

150 Greenberger S, Harats D, Salameh F *et al.* 9-cis-rich β-carotene powder of the alga dunaliella reduces the severity of chronic plaque psoriasis: a randomized, double-blind, placebo-controlled clinical trial. *J Am Coll Nutr* 2012; **31**:320–6.

151 Kaltwasser J, Nash P, Gladman D *et al.* Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum* 2004; **50**:1939–50.

152 Nash P, Thaçi D, Behrens F *et al.* Leflunomide improves psoriasis in patients with psoriatic arthritis: an in-depth analysis of data from the TOPAS study. *Dermatology* 2006; **212**:238–49.

153 Flytström I, Stenberg B, Svensson A *et al.* Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. *Br J Dermatol* 2008; **158**:116–21.

154 Asawanonda P, Nateetongrungsak Y. Methotrexate plus narrowband UVB phototherapy versus narrowband UVB phototherapy alone in the treatment of plaque-type psoriasis: a randomized, placebo-controlled study. *J Am Acad Dermatol* 2006; **54**:1013–18.

155 Ho S, Yeung C, Chan H. Methotrexate versus traditional Chinese medicine in psoriasis: a randomized, placebo-controlled trial to determine efficacy, safety and quality of life. *Clin Exp Dermatol* 2010; **35**:717–22.

156 Gupta A, Langley R, Lynde C *et al.* ISA247: quality of life results from a phase II, randomized, placebo-controlled study. *J Cutan Med Surg* 2008; **12**:268–75.

157 Kunynetz R, Carey W, Thomas R *et al.* Quality of life in plaque psoriasis patients treated with voclosporin: a Canadian phase III, randomized, multicenter, double-blind, placebo-controlled study. *Eur J Dermatol* 2011; **21**:89–94.

158 Drouin R, Moroni O, Cantin K *et al.* A double-blind, placebo-controlled, randomized trial of XP-828L (800 mg) on the quality of life and clinical symptoms of patients with mild-to-moderate psoriasis. *Altern Med Rev* 2008; **13**:145–52.

159 Koek MB, Buskens E, van Weelden H *et al.* Home versus outpatient ultraviolet B phototherapy for mild to severe psoriasis: pragmatic multicentre randomised controlled non-inferiority trial (PLUTO study). *BMJ* 2009; **338**:b1542.

160 Koek MB, Buskens E, Steegmans PH *et al.* UVB phototherapy in an outpatient setting or at home: a pragmatic randomised single-blind trial designed to settle the discussion. The PLUTO study. *BMC Med Res Methodol* 2006; **6**:39.

161 Gahalaut P, Soodan PS, Mishra N *et al.* Clinical efficacy of psoralen+sunlight vs. combination of isotretinoin and psoralen+sunlight for the treatment of chronic plaque-type psoriasis vulgaris: a randomized hospital-based study. *Photodermatol Photoimmunol Photomed* 2014; **30**:294–301.

162 Klein A, Schiffner R, Schiffner-Rohe J *et al.* A randomized clinical trial in psoriasis: synchronous balneophototherapy with bathing in Dead Sea salt solution plus narrowband UVB vs. narrowband UVB alone (TOMESA-study group). *J Eur Acad Dermatol Venereol* 2011; **25**:570–8.

163 Choonhakarn C, Busaracome P, Sripanidkulchai B *et al.* A prospective, randomized clinical trial comparing topical aloe vera with 0.1% triamcinolone acetonide in mild to moderate plaque psoriasis. *J Eur Acad Dermatol Venereol* 2010; **24**:168–72.

164 Ortonne JP, Esposito M, Chimenti S *et al.* Betamethasone valerate dressing is non-inferior to calcipotriol–betamethasone dipropionate ointment in the treatment of patients with mild-to-moderate chronic plaque psoriasis: results of a randomized assessor-blinded multicentre trial. *J Eur Acad Dermatol Venereol* 2014; **28**:1226–34.

165 Ortonne J, Ganslandt C, Tan J *et al.* Quality of life in patients with scalp psoriasis treated with calcipotriol/betamethasone dipropionate scalp formulation: a randomized controlled trial. *J Eur Acad Dermatol Venereol* 2009; **23**:919–26.

166 Kragballe K, Hoffmann V, Ortonne JP *et al.* Efficacy and safety of calcipotriol plus betamethasone dipropionate scalp formulation compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized controlled trial. *Br J Dermatol* 2009; **161**:159–66.

167 Saraceno R, Andreassi L, Ayala F *et al.* Efficacy, safety and quality of life of calcipotriol/betamethasone dipropionate (Dovobet®) versus calcipotriol (Daivonex®) in the treatment of psoriasis vulgaris: a randomized, multicentre, clinical trial. *J Dermatolog Treat* 2007; **18**:361–5.

168 Zheng Z, Zhu X, Wang B *et al.* Effect of Daivobet® on the quality of life in Chinese patients with stable psoriasis vulgaris: a multicenter, randomized, double-blind, positive controlled and parallel group study. *World Appl Sci J* 2011; **13**:1240–7.

169 van de Kerkhof PCM, van der Valk PGM, Swinkels OQJ *et al.* A comparison of twice-daily calcipotriol ointment with once-daily short-contact dithranol cream therapy: a randomized controlled trial of supervised treatment of psoriasis vulgaris in a day-care setting. *Br J Dermatol* 2006; **155**:800–7.

170 Menter A, Gold LS, Bukhalo M *et al.* Calcipotriene plus betamethasone dipropionate topical suspension for the treatment of mild to moderate psoriasis vulgaris on the body: a randomized, double-blind, vehicle-controlled trial. *J Drugs Dermatol* 2013; **12**:92–8.

171 van de Kerkhof PC. The impact of a two-compound product containing calcipotriol and betamethasone dipropionate (Daivobet/Dovobet) on the quality of life in patients with psoriasis vulgaris: a randomized controlled trial. *Br J Dermatol* 2004; **151**:663–8.

172 Woo WK, McKenna KE. Combination TL01 ultraviolet B phototherapy and topical calcipotriol for psoriasis: a prospective randomized placebo-controlled clinical trial. *Br J Dermatol* 2003; **149**:146–50.

173 Hutchinson PE, Marks R, White J. The efficacy, safety and tolerance of calcitriol 3 μg/g ointment in the treatment of plaque psoriasis: a comparison with short-contact dithranol. *Dermatology* 2000; **201**:139–45.

174 Bergstrom KG, Arambula K, Kimball AB. Medication formulation affects quality of life: a randomized single-blind study of clobetasol propionate foam 0.05% compared with a combined program of clobetasol cream 0.05% and solution 0.05% for the treatment of psoriasis. *Cutis* 2003; **72**:407–11.

175 Mraz S, Leonardi C, Colon LE *et al.* Different treatment outcomes with different formulations of clobetasol propionate 0.05% for the treatment of plaque psoriasis. *J Dermatolog Treat* 2008; **19**:354–9.

176 Sofen H, Hudson CP, Cook-Bolden FE *et al.* Clobetasol propionate 0.05% spray for the management of moderate-to-severe plaque psoriasis of the scalp: results from a randomized controlled trial. *J Drugs Dermatol* 2011; **10**:885–92.

177 Prins M, Krabbe PFM, Swinkels QOJ *et al.* The effect of treatment on quality of life in psoriasis patients. *Acta Derm Venereol* 2005; **85**:304–10.

178 Alora-Palli MB, Perkins AC, Van Cotti A *et al.* Efficacy and tolerability of a cosmetically acceptable coal tar solution in the treatment of moderate plaque psoriasis: a controlled comparison with calcipotriene (calcipotriol) cream. *Am J Clin Dermatol* 2010; **11**:275–83.

179 Bernstein S, Donsky H, Gulliver W *et al.* Treatment of mild to moderate psoriasis with Relieva, a *Mahonia aquifolium* extract – a double-blind, placebo-controlled study. *Am J Ther* 2006; **13**:121–6.

180 Tiplica G, Salavastru C. Mometasone furoate 0.1% and salicylic acid 5% vs. mometasone furoate 0.1% as sequential local therapy in psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009; **23**:905–12.

181 Galvez GJ, Peiro P, Lucas M *et al.* Quality of life and assessment after local application of sulphurous water in the home environment in patients with psoriasis vulgaris: a randomised placebo-controlled pilot study. *Eur J Integr Med* 2012; **4**:e213–18.

182 Lu C, Xiang Y, Xie X *et al.* A randomized controlled single-blind clinical trial on 84 outpatients with psoriasis vulgaris by auricular therapy combined with optimized Yinxieling formula. *Chin J Integr Med* 2012; **18**:186–91.

183 Schmitt J, Wozel G, Garzarolli M *et al.* Effectiveness of interdisciplinary vs. dermatological care of moderate-to-severe psoriasis: a pragmatic randomised controlled trial. *Acta Derm Venereol* 2014; **94**:192–7.

184 Ersser S, Cowdell F, Nicholls P *et al.* A pilot randomized controlled trial to examine the feasibility and efficacy of an educational nursing intervention to improve self-management practices in patients with mild-moderate psoriasis. *J Eur Acad Dermatol Venereol* 2012; **26**:738–45.

185 Bostoen J, Bracke S, Keyser S *et al.* An educational programme for patients with psoriasis and atopic dermatitis: a prospective randomized controlled trial. *Br J Dermatol* 2012; **167**:1025–31.

186 Vedhara K, Morris R, Booth R *et al.* Changes in mood predict disease activity and quality of life in patients with psoriasis following emotional disclosure. *J Psychosom Res* 2007; **62**:611–19.

187 Jensen P, Zachariae C, Christensen R *et al.* Effect of weight loss on the severity of psoriasis: a randomized clinical study. *JAMA Dermatol* 2013; **149**:795–801.

188 Fordham B, Griffiths CEM, Bundy C. A pilot study examining mindfulness-based cognitive therapy in psoriasis. *Psychol Health Med* 2015; **20**:121–7.
189 Chambers C, Parsi K, Schupp C *et al.* Patient-centered online management of psoriasis: a randomized controlled equivalency trial. *J Am Acad Dermatol* 2012; **66**:948–53.
190 Tabolli S, Naldi L, Pagliarello C *et al.* Evaluation of the impact of writing exercises interventions on quality of life in patients with psoriasis undergoing systemic treatments. *Br J Dermatol* 2012; **167**:1254–64.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1. Example search strategy.
Video S1. Author video.

2) Ali, F.M., Salek, M.S. and Finlay, A.Y., 2018. Two Minimal Clinically Important Difference (2MCID): A New Twist on an Old Concept. *Acta Dermato-Venereologica*, *98*(7-8), pp.715-717.

ActaDV Acta Dermato-Venereologica ActaDV Advances in dermatology and venereology

Two Minimal Clinically Important Difference (2MCID): A New Twist on an Old Concept

Faraz M. ALI[1], M. Sam SALEK[2,3] and Andrew Y. FINLAY[1]
[1]Department of Dermatology and Wound Healing, Division of Infection and Immunity, School of Medicine, College of Biomedical and Life Sciences, Cardiff University, Cardiff, [2]School of Life and Medical Sciences, University of Hertfordshire, Hatfield, and [3]Institute for Medicines Development, Cardiff, UK.
Accepted Jan 23, 2018; Epub ahead of print Jan 24, 2018

The minimal clinically important difference (MCID) is a widely used concept to interpret the meaning of health-related quality of life (HRQoL) score changes. However, to give a greater sense of the meaning of score change across a wider spectrum of score changes, we propose a new concept of '2MCID'. This represents a score change of twice the MCID. This approach, novel in dermatology, has been used in other areas (1, 2) and highlights therapies that reach this higher change threshold. We hypothesise that this method would better discriminate between the efficacy of interventions to help guide clinical judgement and patient progress.

HRQoL outcome measures capture several aspects of a patient's overall well-being (3). Such measures are increasingly being implemented in interventional studies alongside clinical objective parameters as important contributors towards morbidity and mortality data (4). Reports of studies often include HRQoL data citing statistical differences pre- and post-intervention, though statistically significant changes may not be reflective of meaningful change in HRQoL, particularly within large sample sizes which may produce statistically significant change despite the change being small (5).

The MCID is the minimum difference needed for a patient to perceive the change as beneficial (6) and may be used to determine whether a medical intervention improves patient perceived outcomes. Factors to consider when calculating the MCID for a particular outcome include: patient baseline severity, particular disease or condition, patient demographics and treatment. There is no consensus on the best methodology for calculating the MCID (7), and values may therefore differ. Despite these limitations, it is still more useful for clinicians to assess intervention effectiveness based on the patient's perspective, rather than solely on statistical significance.

The most commonly utilized quality of life (QoL) tool in psoriasis trials is the Dermatology Life Quality Index (DLQI), with an MCID of 4 points (8, 9). During this systematic review we noted that multiple MCID could provide a further aid to the results' interpretation: we felt this novel concept deserved further exploration. We have therefore applied the 2MCID concept to data from that review (8).

METHODS

A systematic review was presented by Ali et al. (8). We have introduced the concept of 2MCID to that dataset (i.e. DLQI score change of at least 8) to demonstrate comparative efficacy between interventions.

RESULTS

A total of 100 trials were identified by the systematic review, covering diverse interventions. As the DLQI was the most commonly used QoL measure (83% of studies), the 2MCID concept was tested on interventions with documented DLQI scores. **Fig. 1** summarises all the interventions that met the different MCID thresholds.

For topical treatments, clobetasol 0.05% spray showed the greatest improvement at 4 weeks (2MCID, 8 point improvement), followed by calcipotriol plus betamethasone at 8 weeks (6.4 points). These changes are comparable to ustekinumab 90 mg at 12 weeks (mean 2MCID (8 point) improvement) and ciclosporin 3–5 mg/kg at 12 weeks (6.6 point improvement). No other topical therapy reached 2MCID. However, it is important to consider the context of baseline psoriasis severity, treatment duration and long-term QoL maintenance.

Methotrexate 15 mg at 16 weeks was the only systemic intervention over the 2MCID threshold (8.7 points). This was comparable to several biologics, including etanercept 50 mg at 24 weeks and ustekinumab 90 mg at 12 weeks (8.7 points).

Infliximab 5 mg/kg at 16 weeks and secukinumab 300 mg at 12 weeks demonstrated the largest improvement in DLQI score of a mean of 11.4 (>2MCID), just short of 3MCID. Amongst other interventions, an energy-restricted diet with immunosuppressive therapy at 24 weeks recorded DLQI improvement of 14.4 (3MCID). DLQI at 12 weeks improved by 11.2 (>2MCID) with PUVAsol 0.6 mg/kg + isotretinoin 0.5 mg/kg: for PUVAsol alone, DLQI improvement was 6.8.

For studies with treatment endpoint and assessment at 12 weeks, the interventions with the greatest mean DLQI impact in each category were secukinumab 300 mg (2MCID, 11.4 points), ciclosporin 3–5 mg/kg (1MCID, 6.6 points), PUVAsol 0.6 mg/kg+isotretinoin 0.5 mg/kg (2MCID, 11.2 points), Liquor Carbonis Distillate solution 15% (1MCID, 5.8 points) and educational programme (1MCID, 4 points).

DISCUSSION

Previously, Leaf & Goldfarb (1) described the impact of erythropoiesis stimulating agents on HRQoL using Short-

doi: 10.2340/00015555-2894
Acta Derm Venereol 2018; 98: 715–717

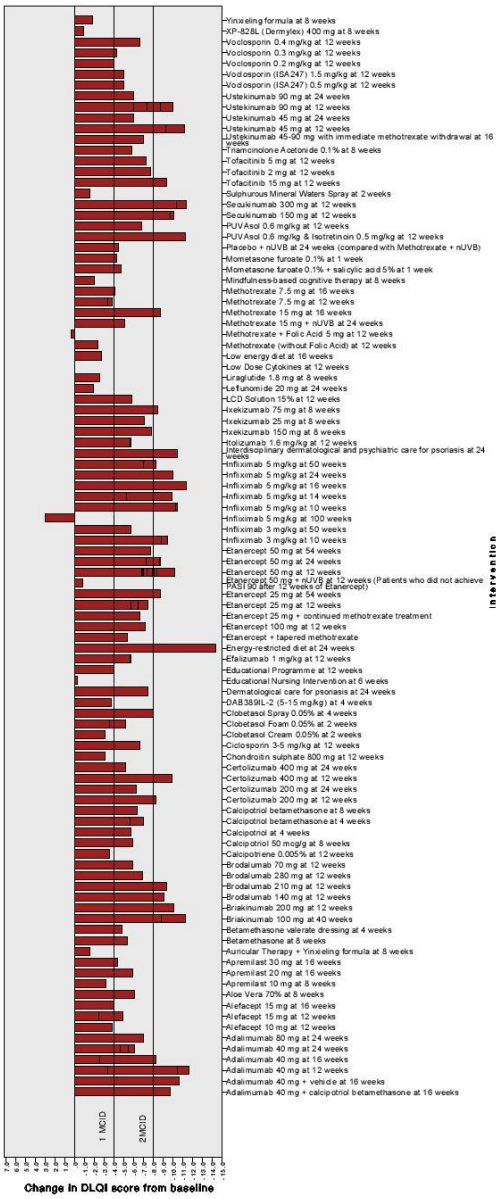


Fig. 1. Mean Dermatology Life Quality Index (DLQI) score change in 83 clinical trials for psoriasis (8), showing those interventions that reached 1 minimal clinically important difference (MCID) and 2 MCID score change.

Form 36 and The Kidney Disease Questionnaire. However, the authors only infrequently arbitrarily refer to score changes using multiples of MCID without formal concept utilization. Similarly, Jones et al. (2) equate a change of 'twice the MCID' to a 'large benefit' when comparing active treatments for COPD against placebo using the St. George's Respiratory Questionnaire. Neither study formally explored or stratified results.

Although score banding descriptors can be used (10) to describe patient numbers within score bands pre- and post-intervention, a method is needed to discriminate between the extent of the effect of interventions on QoL. The concept of 'multiple-MCID' could add meaning to score change when comparing therapies, or when comparing results across different QoL instruments as a 'unit of change'. 2MCID appears to be a practical threshold providing a meaningful 'hurdle' that developers of new interventions might strive to achieve. In the systematic review analysis, only one data set from 83 RCTs demonstrated a change of 3MCID, indicating that a 3MCID 'hurdle' would be a difficult and impractical threshold.

This 'pilot study' of the 'multiple-MCID' concept demonstrates the potential benefit of comparing the extent of impact of different categories of interventions on QoL and interpreting change over time. We have demonstrated that some systemic interventions may impact QoL to the same extent as certain biologic treatments. Similarly, certain topical treatments may be as efficacious as systemic alternatives. However, the systematic review dataset is not homogenous and often patients have different baseline severities. Although MCID values are applied across a spectrum of scores in interpreting change in scores of a measure, in reality the MCID score value may be different if the score change is at the lower or upper end of a HRQoL measure score range. This criticism of the concept of MCID requires further investigation, possibly through meta-regression where the magnitude of effect on DLQI is regressed on baseline severity. The 2MCID concept may be too simplistic: ideally the identification and calculation of a multiple-MCID score should be based on prospective research based on patient assessment of a higher level of change, using an anchor question based on, say, "Major clinically important difference".

Despite these reservations we believe 'multiple-MCID' provides additional meaningful information on clinical improvement and may be of value to clinicians, patients and the pharmaceutical industry. Medications that meet the '2MCID' minimum threshold might be more readily appro-

ved by pharmaceutical regulatory authorities and health technology assessment agencies. This concept may also enable researchers to better distinguish between interventions and comparators in trials, potentially improving patients' access to the most effective new medicines. Prospective longitudinal studies could aim to prove the usefulness of the concept before implementing it more widely. Further work is required before this novel concept is adopted in treatment decision-making and in reimbursement appraisals.

REFERENCES

1. Leaf DE, Goldfarb DS. Interpretation and review of health-related quality of life data in CKD patients receiving treatment for anemia. Kidney Int 2008; 75: 15–24.
2. Jones PW, Gelhorn H, Wilson H, Karlsson N, Menjoge S, Müllerova H, et al. Responder analyses for treatment effects in COPD using the St George's Respiratory Questionnaire. Chronic Obstr Pulm Dis 2017; 4: 124.
3. Revicki DA, Osoba D, Fairclough D, Barofsky I, Berzon R, Leidy N, et al. Recommendations on health-related quality of life research to support labeling and promotional claims in the United States. Qual Life Res 2000; 9: 887–900.
4. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol 2003; 56: 395–407.
5. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998; 16: 139–144.
6. Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Control Clin Trials 1989; 10: 407–415.
7. Gatchel RJ, Lurie JD, Mayer TG. Minimal clinically important difference. Spine 2010; 35: 1739–1743.
8. Ali F, Cueva A, Vyas J, Atwan A, Salek M, Finlay A, et al. A systematic review of the use of quality-of-life instruments in randomized controlled trials for psoriasis. Br J Dermatol 2017; 176: 577–593.
9. Basra MKA, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology 2015; 230: 27–33.
10. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology Life Quality Index Scores Mean? J Invest Dermatol 2005; 125: 659–664.

3) Campbell, N., Ali, F., Finlay, A.Y. and Salek, S.S., 2015. Equivalence of electronic and paper-based patient-reported outcome measures. *Quality of Life Research*, *24*(8), pp.1949-1961.

Qual Life Res (2015) 24:1949–1961
DOI 10.1007/s11136-015-0937-3

REVIEW

Equivalence of electronic and paper-based patient-reported outcome measures

Niloufar Campbell · Faraz Ali · Andrew Y. Finlay · Sam S. Salek

Accepted: 4 February 2015 / Published online: 22 February 2015

Abstract
Aim Electronic formats (ePROs) of paper-based patient-reported outcomes (PROs) should be validated before they can be reliably used. This review aimed to examine studies investigating measurement equivalence between ePROs and their paper originals to identify methodologies used and to determine the extent of such validation.
Methods Three databases (OvidSP, Web of Science and PubMed) were searched using a set of keywords. Results were examined for compliance with inclusion criteria. Articles or abstracts that directly compared screen-based electronic versions of PROs with their validated paper-based originals, with regard to their measurement equivalence, were included. Publications were excluded if the only instruments reported were stand-alone visual analogue scales or interactive voice response formats. Papers published before 2007 were excluded, as a previous meta-analysis examined papers published before this time.
Results Fifty-five studies investigating 79 instruments met the inclusion criteria. 53 % of the 79 instruments studied were condition specific. Several instruments, such as the SF-36, were reported in more than one publication. The most frequently reported formats for ePROs were Web-based versions. In 78 % of the publications, there was evidence of equivalence or comparability between the two formats as judged by study authors. Of the 30 publications that provided preference data, 87 % found that overall participants preferred the electronic format.
Conclusions When examining equivalence between paper and electronic versions of PROs, formats are usually judged by authors to be equivalent. Participants prefer electronic formats. This literature review gives encouragement to the further widespread development and use of ePROs.

Keywords Patient-reported outcome measures · PRO · Electronic PROs · Validation · Equivalence

N. Campbell
Centre for Socioeconomic Research, School of Pharmacy and Pharmaceutical Sciences, Cardiff, UK

F. Ali (✉) · A. Y. Finlay
Department of Dermatology and Wound Healing, School of Medicine, Cardiff University, Glamorgan House, Heath Park, Cardiff CF14 4XN, UK
e-mail: AliFM@cardiff.ac.uk

S. S. Salek
Department of Pharmacy, University of Hertfordshire, Hatfield and Institute for Medicines Development, Cardiff, UK

Introduction

Patient-reported outcome measures (PROs) [1] are increasingly being used in electronic format [2], but often without the instrument being validated using this format. This is potentially a major problem as users may unwittingly generate data that are invalid and scores may not be equivalent to the original paper-based method.

PROs are typically instruments completed by patients or sometimes by others on their behalf [3] and are traditionally paper based. However, electronic PRO (ePRO) instruments can be more convenient to patients, particularly where portable, and can provide real-time data recording and immediate scoring. Automated data entry makes them more convenient to clinicians and improves accuracy by removing human error [4]. Disadvantages, albeit increasingly less common, include patients being less comfortable or having difficulties with the use of electronic devices [2] or lack of availability of Wi-fi.

There is a need for these electronic versions to be validated against the original paper-based formats. This is because it is possible that the mode of delivery of questions may possibly influence the way in which they are answered. If this were so, then the scores and interpretation of the scores might differ depending on mode of delivery, resulting in unreliability of the measurement method. The evidence needed to support the measurement equivalence of different versions has been described [5]. "Equivalence" of two methods of delivering instruments is defined as follows: if a single user were to complete the same instrument by the two methods, the responses and subsequent scores would be the same. The level of evidence required depends on the amount of modification made to the original [5]. ISPOR guidance states that if the psychometric properties of a measure are likely to be impacted during the PRO migration process, then "the measure should be evaluated as if it were a new measure". The main recommendations include "tests of agreement" such as Kappa coefficient or intraclass correlation coefficient (ICC), mean score comparisons, distribution and variance of scores and internal consistency reliability where applicable [5]. Gwaltney et al. [6] undertook a meta-analysis on the subject, examining the literature published before 2007. Forty-six studies were included, and they concluded that written assessments were equivalent whether they were paper or computer based. However, technology has changed greatly since 2007 with the widespread use of smart phones and tablet computers [7, 8]. This review aims to identify and evaluate publications since 2007 that demonstrate the measurement equivalence of electronic versions of paper-based PRO instruments.

Materials and methods

The following databases were searched during March 2014: OvidSP, including the databases EMBASE, MEDLINE and PsycINFO; Web of Science, including Web of Science Core Collection, BIOSIS Citation Index, SciELO Citation Index and MEDLINE; and PubMed.

An identical set of keywords was used for every database that was searched, refined during two pilot searches. The keywords were: patient report* outcome OR quality of life; AND Internet OR touch screen OR web OR tablet OR computer OR electronic*; AND paper; AND questionnaire; AND compar* or equiv*.

The asterisk (*) represents a search on the stem of these words.

Abstracts of all identified articles were first reviewed. If an abstract indicated that the article might be relevant, the full-text article was retrieved and examined. The search was limited to papers published since 2007 to avoid overlap with Gwaltney et al. [6]. Full-text articles or abstracts which directly compared a screen-based electronic version of a validated PRO instrument with its paper-based original, with regard to their measurement equivalence, and publications in English were included. Studies which were published before 2007 or in other languages were excluded. Gwaltney et al. [6] had also excluded interactive voice response (IVR) formats: we likewise excluded IVR formats.

The most important factors were suggested by the lead author and joint agreement reached with all authors. We used a template to record relevant data from each publication and to record data concerning each instrument that was being validated. Where data for IVR formats were reported as part of a larger study, those data were excluded. It was difficult to identify whether stand-alone visual analogue scales (VAS) had been appropriately validated and it was occasionally clear that they had not [9]. Therefore, data from any VAS presented as a stand-alone measure were excluded. Data from validated instruments where items appeared as VAS were still included. Extracted data were tabulated in Microsoft Office Excel for Mac 2011. Data were classified according to the study and instrument characteristics and to the statistical measures used to demonstrate equivalence. Data regarding participant preferences, amount of missing data and completion times for each format were extracted. Data were extracted concerning whether the authors believed they had demonstrated equivalence, as described by the main ISPOR recommendations outlined in the Introduction. As there was very little consistency between the papers reviewed and as we were not able to examine original data, we chose to identify whether the formats under study were equivalent based on the own judgments of authors of the papers. However, the methods used were not consistent, and authors sometimes did not make it clear whether they believed they had found equivalence. Therefore, we had to make an informal assessment concerning the real outcome of such studies. To assess the quality of equivalence assessment undertaken, studies were compared against the recommendations of Coons et al. [5] (Fig. 1).

Different levels of evidence are required depending on the level of modification of the original instrument [5]. It was not always possible to judge how much of the originals had been adapted, so all electronic versions were assumed to be moderately adapted. To simplify analysis as selection criteria, only one relevant statistical method, according to the ISPOR recommendations, was chosen for each study type. However, to provide a wider picture, DIF and Bland–Altman analyses were also always included, if used. If a publication stated that randomisation was undertaken but no details were provided, it was assumed that the method used was appropriate.

Although the ISPOR guidance [5] distinguishes between weighted and un-weighted kappa coefficients, it was not

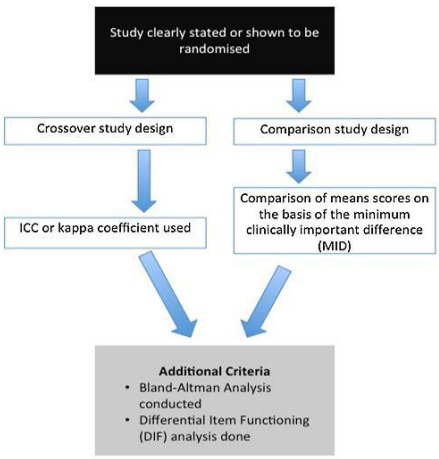


Fig. 1 Flow chart demonstrating the criteria used to assess quality of measurement equivalence techniques used in the literature

always clear which had been used and so if either one were present, this was judged as fitting this criterion.

Results

Database searching identified 501 studies, 55 of which were judged to be relevant according to the inclusion criteria. The way in which 501 abstracts were reduced to 55 is summarised in Fig. 2. Two papers were excluded due to their use of IVR format. Seventy-nine different relevant instruments were described across these publications (Appendix).

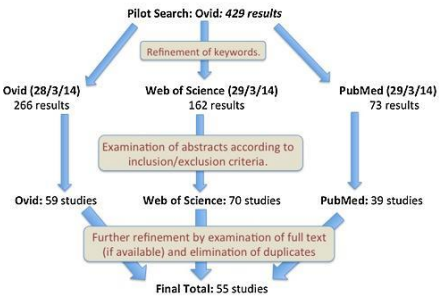


Fig. 2 Flow chart demonstrating the search strategy and filtering process

Of the 55 studies, 75 % (41) were full-text journal articles, with the remaining 25 % consisting of article and conference abstracts. Forty-seven (85 %) of the studies used a crossover study design, whereas six studies (11 %) used a comparison design. It was not clear which design had been used in two studies. Thirty-three (60 %) investigated only one instrument, with the largest number of instruments investigated in one study being 10 [10]. Eleven (20 %) studies used multiple sample sizes, usually employing a different sample size for each instrument investigated. The use of multiple sample sizes in the same study could lead to results having different statistical validities and reliabilities between questionnaires. However, such use was often unavoidable, for example: sometimes the number of patients eligible to complete certain surveys differed and sometimes the number of patients who were lost to follow up differed between questionnaires.

When transposing an instrument from written to an e-delivery format, logically nearly always some changes have to be made, for example instead of saying "Tick one box for each question", one needs to say "Choose one answer for each question" or perhaps this instruction is completely superfluous because the software will only accept one answer. It is a reasonable assumption to make that only moderate changes were made, though most authors did not give any specific information concerning this and so we are not able to identify whether these moderate changes influenced the degree of equivalence between written and e-delivery.

Instrument characteristics

Of the total of 79 PRO instruments identified 42 (53 %) were "condition specific"; 19 (24 %) were specialty specific; and 18 (23 %) were generic measures. The most commonly used instrument was the Short Form 36-item Health Survey (SF-36) that was employed in 10 studies: the version of the SF-36 that was used was not reported by most authors. However, it would be appropriate to assume that, if not mentioned by the authors, the most commonly used version (SF-36) has been employed. The most common format of ePROs tested within studies was the "Internet" (36 %), followed by "touch-screen computers" (20 %).

Overall conclusions of study authors

Forty-three studies (78 %) found equivalence between the standard paper-based PROs and the ePROs. Two studies (4 %) failed to find equivalence. In 10 studies (18 %), the authors' conclusions were not clear. For example, in one study, where two out of the three instruments investigated were not comparable, but one instrument showed

equivalence [11], authors concluded that different versions should not be used in the same trial and individual patient data should not be compared across different formats [12]. Though results for each format were similar on a group level, there was high variability at the individual patient level [13].

Statistical methods used

In examining how often different methods were used to demonstrate equivalence, 80 % (44) of studies used a correlation coefficient, with the most common being the ICC (Fig. 3).

Comparison with ISPOR recommendations

Twenty-five (47 %) publications appeared to fulfil the ISPOR recommended criteria [5] (Table 1). Of these, 60 % (15 studies) were randomised crossover studies that used an ICC or kappa coefficient to measure correlation. Two studies (8 %) were randomised comparison studies that analysed mean scores on the basis of the minimum clinically important difference (MCID). Six (24 %) provided Bland–Altman plots, and two of the reports described DIF analysis. Surprisingly, only 30 (55 %) of the 55 studies presented data on participant format preferences, 16 (29 %) provided comparisons of the amount of missing data, and 19 (35 %) provided data on completion times. On average, nine (47 %) studies reported longer completion times for ePROs, compared to five studies (26 %), which found paper-based PROs, took longer to complete.

Discussion

In the process of demonstrating measurement equivalence, crossover study design was the most commonly used and the commonest electronic format used was the Internet-based online version. It is important to note that in some cases, the authors did not indicate how or whether the Internet was accessed, in which case it was recorded as a separate "device". Most studies used a combination of different statistical tests with correlation coefficients being the most common; however, different authors may use

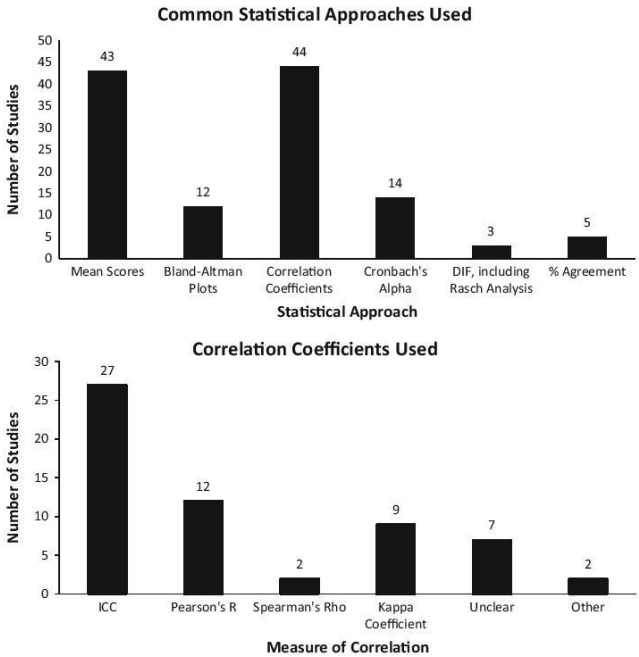


Fig. 3 Graphs presenting data regarding statistical methods used to demonstrate equivalence

Table 1 Number and percentage of studies that fulfilled ISPOR criteria

	Number of studies	Percentage of studies
Randomised crossover + ICC/Kappa coefficient	15	60
Randomised comparison + MID	2	8
Randomised studies + Bland–Altman analysis	6	24
Randomised studies + DIF	2	8
Total number of studies fitting criteria	25	100

different standards. For example, in one [14] of the two studies that stated no equivalence between formats, the authors used an ICC standard of 0.95 to identify concordance, which is higher than that recommended by ISPOR (0.70 at group level and 0.85–0.95 at individual). The authors state that they chose this higher criterion as it was slightly lower than the test–retest reliability value originally produced by the paper version [5].

There may be confusion concerning the interpretation of "equivalence". The strict scientific definition (if a single user were to complete the same instrument by the two methods, the responses and subsequent scores would be the same) may be replaced in practice by a much looser definition, allowing, say, a correlation of 0.8 between two methods of delivery. To clarify this, those reporting equivalence should define their usage of this term.

Less than half of the studies fulfilled the basic ISPOR recommendations [5]. A reason for the low number of studies identified as fitting these criteria may be that it was not always possible to tell whether the criteria had been met, particularly where only an abstract was available. For example, in Naus et al. [15] and Ribeiro et al. [16], which were both full-text journal articles, though the correlations between formats were analysed, the measure of correlation used was not specified.

As end users, patients should have a powerful role to play in influencing the type of assessment that they may be expected to complete. Patients who are already familiar with and comfortable interacting with electronic devices are more likely to prefer this format of delivery, but this should be confirmed by assessing patient preferences. However, patient involvement may not be appropriate in the question of "equivalence" as that requires prospective scientific evaluation. The majority of studies indicated that patients prefer the electronic formats, and comments from patients included that "the PDA was efficient and saved paper" [17]. Some patients suffering from reduced manual function found the touch-screen computer version easier to use [18]. The use of electronic formats is less prone to error, such as missing or ambiguous data entry. The ability to program data validation into the electronic software prevents such errors [19]. This may be considered a disadvantage where a patient deliberately wishes to avoid answering a question. However, it is possible to prevent this problem [17] by alerting patients if they skip any questions. Patients take a longer time to complete electronic versions. Possible explanations include patients' lack of familiarity with electronic devices and hence requiring assistance [10]. As people become more familiar with such devices, it is likely that this problem will diminish. A study limitation commonly identified by authors was the generalizability of their results to populations unfamiliar with the Internet. If Internet access was required for enrolment, participants may have been biased towards the educated and young [11].

A major limitation of the studies reviewed here was the lack of detail provided by authors concerning methodology, for example, over which statistical techniques were utilised [15]. In reviewing such literature in future, it would be of interest to consider patient preference, as the acceptability of electronic formats is essential if they are going to be of practical use. As suggested by Gwaltney et al. [6], a more accurate way to determine whether studies had truly identified equivalence would be to define numerical standards for the statistical methods used and to judge study data directly against these.

Good practice recommendations [5] state that every new electronic version should be validated before use. As two studies did not identify equivalence [14, 20] and 10 studies had ambiguous findings [11–13, 15, 21–26], validation of electronic versions should still be carried out, even though this work indicates that electronic versions are usually judged to be equivalent to the original version.

It is important to highlight some of the similarities and differences between this review and that published by Gwaltney et al. [6] (Table 2). IVR formats were excluded in both reviews as auditory transference of ePROs from a written format presents lower probabilities of equivalence. ICC was identified as the most commonly used correlation technique in both reviews, with a majority of the studies demonstrating equivalence. We also agree with Gwaltney et al. [6] that details of how items were altered to be presented in an electronic format were not elucidated within the individual studies. Therefore, situations where formats of instruments are drastically changed cannot be accounted for in terms of equivalence. Further studies which employ cognitive interviews may be useful to determine whether such changes influence the way in which assessments are

Table 2 Key comparisons with the Gwaltney et al. review [5]

	Gwaltney et al. [5]	Present study
Review year range	Pre-2007	2007–2014
Total studies reviewed	46	55
Most common correlation coefficient used	Intraclass correlation coefficient (ICC)	Intraclass correlation coefficient (ICC)
Number of different instruments identified	278	79
Number of different electronic modalities identified	3	5
	(PC/laptop, PDA, tablet)	(Internet, tablet, computer, touch-screen computer, PDA)

answered. Our review also identified several studies that employed "tablets" and "touch-screen" devices compared to the review by Gwaltney et al. [6]. The use of tablets and touch-screen formats has seen a rise mostly in the last few years, accounting for this disparity. However, whether this innovation in delivery format of PRO instruments provides an additional advantage to that of standard electronic data entry methods needs to be further examined. Both reviews, however, suggest that most studies find equivalence between electronic and paper-based versions of patient-reported outcomes.

ePRO instruments have an expanding role in the provision of patient-centred care, both in clinical practice and by providing a way to gather information from patients during clinical trials. The advantages of computerising paper-based PRO instruments are extensive: they have benefits to patients, such as convenience, and benefits to clinicians and researchers, as they can save time, manpower and money. They can also remove sources of error created when data from paper-and-pencil formats are manually transferred to computer databases. As the public become more experienced in the use of technology, ePRO instruments have high acceptability and are commonly preferred by patients over paper-based versions of the same instrument. There are PRO instruments originally developed in electronic formats [27], thereby not requiring equivalence testing.

There may be disadvantages to computerising PRO instruments, though it appears that fears of computer aversion may be overestimated. The transfer of a PRO instrument to an electronic format may require new psychometric assessment, in order to prove that measurement properties such as reliability and validity are equal or improved from those of the original version. The degree of assessment required depends on the amount of change that is made to the instrument, but major change may require full psychometric evaluation. However, the evidence suggests that where changes appear to have been relatively minor or moderate, equivalency in psychometric values is retained. Gwaltney et al's [6] and our review provide evidence that paper-based and electronic versions of the same measure are comparable and that therefore computerising paper-based PRO instruments is a successful and worthwhile step.

Conflict of interest AYF is joint copyright owner of the DLQI.

Appendix

See Table 3.

Table 3 Reviewed articles

Study authors	Publication type	Relevant instruments investigated	Country	Analysed sample size	Sample size calculation	Study population	Study design	Electronic format
Beaumont et al. [28]	Journal article	COPD Population Screener (COPD-PS)	USA	1006	Y	General population	R Comparison	Internet
Bernstein et al. [29]	Journal article	Sexual Health Inventory for Men (SHIM)	USA	116	N	Male patients	Crossover	Internet
Bruce and Fries [30]	Conference abstract	Health Assessment Questionnaire: Disability Index (HAQ: DI)	USA	378	N	Patients	Comparison	Internet

Table 3 continued

Study authors	Publication type	Relevant instruments investigated	Country	Analysed sample size	Sample size calculation	Study population	Study design	Electronic format
Carlbring et al. [21]	Journal article	Body Sensations Questionnaire (BSQ)	Sweden	Multiple	N	Patients	R Crossover	Internet
		Agoraphobic Cognitions Questionnaire (ACQ)						
		Mobility Inventory (MI)						
		Beck Anxiety Inventory (BAI)						
		Beck Depression Inventory (BDI)						
		Quality of Life Inventory (QOLI)						
		Montgomery Asberg Depression Rating Scale-self-rated (MADRS-S)						
Chang et al. [31]	Journal article	EORTC QLQ-PR25	Taiwan	99	Y	Patients	R Crossover	Touch-screen computer
Chen et al. [33]	Journal article	Short Form-36 (SF-36)	China	150	Y	Patients + university students	R Crossover	Unclear
Chen et al. [34]	Journal article	Short WHO Quality of Life Assessment (WHOQOL-BREF)	Taiwan	72	N	Nurses	Crossover	Internet
Chen and Li [35]	Journal article	Short Form-36 (SF-36)	China	100	N	University students	Crossover	Computer
Chen et al. [32]	Conference abstract	Urogenital Distress Inventory (UDI-6)	China	81	N	Patients	Crossover	Internet
		Incontinence Impact Questionnaire (HQ-7)						
		Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12)						
Clayer and Davis [22]	Journal article	Toronto Extremity Salvage Score (TESS)	Australia	46	N	Patients	Crossover	Internet
Dalal et al. [36]	Journal article	Lung Function Questionnaire (LFQ)	USA	48	Y	General population	R Crossover	Internet
Dinkel et al. [37]	Journal article	Stress Index RadioOncology (SIRO)	Germany	177	N	Patients	Crossover	Tablet
Frennered et al. [23]	Journal article	EuroQol-5 Dimension (EQ-5D)	Sweden	Multiple	N	Patients	Crossover	Touch-screen computer
		General Function Score (GFS)						
		Short Form-36 (SF-36)						
		Zung Depression Scale (ZDS)						
Gudsburgen et al. [38]	Journal article	Knee Injury and Osteoarthritis Outcome Score (KOOS)	Denmark	20	Y (for KOOS)	Patients	R Repeated Crossover	Touch-screen computer
		Short Form-36 (SF-36)						
		Physical Activity Scale						
		painDETECT						
		Activity of Daily Living Questionnaire (ADL)						

Table 3 continued

Study authors	Publication type	Relevant instruments investigated	Country	Analysed sample size	Sample size calculation	Study population	Study design	Electronic format
Handa et al. [19]	Journal article	Pelvic Floor Distress Inventory (PFDI-20)	USA	43	Post hoc power analysis	Female patients	R Crossover	Internet
		Pelvic Floor Impact Questionnaire (PFIQ-7)						
Hedman et al. [39]	Journal article	Liebowitz Social Anxiety Scale-Self Report (LSAS-SR)	Sweden	Multiple	N	Patients	Comparison	Internet
		Social Phobia Scale (SPS)						
		Social Interaction Anxiety Scale (SIAS)						
		Montgomery-Asberg Depression Rating Scale-Self-Rated (MADRS-S)						
		Beck Anxiety Inventory (BAI)						
		Quality of Life Inventory (QOLI)						
Heiberg et al. [40]	Journal article	Rheumatoid Arthritis Disease Activity Index (RADAI)	Norway	38	N	Patients	R Repeated Crossover	PDA
		Modified Health Assessment Questionnaire (MHAQ)						
		Short Form-36 (SF-36)						
Holländare et al. [41]	Journal article	Montgomery-Asberg Depression Rating Scale-Self-Rated (MADRS-S)	Sweden	87	N	Patients	Crossover	Internet
		Beck Depression Inventory (BDI)						
Hollen et al. [42]	Journal article	Lung Cancer Symptom Scale (LCSS)	USA	86	Y	Patients	Crossover	PDA
Howell et al. [43]	Journal article	Satisfaction with Life Scale (SWLS)	USA	173	N	University students	Comparison	Internet
		Subjective Happiness Scale (SHS)						
Juniper et al. [12]	Journal article	Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S))	Denmark	70	N	Patients	R Crossover	PDA
Juniper et al. [14]	Journal article	Asthma Quality of Life Questionnaire (AQLQ(S))	Canada	Multiple	N	Patients	R Crossover	PDA
		Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S))						
		Asthma Control Questionnaire (ACQ)						
Lalanne et al. [44]	Conference abstract	PROQOL-HIV	France	58	N	Patients	R Crossover	Unclear
Lee [45]	Journal article	Cancer-Specific Quality-of-Life Questionnaire (C-QOL)	South Korea	105	Y	Patients	R Crossover	Touch-screen computer
Lee [46]	Abstract	Asthma-Specific Quality-of-Life Questionnaire (A-QOL)	South Korea	261	N	Patients	R Crossover	Touch-screen computer
Lee et al. [47]	Journal article	Diabetes-Specific Quality-of-Life Questionnaire (D-QOL)	South Korea	208	Y	Patients	R Crossover	Touch-screen computer

Table 3 continued

Study authors	Publication type	Relevant instruments investigated	Country	Analysed sample size	Sample size calculation	Study population	Study design	Electronic format
Mackenzie et al. [10]	Journal article	Health Assessment Questionnaire (HAQ)	Canada	Multiple	N	Patients	R Crossover	Internet
		Short Form-36 (SF-36)						
		Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)						
		Bath Ankylosing Spondylitis Functional Index (BASFI)						
		Bath Ankylosing Spondylitis Global Score (BAS-G)						
		Ankylosing Spondylitis Quality of Life Instrument (ASQoL)						
		Modified Fatigue Severity Scale (mFSS)						
		Functional Assessment of Chroinc Illness Therapy (FACIT)						
		Dermatology Life Quality Index (DLQI)						
		EuroQol-5 Dimension (EQ-5D)						
Matthew et al. [17]	Journal article	International Prostate Symptom Score (IPSS)	Canada	Multiple	N	Patients	R Crossover	PDA
		International Index of Erectile Function-5 (IIEF-5)						
		Patient Orientated Prostate Cancer Utility (PORPUS)						
Minard et al. [48]	Conference abstract	Pediatric Caregiver's Asthma Quality of Life (PCAQLQ)	Canada	25	N	Caregivers of child patients	R Crossover	Unclear
Minard et al. [49]	Conference abstract	Mini Pediatric Asthma Quality of Life (Mini PAQLQ)	Canada	18	N	Child patients	R Crossover	Unclear
Naus et al. [15]	Journal article	Beck Depression Inventory (BDI)	USA	76	N	Female university students	R Crossover	Computer
		Short Form-36 (SF-36)						
		Neo-Five Factor Inventory (NEO-FFI)						
Olajos-Clow et al. [50]	Journal article	Mini-Asthma Quality of Life (MiniAQLQ)	Canada	40	Interim analysis	Patients	R Crossover	Computer
Oliveira et al. [51]	Abstract	EORTC-QLQ C30	Portugal	200	N	Patients	Crossover	Touch-screen computer
Oliveira et al. [24]	Journal article	EORTC-QLQ C30	Portugal	193	N	Patients	Unclear	Touch-screen computer
Parnell et al. [52]	Journal article	Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12)	USA	50	Post hoc power analysis	Female patients	R Crossover	Internet
Raat et al. [53]	Journal article	Child Health Questionnaire-Child Form (CHQ-CF)	Netherlands	933	N	Children	R Comparison	Internet

Table 3 continued

Study authors	Publication type	Relevant instruments investigated	Country	Analysed sample size	Sample size calculation	Study population	Study design	Electronic format
Ribeiro et al. [16]	Journal article	Short Form-36 (SF-36)	Portugal	50	N	Patients	Crossover	Touch-screen computer
Ribeiro et al. [54]	Conference abstract	Short Form-36 (SF-36)	Portugal	91	N	Patients	Unclear	Unclear
Richter et al. [55]	Journal article	Hannover Functional Questionnaire (FFbH)	Germany	Multiple	N	Patients	R Crossover	Tablet
		Health Assessment Questionnaire (HAQ)						
		Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)						
		Short Form-36 (SF-36)						
Ring et al. [13]	Abstract	Functional Assessment of Cancer Therapy-Lung (FACT-L)	UK	50	N	Patients	R Crossover	Unclear (Handheld device)
		EuroQol-5 Dimension (EQ-5D)						
Sage et al. [56]	Conference abstract	Rheumatology Paediatric Quality of Life Inventory (RHE-PedsQL)	USA	Multiple	N	Child + adult patients	Crossover	Tablet
		Review of Systems Symptom Checklist (ROS)						
Salaffi et al. [9]	Journal article	Recent-Onset Arthritis Disability (ROAD)	Italy	87	N	Patients	R Crossover	Touch-screen computer
Salaffi et al. [57]	Journal article	Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Italy	55	N	Patients	Crossover	Tablet
		Bath Ankylosing Spondylitis Functional Index (BASFI)						
Saunders et al. [25]	Journal article	Attitudes towards Loss of Hearing Questionnaire (ALHQ)	USA	100	N	Patients	Crossover	Computer
Schefte and Hetland [18]	Journal article	Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Denmark	Multiple	N	Patients	R Crossover	Touch-screen computer
		Bath Ankylosing Spondylitis Functional Index (BASFI)						
		Health Assessment Questionnaire (HAQ)						
Schemmann et al. [58]	Conference abstract	International Hip Outcome Score-12 (iHOT-12)	Germany	60	N	Patients	Unclear	Tablet
Silveira et al. [26]	Abstract	EORTC-QLQ C30	Portugal	54	N	Patients	Crossover	Computer
		EORTC-H&N35						
Sjöstrom et al. [59]	Journal article	ICIQ Lower Urinary Tract Symptoms Quality-of-Life (ICIQ-LUTSqol)	Sweden	54	N	Patients	Crossover	Internet
Swartz et al. [20]	Journal article	Center for Epidemiological Studies Depression Scale (CES-D)	USA	756	Rationale detailed	Patients	R Crossover	PDA

Table 3 continued

Study authors	Publication type	Relevant instruments investigated	Country	Analysed sample size	Sample size calculation	Study population	Study design	Electronic format
Twiss et al. [60]	Conference abstract	Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)	USA	147	N	Patients	Comparison	Unclear
Varni et al. [61]	Journal article	Pediatric Quality of Life Inventory (PedsQL™) (Generic Core Scales): Child Self-Report Pediatric Quality of Life Inventory (PedsQL™): Parent Proxy-Report	USA	Multiple	N	Child patients + caregivers	R Crossover	Internet
Vinney et al. [62]	Journal article	Pediatric Quality of Life Inventory (PedsQL™)	USA	19	Y	Children: General population + patients	R Crossover	PDA
Wu et al. [11]	Journal article	Kansas City Cardiomyopathy Questionnaire (KCCQ) Minnesota Living with Heart Failure Questionnaire (MLHFQ) Self-Care of Heart Failure Index (SCHFI)	Canada	Multiple	Y (for KCCQ)	Patients	R Crossover	Internet
Young et al. [63]	Journal article	Activities Scale for Kids (Performance Version) (ASK) Pediatric Quality of Life Inventory (PedsQL) (Generic Core Scales)	Canada	69	N	Child patients	R Crossover	Internet
Zimmerman and Martinez [64]	Abstract	Clinically Useful Depression Outcome Scale (CUDOS)	USA	53	N	Patients	Crossover	Internet

References

1. Center for Drug Evaluation and Research (CDER). (2009). *Guidance for industry—patient-reported outcome measures: Use in medical product development to support labeling claims*. Silver Spring: Food and Drug Administration.
2. Leidy, N. K., & Vernon, M. (2008). Perspectives on patient-reported outcomes: content validity and qualitative research in a changing clinical trial environment. *Pharmacoeconomics, 26*(5), 363–370.
3. Marshall, S., Haywood, K., & Fitzpatrick, R. (2006). Impact of patient-reported outcome measures on routine practice: A structured review. *Journal of Evaluation in Clinical Practice, 12*(5), 559–568.
4. Lee, S. J., Kavanaugh, A., & Lenert, L. (2007). Electronic and computer-generated patient questionnaires in standard care. *Best Practice and Research Clinical Rheumatology, 21*(4), 637–647.
5. Coons, S. J., Gwaltney, C. J., Hays, R. D., Lundy, J. J., Sloan, J. A., Revicki, D. A., et al. (2009). Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO good research practices task force report. *Value in Health, 12*(4), 419–429.
6. Gwaltney, C. J., Shields, A. L., & Shiffman, S. (2008). Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: A meta-analytic review. *Value in Health, 11*(2), 322–333.
7. Arthur, C. (2012). The history of smartphones: timeline. *The Guardian*, 24 January 2012 (Online). http://www.theguardian.com/technology/2012/jan/24/smartphones-timeline. Accessed 2 May 2014.
8. McLellan, C. (2014). *The History of Tablet Computers: A timeline* (Online). http://www.zdnet.com/the-history-of-tablet-computers-a-timeline-7000026555/. Accessed 2 May 2014.
9. Salaffi, F., Gasparini, S., & Grassi, W. (2009). The use of computer touch-screen technology for the collection of the patient-reported outcome data in rheumatoid arthritis: Comparison to standardised patient questionnaires. *Clinical and Experimental Rheumatology, 27*(3), 459–468.
10. MacKenzie, H., Thavaneswaran, A., Chandran, V., & Gladman, D. D. (2011). Patient-reported outcome in psoriatic arthritis: A comparison of web-based versus paper-completed questionnaires. *The Journal of Rheumatology, 38*(12), 2619–2624.
11. Wu, R. C., Thorpe, K., Math, M., Ross, H., Micevski, V., Marquez, C., Straus, S. E. (2009). Comparing administration of questionnaires via the Internet to pen-and-paper in patients with heart failure: Randomised controlled trial. *Journal of Medical Internet Research* (Online), 11(1). http://www.jmir.org/2009/1/e3/. Accessed 1 May 2014.
12. Juniper, E. F., Riis, B., & Juniper, B. A. (2007). Development and validation of an electronic version of the Rhinoconjunctivitis quality of life questionnaire. *Allergy, 62*(9), 1091–1093.
13. Ring, A. E., Cheong, K. A., Watkins, C. L., Meddis, D., Cella, D., & Harper, P. G. (2008). A randomised study of electronic diary versus paper and pencil collection of patient-reported outcomes in patients with non-small cell lung cancer. *The Patient: Patient-Centered Outcomes Research, 1*(2), 105–113.

14. Juniper, E. F., Langlands, J. M., & Juniper, B. A. (2009). Patients may respond differently to paper and electronic versions of the same questionnaires. *Respiratory Medicine, 103*(6), 932–934.
15. Naus, M. J., Philipp, L. M., & Samsi, M. (2009). From paper to pixels: A comparison of paper and computer formats in psychological assessment. *Computers in Human Behavior, 25*(1), 1–7.
16. Ribeiro, C., Moreira, L., Silveira, A., Silva, I., Gestal, J., & Vasconcelos, C. (2010). Development and use of touch-screen computer-assisted self-interview in Portuguese patients with chronic immune disease: Evaluation of an electronic version of SF-36v2. *Acta Reumatológica Portuguesa, 35*(2), 208–214.
17. Matthew, A. G., Currie, K. L., Irvine, J., Ritvo, P., Mina, D. S., Jamnicky, L., Nam, R., Trachtenberg, J. (2007). Serial personal digital assistant data capture of health-related quality of life: A randomised controlled trial in a prostate cancer clinic. *Health and Quality of Life Outcomes* (Online), 5(38). http://www.hqlo.com/content/5/1/38. Accessed 30 April 2014.
18. Schefte, D. B., & Hetland, M. L. (2010). An open-source, self-explanatory touch screen in routine care. Validity of filling in the bath measures on ankylosing spondylitis disease activity index, function index, the health activity index, function index, the health assessment questionnaire and visual analogue scales in comparison with paper versions. *Rheumatology, 49*(1), 99–104.
19. Handa, V. L., Barber, M. D., Young, S. B., Aronson, M. P., Morse, A., & Cundiff, G. W. (2008). Paper versus web-based administration of the pelvic floor distress inventory 20 and the pelvic floor impact questionnaire 7. *International Urogynecology Journal, 19*(10), 1331–1335.
20. Swartz, R. J., Moor, C. D., Cook, K. F., Fouladi, R. T., Basen-Engquist, K., Eng, C., & Taylor, C. L. C. (2007). Mode effects in the center for epidemiological studies depression (CES-D) scale: Personal digital assistant versus paper and pencil administration. *Quality of Life Research, 16*(5), 803–813.
21. Carlbring, P., Brunt, S., Bohman, S., Austin, D., Richards, J., Öst, L.-G., & Andersson, G. (2007). Internet versus paper and pencil administration of questionnaires commonly used in panic/agoraphobia research. *Computers in Human Behaviour, 23*(3), 1421–1434.
22. Clayer, M., & Davis, A. (2011). Can the Toronto extremity salvage score produce reliable results when used online? *Clinical Orthopaedics and Related Research, 469*(6), 1750–1756.
23. Frennered, K., Hägg, O., & Wessberg, P. (2010). Validity of a computer touch-screen questionnaire system in back patients. *Spine, 35*(6), 697–703.
24. Oliveira, A., Ferreira, P. L., Antunes, B., & Pimentel, F. L. (2011). OnQol: Electronic device to capture QoL data in oncology: Difference between patients 65 years or older and patients younger than 65 years of age. *Journal of Geriatric Oncology, 2*(4), 253–258.
25. Saunders, G., Forsline, A., & Jacobs, P. (2007). The Attitudes towards Loss of Hearing Questionnaire (ALHQ): A comparison of paper and electronic formats. *The Journal of the American Academy of Audiology, 18*(1), 66–77.
26. Silveira, A., Gonçalves, J., Sequeira, T., Ribeiro, C., Lopes, C., Monteiro, E., & Pimentel, F. L. (2011). Computer-based quality-of-life monitoring in head and neck cancer patients: A validation model using the EORTC-QLQ C30 and EORTC-H&N35 Portuguese PC-software version. *Acta Médica Portuguesa, 24*(S2), 347–354.
27. Wright, E. P., Kiely, M., Johnston, C., Smith, A. B., Cull, A., & Selby, P. J. (2005). Development and evaluation of an instrument to assess social difficulties in routine oncology practice. *Quality of Life Research, 14*(2), 373–386.
28. Beaumont, J. L., Victorson, D., Su, J., Baker, C. L., Wortman, K., Shah, H., & Cella, D. (2011). Examining web equivalence and risk factor sensitivity of the COPD Population Screener. *Value in Health, 14*(4), 506–512.
29. Bernstein, A. N., Levinson, A. W., Hobbs, A. R., Lavery, H. J., & Samadi, D. B. (2013). Validation of online administration of the sexual health inventory for men. *The Journal of Urology, 189*(4), 1456–1461.
30. Bruce, B., & Fries, J. F. (2011). Internet versus mailed administration of the health assessment questionnaire disability index. 63(10), pp. S1–S1 256.
31. Chang, Y-J., Chang, C-H., Peng, C-L., Wu, H-C., Lin, H-C., Wang, J-Y., Li, T-C., Yeh, Y-C., Liang, W-M. (2014). Measurement equivalence and feasibility of the EORTC QLQ-PR25: paper-and-pencil versus touch-screen administration. *Health and Quality of Life Outcomes* (Online), 12(23). http://www.hqlo.com/content/12/1/23. Accessed 29 April 2014.
32. Chen, H-L., Tien, S-W., Shih, C-C. (2011). Paper questionnaire versus Web questionnaire for clinical research impact using the short form of the UDI-6, HQ-7, PISQ-12. *International Conference on Engineering and Business Management (EBM2011)*, 1–6, pp. 1293–1297.
33. Chen, T-h, Li, L., Sigle, J. M., Du, Y.-P., Wang, H.-M., & Lei, J. (2007). Crossover randomised controlled trial of the electronic version of the Chinese SF-36. *Journal of Zheijang University Science B, 8*(8), 604–608.
34. Chen, W.-C., Wang, J.-D., Hwang, J.-S., Chen, C.-C., Wu, C.-H., & Yao, G. (2009). Can the web-form WHOQOL-BREF be an alternative to the paper-form? *Social Indicators Research, 94*(1), 97–114.
35. Chen, T-h, & Li, L. (2010). Pilot study of equivalence between the electronic and paper version of the Chinese SF-36. *Journal of Happiness Studies, 11*(2), 151–161.
36. Dalal, A. A., Nelson, L., Gilligan, T., McLeod, L., Lewis, S., & De Muro-Mercon, C. (2011). Evaluating patient-reported outcome measurement comparability between paper and alternative versions, using the lung function questionnaire as an example. *Value in Health, 14*(5), 712–720.
37. Dinkel, A., Berg, P., Pirker, C., Geinitz, H., Sehlen, S., Emrich, M., et al. (2010). Routine psychosocial distress screening in radiotherapy: implementation and evaluation of a computerised procedure. *British Journal of Cancer, 103*, 1489–1495.
38. Gudbergsen, H., Bartels, E. M., Krusager, P., Waehrens, E. E., Christensen, R., Danneskoild-Samsöe, B., Bliddal, H. (2011). Test-retest of computerised health status questionnaires frequently used in the monitoring of knee osteoarthritis: a randomised crossover trial. *BMC Musculoskeletal Disorders* (Online), 12(190). http://www.biomedcentral.com/1471-2474/12/190. Accessed 29 April 2014.
39. Hedman, E., Ljótsson, B., Rück, C., Furmark, T., Carlbring, P., Lindefors, N., & Andersson, G. (2010). Internet administration of self-report measures commonly used in research on social anxiety disorder: A psychometric evaluation. *Computers in Human Behaviour, 26*(4), 736–740.
40. Heiberg, T., Kvien, T. K., Dale, Ø., Mowinckel, P., Aanerud, G. J., Songe-Møller, A. B., et al. (2007). Daily health status registration (patient diary) in patients with rheumatoid arthritis: A comparison between personal digital assistant and paper-pencil format. *Arthritis Care & Research, 57*(3), 454–460.
41. Holländare, F., Andersson, G., Engström, I. (2010). A comparison of psychometric properties between Internet and paper versions of two depression instruments (BDI-II and MADRS-S) administered to clinic patients. *Journal of Medical Internet Research* (Online), 12(5). http://www.jmir.org/2010/5/e49/. Accessed 1 May 2014.
42. Hollen, P. J., Gralla, R. J., Stewart, J. A., Meharchand, J. M., Wierzbicki, R., & Leighl, N. (2013). Can a computerised format replace a paper form in PRO and HRQL evaluation? Psychometric testing of the computer-assisted LCSS instrument (eLCSS-QL). *Supportive Care in Cancer, 21*(1), 165–172.

43. Howell, R. T., Rodzon, K. S., Kurai, M., & Sanchez, A. H. (2010). A validation of well-being and happiness surveys for administration via the Internet. *Behaviour Research Methods, 42*(3), 775–784.
44. Lalanne, C., Herrmann, S., Armstrong, A. R., Cheung-Lung, C., Schwartz, Y., Chassany, O., & Duracinsky, M. (2013). Paper-based and electronic assessment of health-related quality of life specific HIV disease: A reliability study with the PROQOL-HIV questionnaire. *Value in Health, 16*(7), A362.
45. Lee, E.-H. (2009). Touch-screen computerised quality-of-life assessment for patients with cancer. *Asian Nursing Research, 3*(1), 41–48.
46. Lee, E.-H. (2009). Computerised measurement for asthma-specific quality of life: Comparison with a conventional paper-and-pencil questionnaire. *Journal of Korean Academy Nursing, 39*(6), 781–787.
47. Lee, E-H., Lee, Y.W., Lee, K-W., Kim, D.J., Kim, Y-S., Nam, M-S. (2013). Measurement equivalence of touch-screen computerised and paper-based diabetes-specific quality-of-life questionnaires. *International Journal of Nursing Practice* (Online). http://onlinelibrary.wiley.com/doi/10.1111/ijn.12184/abstract. Accessed 30 April 2014.
48. Minard, J. P., Thomas, N., Olajos-Clow, J., Juniper, E. F., Jiang, X., Jenkins, B., Taite, A. K., Turcotte, S., Lougheed, M. D. (2011)a. Validation of an electronic version of the Pediatric Caregiver's Asthma Quality of Life Questionnaire (PACQLQ). *American Journal of Respiratory and Critical Care Medicine* (Online),183. http://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2011.183.1_MeetingAbstracts.A1432. Accessed 30 April 2014.
49. Minard, J.P., Thomas, N., Olajos-Clow, J., Juniper, E. F., Jiang, X., Jenkins, B., Taite, A. K., Turcotte, S., Lougheed, M. D. (2011)b. Validation of an electronic version of the Mini Pediatric Asthmas Quality of Life Questionnaire (Mini PAQLQ). *American Journal of Respiratory and Critical Care Medicine* (Online). http://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2011.183.1_MeetingAbstracts.A1433. Accessed 30 April 2014.
50. Olajos-Clow, J., Minard, J., Szpiro, K., Juniper, E. F., Turcotte, S., Jiang, X., et al. (2010). Validation of an electronic version of the Mini Asthma quality of life questionnaire. *Respiratory Medicine, 104*(5), 658–667.
51. Oliveira, A., Ferreira, P. L., Antunes, B., & Pimentel, F. L. (2010). Quality of life in oncology: Electronic device to collect data. *Acta Médica Portuguesa, 23*(6), 1017–1024.
52. Parnell, B. A., Dunivan, G. C., Connolly, A., Jannelli, M. L., Wells, E. C., & Geller, E. J. (2011). Validation of web-based administration of the pelvic organ prolapse/urinary incontinence sexual function questionnaire (PISQ-12). *International Urogynecology Journal, 22*(3), 357–361.
53. Raat, H., Mangunkusumo, R. T., Landgraf, J. M., Kloek, G., & Brug, J. (2007). Feasibility, reliability and validity of adolescent health status measurement by the Child Health Questionnaire Child Form (CHQ-CF): Internet administration compared with the standard paper version. *Quality of Life Research, 16*(4), 675–685.
54. Ribeiro, C., Silveira, A., Silva, I., Ribeiro, C., Gestal, J., & Vasconcelos, C. (2011). Computerised information-gathering in patients with lupus: An initial evaluation of an electronic version of the short form 36 version 2. *Lupus, 20*(4), 402.
55. Richter, J. G., Becker, A., Koch, T., Nixdorf, M., Willers, R., Monser, R., et al. (2008). Self-assessments of patients via Tablet PC in routine patient care: Comparison with standardised paper questionnaires. *Annals of the Rheumatic Diseases, 67*(12), 1739–1741.
56. Sage, J. M., Ali, A., Farrell, J., Huggins, J. L., Covert, K., Eskra, D., et al. (2012). Moving into the electronic age: Validation of rheumatology self-assessment questionnaires on tablet computers. *Arthritis and Rheumatism, 64*(S10), S1102.
57. Salaffi, F., Gasparini, S., Ciapetti, A., Gutierrez, M., & Grassi, W. (2013). Usability of an innovative and interactive electronic system for collection of patient-reported data in axial spondyloarthritis: Comparison with the traditional paper-administered format. *Rheumatology, 52*(11), 2062–2070.
58. Schemmann, D., Rudolph, J., Haas, H., & Müller-Stromberg, J. (2013). Validation and patient acceptance of a touch tablet version of the iHOT-12 questionnaire. *Arthroscopy, 29*(12), E188.
59. Sjöstrom, M., Stenlund, H., Johansson, S., Umefjord, G., & Samuelsson, E. (2012). Stress urinary incontinence and quality of life: A reliability study of a condition-specific instrument in paper and web-based versions. *Neurology and Urodynamics, 31*(8), 1242–1246.
60. Twiss, J., McKenna, S., Graham, J. E., Swetz, K. M., Sloan, J., & Gomberg-Maitland, M. (2013). Assessing measurement equivalence of different forms of administration of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) using Rasch analysis. *Value in Health, 16*(7), A606.
61. Varni, J. W., Limbers, C. A., Burwinkle, T. M., Bryant, W. P., & Wilson, D. P. (2008). The ePedsQL™ in Type 1 and Type 2 diabetes: Feasibility, reliability, and validity of the Pediatric Quality of Life Inventory™ Internet administration. *Diabetes Care, 31*(4), 672–677.
62. Vinney, L. A., Grade, J. D., & Connor, N. P. (2012). Feasibility of using a handheld electronic device for the collection of patient reported outcomes data from children. *Journal of Communication Disorders, 45*(1), 12–19.
63. Young, N. L., Varni, J. W., Snider, L., McCormick, A., Sawatzky, B., Scott, M., et al. (2009). The Internet is valid and reliable for child-report: An example using the Activities scale for kids (ASK) and the Pediatric quality of life inventory (PedsQL). *Journal of Clinical Epidemiology, 62*(3), 314–320.
64. Zimmerman, M., & Martinez, J. H. (2012). Web-based assessment of depression in patients treated in clinical practice: Reliability, validity and patient acceptance. *Journal of Clinical Psychiatry, 73*(3), 333–338.

4) Ali, F.M., Johns, N., Finlay, A.Y., Salek, M.S. and Piguet, V., 2017. Comparison of the paper-based and electronic versions of the Dermatology Life Quality Index: evidence of equivalence. *British Journal of Dermatology*, *177*(5), pp.1306-1315.

QUALITATIVE RESEARCH

BJD
British Journal of Dermatology

Comparison of the paper-based and electronic versions of the Dermatology Life Quality Index: evidence of equivalence

F.M. Ali,[1] N. Johns,[1,2] A.Y. Finlay,[1] M.S. Salek[3,4] and V. Piguet[1]

[1]Department of Dermatology and Wound Healing, Division of Infection and Immunity, School of Medicine, Cardiff University, Cardiff, U.K.
[2]Faculty of Pharmaceutical Sciences and Melatonin Research Group, Khon Kaen University, Khon Kaen, Thailand
[3]School of Life and Medical Sciences, University of Hertfordshire, Hatfield, U.K.
[4]Institute for Medicines Development, Cardiff, U.K.

Correspondence
Faraz Ali.
E-mail: alifm@cardiff.ac.uk

Accepted for publication
18 January 2017

Funding sources
The study was supported by a research grant from Janssen Pharmaceutica NV.

Conflicts of interest
A.Y.F. is joint copyright owner of the Dermatology Life Quality Index for which Cardiff University (grant no: 509937) and A.Y.F. receive royalties.

DOI 10.1111/bjd.15314

Summary

Background The use of patient-reported outcome measures in electronic format has been increasing. However, these formats are usually not validated or compared with the original paper-based formats, so there is no evidence that they are completed in the same way.

Objectives To compare the conventional paper version with a web-based application (iPad®) version of the Dermatology Life Quality Index (DLQI) to assess equivalence of scores.

Methods The study employed a randomized crossover design using a within-subjects comparison of the two formats of the questionnaire. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines were followed. Participants aged over 18 years with any confirmed skin condition were recruited from a teaching hospital dermatology outpatient clinic. Expected intraclass correlation coefficient (ICC) was 0·9 (α = 0·05).

Results A total of 104 patients were recruited, median age 53·5 years (interquartile range 37·3–67·8; 43% male). The ICC showed high concordance between the total DLQI scores from paper and iPad versions (ICC 0·98; 95% confidence interval 0·97–0·99). Patients took a median of 78 s to complete the electronic version and 73 s for paper (P = 0·008): 76% preferred the electronic version and perceived completion to take a shorter time.

Conclusions There is high concordance and thus equivalence between the iPad and paper versions of the DLQI, with an ICC of 0·98, and a clear patient preference for the iPad version.

What's already known about this topic?

- The use of patient-reported outcome measures (PROs) in electronic format has been increasing.
- Electronic formats are usually not validated or compared with their original paper-based formats, but are assumed without evidence to be comparable.
- The benefits of using electronic PROs include portability, real-time monitoring of patients' quality of life and improved data capture.

What does this study add?

- There is equivalence between completing the Dermatology Life Quality Index (DLQI) on paper and in an electronic format.
- Patients prefer the electronic format to the paper version although the electronic format takes slightly longer to complete.
- This equivalence testing of the electronic format of the DLQI with the paper version will reassure and encourage such use in clinical and research settings.

What are the clinical implications of this work?

- The DLQI application (app) will increase routine assessment of quality of life with negligible addition to consultation time.
- The DLQI app may facilitate transfer of patient data to electronic records, potentially being incorporated into referral systems from primary care.
- It is hoped the results of this study will encourage validation of other patient-reported outcome measures in electronic format in dermatology and other medical specialties.

There is increasing interest in utilizing technology within clinical medicine: innovations include computerized data entry,[1,2] communication initiatives[3] and virtual reality.[4] Within dermatology, there have been several innovations using electronics and information technology.[5–7] The use of patient-reported outcome measures (PROs) in electronic format has also been increasing.[8] However, these formats are usually not validated or compared with their original paper-based versions. This may result in data that are incomparable between the two formats due to the lack of equivalence.[9] Coons *et al.*[10] have proposed guidelines detailing the level of evidence required to demonstrate equivalence, depending on the amount of modification to the original PRO.

The Dermatology Life Quality Index (DLQI)[11] is the most commonly used dermatology-specific quality of life (QoL) measure in clinical trials.[12–14] The DLQI is easy to use in clinical practice due to its brevity and simplicity[15] with an average completion time of 2 min.[16] In the current era of widespread use of digital devices such as tablets and smartphones, clinicians, researchers and patients often use nonvalidated electronic versions instead of the original paper version. However, there is an underlying concern over whether such data are comparable with two decades of data gathered via the validated paper DLQI,[11,14] posing several challenges in data analysis and interpretation. The availability of a DLQI application (app) that had been validated would alleviate such concerns and contribute to better management of patients with skin conditions by having an easy tool for regular monitoring of disease severity from the patient's own perspective. Moreover, this tool could potentially be used by general practitioners to decide which patients need to be referred, as well as provide reassurance for users of electronic QoL measures across dermatology and other medical fields.

This study aimed to compare the conventional paper-based with a novel web-based app version of the DLQI, following International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines,[10] with respect to patient acceptability and preference and in terms of consistency of scores. We also assessed whether there was a carryover effect depending on which format patients completed first (paper vs. iPad®).

Participants and methods

Study participants

The study employed a randomized crossover design using a within-subjects comparison of the two formats of the questionnaire. The study was conducted at the dermatology outpatient department, University Hospital of Wales, Cardiff, U.K. Inclusion criteria were patients aged 18 years or older with any confirmed skin condition, and the ability to read and understand English. The exclusion criteria were patients who were not able to read and/or understand written English; having a coexisting medical or second dermatological condition of considerable severity as determined by the investigator; or physical deformities that would prevent writing or use of an iPad. The study protocol was approved by a local ethics committee (ref. 14/SW/0085, South West – Central Bristol Research Ethics Committee, U.K.) and the Cardiff & Vale University Health Board Research and Development department. Written informed consent was given by each subject prior to entering the study.

The Dermatology Life Quality Index iPad® application

The DLQI consists of 10 questions concerning a dermatology patient's perception of the impact of their skin disease on

different aspects of their QoL over the last week. The items of the DLQI include symptoms and feelings, daily activities, leisure, work or school, personal relationships and the side-effects of treatment. Each item is scored on a 4-point scale: not at all/not relevant, a little, a lot, and very much. Scores of individual items (0–3) are added to yield a total score (0–30); higher scores indicate greater impairment of QoL. The DLQI has been shown to be a strong instrument with respect to its internal consistency, reproducibility, validity and sensitivity to change.[14,15,17–19]

The DLQI was developed into an electronic app on the iPad by Janssen EMEA in conjunction with the original copyright holder (A.Y.F., Cardiff University). Only this particular iOS version was tested for the purpose of studying equivalence. The individual items and their response categories/scale were unchanged, allowing users to select options using touch. The app (Psoriasis 360©) is available without charge and may be downloaded from the Apple App Store (https://appsto.re/gb/-JIFw.i). It is also available from the Google (Android) App Store (https://play.google.com/store/apps/details?id=com.sapnagroup.p360&hl=en_GB). The DLQI paper version and a screenshot of the iPad app version are shown in Figure 1a and b, respectively.

Study procedure

Eligible patients were asked to complete the DLQI, both paper and electronic versions. The order of completing the questionnaires (paper version first vs. iPad version first) was randomized using a random number generator. After 30 min, patients were asked to complete the other format (Fig. 2). A 30-min interval was used to minimize patient waiting time and

(a)

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ■ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes ☐ No ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot ☐ A little ☐ Not at all ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

©AY Finlay, GK Khan, April 1992 www.dermatology.org.uk this must not be copied without the permission of the authors.

Fig 1. (a) The original Dermatology Life Quality Index (DLQI) questionnaire.[11] (b) Example screenshot from the DLQI iPad® app. The DLQI is copyright © A Y Finlay, G K Khan, April 1992. This must not be copied without the permission of the DLQI authors.

(b)

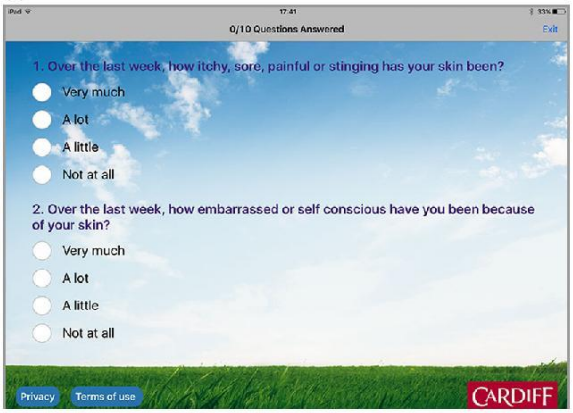


Fig 1. Continued

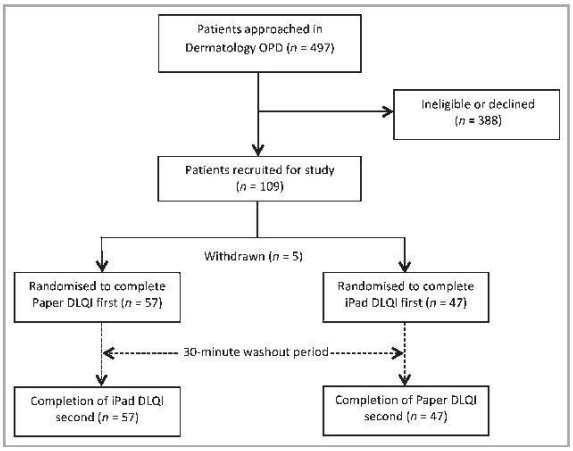


Fig 2. Flow diagram of the study procedure. OPD, outpatients department; DLQI, Dermatology Life Quality Index.

burden, as following up patients to complete the study at a later date would result in a higher cost and increase the chances of change in disease severity.[10] In between testing, the research team ensured that patients read a magazine, talked to staff or used their phones to browse, as forms of distraction.

Training to operate the app was given in person to every subject by a member of the research team, who remained with the patient throughout the duration of completion in case the subject needed assistance. The app also has basic instructions on the home screen and all patients were given time to read this prior to completion. Prior to completing either format of the DLQI, patients also completed a short demographic questionnaire on age, gender, literacy levels, visual and tactile impairments, diagnosis, and previous use of tablet computers or the DLQI. Completion of both versions was conducted in a similar environment; both completions by the participant were either before or after meeting the doctor, in order to reduce the effect of the doctor's consultation upon patient-reported QoL. The time taken to complete the DLQI using the paper version and the app was recorded. Patients were asked to also complete a short questionnaire asking about their perception, attitude and experience with the paper-based and web-based methods, concerning ease or difficulty of administration, acceptability, time requirement, feasibility and being comfortable with disclosing personal information using the novel app-based method.

Sample size

Sample size was calculated in accordance with ISPOR guidelines.[10] The study power was set at 95%, with an expected intraclass correlation coefficient (ICC) of 0·9 ($\alpha = 0{\cdot}05$), resulting in a target sample size of 104 patients.

Data analysis

Data analysis was conducted using SPSS version 20 (IBM, Armonk, NY, U.S.A.). Concordance of DLQI scores between paper- and app-based data was analysed using a two-way fixed-effects ICC model, which is the most commonly utilized statistical measure in equivalence studies of this nature.[20] The Wilcoxon signed-rank test was used to compare DLQI scores and completion times between the two formats; both variables were shown by the Shapiro–Wilk test to be non-normally distributed. A more stringent score difference of 1 point (3%) between the two versions was considered equivalent, although the majority of studies target a maximum of 5% difference.[20] Subanalysis was conducted to identify any carryover effect depending on which format of the DLQI patients completed first. Bland–Altman plots were drawn to measure the limits of agreement between the two formats. Equivalence was considered with limits of agreement ≤4, which is the minimal clinically important difference (MCID) for the DLQI.[21]

Descriptive analysis was used to present demographic data of the patients and their feedback on the preference and experience of using the tools. Linear regression techniques were used to identify correlation of iPad completion times with age.

Results

Sociodemographic characteristics of the study participants

A total of 104 patients were recruited, mean age 52 years ± 18·7; 43% male. Demographic details are given in Table 1. The most common diagnoses were psoriasis (39%), 'skin lesion' (19%) and eczema (13%). The majority of patients (61%) had their highest level of education at school; 17% of patients had never used a tablet before and 46% stated that they were 'a little' or 'not' comfortable with a tablet prior to participating in this study.

Comparisons of validity and reliability

As shown in Table 2, the ICC shows high concordance between total DLQI scores from paper and iPad versions [ICC = 0·98; 95% confidence interval (CI) 0·97–0·99]. The median difference of scores was also within the hypothesized difference of ±1 point (P = 0·006) (Fig. 3). The lower and higher limits of agreement were −3·1 and 4·1, respectively (Fig. 4). Patients took a slightly longer time to complete the DLQI on the iPad than on paper. The median of the individual

Table 1 Demographic characteristics of the study participants

	All (*n* = 104)	Paper first (*n* = 57)	iPad® first (*n* = 47)
Age, years			
Mean ± SD	51·5 ± 18·7	51·5 ± 19·3	51·4 ± 18·2
Median (IQR)	53·5 (37·3–67·8)	54 (33–68)	50 (38–67)
Range	20–89	20–89	20–85
Sex			
Male	43·3 (45)	51 (29)	34 (16)
Female	56·7 (59)	49 (28)	66 (31)
Nationality			
British	91·3 (95)	91 (52)	92 (43)
Other	8·7 (9)	9 (5)	9 (4)
First language			
English	90·4 (94)	88 (50)	94 (44)
Welsh	1·9 (2)	4 (2)	–
Other	7·7 (8)	9 (5)	6 (3)
Education			
Secondary school	60·6 (63)	58 (33)	64 (30)
University	37·6 (41)	42 (24)	36 (17)
Visual impairment			
None	59·6 (62)	65 (37)	53 (25)
Glasses	29·8 (31)	25 (14)	36 (17)
Other condition	5·8 (6)	5 (3)	6 (3)
Unspecified	1·9 (2)	4 (2)	–
Missing data	2·9 (3)	2 (1)	4 (2)
Tactile impairment			
Yes	9·6 (10)	9 (5)	11 (5)
No	90·4 (94)	91 (52)	89 (42)
Diagnosis			
Unknown	2·9 (3)	5 (3)	–
Skin lesion	19·2 (20)	23 (13)	15 (7)
Psoriasis	38·5 (40)	33 (19)	45 (21)
Eczema/dermatitis	13·5 (14)	14 (8)	13 (6)
Alopecia	1·0 (1)	–	2 (1)
Vitiligo	1·9 (2)	2 (1)	2 (1)
Infection	3·8 (4)	4 (2)	4 (2)
Acne/folliculitis	6·7 (7)	5 (3)	9 (4)
Cyst	2·9 (3)	4 (2)	2 (1)
Cutaneous malignancies	1·9 (2)	2 (1)	2 (1)
Allergy	1·0 (1)	2 (1)	–
Hidradenitis	1·9 (2)	4 (2)	–
Autoimmune/ inflammatory condition	1·9 (2)	2 (1)	2 (1)
Missing data	2·9 (3)	2 (1)	–
Tablet use			
Daily	49·0 (51)	40 (23)	60 (28)
Less often	32·7 (34)	44 (25)	19 (9)
Never	17·3 (18)	14 (8)	21 (10)
Missing data	1·0 (1)	2 (1)	–
Tablet comfort			
Very comfortable	52·9 (55)	54 (31)	51 (24)
A little comfortable	30·8 (32)	30 (17)	32 (15)
Not comfortable	15·4 (16)	14 (8)	17 (8)
	1·0 (1)	2 (1)	–
Used DLQI before?			
Yes	9·6 (10)	7 (4)	12·8 (6)
No	89·4 (93)	93 (53)	85 (40
Missing data	1·0 (1)	–	2 (1)

All data are presented as % (*n*) unless otherwise stated. IQR, interquartile range; DLQI, Dermatology Life Quality Index.

Table 2 Equivalence analysis of paper and electronic Dermatology Life Quality Index (DLQI) overall median scores and median completion time

	Paper	iPad®	ICC (95% CI)[a]	Difference (P − I)	Limits of agreement[b]	
					Lower	Upper
DLQI scores (n = 104)						
Median (IQR)	5 (1–12)	4 (1–11)	0·98 (0·97–0·99)	0·0 (0–1)[c]	−3·1	4·1
DLQI times (min:s)						
Median (IQR)	1:13 (00:56–01:36)	1:18 (1:03–1:39)	0·59 (0·39–0·72)	−0:09 (00:25–00:13)[c]		

CI, confidence interval; ICC, intraclass correlation; IQR, interquartile range; P − I, paper score minus iPad score. [a]Hypothesizing coefficient of ≥0·9. [b]Limits of agreement calculated from Bland–Altman plots (Fig. 4). [c]P-value <0·05 calculated from Wilcoxon signed-rank test.

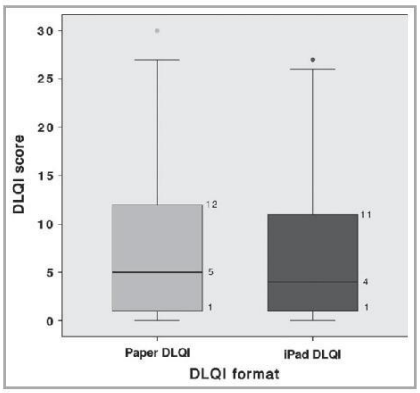


Fig 3. Box plot demonstrating the score distribution of both paper and iPad® Dermatology Life Quality Index (DLQI) formats. The bottom whisker represents the lowest value, and the upper whisker represents the highest value. The dot represents one outlier. The upper level of the box represents the 75th percentile and the lower level of the box represents the 25th percentile. The broad horizontal line in the middle of the box represents the median.

time differences was 9 s [interquartile range (IQR) −25–13; P = 0·008]. However, as shown in Table 3, there was no carryover effect on scores (P = 0·56) or completion times (P = 0·76) regardless of which format of the DLQI was used first. Linear regression demonstrated that the time taken to complete the iPad version was weakly correlated in a positive way with age, with older patients taking slightly longer (R^2 = 0·257; P = 0·012). The estimated increase was 8 s for each 10-year increase in age.

Comparisons of applicability and practicality

Patients were asked: 'On a scale of 1 to 10, where 1 is very uncomfortable and 10 is very comfortable, how comfortable were you using the iPad application version of the DLQI?'. In addition, patients were asked: 'On a scale of 1 to 10, where 1 is very difficult and 10 is very easy, how easy did you find it to use the iPad application version of the DLQI?'. Both questions were also asked about the paper version of the DLQI. Patients found both paper and iPad versions were easy (mean 9·4 ± 1·3 for paper and 9·6 ± 1·3 for iPad) and comfortable to use (mean 9·4 ± 1·1 for paper and 9·6 ± 1·4 for iPad) (Table 4). Overall, 57% of patients reported perceived time to complete the iPad version as shorter than that of the paper version. Which format was used first had an effect on the perceived time of iPad completion: more patients perceived a shorter time with iPad when paper was used first than when iPad was used first (70% vs. 43%; P = 0·023). The feedback results in other areas were the same whether paper or iPad was completed first. The majority of patients (76%) preferred the iPad version to paper. Patient demographics or previous experience with tablets did not have any effect on choice of preference and completion of the questionnaire.

Discussion

PROs in electronic formats are increasingly being used over their paper counterparts due to their inherent benefits, including a more streamlined process as well as increased reliability of data.[20] If not validated alongside the paper format, several new PROs are being validated initially in electronic format[22,23] to facilitate easier and higher quality data analysis and to reduce the overall cost of administration and storage. Paper-based instruments have a number of limitations such as higher rate of missing values; higher error rates in selecting multiple responses for single-option items; data entry error[24] in transferring responses from paper to electronic databases; and higher costs associated with administration, collection and processing the data.[25] These issues can be avoided by the use of computer-based administration (CBA) of QoL questionnaires.

However, CBA of PROs presents several challenges.[26,27] In routine clinical practice, assessment (at each visit) of disease severity and of QoL is labour intensive, requiring a major commitment of resources. Ease of use is one of the most important factors necessary for assessing QoL as part of routine clinical practice. Furthermore, patients may not be accustomed to such input devices or may be hindered by lack of internet connectivity.[8]

CBA of QoL measures such as in the form of web-based apps using touchscreen computers, also called tablets (e.g. iPad), is one of the ways that more frequent assessments can be conducted with minimal burden on patients and clinical

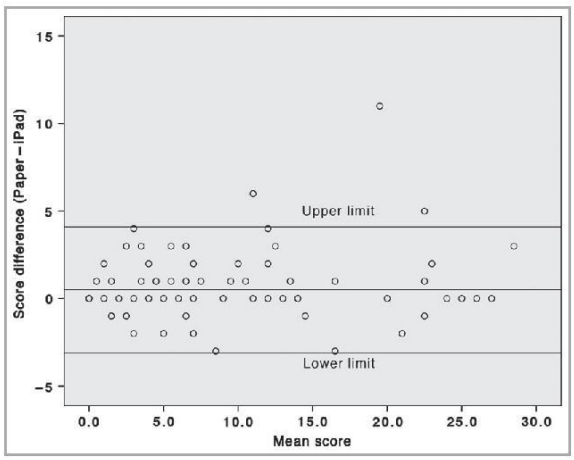


Fig 4. Bland–Altman plot demonstrating Paper and iPad® Dermatology Life Quality Index score agreement.

Table 3 Equivalence and carryover analysis of paper and electronic Dermatology Life Quality Index

	All (n = 104)	Paper first (n = 57)	iPad® first (n = 47)
Paper score			
Median (IQR)	5 (1–12)	5 (1–12·5)	6 (1–12)
Range	0–30	0–26	0–30
iPad score			
Median (IQR)	4 (1–11)	4 (0·5–10)	6 (1–12)
Range	0–27	0–26	0–30
Paper time (min:s)			
Median (IQR)	01:13 (00:56–01:36)	01:24 (01:06–01:40)	01:03 (00:50–01:29)
Range	00:28–04:15	00:28–04:15	00:30–02:49
iPad time (min:s)			
Median (IQR)	01:18 (01:03–01:39)	01:13 (00:58–01:27)	01:25 (01:09–01:53)
Range	00:35–08:24	00:35–08:24	00:49–02:49
Score difference			
Median (IQR)	0 (0–1)	0 (0–1·5)	0 (0–0)
Range	−3–11	−2–11	−3–5
P-value	0·006[a]		
Carryover effect			0·56[a]
Time difference (min:s)			
Median (IQR)	−00:09 (−00:25–00:13)	00:09 (−00:09–00:23·5)	−00:26 (−00:46 to −00:11)
Range	−06:45–00:58	−06:45–00:58	−01:53–00:16
P-value	0·008[a]		
Carryover effect			0·76[a]

IQR, interquartile range. [a]P-value calculated from Wilcoxon signed-rank test.

staff in addition to meeting the requirements outlined above. This computer-based method, which includes not only assessment but also scoring and presentation of QoL results, eliminates the need for a test administrator (interviewer), as usually needed for traditional paper and pencil formats, while providing immediate, 'real-time' feedback. Information from assessments can be displayed in graphic reports as visual aids that help guide discussions about treatment options and care planning. The availability of electronic versions of QoL instruments on various computer-based devices has the potential to reduce both the respondent burden and administrative time required to transfer the results of these PROs such as QoL scores to the clinician's desk, thus enhancing the feasibility and logistics of integrating real-time QoL assessment data for immediate use into routine clinical care to aid decision-making. A further benefit of electronic data capture is the ability to record time and date stamps, a feature particularly useful for diary data, in contrast to paper capture whereby

Table 4 Comparisons of applicability and practicality of paper and electronic versions of the Dermatology Life Quality Index

	All (n = 104)		Paper first (n = 57)		iPad® first (n = 47)	
Score[a]	Paper	iPad®	Paper	iPad	iPad	Paper
Ease of use, median (IQR)	10 (9–10)	10 (10–10)	10 (10–10)	10 (10–10)	10 (9–10)	10 (9–10)
Comfort, median (IQR)	10 (9–10)	10 (10–10)	10 (9–10)	10 (10–10)	10 (10–10)	10 (9–10)
Perceived time to complete iPad version						
Shorter than paper	57·7 (60)		70 (40)		43 (20)	
Same as paper	35·6 (37)		26 (15)		47 (22)	
Longer than paper	5·8 (6)		4 (2)		9 (4)	
Missing data	1·0 (1)		–		2 (1)	
Preference						
Paper	13·5 (14)		16 (9)		11 (5)	
iPad	76·0 (79)		75 (43)		77 (36)	
No preference	10·6 (11)		9 (5)		13 (6)	

Values are presented as % (n) except where otherwise stated. IQR, interquartile range. [a]10 = very easy or very comfortable; 1 = very difficult or very uncomfortable.

completion may occur at a different time to that recorded or intended. The computer-based measurement of QoL was well accepted by patients, who felt this method was a useful tool to inform the clinician about their problems.[28] Data are more complete on electronic questionnaires compared with paper questionnaires, data handling is greatly simplified, and the majority of patients prefer electronic completion.[29] Implementation of an electronic format of the DLQI could potentially streamline referral systems from primary care, allowing more appropriate allocation of appointments and resources. For example, the DLQI is integral to guidelines assessing the severity of psoriasis[30] and chronic hand eczema,[31] and referrals could potentially be triaged according to DLQI severity. In the research setting the availability of a web-based app would facilitate more efficient data collection in multicentre clinical trials and for longitudinal assessments of disease severity.

In response to increasing demand, a web-based app of the DLQI has been developed to encourage its further uptake in the current modernized clinical and research settings in many countries. Although computerized administration of QoL tools in other specialties has been shown to have numerous advantages over traditional paper-based tools,[32] this method of QoL assessment to present an overall disease severity idea has not yet been widely used in dermatology.

Level of education and literacy are important to consider when conducting PRO studies.[33] This study is representative of the general population, with the study participants' education ranging from secondary school (22·9%) to university level (37·6%). Previous experience with use of a tablet device did not affect results, with 17·3% of patients having never used one before and 46·2% stating that they were 'a little comfortable' or 'not comfortable' with using a tablet. Overall, 76% of patients preferred the iPad version, and found it easier to use and more comfortable than the paper version. Furthermore, 93% of patients perceived that the iPad was quicker to complete than the paper version or took the same amount of time, despite on average being slower by a median of 9 s ($P = 0·008$). Similar findings have been reported in many studies comparing electronic and paper PROs.[9,20,34] However, patients were aware of being timed when completing both versions, which could be a potential source of bias. Slower completion times could also be attributed to lack of familiarity of navigating on the iPad and occasional nonresponsiveness of the touchscreen. Investigators reported that various patients did not know how to 'touch' the screen appropriately and often searched for a 'next' button rather than scrolling down, despite instructions provided to the user on every occasion. This may be attributed to a simple design flaw in the app itself; navigation may be updated to become more intuitive. This study indicates that patients enjoy using the iPad more and the extra time spent had a negligible impact on patient experience. One concern expressed by a few patients included potential infection risk with shared iPads, though this may be less of an issue where personal electronic devices are used to monitor QoL changes over a period of time.

There are some limitations to the study. For example, a 30-min washout period may be considered too short and result in a carryover or 'training' effect, although there was no statistical evidence of this (Table 3). Theoretically, this may have occurred only when the iPad was administered first, as patients spent longer on average completing it, possibly giving them more time to remember the questions and answers. However, this effect was counteracted by the crossover study design, and patients were provided with reading material as a 'distraction'. Nevertheless, there is no consensus on the ideal time interval between PRO administrations when carrying out test–retest validation: intervals have ranged from 1 min to 7 years.[35] Other studies have also used 30 min as a washout period.[36] In order to reduce patient time and travel burden, as well as to ensure disease severity did not fluctuate between administrations, the shorter washout period of 30 min was used. Touchscreen surfaces are also prone to accidental touches, which may result in unintentional item responses subsequently

contributing to final score differences. The electronic version of the DLQI utilized in this study does not allow completion until all items are answered, which may impact validity if patients are coerced into answering questions they may have otherwise skipped on a paper format. This could have ethical implications from not giving patients the choice of not responding to a question if they do not wish to do so. In the DLQI, this issue is partly addressed by having a 'not relevant' option in eight of the 10 questions. The median score difference of '0' is unlikely to be clinically significant and strong correlation suggests that the two formats may be used interchangeably. Though the significant P-value of 0·006 for median total score difference is statistically significant, this is likely due to the large sample size.[37] Furthermore, the MCID for the DLQI is 4,[21] therefore the difference in scores is negligible in a clinical context. The limits of agreement from the Bland–Altman plots (−3·4–4·1) are also similarly reassuring. Differential item functioning was not assessed, as the DLQI total score is most relevant in clinical decision-making.[14]

Touchscreen devices offer many advantages, including portability and real-time assessment of QoL status.[38] Though this study did not involve full psychometric evaluation of the DLQI, there is evidence to suggest that where minimal modifications have been made, psychometric properties remain intact and need not be tested again.[10,20,39] While cognitive debriefing is suggested for equivalence studies of electronic PROs where only minor modifications are made,[10] this requirement was circumvented by using a higher threshold for testing equivalence (i.e. by comparing scores). It is hoped this will provide further reassurance for users who may have had concerns regarding the validity of scores from use of the DLQI in the previously nonvalidated electronic formats that have been used for many years. Formally testing such measures in this novel format provides confidence for end users who might otherwise have been reluctant to consider use of such formats because of concerns about validity or applicability. Thus, such studies may have wider and reassuring implications not only for the DLQI but also for other PROs within dermatology and across other medical specialties, encouraging early simultaneous validation of electronic and paper versions. Several challenges remain, including interface design decisions, data collection[40] and adapting electronic PROs to target populations, particularly in patients with physical disabilities or other impairments.[41] Nevertheless, this study has demonstrated that when DLQI migrates to an electronic format, scores are equivalent despite an overall slower completion time, which should become negligible with increased use and improvements to the app interface. This study provides evidence of equivalence for this app in particular (Psoriasis 360©), and future/other iterations of the electronic DLQI may not necessarily be equivalent. However, in most cases the changes to font size and layout are minor and thus repeated equivalence studies may be deemed unnecessary.[10]

The majority of patients preferred the electronic DLQI over the paper format, reflecting the findings of many similar studies.[30,42,43]

In conclusion, this study demonstrates equivalence in the measurement properties of paper and electronic formats, promoting confidence in the use of electronic format of the DLQI in both clinical and research settings, thereby paving the way for the digital era into current practices. The digital era in medicine will continue to be fuelled by a new generation of healthcare professionals who have been trained in this new platform. Patients and healthcare professionals are becoming more comfortable communicating and delivering their clinical expertise within a digital environment. In this context the electronic DLQI would be a valuable instrument in professionals' digital healthcare toolboxes, further facilitating its routine use.[44]

Acknowledgments

The study was supported by an investigator-initiated grant from Janssen to V.P. The authors are grateful to patients and staff who participated in this study. We would also like to thank Professor Richard Kay (Cardiff University) for input and guidance, as well as Cardiff University students Naomi Spencer, Natasha Logier and Zhi Lim for their help during recruitment.

References

1 Bates DW, Leape LL, Cullen DJ *et al.* Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA* 1998; **280**:1311–6.
2 Gill JM, Ewen E, Nsereko M. Impact of an electronic medical record on quality of care in a primary care office. *Del Med J* 2001; **73**:187–94.
3 Guo Q, Cann B, McClement S *et al.* Keep in touch (KIT): perspectives on introducing internet-based communication and information technologies in palliative care. *BMC Palliat Care* 2016; **15**:66.
4 Ershow AG, Peterson CM, Riley WT *et al.* Virtual reality technologies for research and education in obesity and diabetes: research needs and opportunities. *J Diabetes Sci Technol* 2011; **5**:212–24.
5 Hattori Y, Falgout L, Lee W *et al.* Multifunctional skin-like electronics for quantitative, clinical monitoring of cutaneous wound healing. *Adv Healthc Mater* 2014; **3**:1597–607.
6 DeLouise LA. Applications of nanotechnology in dermatology. *J Invest Dermatol* 2012; **132**:964–75.
7 Shaw IJ, de Berker DA. Strengths and weaknesses of electronic referral: comparison of data content and clinical value of electronic and paper referrals in dermatology. *Br J Gen Pract* 2007; **57**:223–4.
8 Leidy NK, Vernon M. Perspectives on patient-reported outcomes. *Pharmacoeconomics* 2008; **26**:363–70.
9 Campbell N, Ali F, Finlay AY *et al.* Equivalence of electronic and paper-based patient-reported outcome measures. *Qual Life Res* 2015; **24**:1949–61.
10 Coons SJ, Gwaltney CJ, Hays RD *et al.* Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force report. *Value Health* 2009; **12**:419–29.

11 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**:210–6.

12 Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. *J Invest Dermatol* 2007; **127**:2726–39.

13 Le Cleach L, Chassany O, Levy A *et al.* Poor reporting of quality of life outcomes in dermatology randomized controlled clinical trials. *Dermatology* 2008; **216**:46–55.

14 Basra MKA, Fenech R, Gatt RM *et al.* The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159**:997–1035.

15 Bronsard V, Paul C, Prey S *et al.* What are the best outcome measures for assessing quality of life in plaque type psoriasis? A systematic review of the literature. *J Eur Acad Dermatol Venereol* 2010; **24** (Suppl. 2):17–22.

16 Loo WJ, Diba VC, Chawla M, Finlay AY. Dermatology Life Quality Index: influence of an illustrated version. *Br J Dermatol* 2003; **148**:279–84.

17 Badia X, Mascaró JM, Lozano R. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQI. *Br J Dermatol* 1999; **141**:698–702.

18 Hahn HB, Melfi CA, Chuang TY *et al.* Use of the Dermatology Life Quality Index (DLQI) in a midwestern US urban clinic. *J Am Acad Dermatol* 2001; **45**:44–8.

19 Mazzotti E, Picardi A, Sampogna F *et al.* Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis. *Br J Dermatol* 2003; **149**:318–22.

20 Gwaltney CJ, Shields AL, Shiffman S. Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. *Value Health* 2008; **11**:322–33.

21 Basra MK, Salek MS, Camilleri L *et al.* Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology* 2015; **230**:27–33.

22 Bächinger D, Röösli C, Ditzen B *et al.* Development and validation of the Zurich chronic middle ear inventory (ZCMEI-21): an electronic questionnaire for assessing quality of life in patients with chronic otitis media. *Eur Arch Otorhinolaryngol* 2016; **273**:3073–81.

23 Deal LS, DiBenedetti DB, Williams VS, Fehnel SE. The development and validation of the daily electronic Endometriosis Pain and Bleeding Diary. *Health Qual Life Outcomes* 2010; **8**:64.

24 Lee SJ, Kavanaugh A, Lenert L. Electronic and computer-generated patient questionnaires in standard care. *Best Pract Res Clin Rheumatol* 2007; **21**:637–47.

25 Saleh KJ, Radosevich DM, Kassim RA *et al.* Comparison of commonly used orthopaedic outcome measures using palm-top computers and paper surveys. *J Orthop Res* 2002; **20**:1146–51.

26 Bezjak A, Ng P, Skeel R *et al.* Oncologists' use of quality of life information: results of a survey of Eastern Cooperative Oncology Group physicians. *Qual Life Res* 2001; **10**:1–13.

27 Carlson LE, Speca M, Hagen N, Taenzer P. Computerized quality-of-life screening in a cancer pain clinic. *J Palliat Care* 2001; **17**:46–52.

28 Velikova G, Brown JM, Smith AB, Selby PJ. Computer-based quality of life questionnaires may contribute to doctor–patient interactions in oncology. *Br J Cancer* 2002; **86**:51–9.

29 Drummond HE, Ghosh S, Ferguson A *et al.* Electronic quality of life questionnaires: a comparison of pen-based electronic questionnaires with conventional paper in a gastrointestinal study. *Qual Life Res* 1995; **4**:21–6.

30 Finlay AY. Current severe psoriasis and the rule of tens. *Br J Dermatol* 2005; **152**:861–7.

31 Paulden M, Rodgers M, Griffin S *et al.* Alitretinoin for the treatment of severe chronic hand eczema. *Health Technol Assess* 2010; **14**:39–46.

32 Hanscom B, Lurie JD, Homa K, Weinstein JN. Computerized questionnaires and the quality of survey data. *Spine* 2002; **27**:1797–801.

33 Bushnell DM, Martin ML, Parasuraman B. Electronic versus paper questionnaires: a further comparison in persons with asthma. *J Asthma* 2003; **40**:751–62.

34 Kleinman L, Leidy NK, Crawley J *et al.* A comparative trial of paper-and-pencil versus computer administration of the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire. *Med Care* 2001; **39**:181–9.

35 Quadri N, Wild DJ, Skerritt B *et al.* A literature review of the variance in interval length between administrations for assessment of test retest reliability and equivalence of PRO measures. *Value Health* 2013; **16**:A40–1.

36 Sun T, West N, Ansermino JM *et al.* A smartphone version of the Faces Pain Scale-Revised and the Color Analog Scale for postoperative pain assessment in children. *Paediatr Anaesth* 2015; **25**:1264–73.

37 Doll H, Carney S. Statistical approaches to uncertainty: P values and confidence intervals unpacked. *Equine Vet J* 2007; **39**:275–6.

38 Dale O, Hagen KB. Despite technical problems personal digital assistants outperform pen and paper when collecting patient diary data. *J Clin Epidemiol* 2007; **60**:8–17.

39 Muehlhausen W, Doll H, Quadri N *et al.* Equivalence of electronic and paper administration of patient-reported outcome measures: a systematic review and meta-analysis of studies conducted between 2007 and 2013. *Health Qual Life Outcomes* 2015; **13**:167.

40 Zbrozek A, Hebert J, Gogates G *et al.* Validation of electronic systems to collect patient-reported outcome (PRO) data—recommendations for clinical trial teams: report of the ISPOR ePRO Systems Validation Good Research Practices Task Force. *Value Health* 2013; **16**:480–9.

41 Hahn EA, Cella D. Health outcomes assessment in vulnerable populations: measurement challenges and recommendations. *Arch Phys Med Rehabil* 2003; **84**:S35–42.

42 Velikova G, Wright EP, Smith AB *et al.* Automated collection of quality-of-life data: a comparison of paper and computer touch-screen questionnaires. *J Clin Oncol* 1999; **17**:998–1007.

43 Ryan JM, Corry JR, Attewell R, Smithson MJ. A comparison of an electronic version of the SF-36 General Health Questionnaire to the standard paper version. *Qual Life Res* 2002; **11**:19–26.

44 Finlay AY, Salek MS, Abeni D *et al.* Why quality of life measurement is important in dermatology clinical practice: an expert-based opinion statement by the EADV Task Force on Quality of Life. *J Eur Acad Dermatol Venereol* 2017; **31**:424–31.

5) Ali, F.M., Kay, R., Finlay, A.Y., Piguet, V., Kupfer, J., Dalgard, F. and Salek, M.S., 2017. Mapping of the DLQI scores to EQ-5D utility values using ordinal logistic regression. *Quality of Life Research*, *26*(11), pp.3025-3034.

Mapping of the DLQI scores to EQ-5D utility values using ordinal logistic regression

Faraz Mahmood Ali, Richard Kay, Andrew Y. Finlay, Vincent Piguet, Joerg Kupfer, Florence Dalgard & M. Sam Salek

Quality of Life Research
An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation - Official Journal of the International Society of Quality of Life Research

ISSN 0962-9343
Volume 26
Number 11

Qual Life Res (2017) 26:3025-3034
DOI 10.1007/s11136-017-1607-4

Springer

Qual Life Res (2017) 26:3025–3034
DOI 10.1007/s11136-017-1607-4

Mapping of the DLQI scores to EQ-5D utility values using ordinal logistic regression

Faraz Mahmood Ali[1] · Richard Kay[2] · Andrew Y. Finlay[1] · Vincent Piguet[1] · Joerg Kupfer[3] · Florence Dalgard[4] · M. Sam Salek[5,6]

Accepted: 27 May 2017 / Published online: 10 June 2017

Abstract

Purpose The Dermatology Life Quality Index (DLQI) and the European Quality of Life-5 Dimension (EQ-5D) are separate measures that may be used to gather health-related quality of life (HRQoL) information from patients. The EQ-5D is a generic measure from which health utility estimates can be derived, whereas the DLQI is a specialty-specific measure to assess HRQoL. To reduce the burden of multiple measures being administered and to enable a more disease-specific calculation of health utility estimates, we explored an established mathematical technique known as ordinal logistic regression (OLR) to develop an appropriate model to map DLQI data to EQ-5D-based health utility estimates.

Methods Retrospective data from 4010 patients were randomly divided five times into two groups for the derivation and testing of the mapping model. Split-half cross-validation was utilized resulting in a total of ten ordinal logistic regression models for each of the five EQ-5D dimensions against age, sex, and all ten items of the DLQI. Using Monte Carlo simulation, predicted health utility estimates were derived and compared against those observed. This method was repeated for both OLR and a previously tested mapping methodology based on linear regression.

Results The model was shown to be highly predictive and its repeated fitting demonstrated a stable model using OLR as well as linear regression. The mean differences between OLR-predicted health utility estimates and observed health utility estimates ranged from 0.0024 to 0.0239 across the ten modeling exercises, with an average overall difference of 0.0120 (a 1.6% underestimate, not of clinical importance).

Conclusions This modeling framework developed in this study will enable researchers to calculate EQ-5D health utility estimates from a specialty-specific study population, reducing patient and economic burden.

Keywords DLQI · Mapping · Utility values · Quality of life · EQ-5D · Ordinal logistic regression

Electronic supplementary material The online version of this article (doi:10.1007/s11136-017-1607-4) contains supplementary material, which is available to authorized users.

✉ Faraz Mahmood Ali
alifm@cardiff.ac.uk

[1] Department of Dermatology and Academic Wound Healing, Division of Infection and Immunity, School of Medicine, Cardiff University, Cardiff CF14 4XN, UK

[2] School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, UK

[3] Institute of Medical Psychology, Justus Liebig University, Giessen, Germany

[4] Department of Dermatology and Venereology, Skåne University Hospital, Lund University, 20502 Malmö, Sweden

[5] School of Life & Medical Sciences, Department of Pharmacy, University of Hertfordshire, Hatfield, UK

[6] Institute for Medicines Development, Cardiff, UK

Introduction

'Health-related quality of life' (HRQoL) data can be used to derive 'Quality-Adjusted Life Years' (QALYs), which are implemented in economic analyses to aid healthcare decision makers. The Dermatology Life Quality Index (DLQI) [1] is the most commonly used dermatology-specific HRQoL instrument [2]. In contrast, the European

Quality of Life-5 Dimension (EQ-5D) [3] is a generic utility measure for use across all diseases [4] that provides health utility estimates, for comparison of disease burden, that has been little used in dermatology [5]. Both measures may be used together, though this may be burdensome, and integrating data from multiple measures presents challenges [6]: it is not clear whether two types of measures should inform the same decision [7].

There are several 'mapping techniques' [8] involving algorithms to predict health utility estimates from disease-specific measures. A linear model [9] was used to predict health utility estimates from the DLQI [10–12]. However, the methodology had limitations including small sample sizes and psoriasis-only populations, which may not be reliably used across a general dermatology population. Subsequent mapping models were derived using multiple linear regression [13] and bivariate/multivariate analysis [14], though the authors did not conduct formal validation to predict utility values and only went as far as predicting EQ-5D VAS or total scores. Blome et al. [14] pessimistically postulated that 'any prediction of utilities with the DLQI and other variables regularly assessed in psoriasis studies will be vague and not of clinical relevance.' However, Gray et al. [15] succeeded in mapping the Short-Form 12 to categorical EQ-5D responses using ordinal logistic regression (OLR).

There is a wealth of DLQI data from clinical studies over the last two decades without health utility estimate outputs recorded. Therefore, deriving this information from a dermatology-specific population would allow researchers to compare more disease-specific economic data across all conditions. The aim of this study was to create a mapping model using OLR to predict EQ-5D health utility estimates from DLQI scores, and we hypothesized that this can be done reliably. Previous unsatisfactory or failed attempts have used total DLQI scores to calculate health utility estimates for a cohort of patients, whereas a key aspect of OLR methodology is the use of data from individual DLQI items mapped to individual EQ-5D domains. We also aimed to produce health utility estimates utilizing the previous linear regression method employed by Currie and Conway [9] on our dataset, which is larger and more diverse, to compare the accuracy of the two distinct mapping techniques.

Materials and methods

The Dermatology Life Quality Index (DLQI)

The DLQI consists of ten items, with four possible responses to each item: "Very much," "A lot," "A little," and "Not at all." If any item for the DLQI was left unanswered, it was scored zero, following the developers' instructions [16] (see Appendix). The two parts of item 7 were combined as a single item containing scores for both parts, as routinely done in calculating total scores. This allowed a uniform four-level ordinal response system for all DLQI items.

The European Quality of Life-5 Dimension

The EQ-5D consists of two parts: a descriptive system and a visual analogue scale (VAS). The descriptive system contains five dimensions: "mobility," "self-care," "usual activities," "pain/discomfort," and "anxiety/depression." The 3-level version EQ-5D-3L was used, for which there are three possible responses: "no problems," "some problems," and "extreme problems." In our analysis, these outcomes were scored 1, 2, and 3.

The data

Data from 4010 patients with skin diseases [17] were used. The patient dataset was accessed from an international multicenter observational cross-sectional study examining the association between depressive symptoms and dermatological conditions ranging from benign and malignant skin lesions to chronic inflammatory diseases such as psoriasis and lupus erythematosus [17]. The dataset ($n = 4010$) was filtered to exclude subjects with missing age, sex, DLQI, and EQ-5D data (11.7% in total). This resulted in a total of 3542 subjects. The socio-demographic characteristics for the entire patient dataset are given by Dalgard et al. [17], and have been summarized in Table 1. These patients were referred to outpatient dermatology clinics at various centers across Europe between 2011 and 2013. The full methodology has been previously described [17]. Each participant was examined and the main diagnosis recorded. Patients completed several questionnaires, including the DLQI and EQ-5D. This mapping study did not require additional ethics approval.

As no official European time trade-off (TTO) values exist for EQ-5D health states, we applied the UK TTO values throughout the validation process.

Conceptual correlations

We assessed the strength of the conceptual correlations between the DLQI and EQ-5D and found that several key themes were significantly associated (i.e., $p < 0.05$). The key concepts that apply to each DLQI item are shown in Table 2.

Table 1 Socio-demographic data for the complete dataset

	No. of patients
Country	
Belgium	222
Denmark	247
France	116
Germany	254
Hungary	171
Italy	517
Netherlands	209
Norway	468
Poland	247
Russia	269
Spain	274
Turkey	280
UK	268
Most common diagnoses	
Psoriasis	484
Eczema	239
Acne	185

	No. of patients	Average age (years, range)
All subjects	3542	46.29 (18–95)
Sex		
Male (*n*)	1558	47.76 (18–92)
Female (*n*)	1984	45.14 (18–95)
Average DLQI score[a]		6.69

EQ-5D domain (no. of patients)	No problems	Some problems	Extreme problems
Mobility	2692	839	11
Self-care	3162	372	8
Usual activities	2615	874	53
Pain or discomfort	1604	1739	199
Anxiety or depressed	1954	1431	157

[a] DLQI total score range is 0–30, 0 indicating no impairment and 30 indicating maximum impairment of quality of life

For the 'Mobility' EQ-5D domain, DLQI items 3, 7, and 10 were most strongly correlated which cover the concepts of 'daily activities,' 'work and school,' and 'treatment.' The 'Pain' domain was strongly correlated with almost all key concepts of the DLQI including items 1, 3, 6, 8, 9, and 10. It correlated most with Item 1 of the DLQI, in particular, which asks about pain and soreness of the patient's skin condition. The 'Self-care' domain correlated most strongly with item 10 (treatment), as well as items 1, 3, and 7. 'Usual activities' correlated strongly with item 3 (daily activities) as expected, as well as items 1, 5, 6, 7, and 10. Finally, the 'Anxiety' domain was most strongly correlated to item 2, which enquires about 'embarrassment' and whether patients feel 'self-conscious' due to their skin condition, as well as items 4, 5, 7, 9, 10. Overall, all ten DLQI items correlated strongly with the EQ-5D domains, re-emphasizing the strong conceptual correlation between the two questionnaires.

Table 2 Key concepts that apply to each DLQI item [1]

Section	Items
Symptoms and feelings	1, 2
Daily activities	3, 4
Leisure	5, 6
Work and school	7
Personal relationships	8, 9
Treatment	10

Ordinal regression modeling algorithm

Ordinal models produce a set of probabilities for each possible outcome category, as given by the equations:

$$P(Y=1)=\frac{1}{1+e^{(-a_1+b_1x_1+b_2x_2+\cdots+b_mx_m)}}$$

$$P(Y=2)=\frac{1}{1+e^{(-a_2+b_1x_1+b_2x_2+\cdots+b_mx_m)}}-P(Y=1)$$

$$P(Y=3)=1-P(Y=2)-P(Y=1)$$

'Y' represents the outcome of any given EQ-5D domain ("mobility," "self-care," "usual activities," "pain/discomfort," or "anxiety/depression"). The outcome categories $Y=1$, 2, and 3 represent the three possible responses for a given EQ-5D domain, i.e., "no problems," "some problems," or "extreme problems," respectively. Sex was coded as 0 = male and 1 = female. The x-variables are indicator variables derived from DLQI scores, age, fitted as a linear term, and sex, while the b's are the regression coefficients. The b's are essentially 'weights' attached to each indicator of each DLQI item score, age, and sex and they are used to calculate estimated probabilities of each EQ-5D item response. The model is based on the assumption that for each EQ-5D dimension there is an underlying continuous 'latent' variable, for example, measuring mobility. The value of the linear combination $b_1x_1+b_2x_2+\cdots+b_mx_m$ provides a predicted score, Z, on this continuum. If we assume that these scores Z follow a logistic distribution, then the OLR model follows from assuming that if $Z<a_1$, the subjects would record an outcome $Y=1$, if $a_1<Z<a_2$, they would record an outcome of $Y=2$, and if $Z>a_2$ they would record an outcome $Y=3$.

Using all data, a series of ordinal logistic regressions were fitted for each of the five EQ-5D dimensions against the ten individual items of the DLQI, as well as age and sex using SPSS version 22. All ten DLQI items were included for each domain model in order to capture all the correlations induced by each DLQI item. Regressions were run with age and sex alone, DLQI items alone, as well as age and sex combined with DLQI items (Table 3) in order to evaluate the contribution of age and sex, and collectively the ten DLQI items. Model comparisons were undertaken by comparing twice the absolute difference in the maximized log-likelihoods with the Chi-square distribution with degrees of freedom equal to the difference in the number of model terms being evaluated. Note that age and sex were chosen as additional variables as these data are invariably recorded and therefore accessible and have been shown to significantly impact on QoL [18].

Model validation

Split-half cross-validation was employed [19] whereby the dataset was randomly split five times into separate estimation and validation sets using the random number generator in SPSS version 22. The estimation set was used to derive the mapping models, whilst the out-of-sample validation set was utilized for validating the fitted models. This process was repeated with each of the five estimation/validation sets after which the sets were reversed, resulting in a total of 10 complete models.

Bootstrapping has been suggested as an alternative approach to model validation [19] although that technique was evaluated in a somewhat simpler setting than the one considered here, namely with a single binary outcome variable and a single logistic model rather than with five ordinal outcomes and a separate logistic model in each case. As these authors note, however, bootstrapping is likely to offer relevant advantages in datasets with small sample sizes. The issue of small sample sizes and bootstrapping is discussed further in relation to model validation [20] when predictor selection techniques have been employed. In our case, the sample size is sufficiently large and there is no predictor selection, supporting the use of split-half cross-validation.

The model was tested on each validation dataset to produce three predicted probabilities per subject per EQ-5D domain ($Y = 1$, 2, or 3). Using these predicted probabilities, a Monte Carlo simulation was run for each subject resulting in predicted domain responses and consequently health utility estimates. This was repeated five times for each random split to ensure the model output was stable. The five estimation and validation sets were then switched and the process was repeated (split-half cross-validation), resulting in a total of ten models. The average predicted health utility estimate for each validation set was then compared with the observed health utility estimate of the same set.

The proportional odds assumption was assessed using the test for parallelism within SPSS. For each domain, except mobility, this test gave a non-significant result supporting the assumption for proportional odds. For mobility, the p value of 0.01 did indicate some departure from this assumption but this can be explained by the small number of subjects ($n = 11$) in the dataset who have a mobility outcome category of 3. As a consequence, the sub-model that compares categories 1 and 2 combined with category 3 is unstable and the results for the test for parallelism unreliable.

Currie and Conway method: linear regression

The methodology reported above for model derivation, split-half cross-validation, and Monte Carlo simulation was repeated to test the linear regression algorithm utilized by Currie and Conway [9]. This method uses the total DLQI scores and correlates it directly with the final health utility estimates resulting in a linear regression formula in the format: Utility $= a - (b \times$ DLQI total score).

Table 3 The significance of the DLQI items and age and sex compared to the model containing age, sex, and the DLQI items for each EQ-5D domain

EQ-5D domain	Covariates: age/sex			Covariates: DLQI			Covariates: age/sex/DLQI
	−2 log likelihood	Chi-square comparing to full model	Degrees of freedom (*df*)	−2 log likelihood	Chi-square comparing to full model	Degrees of freedom (*df*)	−2 log likelihood
Mobility	507.4	171.9	2	1311	107.0	10	1566
Self-care	430.8	18.7	2	862.5	172.9	10	988.7
Usual activities	610.2	36.6	2	1388.1	269.2	10	1754.1
Pain	783.8	37.5	2	1738	424.9	10	2373.3
Anxiety/depression	772.6	19	2	1787.9	284.4	10	2451.7

The average difference between observed health utility estimates and predicted health utility estimates was calculated for both OLR and linear regression methods, as well as mean square error (MSE) and mean absolute error (MAE).

Results

Model validation

OLR method

For each of the five EQ-5D domains, an ordinal model was derived and used to predict the probability of each EQ-5D response for each subject in each validation set, and subsequently the health utility estimates, using Monte Carlo simulation. The model was shown to be highly predictive, and repeated data splits demonstrated a stable model. In each case, the predicted mean health utility estimate was a slight underestimate of the observed mean health utility estimate and across the ten validation sets, the difference between predicted mean health utility estimates and observed mean health utility estimates ranged from −0.0024 to −0.0239, with an mean overall difference of −0.0120. This 1.59% underestimate represents a clinically unimportant effect [21]. The MSE across all ten splits ranged from 0.0728 to 0.0818 with an average MSE of 0.0766. The MAE across all ten splits ranged from 0.1873 to 0.2009 with an average MAE of 0.1934.

The predictive ability of the model at an individual subject level was also examined using histograms to display the difference between predicted health utility estimates and the observed health utility estimates for each simulation at the individual subject level. The results from a typical split sample are displayed in Fig. 1. The plot depicts a centrality around '0' which indicates the strong predictive collective capability of the OLR models. On average, 37% of the individual health utility estimates were predicted to lie within 0.1 of the observed values, while 62% were predicted to lie within 0.2 and 81% within 0.3 over all 10 validation exercises.

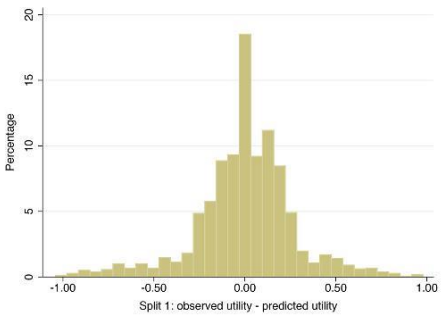


Fig. 1 Histogram displaying the difference between predicted and observed health utility estimates for a typical split sample

To further evaluate its reliability, the OLR mapping method was also applied to different subsets of the study population. A model was derived from psoriasis-only patients ($n = 484$) and tested on patients with all other skin conditions ($n = 3058$). The average difference between the observed and predicted health utility estimates was 0.05 (MSE 0.0844, MAE 0.2037). Thirty-six percent of the individual health utility estimates were predicted to lie within 0.1 of the observed values, while 61% were predicted to lie within 0.2 and 78% within 0.3.

Similarly, the model performance was tested on different geographical groups of patients. As a test exercise, a model derived from patients in Italy ($n = 517$) was tested on patients from Norway ($n = 468$). The average health utility estimate difference for the Norway patients was 0.06 (MSE 0.09. MAE 0.21). Thirty-six percent of the individual health utility estimates were predicted to lie within 0.1 of the observed values, while 59% were predicted to lie within 0.2 and 78% within 0.3.

Despite the small sample sizes for the model building exercise in these two cases, these evaluations support the reliability and robustness of the modeling framework.

Details of the final-fitted OLR models using data from the 3542 subjects are given in Table 4.

Currie and Conway method

For the Currie and Conway linear regression model, the average difference between the observed and predicted estimates was −0.0007. The MSE across all ten splits ranged from 0.0438 to 0.05 with an average MSE of 0.0469. The mean absolute error (MAE) across all ten splits ranged from 0.1527 to 0.1616 with an average MAE of 0.1566. On average, 38% of the individual health utility estimates were predicted to lie within 0.1 of the observed estimates, while 78% were predicted to lie within 0.2 and 89% within 0.3 over all 10 validation exercises.

Discussion

There is increasing interest in correlating and mapping DLQI scores into generic measures, such as the EQ-5D, for cost-analysis and to provide more accurate disease-specific data which generic measures are unable to capture. Schmitt et al. [22] correlated the Work Limitations Questionnaire with the DLQI ($r = 0.47, p < 0.0001$) to derive a model to

Table 4 Final model estimates (standard errors) for each EQ-5D domain

	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/depression
Threshold a_1	4.500 (0.190)	4.854 (0.251)	3.574 (0.171)	2.204 (0.133)	1.469 (0.128)
Threshold a_2	9.506 (0.368)	9.074 (0.438)	7.231 (0.237)	6.052 (0.178)	4.775 (0.162)
Age	0.051 (0.003)	0.033 (0.004)	0.027 (0.003)	0.025 (0.002)	0.003 (0.002)
Sex[a]	0.046 (0.089)	−0.213 (0.120)	0.133 (0.087)	0.177 (0.073)	0.465 (0.073)
DLQI 1	0.087 (0.055)	0.176 (0.074)	0.270 (0.052)	0.685 (0.047)	0.035 (0.044)
DLQI 2	0.013 (0.061)	0.052 (0.079)	−0.114 (0.059)	0.014 (0.049)	0.378 (0.048)
DLQI 3	0.209 (0.068)	0.278 (0.085)	0.351 (0.063)	0.199 (0.060)	0.107 (0.057)
DLQI 4	0.071 (0.058)	0.053 (0.072)	0.051 (0.055)	0.097 (0.050)	−0.099 (0.048)
DLQI 5	0.113 (0.075)	0.064 (0.095)	0.209 (0.070)	−0.122 (0.064)	0.205 (0.062)
DLQI 6	0.116 (0.060)	0.014 (0.071)	0.215 (0.055)	0.310 (0.054)	−0.075 (0.052)
DLQI 7	0.251 (0.053)	0.236 (0.063)	0.283 (0.049)	−0.048 (0.046)	0.186 (0.044)
DLQI 8	−0.008 (0.076)	−0.013 (0.091)	−0.081 (0.071)	0.163 (0.066)	0.121 (0.064)
DLQI 9	−0.094 (0.065)	0.002 (0.075)	0.068 (0.060)	0.132 (0.057)	0.194 (0.054)
DLQI 10	0.233 (0.061)	0.478 (0.071)	0.210 (0.057)	0.245 (0.054)	0.155 (0.052)

The 10 DLQI questions are represented in order by DLQI 1, DLQI 2, etc

[a] Sex was coded male = 0, female = 1

calculate work productivity in psoriasis. Moller et al. [23] state that 'disutility among psoriasis patients are within the ranges of other chronic diseases.' There is, therefore, a need to accurately represent and compare data from dermatology with health utility estimates from other conditions. Furthermore, there are several inherent disadvantages with generic measures [24] such as the EQ-5D or Short-Form 36 (SF-36), e.g., they contain irrelevant questions for patients with severe inflammatory skin conditions, resulting in the inability to perform imputation due to systematically missing responses in the questionnaires. Patients may also develop 'questionnaire fatigue' from repeated completions. Focusing on one specialty- or disease-specific questionnaire, from which health utility estimates may be predicted, provides a perception of relevance encouraging thorough careful completion by patients whilst also reducing study time and costs for researchers. Using OLR, this study has succeeded in mapping DLQI scores to EQ-5D data, from which health utility estimates were calculated. The model reliably predicts EQ-5D scores, in particular at a group level, demonstrated through a split-half cross-validation process resulting in very close health utility estimate predictions. The model is shown also to provide close prediction of health utility estimates at an individual subject level.

There are strong conceptual associations between the DLQI and EQ-5D items. Mapping is more likely to be successful where conceptual overlap between two measures exists [25]. This is so for the DLQI and EQ-5D; many studies have reported a strong association [26–31], which is reaffirmed by this study. Although overall predictions were strongly correlated to the observed scores at a group level, the individual predicting power of the model requires further testing.

The linear regression model utilized by Currie and Conway [9] provided better predictive accuracy when fitted on this study's dataset (average difference between predicted and observed health utility estimates = 0.00065, compared to OLR = 0.0120). This was also reflected in the respective MAE (linear regression = 0.16, OLR = 0.19) and MSE (linear regression = 0.05, OLR = 0.08) values. It is therefore plausible that this mapping method performs better when fitted on a larger and dermatologically diverse dataset, compared to its previous validation study which was limited to a small sample size and to psoriasis patients in the UK [9]. However, there is one structural advantage in the use of the ordinal model over the linear model [9]. Since the DLQI total score always takes a positive value, the maximum utility value derived from the linear regression equation has an upper bound of 'a.' In a typical application, the value of the constant 'a' will approach 1 but will never be equal to 1 and a predicted health utility estimate of '1' ('perfect health') cannot be obtained. In the OLR model and the associated Monte Carlo simulation such an outcome can be achieved. Both models' estimates are derived from a European dataset of over 3500 patients with various dermatological conditions, and the predicted responses may be used to calculate country-specific health utility estimates [32]. This was not possible using the previous linear model [9], derived from a UK dataset, because of differing health utility estimate tariffs between countries [33, 34]. Thus the proposed ordinal model, as well as the revised linear regression model, may be used as mapping tools in other European countries.

There are some limitations that apply to both models. The observed scores for the DLQI and the EQ-5D were sometimes inconsistent within the same subject, e.g., one subject answered 1 on every EQ-5D domain ('perfect health') but 29 on the DLQI (very poor health). This could be due to poor understanding of the items, the reliability or validity of the instruments, or due to random errors. Though these data were included to avoid bias, Van Hout et al. [35] argue that analysis should be restricted to logically consistent responses. Perhaps including more sociodemographic variables in the OLR model, other than age and sex, may improve its predictive performance, though this may result in only marginal improvements that would not outweigh the complexity of running the model [15]. The UK TTO values were used in the derivation of both models; it is worth considering that these health states were elicited in 1993 and therefore may not be up to date with current health valuations. Furthermore, no official European TTO values exist for EQ-5D health states and therefore we applied the UK TTO values throughout the validation process. Further sensitivity analysis may be conducted using preference value-sets from different countries. However, these were not accessible for this study, but would be a useful consideration for future studies. Though there may be cultural variation influencing HRQoL and utility responses, we have not been able to test this specific question in detail. However, when the OLR model was created using only Italian patients and tested on a Norway population, it performed almost as well as the model derived from the complete dataset. Our experience suggests that within the European context there is some uniformity of attitudes, cultural norms, and responses, as the DLQI has undergone over one hundred validated translations, with a significant number in European countries [2]. We believe the methodology remains intact and consistent, regardless of the TTO values utilized.

Though bootstrapping may indeed be the best approach for testing such models, this would require some additional theoretical considerations to extend existing methodology for the binary logistic model to the ordinal setting. We were able to bypass this approach by using 'split-half cross-validation,' which is a valid technique for large sample sizes [19]. Nevertheless, this study presents the opportunity for further statistical research.

There may be concerns regarding the use of these models in different diseases and whether single disease models would provide more accurate utility data. This study includes a wide range of the most common different skin diseases from a wide range of different European countries, giving the models additional strength in terms of universality. However, we successfully derived a model from psoriasis-only patients and tested this on patients with all other conditions, with the predicted results reassuringly similar to the original OLR model validation exercise. Two limitations of this exercise were the sample size of psoriasis patients, which was relatively small ($n = 484$) and that none of the patients had answered 'extreme' for the self-care domain of the EQ-5D. Given the overall sample size from which the OLR model was created, our view is therefore that the model may be implemented successfully across different conditions, limiting the need for condition-specific modeling, which may be practically difficult to create.

Though we initially hypothesized that OLR will improve upon previous attempts at predicting health utility estimates, we have identified that both of the existing templates may be used as a road map across other medical disciplines in instances where similar needs exist. Both methodologies will therefore be useful for researchers interested in deriving generic HRQoL data, including descriptive information, from disease-specific populations without having to implement numerous questionnaires. Though OLR has previously been used for converting measures [15], as far as we are aware this is first time it has been used to convert a specialty-specific instrument into a generic measure. A step-by-step guide is provided to implement the OLR model (Supplementary material) in the particular setting of mapping the DLQI scores to EQ-5D health utility estimates. An excel spreadsheet is also available upon request with pre-programmed formulae to enable EQ-5D domain probability calculations for a cohort of patients, from which health utility estimates may be predicted using Monte Carlo simulation. The DLQI is the most commonly reported outcome measure in dermatology [2, 36], and therefore there are many datasets from which generic EQ-5D and health utility data can now be predicted, using either OLR or linear regression.

Acknowledgements We wish to thank Dr. M.K.A. Basra, Dr. Paul Kamudoni, Mr. Pedro Cruz, and Ms. Sue Wei Chong for their contributions to the early development of this study in Cardiff. We also wish to acknowledge and thank the European Society of Dermatology and Psychiatry (ESDaP) Study Group who collected and validated the patient data for this study [17]. The other ESDaP participants were Uwe Gieler, Department of Dermatology, Justus Liebig University, Giessen, Germany; Lucia Tomas-Aragones, Department of Psychology, University of Zaragoza, Zaragoza, Spain; Lars Lien, Department of Public Health, Hedmark University College, Elverum, Norway; Francoise Poot, Department of Dermatology, Universite Libre de Bruxelles, Brussels, Belgium; Gregor B E Jemec, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; Laurent Misery, Department of Dermatology, University Hospital of Brest, Brest, France; Csanad Szabo, Department of Dermatology, University of Szeged, Szeged, Hungary; Dennis Linder, Department for Dermatology, Padua University Hospital, Padua, Italy; Francesca Sampogna, Health Services Research Unit, Istituto Dermopatico dell'Immacolata, Rome, Italy; Andrea W M Evers, Institute of Psychology Health, University of Leiden, Leiden, the Netherlands; Jon Anders Halvorsen, Department of Dermatology, University of Oslo, Oslo, Norway; Flora Balieva, Department of

Dermatology, Stavanger University Hospital, Stavanger, Norway; Jacek Szepietowski, Department of Dermatology, Wroclaw Medical University, Wroclaw, Poland; Dmitry Romanov, Department of Psychiatry and Psychosomatic Medicine, Sechenov First Moscow State Medical, Moscow, Russia; Servando E Marron, Department of Dermatology, Alcaniz Hospital, Alcaniz, Spain; Ilknur K Altunay, Department of Dermatology, Sisli Etfal Teaching and Research Hospital, Istanbul, Turkey. Finally we would like to thank the journal editors and the reviewers for their insightful comments. These led to considerable improvements in the manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest AY Finlay is joint copyright holder of the DLQI. Cardiff University and AYF receive royalties from its use. Authors FA, RK, VP, FD, JK, and SS declare that they have no conflict of interest.

Ethical approval This article does not describe any new studies with human participants or animals performed by any of the authors: it describes additional analyses of previously reported data.

Appendix

The Dermatology Life Quality Index [1, 16]*

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
	If 'No', over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home **messy**, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

©AY Finlay, GK Khan, April 1992 www.dermatology.org.uk, this must not be copied without the permission of the authors.

*Footnote: how the DLQI is scored [1, 16]

The scoring of each question is as follows

Response	Score
Very much	Scored 3
A lot	Scored 2
A little	Scored 1
Not at all	Scored 0
Not relevant	Scored 0
Question unanswered	Scored 0
Question 7: "prevented work or studying"	Scored 3

References

1. Finlay, A. Y., & Khan, G. (1994). Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clinical and Experimental Dermatology, 19*(3), 210–216.
2. Basra, M. K. A., Fenech, R., Gatt, R. M., Salek, M. S., & Finlay, A. Y. (2008). The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *British Journal of Dermatology, 159*(5), 997–1035.
3. TE Group. (1990). EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy, 16*(3), 199–208.
4. Klassen, A. F., Newton, J. N., & Mallon, E. (2000). Measuring quality of life in people referred for specialist care of acne: comparing generic and disease-specific measures. *Journal of the American Academy of Dermatology, 43*(2), 229–233.
5. Pereira, F. R. A., Basra, M. K., Finlay, A. Y., & Salek, M. S. (2012). The role of the EQ-5D in the economic evaluation of dermatological conditions and therapies. *Dermatology, 225*(1), 45–53.
6. Feeny, D. (2002). Commentary on Jack Dowie, "Decision validity should determine whether a generic or condition-specific HRQOL measure is used in health care decisions". *Health Economics, 11*(1), 13–16.
7. Dowie, J. (2002). Decision validity should determine whether a generic or condition-specific HRQOL measure is used in health care decisions. *Health Economics, 11*(1), 1–8.
8. Mortimer, D., & Segal, L. (2008). Comparing the incomparable? A systematic review of competing techniques for converting descriptive measures of health status into QALY-weights. *Medical Decision Making, 28*(1), 66–89.
9. Currie, C. J., & Conway, P. (2007). PSK11 Evaluation of the association between EQ5D utility and dermatology life quality index (DLQI) score in patients with psoriasis. *Value in Health, 10*(6), A470–A471.
10. Lloyd, A., Reeves, P., Conway, P., Reynolds, A., & Baxter, G. (2009). Economic evaluation of etanercept in the management of chronic plaque psoriasis. *British Journal of Dermatology, 160*(2), 380–386.
11. Blank, P. R., Blank, A. A., & Szucs, T. D. (2010). Cost-effectiveness of oral alitretinoin in patients with severe chronic hand eczema-a long-term analysis from a Swiss perspective. *BMC Dermatology, 10*(1), 1.
12. Rodgers, M. M., Griffin, S., Paulden, M., Slack, R., Duffy, S., Ingram, J. R., et al. (2010). Alitretinoin for severe chronic hand eczema. *Pharmacoeconomics, 28*(5), 351–362.
13. Norlin, J. M., Steen Carlsson, K., Persson, U., & Schmitt-Egenolf, M. (2012). Analysis of three outcome measures in moderate to severe psoriasis: a registry-based study of 2450 patients. *British Journal of Dermatology, 166*(4), 797–802.
14. Blome, C., Beikert, F. C., Rustenbach, S. J., & Augustin, M. (2013). Mapping DLQI on EQ-5D in psoriasis: transformation of skin-specific health-related quality of life into utilities. *Archives of Dermatological Research, 305*(3), 197–204.
15. Gray, A. M., Rivero-Arias, O., & Clarke, P. M. (2006). Estimating the association between SF-12 responses and EQ-5D utility values by response mapping. *Medical Decision Making, 26*(1), 18–29.
16. Cardiff University (2016). DLQI Instructions for use and scoring. http://www.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/dlqi-instructions-for-use-and-scoring/. Accessed 7 June 2017.
17. Dalgard, F. J., Gieler, U., Tomas-Aragones, L., Lien, L., Poot, F., Jemec, G. B., et al. (2015). The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *Journal of Investigative Dermatology, 135*(4), 984–991.
18. Sampogna, F., Chren, M. M., Melchi, C. F., Pasquini, P., Tabolli, S., & Abeni, D. (2006). Age, gender, quality of life and psychological distress in patients hospitalized with psoriasis. *British Journal of Dermatology, 154*(2), 325–331.
19. Steyerberg, E. W., Harrell, F. E., Borsboom, G. J., Eijkemans, M. J. C., Vergouwe, Y., & Habbema, J. D. F. (2001). Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *Journal of Clinical Epidemiology, 54*(8), 774–781.
20. Collins, G. S., Reitsma, J. B., Altman, D. G., & Moons, K. G. (2015). Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMC Medicine, 13*(1), 1.
21. Coretti, S., Ruggeri, M., & McNamee, P. (2014). The minimum clinically important difference for EQ-5D index: a critical review. *Expert Review of Pharmacoeconomics & Outcomes Research, 14*(2), 221–233.
22. Schmitt, J., & Küster, D. (2015). Correlation between Dermatology Life Quality Index (DLQI) scores and Work Limitations Questionnaire (WLQ) allows the calculation of percent work productivity loss in patients with psoriasis. *Archives of Dermatological Research, 307*(5), 451–453.
23. Møller, A. H., Erntoft, S., Vinding, G. R., & Jemec, G. B. (2015). A systematic literature review to compare quality of life in psoriasis with other chronic diseases using EQ-5D-derived utility values. *Patient Related Outcome Measures, 6,* 167.
24. Guyatt, G. H., Feeny, D. H., & Patrick, D. L. (1993). Measuring health-related quality of life. *Annals of Internal Medicine, 118*(8), 622–629.
25. Longworth, L., & Rowen, D. (2011). *NICE DSU technical support document 10: the use of mapping methods to estimate health state utility values* (p. b4). Sheffield: Decision Support Unit, ScHARR, University of Sheffield.
26. Shikiar, R., Heffernan, M., Langley, R. G., Willian, M. K., Okun, M. M., & Revicki, D. A. (2007). Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a Phase II randomized controlled trial. *Journal of Dermatological Treatment, 18*(1), 25–31.
27. Cortesi, P. A., Scalone, L., De Pità, O., Angelini, G., Cristaudo, A., Girolomoni, G., et al. (2011). PSS31 Association between Eq-5D and Dermatology Life Quality Index (Dlqi) in patients with chronic hand eczema. *Value in Health, 14*(7), A507.
28. Scalone, L., De Portu, S., Casati, A., Baranzoni, N., Monzini, M. S., Giannetti, A., et al. (2006). PSK8 Convergent validity and sensitivity to change of the generic instrument EQ-5D and the disease-specific DLQI in atopic dermatitis. *Value in Health, 9*(6), A268–A269.

29. Matusiak, Ł., Bieniek, A., & Szepietowski, J. C. (2010). Psychophysical aspects of hidradenitis suppurativa. *Acta Dermato-Venereologica, 90*(3), 264–268.
30. Hjortsberg, C., Bergman, A., Bjarnason, A., HElkkILä, H., Hjelmgren, J., Svensson, Å., et al. (2011). Are treatment satisfaction, quality of life, and self-assessed disease severity relevant parameters for patient registries? Experiences from Finnish and Swedish patients with psoriasis. *Acta Dermato-Venereologica, 91*(4), 409–414.
31. Radtke, M. A., Schäfer, I., Gajur, A., Langenbruch, A., & Augustin, M. (2009). Willingness-to-pay and quality of life in patients with vitiligo. *British Journal of Dermatology, 161*(1), 134–139.
32. Rivero-Arias, O., Ouellet, M., Gray, A., Wolstenholme, J., Rothwell, P. M., & Luengo-Fernandez, R. (2010). Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. *Medical Decision Making, 30*(3), 341–354.
33. Rutten-van Mölken, M. P., Oostenbrink, J. B., Tashkin, D. P., Burkhart, D., & Monz, B. U. (2006). Does quality of life of COPD patients as measured by the generic EuroQol five-dimension questionnaire differentiate between COPD severity stages? *Chest Journal, 130*(4), 1117–1128.
34. Tsuchiya, A., Ikeda, S., Ikegami, N., Nishimura, S., Sakai, I., Fukuda, T., et al. (2002). Estimating an EQ-5D population value set: the case of Japan. *Health Economics, 11*(4), 341–353.
35. Van Hout, B., Janssen, M. F., Feng, Y. S., Kohlmann, T., Busschbach, J., Golicki, D., et al. (2012). Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in Health, 15*(5), 708–715.
36. Ali, F. M., Cueva, A. C., Vyas, J., Atwan, A. A., Salek, M. S., Finlay, A. Y., et al. (2017). A systematic review of the use of quality-of-life instruments in randomized controlled trials for psoriasis. *British Journal of Dermatology, 176*(3), 577–593.

6) Ali, F.M., Salek, S., Finlay, A.Y. and Piguet, V., 2019. Validation of the electronic Psoriasis Area and Severity Index application: Establishing measurement equivalence. *Journal of the American Academy of Dermatology*, *81*(6), pp.1439-1441.

Correspondence to: Angelica Misitzis, MD, Center for Dermatoepidemiology, Providence VA Medical Center, 830 Chalkstone Ave, Providence, RI 02908-4799

E-mail: angelicamisitzi@gmail.com

REFERENCES

1. Brooks K, Brooks D, Dajani Z, et al. Use of artificial tanning products among young adults. *J Am Acad Dermatol*. 2006;54(6):1060-1066.
2. Trends help. Available at: https://support.google.com/trends/answer/4365533?hl=en&ref_topic=6248052. Accessed June 3, 2019.
3. Reed DD. Google search trends for tanning salons: temporal patterns indicate peak interest in mid spring. *J Am Acad Dermatol*. 2015;73(6):1055-1056.
4. Faurschou A, Wulf HC. Durability of the sun protection factor provided by dihydroxyacetone. *Photodermatol Photoimmunol Photomed*. 2004;20(5):23942.
5. Dixon HG, Warne CD, Scully ML, et al. Does the portrayal of tanning in Australian women's magazines relate to real women's tanning beliefs and behavior? *Health Educ Behav*. 2011;38(2):132-142.

https://doi.org/10.1016/j.jaad.2019.06.017

Validation of the electronic Psoriasis Area and Severity Index application: Establishing measurement equivalence

To the Editor: Despite its many shortcomings, the Psoriasis Area and Severity Index (PASI) remains the standard method worldwide for psoriasis assessment.[1] Several studies have implemented electronic versions without evidence of formal validation, raising the possibility of lack of equivalence with the paper counterpart.[2] This study compared the conventional paper-based and a novel electronic application version of the PASI (Fig 1). International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines[3] were followed to assess rater preference and consistency of scores.

The study used a randomized cross-over design using a within-subjects comparison of the 2 formats of the PASI. The study was conducted at the dermatology outpatient department, University Hospital of Wales, Cardiff, United Kingdom.

Inclusion criteria were patients aged 18 years or older with a clinical diagnosis of chronic plaque psoriasis from a dermatologist and the ability to read and understand English. Raters ranged from medical students to senior trainees and received standardized clinical training for the PASI assessment to ensure uniformity of rating. The study power was 80%, with an expected intraclass correlation coefficient (ICC) of 0.9 ($\alpha = 0.05$), resulting in a target sample size of 44 patients.

All 3 raters showed high correlation in test scores (Pearson correlation, 0.949; $P < .05$; n = 5) demonstrating standardization of the assessment criteria. Forty-four patients (59.1% male) were recruited, with a mean ± standard deviation (SD) age of 45 ± 16 years. The mean duration of chronic plaque psoriasis diagnosis was 19.2 ± 14.8 years (interquartile range, 8-30 years), with PASI severity ranging from 0.7 to 28.5. The ICC showed high concordance between the total PASI scores from paper and the iPad (Apple Inc, Cupertino, CA) format (ICC, 0.993; 95% confidence interval, 0.988-0.996; Table I). The median difference in PASI scores was also within the hypothesized difference of CC = 0.993 ($P = .72$). The lower and higher limits of agreement were −1.4 and 1.4, respectively.

The PASI iPad version demonstrated reduced interrater variability compared with the paper version (Pearson correlation, 0.982 vs 0.949; 5 patients assessed). There was no carryover effect demonstrated with scores ($P = .82$) or time to completion ($P = .16$) regardless of which format of the PASI was used first.

The raters, using a stopwatch, took a median of 147 seconds (iPad) vs 152 seconds (paper), not including calculation time ($P = .81$). Raters reported that the iPad version was easier to use compared with the paper version due to the visual nature of the application allowing accurate assessment and calculation of severity scores, although suggestions were made to improve the user interface.

The future of medical practice is intricately anchored within the evolution of digital technology. There is high correlation, and thus equivalence, between the PASI iPad and paper versions. The raters preferred the iPad version due to the visual nature of the scoring process and the reduced likelihood of calculation errors. The higher interrater reliability and the inherent advantages of electronic tools[4] further reinforces the superiority of the digital format. The validated Psoriasis 360 (Janssen EMEA, Beerse Belgium) application, together with the previously validated Dermatology Life Quality Index[5] component, has the potential to be of considerable value to clinicians, researchers, and patients.

Faraz Mahmood Ali, MBChB, MRCP,[a] Sam Salek, PhD, RPh,[b,c] Andrew Y. Finlay, MBBS, FRCP,[a] and Vincent Piguet, MD, PhD, FRCP[a,d]

From the Division of Infection and Immunity, Department of Dermatology and Academic Wound Healing, School of Medicine, Cardiff University,[a] the School of Life and Medical Sciences, University of Hertfordshire, Hatfield,[b]

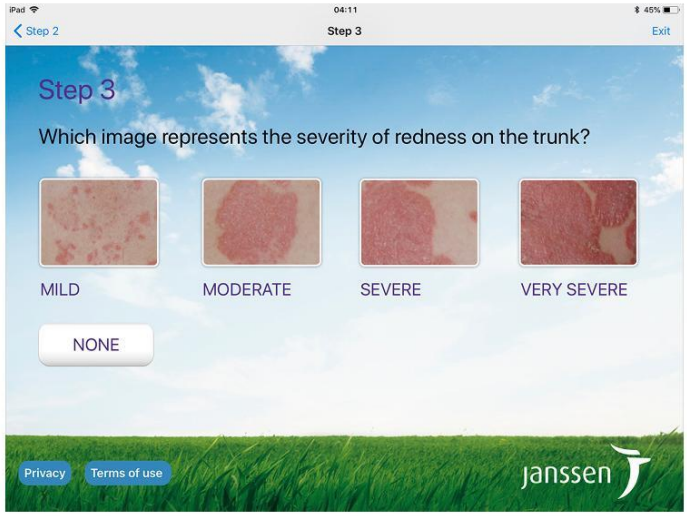


Fig 1. Example screenshot from the Psoriasis Area and Severity Index (PASI) application (Janssen, Beerse Belgium) for the iPad (Apple, Cupertino, CA). Psoriasis 360 is no longer supported by Janssen EMEA. The screenshot is for illustrative purposes only.

Table I. Equivalence analysis of paper and electronic Psoriasis Area and Severity Index (*PASI*) overall mean scores and mean completion time

	Paper	iPad*			Limits of agreement‡	
Variable	Median (IQR)	Median (IQR)	ICC† (95% CI)	Difference (Paper − iPad)	Lower	Upper
PASI scores (n = 104)	5.7 (2.1-10.7)	5.8 (2.7-9.3)	0.993 (0.988-0.996)	0.0 (−0.3 to 0.4)§	−1.4	1.4
PASI times (min:sec)	2:32 (01:55-03:07)	2:27 (01:54-03:00)	0.444 (0.148-0.665)	−00:10 (−00:31 to 00:40)§		

CI, Confidence interval; *ICC*, intraclass correlation coefficient; *IQR*, interquartile range.
*Apple, Cupertino, CA.
†Hypothesizing coefficient of ≥0.9.
‡Limits of agreement calculated from Bland-Altman plots.
§*P* value > .05 calculated by Wilcoxon signed rank test.

and Institute for Medicines Development, Cardiff,[c] United Kingdom; and Division of Dermatology, Department of Medicine, University of Toronto, and Division of Dermatology, Women's College Hospital, Toronto, Ontario, Canada.[d]

Funding sources: The study was supported by a research grant from Janssen-Cilag Limited.

Conflicts of interest: Dr Ali has received travel expenses for attending American Academy of Dermatology meetings from Janssen-Cilag Limited and has received lecture fees from Leo Pharmaceuticals. Dr Finlay is joint copyright owner of the Dermatology Life Quality Index, and he and Cardiff University receive royalties. Dr Finlay is a member of a Novartis advisory board and has received lecture fees and travel expenses from Novartis. Dr Piguet undertakes personal advisory work for Pfizer, AbbVie, Janssen, UCB, Novartis, Almirall, and Celgene and has received departmental support from AbbVie, Bausch Health, Celgene, Janssen, LEO Pharma, Lilly, NAOS, Novartis, Pfizer, Pierre Fabre, and Sanofi. Dr Salek has no conflicts of interest to disclose.

Correspondence to: Faraz Ali, MBChB, MRCP, Department of Dermatology, Division of Infection and Immunity, School of Medicine, Cardiff University, 3rd Floor Glamorgan House, Heath Park, Cardiff CF14 4XN, UK

E-mail: alifm@cardiff.ac.uk

REFERENCES

1. Ashcroft DM, Wan Po AL, Williams HC, Griffiths CEM. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. *Br J Dermatol*. 1999;141:185-191.
2. Campbell N, Ali F, Finlay AY, et al. Equivalence of electronic and paper-based patient-reported outcome measures. *Qual Life Res*. 2015;24:1949-1961.
3. Coons SJ, Gwaltney CJ, Hays RD, et al. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force Report. *Value Health*. 2009;12:419-429.
4. Gill JM, Ewen E, Nsereko M. Impact of an electronic medical record on quality of care in a primary care office. *Del Med J*. 2001;73:187-194.
5. Ali FM, Johns N, Finlay AY, Salek MS, Piguet V. Comparison of the paper-based and electronic versions of the Dermatology Life Quality Index: evidence of equivalence. *Br J Dermatol*. 2017;177:1306-1315.

https://doi.org/10.1016/j.jaad.2019.04.073

An increase in sunscreen use in a population resistant to sun protection

To the Editor: Keratinocyte carcinoma (KC) is the most common malignant neoplasm diagnosed in the United States. Its incidence is increasing, and sunscreen use is a key tool to prevent it.[1] In this study, we describe sunscreen use among patients who were enrolled in the randomized, controlled Veterans Affairs Keratinocyte Carcinoma Chemoprevention (VAKCC) Trial.[2] Participants had heavily sun-damaged skin, defined as having at least 2 KCs in the 5 years before the trial. The study enrolled 932 patients with a mean age of 70 years. Most were male (98%) and white (99%). The median duration of follow-up was 2.8 years.

Characteristics of the participants were obtained by interview and examination at enrollment. They had semiannual counseling and visits, received free sunscreen, and were encouraged to use it. Analysis was performed with Stata 14.2 software (StataCorp LLC, College Station, TX).

Sunscreen use was significantly more common among participants who reported inability to tan, freckles, history of severe sunburns, age younger than 70 years, and residence in southern states. Of the sunscreen users, 90% reported using sun protection factor ≥30. Our findings confirm that people who are more sun sensitive are more likely to use sunscreen.

Fig 1. Proportion of participants who reported never using sunscreen while outside during peak hours during the past week.

At baseline, 71% of participants reported no sunscreen use while outside during peak hours during the past week, and only 19% reported using sunscreen 75% to 100% of the time during the week before enrollment (Fig 1). At 6 months, the proportion of patients who never used sunscreen dropped from 71% to 47%, and the number who almost always used sunscreen doubled from 19% to 37%.

Prior literature reports significant increases in sun protection after a history of skin cancer.[3] Only 19% of our population reported sunscreen use at baseline.

Another study observed only a 12% increase in sunscreen users after their consult intervention.[4] Their population was younger and mainly female.[4] We consider the increase we observed to be important, because our population was male and older, both of which have been associated with less sun protection.

Sunscreen use is affected by socioeconomic factors.[5] In our study, sunscreen provision was free, suggesting that no cost might have contributed to the noted increase.

Limitations include the homogenous veteran population and that the effects might not be observed outside of the setting of this trial.

Our results suggest that the combination of no cost with the follow-up and counseling involved in the participation of our trial may have been responsible for the increase in sunscreen use even in a population resistant to sun protection.

Appendix: Key personnel of the VAKCC Trial is available at https://data.mendeley.com/datasets/8w3cy2txw6/draft?a=81889ed9-415a-4620-b37d-26b2a6d8e305.

Angelica Misitzis, MD,[a,b] Meghan Beatson, BS,[a,b] Julia A. Siegel, MD,[a] and Kaveri Korgavkar, MD[a] Joanna Walker, MD,[a,b] and Martin A. Weinstock,

7) Ali, F.M., Johns, N., Salek, S. and Finlay, A.Y., 2018. Correlating the Dermatology Life Quality Index with psychiatric measures: A systematic review. *Clinics in dermatology*, *36*(6), pp.691-697.

Clinics in Dermatology (2018) 36, 691–697

ELSEVIER

Clinics in Dermatology

Correlating the Dermatology Life Quality Index with psychiatric measures: A systematic review

Faraz M. Ali, MBChB, MRCP[a,*], Nutjaree Johns, PharmD, PhD[a,b], Sam Salek, PhD, FFPM, FRPS[c,d], Andrew Y. Finlay, MBBS, FRCP[a]

[a]*Department of Dermatology and Academic Wound Healing, Division of Infection and Immunity, School of Medicine, Cardiff University, Cardiff, UK*
[b]*Faculty of Pharmaceutical Sciences and Melatonin Research Group, Khon Kaen University, Khon Kaen, Thailand*
[c]*School of Life and Medical Sciences, University of Hertfordshire, Hatfield, UK*
[d]*Institute for Medicines Development, Cardiff, UK*

Abstract Skin conditions may have a major impact on the psychologic well-being of patients, ranging from depression to anxiety. The Dermatology Life Quality Index (DLQI) is the most commonly used quality of life tool in dermatology, though it has yet to be correlated with psychiatric measures used in clinical therapeutic trials. We conducted a systematic review to determine whether there is any correlation between the DLQI and psychiatric measure scores, potentially allowing the DLQI to be used as a surrogate measure for depression or psychiatric screening. Six databases were searched using the following keywords: "DLQI," "Dermatology Life Quality Index," "Psych*," "depression," "anxiety," "stress," and "trial*." All randomized trials where full DLQI and psychiatric scores were provided were included. PRISMA guidelines were followed. In all, 462 records were screened, but only seven met inclusion criteria. Hospital Anxiety and Depression Scale (HADS) was the most commonly used psychiatric measure; the "depression" component score changes correlated strongly with the DLQI ($r = 0.715$). There needs to be guidance on psychiatric measurement and reporting in clinical trials. Although the DLQI correlated well with the "depression" domain of the HADS scale, interviews and screening for depression are still vital for full assessment of patient psychologic well-being.

Introduction

Skin conditions may have significant implications for a patient's quality of life (QoL), affecting various aspects of their day-to-day living.[1] This includes routine activities, household chores, social interactions, and relationships. There is a well-documented impact on psychologic well-being, often manifesting in psychiatric problems that may range from

Conflicts of interest: AYF is joint copyright owner of the DLQI, and Cardiff University and AYF receive royalties. FA, NJ, and SS declare no conflicts of interest.

* Corresponding author. Tel.: +44 2920 744721.
E-mail address: AliFM@cardiff.ac.uk (F.M. Ali).

https://doi.org/10.1016/j.clindermatol.2018.08.014
0738-081X/

depression to anxiety.[2] Several studies have examined the relationship between psychiatric morbidity and skin diseases.[3–7] For example, psoriasis is associated with psychologic disorders, with sexual and sleep complaints being the most prevalent.[3] Anxiety and depression are strongly correlated in such conditions as alopecia areata,[4] vitiligo,[5] rosacea,[6] and hirsutism.[7]

The Dermatology Life Quality Index[8] (DLQI, score range 0-30) has been used in many skin conditions and across a wide range of disease severities.[9,10] It is a dermatology-specific tool that assesses the QoL impairment in the past week for those aged 16 and older. It has 10 questions and evaluates 6 parameters: clinical manifestations and feelings, daily activities, leisure, work/school, personal relationships, and treatment. The total possible score ranges from 0 to 30, where a higher score signifies a larger impairment in the patient's QoL caused by the skin disease. The minimal clinically important difference, that is, the minimum change in score that has clinical relevance, is 4,[11] and score ranges have also been banded to aid interpretation of QoL severity.[12] It has high patient acceptability,[13] short completion time of around two minutes[14] and extensive validation,[9] resulting in its widespread use in both clinical settings and clinical therapeutic research trials globally.[15] The DLQI is also integral to several national registries and guidelines, for example, the National Institute for Health and Clinical Excellence guidelines for biologics in the treatment of psoriasis.[10] The psychosocial aspects captured by the DLQI are well documented.[10] Despite this, the DLQI has yet to be compared and correlated with other psychiatric morbidity measures in randomized controlled trials.

We have conducted a systematic review to identify the various validated psychiatric measures that have been utilized in conjunction with the DLQI in randomized controlled trials. This might also reveal whether there is any correlation between the scores that would potentially allow the DLQI to be used as a surrogate measure for depression or psychiatric screening.

Materials and methods

Data sources

Six computerized bibliographic databases were searched up to May 19, 2016: Ovid MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, Web of Science Core Collection, Scopus, and PsycINFO. The search was not restricted by language and was conducted using PRISMA guidelines.

Keywords used were "DLQI," "Dermatology Life Quality Index," "Psych*," "depression," "anxiety," "stress," and "trial*."

Search filters are given in the Supplementary Material. We ran supplementary searches and reviewed trial registers and gray literature. Reference lists of all included studies and of recent reviews were also assessed. Electronic publications in advance of print were also included.

Selection criteria

We included all randomized controlled trials for any condition where the DLQI was used. This included crossover trials and trials with open-label extensions, in all languages studying the adult population (aged 18 and over) of either sex and of any ethnicity. Only papers where the absolute scores or change in scores for the DLQI and for psychiatric measures were provided were included.

Exclusion criteria

The exclusion criteria for the systematic review were as follows: studies that included any patient younger than 18 years of age, and publications in which the change in scores could not be reliably calculated for the DLQI or any psychiatric morbidity scale (including graphical representation). Abstracts and posters were excluded where further data were not available after contacting the author(s).

Outcome measures extracted

Primary outcome

Data recorded included DLQI scores and psychiatric morbidity scales being utilized. Scores for these measures were recorded at baseline, treatment, and follow-up endpoints, as well as the change in these scores attributed to treatment. For studies with an open-label extension, the data were extracted only for the period of the study randomized and controlled.

Secondary outcomes

Correlation between the sensitivity of the DLQI and psychiatric measures to change.

Data extraction and synthesis

Two reviewers (FA and NJ) extracted data independently from all eligible published studies, discussed any disagreements, and if necessary, involved a third reviewer (Dr. Jui Vyas, Cardiff University) for resolution. We adapted a form, which included the Cochrane Risk of Bias tool, for recording data[16] that included study design, details of administration, methodologic quality, and duration of treatment and follow-up. The quality of each presentation was quantitatively rated using the Jadad score.[17]

Results

Characteristics and attributes of the studies selected

In all, 462 records were screened from the initial database search, of which only seven interventional randomized controlled trials met the inclusion criteria; six studies were for

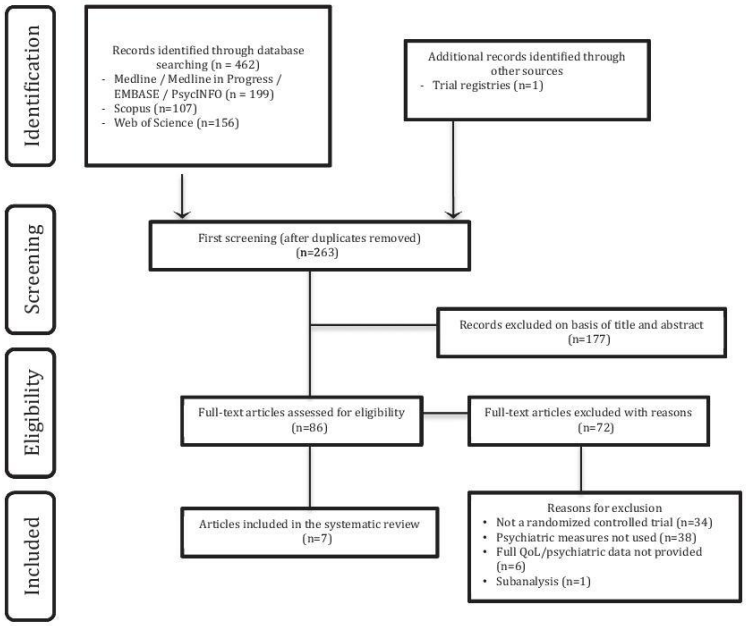


Fig. 1 Flow diagram of publication selection. QoL, quality of life.

psoriasis and one for atopic dermatitis. One study, for which results were available, was identified by searching trial registries (Figure 1). The data described results from 5578 adult patients, with an average age of 45 years. Approximately 63.8% of the study population were men. Table 1 contains the studies identified by the systematic review.

The most common psychiatric tools used alongside the DLQI were the Beck Depression Inventory (BDI, 2 studies) and the Hospital Anxiety and Depression Scale (HADS, 5 studies). The BDI, published in 1961,[18] is a 21-item patient-reported outcome measure (score range 0-63) and is commonly used in studies to assess the severity of depression.

Table 1 Table of included studies, basic demographic information, and psychiatric measures used

Author, year	Jadad score	Interventional study arm	Condition	Study duration (weeks)	Average participant age	Total no. of study participants	Psychiatric measure used
Bostoen 2012[27]	4	Educational Program	Atopic dermatitis	12	38.5	16	BDI
Bundy 2013[28]	2	eTIPS	Psoriasis	6	45.8	61	HADS
Dauden 2009[29]	1	Etanercept (Continuous)	Psoriasis	54	44.8	352	HADS
		Etanercept (Paused)			45.2	359	
Gelfand 2008[30]	1	Etanercept (Continuous)	Psoriasis	12	45.8	1272	BDI
		Etanercept (Interrupted)			44.9	1274	
Gniadecki 2012[31]	3	Etanercept BIW	Psoriasis	12	46.1	379	HADS
		Etanercept QW			46.9	373	
Langley 2010[32]	4	Ustekinumab 45 mg	Psoriasis	52	45.1	409	HADS
		Ustekinumab 90 mg			46.6	411	
Trial No: NCT01309737[33]	N/A	CP-690,550 5 mg	Psoriasis	52	45.9	331	HADS
		CP-690,550 10 mg			44.3	341	

BDI, Beck Depression Inventory; BIW, twice weekly; eTIPS, electronic Targeted Intervention for Psoriasis; HADS, Hospital Anxiety and Depression Scale; QW, once weekly.

Table 2 Baseline scores and change in scores after treatment as reported in each study

Author, year	Interventional study arm	Baseline score HADS-D	Baseline score HADS-A	Baseline score DLQI	Change in score HADS-D	Change in score HADS-A	Change in score DLQI	Expected DLQI score change for 1 HADS-D point	Expected DLQI score change for 1 HADS-A point
Bundy 2013[28]	eTIPS	5.0	7.6	6.6	-0.6	-0.8	-2.5	4.0	3.2
Dauden 2009[29]	Etanercept (Continuous)	5.7	7.2	12.8	-1.8	-2.0	-8.8	5.0	4.4
	Etanercept (Paused)	6.2	7.7	13.8	-1.5	-1.8	-7.7	5.0	4.2
Gniadecki 2012[31]	Etanercept BIW	6.6	8.3	12.3	-1.6	-1.9	-7.9	4.9	4.2
	Etanercept QW	6.4	8.0	12.3	-1.4	-1.7	-6.8	4.9	4.0
Langley 2010[32]	Ustekinumab 45 mg	4.9	6.8	12.2	-1.7	-1.6	-9.3	5.4	5.8
	Ustekinumab 90 mg	5.4	6.9	12.6	-2.1	-1.6	-10.0	4.8	6.3
Trial No: NCT01309737[33]	CP-690,550 5 mg	6.0	7.1	13.2	-2.4	-2.7	-8.2	3.4	3.0
	CP-690,550 10 mg	5.6	6.9	12.7	-2.5	-2.6	-9.4	3.8	3.6
Mean (SD)		5.8 (0.6)	7.4 (0.5)	11.1 (2.2)	-1.7 (0.6)	-1.9 (0.6)	-7.8	4.6	4.3
Range		4.9-6.6	6.8-8.3	6.6-13.8	-2.5 to -0.6	-2.7 to -0.8	-10.0 to -2.5	3.4-5.5	3.0-6.3

BIW, twice weekly; DLQI, Dermatology Life Quality Index; eTIPS, electronic Targeted Intervention for Psoriasis; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale–Depression; QW, once weekly.

The inventory covers various aspects of mental health and depression as well as physical clinical manifestations and relationships. The HADS scale was developed in 1983[19] as a screening tool and consists of 14 items (score range 0-21). The questions encapsulate two domains: anxiety (HADS-A) and depression (HADS-D), each containing seven questions with a four-level response system. Scores ranging from 0 to 7 are considered "normal," 8 to 10 "borderline abnormal," and 11 to 21 "abnormal."

DLQI and the psychiatric measures scores

Mean scores at baseline ranged from 6.6-13.8 for the DLQI, 8.1-12.3 for the BDI, 5.0-6.6 for HADS-D, and 6.8-8.3 for the HADS-A. At treatment endpoint, the scores ranged from 2.6-6.1 for the DLQI, 5.8-10.5 for BDI, 3.1-5.00 for HADS-D, and 4.3-6.1 for HADS-A (Table 2). In five studies, the DLQI was measured more frequently than the psychiatric scores throughout the study duration; however, only measurement scores for simultaneous assessment points of the two measures (ie, DLQI, HADS, or BDI) were examined.

Relationships between the DLQI and psychiatric measures

Change in score for these measures at treatment endpoint were recorded, or calculated where needed from the absolute data provided. As the HADS was the most commonly used tool (5 out of 7 studies), DLQI scores were correlated with this measure (Figure 2A and B). Both domains of the HADS were strongly correlated to the DLQI (HADS-D index: R^2= 0.715, and HADS-A index: R^2= 0.423).

Relevance of accumulative change of scores for the DLQI and HAD Scale

Table 2 demonstrates a mean baseline HADS-D score across all studies of 5.8 ("normal" according to the HADS-D scoring index[19]) and a mean baseline HADS-A score of 7.4 ("borderline abnormal"). The expected DLQI score change per HADS-D point is 4.59 and 4.29 for the HADS-A. This suggests that there is a relationship between the two scales, where improvement in DLQI scores may indicate incremental changes in HADS scores.

Discussion

Depression and other psychiatric issues continue to be significant problems experienced by dermatology patients, potentially affecting treatment compliance and leading to premature treatment discontinuation and alteration of the disease course.[20] The implications extend beyond QoL for concerned individuals, with concurrent economic repercussions through

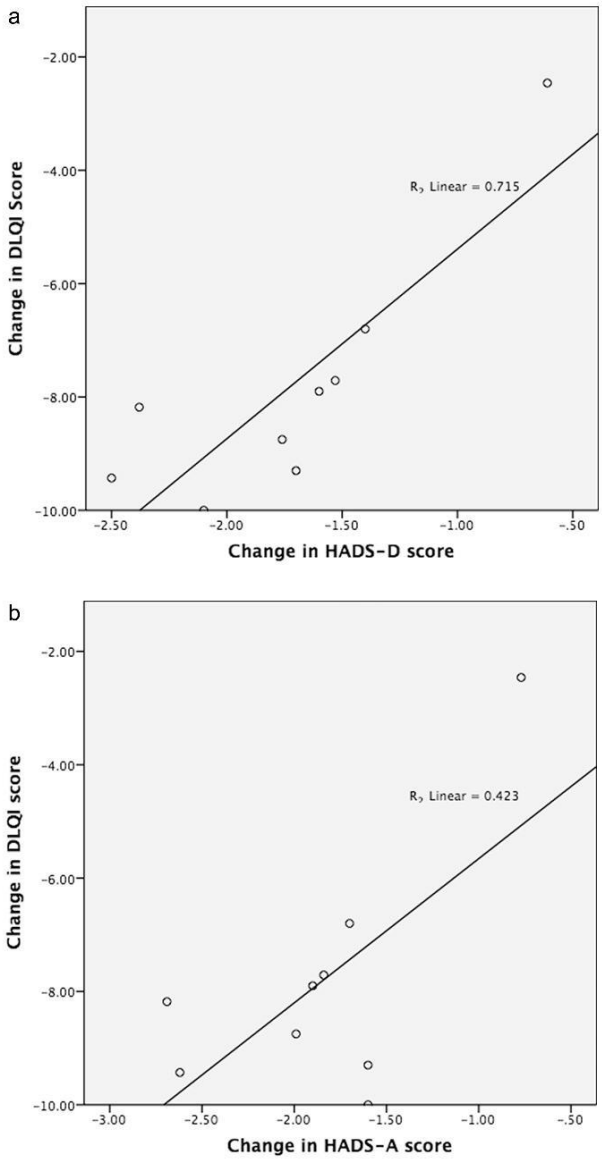


Fig. 2 **(a)** Correlation between change in DLQI scores and HADS-D scores. **(b)** Correlation between change in DLQI scores and HADS-A scores. DLQI, Dermatology Life Quality Index; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale–Depression.

lost productivity and sick leave.[21,22] Researchers often administer QoL tools, which encompass a psychologic component alongside psychiatric measures where appropriate to gather holistic efficacy data, though these are predominantly cited as secondary outcomes. This systematic review highlights the need for more frequent psychiatric assessment in randomized controlled trials, particularly where quality of life is measured; several studies had to be excluded from this review as a result. Full scores for psychiatric measures are not always provided, with researchers favoring clinical data. Although primary outcomes are centered on these clinical parameters, psychiatric morbidity should not be sidelined, given its prevalence in this population.[2–7]

Although the HADS is commonly used to assess clinical manifestations of depression and anxiety, it is most appropriate as a screening tool, with routine clinical psychiatric assessment considered as the primary diagnostic method.[23] The DLQI contains questions on various aspects of quality of life, including "embarrassment" and "self-consciousness," but it does not overtly record data on depression or anxiety.[8] The total DLQI score correlates well with score changes in the Depression component of the HADS, though not as well as with the Anxiety component (Figure 2A and B). It may be possible to consider depression and anxiety in patients using DLQI scores, especially in the absence of an appropriate psychiatric measure; a DLQI score change of 4.59 and 4.29 results in a point change for the HADS-D and HADS-A, respectively. However, a significant limitation of this systematic review is that there was very little data in interventional trials where both DLQI and HADS values were provided, thereby necessitating further work on more expansive data sets for more accurate and refined correlation values.

Several studies used inappropriate or nonvalidated scales to assess psychiatric morbidity, which led to their exclusion in this systematic review. The frequency at which this data was recorded compared with quality of life also varied across studies, despite the majority of the identified studies belonging to the same intervention group. Generic and disease-specific QoL questionnaires may capture elements of depression and other mental health disorders, though these have not been validated as such for their primary purpose. Where psychiatric scores were provided, on occasion, the authors omitted commenting on the results and therefore deducing worthwhile conclusions. We suggest guidelines to ensure routine and correct measurement of psychiatric clinical manifestations using appropriate measures, alongside QoL assessment. The diverse and inconsistent nature of the data-reporting limits the potential to analyze and compare data between trials, while potentially missing cases of depression or other significant mental health issues. Almost all the studies identified in this review assessed psoriasis, a condition commonly linked with psychologic distress.[24] In such cases, psychotherapy may be a significant adjuvant to traditional topical and systemic dermatologic treatment, further highlighting the need for full and accurate reporting of psychologic data.

There are several limitations to this review. Though the focus was primarily on interventional studies, to capture more extensive correlation data, observational studies could also have been included. We studied only DLQI data, given its widespread implementation[15]; further research correlating other QoL measures may highlight other patterns of data reporting. The mean baseline HADS-D score of 5.8 is rated "normal" according to the screening cut-off[19] and 7.4 "borderline abnormal" for the HADS-A. This highlights that mostly patients without, or with minimal, psychiatric morbidity were recruited, emphasizing the limited availability of such data in trials. Perhaps if data with patients suffering with more significant psychiatric morbidity were available for randomized controlled trials, we might see higher score changes in the HAD scale and subsequently more sensitive DLQI correlation values (Table 2).

Conclusions

The results of this systematic review echo our recent calls for guidance on the reporting of QoL scores[15]; we extend these suggestions for psychiatric morbidity reporting. Given the widespread adoption of the DLQI by health care policy makers, it is important that clinicians understand its potential value in informing routine decision-making.[25] Chronic skin conditions are associated with impaired QoL and morbidity rather than mortality; thus such questionnaires are perceived to be more relevant by patients. This in turn encourages patients to be more actively involved in their health care decisions.[26] Though skin diseases are assessed using clinical parameters, their visible nature means that patients often suffer with depression and suicidal ideation.[23] If appropriate measures such as the HADS are not administered, these potentially serious clinical manifestations may be missed, perhaps leading to avoidable detrimental consequences.

References

1. Finlay AY, Ryan TJ. Disability and handicap in dermatology. *Int J Dermatol.* 1996;35:305-311.
2. Jowett S, Ryan TJ. Skin disease and handicap: an analysis of the impact of skin conditions. *Soc Sci Med.* 1985;20:425-429.
3. Ferreira BI, Abreu JL, Dos Reis JP, et al. Psoriasis and associated psychiatric disorders: a systematic review on etiopathogenesis and clinical correlation. *J Clin Aesthet Dermatol.* 2016;9:36-43.
4. Karia SB, De Sousa A, Shah N, et al. Psychiatric morbidity and quality of life in skin diseases: a comparison of alopecia areata and psoriasis. *Ind Psychiatry J.* 2015;24:125-128.
5. Hedayat K, Karbakhsh M, Ghiasi M, et al. Quality of life in patients with vitiligo: a cross-sectional study based on Vitiligo Quality of Life index (VitiQoL). *Health Qual Life Outcomes.* 2016;14:1.
6. Egeberg A, Hansen PR, Gislason GH, et al. Patients with rosacea have increased risk of depression and anxiety disorders: a Danish nationwide cohort study. *Dermatology.* 2016;232:208-213.
7. Ekbäck MP, Lindberg M, Benzein E, et al. Health-related quality of life, depression and anxiety correlate with the degree of hirsutism. *Dermatology.* 2013;227:278-284.

8. Finlay AY, Khan G. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol.* 1994;19:210-216.
9. Mease PJ, Menter MA. Quality-of-life issues in psoriasis and psoriatic arthritis: outcome measures and therapies from a dermatological perspective. *J Am Acad Dermatol.* 2006;54:685-704.
10. Basra MKA, Fenech R, Gatt RM, et al. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol.* 2008;159:997-1035.
11. Basra MKA, Salek MS, Camilleri L, et al. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology.* 2015;230:27-33.
12. Hongbo Y, Thomas CL, Harrison MA, et al. Translating the science of quality of life into practice: what do Dermatology Life Quality Index scores mean? *J Invest Dermatol.* 2005;125:659-664.
13. Bronsard V, Paul C, Prey S, et al. What are the best outcome measures for assessing quality of life in plaque type psoriasis? A systematic review of the literature. *J Eur Acad Dermatol Venereol.* 2010;24:17-22.
14. Loo WJ, Diba V, Chawla M, et al. Dermatology Life Quality Index: influence of an illustrated version. *Br J Dermatol.* 2003;148:279-284.
15. Ali FM, Cueva AC, Vyas J, et al. A systematic review of the use of quality of life instruments in randomized controlled trials for psoriasis. *Br J Dermatol.* 2017;176:577-593.
16. Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions.* Vol 5. Wiley Online Library; 2008.
17. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17:1-12.
18. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961;4:561-571.
19. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67:361-370.
20. Cvetkovski RS, Zachariae R, Jensen H, et al. Quality of life and depression in a population of occupational hand eczema patients. *Contact Dermatitis.* 2002;54:106-111.
21. Diepgen TL. Occupational skin-disease data in Europe. *Int Arch Occup Environ Health.* 2003;76:331-338.
22. Simon GE, Barber C, Birnbaum HG. Depression and work productivity: the comparative costs of treatment versus non treatment. *J Occup Environ Med.* 2001;43:2-9.
23. Boehm D, Schmid-Ott G, Finkeldey F, et al. Anxiety, depression and impaired health-related quality of life in patients with occupational hand eczema. *Contact Dermatitis.* 2012;67:184-192.
24. Russo PA, Ilchef R, Cooper AJ. Psychiatric morbidity in psoriasis: a review. *Australas J Dermatol.* 2004;45:155-161.
25. Finlay AY, Salek MS, Abeni D, et al. Why quality of life measurement is important in dermatology clinical practice: an expert-based opinion statement by the EADV Task Force on Quality of Life. *J Eur Acad Dermatol Venereol.* 2017;31:424-431.
26. Frost MH, Reeve BB, Liepa AM, et al. What is sufficient evidence for the reliability and validity of patient-reported outcome measures? *Value Health.* 2007;10:S94-S105.
27. Bostoen J, Bracke S, De Keyser S, et al. An educational programme for patients with psoriasis and atopic dermatitis: a prospective randomized controlled trial. *Br J Dermatol.* 2012;167:1025-1031.
28. Bundy C, Pinder B, Bucci S, et al. A novel, web-based, psychological intervention for people with psoriasis: the electronic Targeted Intervention for Psoriasis (eTIPs) study. *Br J Dermatol.* 2013;169:329-336.
29. Dauden E, Griffiths CE, Ortonne JP, et al. Improvements in patient-reported outcomes in moderate-to-severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. *J Eur Acad Dermatol Venereol.* 2009;23:1374-1382.
30. Gelfand JM, Kimball AB, Mostow EN, et al. Patient-reported outcomes and health-care resource utilization in patients with psoriasis treated with etanercept: continuous versus interrupted treatment. *Value Health.* 2008;11:400-407.
31. Gniadecki R, Robertson D, Molta CT, et al. Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. *J Eur Acad Dermatol Venereol.* 2012;26:1436-1443.
32. Langley RG, Feldman SR, Han C, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: results from a randomized, double-blind, placebo-controlled phase III trial. *J Am Acad Dermatol.* 2010;63:457-465.
33. ClinicalTrials.gov. A phase 3, multi-site, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of 2 oral doses of CP-690,550 in subjects with moderate to severe chronic plaque psoriasis. Available at:https://clinicaltrials.gov/ct2/show/study/NCT01309737?term=%22DLQI%22+AND+%22Depression%22&rank=3&sect=Xb0156_0a. Accessed October 30, 2016.

Appendices

Appendix I: Systematic review protocol

PROTOCOL FOR A SYSTEMATIC REVIEW
*Based on PRISMA-P

Section 1: Administrative Information

Title:
What evidence is there that any therapies for Psoriasis have an impact on Health-Related Quality of Life. Protocol for a Systematic Review

Registration
PROSPERO registry number:
In accordance with the guidelines, our systematic review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 13/05/2015 (registration number CRD42015009193)

Corresponding Author: Faraz Mahmood Ali. Clinical Research Fellow in Dermatology. Department of Dermatology, School of Medicine, Cardiff University, 3rd Floor Glamorgan House, Heath Park, Cardiff, Wales, UK, CF14 4XN. alifm@cf.ac.uk

Investigators:

Dr. Faraz Mahmood Ali: Clinical Research Fellow, Dept. of Dermatology and Wound Healing, Cardiff University School of Medicine.
Email: alifm@cardiff.ac.uk
Andrea Cueva, Honorary Research Fellow. Ecuadorian National government through the National Institution of Higher Education, Science, Technology and Innovation (SENESCYT).
Email: andrea.c.cueva@hotmail.com
Professor Andrew Finlay: Former Head of Department of Dermatology and Wound Healing, Cardiff University School of Medicine.
Email: FinlayAY@cardiff.ac.uk
Professor Sam Salek: Department of Pharmacy, University of Hertfordshire, Hatfield and Institute for Medicines Development, Cardiff, UK.

Email: mssalek@gmail.com
Professor Vincent Piguet: Head of Department of Dermatology and Wound Healing, Cardiff University School of Medicine
Email: PIguetV@cardiff.ac.uk
Dr. Jui Vyas: Senior Clinical Lecturer, Dept. of Dermatology and Wound Healing, Cardiff University School of Medicine

Email: VyasJJ@cardiff.ac.uk
Dr. Ausama Atwan: Clinical Lecturer, Dept. of Dermatology and Wound Healing, Cardiff University School of Medicine
Email: AtwanAA@cardiff.ac.uk

Contributions:
Faraz Ali
Andrea Cueva
Ausama Atwan
Jui Vyas
Andrew Finlay
Sam Salek
Vincent Piguet

Support: **The present study will be funded as part of a research post at Cardiff University**

Sponsor
Site: Department of Dermatology, School of Medicine, Cardiff University, 3rd Floor Glamorgan House, Heath Park, Cardiff, Wales, UK, CF14 4XN
Study commencement date: November 2014
Study duration (post- ethical permission): 1-2 years

Introduction

Psoriasis is a chronic incurable disfiguring skin condition that runs a remitting-relapsing course characterised by fluctuations in clinical severity and perhaps in quality of life in some patients. Patients with more widespread psoriasis require long term systemic therapy and regular and frequent monitoring for potential adverse effects of the systemic drugs. Consequently frequent assessments of disease severity and quality of life are necessary to help guide optimal treatment planning and decision-making. Treatments range from topical applications to systemic therapies and biologics. But how effective are various treatments in Psoriasis in impacting Health-related Quality of Life (HRQoL)?

The measurement of the impact of skin disease on the lives of patients (Finlay 1998; Basra and Shahrukh 2009) is increasingly being recognised as an essential aspect in the assessment of the burden of skin disease. The Dermatology Life Quality Index (DLQI) (Finlay and Khan 1994; Basra et al 2008) is a dermatology-specific quality of life measure that has been widely used as a patient reported outcome measure in dermatology clinical research as well as in clinical practice.

Dermatological Life Quality Index (DLQI)

A dermatology specific quality of life instrument with 10 items assessing the impact of any skin disease on the everyday life of an individual. Scoring see www.dermatology.org.uk
This instrument has been widely used among dermatological patients from all over the world (Basra et al 2008). The scoring is from 0 to 30, a higher score indicates greater quality of life impairment; a DLQI score of more than 10 means a very large effect on patient's life (Hongbo et al, 2005).
The DLQI has been used in many dermatological conditions and across a wide range of disease severities (Mease and Menter, 2006; Basra et al, 2008). The DLQI has a high validity, reliability and internal consistency (Mease and Menter, 2006), acceptability (mean of 2 minutes to complete the questionnaire), good interpretability and availability of many language translations (Bronsard et al, 2010).

Objectives

To do a literature search till date of all the Randomised Controlled Trials and Studies on Psoriasis involving interventions with HRQoL outcomes measured. A Systematic Review will then be performed to identify, appraise and synthesise all high quality research evidence to identify if any interventions impact HRQoL in Psoriasis.

Ethical consideration

Formal ethical permission may not be needed as historical data is being used from existing literature.

Methodology

Eligibility Criteria

Types of studies

We included randomised controlled trials including cross-over trials and trials with open-label extensions.
Only papers where the total scores for the QoL tools were provided were included. An exception is when the QoL questionnaires are validated to be reported as subscales.
Types of participants

Adults (age 18 and over) of either sex and of any ethnicity, with a clinical diagnosis of psoriasis. We included all subtypes of psoriasis.

If the subjects suffer with a co-morbidity such as psoriatic arthritis, a skin-related quality of life scale must be included

Types of interventions

We included all randomised controlled trials with any intervention used for the treatment of psoriasis including, but not limited to: systemic therapy, topical therapy and psychological therapy.
These trials included comparisons of any intervention with placebo or another active intervention

Types of outcome measures

Primary Outcomes

1. All quality of life scores with any quality of life scale

Secondary outcomes

Evidence that the study used a psoriasis severity scale for clinical correlation:

4. Psoriasis Area and Severity Index (PASI) score OR
5. The proportion of participants attaining PASI 50, 75, and 90, defined as a 50%, 75%, or 90% reduction in PASI score relative to the baseline PASI score immediately prior to treatment initiation OR
6. If 1 or 2 not available, the primary Psoriasis Severity Scale used will be recorded

Exclusion criteria

Psoriatic arthritis studies where it is not possible to differentiate arthritis' quality of life from psoriasis' quality of life data will be excluded.
Studies which include any patient less than 18 years of age.
Articles where the change in QoL values cannot be reliably calculated will be excluded. This includes graphical representation.
For consistency, QoL data only presented as sub-scales, where total scores are usually calculated, were excluded. Abstracts and posters where further data is not available upon contacting the author, were also excluded.
For studies with an open label extension, the data will only be extracted for the period of the study while it was randomised and controlled.
For cross-over trials, the data will only be extracted prior to the crossover.

Search methods for identification of studies

We aimed to identify all relevant randomised controlled trials (RCTs) in the English language regardless of publication status (published, unpublished, in press, or in progress).

Information Sources

Electronic searches

We searched the following databases up to 10 November 2014:

- OVID Medline using the search strategy in Appendix II
- OVID Medline: In Process using the search strategy in Appendix III
- Embase using the search strategy in Appendix IV
- Web of Science Core Collection using the search strategy in Appendix V
- Scopus using the search strategy in Appendix VI
- Cochrane Database using the search strategy in Appendix VII

Searching other resources

Trials registers

We searched the following trials registers:

- The metaRegister of Controlled Trials (http://www.isrctn.com).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
- The EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

Handsearching

In order to identify other potential RCTs for inclusion, FA and AC will hand-search the abstracts of proceedings from the following major dermatology conferences that were not already recorded in the Cochrane Skin Group Specialised Register:

- American Academy of Dermatology;
- British Association of Dermatologists;
- European Academy of Dermatology and Venereology (EADV);
- European Society for Dermatological Research (ESDR);

- International Investigative Dermatology; and
- Society for Investigative Dermatology (SID).

Grey literature

We will check the reference lists of included and excluded studies for further references to relevant trials
We will contact by email authors of conference abstracts, meeting posters, letters to editors to check for unpublished RCTs. If there is no response and if data is inadequate, the citation will be discarded.

Search Strategy

Search strategy for databases included on Appendix II

Correspondence

We corresponded with authors where necessary to determine if a study met the criteria for inclusion and to obtain additional data where necessary

Data management

Selection of studies

Two authors (FA and AC) will independently compare the titles and abstracts of the studies retrieved by the searches with the inclusion criteria. They will examine the full texts of studies that potentially meet the criteria, as well as the studies whose abstracts do not provide sufficient information. A third author (AA) will resolve any disagreements in terms of final study selection. We will record the reasons for exclusion of studies.

Data extraction and management

Two authors (FA and AC) will independently extract data using a data extraction form based on the 'Checklist of items to consider in data collection or data extraction' found in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). A third author (AA) will resolve any disagreements. Two authors (FA and AC) will pilot the data collection form prior to use.

Dealing with missing data

Articles where the QoL data has not been provided or has partially been provided on a graphic representation, which do not include numerical or percentual values and therefore its data cannot be extracted will be excluded.

Recording of data and retention of documents

Throughout the course of the study and at the completion of each stage research data will be entered onto data collection sheets and entered into SPSS version 16. At the end of the final study all the data will be collected and subjected to thorough analysis. All the research documents will be kept in a secure place under lock in the Dept. of Dermatology of UHW. Only the key researchers will have access to these data.

Risk of bias in individual studies

Two authors (FA and AC) will independently assess the methodological quality of included studies using the The Cochrane Collaboration's 'Risk of bias' tool (Higgins 2011). The risk of bias will be graded as 'low', 'high', or 'unclear' for each of the following domains:
(a) random sequence generation;
(b) allocation concealment;
(c) blinding of participants, personnel, and outcome assessment;
(d) incomplete outcome data;
(e) selective outcome reporting (we will check trial databases to ensure that reported outcomes match to those prospectively listed); and
(f) other sources of bias.

Data analysis

Data will be analysed using SPSS version 22 and Microsoft Excel 2011. The data will be mostly qualitative with basic quantitative analyses.

Confidence in cumulative evidence

Jadad scoring will be used to grade the evidence

Publication of Results

At the end of study the results will be submitted for presentation at national and international research meetings and for publication.

Conflict of Interests

Andrew Y. Finlay is joint copyright owner of the DLQI. The other authors state no conflict of intere

References

Basra MKA, Fenech R, Gatt RM, *et al* (2008). The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J of Dermatol* 159: 997-1035.

Basra MKA, Shahrukh M (2009). Burden of skin diseases. *Expert Rev. Pharmacoeconomics Outcomes Res.* 9(3): 271-283.

Bronsard V, Paul C, Prey S, *et al* (2010). What are the best outcome measures for assessing quality of life in plaque type psoriasis? A systematic review of the literature. *JEADV* 24 (2): 17-22

Finlay AY, Khan GK (1994). Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. *Clin Exp Dermatol* 19: 210-216

Finlay AY (1998). Quality of Life Assessments in Dermatology. *Semin in Cutan Med Surg* 17(4): 291-296

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March
2011]. The Cochrane Collaboration 2011. Available from www.cochrane-handbook.org

Hjortsberg, C. et al. 2011. Are Treatment Satisfaction, Quality of Life, and Self-assessed Disease Severity Relevant Parameters for Patient Registries? Experiences from Finnish and Swedish Patients with Psoriasis. Acta Dermato-Venereologica 91(4), pp. 409-414.

Hongbo Y, Thomas CL, Harrison MA, *et al* (2005). Translating the Science of Quality of Life into Practice: What Do Dermatology Life Quality Index Score Mean? *J Invest Dermatol* 125: 659-664

Longworth, L. and Rowen, D. 2011. NICE DSU Technical Support Document 10:The use of mapping methods to estimate health state utility values. Report by the Decision Support Unit. Sheffield: National Institute for Health and Clinical Excellence (NICE): Decision Support Unit.

Mease PJ, Menter MA (2006). Quality-of-life issues in psoriasis and psoriatic arthritis: Outcome measures and therapies from a dermatological perspective. *J Am Acad Dermatol* 54(4): 685-704

Matusiak, L. et al. 2010. Psychophysical Aspects of Hidradenitis Suppurativa. Acta Dermato-Venereologica 90(3), pp. 264-268.

Radtke, M. A. et al. 2009. Willingness-to-pay and quality of life in patients with vitiligo. British Journal of Dermatology 161(1), pp. 134-139.

Scalone, L. et al. 2006. PSK8 Convergent validity and sensitivity to change of the generic instrument EQ-5D and the disease-specific DLQI in atopic dermatitis. Value in Health 9(6), pp. A268-A269. Abstract only.
Shikiar, R. et al. 2007. Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: Patient-reported outcomes from a Phase II randomised controlled trial. Journal of Dermatological Treatment 18(1), pp. 25-31.
Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D Scores for the United Kingdom. Med Decis Making. 2011.

Appendix II: Medline OVID search strategy

1.psoriasis.mp.orexpPsoriasis/
2.psoria*.mp.
3.erythrodermicpsoriasis.mp.
4.guttatepsoriasis.mp.
5.pustularpsoriasis.mp.
6.palmoplantarpsoriasis.mp.
7.psoriasisvulgaris.mp.
8.plaquepsoriasis.mp.
9.localisedpustularpsoriasis.mp.
10.localizedpustularpsoriasis.mp.
11.inversepsoriasis.mp.
12.scalppsoriasis.mp.
13.nailpsoriasis.mp.
14.inflammatorypsoriasis.mp.
15.or/1-14
16.intervention*.mp.
17.treatment*.mp.
18.topical.mp.
19.systemic.mp.
20.immunosuppressivedrug.mp.
21.ImmunosuppressiveAgents/
22.NonprescriptionDrugs/
23.over-the-counter.mp.
24.otc.mp.
25.expTars/
26.(tarortars).tw.
27.expSteroids/
28.expRetinoids/
29.retinoid*.tw.
30.steroid*.tw.
31.expemollientagent/
32.emollient*.tw.
33.expTacrolimus/
34.tacrolimus.tw.
35.topicalimmunemodulator*.tw.

36.(topicaladj3therap*).tw.
37.(topicaladj3treatment*).tw.
38.(topicaladj3agent*).tw.
39.vitaminDanalogues.mp.
40.calcipotriol.mp.
41.dovonex.tw.
42.dovobet.tw.
43.xamiol.tw.
44.calcipotriene.mp.
45.taclonex.tw.
46.Calcitriol/orcalcitriol.mp.
47.silkis.tw.
48.tacalcitol.mp.
49.curatoderm.tw.
50.vitaminD.tw.
51.tars.mp.orTars/
52.(calamineandcoaltarointment).mp.
53.coaltar.mp.
54.calamine.mp.
55.(coaltarandsalicylicacidointment).mp.
56.coaltarpaste.mp.
57.(zincandcoaltarpaste).mp.
58.zincoxide.mp.
59.alphosyl.mp.
60.crudecoaltar.mp.
61.dithranol.mp.
62.anthralin.mp.orAnthralin/
63.dithrocream.tw.
64.micanol.tw.
65.psorin.tw.
66.zithranol.tw.
67.topicalretinoids.mp.
68.tazarotene.mp.
69.zorac.tw.
70.tazorac.tw.
71.corticosteroid.mp.
72.hydrocortisone.mp.orHydrocortisone/

73.dioderm.tw.
74.mildison.tw.
75.alphaderm.tw.
76.calmuridHC.tw.
77.eurax-hydrocortisone.tw.
78.canestenHC.tw.
79.daktacort.tw.
80.fucidinH.tw.
81.nystaform-HC.tw.
82.timodine.tw.
83.hydrocortisonebutyrate.mp.
84.locoid.tw.
85.locoidcrelo.tw.
86.alclometasonedipropionate.mp.
87.modrasone.tw.
88.betamethasoneesters.mp.
89.betamethasonevalerate.tw.
90.betacap.tw.
91.betesil.tw.
92.betnovate.tw.
93.betnovate-rd.tw.
94.bettamousse.tw.
95.diprosone.tw.
96.diprosalic.tw.
97.betnovate-c.tw.
98.betnovate-n.tw.
99.fucibet.tw.
100.lotriderm.tw.
101.clobetasolpropionate.mp.
102.clarelux.tw.
103.dermovate.tw.
104.etrivex.tw.
105.dermovate-nn.tw.
106.clobetasonebutyrate.mp.
107.eumovate.tw.
108.diflucortolonevalerate.mp.
109.nerisone.tw.

110.nerisoneforte.tw.
111.fludroxycortide.mp.
112.flurandrenolone.tw.
113.haelan.tw.
114.fluocinoloneacetonide.mp.orFluocinoloneAcetonide/
115.synalar1in4dilution.tw.
116.synalar1in10dilution.tw.
117.synalarc.tw.
118.synalarn.tw.
119.fluocinonide.mp.orFluocinonide/
120.metosyn.tw.
121.fluocortolone.mp.orFluocortolone/
122.ultralanumplain.tw.
123.fluticasonepropionate.mp.
124.cutivate.tw.
125.mometasonefuroate.mp.
126.elocon.tw.
127.triamcinoloneacetonide.mp.orTriamcinoloneAcetonide/
128.aureocort.tw.
129.KeratolyticAgents/orkeratolytic.mp.
130.salicylicacid.mp.orSalicylicAcid/
131.zinc.mp.andsalicylicacidpaste.tw.
132.Sulfur/orsulphur.mp.
133.expUltravioletRays/
134.expUltravioletTherapy/
135.ultraviolet*.tw.
136.(uvorUVBorUVA).tw.
137.phototherapy.mp.orPhototherapy/
138.ultravioletb.mp.
139.UVB.mp.
140.narrowbandUVB.mp.
141.narrow-bandUVB.mp.
142.narrowbandUVBtherapy.mp.
143.broadbandlighttherapy.mp.
144.ultravioletlight.mp.
145.UVlight.mp.
146.naturallight.mp.

147.combinationlighttherapy.mp.
148.photochemotherapy.mp.orPhotochemotherapy/
149.psoralen.mp.
150.PUVA.mp.
151.oralretinoids.mp.
152.acitretin.mp.orAcitretin/
153.neotigason.tw.
154.cyclosporin.mp.orCyclosporine/
155.ciclosporin.mp.
156.deximune.tw.
157.neoral.tw.
158.sandimmune.tw.
159.hydroxycarbamide.mp.
160.hydrea.tw.
161.hydroxyurea.mp.orHydroxyurea/
162.methotrexate.mp.orMethotrexate/
163.metoject.tw.
164.cytokinemodulators.mp.
165.etanercept.mp.
166.enbrel.tw.
167.adalimumab.mp.
168.humira.tw.
169.infliximab.mp.
170.remicade.tw.
171.ustekinumab.mp.
172.stelara.tw.
173.efalizumab.mp.
174.raptiva.tw.
175.biologic*.mp.
176.Psychotherapy/
177.(psycho*adj3therap*).tw.
178.psychotherap*.tw.
179.expCognitiveTherapy/
180.(cognit*adj3therap*).tw.
181.((behaviourorbehavior)adj3therap*).tw.
182.psychoeducation.tw.
183.CBT.tw.

184.expPeerGroup/
185.expSelf-HelpGroups/
186.(peeradj3group*).tw.
187.((supportorself-helporselfhelp)adj3group*).tw.
188.alternativetherapy.mp.
189.homeopathy.mp.orHomeopathy/
190.Relaxation/orrelaxation.mp.
191.oreganooil.mp.
192.traditionaltreatment*.mp.
193.oatextracts.mp.
194.coldwaterfishoils.mp.
195.eveningprimroseoil.mp.
196.teatreeoil.mp.or"TeaTreeOil"/
197.aloevera.mp.orAloe/
198.taichi.mp.
199.yoga.mp.orYoga/
200.laser.mp.
201.herbalmedication.mp.
202.petroleumjelly.mp.
203.massage*.mp.
204.sharkcartilageextract.mp.
205.meditation.mp.orMeditation/
206.complementarytherapy.mp.orComplementaryTherapies/
207.hypnotherapy.mp.
208.milkthistle.mp.orMilkThistle/
209.expMotorActivity/
210.(physicaladj3activit$).tw.
211.expExercise/
212.expExerciseTherapy/
213.exercis$.tw.
214.expLifeStyle/
215.lifestyle$.tw.
216.(lifeadj3style$).tw.
217.expHealthBehavior/
218.(healthadj3(behavior$orbehaviour$)).tw.
219.expDiet/
220.expDietarySupplements/

221.diet$.tw.
222.nutrition$.tw.
223.expObesity/
224.expBodyWeight/
225.obes$.tw.
226.weight$.tw.
227.expSmoking/
228.(smokingorsmoker*).tw.
229.expAlcohol-RelatedDisorders/
230.expAlcoholicBeverages/
231.alcohol*.tw.
232.drinking.tw.
233.expEmployment/
234.expOccupations/
235.(employment*oroccupation*orwork).tw.
236.goeckermantherapy.mp.
237.excimertherapy.mp.
238.scalelifters.mp.
239.non-biologicalmedications.mp.
240.FishOils/orfishoil*.mp.
241.vitamins.mp.orVitamins/
242.vitaminE.mp.orVitaminE/
243.VitaminA/orvitaminA.mp.
244.mineral*.mp.
245.selenium.mp.orSelenium/
246.Antimetabolites/orantimetabolite*.mp.
247.thioguanine.mp.orThioguanine/
248.tioguanine.mp.
249.miscellaneous.mp.
250.immunomodulatoragents.mp.
251.immunomodulatordrugs.mp.
252.calcineurininhibitors.mp.
253.anti-itch.mp.
254.e45cream.mp.
255.fumaricacidesters.mp.
256.fumaricacidesters.mp.
257.FAE.mp.

258.sorbelene.mp.
259.anti-fungal.mp.
260.skinbiopsy.mp.
261.alefacept.mp.
262.amevive.tw.
263.or/16-262
264.QOL.mp.
265.qualityoflife.mp.or"QualityofLife"/
266.healthrelatedqualityoflife.mp.
267.HRQOL.mp.
268.EQ5D.mp.
269.nationalpsoriasisfoundation.mp.
270.skindex.mp.
271.DLQI.mp.
272.dermatologylifequalityindex.mp.
273.burdenofskindisease.mp.
274.patientreportedoutcomemeasure.mp.
275.qualityoflifeimpairment.mp.
276.outcomemeasurement.mp.
277."OutcomeAssessment(HealthCare)"/oroutcomeassessment.mp.
278.QOLtools.mp.
279.patientreportedoutcome.mp.
280.PRO.mp.
281.NHP.mp.
282.WHO-QOL.mp.
283.psoriasisdisabilityindex.mp.
284.PDI.mp.
285.salfordpsoriasisindex.mp.
286.SPI.mp.
287.FDLQI.mp.
288.PFI.mp.
289.skindex-16.mp.
290.skindex-29.mp.
291.skindex-teen.mp.
292.childrensdermatologylifequalityindex.mp.
293.CDLQI.mp.
294.familydermatologylifequalityindex.mp.

295.psoriasis-specificmeasureofqualityoflife.mp.

296.PSORIQoL.mp.

297.USPSORIQoL.mp.

298.skindex-17.mp.

299.DQOLS.mp.

300.dermatologyqualityoflifescales.mp.

301.shortform-36.mp.

302.KMPI.mp.

303.PDI.mp.

304.nationalpsoriasisfoundationpsoriasisscore.mp.

305.NPF-PS.mp.

306.physicianstaticglobalassessment.mp.

307.PSGA.mp.

308.overalllesionassessment.mp.

309.OLA.mp.

310.physiciandynamicglobalassessment.mp.

311.physiciandynamicglobalassessment.mp.

312.PDGA.mp.

313.latticesystemglobalpsoriasisscore.mp.

314.LS-GPS.mp.

315.PsAQoL.mp.

316.dermatologyindexofdiseaseseverity.mp.

317.DIDS.mp.

318.psoriasislifestressinventory.mp.

319.PLSI.mp.

320.WHOQOL-26.mp.

321.WHOQOL-100.mp.

322.patientgeneralindex.mp.

323.PGI.mp.

324.DIELH.mp.

325.VQ-dermato.mp.

326.impactofchronicskindiseaseondailylife.mp.

327.ISDL.mp.

328.freiberglifequalityassessment.mp.

329.FLQA.mp.

330.SF-29.mp.

331.valueoflife/

332.qualityadjustedlifeyear/
333.qualityadjustedlife.tw.
334.(qaly$orqald$orqale$orqtime$).tw.
335.disabilityadjustedlife.tw.
336.daly$.tw.
337.healthstatusindicators/
338.(sf36orsf36orshortform36orshortform36orsfthirtysixorsfthirtysixorshortformthirtysixorshortformthirtysixorshortformthirtysixorshortformthirtysix).tw.
339.(sf6orsf6orshortform6orshortform6orsfsixorsfsixorshortformsixorshortformsix).tw.
340.(sf12orsf12orshortform12orshortform12orsftwelveorsftwelveorshortformtwelveorshortformtwelve).tw.
341.(sf16orsf16orshortform16orshortform16orsfsixteenorsfsixteenorshortformsixteenorshortformsixteen).tw.
342.(sf20orsf20orshortform20orshortform20orsftwentyorsftwentyorshortformtwentyorshortformtwenty).tw.
343.(euroqoloreuroqoloreq5doreq5d).tw.
344.(hqlorhqolorhqolorhrqolorhrqol).tw.
345.(hyeorhyes).tw.
346.health$year$equivalent$.tw.
347.healthutilit$.tw.
348.(huiorhui1orhui2orhui3).tw.
349.disutili$.tw.
350.rosser.tw.
351.qualityofwellbeing.tw.
352.qwb.tw.
353.willingnesstopay.tw.
354.standardgamble$.tw.
355.timetradeoff.tw.
356.timetradeoff.tw.
357.tto.tw.
358.or/264-357
359.RandomisedControlledTrialsasTopic/
360.Randomi?edcontrolledtrial/
361.RandomAllocation/
362.DoubleBlindMethod/
363.SingleBlindMethod/
364.clinicaltrial/

365.clinicaltrial,phasei.pt.

366.clinicaltrial,phaseii.pt.

367.clinicaltrial,phaseiii.pt.

368.clinicaltrial,phaseiv.pt.

369.controlledclinicaltrial.pt.

370.randomi?edcontrolledtrial.pt.

371.multicenterstudy.pt.

372.clinicaltrial.pt.

373.expClinicalTrialsastopic/

374.randomly.ab.

375.trial.ab.

376.groups.ab.

377.or/359-376

378.(clinicaladjtrial$).tw.

379.((singl$ordoubl$ortreb$ortripl$)adj(blind$3ormask$3)).tw.

380.PLACEBOS/

381.placebo$.tw.

382.randomlyallocated.tw.

383.(allocatedadj2random$).tw.

384.or/378-383

385.377or384

386.casereport.tw.

387.letter/

388.historicalarticle/

389.or/386-388

390.385not389

391.15and263and358and390

Appendix III: Ovid Medline in Process search strategy

1.psoriasis.mp.orexpPsoriasis/
2.psoria*.mp.
3.erythrodermicpsoriasis.mp.
4.guttatepsoriasis.mp.
5.pustularpsoriasis.mp.
6.palmoplantarpsoriasis.mp.
7.psoriasisvulgaris.mp.
8.plaquepsoriasis.mp.
9.localisedpustularpsoriasis.mp.
10.localizedpustularpsoriasis.mp.
11.inversepsoriasis.mp.
12.scalppsoriasis.mp.
13.nailpsoriasis.mp.
14.inflammatorypsoriasis.mp.
15.or/1-14
16.intervention*.mp.
17.treatment*.mp.
18.topical.mp.
19.systemic.mp.
20.immunosuppressivedrug.mp.
21.ImmunosuppressiveAgents/
22.NonprescriptionDrugs/
23.over-the-counter.mp.
24.otc.mp.
25.expTars/
26.(tarortars).tw.
27.expSteroids/
28.expRetinoids/
29.retinoid*.tw.
30.steroid*.tw.
31.expemollientagent/
32.emollient*.tw.
33.expTacrolimus/
34.tacrolimus.tw.
35.topicalimmunemodulator*.tw.

36.(topicaladj3therap*).tw.
37.(topicaladj3treatment*).tw.
38.(topicaladj3agent*).tw.
39.vitaminDanalogues.mp.
40.calcipotriol.mp.
41.dovonex.tw.
42.dovobet.tw.
43.xamiol.tw.
44.calcipotriene.mp.
45.taclonex.tw.
46.Calcitriol/orcalcitriol.mp.
47.silkis.tw.
48.tacalcitol.mp.
49.curatoderm.tw.
50.vitaminD.tw.
51.tars.mp.orTars/
52.(calamineandcoaltarointment).mp.
53.coaltar.mp.
54.calamine.mp.
55.(coaltarandsalicylicacidointment).mp.
56.coaltarpaste.mp.
57.(zincandcoaltarpaste).mp.
58.zincoxide.mp.
59.alphosyl.mp.
60.crudecoaltar.mp.
61.dithranol.mp.
62.anthralin.mp.orAnthralin/
63.dithrocream.tw.
64.micanol.tw.
65.psorin.tw.
66.zithranol.tw.
67.topicalretinoids.mp.
68.tazarotene.mp.
69.zorac.tw.
70.tazorac.tw.
71.corticosteroid.mp.
72.hydrocortisone.mp.orHydrocortisone/

73.dioderm.tw.
74.mildison.tw.
75.alphaderm.tw.
76.calmuridHC.tw.
77.eurax-hydrocortisone.tw.
78.canestenHC.tw.
79.daktacort.tw.
80.fucidinH.tw.
81.nystaform-HC.tw.
82.timodine.tw.
83.hydrocortisonebutyrate.mp.
84.locoid.tw.
85.locoidcrelo.tw.
86.alclometasonedipropionate.mp.
87.modrasone.tw.
88.betamethasoneesters.mp.
89.betamethasonevalerate.tw.
90.betacap.tw.
91.betesil.tw.
92.betnovate.tw.
93.betnovate-rd.tw.
94.bettamousse.tw.
95.diprosone.tw.
96.diprosalic.tw.
97.betnovate-c.tw.
98.betnovate-n.tw.
99.fucibet.tw.
100.lotriderm.tw.
101.clobetasolpropionate.mp.
102.clarelux.tw.
103.dermovate.tw.
104.etrivex.tw.
105.dermovate-nn.tw.
106.clobetasonebutyrate.mp.
107.eumovate.tw.
108.diflucortolonevalerate.mp.
109.nerisone.tw.

110.nerisoneforte.tw.
111.fludroxycortide.mp.
112.flurandrenolone.tw.
113.haelan.tw.
114.fluocinoloneacetonide.mp.orFluocinoloneAcetonide/
115.synalar1in4dilution.tw.
116.synalar1in10dilution.tw.
117.synalarc.tw.
118.synalarn.tw.
119.fluocinonide.mp.orFluocinonide/
120.metosyn.tw.
121.fluocortolone.mp.orFluocortolone/
122.ultralanumplain.tw.
123.fluticasonepropionate.mp.
124.cutivate.tw.
125.mometasonefuroate.mp.
126.elocon.tw.
127.triamcinoloneacetonide.mp.orTriamcinoloneAcetonide/
128.aureocort.tw.
129.KeratolyticAgents/orkeratolytic.mp.
130.salicylicacid.mp.orSalicylicAcid/
131.zinc.mp.andsalicylicacidpaste.tw.
132.Sulfur/orsulphur.mp.
133.expUltravioletRays/
134.expUltravioletTherapy/
135.ultraviolet*.tw.
136.(uvorUVBorUVA).tw.
137.phototherapy.mp.orPhototherapy/
138.ultravioletb.mp.
139.UVB.mp.
140.narrowbandUVB.mp.
141.narrow-bandUVB.mp.
142.narrowbandUVBtherapy.mp.
143.broadbandlighttherapy.mp.
144.ultravioletlight.mp.
145.UVlight.mp.
146.naturallight.mp.

147.combinationlighttherapy.mp.
148.photochemotherapy.mp.orPhotochemotherapy/
149.psoralen.mp.
150.PUVA.mp.
151.oralretinoids.mp.
152.acitretin.mp.orAcitretin/
153.neotigason.tw.
154.cyclosporin.mp.orCyclosporine/
155.ciclosporin.mp.
156.deximune.tw.
157.neoral.tw.
158.sandimmune.tw.
159.hydroxycarbamide.mp.
160.hydrea.tw.
161.hydroxyurea.mp.orHydroxyurea/
162.methotrexate.mp.orMethotrexate/
163.metoject.tw.
164.cytokinemodulators.mp.
165.etanercept.mp.
166.enbrel.tw.
167.adalimumab.mp.
168.humira.tw.
169.infliximab.mp.
170.remicade.tw.
171.ustekinumab.mp.
172.stelara.tw.
173.efalizumab.mp.
174.raptiva.tw.
175.biologic*.mp.
176.Psychotherapy/
177.(psycho*adj3therap*).tw.
178.psychotherap*.tw.
179.expCognitiveTherapy/
180.(cognit*adj3therap*).tw.
181.((behaviourorbehavior)adj3therap*).tw.
182.psychoeducation.tw.
183.CBT.tw.

184.expPeerGroup/
185.expSelf-HelpGroups/
186.(peeradj3group*).tw.
187.((supportorself-helporselfhelp)adj3group*).tw.
188.alternativetherapy.mp.
189.homeopathy.mp.orHomeopathy/
190.Relaxation/orrelaxation.mp.
191.oreganooil.mp.
192.traditionaltreatment*.mp.
193.oatextracts.mp.
194.coldwaterfishoils.mp.
195.eveningprimroseoil.mp.
196.teatreeoil.mp.or"TeaTreeOil"/
197.aloevera.mp.orAloe/
198.taichi.mp.
199.yoga.mp.orYoga/
200.laser.mp.
201.herbalmedication.mp.
202.petroleumjelly.mp.
203.massage*.mp.
204.sharkcartilageextract.mp.
205.meditation.mp.orMeditation/
206.complementarytherapy.mp.orComplementaryTherapies/
207.hypnotherapy.mp.
208.milkthistle.mp.orMilkThistle/
209.expMotorActivity/
210.(physicaladj3activit$).tw.
211.expExercise/
212.expExerciseTherapy/
213.exercis$.tw.
214.expLifeStyle/
215.lifestyle$.tw.
216.(lifeadj3style$).tw.
217.expHealthBehavior/
218.(healthadj3(behavior$orbehaviour$)).tw.
219.expDiet/
220.expDietarySupplements/

221.diet$.tw.
222.nutrition$.tw.
223.expObesity/
224.expBodyWeight/
225.obes$.tw.
226.weight$.tw.
227.expSmoking/
228.(smokingorsmoker*).tw.
229.expAlcohol-RelatedDisorders/
230.expAlcoholicBeverages/
231.alcohol*.tw.
232.drinking.tw.
233.expEmployment/
234.expOccupations/
235.(employment*oroccupation*orwork).tw.
236.goeckermantherapy.mp.
237.excimertherapy.mp.
238.scalelifters.mp.
239.non-biologicalmedications.mp.
240.FishOils/orfishoil*.mp.
241.vitamins.mp.orVitamins/
242.vitaminE.mp.orVitaminE/
243.VitaminA/orvitaminA.mp.
244.mineral*.mp.
245.selenium.mp.orSelenium/
246.Antimetabolites/orantimetabolite*.mp.
247.thioguanine.mp.orThioguanine/
248.tioguanine.mp.
249.miscellaneous.mp.
250.immunomodulatoragents.mp.
251.immunomodulatordrugs.mp.
252.calcineurininhibitors.mp.
253.anti-itch.mp.
254.e45cream.mp.
255.fumaricacidesters.mp.
256.fumaricacidesters.mp.
257.FAE.mp.

258.sorbelene.mp.
259.anti-fungal.mp.
260.skinbiopsy.mp.
261.alefacept.mp.
262.amevive.tw.
263.or/16-262
264.QOL.mp.
265.qualityoflife.mp.or"QualityofLife"/
266.healthrelatedqualityoflife.mp.
267.HRQOL.mp.
268.EQ5D.mp.
269.nationalpsoriasisfoundation.mp.
270.skindex.mp.
271.DLQI.mp.
272.dermatologylifequalityindex.mp.
273.burdenofskindisease.mp.
274.patientreportedoutcomemeasure.mp.
275.qualityoflifeimpairment.mp.
276.outcomemeasurement.mp.
277."OutcomeAssessment(HealthCare)"/oroutcomeassessment.mp.
278.QOLtools.mp.
279.patientreportedoutcome.mp.
280.PRO.mp.
281.NHP.mp.
282.WHO-QOL.mp.
283.psoriasisdisabilityindex.mp.
284.PDI.mp.
285.salfordpsoriasisindex.mp.
286.SPI.mp.
287.FDLQI.mp.
288.PFI.mp.
289.skindex-16.mp.
290.skindex-29.mp.
291.skindex-teen.mp.
292.childrensdermatologylifequalityindex.mp.
293.CDLQI.mp.
294.familydermatologylifequalityindex.mp.

295.psoriasis-specificmeasureofqualityoflife.mp.

296.PSORIQoL.mp.

297.USPSORIQoL.mp.

298.skindex-17.mp.

299.DQOLS.mp.

300.dermatologyqualityoflifescales.mp.

301.shortform-36.mp.

302.KMPI.mp.

303.PDI.mp.

304.nationalpsoriasisfoundationpsoriasisscore.mp.

305.NPF-PS.mp.

306.physicianstaticglobalassessment.mp.

307.PSGA.mp.

308.overalllesionassessment.mp.

309.OLA.mp.

310.physiciandynamicglobalassessment.mp.

311.physiciandynamicglobalassessment.mp.

312.PDGA.mp.

313.latticesystemglobalpsoriasisscore.mp.

314.LS-GPS.mp.

315.PsAQoL.mp.

316.dermatologyindexofdiseaseseverity.mp.

317.DIDS.mp.

318.psoriasislifestressinventory.mp.

319.PLSI.mp.

320.WHOQOL-26.mp.

321.WHOQOL-100.mp.

322.patientgeneralindex.mp.

323.PGI.mp.

324.DIELH.mp.

325.VQ-dermato.mp.

326.impactofchronicskindiseaseondailylife.mp.

327.ISDL.mp.

328.freiberglifequalityassessment.mp.

329.FLQA.mp.

330.SF-29.mp.

331.valueoflife/

332.qualityadjustedlifeyear/
333.qualityadjustedlife.tw.
334.(qaly$orqald$orqale$orqtime$).tw.
335.disabilityadjustedlife.tw.
336.daly$.tw.
337.healthstatusindicators/
338.(sf36orsf36orshortform36orshortform36orsfthirtysixorsfthirtysixorshortformthirtysixorshortformthirtysixorshortformthirtysixorshortformthirtysix).tw.
339.(sf6orsf6orshortform6orshortform6orsfsixorsfsixorshortformsixorshortformsix).tw.
340.(sf12orsf12orshortform12orshortform12orsftwelveorsftwelveorshortformtwelveorshortformtwelve).tw.
341.(sf16orsf16orshortform16orshortform16orsfsixteenorsfsixteenorshortformsixteenorshortformsixteen).tw.
342.(sf20orsf20orshortform20orshortform20orsftwentyorsftwentyorshortformtwentyorshortformtwenty).tw.
343.(euroqoloreuroqoloreq5doreq5d).tw.
344.(hqlorhqolorhqolorhrqolorhrqol).tw.
345.(hyeorhyes).tw.
346.health$year$equivalent$.tw.
347.healthutilit$.tw.
348.(huiorhui1orhui2orhui3).tw.
349.disutili$.tw.
350.rosser.tw.
351.qualityofwellbeing.tw.
352.qwb.tw.
353.willingnesstopay.tw.
354.standardgamble$.tw.
355.timetradeoff.tw.
356.timetradeoff.tw.
357.tto.tw.
358.or/264-357
359.RandomisedControlledTrialsasTopic/
360.Randomi?edcontrolledtrial/
361.RandomAllocation/
362.DoubleBlindMethod/
363.SingleBlindMethod/
364.clinicaltrial/

365.clinicaltrial,phasei.pt.

366.clinicaltrial,phaseii.pt.

367.clinicaltrial,phaseiii.pt.

368.clinicaltrial,phaseiv.pt.

369.controlledclinicaltrial.pt.

370.randomi?edcontrolledtrial.pt.

371.multicenterstudy.pt.

372.clinicaltrial.pt.

373.expClinicalTrialsastopic/

374.randomly.ab.

375.trial.ab.

376.groups.ab.

377.or/359-376

378.(clinicaladjtrial$).tw.

379.((singl$ordoubl$ortreb$ortripl$)adj(blind$3ormask$3)).tw.

380.PLACEBOS/

381.placebo$.tw.

382.randomlyallocated.tw.

383.(allocatedadj2random$).tw.

384.or/378-383

385.377or384

386.casereport.tw.

387.letter/

388.historicalarticle/

389.or/386-388

390.385not389

391.15and263and358and390

Appendix IV: Web of Science core collection search strategy

(TS= (psoriasis)
OR TS= (psoria*)
OR TS= (erythrodermic psoriasis)
OR TS= (guttate psoriasis)
OR TS= (pustular psoriasis)
OR TS= (palmoplantar psoriasis)
OR TS= (psoriasis vulgaris)
OR TS= (plaque psoriasis)
OR TS= (localised pustular psoriasis)
OR TS= (localized pustular psoriasis)
OR TS= (inverse psoriasis)
OR TS= (scalp psoriasis)
OR TS= (nail psoriasis)
OR TS= (inflammatory psoriasis))

AND

(TS= (intervention*)
OR TS= (treatment*)
OR TS= (topical)
OR TS= (systemic)
OR TS= (immunosuppressive drug)
OR TS= (Immunosuppressive Agents)
OR TS= (Nonprescription Drugs)
OR TS= (over-the-counter)
OR TS= (otc)
OR TS= (Tars)
OR TS= (tar or tars)
OR TS= (Steroids)
OR TS= (Adrenal Cortex Hormones)
OR TS= (Retinoids)
OR TS= (retinoid*)
OR TS= (steroid*)
OR TS= (emollient agent)
OR TS= (emollient*)

OR TS= (Tacrolimus)
OR TS= (tacrolimus)
OR TS= (topical immune modulator*)
OR TS= (topical adj3 therap*)
OR TS= (topical adj3 treatment*)
OR TS= (topical adj3 agent*)
OR TS= (vitamin D analogues)
OR TS= (calcipotriol)
OR TS= (dovonex)
OR TS= (dovobet)
OR TS= (xamiol)
OR TS= (calcipotriene)
OR TS= (taclonex)
OR TS= (Calcitriol or calcitriol)
OR TS= (silkis)
OR TS= (tacalcitol)
OR TS= (curatoderm)
OR TS= (vitamin D)
OR TS= (calamine and coal tar ointment)
OR TS= (coal tar)
OR TS= (calamine)
OR TS= (coal tar and salicylic acid ointment)
OR TS= (coal tar paste)
OR TS= (zinc and coal tar paste)
OR TS= (zinc oxide)
OR TS= (alphosyl)
OR TS= (crude coal tar)
OR TS= (dithranol)
OR TS= (anthralin or Anthralin)
OR TS= (dithrocream)
OR TS= (micanol)
OR TS= (psorin)
OR TS= (zithranol)
OR TS= (topical retinoids)
OR TS= (tazarotene)
OR TS= (zorac)
OR TS= (tazorac)

OR TS= (corticosteroid)
OR TS= (hydrocortisone or Hydrocortisone)
OR TS= (dioderm)
OR TS= (mildison)
OR TS= (alphaderm)
OR TS= (calmurid HC)
OR TS= (eurax-hydrocortisone)
OR TS= (canesten HC)
OR TS= (daktacort)
OR TS= (fucidin H)
OR TS= (nystaform-HC)
OR TS= (timodine)
OR TS= (hydrocortisone butyrate)
OR TS= (locoid)
OR TS= (locoid crelo)
OR TS= (alclometasone dipropionate)
OR TS= (modrasone)
OR TS= (betamethasone esters)
OR TS= (betamethasone valerate)
OR TS= (betacap)
OR TS= (betesil)
OR TS= (betnovate)
OR TS= (betnovate-rd)
OR TS= (bettamousse)
OR TS= (diprosone)
OR TS= (diprosalic)
OR TS= (betnovate-c)
OR TS= (betnovate-n)
OR TS= (fucibet)
OR TS= (lotriderm)
OR TS= (clobetasol propionate)
OR TS= (clarelux)
OR TS= (dermovate)
OR TS= (etrivex)
OR TS= (dermovate-nn)
OR TS= (clobetasone butyrate)
OR TS= (eumovate)

OR TS= (diflucortolone valerate)

OR TS= (nerisone)

OR TS= (nerisone forte)

OR TS= (fludroxycortide)

OR TS= (flurandrenolone)

OR TS= (haelan)

OR TS= (fluocinolone acetonide or Fluocinolone Acetonide)

OR TS= (synalar 1 in 4 dilution)

OR TS= (synalar 1 in 10 dilution)

OR TS= (synalar c)

OR TS= (synalar n)

OR TS= (fluocinonide or Fluocinonide)

OR TS= (metosyn)

OR TS= (fluocortolone or Fluocortolone)

OR TS= (ultralanum plain)

OR TS= (fluticasone propionate)

OR TS= (cutivate)

OR TS= (mometasone furoate)

OR TS= (elocon)

OR TS= (triamcinolone acetonide or Triamcinolone Acetonide)

OR TS= (aureocort)

OR TS= (Keratolytic Agents or keratolytic)

OR TS= (salicylic acid or Salicylic Acid)

OR TS= (zinc and salicylic acid paste)

OR TS= (Sulfur or sulphur)

OR TS= (Ultraviolet Rays)

OR TS= (Ultraviolet Therapy)

OR TS= (ultraviolet*)

OR TS= (uv or UVB or UVA)

OR TS= (phototherapy or Phototherapy)

OR TS= (ultraviolet b)

OR TS= (UVB)

OR TS= (narrow band UVB)

OR TS= (narrow-band UVB)

OR TS= (narrow band UVB therapy)

OR TS= (broadband light therapy)

OR TS= (ultraviolet light)

OR TS= (UV light)
OR TS= (artificial light)
OR TS= (natural light)
OR TS= (combination light therapy)
OR TS= (photochemotherapy or Photochemotherapy)
OR TS= (psoralen)
OR TS= (PUVA)
OR TS= (oral retinoids)
OR TS= (acitretin or Acitretin)
OR TS= (neotigason)
OR TS= (cyclosporin or Cyclosporine)
OR TS= (ciclosporin)
OR TS= (deximune)
OR TS= (neoral)
OR TS= (sandimmune)
OR TS= (hydroxycarbamide)
OR TS= (hydrea)
OR TS= (hydroxyurea or Hydroxyurea)
OR TS= (methotrexate or Methotrexate)
OR TS= (metoject)
OR TS= (cytokine modulators)
OR TS= (etanercept)
OR TS= (enbrel)
OR TS= (adalimumab)
OR TS= (humira)
OR TS= (infliximab)
OR TS= (remicade)
OR TS= (ustekinumab)
OR TS= (stelara)
OR TS= (efalizumab)
OR TS= (raptiva)
OR TS= (biologic*)
OR TS= (Psychotherapy)
OR TS= (psycho* adj3 therap*)
OR TS= (psychotherap*)
OR TS= (Cognitive Therapy)
OR TS= (cognit* adj3 therap*)

OR TS= ((behaviour or behavior) adj3 therap*)

OR TS= (psychoeducation)

OR TS= (CBT)

OR TS= (Peer Group)

OR TS= (Self-Help Groups)

OR TS= (peer adj3 group*)

OR TS= ((support or self-help or self help) adj3 group*)

OR TS= (alternative therapy)

OR TS= (homeopathy or Homeopathy)

OR TS= (Relaxation or relaxation)

OR TS= (oregano oil)

OR TS= (traditional treatment*)

OR TS= (oat extracts)

OR TS= (cold water fish oils)

OR TS= (evening primrose oil)

OR TS= (tea tree oil)

OR TS= (aloe vera or Aloe)

OR TS= (tai chi)

OR TS= (yoga or Yoga)

OR TS= (laser)

OR TS= (herbal medication)

OR TS= (petroleum jelly)

OR TS= (massage*)

OR TS= (shark cartilage extract)

OR TS= (meditation or Meditation)

OR TS= (complementary therapy or Complementary Therapies)

OR TS= (hypnotherapy)

OR TS= (milk thistle or Milk Thistle)

OR TS= (Motor Activity)

OR TS= (physical adj3 activit$)

OR TS= (Exercise)

OR TS= (Exercise Therapy)

OR TS= (exercise$)

OR TS= (Life Style)

OR TS= (lifestyle$)

OR TS= (life adj3 style$)

OR TS= (Health Behavior)

OR TS= (health adj3 (behavior$ or behaviour$))

OR TS= (Diet)

OR TS= (Dietary Supplements)

OR TS= (diet$)

OR TS= (nutrition$)

OR TS= (Obesity)

OR TS= (Body Weight)

OR TS= (obes$)

OR TS= (weight$)

OR TS= (Smoking)

OR TS= (smoking or smoker*)

OR TS= (Alcohol-Related Disorders)

OR TS= (Alcoholic Beverages)

OR TS= (alcohol*)

OR TS= (drinking)

OR TS= (Employment)

OR TS= (Occupations)

OR TS= (employment* or occupation* or work)

OR TS= (goeckerman therapy)

OR TS= (excimer therapy)

OR TS= (scale lifters)

OR TS= (non-biological medications)

OR TS= (Fish Oils or fish oil*)

OR TS= (vitamins or Vitamins)

OR TS= (vitamin E or Vitamin E)

OR TS= (Vitamin A or vitamin A)

OR TS= (mineral*)

OR TS= (selenium or Selenium)

OR TS= (Antimetabolites or antimetabolite*)

OR TS= (thioguanine or Thioguanine)

OR TS= (tioguanine)

OR TS= (miscellaneous)

OR TS= (immunomodulator agents)

OR TS= (immunomodulator drugs)

OR TS= (calcineurin inhibitors)

OR TS= (anti-itch)

OR TS= (e45 cream)

OR TS= (fumaric acid esters)
OR TS= (FAE)
OR TS= (sorbelene)
OR TS= (anti-fungal)
OR TS= (skin biopsy)
OR TS= (alefacept)
OR TS= (amevive))
AND

(TS= (QOL)
OR TS= (quality of life)
OR TS= (health related quality of life)
OR TS= (HRQOL)
OR TS= (EQ5D)
OR TS= (national psoriasis foundation)
OR TS= (skindex)
OR TS= (DLQI)
OR TS= (dermatology life quality index)
OR TS= (burden of skin disease)
OR TS= (patient reported outcome measure)
OR TS= (quality of life impairment)
OR TS= (outcome measurement)
OR TS= (outcome assessment)
OR TS= (QOL tools)
OR TS= (patient reported outcome)
OR TS= (PRO)
OR TS= (NHP)
OR TS= (WHO- QOL)
OR TS= (psoriasis disability index)
OR TS= (PDI)
OR TS= (salford psoriasis index)
OR TS= (SPI)
OR TS= (FDLQI)
OR TS= (PFI)
OR TS= (skindex-16)
OR TS= (skindex-29)
OR TS= (skindex-teen)

OR TS= (childrens dermatology life quality index)

OR TS= (CDLQI)

OR TS= (family dermatology life quality index)

OR TS= (FDLQIDELETE AS IT IS DUPLICATE)

OR TS= (psoriasis-specific measure of quality of life)

OR TS= (PSORIQoL)

OR TS= (US PSORIQoL)

OR TS= (skindex-17)

OR TS= (DQOLS)

OR TS= (dermatology quality of life scales)

OR TS= (short form-36)

OR TS= (KMPI)

OR TS= (PDI)

OR TS= (national psoriasis foundation psoriasis score)

OR TS= (NPF-PS)

OR TS= (physician static global assessment)

OR TS= (PSGA)

OR TS= (overall lesion assessment)

OR TS= (OLA)

OR TS= (physician dynamic global assessment)

OR TS= (PDGA)

OR TS= (lattice system global psoriasis score)

OR TS= (LS- GPS)

OR TS= (PsAQoL)

OR TS= (dermatology index of disease severity)

OR TS= (DIDS)

OR TS= (psoriasis life stress inventory)

OR TS= (PLSI)

OR TS= (WHO QOL-26)

OR TS= (WHO QOL-100)

OR TS= (patient general index)

OR TS= (PGI)

OR TS= (DIELH)

OR TS= (VQ-dermato)

OR TS= (impact of chronic skin disease on daily life)

OR TS= (ISDL)

OR TS= (freiberg life quality assessment)

OR TS= (FLQA)
OR TS= (SF-29)
OR TS= (value of life)
OR TS= (quality adjusted life year)
OR TS= (quality adjusted life)
OR TS= ((qaly$ or qald$ or qale$ or qtime$))
OR TS= (disability adjusted life)
OR TS= (daly$)
OR TS= (health status indicators)
OR TS= (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
OR TS= (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
OR TS= (sf12 or sf 12 or short form 12 or shortform 12 or sf elve or sfelve or shortform elve or short form elve)
OR TS= (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen)
OR TS= (sf20 or sf 20 or short form 20 or shortform 20 or sf enty or sfenty or shortform enty or short form enty)
OR TS= (euroqol or euro qol or eq5d or eq 5d)
OR TS= (hql or hqol or h qol or hrqol or hr qol)
OR TS= (hye or hyes)
OR TS= (health$ year$ equivalent$)
OR TS= (health utilit$)
OR TS= (hui or hui1 or hui2 or hui3)
OR TS= (disutili$)
OR TS= (rosser)
OR TS= (quality of wellbeing)
OR TS= (qwb)
OR TS= (willingness to pay)
OR TS= (standard gamble$)
OR TS= (time trade off)
OR TS= (time tradeoff)
OR TS= (tto))

AND

(TS= (Randomised Controlled Trials)
OR TS= (Randomi?ed controlled trial)
OR TS= (Random Allocation)
OR TS= (Double Blind Method)
OR TS= (Single Blind Method)
OR TS= (clinical trial)
OR TS= (clinical trial, phase ipt)
OR TS= (clinical trial, phase iipt)
OR TS= (clinical trial, phase iiipt)
OR TS= (clinical trial, phase ivpt)
OR TS= (controlled clinical trialpt)
OR TS= (randomi?ed controlled trial)
OR TS= (multicenter study)
OR TS= (clinical trial)
OR TS= (Clinical Trials as topic)
OR TS= (randomly)
OR TS= (trial)
OR TS= (groups)
OR TS= (clinical adj trial$)
OR TS= ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3))
OR TS= (PLACEBOS)
OR TS= (placebo$)
OR TS= (randomly allocated)
OR TS= (allocated adj2 random$)
NOT TS= (case report)
NOT TS= (LETTER)
NOT TS= (historical article))

Appendix V: EMBASE search strategy

1. psoriasis.mp. or exp Psoriasis/
2. psoria*.mp.
3. erythrodermic psoriasis.mp.
4. guttate psoriasis.mp.
5. pustular psoriasis.mp.
6. palmoplantar psoriasis.mp.
7. psoriasis vulgaris.mp.
8. plaque psoriasis.mp.
9. localised pustular psoriasis.mp.
10. localized pustular psoriasis.mp.
11. inverse psoriasis.mp.
12. scalp psoriasis.mp.
13. nail psoriasis.mp.
14. inflammatory psoriasis.mp.
15. or/1-14
16. intervention*.mp.
17. treatment*.mp.
18. topical.mp.
19. systemic.mp.
20. immunosuppressive drug.mp.
21. Immunosuppressive Agents/
22. Nonprescription Drugs/
23. over-the-counter.mp.
24. otc.mp.
25. exp Tars/
26. (tar or tars).tw.
27. exp Steroids/
28. exp Retinoids/
29. retinoid*.tw.
30. steroid*.tw.
31. exp emollient agent/
32. emollient*.tw.
33. exp Tacrolimus/
34. tacrolimus.tw.
35. topical immune modulator*.tw.

36. (topical adj3 therap*).tw.
37. (topical adj3 treatment*).tw.
38. (topical adj3 agent*).tw.
39. vitamin D analogues.mp.
40. calcipotriol.mp.
41. dovonex.tw.
42. dovobet.tw.
43. xamiol.tw.
44. calcipotriene.mp.
45. taclonex.tw.
46. Calcitriol/ or calcitriol.mp.
47. silkis.tw.
48. tacalcitol.mp.
49. curatoderm.tw.
50. vitamin D.tw.
51. tars.mp. or Tars/
52. (calamine and coal tar ointment).mp.
53. coal tar.mp.
54. calamine.mp.
55. (coal tar and salicylic acid ointment).mp.
56. coal tar paste.mp.
57. (zinc and coal tar paste).mp.
58. zinc oxide.mp.
59. alphosyl.mp.
60. crude coal tar.mp.
61. dithranol.mp.
62. anthralin.mp. or Anthralin/
63. dithrocream.tw.
64. micanol.tw.
65. psorin.tw.
66. zithranol.tw.
67. topical retinoids.mp.
68. tazarotene.mp.
69. zorac.tw.
70. tazorac.tw.
71. corticosteroid.mp.
72. hydrocortisone.mp. or Hydrocortisone/

73. dioderm.tw.
74. mildison.tw.
75. alphaderm.tw.
76. calmurid HC.tw.
77. eurax-hydrocortisone.tw.
78. canesten HC.tw.
79. daktacort.tw.
80. fucidin H.tw.
81. nystaform-HC.tw.
82. timodine.tw.
83. hydrocortisone butyrate.mp.
84. locoid.tw.
85. locoid crelo.tw.
86. alclometasone dipropionate.mp.
87. modrasone.tw.
88. betamethasone esters.mp.
89. betamethasone valerate.tw.
90. betacap.tw.
91. betesil.tw.
92. betnovate.tw.
93. betnovate-rd.tw.
94. bettamousse.tw.
95. diprosone.tw.
96. diprosalic.tw.
97. betnovate-c.tw.
98. betnovate-n.tw.
99. fucibet.tw.
100. lotriderm.tw.
101. clobetasol propionate.mp.
102. clarelux.tw.
103. dermovate.tw.
104. etrivex.tw.
105. dermovate-nn.tw.
106. clobetasone butyrate.mp.
107. eumovate.tw.
108. diflucortolone valerate.mp.
109. nerisone.tw.

110. nerisone forte.tw.
111. fludroxycortide.mp.
112. flurandrenolone.tw.
113. haelan.tw.
114. fluocinolone acetonide.mp. or Fluocinolone Acetonide/
115. synalar 1 in 4 dilution.tw.
116. synalar 1 in 10 dilution.tw.
117. synalar c.tw.
118. synalar n.tw.
119. fluocinonide.mp. or Fluocinonide/
120. metosyn.tw.
121. fluocortolone.mp. or Fluocortolone/
122. ultralanum plain.tw.
123. fluticasone propionate.mp.
124. cutivate.tw.
125. mometasone furoate.mp.
126. elocon.tw.
127. triamcinolone acetonide.mp. or Triamcinolone Acetonide/
128. aureocort.tw.
129. Keratolytic Agents/ or keratolytic.mp.
130. salicylic acid.mp. or Salicylic Acid/
131. zinc.mp. and salicylic acid paste.tw.
132. Sulfur/ or sulphur.mp.
133. exp Ultraviolet Rays/
134. exp Ultraviolet Therapy/
135. ultraviolet*.tw.
136. (uv or UVB or UVA).tw.
137. phototherapy.mp. or Phototherapy/
138. ultraviolet b.mp.
139. UVB.mp.
140. narrow band UVB.mp.
141. narrow-band UVB.mp.
142. narrow band UVB therapy.mp.
143. broadband light therapy.mp.
144. ultraviolet light.mp.
145. UV light.mp.
146. natural light.mp.

147. combination light therapy.mp.
148. photochemotherapy.mp. or Photochemotherapy/
149. psoralen.mp.
150. PUVA.mp.
151. oral retinoids.mp.
152. acitretin.mp. or Acitretin/
153. neotigason.tw.
154. cyclosporin.mp. or Cyclosporine/
155. ciclosporin.mp.
156. deximune.tw.
157. neoral.tw.
158. sandimmune.tw.
159. hydroxycarbamide.mp.
160. hydrea.tw.
161. hydroxyurea.mp. or Hydroxyurea/
162. methotrexate.mp. or Methotrexate/
163. metoject.tw.
164. cytokine modulators.mp.
165. etanercept.mp.
166. enbrel.tw.
167. adalimumab.mp.
168. humira.tw.
169. infliximab.mp.
170. remicade.tw.
171. ustekinumab.mp.
172. stelara.tw.
173. efalizumab.mp.
174. raptiva.tw.
175. biologic*.mp.
176. Psychotherapy/
177. (psycho* adj3 therap*).tw.
178. psychotherap*.tw.
179. exp Cognitive Therapy/
180. (cognit* adj3 therap*).tw.
181. ((behaviour or behavior) adj3 therap*).tw.
182. psychoeducation.tw.
183. CBT.tw.

184. exp Peer Group/
185. exp Self-Help Groups/
186. (peer adj3 group*).tw.
187. ((support or self-help or self help) adj3 group*).tw.
188. alternative therapy.mp.
189. homeopathy.mp. or Homeopathy/
190. Relaxation/ or relaxation.mp.
191. oregano oil.mp.
192. traditional treatment*.mp.
193. oat extracts.mp.
194. cold water fish oils.mp.
195. evening primrose oil.mp.
196. tea tree oil.mp. or "Tea Tree Oil"/
197. aloe vera.mp. or Aloe/
198. tai chi.mp.
199. yoga.mp. or Yoga/
200. laser.mp.
201. herbal medication.mp.
202. petroleum jelly.mp.
203. massage*.mp.
204. shark cartilage extract.mp.
205. meditation.mp. or Meditation/
206. complementary therapy.mp. or Complementary Therapies/
207. hypnotherapy.mp.
208. milk thistle.mp. or Milk Thistle/
209. exp Motor Activity/
210. (physical adj3 activit$).tw.
211. exp Exercise/
212. exp Exercise Therapy/
213. exercis$.tw.
214. exp Life Style/
215. lifestyle$.tw.
216. (life adj3 style$).tw.
217. exp Health Behavior/
218. (health adj3 (behavior$ or behaviour$)).tw.
219. exp Diet/
220. exp Dietary Supplements/

221. diet$.tw.
222. nutrition$.tw.
223. exp Obesity/
224. exp Body Weight/
225. obes$.tw.
226. weight$.tw.
227. exp Smoking/
228. (smoking or smoker*).tw.
229. exp Alcohol-Related Disorders/
230. exp Alcoholic Beverages/
231. alcohol*.tw.
232. drinking.tw.
233. exp Employment/
234. exp Occupations/
235. (employment* or occupation* or work).tw.
236. goeckerman therapy.mp.
237. excimer therapy.mp.
238. scale lifters.mp.
239. non-biological medications.mp.
240. Fish Oils/ or fish oil*.mp.
241. vitamins.mp. or Vitamins/
242. vitamin E.mp. or Vitamin E/
243. Vitamin A/ or vitamin A.mp.
244. mineral*.mp.
245. selenium.mp. or Selenium/
246. Antimetabolites/ or antimetabolite*.mp.
247. thioguanine.mp. or Thioguanine/
248. tioguanine.mp.
249. miscellaneous.mp.
250. immunomodulator agents.mp.
251. immunomodulator drugs.mp.
252. calcineurin inhibitors.mp.
253. anti-itch.mp.
254. e45 cream.mp.
255. fumaric acid esters.mp.
256. fumaric acid esters.mp.
257. FAE.mp.

258. sorbelene.mp.
259. anti-fungal.mp.
260. skin biopsy.mp.
261. alefacept.mp.
262. amevive.tw.
263. or/16-262
264. QOL.mp.
265. quality of life.mp. or "Quality of Life"/
266. health related quality of life.mp.
267. HRQOL.mp.
268. EQ5D.mp.
269. national psoriasis foundation.mp.
270. skindex.mp.
271. DLQI.mp.
272. dermatology life quality index.mp.
273. burden of skin disease.mp.
274. patient reported outcome measure.mp.
275. quality of life impairment.mp.
276. outcome measurement.mp.
277. "Outcome Assessment (Health Care)"/ or outcome assessment.mp.
278. QOL tools.mp.
279. patient reported outcome.mp.
280. PRO.mp.
281. NHP.mp.
282. WHO- QOL.mp.
283. psoriasis disability index.mp.
284. PDI.mp.
285. salford psoriasis index.mp.
286. SPI.mp.
287. FDLQI.mp.
288. PFI.mp.
289. skindex-16.mp.
290. skindex-29.mp.
291. skindex-teen.mp.
292. childrens dermatology life quality index.mp.
293. CDLQI.mp.
294. family dermatology life quality index.mp.

295. psoriasis-specific measure of quality of life.mp.
296. PSORIQoL.mp.
297. US PSORIQoL.mp.
298. skindex-17.mp.
299. DQOLS.mp.
300. dermatology quality of life scales.mp.
301. short form-36.mp.
302. KMPI.mp.
303. PDI.mp.
304. national psoriasis foundation psoriasis score.mp.
305. NPF-PS.mp.
306. physician static global assessment.mp.
307. PSGA.mp.
308. overall lesion assessment.mp.
309. OLA.mp.
310. physician dynamic global assessment.mp.
311. physician dynamic global assessment.mp.
312. PDGA.mp.
313. lattice system global psoriasis score.mp.
314. LS- GPS.mp.
315. PsAQoL.mp.
316. dermatology index of disease severity.mp.
317. DIDS.mp.
318. psoriasis life stress inventory.mp.
319. PLSI.mp.
320. WHO QOL-26.mp.
321. WHO QOL-100.mp.
322. patient general index.mp.
323. PGI.mp.
324. DIELH.mp.
325. VQ-dermato.mp.
326. impact of chronic skin disease on daily life.mp.
327. ISDL.mp.
328. freiberg life quality assessment.mp.
329. FLQA.mp.
330. SF-29.mp.
331. exp socioeconomics/

332. quality adjusted life year/
333. quality adjusted life.tw.
334. (qaly$ or qald$ or qale$ or qtime$).tw.
335. disability adjusted life.tw.
336. daly$.tw.
337. health survey/
338. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
339. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
340. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
341. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
342. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
343. (euroqol or euro qol or eq5d or eq 5d).tw.
344. (hql or hqol or h qol or hrqol or hr qol).tw.
345. (hye or hyes).tw.
346. health$ year$ equivalent$.tw.
347. health utilit$.tw.
348. (hui or hui1 or hui2 or hui3).tw.
349. disutili$.tw.
350. rosser.tw.
351. quality of wellbeing.tw.
352. qwb.tw.
353. willingness to pay.tw.
354. standard gamble$.tw.
355. time trade off.tw.
356. time tradeoff.tw.
357. tto.tw.
358. or/264-357
359. Clinical trial/
360. Randomised controlled trial/
361. Randomization/
362. Single blind procedure/
363. Double blind procedure/

364. Crossover procedure/
365. Placebo/
366. Randomi?ed controlled trial$.tw.
367. Rct.tw.
368. Random allocation.tw.
369. Randomly allocated.tw.
370. Allocated randomly.tw.
371. (allocated adj2 random).tw.
372. Single blind$.tw.
373. Double blind$.tw.
374. ((treble or triple) adj blind$).tw.
375. Placebo$.tw.
376. Prospective study/
377. randomly.ab.
378. trial.ab.
379. groups.ab.
380. or/359-379
381. Case study/
382. Case report.tw.
383. Abstract report/ or letter/
384. or/381-383
385. 380 not 384
386. 15 and 263 and 358 and 385
387. limit 386 to (english language and (clinical trial or randomised controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) and (article or conference abstract or conference paper or conference proceeding or "conference review"))

Appendix VI: Scopus search strategy

(TITLE-ABS-KEY("psoriasis") OR TITLE-ABS-KEY("psoria*") OR TITLE-ABS-KEY("erythrodermic psoriasis") OR TITLE-ABS-KEY("guttate psoriasis") OR TITLE-ABS-KEY("pustular psoriasis") OR TITLE-ABS-KEY("palmoplantar psoriasis") OR TITLE-ABS-KEY("psoriasis vulgaris") OR TITLE-ABS-KEY("plaque psoriasis") OR TITLE-ABS-KEY("localised pustular psoriasis") OR TITLE-ABS-KEY("localized pustular psoriasis") OR TITLE-ABS-KEY("inverse psoriasis") OR TITLE-ABS-KEY("scalp psoriasis") OR TITLE-ABS-KEY("nail psoriasis") OR TITLE-ABS-KEY("inflammatory psoriasis")) AND ((TITLE-ABS-KEY("intervention*")) OR (TITLE-ABS-KEY("treatment*")) OR (TITLE-ABS-KEY("topical")) OR (TITLE-ABS-KEY("systemic")) OR (TITLE-ABS-KEY("immunosuppressive drug")) OR (TITLE-ABS-KEY("Immunosuppressive Agents")) OR (TITLE-ABS-KEY("Nonprescription Drugs")) OR (TITLE-ABS-KEY("over-the-counter")) OR (TITLE-ABS-KEY("otc")) OR (TITLE-ABS-KEY("Tars")) OR (TITLE-ABS-KEY("tar")) OR (TITLE-ABS-KEY(" Steroids")) OR (TITLE-ABS-KEY(" Adrenal Cortex Hormones")) OR (TITLE-ABS-KEY(" Retinoids")) OR (TITLE-ABS-KEY("retinoid*")) OR (TITLE-ABS-KEY("steroid*")) OR (TITLE-ABS-KEY(" emollient agent")) OR (TITLE-ABS-KEY("emollient*")) OR (TITLE-ABS-KEY(" Tacrolimus")) OR (TITLE-ABS-KEY("tacrolimus")) OR (TITLE-ABS-KEY("topical immune modulator*")) OR (TITLE-ABS-KEY("topical adj therap*")) OR (TITLE-ABS-KEY("topical adj treatment*")) OR (TITLE-ABS-KEY("topical adj agent*")) OR (TITLE-ABS-KEY("vitamin D analogues")) OR (TITLE-ABS-KEY("calcipotriol")) OR (TITLE-ABS-KEY("dovonex")) OR (TITLE-ABS-KEY("dovobet")) OR (TITLE-ABS-KEY("xamiol")) OR (TITLE-ABS-KEY("calcipotriene")) OR (TITLE-ABS-KEY("taclonex")) OR (TITLE-ABS-KEY("Calcitriol")) OR (TITLE-ABS-KEY("silkis")) OR (TITLE-ABS-KEY("tacalcitol")) OR (TITLE-ABS-KEY("curatoderm")) OR (TITLE-ABS-KEY("vitamin D")) OR (TITLE-ABS-KEY("calamine and coal tar ointment")) OR (TITLE-ABS-KEY("coal tar")) OR (TITLE-ABS-KEY("calamine")) OR (TITLE-ABS-KEY("coal tar and salicylic acid ointment")) OR (TITLE-ABS-KEY("coal tar paste")) OR (TITLE-ABS-KEY("zinc and coal tar paste")) OR (TITLE-ABS-KEY("zinc oxide")) OR (TITLE-ABS-KEY("alphosyl")) OR (TITLE-ABS-KEY("crude coal tar")) OR (TITLE-ABS-KEY("dithranol")) OR (TITLE-ABS-KEY("anthralin")) OR (TITLE-ABS-KEY("dithrocream")) OR (TITLE-ABS-KEY("micanol")) OR (TITLE-ABS-KEY("psorin")) OR (TITLE-ABS-KEY("zithranol")) OR (TITLE-ABS-KEY("topical retinoids")) OR (TITLE-ABS-KEY("tazarotene")) OR (TITLE-ABS-KEY("zorac")) OR (TITLE-ABS-KEY("tazorac")) OR (TITLE-ABS-KEY("corticosteroid")) OR (TITLE-ABS-KEY("hydrocortisone")) OR (TITLE-ABS-KEY("dioderm")) OR (TITLE-ABS-KEY("mildison")) OR (TITLE-ABS-KEY("alphaderm")) OR (TITLE-ABS-KEY("calmurid HC")) OR (TITLE-ABS-KEY("eurax-hydrocortisone")) OR (TITLE-ABS-KEY("canesten HC")) OR (TITLE-ABS-KEY("daktacort")) OR (TITLE-ABS-KEY("fucidin

H")) OR (TITLE-ABS-KEY("nystaform-HC")) OR (TITLE-ABS-KEY("timodine")) OR (TITLE-ABS-KEY("hydrocortisone butyrate")) OR (TITLE-ABS-KEY("locoid")) OR (TITLE-ABS-KEY("locoid crelo")) OR (TITLE-ABS-KEY("alclometasone dipropionate")) OR (TITLE-ABS-KEY("modrasone")) OR (TITLE-ABS-KEY("betamethasone esters")) OR (TITLE-ABS-KEY("betamethasone valerate")) OR (TITLE-ABS-KEY("betacap")) OR (TITLE-ABS-KEY("betesil")) OR (TITLE-ABS-KEY("betnovate")) OR (TITLE-ABS-KEY("betnovate-rd")) OR (TITLE-ABS-KEY("bettamousse")) OR (TITLE-ABS-KEY("diprosone")) OR (TITLE-ABS-KEY("diprosalic")) OR (TITLE-ABS-KEY("betnovate-c")) OR (TITLE-ABS-KEY("betnovate-n")) OR (TITLE-ABS-KEY("fucibet")) OR (TITLE-ABS-KEY("lotriderm")) OR (TITLE-ABS-KEY("clobetasol propionate")) OR (TITLE-ABS-KEY("clarelux")) OR (TITLE-ABS-KEY("dermovate")) OR (TITLE-ABS-KEY("etrivex")) OR (TITLE-ABS-KEY("dermovate-nn")) OR (TITLE-ABS-KEY("clobetasone butyrate")) OR (TITLE-ABS-KEY("eumovate")) OR (TITLE-ABS-KEY("diflucortolone valerate")) OR (TITLE-ABS-KEY("nerisone")) OR (TITLE-ABS-KEY("nerisone forte")) OR (TITLE-ABS-KEY("fludroxycortide")) OR (TITLE-ABS-KEY("flurandrenolone")) OR (TITLE-ABS-KEY("haelan")) OR (TITLE-ABS-KEY("fluocinolone acetonide")) OR (TITLE-ABS-KEY("synalar 1 in 4 dilution")) OR (TITLE-ABS-KEY("synalar 1 in 10 dilution")) OR (TITLE-ABS-KEY("synalar c")) OR (TITLE-ABS-KEY("synalar n")) OR (TITLE-ABS-KEY("fluocinonide ")) OR (TITLE-ABS-KEY("metosyn")) OR (TITLE-ABS-KEY("fluocortolone ")) OR (TITLE-ABS-KEY("ultralanum plain")) OR (TITLE-ABS-KEY("fluticasone propionate")) OR (TITLE-ABS-KEY("cutivate")) OR (TITLE-ABS-KEY("mometasone furoate")) OR (TITLE-ABS-KEY("elocon")) OR (TITLE-ABS-KEY("triamcinolone acetonide")) OR (TITLE-ABS-KEY("aureocort")) OR (TITLE-ABS-KEY("Keratolytic Agents")) OR (TITLE-ABS-KEY("keratolytic")) OR (TITLE-ABS-KEY("salicylic acid")) OR (TITLE-ABS-KEY("zinc and salicylic acid paste")) OR (TITLE-ABS-KEY("Sulfur")) OR (TITLE-ABS-KEY(" Ultraviolet Rays")) OR (TITLE-ABS-KEY(" Ultraviolet Therapy")) OR (TITLE-ABS-KEY("ultraviolet*")) OR (TITLE-ABS-KEY("phototherapy")) OR (TITLE-ABS-KEY("ultraviolet b")) OR (TITLE-ABS-KEY("UVB")) OR (TITLE-ABS-KEY("narrow band UVB")) OR (TITLE-ABS-KEY("narrow-band UVB")) OR (TITLE-ABS-KEY("narrow band UVB therapy")) OR (TITLE-ABS-KEY("broadband light therapy")) OR (TITLE-ABS-KEY("ultraviolet light")) OR (TITLE-ABS-KEY("UV light")) OR (TITLE-ABS-KEY("artificial light")) OR (TITLE-ABS-KEY("natural light")) OR (TITLE-ABS-KEY("combination light therapy")) OR (TITLE-ABS-KEY("photochemotherapy")) OR (TITLE-ABS-KEY("psoralen")) OR (TITLE-ABS-KEY("PUVA")) OR (TITLE-ABS-KEY("oral retinoids")) OR (TITLE-ABS-KEY("acitretin neotigason")) OR (TITLE-ABS-KEY("Cyclosporine")) OR (TITLE-ABS-KEY("ciclosporin")) OR (TITLE-ABS-KEY("deximune")) OR (TITLE-ABS-KEY("neoral")) OR (TITLE-ABS-KEY("sandimmune")) OR (TITLE-ABS-KEY("hydroxycarbamide")) OR (TITLE-ABS-KEY("hydrea")) OR (TITLE-ABS-

KEY("hydroxyurea")) OR (TITLE-ABS-KEY("methotrexate")) OR (TITLE-ABS-KEY("metoject")) OR (TITLE-ABS-KEY("cytokine modulators")) OR (TITLE-ABS-KEY("etanercept")) OR (TITLE-ABS-KEY("enbrel")) OR (TITLE-ABS-KEY("adalimumab")) OR (TITLE-ABS-KEY("humira")) OR (TITLE-ABS-KEY("infliximab")) OR (TITLE-ABS-KEY("remicade")) OR (TITLE-ABS-KEY("ustekinumab")) OR (TITLE-ABS-KEY("stelara")) OR (TITLE-ABS-KEY("efalizumab")) OR (TITLE-ABS-KEY("raptiva")) OR (TITLE-ABS-KEY("biologic*")) OR (TITLE-ABS-KEY("Psychotherapy")) OR (TITLE-ABS-KEY("psycho* adj therap*")) OR (TITLE-ABS-KEY("psychotherap*")) OR (TITLE-ABS-KEY("Cognitive Therapy")) OR (TITLE-ABS-KEY("cognit* adj therap*")) OR (TITLE-ABS-KEY("behav* adj therap*")) OR (TITLE-ABS-KEY("psychoeducation")) OR (TITLE-ABS-KEY("CBT")) OR (TITLE-ABS-KEY(" Peer Group")) OR (TITLE-ABS-KEY(" Self-Help Groups")) OR (TITLE-ABS-KEY("peer adj group*")) OR (TITLE-ABS-KEY("support adj group*")) OR (TITLE-ABS-KEY("alternative therapy")) OR (TITLE-ABS-KEY("homeopathy")) OR (TITLE-ABS-KEY("Relaxation")) OR (TITLE-ABS-KEY("oregano oil")) OR (TITLE-ABS-KEY("traditional treatment*")) OR (TITLE-ABS-KEY("oat extracts")) OR (TITLE-ABS-KEY("cold water fish oils")) OR (TITLE-ABS-KEY("evening primrose oil")) OR (TITLE-ABS-KEY("tea tree oil")) OR (TITLE-ABS-KEY("aloe")) OR (TITLE-ABS-KEY("tai chi")) OR (TITLE-ABS-KEY("yoga")) OR (TITLE-ABS-KEY("laser")) OR (TITLE-ABS-KEY("herbal medication")) OR (TITLE-ABS-KEY("petroleum jelly")) OR (TITLE-ABS-KEY("massage*")) OR (TITLE-ABS-KEY("shark cartilage extract")) OR (TITLE-ABS-KEY("meditation")) OR (TITLE-ABS-KEY("complementary therap*")) OR (TITLE-ABS-KEY("hypnotherapy")) OR (TITLE-ABS-KEY("milk thistle")) OR (TITLE-ABS-KEY(" Motor Activity")) OR (TITLE-ABS-KEY("physical adj activit*")) OR (TITLE-ABS-KEY(" Exercise")) OR (TITLE-ABS-KEY(" Exercise Therapy")) OR (TITLE-ABS-KEY("exercis*")) OR (TITLE-ABS-KEY(" Life Style")) OR (TITLE-ABS-KEY("lifestyle*")) OR (TITLE-ABS-KEY("life adj style*")) OR (TITLE-ABS-KEY(" Health Behavior")) OR (TITLE-ABS-KEY("health adj behave*")) OR (TITLE-ABS-KEY(" Diet")) OR (TITLE-ABS-KEY(" Dietary Supplements")) OR (TITLE-ABS-KEY("diet*")) OR (TITLE-ABS-KEY("nutrition*")) OR (TITLE-ABS-KEY(" Obesity")) OR (TITLE-ABS-KEY(" Body Weight")) OR (TITLE-ABS-KEY("obes*")) OR (TITLE-ABS-KEY("weight*")) OR (TITLE-ABS-KEY(" Smoking")) OR (TITLE-ABS-KEY("smoking")) OR (TITLE-ABS-KEY("smoker*")) OR (TITLE-ABS-KEY(" Alcohol-Related Disorders")) OR (TITLE-ABS-KEY(" Alcoholic Beverages")) OR (TITLE-ABS-KEY("alcohol*")) OR (TITLE-ABS-KEY("drinking")) OR (TITLE-ABS-KEY(" Employment")) OR (TITLE-ABS-KEY(" Occupations")) OR (TITLE-ABS-KEY("goeckerman therapy")) OR (TITLE-ABS-KEY("excimer therapy")) OR (TITLE-ABS-KEY("scale lifters")) OR (TITLE-ABS-KEY("non-biological medications")) OR (TITLE-ABS-KEY("Fish Oil*")) OR (TITLE-ABS-KEY("Vitamin*")) OR (TITLE-ABS-KEY("vitamin E")) OR (TITLE-ABS-KEY("Vitamin A")) OR (TITLE-ABS-KEY("mineral* ")) OR (TITLE-ABS-KEY("selenium")) OR

(TITLE-ABS-KEY("Antimetabolite*")) OR (TITLE-ABS-KEY("thioguanine")) OR (TITLE-ABS-KEY("tioguanine")) OR (TITLE-ABS-KEY("miscellaneous")) OR (TITLE-ABS-KEY("immunomodulator agents")) OR (TITLE-ABS-KEY("immunomodulator drugs")) OR (TITLE-ABS-KEY("calcineurin inhibitors")) OR (TITLE-ABS-KEY("anti-itch")) OR (TITLE-ABS-KEY("e45 cream")) OR (TITLE-ABS-KEY("fumaric acid esters")) OR (TITLE-ABS-KEY("FAE")) OR (TITLE-ABS-KEY("sorbelene")) OR (TITLE-ABS-KEY("anti-fungal")) OR (TITLE-ABS-KEY("skin biopsy")) OR (TITLE-ABS-KEY("alefacept")) OR (TITLE-ABS-KEY("amevive"))) AND
(TITLE-ABS-KEY(“Qol”) OR TITLE-ABS-KEY("Quality of Life") OR TITLE-ABS-KEY("Health related quality of life") OR TITLE-ABS-KEY(“HRQOL”) OR TITLE-ABS-KEY("EQ5D") OR TITLE-ABS-KEY("National psoriasis foundation") OR TITLE-ABS-KEY("Skindex") OR TITLE-ABS-KEY("DLQI") OR TITLE-ABS-KEY("Dermatology Life Quality Index") OR TITLE-ABS-KEY("Burden of Skin Disease") OR TITLE-ABS-KEY("Dermatology-specific quality of life measure") OR TITLE-ABS-KEY("Patient reported outcome measure") OR TITLE-ABS-KEY("Quality of Life Impairment") OR TITLE-ABS-KEY("Outcome Measurement") OR TITLE-ABS-KEY("Outcome Assessment") OR TITLE-ABS-KEY("QoL Tools") OR TITLE-ABS-KEY("Patient reported Outcome") OR TITLE-ABS-KEY("PRO") OR TITLE-ABS-KEY("NHP") OR TITLE-ABS-KEY("WHO-QoL") OR TITLE-ABS-KEY("Psoriasis Disability Index") OR TITLE-ABS-KEY("PDI") OR TITLE-ABS-KEY("SPI") OR TITLE-ABS-KEY("Salford Psoriasis Index") OR TITLE-ABS-KEY("FDLQI") OR TITLE-ABS-KEY("PFI") OR TITLE-ABS-KEY("Skindex-16") OR TITLE-ABS-KEY("Skindex-29") OR TITLE-ABS-KEY("Skindex-Teen") OR TITLE-ABS-KEY("Children's Dermatology Life Quality Index") OR TITLE-ABS-KEY("CDLQI") OR TITLE-ABS-KEY("Family Dermatology Life Quality Index") OR TITLE-ABS-KEY("Psoriasis-Specific Measure of Quality of Life") OR TITLE-ABS-KEY("PSORIQoL") OR TITLE-ABS-KEY("US PSORIQoL") OR TITLE-ABS-KEY("Skindex-17") OR TITLE-ABS-KEY("DQOLS") OR TITLE-ABS-KEY("Dermatology Quality of Life Scales") OR TITLE-ABS-KEY("Short Form-36") OR TITLE-ABS-KEY("KMPI") OR TITLE-ABS-KEY(“PDI”) OR TITLE-ABS-KEY("National Psoriasis Foundation Psoriasis Score") OR TITLE-ABS-KEY("NPF-PS") OR TITLE-ABS-KEY("Physician Static Global Assessment") OR TITLE-ABS-KEY("PSGA") OR TITLE-ABS-KEY("Overall Lesion Assessment") OR TITLE-ABS-KEY("OLA") OR TITLE-ABS-KEY("Physician Dynamic Global Assessment") OR TITLE-ABS-KEY("PDGA") OR TITLE-ABS-KEY("Lattice System Global Psoriasis Score") OR TITLE-ABS-KEY("LS- GPS") OR TITLE-ABS-KEY("PsAQoL") OR TITLE-ABS-KEY("Dermatology Index of Disease Severity") OR TITLE-ABS-KEY("DIDS") OR TITLE-ABS-KEY("Psoriasis Life Stress Inventory") OR TITLE-ABS-KEY("PLSI") OR TITLE-ABS-KEY("WHO QoL-26") OR TITLE-ABS-KEY("WHO QoL-100") OR TITLE-ABS-KEY("Patient General Index") OR TITLE-ABS-KEY("PGI") OR TITLE-ABS-KEY("DIELH") OR TITLE-ABS-KEY("VQ-Dermato") OR TITLE-

ABS-KEY("Impact of Chronic Skin Disease on Daily Life") OR TITLE-ABS-KEY("ISDL") OR TITLE-ABS-KEY("Freiberg Life Quality Assessment") OR TITLE-ABS-KEY("FLQA") OR TITLE-ABS-KEY("SF-29") OR TITLE-ABS-KEY("value of life") OR TITLE-ABS-KEY("quality adjusted life year") OR TITLE-ABS-KEY("quality adjusted life") OR TITLE-ABS-KEY(qaly or qald* or qale* or qtime*) OR TITLE-ABS-KEY("disability adjusted life") OR TITLE-ABS-KEY("daly*") OR TITLE-ABS-KEY("health status indicators") OR TITLE-ABS-KEY(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) OR TITLE-ABS-KEY(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) OR TITLE-ABS-KEY(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) OR TITLE-ABS-KEY(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen) OR TITLE-ABS-KEY(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) OR TITLE-ABS-KEY(euroqol or euro qol or eq5d or eq 5d) OR TITLE-ABS-KEY(hql or hqol or h qol or hrqol or hr qol) OR (hye or hyes) OR TITLE-ABS-KEY("health year equivalent") OR TITLE-ABS-KEY("health utility*") OR TITLE-ABS-KEY(hui or hui1 or hui2 or hui3) OR TITLE-ABS-KEY("Disutili*") OR TITLE-ABS-KEY("rosser") OR TITLE-ABS-KEY("quality of wellbeing") OR TITLE-ABS-KEY("qwb") OR TITLE-ABS-KEY("willigness to pay") OR TITLE-ABS-KEY("standard gamble*") OR TITLE-ABS-KEY("time trade off") OR TITLE-ABS-KEY("time tradeoff") OR TITLE-ABS-KEY("Tto")) AND ((TITLE-ABS-KEY("Randomised Controlled Trials") OR TITLE-ABS-KEY("Randomised controlled trial*") OR TITLE-ABS-KEY("Random Allocation") OR TITLE-ABS-KEY("Double Blind Method") OR TITLE-ABS-KEY("Single Blind Method") OR TITLE-ABS-KEY("clinical trial") OR TITLE-ABS-KEY("clinical trial, phase I") OR TITLE-ABS-KEY("clinical trial, phase ii") OR TITLE-ABS-KEY("clinical trial, phase iii") OR TITLE-ABS-KEY("clinical trial, phase iv") OR TITLE-ABS-KEY("controlled clinical trial") OR TITLE-ABS-KEY("randomised controlled trial") OR TITLE-ABS-KEY("multicenter study") OR TITLE-ABS-KEY("clinical trial*") OR TITLE-ABS-KEY("Clinical Trials") OR TITLE-ABS-KEY("Randomly") OR TITLE-ABS-KEY("trial") OR TITLE-ABS-KEY("Groups") OR TITLE-ABS-KEY(Placebo*) OR TITLE-ABS-KEY("randomly allocated") OR TITLE-ABS-KEY("allocated random*")) AND NOT ("case report" OR "letter" OR "historical article"))

Appendix VII: Cochrane database search strategy

#1	psoriasis or exp Psoriasis	3447
#2	psoria*	3729
#3	erythrodermic psoriasis	20
#4	guttate psoriasis	30
#5	pustular psoriasis	47
#6	palmoplantar psoriasis	47
#7	psoriasis vulgaris	454
#8	plaque psoriasis	1050
#9	localised pustular psoriasis	11
#10	localized pustular psoriasis	11
#11	inverse psoriasis	36
#12	scalp psoriasis	185
#13	nail psoriasis	80
#14	inflammatory psoriasis	547
#15	(Groff et al. -#14)	3729
#16	MeSH descriptor: [Quality of Life] explode all trees	14948
#17	"dermatology index of disease severity"	1
#18	"value of life"	167
#19	"life quality"	1498
#20	"quality of wellbeing"	4
#21	"DLQI"	188
#22	"dermatology life quality index"	258
#23	(or #16 - #22)	16129
#24	#15 and #23	223
#25	intervention*	121446
#26	treatment*	373942
#27	topical	17258
#28	systemic	22829
#29	immunosuppressive drug	4991
#30	Nonprescription Drugs	254
#31	over-the-counter	859
#32	Tar	349
#33	retinoid*	579
#34	steroid*	19956
#35	emollient*	583

#36 (topical near/3 therap*) 2953
#37 (topical near/3 treatment*) 2448
#38 (systemic near/3 therap*) 2207
#39 (systemic near/3 treatment*) 1527
#40 vitamin D analogue* 338
#41 ultraviolet* 2071
#42 MeSH descriptor: [Phototherapy] explode all trees 2242
#43 cytokine modulators 40
#44 biologic* 29894
#45 (psycho* near/3 therap*) 24489
#46 psychotherap* 9269
#47 (cognit* near/3 therap*) 11174
#48 ((behaviour or behavior) near/3 therap*) 9805
#49 alternative therapy 18399
#50 homeopathy 504
#51 Relaxation 6703
#52 Laser* 10504
#53 complementary therap* 4269
#54 (physical near/3 activit$) 30
#55 Exercise Therapy 24012
#56 Life Style 3109
#57 nutrition$ 27008
#58 (smoking or smoker*) 17917
#59 alcohol* 16716
#60 medications 41679
#61 immunomodulator agents 143
#62 immunomodulator drugs 250
#63 (Papp et al. -#62) 510856
#64 #24 and #63 210
#65 #15 and #23 and #63 210

OF THE RESULTS ONLY TRIALS WERE SELECTED

Appendix VIII: Data capture form for systematic review – psoriasis treatments and quality of life (version 4 – 6/12/14)

ID Information

Study ID *(first author and date)*	
Contact details of study authors *(e-mail)*	
Notes:	

General Information

Initials of person extracting data	
Date form completed	
Reference citation	

Study eligibility (refer to pages 3-4 in the protocol)

Type of study	Randomised controlled trial
Participants (Adults, type of psoriasis, severity scale value)	Adults with moderate-to-severe psoriasis
Types of intervention	

Types of comparison	
Types of relevant outcome measures (QoL and PSS)	PASI DLQI
☐ **INCLUDE**	☐ **EXCLUDE** *(Do not proceed if study excluded from review)*

Methods (refer to pages 3-4 in the protocol)

Design (include single or multi-centre)		
Total study duration including follow-up *(short term <12 wks, intermediate 12 wks-6 months, long-term >6 months)*		
Duration of treatment phase		
Duration of follow up phase		
Random sequence generation. (If not mentioned mark as high risk and unclear)	☐ Low risk ☐ high risk ☐ unclear	**Notes:**
Allocation concealment (If not mentioned mark as high risk and unclear)	☐ Low risk ☐ high risk ☐ unclear	**Notes:**
Blinding	☐ Single ☐ double ☐ open	**Notes:**
Adverse events reported	☐ Low risk ☐ high risk ☐ unclear	**Notes:**

Blinding of participants and personnel (any blinding provides low risk)	☐ Low risk ☐ high risk ☐ unclear	**Notes:**
Incomplete outcome data (were dropouts accounted for when measuring QoL or Psoriasis Severity)	☐ Low risk ☐ high risk ☐ unclear	**Notes:**
Selective reporting	☐ Low risk ☐ high risk ☐ unclear	**Notes:**
Other bias/critique		

Participants (We shall include individuals of either sex and any age and ethnicity, with a clinical diagnosis of psoriasis ma de by a medical practitioner. We will include all subtypes of psoriasis).

Number screened		
Number randomised		
Power analysis used		
Country or Lead Country if multi-centre		
Age for each arm (**mean±SD)**		
Sex a or b	a. Sex for each arm **n (%)**	M F M F
	b. Sex male **n (%)**	
Type of psoriasis		moderate-to-severe psoriasis

Associations as per title or per methodology *(psoriatic arthritis, nail disease, etc)*	
Psoriasis severity for eligibility *(PASI, QoL, BSA, etc)*	

Intervention groups

Number of groups/arms	
Randomisation ratio	
Duration of intervention period (weeks)	
Intervention 1	
Details *(formulation, dose, frequency, etc)*	
Intervention 2	
Details	
Intervention 3	
Details	
Intervention 4	
Details	

Outcomes (refer to pages 3-4 in the protocol)

QoL scales used (scale range) *i.e DLQI (0-30)*	
Psoriasis severity scale used (scale range)	

Treatment endpoint for PSS and QoL include weeks and tool used	# week PASI # week DLQI
Follow up endpoint for PSS and QoL include weeks and tool used	# weeks PASI # weeks DLQI
Time points when both PSS and QoL are measured	weeks

Results

Number of participants allocated to each intervention		
Intention-to-treat analysis		
Psoriasis severity score (Add here name of score**)**		
Baseline data **mean ±SD** (include *n*)		
Treatment endpoint data (include *n*)	Full value **mean ±SD** (*n*)	
	Change value or percentage (*n*)	
	PASI 90 **n (%)** (include *n*)	
	PASI 75 **n (%)** (include *n*)	
	PASI 50 **n (%)** (include *n*)	
Effect estimate with confidence interval (CI) / P value		
Follow-up endpoint data (include *n*)	Full value **mean ±SD** (include *n*)	
	Change value or percentage	

	PASI 90 **n (%)**					
	PASI 75 **n (%)**					
	PASI 50 **n (%)**					
Effect estimate with confidence interval (CI) / P value						
QoL tool 1 (Add here name of score**)**						
What does the study include (answer Yes or No)		Full scores baseline+ F/U	Score Change	Percentage change	Graphic	MCID reported
Baseline data **mean ±SD** (include *n*)						
Summary data up to treatment endpoint	Full value **mean ±SD** (include *n*)					
	Change value or percentage (include *n*)					
	Divided data (include *n*)					
Summary data up to follow-up endpoint	Full value **mean ±SD** (include *n*)					
	Change value or percentage (include *n*)					
	Divided data (include *n*)					
Effect estimate with confidence interval (CI) / P value						

QoL tool 2 (Add here name of score**)**						
What does the study include (answer Yes or No)		Full scores baseline+ F/U	Score Change	Percentage change	Graphic	MCID reported
Baseline data **mean ±SD** (include *n*)						
Summary data up to treatment endpoint	Full value **mean ±SD** (include *n*)					
	Change value or percentage (include *n*)					
	Divided data (include *n*)					
Summary data up to follow-up endpoint	Full value **mean ±SD** (include *n*)					
	Change value or percentage (include *n*)					
	Divided data (include *n*)					
Effect estimate with confidence interval (CI) / P value						
QoL tool 3 (Add here name of score**)**						
What does the study include (answer Yes or No)		Full scores baseline+ F/U	Score Change	Percentage change	Graphic	MCID reported

Baseline data **mean ±SD** (include *n*)		
Summary data up to treatment endpoint	Full value **mean ±SD** (include *n*)	
	Change value or percentage (include *n*)	
	Divided data (include *n*)	
Summary data up to follow-up endpoint	Full value **mean ±SD** (include *n*)	
	Change value or percentage (include *n*)	
	Divided data (include *n*)	
Effect estimate with confidence interval (CI) / P value		

Conflict of Interest and Conclusions

Miscellaneous	
Study funding sources	
Possible conflicts of interest	
Key conclusions of study authors in terms of QoL	
Miscellaneous comments of study authors in terms of QoL	
Reference to other relevant studies	

Correspondence required?	
Miscellaneous comments of Cochrane author	

Appendix IX: Jadad scoring procedure

		RANDOMISED		DOUBLE-BLINDED		WITHDRAWALS AND DROPOUTS	TOTAL
STUDY NO	AUTHOR NAME	mentioned	appropriate method	mentioned	appropriate method		
1	Alora Palli 2010.docx	1	1	0	0	0	2
2	Asahina 2010.docx	1	0	1	0	1	3
3	Asawanonda 2006.docx	1	1	1	0	1	4
4	Bagel 1998.docx	1	0	1	0	0	2
5	Barker 2011.docx	1	1	0	0	1	3
6	Beissert 2009.docx	1	1	0	0	1	3
7	Bergstrom 2003.docx	1	0	0	0	0	1
8	Bernstein 2006.docx	1	0	1	0	0	2
9	Bissonnette 2011.docx	1	1	1	1	1	5
10	Bostoen 2012.docx	1	1	1	0	1	4
11	Cassano 2006.docx	1	0	0	0	0	1
12	Chambers 2012.docx	1	1	0	0	0	2
13	Choonhakarn 2010.docx	1	1	1	1	0	4
14	Dauden 2009.docx	1	0	0	0	0	1
15	De Korte 2008.docx	1	1	0	0	1	3
16	Drouin 2008.docx	1	1	1	1	1	5
17	Ellis 2003.docx	1	1	1	1	0	4
18	Ersser 2012.docx	1	1	0	0	0	2
19	Faurschou 2014.docx	1	1	1	1	0	4
20	Feldman 2005 etanercept.docx	1	1	1	1	1	5
21	Feldman 2005 infliximab.docx	1	1	1	1	1	5
22	Feldman 2008.docx	1	1	1	1	0	4

23	Finlay 2003.docx	1	1	1	1	0	4
24	Flytström 2008.docx	1	1	0	0	1	3
25	Fordham 2014.docx	1	1	0	0	0	2
26	Gahalaut 2014.docx	1	1	0	0	0	2
27	Galvez 2012.docx	1	0	1	1	0	3
28	Genovese 2007.docx	1	1	1	1	0	4
29	Gladman 2014.docx	1	0	1	1	0	3
30	Gniadecki 2012.docx	1	0	1	1	0	3
31	Gordon 2003.docx	1	1	1	1	1	5
32	Gordon 2012.docx	1	1	1	1	1	5
33	Gordon 2014.docx	1	1	1	1	1	5
34	Gottlieb 2003.docx	1	1	1	1	1	5
35	Greenberger 2012.docx	1	0	1	1	0	3
36	Guida 2014.docx	1	1	0	0	0	2
37	Gupta 2008.docx	1	0	1	1	0	3
38	Ho 2010.docx	1	1	0	0	0	2
39	Hutchinson, 2000.docx	1	0	0	0	0	1
40	Igarashi 2012.docx	1	0	1	1	0	3
41	Jensen 2013.docx	1	1	0	0	0	2
42	Kaltwasser 2004.docx	1	1	1	1	1	5
43	Kavanaugh 2010.docx	1	1	1	1	1	5
44	Kimball 2012.docx	1	1	1	0	0	3
45	Klein 2011.docx	1	1	0	0	0	2
46	Koek 2006.docx	1	1	0	0	0	2
47	Krueger 2005.docx	1	1	1	1	0	4
48	Krupashankar 2014.docx	1	0	1	1	1	4
49	Kunynetz 2011.docx	1	1	1	1	1	5
50	Langley 2010.docx	1	1	1	1	0	4
51	Langley 2014	1	1	1	1	0	4

	ERASURE.docx						
52	Langley 2014 FIXTURE.docx	1	1	1	1	0	4
53	Leonardi 2012.docx	1	1	1	1	1	5
54	Lu 2012.docx	1	1	0	0	0	2
55	Lui 2012.docx	1	1	0	0	0	2
56	Lynde 2012.docx	1	1	0	0	1	3
57	Mamolo 2014.docx	1	1	1	1	0	4
58	McInnes 2013.docx	1	1	1	1	0	4
59	Mease 2005.docx	1	0	1	1	1	4
60	Menter 2013.docx	1	1	1	1	0	4
61	Menter, 2009.docx	1	0	0	0	0	1
62	Möller 2010.docx	1	1	1	1	0	4
63	Moore 2007.docx	1	0	0	0	1	2
64	Mraz 2008.docx	1	0	0	0	0	1
65	Ortonne 2009.docx	1	1	0	0	0	2
66	Ortonne 2013.docx	1	1	0	0	1	3
67	Ortonne, 2005.docx	1	1	1	1	0	4
68	Ortonne, 2014.docx	1	1	1	1	1	5
69	Papp 2012.docx	1	1	1	1	1	5
70	Paul 2014.docx	1	1	0	0	0	2
71	Prins 2005.docx	1	1	0	0	0	2
72	Reich 2006.docx	1	1	1	1	1	5
73	Reich 2009.docx	1	1	1	1	1	5
74	Reich 2012.docx	1	1	1	1	1	5
75	Reich 2013.docx	1	1	0	0	0	2
76	Revicki 2007.docx	1	1	1	1	1	5
77	Revicki 2008.docx	1	1	1	1	1	5
78	Roberti 2014.docx	1	1	1	1	0	4

79	Salim 2006.docx	1	1	1	1	1	5
80	Saraceno 2007.docx	1	1	0	0	0	2
81	Schmitt 2014.docx	1	1	0	0	1	3
82	Shikiar 2007.docx	1	0	1	1	1	4
83	Sofen 2011.docx	1	0	1	0	0	2
84	Tabolli 2012.docx	1	1	0	0	0	2
85	Thaci 2002.docx	1	1	1	1	0	4
86	Thaci 2010.docx	1	1	1	1	1	5
87	Thaci, 2014.docx	1	0	1	0	1	3
88	Tiplica, 2009.docx	1	1	0	0	1	3
89	Torii, 2010.docx	1	0	1	1	1	4
90	Tsai, 2011.docx	1	1	1	1	1	5
91	Tyring, 2007.docx	1	1	1	1	1	5
92	Van De Kerkhof, 2004.docx	1	1	1	1	0	4
93	Vedhara, 2007.docx	1	1	0	0	0	2
94	Wall, 1998.docx	1	0	0	0	0	1
95	Woo, 2003.docx	1	1	1	1	1	5
96	Yan, 2011.docx	1	1	1	1	0	4
97	Yang, 2012.docx	1	0	1	0	0	2
98	Zachariae, 2008.docx	1	1	0	0	1	3
99	Zheng, 2011.docx	1	0	1	0	0	2
100	Zhu, 2013.docx	1	0	1	0	1	3

Appendix X: Systematic review course certificate

Uned Cefnogi Tystiolaeth Ymchwil
SURE
Support Unit for Research Evidence

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD
information services
gwasanaethau gwybodaeth

This is to certify that

Faraz Ali

successfully completed

CONDUCTING A SYSTEMATIC REVIEW:

A practical guide

Approved by the Federation of the Royal College of Physicians of the United Kingdom
for 20 category 1 (external) CPD credits
RCP Activity Code Number: 80887

Held on

24 –27th June 2013

at

Cardiff University

Fiona Morgan

Fiona Morgan
Course Leader

NISCHR
Canolfan Ymchwil Clinigol CRC Clinical Research Centre

Today's **Research**; Tomorrow's **Care**
Ymchwil Heddiw; **Gofal** Yfory

NISCHR CRC is part of the research infrastructure for Wales funded by NISCHR, Welsh Government www.wales.gov.uk/nischr

Appendix XI: Results of literature review on equivalence of electronic and paper based patient reported outcomes

Study Authors	Publication Type	Relevant Instruments Investigated	Country	Analysed Sample Size	Sample Size Calculation	Study Population	Study Design	Electronic Format
Beaumont et al (2011)	Journal article	COPD Population Screener (COPD-PS)	USA	1006	Y	General population	R Comparison	Internet
Bernstein et al (2013)	Journal article	Sexual Health Inventory for Men (SHIM)	USA	116	N	Male patients	Crossover	Internet
Bruce & Fries (2011)	Conference abstract	Health Assessment Questionnaire: Disability Index (HAQ: DI)	USA	378	N	Patients	Comparison	Internet
Carlbring et al (2007)	Journal article	Body Sensations Questionnaire (BSQ)	Sweden	Multiple	N	Patients	R Crossover	Internet
		Agoraphobic Cognitions Questionnaire (ACQ)						
		Mobility Inventory (MI)						
		Beck Anxiety Inventory (BAI)						
		Beck Depression Inventory (BDI)						
		Quality of Life Inventory (QOLI)						
		Montgomery Asberg Depression Rating Scale - self-rated (MADRS-S)						
Chang et al (2014)	Journal article	EORTC QLQ-PR25	Taiwan	99	Y	Patients	R Crossover	Touch-screen computer
Chen et al (2007)	Journal article	Short Form-36 (SF-36)	China	150	Y	Patients + university students	R Crossover	Unclear
Chen et al (2009)	Journal article	Short WHO Quality of Life Assessment (WHOQOL-BREF)	Taiwan	72	N	Nurses	Crossover	Internet
Chen & Li (2010)	Journal article	Short Form-36 (SF-36)	China	100	N	University students	Crossover	Computer
Chen et al (2011)	Conference abstract	Urogenital Distress Inventory (UDI-6)	China	81	N	Patients	Crossover	Internet
		Incontinence Impact Questionnaire (HQ-7)						
		Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12)						
Clayer & Davis (2011)	Journal article	Toronto Extremity Salvage Score (TESS)	Australia	46	N	Patients	Crossover	Internet
Dalal et al (2011)	Journal article	Lung Function Questionnaire (LFQ)	USA	48	Y	General population	R Crossover	Internet
Dinkel et al (2010)	Journal article	Stress Index RadioOncology (SIRO)	Germany	177	N	Patients	Crossover	Tablet
Frennered et al (2010)	Journal article	EuroQol-5 Dimension (EQ-5D)	Sweden	Multiple	N	Patients	Crossover	Touch-screen computer
		General Function Score (GFS)						
		Short Form-36 (SF-36)						
		Zung Depression Scale (ZDS)						
Guldsburgen et al (2011)	Journal article	Knee Injury and Osteoarthritis Outcome Score (KOOS)	Denmark	20	Y (for KOOS)	Patients	R Repeated Crossover	Touch-screen computer
		Short Form-36 (SF-36)						
		Physical Activity Scale						
		painDETECT						
		Activity of Daily Living Questionnaire (ADL)						

Study Authors	Publication Type	Relevant Instruments Investigated	Country	Analysed Sample Size	Sample Size Calculation	Study Population	Study Design	Electronic Format
Handa et al (2008)	Journal article	Pelvic Floor Distress Inventory (PFDI-20)	USA	43	Post-hoc power analysis	Female patients	R Crossover	Internet
		Pelvic Floor Impact Questionnaire (PFIQ-7)						
Hedman et al (2010)	Journal article	Liebowitz Social Anxiety Scale-Self Report (LSAS-SR)	Sweden	Multiple	N	Patients	Comparison	Internet
		Social Phobia Scale (SPS)						
		Social Interaction Anxiety Scale (SIAS)						
		Montgomery-Asberg Depression Rating Scale - Self-Rated (MADRS-S)						
		Beck Anxiety Inventory (BAI)						
		Quality of Life Inventory (QOLI)						
Heiberg et al (2007)	Journal article	Rheumatoid Arthritis Disease Activity Index (RADAI)	Norway	38	N	Patients	R Repeated Crossover	PDA
		Modified Health Assessment Questionnaire (MHAQ)						
		Short Form-36 (SF-36)						
Hollandere et al (2010)	Journal article	Montgomery-Asberg Depression Rating Scale - Self-Rated (MADRS-S)	Sweden	87	N	Patients	Crossover	Internet
		Beck Depression Inventory (BDI)						
Hollen et al (2013)	Journal article	Lung Cancer Symptom Scale (LCSS)	USA	86	Y	Patients	Crossover	PDA
Howell et al (2010)	Journal article	Satisfaction with Life Scale (SWLS)	USA	173	N	University students	Comparison	Internet
		Subjective Happiness Scale (SHS)						
Juniper et al (2007)	Journal article	Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S))	Denmark	70	N	Patients	R Crossover	PDA
Juniper et al (2009)	Journal article	Asthma Quality of Life Questionnaire (AQLQ(S))	Canada	Multiple	N	Patients	R Crossover	PDA
		Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S))						
		Asthma Control Questionnaire (ACQ)						
Lalanne et al (2013)	Conference abstract	PROQOL-HIV	France	58	N	Patients	R Crossover	Unclear
Lee (2009a)	Journal article	Cancer-Specific Quality-of-Life Questionnaire (C-QOL)	South Korea	105	Y	Patients	R Crossover	Touch-screen computer
Lee (2009b)	Abstract	Asthma-Specific Quality-of-Life Questionnaire (A-QOL)	South Korea	261	N	Patients	R Crossover	Touch-screen computer
Lee et al (2013)	Journal article	Diabetes-Specific Quality-of-Life Questionnaire (D-QOL)	South Korea	208	Y	Patients	R Crossover	Touch-screen computer

Study Authors	Publication Type	Relevant Instruments Investigated	Country	Analysed Sample Size	Sample Size Calculation	Study Population	Study Design	Electronic Format
Mackenzie et al (2011)	Journal article	Health Assessment Questionnaire (HAQ)	Canada	Multiple	N	Patients	R Crossover	Internet
		Short Form-36 (SF-36)						
		Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)						
		Bath Ankylosing Spondylitis Functional Index (BASFI)						
		Bath Ankylosing Spondylitis Global Score (BAS-G)						
		Ankylosing Spondylitis Quality of Life Instrument (ASQoL)						
		Modified Fatigue Severity Scale (mFSS)						
		Functional Assessment of Chroinc Illness Therapy (FACIT)						
		Dermatology Life Quality Index (DLQI)						
		EuroQol-5 Dimension (EQ-5D)						
Matthew et al (2007)	Journal article	International Prostate Symptom Score (IPSS)	Canada	Multiple	N	Patients	R Crossover	PDA
		International Index of Erectile Function-5 (IIEF-5)						
		Patient Orientated Prostate Cancer Utility (PORPUS)						
Minard et al (2011a)	Conference abstract	Pediatric Caregiver's Asthma Quality of Life (PCAQLQ)	Canada	25	N	Caregivers of child patients	R Crossover	Unclear
Minard et al (2011b)	Conference abstract	Mini Pediatric Asthma Quality of Life (Mini PAQLQ)	Canada	18	N	Child patients	R Crossover	Unclear
Naus et al (2009)	Journal article	Beck Depression Inventory (BDI)	USA	76	N	Female university students	R Crossover	Computer
		Short Form-36 (SF-36)						
		Neo-Five Factor Inventory (NEO-FFI)						
Olajos-Clow et al (2010)	Journal article	Mini-Asthma Quality of Life (MiniAQLQ)	Canada	40	Interim analysis	Patients	R Crossover	Computer
Oliveira et al (2010)	Abstract	EORTC-QLQ C30	Portugal	200	N	Patients	Crossover	Touch-screen computer
Oliveira et al (2011)	Journal article	EORTC-QLQ C30	Portugal	193	N	Patients	Unclear	Touch-screen computer
Parnell et al (2011)	Journal article	Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12)	USA	50	Post-hoc power analysis	Female patients	R Crossover	Internet
Raat et al (2007)	Journal article	Child Health Questionnaire - Child Form (CHQ-CF)	Netherlands	933	N	Children	R Comparison	Internet
Ribeiro et al (2010)	Journal article	Short Form-36 (SF-36)	Portugal	50	N	Patients	Crossover	Touch-screen computer
Ribeiro et al (2011)	Conference abstract	Short Form-36 (SF-36)	Portugal	91	N	Patients	Unclear	Unclear

Study Authors	Publication Type	Relevant Instruments Investigated	Country	Analysed Sample Size	Sample Size Calculation	Study Population	Study Design	Electronic Format
Richter et al (2008)	Journal article	Hannover Functional Questionnaire (FFbH)	Germany	Multiple	N	Patients	R Crossover	Tablet
		Health Assessment Questionnaire (HAQ)						
		Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)						
		Short Form-36 (SF-36)						
Ring et al (2008)	Abstract	Functional Assessment of Cancer Therapy - Lung (FACT-L)	UK	50	N	Patients	R Crossover	Unclear (Handheld device)
		EuroQol-5 Dimension (EQ-5D)						
Sage et al (2012)	Conference abstract	Rheumatology Paediatric Quality of Life Inventory (RHE-PedsQL)	USA	Multiple	N	Child + adult patients	Crossover	Tablet
		Review of Systems Symptom Checklist (ROS)						
Salaffi et al (2009)	Journal article	Recent-Onset Arthritis Disability (ROAD)	Italy	87	N	Patients	R Crossover	Touch-screen computer
Salaffi et al (2013)	Journal article	Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Italy	55	N	Patients	Crossover	Tablet
		Bath Ankylosing Spondylitis Functional Index (BASFI)						
Saunders et al (2007)	Journal article	Attitudes towards Loss of Hearing Questionnaire (ALHQ)	USA	100	N	Patients	Crossover	Computer
Schefte & Hetland (2010)	Journal article	Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Denmark	Multiple	N	Patients	R Crossover	Touch-screen computer
		Bath Ankylosing Spondylitis Functional Index (BASFI)						
		Health Assessment Questionnaire (HAQ)						
Schemmann et al (2013)	Conference abstract	International Hip Outcome Score-12 (iHOT-12)	Germany	60	N	Patients	Unclear	Tablet
Silveira et al (2011)	Abstract	EORTC-QLQ C30	Portugal	54	N	Patients	Crossover	Computer
		EORTC-H&N35						
Sjostrom et al (2012)	Journal article	ICIQ Lower Urinary Tract Symptoms Quality-of-Life (ICIQ-LUTSqol)	Sweden	54	N	Patients	Crossover	Internet
Swartz et al (2007)	Journal article	Center for Epidemiological Studies Depression Scale (CES-D)	USA	756	Rationale detailed	Patients	R Crossover	PDA
Twiss et al (2013)	Conference abstract	Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)	USA	147	N	Patients	Comparison	Unclear
Varni et al (2008)	Journal article	Pediatric Quality of Life Inventory (PedsQL™) (Generic Core Scales): Child Self-Report	USA	Multiple	N	Child patients + caregivers	R Crossover	Internet
		Pediatric Quality of Life Inventory (PedsQL™): Parent Proxy-Report						
Vinney et al (2012)	Journal article	Pediatric Quality of Life Inventory (PedsQL™)	USA	19	Y	Children: General population + patients	R Crossover	PDA
Wu et al (2009)	Journal article	Kansas City Cardiomyopathy Questionnaire (KCCQ)	Canada	Multiple	Y (for KCCQ)	Patients	R Crossover	Internet
		Minnesota Living with Heart Failure Questionnaire (MLHFQ)						
		Self-Care of Heart Failure Index (SCHFI)						
Young et al (2009)	Journal article	Activities Scale for Kids (Performance Version) (ASK)	Canada	69	N	Child patients	R Crossover	Internet
		Pediatric Quality of Life Inventory (PedsQL) (Generic Core Scales)						
Zimmerman & Martinez (2012)	Abstract	Clinically Useful Depression Outcome Scale (CUDOS)	USA	53	N	Patients	Crossover	Internet

Appendix XII: Literature review update

Authors	Publication Type	Instrument	Statistical evidence of equivalence	Electronic Format
Crist and Pashuck (2018)	Article	EQ-5D and musculoskeletal functional assessment	Score difference	Computer
Goswami et al. (2019)	Article	Hematological malignancy-patient-reported outcome (HM-PRO)	ICC / Spearman's rank	Not specified
Chai-Adisaksopha et al. (2019)	Article	PROBE questionnaire	Kappa co-efficients	Web-based
Hudgens et al. (2019)	Article	FSIQ-RMS: A New Patient-Reported Questionnaire to Assess Symptoms and Impacts of Fatigue in Relapsing Multiple Sclerosis	Conceptual equivalence	Smartphone
Martin et al. (2018)	Article	The Patient Assessment for Low Back Pain - Symptoms (PAL-S)	Interview assessment	Web-based
Palmer et al. (2018)	Article	iList questionnaire (OABSS and PPBC)	2-sided Z-test (patient-assessment)	iPad
Inderjeeth et al. (2017)	Conference abstract	Patient assessment of pain (PAAP), Patient assessment of global disease activity (PtGADA) and Bristol Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ)	'Correlation / agreement'	Not stated
Takegami et al. (2019)	Article	Japanese Orthopaedic Association Hip Disease Evaluation Questionnaire	ICC	Web-based
Keilmann et al. (2019)	Conference abstract	EORTC QLQ-C30	Wilcoxon test, Spearman's rho and agreement rates for single items, Person's correlation, Kendall's tau	Tablet
Hofstedt et al. (2019)	Article	Bath Ankylosing Spondylitis Disease Activity Index and Functional Index (BASDAI and BASFI),	ICC	Internet-based
Bagattini et al. (2018)	Article	Brazilian EQ-5D	ICC / Kappa coefficient	Tablet

Nishimura et al. (2017)	Conference abstract	Evaluating Respiratory Symptoms in COPD (E-RS) and the COPD Assessment Test (CAT)	ICC	Tablet
Dang et al. (2018)	Conference abstract	Physical/functional (COMI-back, ODI, EQ-5D-VAS) and mental health status (PHQ-2 - depression, GAD-2 - anxiety)	Patient preference	Tablet
Pompili et al. (2018)	Conference abstract	PROMs in 'Life After Cancer'	Chi-square	Web-based
Solé et al. (2018)	Article	Cystic Fibrosis Questionnaire (CFQ-R Teen/Adult)	ICC	Not specified
Ali et al. (2017b)	Article	Dermatology Life Quality Index (DLQI)	ICC and patient preference	Tablet
O'Donohoe et al. (2015)	Conference abstract	St. George's Hospital Respiratory Questionnaire for COPD Patients (SGRQ-C) and the COPD Assessment Test (CAT)	Cognitive debriefing	Tablet
Petersen et al. (2016)	Conference abstract	EORTC QLQ-CAT	Patient interviews	Web-based
Peters et al. (2016)	Conference abstract	Coeliac disease assessment questionnaire (CDAQ)	Internal consistency	Web-based
Schougaard et al. (2018)	Article	Epilepsy PRO	Weighted Kappa	Web-based
Byrom et al. (2018)	Article	'Bring Your Own Device' PROM	ICC	Mobile-device
Storck et al. (2018)	Article	Mobile patient survey (pruritus)	Coefficient RC, Weighted Kappa	Mobile-device
Tan and Caird (2016)	Conference abstract	Electronic Integrated Text, Visual and Audio Questionnaire (EITVAQ)	Pearson Chi-Square Test	Not specified
Bandarian-Balooch et al. (2017)	Article	Headache Disability Inventory, SF-36, Depression Anxiety Stress Scales, Measure of Acceptance Questionnaire	Patient evaluation / convergent validity	Web-based
El Miedany et al. (2016)	Article	Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index	Score comparison	Web-based
Eshoj et al. (2017)	Article	Danish Western Ontario Shoulder Instability (WOSI) questionnaire	Pearson's (r) and Concordance	Not specified

			Correlation Coefficients (CCC)	
Knoerl et al. (2017)	Article	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy Scale (QLQ-CIPN20), National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), QLQ-CIPN20, Neuropathy Screening Question (NSQ)	ICC	Not specified
Nitikman et al. (2017)	Article	Pediatric Outcomes Data Collection Instrument (PODCI), Scoliosis Research Society 30 (SRS-30)	Paired sample T-test	Web-based
Rosato et al. (2017)	Conference Abstract	MSQOL-29	ICC/Mixed-effect Model	Not specified
Sharma et al. (2016)	Article	Expanded Prostate Cancer Index Composite (EPIC)	Signed-rank test	Not specified
Kim et al. (2016)	Article	M.D. Anderson Symptom Inventory (MDASI-K) and the Brief Fatigue Inventory (BFI-K)	ICC and patient preference	Tablet
Dang et al. (2016)	Article	Eyelash Satisfaction Questionnaire (ESQ)	Cronbach's alpha	Web-based
Bennett et al. (2016b)	Article	MSKCC Bowel Function Instrument (BFI), the LASA Quality of Life (QOL) scale, and the Subjective Significance Questionnaire (SSQ)	ICC	Web, interactive voice response system
Touchèque et al. (2016)	Article	Quality of Life Systemic Inventory for Children (QLSI-C)	ICC, Paired t test and Pearson's correlations	Tablet
Rasmussen et al. (2016)	Article	Thyroid-related quality-of-life questionnaire ThyPRO	ICC, Paired t tests and Bland-Altman plots	Not specified
Bennett et al. (2016a)	Article	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)	ICC, Mixed-models	Tablet
Minard et al. (2016)	Article	Mini Pediatric and Pediatric Asthma Caregiver's Quality of	ICC	Not specified

		Life Questionnaires (MiniPAQLQ and PACQLQ, respectively)		
Robson et al. (2016)	Conference abstract	ANCA-associated vasculitis PRO (AAV-PRO)	ICC	Web-based
Sydor and Spertus (2016)	Conference abstract	Kansas City Cardiomyopathy Questionnaire (KCCQ)	Cognitive interviews	Not specified
Simpson et al. (2016)	Conference abstract	English Quality of Life-Bronchiectasis (QOL-B)	Cognitive debriefing and usability testing	Tablet
Eremenco et al. (2014)	Conference abstract	Pain Visual Analogue Scale (VAS), Global Disease VAS, HAQ-DI, MOS Sleep Scale, WPAI:RA, Rheumatology Attitudes Index, Sexual Impairment due to RA, Perception of Ultrasound in Management of RA, TSQM, FACIT-Fatigue Scale, Compliance Questionnaire Rheumatology, and RA-WIS	Patient preference / score comparison	Touchscreen + Stylus
Robles et al. (2015)	Article	Spanish and Catalan versions of the Euroqol 5D-Y	Percentage agreement, Kappa Index, ICC	Web-based
Kesterke et al. (2015)	Article	Western Ontario and McMaster Universities (WOMAC) osteoarthritis score, Forgotten Joint Score-12 (FJS-12)	T-test, Mann-Whitney U test, Fisher's exact test, and Wilcoxon test	Tablet
Cunha-Miranda et al. (2015)	Article	Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Quality of Life scale (ASQoL), Short-Form 36 (SF-36), Health Assessment Questionnaire (HAQ) and visual analogue scales (VAS)	ICC	Touchscreen
Sorenson et al. (2015)	Article	Trojan Lifetime Champions (TLC) Health Survey	ICC, Kappa	Not specified
Richter et al.	Conference	HAQ; RA disease	Score	Smartphone/Tablet

(2015)	abstract	activity index (RADAI)	comparison (not specified)	'Bring Your Own Device'
Eremenco et al. (2015a)	Conference abstract	Fatigue symptoms and impacts questionnaire-relapsing multiple sclerosis (FSIQ-RMSTM)	Patient interviews	Smartphone
Eremenco et al. (2015c)	Conference abstract	Dysmenorrhea (DYS), Non-menstrual Pelvic Pain (NMPP), Dyspareunia, Uterine Bleeding, Numeric Rating Scale (NRS), and Menstrual Period	Patient interviews	eDiary
Eremenco et al. (2015b)	Conference abstract	Menstrual Bleeding Scale, Uterine Fibroid Daily Symptom Scale, Non-Bleeding Uterine Fibroids Symptom (NBUFSQ) Questionnaire-Morning, and NBUFSQ-Evening	Patient interviews	eDiary
Skerritt et al. (2015)	Conference abstract	EORTC Quality of Life Questionnaire (EORTC QLQ-C30;v3.0) and its Breast Cancer Module (QLQ-BR23;v1.0)	Patient interviews	Tablet + Handheld device
Elash et al. (2015)	Conference abstract	SF-36v2 Health Survey (Standard), Bath Ankylosing Spondylitis Disease Activity Index, Health Assessment Questionnaire, Dermatology Quality of Life Instrument, Patient Global Assessment of Disease Activity, Subject Assessment of Pain, and, Fatigue Visual Analogue Scale	ICC	Tablet
Acaster et al. (2015)	Conference abstract	Symptom bother VAS ('Allergy Diary by MACVIA ARIA')	ICC	Touchscreen
Katusiime et al. (2015)	Conference abstract	Living with Medicines Questionnaire©	Chi-square test	Web-based
Morley et al. (2015)	Conference abstract	Parkinson's disease Questionnaire (PDQ-39)	Item-total correlations, Cronbach's alpha and construct validity	Computer-based
Rajmil et al. (2014)	Article	KIDSCREEN-52, Strengths and Difficulties Questionnaire (SDQ)	ICC	Web-based
Linehan et al. (2014)	Article	Electronic personal assessment	Not specified	Not specified

		questionnaire (ePAQ-PF)		
Chang et al. (2014)	Article	Taiwan Chinese version of the EORTC QLQ-PR25	Rasch rating scale	Touchscreen
Bjorner et al. (2014)	Article	Patient Reported Outcomes Measurement Information System (PROMIS)	ICC	Interactive voice response (IVR) technology, personal digital assistant (PDA), or personal computer (PC)
Lee et al. (2014)	Article	Diabetes-Specific Quality-of-Life questionnaire (cD-QOL)	Kappa coefficients, ICC and Cronbach's alpha	'Computerised'
Broering et al. (2014)	Article	Medical Outcomes Study (MOS) Short Form-36 (SF-36) and the University of California Los Angeles Prostate Cancer Index (UCLA-PCI)	ICC	Web-based
Duracinsky et al. (2014)	Article	Patient-Reported Outcomes Quality of Life-human immunodeficiency virus (PROQOL-HIV)	Pearson correlation, ICC	'Computerised'
O'Gorman et al. (2014)	Conference abstract	EQ-5D-5L	Anova	Mobile device
Salaffi et al. (2014)	Conference abstract	Recent-Onset Arthritis Disability (ROAD) and PRO-CLinical ARthritis Activity (PRO-CLARA)	Student's t-test, ICC	Touchscreen
Bushnell et al. (2018)	Article	Low Back Pain-Impacts (PAL-I)	Patient interviews	Not specified
Delgado-Herrera et al. (2017)	Article	IBS-D Daily Symptom Diary and IBS-D Symptom Event Log	Patient interviews	Mobile device
Norquist et al. (2017)	Article	EORTC QLQ-H&N35	Patient interviews	Not specified
Caetano et al. (2016)	Article	Denture satisfaction item (100-mm VAS) and OHIP-EDENT	Cronbach's alpha, Paried t-test	Tablet
Hafner et al. (2016)	Article	Prosthetic Limb Users Survey of Mobility, Prosthesis Evaluation Questionnaire-Mobility Subscale, Activities-Specific Balance Confidence Scale, Quality of Life in Neurological Conditions-Applied Cognition/General Concerns, Patient-Reported Outcomes	ICC	Not specified

		Measurement Information System Profile, and Socket Comfort Score		
El Miedany et al. (2016)	Article	Routine Assessment of Patient Index Data 3 (RAPID-3), 28-joint Disease Activity Score (DAS28)	Patient adherence, no other specification	Not specified
Sun et al. (2016)	Article	Pelvic Floor Impact Questionnaire Short Form 7 questionnaire	ICC, Bland-Altman	Not specified
Wæhrens et al. (2015)	Article	Fibromyalgia Impact Questionnaire (FIQ), the Major Depression Inventory (MDI), the 36-item Short Form Health Survey (SF-36), the painDETECT questionnaire (PDQ), the Coping Strategies Questionnaire (CSQ), and the Generalized Anxiety Disorder Self-Assessment Questionnaire (GAD-10)	ICC, Spearman's coefficient	Touchscreen
Spangenberg et al. (2015)	Article	Patient Health Questionnaire (PHQ-9), Aachen Depression Item Bank (ADIB)	ICC, mixed-effects regression, and differential item functioning (DIF)	Tablet

Appendix XIII: Study protocol – Version 7 (21.05.14)

Title: Comparison of the paper-based and web-based application versions of the Dermatology Life Quality Index [DLQI] and Psoriasis Area and Severity [PASI] Index

Investigators: Faraz Ali, Andrew Finlay, Sam Salek, Vincent Piguet

Site: Dermatology outpatient clinic, University Hospital of Wales, Cardiff

Study commencement date: April 2014

Study duration (post- ethical permission): 1 year

Background

Skin diseases are very common in the community and although most are not life threatening, many are chronic and incurable. Skin diseases can have a significant impact on patients' quality of life (QoL). These effects on patients may not be captured using traditional biomedical outcome measures. This is the reason why QoL assessment has become an important endpoint in clinical research in addition to traditional clinical outcomes. The clinical uses of QoL assessment may extend beyond the application of research findings. Routine assessment of QoL as part of clinical practice has the potential to improve communication between patients and providers (Detmar and Aaronson 1998), identify

frequently overlooked problems, prioritise problems, and evaluate the impact of therapeutic efforts at the individual patient level. QoL discussions help patients feel understood both physically and emotionally (Detmar and Aaronson 1998). Because of the increasing recognition of its importance, QoL is increasingly being incorporated into patient service evaluation and policy making and for health resource allocation. Last but not least, the use of QoL and other patient-reported outcomes has become a regulatory requirement for the pharmaceutical industry to support labeling claims (Patrick et al, 2007).

Standardised questionnaires for self-rating by the respondents are useful for recording QoL not only because of their ease of use but also because they are quicker to complete and allow data recording independent of the investigator, thus avoiding the influence of the examiner on the respondent (Augustin et al, 2000). A standardised measurement of patients' QoL may support clinicians in identifying important problems for discussion during the limited time of the medical consultations. However, the assessments made by the use of the questionnaires need to be understandable, user-friendly, and short (Bezjak et al 2001) If not, health-care providers are less likely to use the measures (Bezjak et al 2001). Scores must be clinically meaningful to both providers and patients. Results must be presented in a format that is easy to read, provides useful information, and facilitates direct discussion about topics such as treatment options and general and specific aspects of QoL (Bezjak et al 2001; Carlson 2001). Additionally, results must be ready in "real-time," at the visit when the data are gathered. Ease of use is one of the most important factors necessary for assessing QoL as part of routine clinical practice. Paper-based instruments have a number of limitations such as higher rate of missing values, higher error rates in selecting multiple responses for single option items, data entry error in transferring responses from a paper form to the electronic databases and higher costs associated with administration, collection and entering the data (Saleh et al, 2002). On the other hand, these issues can be effectively handled by the use of computer-based administration of QoL questionnaires. Computer-based administration (CBA) of QoL measures such as in the form of web-based applications (see Appendix 1) using screen-touch computers also called tablets is one of the ways that more frequent assessments can be conducted with minimal burden on patients and clinical staff in addition to meeting all the requirements mentioned above. This method that includes not only computer-based administration but also scoring and presentation of QoL results, eliminates the need for a test administrator, as usually needed for traditional paper and pencil formats while providing immediate "real-time" feedback. Information from assessments can be displayed in graphic reports as visual aids that help guide discussions about treatment options and care planning.

Psoriasis is a chronic incurable disfiguring skin condition that runs a remitting-relapsing course characterised by fluctuations in clinical severity and perhaps in QoL in some patients. Patients with more widespread psoriasis require long term systemic therapy and regular and frequent monitoring for potential adverse effects of the systemic drugs. Consequently frequent assessments of disease severity and QoL are necessary to help guide optimal treatment planning and decision-making. It follows that routine assessment (at each visit) of disease severity and QoL will require a major commitment of resources. However, the availability of a CBA has the potential to reduce both the respondent burden (as mentioned above) and administrative time required to transfer the results of these patient-reported outcomes e.g. QoL scores to the clinician's desk enhancing the feasibility and logistics of integrating real-time disease severity/QoL assessment data for immediate use into routine clinical care (Paul et al 2002). There is evidence to show that the computer-based measurement of QoL was well accepted by patients who felt that this method was a useful tool to tell the clinician about their problems (Velikova et al, 2002). The clinicians perceived that the QoL data broadened the range of the clinical inquiry and helped them identify issues for discussion. Having symptoms and functional problems expressed quantitatively on a scale was useful for detection of change over time. Further evidence shows that data are more complete on the electronic questionnaires compared with paper questionnaires, data handling greatly simplified and majority of patients prefer the former (Drummond et al, 1995).

Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI; Finlay and Khan, 1994) is currently the most commonly used dermatology-specific QoL measure in clinical trials of skin diseases (Both et al 2007; le Cleach et al 2008). It has been used in more than 36 skin diseases (inflammatory, non-inflammatory and skin cancers), in more than 32 countries and is available in over 55 international language versions (Basra et al, 2008). The DLQI has been shown to be easy to use in clinical practice due to its simplicity and brevity (Bronsard et al 2010) with an average completion time of around 2 minutes (Loo et al 2003). It consists of 10 questions concerning dermatological patients' perception of the impact of skin diseases on different aspects of their QoL over the last week. The items of the DLQI encompass aspects such as symptoms and feelings, daily activities, leisure, work or school, personal relationships and the side effects of treatment. Each item is scored on a 4-point scale: not at all/not relevant, a little, a lot and very much. Scores of individual items (0-3) are added to yield a total score (0-30); higher scores mean greater impairment of patient's QoL. In 2005, Hongbo et al introduced the

much needed banding of the DLQI scores to facilitate the clinical interpretation of scores (Hongbo et al, 2005). According to this banding system a DLQI score of 0 and 1 means no impact on patient's QoL while a score of 2-5, 6-10, 11-20 and 21-30 indicate a small, moderate, large and extremely large effect on patient's QoL respectively. Psychometrically, the DLQI has been shown to be a strong instrument with respect to its internal consistency, reproducibility, validity and sensitivity to change (Bronsard et al 2010, Badia et al, 1999; Hahn et al, 2001; Mazzotti et al, 2003). The strong psychometric properties of the DLQI have resulted in the increasing popularity of the DLQI in both clinical research and in clinical practice. Moreover, the content of the DLQI has been shown to include all important and relevant concepts from the perspective of patients with moderate to severe plaque psoriasis supporting its content validity in psoriasis patients (Safikhani et al, 2011)

Psoriasis Area and Severity Index (PASI)

Psoriasis Area and Severity Index is a widely used tool to assess the severity of psoriasis (Fredriksson and Pattersson, 1978) that is mostly completed by trained health care professionals and study investigators. Although PASI has been criticised for being resource intensive, lacking sensitivity and being complex, in the absence of a "gold standard", it has become an almost universal outcome measure in clinical trials of drugs used for psoriasis (Ashcroft et al, 1999). PASI scoring system assesses four body areas: head (corresponding to 10% of total body surface area), upper extremities (20%), trunk (30%) and lower extremities (40%). The area of psoriasis involvement for each of the 4 body regions is assigned a numerical value of 0-6 corresponding to 0-100% involvement as follows:

0=no involvement; 1= up to 9% involvement; 2= 10-29% involvement; 3=30-49%; 4=50-69%; 5=70-89% and 6=90-100% involvement.

For each body region, erythema, induration and desquamation are rated according to a 5 point scale as follows:

0= no involvement; 1=slight involvement; 2=moderate involvement; 3=marked involvement and 4=very marked involvement

The PASI score is calculated by applying a standard formula. The score can vary in increments of 0.1 units and range from 0 to 72; higher score indicates greater degree of severity.

Although PASI has been administered in various formats such as conventional paper-based format and computerised (including hand-held touch screen) devices but there is no published evidence to show its use as a web-based application.

DLQI/PASI web-based application and its clinical and research implications

In response to the increasing demand, a web-based application of the DLQI/PASI has been developed (see Appendix 2) to encourage its further uptake in the current modernised clinical and research settings in many countries. Although computerised administration of QoL tools in other specialities has been shown to have numerous advantages over traditional paper-based tools (Hanscom et al 2002), this method of QoL/disease severity assessment to present an overall disease severity idea has not been introduced in dermatology yet, and hence quantitative comparisons have not been made for the web-based application and paper-versions of the DLQI and PASI, both being so far the most widely used outcome measures in psoriasis clinical trials. More importantly in clinical practice, to-date there is no method to allow "real-time" monitoring of patient's QoL and disease severity during flare-up of their psoriasis (known for its remitting and relapsing nature). The availability of a DLQI/PASI application to patients would be expected to facilitate the monitoring of psoriasis in a more efficient way.

It is hoped that the availability of a validated DLQI/PASI application will help in better management of psoriasis by having an easy tool for regular monitoring of the disease severity from patient's own perspective including both impact on QoL and self-assessed disease severity. Moreover, this tool could potentially be used by GPs to decide which patients need to be referred.

In the research setting the availability of a web-based application would facilitate more efficient data collection in clinical trials, sometimes even from multiple centre/countries such as for longitudinal assessments of disease severity.

Study Objectives

The objective of this pilot study are:

Primary objective:

- To compare the conventional paper-based and the novel web-based application versions of the DLQI and the PASI in terms of patient and investigator acceptability and preference and in terms of consistency of their scores, respectively.

Secondary objectives:

- To assess the correlation between DLQI scores assessed by two different methods: standard paper-based DLQI and the DLQI application
- To assess the correlation between PASI scores assessed by investigator using conventional PASI and web-based PASI application
- To assess the internal consistency reliability of the web-based DLQI application
- To assess the feasibility of web-based DLQI/PASI application in the dermatology outpatient clinic
- To compare the response burden between the two formats in terms of time spent on completion both for the DLQI and the PASI
- To compare patients' preferences for the use of the web-based DLQI and PASI application versus conventional versions of these tools in terms of ease of use etc.

Ethical consideration

Based on the advice sought from the Research and Commercial Division (RACD) of Cardiff University and the Research and Development (R&D) Department of Cardiff and Vale University Health Board this study has been classified as original research using a new technology and will need full ethics approval. Therefore, an application will be submitted for full ethical permission to R&D department of Cardiff and Vale LHB and to the South West-Central Bristol Research Ethics Committee after favourable independent scientific review report.

Detailed Patient Information sheet and consent forms will be prepared and submitted for ethical approval along with the study protocol/proposal.

Methodology

The study will employ a within-subjects comparison design involving quantitative method for data collection. Patients with all skin conditions will be recruited, and they will be invited to complete the DLQI (both paper and electronic versions). However, those with Psoriasis will also be assessed using PASI by the investigator (both electronic and paper

versions). Who receives which format first will be randomised on the day, but every patient and investigator will have used both electronic and paper versions. Before the start of the pilot study, the investigators will be given training on the use of the touch-screen web-based application of the DLQI/PASI and the interpretation of the results.

Study participants

A cohort of up to 400 adult patients with different skin diseases on the waiting list for outpatient dermatology appointments and those for routine follow-up appointments will be approached through their respective consultants by post prior to their scheduled appointments. A number of 400 was decided upon based on previous similar studies conducted by the investigators. Patient will be provided information sheet about the study and asked whether they would be willing to participate. Patients can demonstrate their willingness to participate by filling in a reply form. They will also be given the option to arrive at least one hour ahead of their scheduled appointment time or for the study to be conducted immediately after for an hour. This will allow time for study briefing, consenting and administering the questionnaires (as described below in more detail).

Inclusion criteria:

- Ages 18 years and older
- Having any confirmed skin condition for the electronic DLQI (eDLQI)validation
- Having a confirmed diagnosis of psoriasis for electronic PASI (ePASI) validation
- Able to read, write and understand English

Exclusion criteria:

- Ages under 18 years
- Having a co-existing non-dermatological medical condition of considerable severity, as determined by the investigator
- Having a co-existing dermatological condition of considerable severity, as determined by the investigator
- Not able to read and or understand written English

Study procedure

This study will be carried out in the following manner:

a. Patients attending the Dermatology outpatient department, who will be willing to participate after reading the information sheet will be asked to give written

informed consent. At this stage, their demographic details will be recorded including age, gender, literacy level, diagnosis, educational background, any visual or tactile impairment, familiarity with electronic media/computer, previous experience in using touch-screen computers and previous use of iPhone/Android applications etc.

b. Following this, participants with any primary skin condition will be randomised to whether they first complete the DLQI either using the paper-based version or the web-based DLQI/PASI application version provided on an iPad. For psoriasis-only patients, the investigator will also assess the PASI using either the web application or the traditional PASI (randomised). Time taken by participants to complete the DLQI using the paper version and the application and by the investigator to do the PASI using either method will be recorded.
c. After completing this part of stage 1, 30 minutes later, study participants will be asked to complete the DLQI again using the paper-based or the application (DLQI/PASI) version depending on their initial mode of administration. For example, participants who will have been randomised to complete the paper-based version of the DLQI first will now be asked to complete it using the application version and vice versa. Similarly, in patients with psoriasis, the investigator will also assess the patient's PASI using either the conventional PASI or the PASI application, depending on which method was used first. Timing will be calculated as before. Therefore, every patient receives the same standard of management.
d. At the end, a short questionnaire will be filled which would gather data on their perception and experience (i.e. attitude) with the use of both methods i.e. paper-based and web-based application, with regard to various practical aspects such as ease or difficulty of administration, acceptability, time requirement, feasibility, being comfortable with this information disclosure using the novel application-based method.
e. The above will take place entirely either prior to the patient's clinic appointment or for an hour after - depending on patient preference. The study will not have an impact on the patient's clinic appointment itself.

Outcomes and data analysis

The main outcome measures will be:

- patients' perceptions about the web application (and hence the feasibility of this mode of QoL/disease severity assessment)
- the assessment of correlation of the web-based application with the conventional paper-based version of the DLQI/PASI

The latter will be assessed using Intraclass correlation coefficient to see the concordance between paper-based and the application data. Internal consistency of the web-based application will be assessed by using Cronbach's alpha coefficient. Descriptive analysis will be used to present the data from patient feedback questionnaires and to present the results of various quantitative variables such as participants' age, gender, diagnoses, mean/median DLQI scores for the paper-based and web-application versions and the mean/median completion time for the two versions. Independent sample t-test will be used to assess the difference in the scores between the two DLQI (completed by patients) and PASI (completed by both the investigator and patients) versions and to analyse difference in the completion time between the two versions. Linear and logistic regression techniques will be used to identify demographic variables significantly associated with successful use of the DLQI/PASI application (in terms of completeness of DLQI data obtained).

Recording of data and retention of documents

Throughout the course of the study and at the completion of each stage research data will be entered onto data collection sheets and entered into SPSS version 16. At the end of the final study all the data will be collected and subjected to thorough analysis. All the research documents will be kept in a secure place under lock in the Dept. of Dermatology of UHW. Only the key researchers will have access to these data.

Funding

The study will be funded by a pharmaceutical company (Janssen) who are also providing financial and technical support in the development of the new DLQI/PASI application.

Publication of Results

At the end of study the results will be submitted for presentation at national and international research meetings and for publication.

Research staff

1. Dr. Faraz Mahmood Ali: Clinical Research Fellow, Dept. of Dermatology and Wound Healing, Cardiff University School of Medicine

2. Professor Andrew Finlay: Former Head of Department of Dermatology and Wound Healing, Cardiff University School of Medicine.
3. Professor Sam Salek: Chair in Pharmacoepidemiology, Cardiff University
4. Professor Vincent Piguet: Head of Department of Dermatology and Wound Healing, Cardiff University School of Medicine

References

Ashcroft DM, Wan Po AL, Williams HC, Griffiths CEM. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. Br J Dermatol 1999; 141: 185-191.

Augustin M, Amon U, Bullinger M, Gieler U. Recommendations for the Assessment of Quality of Life in Dermatology. Dermato Psychosom 2000; 1: 84-87.

Badia X, Mascaro JM, Lozano R. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: Clinical validity, reliability and sensitivity to change of the DLQI. Br J Dermatol 1999; 141: 698-702.

Basra MKA, Fenech R, Gatt RM et al. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol 2008; 159: 997-1035.

Bezjak A, Ng P, Skeel R, et al: Oncologists' use of quality of life information: Results of a survey of Eastern Cooperative Oncology Group Physicians. Qual Life Res 10:1-13, 2001.

Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. J Invest dermatol 2007; 127: 2726-2739.

Bronsard V, Paul C, Prey S et al. What are the best outcome measures for assessing quality of life in plaque type psoriasis? A systematic review of the literature. JEADV 2010; 24 (Suppl 2): 17-22.

Carlson L, Speca M, Hagen N, et al: Computerized quality of life screening in a cancer pain clinic. J Palliative Care 17:46-52, 2001.

Detmar S, Aaronson N: Quality of life assessment in daily clinical oncology practice: A feasibility study. Eur J Cancer 1998; 34: 1181-1186.

Drummond HE, Ghosh S, Ferguson A et al. Electronic quality of life questionnaires: a comparison of pen-based electronic questionnaires with conventional paper in a gastrointestinal study. Qual Life Res 1995; 4: 21-26.

Feldman SR, Fleischer AB, Reboussin DM et al. The Self-Administered Psoriasis Area and Severity Index is Valid and Relaible. J Invest Dermatol 1996; 106: 183-186.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol 1994; 19: 210-6.

Fleischer A, Rapp SR, Reboussin DM et al. Patient measurement of psoriasis disease severity with a structred instrument. J Invest Dermatol 1994; 102: 967-969.

Fredriksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. Dermatologica 1978; 157: 238-244.

Hahn HB, Catherine A. Melfi CA, Chuang TY et al. Use of the Dermatology Life Quality Index (DLQI) in a midwestern US urban clinic. J Am Acad Dermatol 2001; 45: 44-48.

Hanscom, Brett , Lurie, Jon D. , Homa, Karen, Weinstein, James N. Computerized Questionnaires and the Quality of Survey Data. Spine 2002; 27 - Issue 16: 1797-1801

Hongbo Y, Thomas CL, Harrison MA, Salek S, Finlay AY. Translating the Science of Quality of Life into Practice: What Do Dermatology Life Quality Index Scores Mean? J Invest Dermatol 2005; 125: 659-664.

Jacobsen PB, Davis K, Cella D. Assessing Quality of Life in Research and Clinical Practice. Oncology 2002; 16 No. 910.

Loo WJ, Diba VC, Chawla M, Finlay AY. Dermatology Life Quality Index: influence of an illustrated version. Br J Dermatol 2003; 148: 279-284.

Le Cleach L, Chassany O, Levy A et al. Poor reporting of quality of life outcomes in dermatology randomised controlled clinical trials. Dermatology 2008; 216: 46-55.

Mazzotti E, Picardi A, Sampogna F et al. Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis. Br J Dermatol 2003; 149: 318-322.

Patrick DL, Laurie B. Burke LB, John H. Powers JH et al. Patient-Reported Outcomes to Support Medical Product Labelling Claims: FDA Perspective. Value in Health 2007; 10 (suppl s2): s125-137.

Safikhani S, Sundaram M, Bao Y, Mulani P, Revicki DA. Qualitative assessment of the content validity of the Dermatology Life Quality Index in patients with moderate to severe psoriasis. J Dermatol Treatment 2011; Early Online publication (doi:10.3109/09546634.2011.631980)

Saleh KJ, Radosevich DM, Kassim RA et al. Comparison of commonly used orthopaedic outcome measures using palm-top computers and paper surveys. J Orthopaedic Research 2002; 20: 1146-1151.

Velikova G, Brown JM, Smith AB, Selby PJ. Computer-based quality of life questionnaires may contribute to doctor–patient interactions in oncology. British Journal of Cancer 2002; 86: 51–59.

Appendix XIV: Study Protocol – Version 8 (22.10.14)

Title: Comparison of the paper-based and web-based application versions of the Dermatology Life Quality Index [DLQI] and Psoriasis Area and Severity [PASI] Index

Investigators: Faraz Ali, Andrew Finlay, Sam Salek, Vincent Piguet

Site: Dermatology outpatient clinic, University Hospital of Wales, Cardiff

Study commencement date: April 2014

Study duration (post- ethical permission): 1 year

Background

Skin diseases are very common in the community and although most are not life threatening, many are chronic and incurable. Skin diseases can have a significant impact on patients' quality of life (QoL). These effects on patients may not be captured using traditional biomedical outcome measures. This is the reason why QoL assessment has become an important endpoint in clinical research in addition to traditional clinical outcomes. The

clinical uses of QoL assessment may extend beyond the application of research findings. Routine assessment of QoL as part of clinical practice has the potential to improve communication between patients and providers (Detmar and Aaronson 1998), identify frequently overlooked problems, prioritise problems, and evaluate the impact of therapeutic efforts at the individual patient level. QoL discussions help patients feel understood both physically and emotionally (Detmar and Aaronson 1998). Because of the increasing recognition of its importance, QoL is increasingly being incorporated into patient service evaluation and policy making and for health resource allocation. Last but not least, the use of QoL and other patient-reported outcomes has become a regulatory requirement for the pharmaceutical industry to support labeling claims (Patrick et al, 2007).

Standardised questionnaires for self-rating by the respondents are useful for recording QoL not only because of their ease of use but also because they are quicker to complete and allow data recording independent of the investigator, thus avoiding the influence of the examiner on the respondent (Augustin et al, 2000). A standardised measurement of patients' QoL may support clinicians in identifying important problems for discussion during the limited time of the medical consultations. However, the assessments made by the use of the questionnaires need to be understandable, user-friendly, and short (Bezjak et al 2001) If not, health-care providers are less likely to use the measures (Bezjak et al 2001). Scores must be clinically meaningful to both providers and patients. Results must be presented in a format that is easy to read, provides useful information, and facilitates direct discussion about topics such as treatment options and general and specific aspects of QoL (Bezjak et al 2001; Carlson 2001). Additionally, results must be ready in "real-time," at the visit when the data are gathered. Ease of use is one of the most important factors necessary for assessing QoL as part of routine clinical practice. Paper-based instruments have a number of limitations such as higher rate of missing values, higher error rates in selecting multiple responses for single option items, data entry error in transferring responses from a paper form to the electronic databases and higher costs associated with administration, collection and entering the data (Saleh et al, 2002). On the other hand, these issues can be effectively handled by the use of computer-based administration of QoL questionnaires. Computer-based administration (CBA) of QoL measures such as in the form of web-based applications (see Appendix 1) using screen-touch computers also called tablets is one of the ways that more frequent assessments can be conducted with minimal burden on patients and clinical staff in addition to meeting all the requirements mentioned above. This method that includes not only computer-based administration but also scoring and presentation of QoL results, eliminates the need for a test

administrator, as usually needed for traditional paper and pencil formats while providing immediate "real-time" feedback. Information from assessments can be displayed in graphic reports as visual aids that help guide discussions about treatment options and care planning.

Psoriasis is a chronic incurable disfiguring skin condition that runs a remitting-relapsing course characterised by fluctuations in clinical severity and perhaps in QoL in some patients. Patients with more widespread psoriasis require long term systemic therapy and regular and frequent monitoring for potential adverse effects of the systemic drugs. Consequently frequent assessments of disease severity and QoL are necessary to help guide optimal treatment planning and decision-making. It follows that routine assessment (at each visit) of disease severity and QoL will require a major commitment of resources. However, the availability of a CBA has the potential to reduce both the respondent burden (as mentioned above) and administrative time required to transfer the results of these patient-reported outcomes e.g. QoL scores to the clinician's desk enhancing the feasibility and logistics of integrating real-time disease severity/QoL assessment data for immediate use into routine clinical care (Paul et al 2002). There is evidence to show that the computer-based measurement of QoL was well accepted by patients who felt that this method was a useful tool to tell the clinician about their problems (Velikova et al, 2002). The clinicians perceived that the QoL data broadened the range of the clinical inquiry and helped them identify issues for discussion. Having symptoms and functional problems expressed quantitatively on a scale was useful for detection of change over time. Further evidence shows that data are more complete on the electronic questionnaires compared with paper questionnaires, data handling greatly simplified and majority of patients prefer the former (Drummond et al, 1995).

Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI; Finlay and Khan, 1994) is currently the most commonly used dermatology-specific QoL measure in clinical trials of skin diseases (Both et al 2007; le Cleach et al 2008). It has been used in more than 36 skin diseases (inflammatory, non-inflammatory and skin cancers), in more than 32 countries and is available in over 55 international language versions (Basra et al, 2008). The DLQI has been shown to be easy to use in clinical practice due to its simplicity and brevity (Bronsard et al 2010) with an average completion time of around 2 minutes (Loo et al 2003). It consists of 10 questions concerning dermatological patients' perception of the impact of skin diseases on different aspects of their QoL over the last week. The items of the DLQI encompass aspects such as

symptoms and feelings, daily activities, leisure, work or school, personal relationships and the side effects of treatment. Each item is scored on a 4-point scale: not at all/not relevant, a little, a lot and very much. Scores of individual items (0-3) are added to yield a total score (0-30); higher scores mean greater impairment of patient's QoL. In 2005, Hongbo et al introduced the much needed banding of the DLQI scores to facilitate the clinical interpretation of scores (Hongbo et al, 2005). According to this banding system a DLQI score of 0 and 1 means no impact on patient's QoL while a score of 2-5, 6-10, 11-20 and 21-30 indicate a small, moderate, large and extremely large effect on patient's QoL respectively. Psychometrically, the DLQI has been shown to be a strong instrument with respect to its internal consistency, reproducibility, validity and sensitivity to change (Bronsard et al 2010, Badia et al, 1999; Hahn et al, 2001; Mazzotti et al, 2003). The strong psychometric properties of the DLQI have resulted in the increasing popularity of the DLQI in both clinical research and in clinical practice. Moreover, the content of the DLQI has been shown to include all important and relevant concepts from the perspective of patients with moderate to severe plaque psoriasis supporting its content validity in psoriasis patients (Safikhani et al, 2011)

Psoriasis Area and Severity Index (PASI)

Psoriasis Area and Severity Index is a widely used tool to assess the severity of psoriasis (Fredriksson and Pattersson, 1978) that is mostly completed by trained health care professionals and study investigators. Although PASI has been criticised for being resource intensive, lacking sensitivity and being complex, in the absence of a "gold standard", it has become an almost universal outcome measure in clinical trials of drugs used for psoriasis (Ashcroft et al, 1999). PASI scoring system assesses four body areas: head (corresponding to 10% of total body surface area), upper extremities (20%), trunk (30%) and lower extremities (40%). The area of psoriasis involvement for each of the 4 body regions is assigned a numerical value of 0-6 corresponding to 0-100% involvement as follows:

0=no involvement; 1= up to 9% involvement; 2= 10-29% involvement; 3=30-49%; 4=50-69%; 5=70-89% and 6=90-100% involvement.

For each body region, erythema, induration and desquamation are rated according to a 5 point scale as follows:

0= no involvement; 1=slight involvement; 2=moderate involvement; 3=marked involvement and 4=very marked involvement

The PASI score is calculated by applying a standard formula. The score can vary in increments of 0.1 units and range from 0 to 72; higher score indicates greater degree of severity.

Although PASI has been administered in various formats such as conventional paper-based format and computerised (including hand-held touch screen) devices but there is no published evidence to show its use as a web-based application.

DLQI/PASI web-based application and its clinical and research implications

In response to the increasing demand, a web-based application of the DLQI/PASI has been developed (see Appendix 2) to encourage its further uptake in the current modernised clinical and research settings in many countries. Although computerised administration of QoL tools in other specialities has been shown to have numerous advantages over traditional paper-based tools (Hanscom et al 2002), this method of QoL/disease severity assessment to present an overall disease severity idea has not been introduced in dermatology yet, and hence quantitative comparisons have not been made for the web-based application and paper-versions of the DLQI and PASI, both being so far the most widely used outcome measures in psoriasis clinical trials. More importantly in clinical practice, to-date there is no method to allow "real-time" monitoring of patient's QoL and disease severity during flare-up of their psoriasis (known for its remitting and relapsing nature). The availability of a DLQI/PASI application to patients would be expected to facilitate the monitoring of psoriasis in a more efficient way.

It is hoped that the availability of a validated DLQI/PASI application will help in better management of psoriasis by having an easy tool for regular monitoring of the disease severity from patient's own perspective including both impact on QoL and self-assessed disease severity. Moreover, this tool could potentially be used by GPs to decide which patients need to be referred.

In the research setting the availability of a web-based application would facilitate more efficient data collection in clinical trials, sometimes even from multiple centre/countries such as for longitudinal assessments of disease severity.

Study Objectives

The objective of this pilot study are:

Primary objective:

- To compare the conventional paper-based and the novel web-based application versions of the DLQI and the PASI in terms of patient and investigator acceptability and preference and in terms of consistency of their scores, respectively.

Secondary objectives:

- To assess the correlation between DLQI scores assessed by two different methods: standard paper-based DLQI and the DLQI application
- To assess the correlation between PASI scores assessed by investigator using conventional PASI and web-based PASI application
- To assess the internal consistency reliability of the web-based DLQI application
- To assess the feasibility of web-based DLQI/PASI application in the dermatology outpatient clinic
- To compare the response burden between the two formats in terms of time spent on completion both for the DLQI and the PASI
- To compare patients' preferences for the use of the web-based DLQI and PASI application versus conventional versions of these tools in terms of ease of use etc.

Ethical consideration

Based on the advice sought from the Research and Commercial Division (RACD) of Cardiff University and the Research and Development (R&D) Department of Cardiff and Vale University Health Board this study has been classified as original research using a new technology and will need full ethics approval. Therefore, an application will be submitted for full ethical permission to R&D department of Cardiff and Vale LHB and to the South West-Central Bristol Research Ethics Committee after favourable independent scientific review report.

Detailed Patient Information sheet and consent forms will be prepared and submitted for ethical approval along with the study protocol/proposal.

Methodology

The study will employ a within-subjects comparison design involving quantitative method for data collection. Patients with all skin conditions will be recruited, and they will be invited to complete the DLQI (both paper and electronic versions). However, those with

Psoriasis will also be assessed using PASI by the investigator (both electronic and paper versions). Who receives which format first will be randomised on the day, but every patient and investigator will have used both electronic and paper versions. Before the start of the pilot study, the investigators will be given training on the use of the touch-screen web-based application of the DLQI/PASI and the interpretation of the results.

Study participants

A cohort of up to 400 adult patients with different skin diseases attending outpatient dermatology appointments will be approached **when they attend their scheduled appointments.** A number of 400 was decided upon based on previous similar studies conducted by the investigators. **Patients will be given the information sheet: they will be given the option to take the information sheet home and will be given a reply slip with a prepaid envelope should they wish to have more time to think about it. They may then decide in their own time if they would like to participate at their next appointment and can return the reply slip.**

However patients will also be given the opportunity, should they wish, to participate immediately after they have had their appointment. Most patients arrive up to half an hour prior to their appointment which should provide ample opportunity to consider participation, eligibility and to present any questions to the researchers.

Should the patient agree to participate on the same day and if they are assessed to be eligible, the study will be conducted immediately after their appointment and will not take longer than an hour. This will include study briefing, consenting and administering the questionnaires. The study will not have an impact on the patient's clinic appointment itself.

Inclusion criteria:

- Ages 18 years and older
- Having any confirmed skin condition for the electronic DLQI (eDLQI)validation
- Having a confirmed diagnosis of psoriasis for electronic PASI (ePASI) validation
- Able to read, write and understand English

Exclusion criteria:

- Ages under 18 years
- Having a co-existing non-dermatological medical condition of considerable severity, as determined by the investigator

- Having a co-existing dermatological condition of considerable severity, as determined by the investigator
- Not able to read and or understand written English

Study procedure

This study will be carried out in the following manner:

f. Patients attending the Dermatology outpatient department, who will be willing to participate after reading the information sheet will be asked to give written informed consent. At this stage, their demographic details will be recorded including age, gender, literacy level, diagnosis, educational background, any visual or tactile impairment, familiarity with electronic media/computer, previous experience in using touch-screen computers and previous use of iPhone/Android applications etc.

g. Following this, participants with any primary skin condition will be randomised to whether they first complete the DLQI either using the paper-based version or the web-based DLQI/PASI application version provided on an iPad. For psoriasis-only patients, the investigator will also assess the PASI using either the web application or the traditional PASI (randomised). Time taken by participants to complete the DLQI using the paper version and the application and by the investigator to do the PASI using either method will be recorded.

h. After completing this part of stage 1, 30 minutes later, study participants will be asked to complete the DLQI again using the paper-based or the application (DLQI/PASI) version depending on their initial mode of administration. For example, participants who will have been randomised to complete the paper-based version of the DLQI first will now be asked to complete it using the application version and vice versa. Similarly, in patients with psoriasis, the investigator will also assess the patient's PASI using either the conventional PASI or the PASI application, depending on which method was used first. Timing will be calculated as before. Therefore, every patient receives the same standard of management.

i. At the end, a short questionnaire will be filled which would gather data on their perception and experience (i.e. attitude) with the use of both methods i.e. paper-based and web-based application, with regard to various practical aspects such as

ease or difficulty of administration, acceptability, time requirement, feasibility, being comfortable with this information disclosure using the novel application-based method.

j. **The above will take place after the clinic appointment, should the patient decide to participate on the same day. Should the patient decide they need more time, they will be able to take a reply slip home with a prepaid envelope. They may then decide in their own time if they would like to participate at their next appointment. The study will not have an impact on the patient's clinic appointment itself.**

Outcomes and data analysis

The main outcome measures will be:

- patients' perceptions about the web application (and hence the feasibility of this mode of QoL/disease severity assessment)
- the assessment of correlation of the web-based application with the conventional paper-based version of the DLQI/PASI

The latter will be assessed using Intraclass correlation coefficient to see the concordance between paper-based and the application data. Internal consistency of the web-based application will be assessed by using Cronbach's alpha coefficient. Descriptive analysis will be used to present the data from patient feedback questionnaires and to present the results of various quantitative variables such as participants' age, gender, diagnoses, mean/median DLQI scores for the paper-based and web-application versions and the mean/median completion time for the two versions. Independent sample t-test will be used to assess the difference in the scores between the two DLQI (completed by patients) and PASI (completed by both the investigator and patients) versions and to analyse difference in the completion time between the two versions. Linear and logistic regression techniques will be used to identify demographic variables significantly associated with successful use of the DLQI/PASI application (in terms of completeness of DLQI data obtained).

Recording of data and retention of documents

Throughout the course of the study and at the completion of each stage research data will be entered onto data collection sheets and entered into SPSS version 16. At the end of the final study all the data will be collected and subjected to thorough analysis. All the research

documents will be kept in a secure place under lock in the Dept. of Dermatology of UHW. Only the key researchers will have access to these data.

Funding

The study will be funded by a pharmaceutical company (Janssen) who are also providing financial and technical support in the development of the new DLQI/PASI application.

Publication of Results

At the end of study the results will be submitted for presentation at national and international research meetings and for publication.

Research staff

5. Dr. Faraz Mahmood Ali: Clinical Research Fellow, Dept. of Dermatology and Wound Healing, Cardiff University School of Medicine
6. Professor Andrew Finlay: Former Head of Department of Dermatology and Wound Healing, Cardiff University School of Medicine.
7. Professor Sam Salek: Chair in Pharmacoepidemiology, Cardiff University
8. Professor Vincent Piguet: Head of Department of Dermatology and Wound Healing, Cardiff University School of Medicine

References

Ashcroft DM, Wan Po AL, Williams HC, Griffiths CEM. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. Br J Dermatol 1999; 141: 185-191.

Augustin M, Amon U, Bullinger M, Gieler U. Recommendations for the Assessment of Quality of Life in Dermatology. Dermato Psychosom 2000; 1: 84-87.

Badia X, Mascaro JM, Lozano R. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: Clinical validity, reliability and sensitivity to change of the DLQI. Br J Dermatol 1999; 141: 698-702.

Basra MKA, Fenech R, Gatt RM et al. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol 2008; 159: 997-1035.

Bezjak A, Ng P, Skeel R, et al: Oncologists' use of quality of life information: Results of a survey of Eastern Cooperative Oncology Group Physicians. Qual Life Res 10:1-13, 2001.

Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. J Invest dermatol 2007; 127: 2726-2739.
Bronsard V, Paul C, Prey S et al. What are the best outcome measures for assessing quality of life in plaque type psoriasis? A systematic review of the literature. JEADV 2010; 24 (Suppl 2): 17-22.

Carlson L, Speca M, Hagen N, et al: Computerized quality of life screening in a cancer pain clinic. J Palliative Care 17:46-52, 2001.

Detmar S, Aaronson N: Quality of life assessment in daily clinical oncology practice: A feasibility study. Eur J Cancer 1998; 34: 1181-1186.

Drummond HE, Ghosh S, Ferguson A et al. Electronic quality of life questionnaires: a comparison of pen-based electronic questionnaires with conventional paper in a gastrointestinal study. Qual Life Res 1995; 4: 21-26.

Feldman SR, Fleischer AB, Reboussin DM et al. The Self-Administered Psoriasis Area and Severity Index is Valid and Relaible. J Invest Dermatol 1996; 106: 183-186.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol 1994; 19: 210-6.

Fleischer A, Rapp SR, Reboussin DM et al. Patient measurement of psoriasis disease severity with a structred instrument. J Invest Dermatol 1994; 102: 967-969.

Fredriksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. Dermatologica 1978; 157: 238-244.

Hahn HB, Catherine A. Melfi CA, Chuang TY et al. Use of the Dermatology Life Quality Index (DLQI) in a midwestern US urban clinic. J Am Acad Dermatol 2001; 45: 44-48.
Hanscom, Brett , Lurie, Jon D. , Homa, Karen, Weinstein, James N. Computerized Questionnaires and the Quality of Survey Data. Spine 2002; 27 - Issue 16: 1797-1801

Hongbo Y, Thomas CL, Harrison MA, Salek S, Finlay AY. Translating the Science of Quality of Life into Practice: What Do Dermatology Life Quality Index Scores Mean? J Invest Dermatol 2005; 125: 659-664.

Jacobsen PB, Davis K, Cella D. Assessing Quality of Life in Research and Clinical Practice. Oncology 2002; 16 No. 910.

Loo WJ, Diba VC, Chawla M, Finlay AY. Dermatology Life Quality Index: influence of an illustrated version. Br J Dermatol 2003; 148: 279-284.
Le Cleach L, Chassany O, Levy A et al. Poor reporting of quality of life outcomes in dermatology randomised controlled clinical trials. Dermatology 2008; 216: 46-55.

Mazzotti E, Picardi A, Sampogna F et al. Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis. Br J Dermatol 2003; 149: 318-322.

Patrick DL, Laurie B. Burke LB, John H. Powers JH et al. Patient-Reported Outcomes to Support Medical Product Labelling Claims: FDA Perspective. Value in Health 2007; 10 (suppl s2): s125-137.

Safikhani S, Sundaram M, Bao Y, Mulani P, Revicki DA. Qualitative assessment of the content validity of the Dermatology Life Quality Index in patients with moderate to severe psoriasis. J Dermatol Treatment 2011; Early Online publication (doi:10.3109/09546634.2011.631980)

Saleh KJ, Radosevich DM, Kassim RA et al. Comparison of commonly used orthopaedic outcome measures using palm-top computers and paper surveys. J Orthopaedic Research 2002; 20: 1146-1151.

Velikova G, Brown JM, Smith AB, Selby PJ. Computer-based quality of life questionnaires may contribute to doctor–patient interactions in oncology. British Journal of Cancer 2002; 86: 51–59.

Appendix XV: Approval of original protocol by the NRES Committee, South West-Central Bristol, UK

NHS
Health Research Authority
NRES Committee South West - Central Bristol
Whitefriars
Level 3, Block B
Lewin's Mead
Bristol BS1 2NT
Email: nrescommittee.southwest-bristol@nhs.net

Telephone: 0117 342 1335
Fax:0117 342 0445

12 June 2014

Dr. Faraz Mahmood Ali
Clinical Research Fellow
Cardiff University
Department of Dermatology and Wound Healing
Cardiff University, School of Medicine, Heath Park
Cardiff CF14 4XN]

Dear Dr Ali

Study title:	**Comparison of the paper-based and web-based application versions of the Dermatology Life Quality Index [DLQI] and Psoriasis Area and Severity [PASI] Index**
REC reference:	**14/SW/0085**
IRAS project ID:	**151474**

Thank you for your letter of 28 May 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Naazneen Nathoo, nrescommittee.southwest-bristol@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper		26 March 2014
Covering letter on headed paper		28 May 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		26 July 2013
GP/consultant information sheets or letters	Consultant Email: 4	26 March 2014
Letter from sponsor		27 March 2014
Letters of invitation to participant	4	21 May 2014
Non-validated questionnaire [Dermatology Life Quality Index]		
Other [Screen Shots of Psoriasis 360 App]	1.0.76	24 February 2014
Other [Letter From Funder]		02 April 2014
Participant consent form	3	06 March 2014
Participant information sheet (PIS)	4	21 May 2014
REC Application Form		27 March 2014
Referee's report or other scientific critique report	Dr Katugampola	
Referee's report or other scientific critique report	Professor Cohen	
Referee's report or other scientific critique report	Dr Inaam-ul Haq	
Research protocol or project proposal	7	21 May 2014
Response to Request for Further Information		28 May 2014
Summary CV for Chief Investigator (CI)	Dr Faraz Mahmood Ali	26 March 2014
Validated questionnaire [Feedback Form]	1	20 February 2014
Validated questionnaire [Psoriasis Area and Severity Index (PASI) Worksheet]		
Validated questionnaire [Study Demographic Questionnaire]	4	21 May 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/SW/0085	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

[redacted]

pp. Dr Pamela Cairns
Chair

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: *Mrs Helen Falconer*
Mr Christopher Fegan, Cardiff and Vale University Health Board

A Research Ethics Committee established by the Health Research Authority

Appendix XVI: Accepted protocol amendment

NHS
Health Research Authority

NRES Committee South West - Central Bristol
Whitefriars
Level 3, Block B
Lewin's Mead
Bristol
BS1 2NT
Email: nrescommittee.southwest-bristol@nhs.net

Tel: 0117 342 1335

17 November 2014

Dr Faraz Mahmood Ali
Clinical Research Fellow
Department of Dermatology and Wound Healing
Cardiff University, School of Medicine, Heath Park
Cardiff
CF14 4XN

Dear Dr Ali

Study title:	**Comparison of the paper-based and web-based application versions of the Dermatology Life Quality Index [DLQI] and Psoriasis Area and Severity [PASI] Index**
REC reference:	**14/SW/0085**
Amendment number:	**1**
Amendment date:	**22 October 2014**
IRAS project ID:	**151474**

The above amendment was reviewed the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

As a result of this amendment you will be able to change the method of recruiting potential participants for the study and approach patients when they attend their scheduled dermatology outpatient appointment.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Letters of invitation to participant [Study Patient Invitation Letter]	6	22 October 2014
Notice of Substantial Amendment (non-CTIMP) [14 SW 0085 Amendment Form]	1	22 October 2014

Other [Response form the researcher 14 SW 0085_ 13 Nov 2014]		13 November 2014
Participant consent form [Study Patient Consent Form]	5	22 October 2014
Participant information sheet (PIS) [Study Patient Information Sheet]	5	22 October 2014
Research protocol or project proposal [Study Protocol DLQI.PASI app]	8	22 October 2014

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/SW/0085:	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

Mr Trevor Beswick
Chair

E-mail: nrescommittee.southwest-bristol@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mr Christopher Fegan, Cardiff and Vale University Health Board*
Mrs Helen Falconer

NRES Committee South West - Central Bristol

Attendance at Sub-Committee of the REC meeting

Committee Members:

Name	*Profession*	*Present*
Dr Robert Beetham	Retired Consultant Clinical Biochemist	Yes
Mr Trevor Beswick	Director - SW Medicines, Information & Training	Yes

Also in attendance:

Name	*Position (or reason for attending)*
Tatiana Muravyeva	REC Administration Assistant

Appendix XVII: Patient Consent Form (Version 5: 22/10/14)

Code No:
Study Title: Comparison of the paper-based and web-based application versions of the Dermatology Life Quality Index [DLQI] and Psoriasis Area and Severity [PASI] Index
Please initial the boxes when you have read and agreed with each statement.

1) I confirm that I have fully read the Patient Information Sheet **(Version 5: 22/10/14).** I understand the intent of the study. I have had the opportunity to consider the information provided and to ask questions, and have had any questions answered satisfactorily. ☐

2) I understand that I am participating voluntarily and that I am free to withdraw from the study at any time, without needing to give any reason, without affecting my medical care or legal rights. ☐

3) I hereby give my written consent to participate in this study, which involves me completing several questionnaires. ☐

4) If my primary diagnosed skin condition is psoriasis, I hereby give my written consent to have an investigator undertake two assessments of my psoriasis using the PASI. ☐

5) I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the NHS Trust or by study investigators, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

Participant	**Investigator**
Name:	Name:
Date:	Date:
Signature:	Signature:

Appendix XVIII: Study grant

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Dr Faraz Mahmood Ali
Department of Dermatology
School of Medicine, Cardiff University
3rd Floor Glamorgan House
Heath Park
Cardiff, Wales, UK

2nd April 2014

Dear Dr Ali,

As requested please find below the information required for your ethics application.

This project has been approved at a local level and has been submitted for approval at EMEA and Global levels. Based on discussions with our EMEA colleagues the project is viewed very positively and an important one to support. Please note that this funding is not yet confirmed until we have completed all the relevant processes internally within Janssen.

Organisation:	Janssen-Cilag Ltd
Address:	50-100 Holmers Farm Way, High Wycombe, Buckinghamshire
Postcode:	HP12 4EG
Telephone:	+44 7827 285308
Fax:	NA
Mobile:	+44 7827 285308
Email:	cclibbor@its.jnj.com

Funding application status:	In progress
Date funding decision expected:	May 2014
Amount:	£45,872 (as per your costing)
Duration:	6-9 months

Please do not hesitate to contact me should you require any further information.

Kind regards,

[redacted]

Dr Claire S Clibborn, PhD
Scientific Advisor
Janssen-Cilag Ltd

Janssen-Cilag Ltd
50 -100 Holmers Farm Way, High Wycombe
Buckinghamshire HP12 4EG United Kingdom
tel: 01494 567567 fax: 01494 567404
Website: www.janssen-cilag.co.uk
Registered in England 1027904

Appendix XIX: Patient Letter (Version 5: 21/5/14)

Dear Sir/Madam,

I am writing to invite you to participate in a study conducted by the doctors in the Dermatology Department of the University Hospital of Wales.

The purpose of this study is to compare a newly developed electronic form of the Dermatology Life Quality Index (DLQI) questionnaire and the Psoriasis Area Severity Index (PASI) tool, with the currently used paper-based versions. The study aims to see whether it is acceptable to use the electronic versions in situations (for example, outpatient clinics) where the use of paper-based versions are the current practice. It is hoped that the findings of the study will allow us to improve the standard of care provided to people with skin conditions such as yourself.

You have been asked to take part in this study as you are an adult who has been diagnosed with a skin condition, and who is attending a dermatology outpatient clinic at the University Hospital of Wales. You can only take part in this study if you have no other severe medical conditions, including other co-existing severe skin conditions. We will be delivering the questionnaires using iPads, which function the same as iPhones, and the two questionnaires are installed like any other app used on this and other similar devices.

If you would like to take part, the study will involve you meeting with one of the Dermatology team members before your next scheduled clinic appointment with myself and completing several questionnaires, including the DLQI. If you have been diagnosed with psoriasis, an investigator will also use the PASI to assess your condition.

You do not have to take part in the study if you do not wish to. Before you begin, you will have a chance to speak directly to a Dermatology team member to raise any questions or concerns you may have, and you will be asked to sign a written consent form (Version 4: 21/5/14). After you have given your consent, you still have the right to withdraw it any time. This would not affect your medical care in any way.

I have included a copy of the Patient Information Sheet (Version 4: 21/5/14). Please take time to read this carefully as it contains all the important information about the study and your role in it. If you have any questions or concerns, please do not hesitate to contact myself or the research team through the information given on the information sheet and below.

I would be very grateful if you could kindly fill out the reply form on the next **page to confirm if you are eligible** and whether you would or wouldn't be happy to participate in the study. Alternatively, you may contact Dr. Faraz Ali, who is our lead researcher, directly via the telephone number provided.

If you are eligible and agree to take part, please arrive at the usual location for your clinic appointment at your preferred time as selected below.

Thank you very much for reading this letter and considering helping with this study.

Yours sincerely,

Dr. XXX
Consultant Dermatologist

PLEASE KINDLY COMPLETE AND RETURN BEFORE YOUR NEXT DERMATOLOGY CLINIC APPOINTMENT IN THE ENCLOSED ENVELOPE

Name:

Date of Birth:

Please tick those that apply:

- I confirm that I am 18 years or older ☐
- I confirm that I suffer with only one skin condition, and no other severe skin conditions ☐
- I confirm that I have no other severe medical conditions ☐
- I confirm that I can read, write and understand English ☐

Please note that in order to classify something as 'severe' it needs to have a significant impact on your life. If you have ticked all of the boxes above, you **are eligible** to take part in the study. If however, **you have not ticked all the boxes, then unfortunately you would not be eligible to take part.**

Please note the study will take place during your next clinic appointment. If you are eligible, please confirm whether you would/wouldn't be interested in participating (PLEASE TICK). NB This form is to register your interest in the study and is NOT a consent form:

- I WOULD be interested in participating in this study, and prefer to hear more about the study at the time selected below. I understand that I will be fully consented on the day of my clinic appointment. ☐
- I WOULD NOT be interested in participating in this study ☐

Please choose your preferred time:

- One hour before the appointment (the study will be completed by the appointment time) ☐
- Immediately after the appointment (the study will be completed within an hour after) ☐

Please kindly return this page in the enclosed pre-stamped envelope. If you are unsure whether you are eligible or not, or for any other queries, please contact the lead researcher, Dr Faraz Ali, on: 02920 745874, or 07877 389476.

Appendix XX: Patient Information Sheet (Version 5: 22/10/14)

Study Title: Comparison of the paper-based and web-based application versions of the Dermatology Life Quality Index (DLQI) and Psoriasis Area and Severity (PASI) Index

We would like to invite you to take part in our study.

Before you agree to take part, you must know why the study is being done, whether you are eligible and what you will be required to do. Please take your time to read the following information carefully. If you have any further questions or feel anything is not clear, please contact us through the details provided below. If you would like to take part in the study, you will be able to discuss any questions you have with one of the researchers in person.

Thank you for reading this information.

Am I eligible to take part in this study?

You may be eligible to take part in this study if you fulfil the following criteria:

- You are 18 years or older
- You only suffer with only one skin condition, and no other severe skin conditions (multiple less severe skin conditions would not exclude you from the study)
- You have no other severe medical conditions
- You can read, write and understand English

Please note that in order to classify something as 'severe' it needs to have a significant impact on your life. If you do not fit the above criteria, unfortunately you will not be able to participate in the study.

What is the purpose of the study?

It is well known that psoriasis and other skin conditions can have a major impact on a patient's quality of life. It can cause them both physical discomfort and psychological and social problems. It's important that doctors can reliably measure how much a patient's quality of life is being affected by their skin condition. For example, patient quality of life may help us assess if a particular drug is working or not.

The DLQI and PASI are two tools used to measure a patient's quality of life. The DLQI is a short 10 question questionnaire. The PASI is a tool used to assess the severity of a patient's psoriasis. It is used to examine how much of a patient's skin is currently showing signs of psoriasis. They are usually used in day to day clinical practice and you may have used them previously. To make these tools easier to use for both patients and doctors, an electronic iPad app has been developed. These can be used instead of the paper-based versions that would ordinarily be used in places like outpatient clinics anyway. Electronic versions of quality of life tools might be better as they can save the NHS time and money, and patients often prefer them.

The purpose of this study is to compare patients' results from the paper-based version with those from the iPad version. This may allow us to see whether the new version is as reliable as the old version, and to see how patients feel about it.

Why have I been asked to take part?

You have been asked to take part in this study **because you are attending a dermatology outpatient clinic at University Hospital of Wales (UHW).** You may be eligible to participate in this study if you are an adult who has been diagnosed with a skin condition and as long as you meet the minimum requirements for the study as outlined above. We need up to 400 adults like yourself to take part.

Do I have to take part in this study?

It is your choice to take part in this study or not. **If you would like to take part after your appointment today, you will be assessed for eligibility and may participate immediately after your appointment. You also have the choice of participating at a later stage, in which case please fill the reply slip on your invitation letter and send it back to the researchers in the pre-paid envelope provided. In such as case, the study** will be conducted at your next clinic appointment at your preferred time. This will be either an hour before clinic or for an hour immediately after, as indicated on your reply slip. You will have the opportunity to ask any further questions and will be asked to sign a consent form **(version 5 dated 22/10/14)**. Even after you have agreed to take part, you can still choose to withdraw from the study at any time. This would not affect your standard of care in any way.

Do I need to be computer literate to participate in this study?

We do not need our patients to be computer literate. Our researchers will be able to offer advice and assistance on the day if you have any queries or problems using the iPad application.

What will happen to me if I take part?

When we have taken written consent from you, we will ask you to complete the 'Demographic Questionnaire' (Version 4 21/05/14). This is so we can collect general information, for example about your age, gender and experience using iPads.

You will then be asked to complete either the paper or the iPad version of the DLQI. If your diagnosed skin condition is psoriasis, the study investigator will conduct an assessment using either the paper-based or electronic version of the PASI. These are both very short questionnaires, which can be completed within a few minutes. After approximately half an hour, we will ask you to complete the other version of the DLQI (and be assessed by the other version of the PASI, if this is relevant to you). For example, if you are asked to complete the paper-based DLQI first, half an hour later you will be asked to complete the iPad version. We will then ask you to complete a very short feedback form to get your opinions on the different versions.

This study will not impact on your consultation in any way.

How long will it take?

The study will take up to an hour after your appointment. If you decide to do the study at a later appointment, it will be up to you whether you would like to carry out the study an hour before, or for an hour after your next clinic appointment. The study in total should take no longer than this. You will be given a reply slip with a prepaid envelope

and we would be grateful if you could kindly ensure that the lead investigator Dr Faraz Ali (details below) is aware of your preferences prior to your next clinic appointment.

We expect it to take approximately 20 minutes in total for you to sign the consent form and to complete the demographic questionnaire and the DLQI and for the investigator to complete the PASI if necessary. After taking a break of about half an hour, we expect it to take no more than 20 minutes to complete the questionnaires again, as well as to complete the feedback form. There will be reading material available on the day whilst you wait to complete the second half of the study. We would also encourage participants to bring their own reading material. This is why we have given an approximate time of one hour to complete the entire study, **though in reality may be less.** Please note that parking costs for up to an hour will be reimbursed upon request.

What if I don't want to take part in this study?

It is entirely your choice to take part, and it is totally voluntary. If you don't want to take part, you do not need to.

What are the possible benefits of taking part?

In the short-term, there are no direct benefits to you from taking part in this study. But your participation helps us to assess whether it is as good, if not better, to use the new iPad version of these tools. In the long-term that means we may be able to improve the way these tools are used and so improve the care that patients like you receive.

What are the possible risks of taking part?

As the study involves filling in several questionnaires, two of which are typically used in routine practice, there are no risks from taking part.

What will happen to the results?

The collective results will be published in a scientific journal. The information generated from the questionnaires you complete will be totally anonymised, so neither your name nor any identifying information will appear anywhere. If you are interested, you will be provided with a copy of the publication.

Will my taking part in this study be kept confidential?

All information about you and provided by you will be handled in confidence. All information collected about you will be kept strictly confidential. Each person participating in the study will be given a code number. Only the investigators will have access to the patient details that link with this code number. These will be kept in a secure place within the dermatology department of UHW. The results of the study will not reveal your name, address, or any identifying information.

Will my medical records be accessed?

Your medical records have not been accessed by the research team. Once you have given consent, they will only be accessed by the researchers. This may be useful in case it is found that questionnaires have not been completed fully. If you don't want us to access your records, you can tell us not to.

Who is organising and funding the study?

The study is being organised by the Department of Dermatology (of the School of Medicine) and the Centre for Socioeconomic Research (of the School of Pharmacy and Pharmaceutical Sciences), of Cardiff University. Funding was provided by a pharmaceutical company, JNJ (Janssen), for the development of the electronic applications.

Who has reviewed the study?

The study has been reviewed by the Cardiff and Vale University Health Board Research & Development Department. It has also been reviewed by the NRES Committee South West – Central Bristol REC

What should I do if I have any concerns or questions about the study?

If you are concerned about any aspect of this study, you should ask to speak to the chief investigator, who will do his best to answer your questions:

Dr Faraz Mahmood Ali Tel: 029 2074 5874

If your question remains unresolved and you wish to make a formal complaint, this can be made through the NHS Concerns Procedure. The Complaints Department of Cardiff and Vale University Health Board can be contacted by emailing concerns@wales.nhs.uk or telephoning 029 2074 4095.

Appendix XXI: Ethical approval for study 13/WA/0363

South East Wales Research Ethics Committee B
6th Floor Churchill House
17 Churchill Way
Cardiff
CF10 2TW

Telephone : 02920 376823
E-mail : carl.phillips@wales.nhs.uk
Website : www.nres.nhs.uk

15 November 2013

Dr Faraz Mahmood Ali
Clinical Research Fellow
Department of Dermatology and Wound Healing
3rd Floor, Glamorgan House
Cardiff University, School of Medicine
Heath Park, Cardiff
CF14 4XN

Dear Dr Ali

Study title:	**A European Multicenter study on depression, anxiety, quality of life and attachment among adult patients with common skin disorders**
REC reference:	**13/WA/0363**
Protocol number:	**SPON1250-13**
IRAS project ID:	**142953**

The Research Ethics Committee reviewed the above application at the meeting held on the 13 November 2013.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Executive Officer, Mr Carl Phillips, Carl.phillips@wales.nhs.uk.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

Appendix XXII: Forward stepwise variable methodology: final ordinal regression model estimates using complete patient dataset

Mobility

$$P(Mobility = 1) = \frac{1}{1 + e^{(-Mobiity\,1 + DLQI3 + DLQI7 + DLQI10 + DLQI2 + DLQI5 + DLQI1 + DLQI6)}}$$

$$P(Mobiity = 2) = \frac{1}{1 + e^{(-Mobiity\,2 + DLQI3 + DLQI7 + DLQI10 + DLQI2 + DLQI5 + DLQI1 + DLQI6)}} - P(Y = 1)$$

$$P(Mobility = 3) = 1 - P(Y = 2) - P(Y = 1)$$

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	-.761	.211	12.947	1	.000	-1.176	-.346
	[eq5dmob = 2]	4.081	.359	128.945	1	.000	3.377	4.785
Location	[dlqi3=0]	-.632	.211	8.998	1	.003	-1.045	-.219
	[dlqi3=1]	-.080	.204	.155	1	.693	-.480	.319
	[dlqi3=2]	.250	.192	1.688	1	.194	-.127	.627
	[dlqi3=3]	0[a]	.	.	0	.	.	.
	[dlqi7=0]	-.268	.142	3.548	1	.060	-.547	.011
	[dlqi7=1]	-.722	.154	21.996	1	.000	-1.024	-.420
	[dlqi7=2]	-.690	.204	11.489	1	.001	-1.089	-.291
	[dlqi7=3]	0[a]	.	.	0	.	.	.
	[dlqi10=0]	-.728	.195	13.964	1	.000	-1.110	-.346

[dlqi10=1]	-.357	.200	3.174	1	.075	-.749	.036
[dlqi10=2]	-.155	.207	.556	1	.456	-.561	.252
[dlqi10=3]	0[a]	.	.	0	.	.	.
[dlqi2=0]	.448	.172	6.761	1	.009	.110	.785
[dlqi2=1]	.381	.159	5.769	1	.016	.070	.692
[dlqi2=2]	.024	.156	.024	1	.876	-.281	.329
[dlqi2=3]	0[a]	.	.	0	.	.	.
[dlqi5=0]	-.396	.216	3.356	1	.067	-.819	.028
[dlqi5=1]	-.201	.205	.965	1	.326	-.602	.200
[dlqi5=2]	-.149	.193	.596	1	.440	-.529	.230
[dlqi5=3]	0[a]	.	.	0	.	.	.
[dlqi1=0]	-.469	.160	8.564	1	.003	-.784	-.155
[dlqi1=1]	-.329	.145	5.130	1	.024	-.615	-.044
[dlqi1=2]	-.181	.141	1.643	1	.200	-.457	.096
[dlqi1=3]	0[a]	.	.	0	.	.	.
[dlqi6=0]	-.392	.183	4.599	1	.032	-.750	-.034
[dlqi6=1]	-.642	.203	10.035	1	.002	-1.039	-.245
[dlqi6=2]	-.298	.205	2.113	1	.146	-.699	.104
[dlqi6=3]	0[a]	.	.	0	.	.	.

Link function: Logit.

a. This parameter is set to zero because it is redundant.

Self-care

$$P(Selfcare = 1) = \frac{1}{1 + e^{(-Selfcare\,1 + DLQI10 + DLQI3 + DLQI7 + DLQI1 + DLQI8 + DLQI9 + DLQI2 + DLQI5 + DLQI4 + DLQI6)}}$$

$$P(Selfcare = 2) = \frac{1}{1 + e^{(-Selfcare\,2 + DLQI10 + DLQI3 + DLQI7 + DLQI1 + DLQI8 + DLQI19 + DLQI2 + DLQI5 + DLQI4 + DLQI6)}} - P(Y = 1)$$

$$P(Selfcare = 3) = 1 - P(Y = 2) - P(Y = 1)$$

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	.077	.257	.089	1	.766	-.428	.581
	[eq5dselfcar = 2]	3.859	.378	104.226	1	.000	3.118	4.600
Location	[dlqi10=0]	-1.404	.230	37.188	1	.000	-1.855	-.953
	[dlqi10=1]	-.935	.231	16.425	1	.000	-1.388	-.483
	[dlqi10=2]	-.365	.225	2.632	1	.105	-.807	.076
	[dlqi10=3]	0[a]	.	.	0	.	.	.
	[dlqi3=0]	-.884	.263	11.333	1	.001	-1.399	-.369
	[dlqi3=1]	-.524	.247	4.511	1	.034	-1.008	-.040
	[dlqi3=2]	.018	.219	.007	1	.933	-.412	.449
	[dlqi3=3]	0[a]	.	.	0	.	.	.
	[dlqi7=0]	-.355	.179	3.928	1	.047	-.705	-.004
	[dlqi7=1]	-.676	.196	11.962	1	.001	-1.060	-.293
	[dlqi7=2]	-.537	.243	4.878	1	.027	-1.014	-.060
	[dlqi7=3]	0[a]	.	.	0	.	.	.
	[dlqi1=0]	-.636	.228	7.753	1	.005	-1.083	-.188
	[dlqi1=1]	-.386	.187	4.286	1	.038	-.752	-.021
	[dlqi1=2]	-.233	.173	1.803	1	.179	-.572	.107
	[dlqi1=3]	0[a]	.	.	0	.	.	.
	[dlqi8=0]	.262	.303	.746	1	.388	-.332	.856
	[dlqi8=1]	.307	.293	1.097	1	.295	-.267	.880

[dlqi8=2]	.428	.268	2.547	1	.111	-.098	.953
[dlqi8=3]	0[a]	.	.	0	.	.	.
[dlqi9=0]	-.172	.236	.533	1	.465	-.635	.290
[dlqi9=1]	-.153	.263	.336	1	.562	-.669	.364
[dlqi9=2]	-.590	.282	4.374	1	.036	-1.142	-.037
[dlqi9=3]	0[a]	.	.	0	.	.	.
[dlqi2=0]	.101	.237	.181	1	.671	-.364	.566
[dlqi2=1]	.182	.203	.805	1	.370	-.216	.581
[dlqi2=2]	-.156	.193	.651	1	.420	-.534	.223
[dlqi2=3]	0[a]	.	.	0	.	.	.
[dlqi5=0]	-.254	.297	.733	1	.392	-.836	.328
[dlqi5=1]	.077	.268	.083	1	.774	-.447	.601
[dlqi5=2]	.012	.242	.003	1	.960	-.462	.486
[dlqi5=3]	0[a]	.	.	0	.	.	.
[dlqi4=0]	.154	.230	.448	1	.503	-.297	.604
[dlqi4=1]	.339	.225	2.273	1	.132	-.102	.780
[dlqi4=2]	.556	.214	6.767	1	.009	.137	.975
[dlqi4=3]	0[a]	.	.	0	.	.	.
[dlqi6=0]	-.063	.230	.075	1	.785	-.514	.388
[dlqi6=1]	-.253	.257	.968	1	.325	-.756	.251
[dlqi6=2]	.104	.248	.177	1	.674	-.381	.590
[dlqi6=3]	0[a]	.	.	0	.	.	.

Link function: Logit.

a. This parameter is set to zero because it is redundant.

Usual Activities

$$P(Usual\ Activities = 1) = \frac{1}{1 + e^{(-Usual\ Activities\ 1 + DLQI3 + DLQI10 + DLQI7 + DLQI6 + DLQI1 + DLQI2 + DLQI5 + DLQI4)}}$$

$$P(Usual\ Activities = 2) = \frac{1}{1 + e^{(-Usual\ Activities\ 2 + DLQI3 + DLQI10 + DLQI7 + DLQI6 + DLQI1 + DLQI2 + DLQI5 + DLQI4)}} - P(Y = 1)$$

$$P(Usual\ Activities = 3) = 1 - P(Y = 2) - P(Y = 1)$$

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	-1.632	.222	54.061	1	.000	-2.066	-1.197
	[eq5dactiv = 2]	1.939	.236	67.681	1	.000	1.477	2.401
Location	[dlqi3=0]	-1.034	.206	25.208	1	.000	-1.437	-.630
	[dlqi3=1]	-.557	.199	7.822	1	.005	-.948	-.167
	[dlqi3=2]	-.030	.190	.025	1	.874	-.402	.341
	[dlqi3=3]	0[a]	.	.	0	.	.	.
	[dlqi10=0]	-.616	.197	9.798	1	.002	-1.002	-.230
	[dlqi10=1]	-.302	.202	2.242	1	.134	-.698	.093
	[dlqi10=2]	-.069	.208	.109	1	.741	-.477	.339
	[dlqi10=3]	0[a]	.	.	0	.	.	.
	[dlqi7=0]	-.552	.140	15.469	1	.000	-.826	-.277
	[dlqi7=1]	-.741	.149	24.627	1	.000	-1.033	-.448
	[dlqi7=2]	-.422	.193	4.779	1	.029	-.801	-.044
	[dlqi7=3]	0[a]	.	.	0	.	.	.

[dlqi6=0]	-.766	.182	17.692	1	.000	-1.124	-.409
[dlqi6=1]	-.684	.198	11.890	1	.001	-1.073	-.295
[dlqi6=2]	-.490	.203	5.795	1	.016	-.888	-.091
[dlqi6=3]	0[a]	.	.	0	.	.	.
[dlqi1=0]	-.879	.164	28.701	1	.000	-1.201	-.558
[dlqi1=1]	-.436	.143	9.271	1	.002	-.717	-.155
[dlqi1=2]	-.097	.138	.489	1	.484	-.367	.174
[dlqi1=3]	0[a]	.	.	0	.	.	.
[dlqi2=0]	.606	.177	11.768	1	.001	.260	.953
[dlqi2=1]	.531	.160	11.008	1	.001	.217	.845
[dlqi2=2]	.135	.155	.764	1	.382	-.168	.439
[dlqi2=3]	0[a]	.	.	0	.	.	.
[dlqi5=0]	-.620	.219	8.019	1	.005	-1.049	-.191
[dlqi5=1]	-.336	.206	2.674	1	.102	-.739	.067
[dlqi5=2]	-.207	.194	1.144	1	.285	-.587	.172
[dlqi5=3]	0[a]	.	.	0	.	.	.
[dlqi4=0]	.070	.173	.162	1	.688	-.270	.409
[dlqi4=1]	.088	.173	.257	1	.612	-.252	.427
[dlqi4=2]	.330	.172	3.656	1	.056	-.008	.668
[dlqi4=3]	0[a]	.	.	0	.	.	.

Link function: Logit.

a. This parameter is set to zero because it is redundant.

Pain / Discomfort

$$P(Pain/Discomfort = 1) = \frac{1}{1 + e^{(-Pain/discomfort\ 1 + DLQI1 + DLQI6 + DLQI10 + DLQI4 + DLQI7 + DLQI3)}}$$

$$P(Pain/Discomfort = 2) = \frac{1}{1 + e^{(-Pain/discomfort\ 2 + DLQI1 + DLQI6 + DLQI10 + DLQI4 + DLQI7 + DLQI3)}} - P(Y = 1)$$

$$P(Pain/Discomfort = 3) = 1 - P(Y = 2) - P(Y = 1)$$

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	-3.148	.225	196.440	1	.000	-3.588	-2.707
	[eq5dpain = 2]	.524	.210	6.219	1	.013	.112	.935
Location	[dlqi1=0]	-1.981	.145	186.180	1	.000	-2.266	-1.697
	[dlqi1=1]	-1.133	.136	68.999	1	.000	-1.400	-.865
	[dlqi1=2]	-.490	.135	13.139	1	.000	-.756	-.225
	[dlqi1=3]	0[a]	.	.	0	.	.	.
	[dlqi6=0]	-.936	.173	29.462	1	.000	-1.275	-.598
	[dlqi6=1]	-.676	.187	13.062	1	.000	-1.043	-.309
	[dlqi6=2]	-.422	.195	4.668	1	.031	-.805	-.039
	[dlqi6=3]	0[a]	.	.	0	.	.	.
	[dlqi10=0]	-.843	.193	19.052	1	.000	-1.221	-.464
	[dlqi10=1]	-.481	.198	5.899	1	.015	-.870	-.093
	[dlqi10=2]	-.241	.206	1.366	1	.242	-.646	.163
	[dlqi10=3]	0[a]	.	.	0	.	.	.
	[dlqi4=0]	-.140	.154	.832	1	.362	-.442	.161
	[dlqi4=1]	.024	.158	.023	1	.880	-.286	.334

	[dlqi4=2]	.214	.165	1.676	1	.195	-.110	.537
	[dlqi4=3]	0[a]	.	.	0	.	.	.
	[dlqi7=0]	.431	.135	10.150	1	.001	.166	.696
	[dlqi7=1]	.171	.143	1.436	1	.231	-.109	.451
	[dlqi7=2]	.353	.190	3.451	1	.063	-.019	.726
	[dlqi7=3]	0[a]	.	.	0	.	.	.
	[dlqi3=0]	-.656	.192	11.695	1	.001	-1.032	-.280
	[dlqi3=1]	-.312	.191	2.671	1	.102	-.686	.062
	[dlqi3=2]	-.150	.186	.645	1	.422	-.515	.216
	[dlqi3=3]	0[a]	.	.	0	.	.	.

Link function: Logit.

a. This parameter is set to zero because it is redundant.

Anxiety / Depression

$$P(Anxiety/Depression = 1) = \frac{1}{1 + e^{(-Anxiety/Depression\,1 + DLQI2 + DLQI7 + DLQI9 + DLQI3 + DLQI1 + DLQ10 + DLQI8 + DLQI4)}}$$

$$P(Anxiety/Depression = 2) = \frac{1}{1 + e^{(-Anxiety/Depression\,2 + DLQI2 + DLQI7 + DLQI9 + DLQI3 + DLQI1 + DLQ10 + DLQI8 + DLQI4)}} - P(Y = 1)$$

$$P(Anxiety/Depression = 3) = 1 - P(Y = 2) - P(Y = 1)$$

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	-2.576	.235	120.146	1	.000	-3.037	-2.115
	[eq5danxdep = 2]	.711	.226	9.846	1	.002	.267	1.154

Location	[dlqi2=0]	-1.215	.144	71.611	1	.000	-1.496	-.933
	[dlqi2=1]	-.829	.135	37.515	1	.000	-1.094	-.563
	[dlqi2=2]	-.388	.136	8.183	1	.004	-.654	-.122
	[dlqi2=3]	0[a]	.	.	0	.	.	.
	[dlqi7=0]	-.510	.131	15.142	1	.000	-.768	-.253
	[dlqi7=1]	-.281	.138	4.176	1	.041	-.551	-.012
	[dlqi7=2]	-.114	.185	.379	1	.538	-.476	.248
	[dlqi7=3]	0[a]	.	.	0	.	.	.
	[dlqi9=0]	-.442	.183	5.867	1	.015	-.800	-.084
	[dlqi9=1]	-.395	.198	3.956	1	.047	-.783	-.006
	[dlqi9=2]	-.073	.214	.116	1	.734	-.493	.347
	[dlqi9=3]	0[a]	.	.	0	.	.	.
	[dlqi3=0]	-.351	.192	3.346	1	.067	-.727	.025
	[dlqi3=1]	-.111	.190	.339	1	.561	-.483	.262
	[dlqi3=2]	.028	.185	.022	1	.881	-.334	.389
	[dlqi3=3]	0[a]	.	.	0	.	.	.
	[dlqi1=0]	-.224	.142	2.486	1	.115	-.501	.054
	[dlqi1=1]	-.254	.132	3.698	1	.054	-.514	.005
	[dlqi1=2]	-.246	.132	3.498	1	.061	-.504	.012
	[dlqi1=3]	0[a]	.	.	0	.	.	.
	[dlqi10=0]	-.571	.192	8.854	1	.003	-.947	-.195
	[dlqi10=1]	-.540	.197	7.513	1	.006	-.926	-.154
	[dlqi10=2]	-.337	.204	2.723	1	.099	-.738	.063
	[dlqi10=3]	0[a]	.	.	0	.	.	.
	[dlqi8=0]	-.426	.224	3.613	1	.057	-.866	.013

[dlqi8=1]	-.263	.220	1.422	1	.233	-.694	.169
[dlqi8=2]	-.124	.214	.335	1	.562	-.543	.295
[dlqi8=3]	0[a]	.	.	0	.	.	.
[dlqi4=0]	.142	.153	.865	1	.352	-.158	.442
[dlqi4=1]	.050	.157	.102	1	.750	-.257	.357
[dlqi4=2]	.191	.162	1.397	1	.237	-.126	.508
[dlqi4=3]	0[a]	.	.	0	.	.	.

Link function: Logit.

a. This parameter is set to zero because it is redundant.

Appendix XXIII: Final Excel Formulae

Mobility: Qs 3, 7, 10, 2, 5, 1, 6

P (Mobility = 1)
=1/(1+EXP(0.761+((IF(D4=0,-0.632,0))+(IF(D4=1,-0.080,0))+(IF(D4=2,0.250,0))+(IF(H4=0,-0.268,0))+(IF(H4=1,-0.722,0))+(IF(H4=2,-0.690,0))+(IF(K4=0,-0.728,0))+(IF(K4=1,-0.357,0))+(IF(K4=2,-0.155,0))+(IF(C4=0,0.448,0))+(IF(C4=1,0.381,0))+(IF(C4=2,0.024,0))+(IF(F4=0,-0.396,0))+(IF(F4=1,-0.201,0))+(IF(F4=2,-0.149,0))+(IF(B4=0,-0.469,0))+(IF(B4=1,-0.329,0))+(IF(B4=2,-0.181,0))+(IF(G4=0,-0.392,0))+(IF(G4=1,-0.642,0))+(IF(G4=2,-0.298,0)))))

P (Mobility = 2)
=1/(1+EXP(-4.081+((IF(D4=0,-0.632,0))+(IF(D4=1,-0.080,0))+(IF(D4=2,0.250,0))+(IF(H4=0,-0.268,0))+(IF(H4=1,-0.722,0))+(IF(H4=2,-0.690,0))+(IF(K4=0,-0.728,0))+(IF(K4=1,-0.357,0))+(IF(K4=2,-0.155,0))+(IF(C4=0,0.448,0))+(IF(C4=1,0.381,0))+(IF(C4=2,0.024,0))+(IF(F4=0,-0.396,0))+(IF(F4=1,-0.201,0))+(IF(F4=2,-0.149,0))+(IF(B4=0,-0.469,0))+(IF(B4=1,-0.329,0))+(IF(B4=2,-0.181,0))+(IF(G4=0,-0.392,0))+(IF(G4=1,-0.642,0))+(IF(G4=2,-0.298,0)))))-M4

Self-care: Qs 10, 3, 7, 1, 8, 9, 2, 5, 4, 6

P (Self-care = 1)
=1/(1+EXP(-0.077+((IF(K4=0,-1.404,0))+(IF(K4=1,-0.935,0))+(IF(K4=2,-0.365,0))+(IF(D4=0,-0.884,0))+(IF(D4=1,-0.524,0))+(IF(D4=2,0.018,0))+(IF(H4=0,-0.355,0))+(IF(H4=1,-0.676,0))+(IF(H4=2,-0.537,0))+(IF(B4=0,-0.636,0))+(IF(B4=1,-0.386,0))+(IF(B4=2,-0.233,0))+(IF(I4=0,0.262,0))+(IF(I4=1,0.307,0))+(IF(I4=2,0.428,0))+(IF(J4=0,-0.172,0))+(IF(J4=1,-0.153,0))+(IF(J4=2,-0.590,0))+(IF(C4=0,0.101,0))+(IF(C4=1,0.182,0))+(IF(C4=2,-0.156,0))+(IF(F4=0,-0.254,0))+(IF(F4=1,0.077,0))+(IF(F4=2,0.012,0))+(IF(E4=0,0.154,0))+(IF(E4=1,0.339,0))+(IF(E4=2,0.556,0))+(IF(G4=0,-0.063,0))+(IF(G4=1,-0.253,0))+(IF(G4=2,0.104,0)))))

P (Self-care = 2)
=1/(1+EXP(-3.859+((IF(K4=0,-1.404,0))+(IF(K4=1,-0.935,0))+(IF(K4=2,-0.365,0))+(IF(D4=0,-0.884,0))+(IF(D4=1,-0.524,0))+(IF(D4=2,0.018,0))+(IF(H4=0,-0.355,0))+(IF(H4=1,-0.676,0))+(IF(H4=2,-0.537,0))+(IF(B4=0,-0.636,0))+(IF(B4=1,-0.386,0))+(IF(B4=2,-0.233,0))+(IF(I4=0,0.262,0))+(IF(I4=1,0.307,0))+(IF(I4=2,0.428,0))+(IF(J4=0,-0.172,0))+(IF(J4=1,-0.153,0))+(IF(J4=2,-0.59,0))+(IF(C4=0,0.101,0))+(IF(C4=1,0.182,0))+(IF(C4=2,-0.156,0))+(IF(F4=0,-0.254,0))+(IF(F4=1,0.077,0))+(IF(F4=2,0.012,0))+(IF(E4=0,0.154,0))+(IF(E4=1,0.339,0))+(IF(E4=2,0.556,0))+(IF(G4=0,-0.063,0))+(IF(G4=1,-0.253,0))+(IF(G4=2,0.104,0)))))-P4

Usual Activities: Qs 3, 10, 7, 6, 1, 2, 5, 4

P (Usual Activities = 1)
=1/(1+EXP(1.632+((IF(D4=0,-1.034,0))+(IF(D4=1,-0.557,0))+(IF(D4=2,-0.03,0)+(IF(K4=0,-0.616,0))+(IF(K4=1,-0.302,0))+(IF(K4=2,-0.069,0))+(IF(H4=0,-0.552,0))+(IF(H4=1,-0.741,0))+(IF(H4=2,-0.422,0))+(IF(G4=0,-0.766,0))+(IF(G4=1,-0.684,0))+(IF(G4=2,-0.49,0))+(IF(B4=0,-0.879,0))+(IF(B4=1,-0.436,0))+(IF(B4=2,-0.097,0))+(IF(C4=0,0.606,0))+(IF(C4=1,0.531,0))+(IF(C4=2,0.135,0))+(IF(F4=0,-0.62,0))+(IF(F4=1,-0.336,0))+(IF(F4=2,-0.207,0))+(IF(E4=0,0.07,0))+(IF(E4=1,0.088,0))+(IF(E4=2,0.33,0))))))

P (Usual Activities = 2)
=1/(1+EXP(-1.939+((IF(D4=0,-1.034,0))+(IF(D4=1,-0.557,0))+(IF(D4=2,-0.030,0)+(IF(K4=0,-0.616,0))+(IF(K4=1,-0.302,0))+(IF(K4=2,-0.069,0))+(IF(H4=0,-0.552,0))+(IF(H4=1,-0.741,0))+(IF(H4=2,-0.422,0))+(IF(G4=0,-0.766,0))+(IF(G4=1,-0.684,0))+(IF(G4=2,-0.490,0))+(IF(B4=0,-0.879,0))+(IF(B4=1,-0.436,0))+(IF(B4=2,-0.097,0))+(IF(C4=0,0.606,0))+(IF(C4=1,0.531,0))+(IF(C4=2,0.135,0))+(IF(F4=0,-0.620,0))+(IF(F4=1,-0.336,0))+(IF(F4=2,-0.207,0))+(IF(E4=0,0.070,0))+(IF(E4=1,0.088,0))+(IF(E4=2,0.330,0))))))-S4

Pain: Qs 1, 6, 10, 4, 7, 3

P (Pain = 1)
=1/(1+EXP(3.148+((IF(B4=0,-1.981,0))+(IF(B4=1,-1.133,0))+(IF(B4=2,-0.490,0))+(IF(G4=0,-0.936,0))+(IF(G4=1,-0.676,0))+(IF(G4=2,-0.422,0))+(IF(K4=0,-0.843,0))+(IF(K4=1,-0.481,0))+(IF(K4=2,-0.241,0))+(IF(E4=0,-0.140,0))+(IF(E4=1,0.024,0))+(IF(E4=2,0.214,0))+(IF(H4=0,0.431,0))+(IF(H4=1,0.171,0))+(IF(H4=2,0.353,0))+(IF(D4=0,-0.656,0))+(IF(D4=1,-0.312,0))+(IF(D4=2,-0.150,0)))))

P (Pain = 2)
=1/(1+EXP(-0.524+((IF(B4=0,-1.981,0))+(IF(B4=1,-1.133,0))+(IF(B4=2,-0.49,0))+(IF(G4=0,-0.936,0))+(IF(G4=1,-0.676,0))+(IF(G4=2,-0.422,0))+(IF(K4=0,-0.843,0))+(IF(K4=1,-0.481,0))+(IF(K4=2,-0.241,0))+(IF(E4=0,-0.14,0))+(IF(E4=1,0.024,0))+(IF(E4=2,0.214,0))+(IF(H4=0,0.431,0))+(IF(H4=1,0.171,0))+(IF(H4=2,0.353,0))+(IF(D4=0,-0.656,0))+(IF(D4=1,-0.312,0))+(IF(D4=2,-0.15,0)))))–V4

Anxiety: Qs 2, 7, 9, 3, 1, 10, 8, 4

P (Anxiety = 1)
=1/(1+EXP(2.576+((IF(C4=0,-1.215,0))+(IF(C4=1,-0.829,0))+(IF(C4=2,-0.388,0))+(IF(H4=0,-0.51,0))+(IF(H4=1,-0.281,0))+(IF(H4=2,-0.114,0))+(IF(J4=0,-0.442,0))+(IF(J4=1,-0.395,0))+(IF(J4=2,-0.073,0))+(IF(D4=0,-0.351,0))+(IF(D4=1,-0.111,0))+(IF(D4=2,0.028,0))+(IF(B4=0,-0.224,0))+(IF(B4=1,-0.254,0))+(IF(B4=2,-0.246,0))+(IF(K4=0,-0.571,0))+(IF(K4=1,-0.54,0))+(IF(K4=2,-0.337,0))+(IF(I4=0,-0.426,0))+(IF(I4=1,-0.263,0))+(IF(I4=2,-0.124,0))+(IF(E4=0,0.142,0))+(IF(E4=1,0.05,0))+(IF(E4=2,0.191,0)))))

P (Anxiety = 2)
=1/(1+EXP(-0.711+((IF(C4=0,-1.215,0))+(IF(C4=1,-0.829,0))+(IF(C4=2,-0.388,0))+(IF(H4=0,-0.51,0))+(IF(H4=1,-0.281,0))+(IF(H4=2,-0.114,0))+(IF(J4=0,-0.442,0))+(IF(J4=1,-0.395,0))+(IF(J4=2,-0.073,0))+(IF(D4=0,-0.351,0))+(IF(D4=1,-0.111,0))+(IF(D4=2,0.028,0))+(IF(B4=0,-0.224,0))+(IF(B4=1,-0.254,0))+(IF(B4=2,-0.246,0))+(IF(K4=0,-0.571,0))+(IF(K4=1,-0.54,0))+(IF(K4=2,-0.337,0))+(IF(I4=0,-0.426,0))+(IF(I4=1,-0.263,0))+(IF(I4=2,-0.124,0))+(IF(E4=0,0.142,0))+(IF(E4=1,0.05,0))+(IF(E4=2,0.191,0)))))–Y4

Appendix XXIV: Method Three - External Validation: Parameter estimates based on all ten DLQI items, age and sex

$$P(Y=1)=\frac{1}{1+e^{(-a_1+b_1x_1+b_2x_2+\cdots+b_mx_m)}}$$

$$P(Y=2)=\frac{1}{1+e^{(-a_2+b_1x_1+b_2x_2+\cdots+b_mx_m)}}-P(Y=1)$$

$$P(Y=3)=\ 1-P(Y=2)-\ P(Y=1)$$

Anxiety / Depression

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	1.947	.240	65.891	1	.000	1.477	2.417
	[eq5danxdep = 2]	5.276	.283	348.078	1	.000	4.722	5.830
Location	age	.004	.003	2.331	1	.127	-.001	.010
	sex	.420	.102	16.813	1	.000	.219	.620
	dlqi1	.088	.064	1.910	1	.167	-.037	.214
	dlqi2	.388	.068	32.854	1	.000	.255	.520
	dlqi3	.087	.082	1.116	1	.291	-.074	.247
	dlqi4	-.125	.069	3.246	1	.072	-.260	.011

	dlqi5	.160	.089	3.244	1	.072	-.014	.335
	dlqi6	-.088	.072	1.509	1	.219	-.228	.052
	dlqi7	.207	.062	11.056	1	.001	.085	.330
	dlqi8	.076	.093	.667	1	.414	-.106	.257
	dlqi9	.216	.078	7.785	1	.005	.064	.368
	dlqi10	.206	.072	8.126	1	.004	.064	.347

Link function: Logit.

P(Y=1) =1/(1+EXP(-1.947+(Z2*0.088)+(AA2*0.388)+(AB2*0.087)+(AC2*-0.125)+(AD2*0.160)+(AE2*-0.088)+(AH2*0.207)+(AI2*0.076)+(AJ2*0.216)+(AK2*0.206)+(E2*0.004)+(F2*0.420)))

P(Y=2) =(1/(1+EXP(-5.276+(Z2*0.088)+(AA2*0.388)+(AB2*0.087)+(AC2*-0.125)+(AD2*0.160)+(AE2*-0.088)+(AH2*0.207)+(AI2*0.076)+(AJ2*0.216)+(AK2*0.206)+(E2*0.004)+(F2*0.420))))-BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	4.669	.336	193.325	1	.000	4.011	5.327
	[eq5dmob = 2]	9.577	.547	307.059	1	.000	8.505	10.648
Location	age	.054	.004	176.122	1	.000	.046	.062
	sex	.076	.125	.367	1	.545	-.169	.321
	dlqi1	.105	.080	1.706	1	.192	-.052	.262
	dlqi2	-.102	.088	1.352	1	.245	-.275	.070
	dlqi3	.090	.099	.819	1	.365	-.105	.285

dlqi4	.067	.085	.619	1	.431	-.099	.232
dlqi5	.186	.108	2.966	1	.085	-.026	.398
dlqi6	.047	.084	.316	1	.574	-.117	.212
dlqi7	.368	.074	24.549	1	.000	.223	.514
dlqi8	-.022	.113	.038	1	.845	-.244	.199
dlqi9	-.009	.093	.009	1	.924	-.190	.173
dlqi10	.223	.086	6.766	1	.009	.055	.391

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.669+(Z2*0.105)+(AA2*-0.102)+(AB2*0.090)+(AC2*0.067)+(AD2*0.186)+(AE2*0.047)+(AH2*0.368)+(AI2*-0.022)+(AJ2*-0.009)+(AK2*0.223)+(E2*0.054)+(F2*0.076)))

P(Y=2) =(1/(1+EXP(-9.577+(Z2*0.105)+(AA2*-0.102)+(AB2*0.090)+(AC2*0.067)+(AD2*0.186)+(AE2*0.047)+(AH2*0.368)+(AI2*-0.022)+(AJ2*-0.009)+(AK2*0.223)+(E2*0.054)+(F2*0.076))))-AS2

P(Y=3)=1-AT2-AS2

Pain

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.463	.246	100.560	1	.000	1.982	2.945
	[eq5dpain = 2]	6.308	.301	440.018	1	.000	5.718	6.897
Location	age	.024	.003	64.650	1	.000	.018	.030
	sex	.226	.103	4.827	1	.028	.024	.427

dlqi1	.700	.068	106.398	1	.000	.567	.833
dlqi2	.055	.070	.617	1	.432	-.082	.192
dlqi3	.145	.085	2.905	1	.088	-.022	.311
dlqi4	.083	.071	1.346	1	.246	-.057	.223
dlqi5	-.094	.092	1.045	1	.307	-.275	.087
dlqi6	.303	.075	16.360	1	.000	.156	.449
dlqi7	-.031	.065	.236	1	.627	-.158	.095
dlqi8	.113	.096	1.379	1	.240	-.075	.301
dlqi9	.164	.080	4.174	1	.041	.007	.322
dlqi10	.228	.075	9.239	1	.002	.081	.375

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.463+(Z2*0.700)+(AA2*0.055)+(AB2*0.145)+(AC2*0.083)+(AD2*-0.094)+(AE2*0.303)+(AH2*-0.031)+(AI2*0.113)+(AJ2*0.164)+(AK2*0.228)+(E2*0.024)+(F2*0.226)))

P(Y=2) =(1/(1+EXP(-6.308+(Z2*0.700)+(AA2*0.055)+(AB2*0.145)+(AC2*0.083)+(AD2*-0.094)+(AE2*0.303)+(AH2*-0.031)+(AI2*0.113)+(AJ2*0.164)+(AK2*0.228)+(E2*0.024)+(F2*0.226))))-BB2

P(Y=3)=1-BC2-BB2

Self-care

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	4.438	.436	103.522	1	.000	3.583	5.293
	[eq5dselfcar = 2]	8.390	.632	176.292	1	.000	7.152	9.629

Location	age	.028	.005	29.681	1	.000	.018	.039
	sex	-.268	.173	2.420	1	.120	-.607	.070
	dlqi1	.226	.109	4.343	1	.037	.013	.439
	dlqi2	.003	.114	.001	1	.976	-.219	.226
	dlqi3	.247	.125	3.927	1	.048	.003	.491
	dlqi4	-.028	.105	.073	1	.787	-.234	.178
	dlqi5	.214	.136	2.471	1	.116	-.053	.481
	dlqi6	-.050	.100	.248	1	.618	-.246	.146
	dlqi7	.284	.088	10.304	1	.001	.110	.457
	dlqi8	-.120	.135	.785	1	.375	-.385	.145
	dlqi9	.041	.109	.145	1	.703	-.172	.254
	dlqi10	.526	.101	27.180	1	.000	.328	.724

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.438+(Z2*0.226)+(AA2*0.003)+(AB2*0.247)+(AC2*-0.028)+(AD2*0.214)+(AE2*-0.050)+(AH2*0.284)+(AI2*-0.120)+(AJ2*0.041)+(AK2*0.526)+(E2*0.028)+(F2*-0.268)))

P(Y=2) =(1/(1+EXP(-8.390+(Z2*0.226)+(AA2*0.003)+(AB2*0.247)+(AC2*-0.028)+(AD2*0.214)+(AE2*-0.050)+(AH2*0.284)+(AI2*-0.120)+(AJ2*0.041)+(AK2*0.526)+(E2*0.028)+(F2*-0.268))))-AV2

P(Y=3) =1-AW2-AV2

Usual Activities

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.616	.305	140.338	1	.000	3.017	4.214

	[eq5dactiv = 2]	7.480	.398	353.744	1	.000	6.700	8.259
Location	age	.029	.004	62.983	1	.000	.022	.036
	sex	.116	.122	.903	1	.342	-.123	.355
	dlqi1	.221	.076	8.426	1	.004	.072	.370
	dlqi2	-.107	.083	1.631	1	.202	-.270	.057
	dlqi3	.254	.092	7.623	1	.006	.074	.434
	dlqi4	-.047	.080	.343	1	.558	-.203	.110
	dlqi5	.230	.101	5.195	1	.023	.032	.427
	dlqi6	.156	.077	4.044	1	.044	.004	.308
	dlqi7	.293	.069	18.248	1	.000	.159	.428
	dlqi8	-.098	.106	.855	1	.355	-.305	.110
	dlqi9	.153	.086	3.206	1	.073	-.015	.321
	dlqi10	.314	.080	15.532	1	.000	.158	.470

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.616+(Z2*0.221)+(AA2*-0.107)+(AB2*0.254)+(AC2*-0.047)+(AD2*0.230)+(AE2*0.156)+(AH2*0.293)+(AI2*-0.098)+(AJ2*0.153)+(AK2*0.314)+(E2*0.029)+(F2*0.116)))

P(Y=2) =(1/(1+EXP(-7.480+(Z2*0.221)+(AA2*-0.107)+(AB2*0.254)+(AC2*-0.047)+(AD2*0.230)+(AE2*0.156)+(AH2*0.293)+(AI2*-0.098)+(AJ2*0.153)+(AK2*0.314)+(E2*0.029)+(F2*0.116))))-AY2

P(Y=3) =1-AZ2-AY2

Appendix XXV: Z1 'All Ones' - Binary (Ordinal) Logistic Regression (after missing DLQI/EQ5D cases deleted)

'Not All Ones' = 1
'All Ones' = 0

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[AllOnes = .00]	-5.135	.883	33.853	1	.000	-6.865	-3.405
Location	[dlqi1=0]	-1.667	.358	21.630	1	.000	-2.370	-.965
	[dlqi1=1]	-1.245	.353	12.411	1	.000	-1.937	-.552
	[dlqi1=2]	-.523	.375	1.938	1	.164	-1.259	.213
	[dlqi1=3]	0[a]	.	.	0	.	.	.
	[dlqi2=0]	-.347	.305	1.289	1	.256	-.945	.252
	[dlqi2=1]	-.059	.303	.038	1	.846	-.653	.535
	[dlqi2=2]	.084	.324	.067	1	.796	-.551	.719
	[dlqi2=3]	0[a]	.	.	0	.	.	.
	[dlqi3=0]	-.310	.512	.366	1	.545	-1.314	.694
	[dlqi3=1]	.211	.522	.163	1	.686	-.812	1.234
	[dlqi3=2]	.036	.544	.004	1	.947	-1.031	1.103
	[dlqi3=3]	0[a]	.	.	0	.	.	.
	[dlqi4=0]	.208	.347	.360	1	.549	-.472	.889
	[dlqi4=1]	.425	.356	1.421	1	.233	-.274	1.123
	[dlqi4=2]	.360	.394	.837	1	.360	-.412	1.133

[dlqi4=3]	0[a]	.	.	0	.	.	.
[dlqi5=0]	.732	.491	2.219	1	.136	-.231	1.695
[dlqi5=1]	.972	.487	3.993	1	.046	.019	1.926
[dlqi5=2]	.990	.503	3.874	1	.049	.004	1.975
[dlqi5=3]	0[a]	.	.	0	.	.	.
[dlqi6=0]	-1.171	.551	4.521	1	.033	-2.250	-.092
[dlqi6=1]	-1.161	.573	4.100	1	.043	-2.284	-.037
[dlqi6=2]	-.893	.626	2.033	1	.154	-2.120	.335
[dlqi6=3]	0[a]	.	.	0	.	.	.
[dlqi7=0]	-.841	.367	5.247	1	.022	-1.560	-.121
[dlqi7=1]	-.977	.377	6.713	1	.010	-1.717	-.238
[dlqi7=2]	-1.077	.502	4.600	1	.032	-2.061	-.093
[dlqi7=3]	0[a]	.	.	0	.	.	.
[dlqi8=0]	-.972	.716	1.842	1	.175	-2.375	.432
[dlqi8=1]	-.862	.715	1.454	1	.228	-2.262	.539
[dlqi8=2]	-.766	.720	1.131	1	.288	-2.176	.645
[dlqi8=3]	0[a]	.	.	0	.	.	.
[dlqi9=0]	-.772	.501	2.372	1	.124	-1.753	.210
[dlqi9=1]	-.920	.527	3.046	1	.081	-1.953	.113
[dlqi9=2]	.159	.716	.050	1	.824	-1.244	1.563
[dlqi9=3]	0[a]	.	.	0	.	.	.
[dlqi10=0]	-.152	.446	.116	1	.733	-1.026	.722
[dlqi10=1]	.234	.463	.255	1	.613	-.673	1.141
[dlqi10=2]	.457	.549	.693	1	.405	-.619	1.534
[dlqi10=3]	0[a]	.	.	0	.	.	.

Link function: Logit.

a. This parameter is set to zero because it is redundant.

Binary Logistic Formula to predict probability of Z1 ('All ones')

$$P(Z1 = 0) = \frac{1}{1 + e^{(-a_1 + b_1x_1 + b_2x_2 + b_3x_3)}}$$

$$P(Z1 = 1) = 1 - P(Z1 = 0)$$

$$P(EQ5D\ scores\ all\ ones) = \frac{1}{1 + e^{(-constant + DLQI1... + DLQI10)}}$$

$$P(EQ5D\ scores\ anything\ else) = 1 - P(Z1 = 0)$$

P Z1=0

=1/(1+EXP(5.135+((IF(J2=0,-1.667,0))+(IF(J2=1,-1.245,0))+(IF(J2=2,-0.523,0))+(IF(J2=3,0,0))+(IF(L2=0,-0.347,0))+(IF(L2=1,-0.059,0))+(IF(L2=2,0.084,0))+(IF(L2=3,0,0))+(IF(M2=0,-0.310,0))+(IF(M2=1,0.211,0))+(IF(M2=2,0.036,0))+(IF(M2=3,0,0))+(IF(N2=0,0.208,0))+(IF(N2=1,0.425,0))+(IF(N2=2,0.360,0))+(IF(N2=3,0,0))+(IF(O2=0,0.732,0))+(IF(O2=1,0.972,0))+(IF(O2=2,0.990,0))+(IF(O2=3,0,0))+(IF(P2=0,-1.171,0))+(IF(P2=1,-1.161,0))+(IF(P2=2,-0.893,0))+(IF(P2=3,0,0))+(IF(Q2=0,-0.841,0))+(IF(Q2=1,-0.977,0))+(IF(Q2=2,-1.077,0))+(IF(Q2=3,0,0)) +(IF(S2=0,-0.972,0))+(IF(S2=1,-0.862,0))+(IF(S2=2,-0.766,0))+(IF(S2=3,0,0)) +(IF(T2=0,-0.772,0))+(IF(T2=1,-0.920,0))+(IF(T2=2,0.159,0))+(IF(T2=3,0,0)) +(IF(K2=0,-0.152,0))+(IF(K2=1,0.234,0))+(IF(K2=2,0.457,0))+(IF(K2=3,0,0)))))

P Z1=1

= 1 – P(Z1=0)

Z2 'At least one three' - Binary (Ordinal) Logistic Regression (after missing DLQI/EQ5D cases deleted)

'At least one three' = 1
'No threes' = 0

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[NoThrees = .00]	-.270	.391	.479	1	.489	-1.036	.495
Location	[dlqi1=0]	-1.240	.350	12.559	1	.000	-1.925	-.554
	[dlqi1=1]	-.897	.288	9.722	1	.002	-1.460	-.333
	[dlqi1=2]	-.419	.256	2.684	1	.101	-.921	.082
	[dlqi1=3]	0[a]	.	.	0	.	.	.
	[dlqi2=0]	-.260	.337	.595	1	.440	-.921	.401
	[dlqi2=1]	-.712	.313	5.154	1	.023	-1.326	-.097
	[dlqi2=2]	-.516	.290	3.165	1	.075	-1.085	.053
	[dlqi2=3]	0[a]	.	.	0	.	.	.
	[dlqi3=0]	.245	.408	.360	1	.548	-.555	1.045
	[dlqi3=1]	-.084	.394	.046	1	.830	-.856	.687
	[dlqi3=2]	-.032	.346	.008	1	.927	-.710	.646
	[dlqi3=3]	0[a]	.	.	0	.	.	.
	[dlqi4=0]	.638	.351	3.310	1	.069	-.049	1.325
	[dlqi4=1]	.290	.359	.654	1	.419	-.413	.994
	[dlqi4=2]	.853	.330	6.677	1	.010	.206	1.500
	[dlqi4=3]	0[a]	.	.	0	.	.	.
	[dlqi5=0]	-.374	.435	.739	1	.390	-1.226	.478
	[dlqi5=1]	-.292	.392	.557	1	.456	-1.061	.476

[dlqi5=2]	-.170	.365	.217	1	.641	-.885	.545
[dlqi5=3]	0[a]	.	.	0	.	.	.
[dlqi6=0]	-.648	.325	3.968	1	.046	-1.286	-.010
[dlqi6=1]	-.932	.385	5.867	1	.015	-1.686	-.178
[dlqi6=2]	-.516	.381	1.834	1	.176	-1.262	.231
[dlqi6=3]	0[a]	.	.	0	.	.	.
[dlqi7=0]	-.352	.288	1.495	1	.221	-.916	.212
[dlqi7=1]	-.242	.305	.630	1	.427	-.840	.356
[dlqi7=2]	.311	.373	.697	1	.404	-.419	1.042
[dlqi7=3]	0[a]	.	.	0	.	.	.
[dlqi8=0]	-.480	.442	1.184	1	.277	-1.346	.385
[dlqi8=1]	-.204	.418	.238	1	.626	-1.023	.615
[dlqi8=2]	.206	.379	.294	1	.588	-.538	.949
[dlqi8=3]	0[a]	.	.	0	.	.	.
[dlqi9=0]	-.362	.336	1.161	1	.281	-1.020	.296
[dlqi9=1]	-.401	.390	1.055	1	.304	-1.166	.364
[dlqi9=2]	-.410	.421	.950	1	.330	-1.235	.415
[dlqi9=3]	0[a]	.	.	0	.	.	.
[dlqi10=0]	-.682	.354	3.711	1	.054	-1.376	.012
[dlqi10=1]	-.408	.378	1.167	1	.280	-1.149	.332
[dlqi10=2]	.187	.355	.279	1	.597	-.508	.882
[dlqi10=3]	0[a]	.	.	0	.	.	.

Link function: Logit.

a. This parameter is set to zero because it is redundant.

Binary Logistic Formula to predict probability of Z2 ('At least one three')

$$P(Z2 = 0) = \frac{1}{1 + e^{(-a_1 + b_1x_1 + b_2x_2 + b_3x_3)}}$$

$$P(Z2 = 1) = 1 - P(Z2 = 0)$$

$$P(EQ5D\ scores\ no\ threes) = \frac{1}{1 + e^{(-constant + DLQI1 \ldots + DLQI10)}}$$

$$P(EQ5D\ scores\ at\ least\ one\ three) = 1 - P(Z1 = 0)$$

P Z2=0

=1/(1+EXP(0.270+((IF(J2=0,-1.240,0))+(IF(J2=1,-0.897,0))+(IF(J2=2,-0.419,0))+(IF(J2=3,0,0))+(IF(L2=0,-0.260,0))+(IF(L2=1,-0.712,0))+(IF(L2=2,-0.516,0))+(IF(L2=3,0,0))+(IF(M2=0,0.245,0))+(IF(M2=1,-0.084,0))+(IF(M2=2,-0.032,0))+(IF(M2=3,0,0))+(IF(N2=0,0.638,0))+(IF(N2=1,0.290,0))+(IF(N2=2,0.853,0))+(IF(N2=3,0,0))+(IF(O2=0,-0.374,0))+(IF(O2=1,-0.292,0))+(IF(O2=2,-0.170,0))+(IF(O2=3,0,0))+(IF(P2=0,-0.648,0))+(IF(P2=1,-0.932,0))+(IF(P2=2,-0.516,0))+(IF(P2=3,0,0))+(IF(Q2=0,-0.352,0))+(IF(Q2=1,-0.242,0))+(IF(Q2=2,0.311,0))+(IF(Q2=3,0,0)) +(IF(S2=0,-0.480,0))+(IF(S2=1,-0.204,0))+(IF(S2=2,0.206,0))+(IF(S2=3,0,0)) +(IF(T2=0,-0.362,0))+(IF(T2=1,-0.401,0))+(IF(T2=2,-0.410,0))+(IF(T2=3,0,0)) +(IF(K2=0,-0.682,0))+(IF(K2=1,-0.408,0))+(IF(K2=2,0.187,0))+(IF(K2=3,0,0)))))

P Z2=1

= 1 – P(Z2=0)

Final Expected Utility Value, based on UK TTO values:

=1-0-(AT2*0.071)-(AU2*0.236)-0-(AW2*0.069)-(AX2*0.314)-0-(AZ2*0.123)-(BA2*0.386)-0-(BC2*0.104)-(BD2*0.214)-0-(BF2*0.036)-(BG2*0.094)-(BJ2*0.081)-(BL2*0.269)

Appendix XXVI: External validation: Split Half Cross Validation (Set One)

$$P(Y=1)=\frac{1}{1+e^{(-a_1+b_1x_1+b_2x_2+\cdots+b_mx_m)}}$$

$$P(Y=2)=\frac{1}{1+e^{(-a_2+b_1x_1+b_2x_2+\cdots+b_mx_m)}}-P(Y=1)$$

$$P(Y=3)=1-P(Y=2)-P(Y=1)$$

Anxiety / Depression

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	1.394	.182	58.389	1	.000	1.036	1.751
	[eq5danxdep = 2]	4.933	.237	432.334	1	.000	4.468	5.398
Location	age	.000	.003	.026	1	.873	-.006	.005
	sex	.544	.106	26.472	1	.000	.337	.751
	dlqi1	.004	.064	.003	1	.954	-.123	.130
	dlqi2	.399	.068	34.138	1	.000	.265	.533

dlqi3	.113	.081	1.934	1	.164	-.046	.273
dlqi4	-.136	.068	4.043	1	.044	-.269	-.003
dlqi5	.312	.089	12.355	1	.000	.138	.485
dlqi6	-.061	.073	.692	1	.406	-.205	.083
dlqi7	.140	.063	4.983	1	.026	.017	.262
dlqi8	.144	.092	2.457	1	.117	-.036	.323
dlqi9	.177	.077	5.241	1	.022	.025	.328
dlqi10	.099	.074	1.818	1	.178	-.045	.244

Link function: Logit.

P(Y=1) =1/(1+EXP(-1.394+(Z2*0.004)+(AA2*0.399)+(AB2*0.113)+(AC2*-0.136)+(AD2*0.312)+(AE2*-0.061)+(AH2*0.140)+(AI2*0.144)+(AJ2*0.177)+(AK2*0.099)+(E2*0.000)+(F2*0.544)))

P(Y=2) =(1/(1+EXP(-4.933+(Z2*0.004)+(AA2*0.399)+(AB2*0.113)+(AC2*-0.136)+(AD2*0.312)+(AE2*-0.061)+(AH2*0.140)+(AI2*0.144)+(AJ2*0.177)+(AK2*0.099)+(E2*0.000)+(F2*0.544))))-BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	4.327	.265	265.971	1	.000	3.807	4.847
	[eq5dmob = 2]	9.134	.480	362.102	1	.000	8.194	10.075
Location	age	.050	.004	157.536	1	.000	.042	.057

sex	-.068	.126	.292	1	.589	-.315	.179
dlqi1	.031	.079	.157	1	.692	-.124	.187
dlqi2	.034	.086	.159	1	.690	-.133	.202
dlqi3	.402	.096	17.442	1	.000	.213	.590
dlqi4	-.065	.083	.609	1	.435	-.227	.098
dlqi5	.070	.108	.424	1	.515	-.142	.282
dlqi6	.136	.084	2.592	1	.107	-.029	.301
dlqi7	.321	.074	18.939	1	.000	.176	.465
dlqi8	-.111	.109	1.034	1	.309	-.324	.103
dlqi9	-.068	.091	.562	1	.453	-.247	.110
dlqi10	.255	.085	8.992	1	.003	.088	.421

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.327+(Z2*0.031)+(AA2*0.034)+(AB2*0.402)+(AC2*-0.065)+(AD2*0.070)+(AE2*0.136)+(AH2*0.321)+(AI2*-0.111)+(AJ2*-0.068)+(AK2*0.255)+(E2*0.050)+(F2*-0.068)))

P(Y=2) =(1/(1+EXP(-9.134+(Z2*0.031)+(AA2*0.034)+(AB2*0.402)+(AC2*-0.065)+(AD2*0.070)+(AE2*0.136)+(AH2*0.321)+(AI2*-0.111)+(AJ2*-0.068)+(AK2*0.255)+(E2*0.050)+(F2*-0.068))))-AS2

P(Y=3)=1-AT2-AS2

Pain

Parameter Estimates

	Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval

							95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.016	.186	117.236	1	.000	1.651	2.381
	[eq5dpain = 2]	6.005	.253	562.500	1	.000	5.508	6.501
Location	age	.021	.003	50.389	1	.000	.015	.027
	sex	.180	.104	3.000	1	.083	-.024	.384
	dlqi1	.691	.067	106.197	1	.000	.559	.822
	dlqi2	.034	.070	.244	1	.622	-.102	.171
	dlqi3	.255	.084	9.122	1	.003	.090	.421
	dlqi4	.038	.069	.296	1	.586	-.098	.173
	dlqi5	-.196	.092	4.576	1	.032	-.376	-.016
	dlqi6	.407	.077	27.988	1	.000	.256	.558
	dlqi7	-.011	.065	.031	1	.859	-.138	.115
	dlqi8	.165	.095	3.044	1	.081	-.020	.351
	dlqi9	.087	.079	1.204	1	.273	-.068	.242
	dlqi10	.209	.076	7.630	1	.006	.061	.358

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.016+(Z2*0.691)+(AA2*0.034)+(AB2*0.255)+(AC2*0.038)+(AD2*-0.196)+(AE2*0.407)+(AH2*-0.011)+(AI2*0.165)+(AJ2*0.087)+(AK2*0.209)+(E2*0.021)+(F2*0.180)))

P(Y=2) =(1/(1+EXP(-6.005+(Z2*0.691)+(AA2*0.034)+(AB2*0.255)+(AC2*0.038)+(AD2*-0.196)+(AE2*0.407)+(AH2*-0.011)+(AI2*0.165)+(AJ2*0.087)+(AK2*0.209)+(E2*0.021)+(F2*0.180))))-BB2

P(Y=3)=1-BC2-BB2

Self-care

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	4.700	.353	177.683	1	.000	4.009	5.391
	[eq5dselfcar = 2]	9.246	.680	184.924	1	.000	7.913	10.579
Location	age	.029	.005	30.862	1	.000	.018	.039
	sex	-.174	.170	1.041	1	.308	-.507	.160
	dlqi1	.149	.106	1.964	1	.161	-.059	.356
	dlqi2	.100	.109	.839	1	.360	-.114	.314
	dlqi3	.315	.119	7.003	1	.008	.082	.549
	dlqi4	.026	.100	.068	1	.794	-.169	.222
	dlqi5	-.017	.133	.017	1	.897	-.278	.244
	dlqi6	.023	.100	.052	1	.820	-.173	.218
	dlqi7	.308	.088	12.194	1	.000	.135	.481
	dlqi8	.001	.128	.000	1	.995	-.250	.251
	dlqi9	.044	.104	.181	1	.670	-.160	.249
	dlqi10	.439	.099	19.488	1	.000	.244	.634

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.700+(Z2*0.149)+(AA2*0.100)+(AB2*0.315)+(AC2*0.026)+(AD2*-0.017)+(AE2*0.023)+(AH2*0.308)+(AI2*0.001)+(AJ2*0.044)+(AK2*0.439)+(E2*0.029)+(F2*-0.174)))

P(Y=2) =(1/(1+EXP(-9.246+(Z2*0.149)+(AA2*0.100)+(AB2*0.315)+(AC2*0.026)+(AD2*-0.017)+(AE2*0.023)+(AH2*0.308)+(AI2*0.001)+(AJ2*0.044)+(AK2*0.439)+(E2*0.029)+(F2*-0.174))))-AV2

P(Y=3) =1-AW2-AV2

Usual Activities

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.593	.243	218.907	1	.000	3.117	4.069
	[eq5dactiv = 2]	7.473	.343	475.741	1	.000	6.801	8.144
Location	age	.027	.004	54.018	1	.000	.020	.034
	sex	.264	.125	4.479	1	.034	.020	.508
	dlqi1	.378	.075	25.290	1	.000	.231	.525
	dlqi2	-.198	.084	5.601	1	.018	-.363	-.034
	dlqi3	.492	.090	29.980	1	.000	.316	.668
	dlqi4	-.042	.078	.292	1	.589	-.194	.110
	dlqi5	.267	.100	7.185	1	.007	.072	.462
	dlqi6	.217	.079	7.620	1	.006	.063	.371
	dlqi7	.264	.069	14.654	1	.000	.129	.399
	dlqi8	-.063	.103	.374	1	.541	-.264	.138
	dlqi9	.016	.085	.035	1	.852	-.151	.183
	dlqi10	.152	.081	3.501	1	.061	-.007	.311

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.593+(Z2*0.378)+(AA2*-0.198)+(AB2*0.492)+(AC2*-0.042)+(AD2*0.267)+(AE2*0.217)+(AH2*0.264)+(AI2*-0.063)+(AJ2*0.016)+(AK2*0.152)+(E2*0.027)+(F2*0.264)))

P(Y=2) =(1/(1+EXP(-7.473+(Z2*0.378)+(AA2*-0.198)+(AB2*0.492)+(AC2*-0.042)+(AD2*0.267)+(AE2*0.217)+(AH2*0.264)+(AI2*-0.063)+(AJ2*0.016)+(AK2*0.152)+(E2*0.027)+(F2*0.264))))-AY2

P(Y=3) =1-AZ2-AY2

External validation: Split Half Cross Validation (Set Two)

$$P(Y=1) = \frac{1}{1+e^{(-a_1+b_1x_1+b_2x_2+\cdots+b_mx_m)}}$$

$$P(Y=2) = \frac{1}{1+e^{(-a_2+b_1x_1+b_2x_2+\cdots+b_mx_m)}} - P(Y=1)$$

$$P(Y=3) = 1 - P(Y=2) - P(Y=1)$$

Anxiety / Depression

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	1.559	.183	72.924	1	.000	1.201	1.917
	[eq5danxdep = 2]	5.021	.236	453.085	1	.000	4.558	5.483

Location	age	.004	.003	2.149	1	.143	-.001	.010
	sex	.589	.104	32.068	1	.000	.385	.792
	dlqi1	-.037	.065	.327	1	.568	-.164	.090
	dlqi2	.364	.068	28.462	1	.000	.230	.497
	dlqi3	.174	.084	4.304	1	.038	.010	.338
	dlqi4	-.150	.070	4.645	1	.031	-.287	-.014
	dlqi5	.220	.092	5.795	1	.016	.041	.400
	dlqi6	-.062	.076	.662	1	.416	-.210	.087
	dlqi7	.193	.064	9.153	1	.002	.068	.317
	dlqi8	.239	.089	7.165	1	.007	.064	.414
	dlqi9	.115	.079	2.132	1	.144	-.039	.269
	dlqi10	.134	.076	3.122	1	.077	-.015	.283

Link function: Logit.

P(Y=1) =1/(1+EXP(-1.559+(Z2*-0.037)+(AA2*0.364)+(AB2*0.174)+(AC2*-0.150)+(AD2*0.220)+(AE2*-0.062)+(AH2*0.193)+(AI2*0.239)+(AJ2*0.115)+(AK2*0.134)+(E2*0.004)+(F2*0.589)))

P(Y=2) =(1/(1+EXP(-5.021+(Z2*-0.037)+(AA2*0.364)+(AB2*0.174)+(AC2*-0.150)+(AD2*0.220)+(AE2*-0.062)+(AH2*0.193)+(AI2*0.239)+(AJ2*0.115)+(AK2*0.134)+(E2*0.004)+(F2*0.589))))-BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

	Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval

							95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	4.594	.275	279.993	1	.000	4.056	5.132
	[eq5dmob = 2]	10.178	.650	245.387	1	.000	8.905	11.451
Location	age	.054	.004	168.417	1	.000	.046	.062
	sex	.001	.127	.000	1	.996	-.248	.249
	dlqi1	.078	.081	.920	1	.338	-.081	.236
	dlqi2	.038	.088	.187	1	.665	-.134	.210
	dlqi3	.193	.101	3.682	1	.055	-.004	.391
	dlqi4	.074	.085	.767	1	.381	-.092	.240
	dlqi5	.073	.113	.427	1	.514	-.147	.294
	dlqi6	.287	.088	10.660	1	.001	.115	.459
	dlqi7	.188	.078	5.881	1	.015	.036	.341
	dlqi8	-.096	.109	.778	1	.378	-.311	.118
	dlqi9	-.106	.094	1.247	1	.264	-.291	.080
	dlqi10	.255	.090	8.056	1	.005	.079	.432

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.594+(Z2*0.078)+(AA2*0.038)+(AB2*0.193)+(AC2*0.074)+(AD2*0.073)+(AE2*0.287)+(AH2*0.188)+(AI2*-0.096)+(AJ2*-0.106)+(AK2*0.255)+(E2*0.054)+(F2*-0.001)))

P(Y=2) =(1/(1+EXP(-10.178 +(Z2*0.078)+(AA2*0.038)+(AB2*0.193)+(AC2*0.074)+(AD2*0.073)+(AE2*0.287)+(AH2*0.188)+(AI2*-0.096)+(AJ2*-0.106)+(AK2*0.255)+(E2*0.054)+(F2*-0.001))))-AS2

P(Y=3)=1-AT2-AS2

Pain

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.416	.190	162.165	1	.000	2.044	2.788
	[eq5dpain = 2]	6.276	.256	602.455	1	.000	5.775	6.777
Location	age	.031	.003	96.748	1	.000	.024	.037
	sex	.194	.103	3.547	1	.060	-.008	.396
	dlqi1	.707	.068	109.207	1	.000	.575	.840
	dlqi2	.009	.070	.017	1	.898	-.129	.147
	dlqi3	.268	.086	9.665	1	.002	.099	.438
	dlqi4	.133	.071	3.561	1	.059	-.005	.272
	dlqi5	-.242	.095	6.532	1	.011	-.427	-.056
	dlqi6	.359	.079	20.939	1	.000	.205	.513
	dlqi7	-.030	.066	.213	1	.645	-.159	.098
	dlqi8	.206	.092	4.991	1	.025	.025	.386
	dlqi9	.148	.081	3.364	1	.067	-.010	.306
	dlqi10	.111	.078	2.042	1	.153	-.041	.263

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.416+(Z2*0.707)+(AA2*0.009)+(AB2*0.268)+(AC2*0.133)+(AD2*-0.242)+(AE2*0.359)+(AH2*-0.030)+(AI2*0.206)+(AJ2*0.148)+(AK2*0.111)+(E2*0.031)+(F2*0.194)))

P(Y=2) =(1/(1+EXP(-6.276+(Z2*0.707)+(AA2*0.009)+(AB2*0.268)+(AC2*0.133)+(AD2*-0.242)+(AE2*0.359)+(AH2*-

0.030)+(AI2*0.206)+(AJ2*0.148)+(AK2*0.111)+(E2*0.031)+(F2*0.194)))-BB2

P(Y=3)=1-BC2-BB2

Self-care

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	5.086	.361	198.696	1	.000	4.379	5.793
	[eq5dselfcar = 2]	9.437	.626	227.062	1	.000	8.209	10.664
Location	age	.037	.005	49.345	1	.000	.027	.048
	sex	-.291	.167	3.033	1	.082	-.619	.037
	dlqi1	.179	.105	2.917	1	.088	-.026	.384
	dlqi2	.180	.110	2.676	1	.102	-.036	.395
	dlqi3	.350	.120	8.488	1	.004	.114	.585
	dlqi4	.062	.102	.369	1	.544	-.138	.263
	dlqi5	-.155	.136	1.300	1	.254	-.422	.112
	dlqi6	.150	.103	2.123	1	.145	-.052	.352
	dlqi7	.355	.089	15.833	1	.000	.180	.530
	dlqi8	-.025	.125	.042	1	.838	-.270	.219
	dlqi9	.009	.106	.008	1	.930	-.199	.217
	dlqi10	.317	.103	9.444	1	.002	.115	.519

Link function: Logit.

P(Y=1) =1/(1+EXP(-5.086+(Z2*0.179)+(AA2*0.180)+(AB2*0.350)+(AC2*0.062)+(AD2*-0.155)+(AE2*0.150)+(AH2*0.355)+(AI2*-0.025)+(AJ2*0.009)+(AK2*0.317)+(E2*0.037)+(F2*-0.291)))

P(Y=2) =(1/(1+EXP(-9.437+(Z2*0.179)+(AA2*0.180)+(AB2*0.350)+(AC2*0.062)+(AD2*-0.155)+(AE2*0.150)+(AH2*0.355)+(AI2*-0.025)+(AJ2*0.009)+(AK2*0.317)+(E2*0.037)+(F2*-0.291))))-AV2

P(Y=3) =1-AW2-AV2

Usual Activities

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.564	.244	213.483	1	.000	3.086	4.042
	[eq5dactiv = 2]	7.317	.339	464.819	1	.000	6.652	7.982
Location	age	.030	.004	65.590	1	.000	.023	.038
	sex	.011	.123	.007	1	.932	-.231	.252
	dlqi1	.236	.077	9.456	1	.002	.086	.387
	dlqi2	-.095	.085	1.255	1	.263	-.261	.071
	dlqi3	.374	.094	15.976	1	.000	.191	.557
	dlqi4	.041	.079	.271	1	.602	-.114	.197
	dlqi5	.097	.104	.860	1	.354	-.108	.301
	dlqi6	.364	.081	20.094	1	.000	.205	.524
	dlqi7	.280	.071	15.626	1	.000	.141	.418

dlqi8	-.140	.102	1.867	1	.172	-.340	.061
dlqi9	.073	.088	.697	1	.404	-.099	.245
dlqi10	.232	.084	7.599	1	.006	.067	.397

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.564+(Z2*0.236)+(AA2*-0.095)+(AB2*0.374)+(AC2*-0.041)+(AD2*0.097)+(AE2*0.364)+(AH2*0.280)+(AI2*-0.140)+(AJ2*0.073)+(AK2*0.232)+(E2*0.030)+(F2*0.011)))

P(Y=2) =(1/(1+EXP(-7.317+(Z2*0.236)+(AA2*-0.095)+(AB2*0.374)+(AC2*-0.041)+(AD2*0.097)+(AE2*0.364)+(AH2*0.280)+(AI2*-0.140)+(AJ2*0.073)+(AK2*0.232)+(E2*0.030)+(F2*0.011))))-AY2

P(Y=3) =1-AZ2-AY2

External validation: Split Half Cross Validation (Set Three)

$$P(Y=1)=\frac{1}{1+e^{(-a_1+b_1x_1+b_2x_2+\cdots+b_mx_m)}}$$

$$P(Y=2)=\frac{1}{1+e^{(-a_2+b_1x_1+b_2x_2+\cdots+b_mx_m)}}-P(Y=1)$$

$$P(Y = 3) = 1 - P(Y = 2) - P(Y = 1)$$

Anxiety / Depression

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	1.394	.182	58.389	1	.000	1.036	1.751
	[eq5danxdep = 2]	4.933	.237	432.334	1	.000	4.468	5.398
Location	age	.000	.003	.026	1	.873	-.006	.005
	sex	.544	.106	26.472	1	.000	.337	.751
	dlqi1	.004	.064	.003	1	.954	-.123	.130
	dlqi2	.399	.068	34.138	1	.000	.265	.533
	dlqi3	.113	.081	1.934	1	.164	-.046	.273
	dlqi4	-.136	.068	4.043	1	.044	-.269	-.003
	dlqi5	.312	.089	12.355	1	.000	.138	.485
	dlqi6	-.061	.073	.692	1	.406	-.205	.083
	dlqi7	.140	.063	4.983	1	.026	.017	.262
	dlqi8	.144	.092	2.457	1	.117	-.036	.323
	dlqi9	.177	.077	5.241	1	.022	.025	.328
	dlqi10	.099	.074	1.818	1	.178	-.045	.244

Link function: Logit.

P(Y=1) =1/(1+EXP(-1.394+(Z2*0.004)+(AA2*0.399)+(AB2*0.113)+(AC2*-0.136)+(AD2*0.312)+(AE2*-

0.061)+(AH2*0.140)+(AI2*0.144)+(AJ2*0.177)+(AK2*0.099)+(E2*0.000)+(F2*0.544)))

P(Y=2) =(1/(1+EXP(-4.933+(Z2*0.004)+(AA2*0.399)+(AB2*0.113)+(AC2*-0.136)+(AD2*0.312)+(AE2*-0.061)+(AH2*0.140)+(AI2*0.144)+(AJ2*0.177)+(AK2*0.099)+(E2*0.000)+(F2*0.544))))-BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	4.327	.265	265.971	1	.000	3.807	4.847
	[eq5dmob = 2]	9.134	.480	362.102	1	.000	8.194	10.075
Location	age	.050	.004	157.536	1	.000	.042	.057
	sex	-.068	.126	.292	1	.589	-.315	.179
	dlqi1	.031	.079	.157	1	.692	-.124	.187
	dlqi2	.034	.086	.159	1	.690	-.133	.202
	dlqi3	.402	.096	17.442	1	.000	.213	.590
	dlqi4	-.065	.083	.609	1	.435	-.227	.098
	dlqi5	.070	.108	.424	1	.515	-.142	.282
	dlqi6	.136	.084	2.592	1	.107	-.029	.301
	dlqi7	.321	.074	18.939	1	.000	.176	.465
	dlqi8	-.111	.109	1.034	1	.309	-.324	.103
	dlqi9	-.068	.091	.562	1	.453	-.247	.110
	dlqi10	.255	.085	8.992	1	.003	.088	.421

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.327+(Z2*0.031)+(AA2*0.034)+(AB2*0.402)+(AC2*-0.065)+(AD2*0.070)+(AE2*0.136)+(AH2*0.321)+(AI2*-0.111)+(AJ2*-0.068)+(AK2*0.255)+(E2*0.050)+(F2*-0.068)))

P(Y=2) =(1/(1+EXP(-9.134+(Z2*0.031)+(AA2*0.034)+(AB2*0.402)+(AC2*-0.065)+(AD2*0.070)+(AE2*0.136)+(AH2*0.321)+(AI2*-0.111)+(AJ2*-0.068)+(AK2*0.255)+(E2*0.050)+(F2*-0.068))))-AS2

P(Y=3)=1-AT2-AS2

Pain

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.016	.186	117.236	1	.000	1.651	2.381
	[eq5dpain = 2]	6.005	.253	562.500	1	.000	5.508	6.501
Location	age	.021	.003	50.389	1	.000	.015	.027
	sex	.180	.104	3.000	1	.083	-.024	.384
	dlqi1	.691	.067	106.197	1	.000	.559	.822
	dlqi2	.034	.070	.244	1	.622	-.102	.171
	dlqi3	.255	.084	9.122	1	.003	.090	.421
	dlqi4	.038	.069	.296	1	.586	-.098	.173

	dlqi5	-.196	.092	4.576	1	.032	-.376	-.016
	dlqi6	.407	.077	27.988	1	.000	.256	.558
	dlqi7	-.011	.065	.031	1	.859	-.138	.115
	dlqi8	.165	.095	3.044	1	.081	-.020	.351
	dlqi9	.087	.079	1.204	1	.273	-.068	.242
	dlqi10	.209	.076	7.630	1	.006	.061	.358

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.016+(Z2*0.691)+(AA2*0.034)+(AB2*0.255)+(AC2*0.038)+(AD2*-0.196)+(AE2*0.407)+(AH2*-0.011)+(AI2*0.165)+(AJ2*0.087)+(AK2*0.209)+(E2*0.021)+(F2*0.180)))

P(Y=2) =(1/(1+EXP(-6.005+(Z2*0.691)+(AA2*0.034)+(AB2*0.255)+(AC2*0.038)+(AD2*-0.196)+(AE2*0.407)+(AH2*-0.011)+(AI2*0.165)+(AJ2*0.087)+(AK2*0.209)+(E2*0.021)+(F2*0.180))))-BB2

P(Y=3)=1-BC2-BB2

Self-care

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	4.700	.353	177.683	1	.000	4.009	5.391
	[eq5dselfcar = 2]	9.246	.680	184.924	1	.000	7.913	10.579
Location	age	.029	.005	30.862	1	.000	.018	.039
	sex	-.174	.170	1.041	1	.308	-.507	.160

dlqi1	.149	.106	1.964	1	.161	-.059	.356
dlqi2	.100	.109	.839	1	.360	-.114	.314
dlqi3	.315	.119	7.003	1	.008	.082	.549
dlqi4	.026	.100	.068	1	.794	-.169	.222
dlqi5	-.017	.133	.017	1	.897	-.278	.244
dlqi6	.023	.100	.052	1	.820	-.173	.218
dlqi7	.308	.088	12.194	1	.000	.135	.481
dlqi8	.001	.128	.000	1	.995	-.250	.251
dlqi9	.044	.104	.181	1	.670	-.160	.249
dlqi10	.439	.099	19.488	1	.000	.244	.634

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.700+(Z2*0.149)+(AA2*0.100)+(AB2*0.315)+(AC2*0.026)+(AD2*-0.017)+(AE2*0.023)+(AH2*0.308)+(AI2*0.001)+(AJ2*0.044)+(AK2*0.439)+(E2*0.029)+(F2*-0.174)))

P(Y=2) =(1/(1+EXP(-9.246+(Z2*0.149)+(AA2*0.100)+(AB2*0.315)+(AC2*0.026)+(AD2*-0.017)+(AE2*0.023)+(AH2*0.308)+(AI2*0.001)+(AJ2*0.044)+(AK2*0.439)+(E2*0.029)+(F2*-0.174))))-AV2

P(Y=3) =1-AW2-AV2

Usual Activities

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.593	.243	218.907	1	.000	3.117	4.069
	[eq5dactiv = 2]	7.473	.343	475.741	1	.000	6.801	8.144
Location	age	.027	.004	54.018	1	.000	.020	.034
	sex	.264	.125	4.479	1	.034	.020	.508
	dlqi1	.378	.075	25.290	1	.000	.231	.525
	dlqi2	-.198	.084	5.601	1	.018	-.363	-.034
	dlqi3	.492	.090	29.980	1	.000	.316	.668
	dlqi4	-.042	.078	.292	1	.589	-.194	.110
	dlqi5	.267	.100	7.185	1	.007	.072	.462
	dlqi6	.217	.079	7.620	1	.006	.063	.371
	dlqi7	.264	.069	14.654	1	.000	.129	.399
	dlqi8	-.063	.103	.374	1	.541	-.264	.138
	dlqi9	.016	.085	.035	1	.852	-.151	.183
	dlqi10	.152	.081	3.501	1	.061	-.007	.311

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.593+(Z2*0.378)+(AA2*-0.198)+(AB2*0.492)+(AC2*-0.042)+(AD2*0.267)+(AE2*0.217)+(AH2*0.264)+(AI2*-0.063)+(AJ2*0.016)+(AK2*0.152)+(E2*0.027)+(F2*0.264)))

P(Y=2) =(1/(1+EXP(-7.473+(Z2*0.378)+(AA2*-0.198)+(AB2*0.492)+(AC2*-0.042)+(AD2*0.267)+(AE2*0.217)+(AH2*0.264)+(AI2*-0.063)+(AJ2*0.016)+(AK2*0.152)+(E2*0.027)+(F2*0.264))))-AY2

P(Y=3) =1-AZ2-AY2

External validation: Split Half Cross Validation (Set Four)

$$P(Y=1)=\frac{1}{1+e^{(-a_1+b_1x_1+b_2x_2+\cdots+b_mx_m)}}$$

$$P(Y=2)=\frac{1}{1+e^{(-a_2+b_1x_1+b_2x_2+\cdots+b_mx_m)}}-P(Y=1)$$

$$P(Y=3)=1-P(Y=2)-P(Y=1)$$

Anxiety / Depression

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	1.492	.184	65.423	1	.000	1.130	1.853
	[eq5danxdep = 2]	4.878	.233	437.115	1	.000	4.421	5.335
Location	age	.004	.003	1.687	1	.194	-.002	.010
	sex	.530	.103	26.324	1	.000	.328	.733
	dlqi1	.017	.063	.072	1	.788	-.106	.140
	dlqi2	.420	.067	38.760	1	.000	.288	.552

	dlqi3	.094	.081	1.361	1	.243	-.064	.253
	dlqi4	-.183	.070	6.816	1	.009	-.321	-.046
	dlqi5	.156	.087	3.232	1	.072	-.014	.326
	dlqi6	-.081	.073	1.213	1	.271	-.225	.063
	dlqi7	.264	.063	17.520	1	.000	.141	.388
	dlqi8	.108	.090	1.431	1	.232	-.069	.285
	dlqi9	.239	.080	8.978	1	.003	.083	.396
	dlqi10	.152	.075	4.147	1	.042	.006	.298

Link function: Logit.

P(Y=1) =1/(1+EXP(-1.492+(Z2*0.017)+(AA2*0.420)+(AB2*0.094)+(AC2*-0.183)+(AD2*0.156)+(AE2*-0.081)+(AH2*0.264)+(AI2*0.108)+(AJ2*0.239)+(AK2*0.152)+(E2*0.004)+(F2*0.530)))

P(Y=2) =(1/(1+EXP(-4.878+(Z2*0.017)+(AA2*0.420)+(AB2*0.094)+(AC2*-0.183)+(AD2*0.156)+(AE2*-0.081)+(AH2*0.264)+(AI2*0.108)+(AJ2*0.239)+(AK2*0.152)+(E2*0.004)+(F2*0.530))))-BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	4.336	.268	261.177	1	.000	3.810	4.862
	[eq5dmob = 2]	9.027	.464	378.763	1	.000	8.118	9.936
Location	age	.050	.004	155.738	1	.000	.042	.058
	sex	.067	.124	.292	1	.589	-.177	.311

dlqi1	.006	.078	.006	1	.937	-.146	.158
dlqi2	.006	.085	.006	1	.939	-.160	.173
dlqi3	.186	.095	3.869	1	.049	.001	.371
dlqi4	.011	.083	.016	1	.899	-.152	.173
dlqi5	.122	.104	1.385	1	.239	-.081	.326
dlqi6	.127	.084	2.301	1	.129	-.037	.291
dlqi7	.344	.073	21.920	1	.000	.200	.487
dlqi8	-.107	.107	1.005	1	.316	-.318	.103
dlqi9	-.075	.094	.628	1	.428	-.259	.110
dlqi10	.343	.086	15.889	1	.000	.175	.512

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.336+(Z2*0.006)+(AA2*0.006)+(AB2*0.186)+(AC2*0.011)+(AD2*0.122)+(AE2*0.127)+(AH2*0.344)+(AI2*-0.107)+(AJ2*-0.075)+(AK2*0.343)+(E2*0.050)+(F2*0.067)))

P(Y=2) =(1/(1+EXP(-9.027+(Z2*0.006)+(AA2*0.006)+(AB2*0.186)+(AC2*0.011)+(AD2*0.122)+(AE2*0.127)+(AH2*0.344)+(AI2*-0.107)+(AJ2*-0.075)+(AK2*0.343)+(E2*0.050)+(F2*0.067))))-AS2

P(Y=3)=1-AT2-AS2

Pain

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.170	.190	130.167	1	.000	1.797	2.543
	[eq5dpain = 2]	6.005	.253	565.066	1	.000	5.510	6.500

Location	age	.025	.003	66.638	1	.000	.019	.031
	sex	.132	.103	1.634	1	.201	-.070	.333
	dlqi1	.680	.066	105.810	1	.000	.551	.810
	dlqi2	.034	.069	.238	1	.626	-.102	.169
	dlqi3	.179	.084	4.546	1	.033	.014	.343
	dlqi4	.067	.072	.868	1	.352	-.074	.207
	dlqi5	-.111	.089	1.544	1	.214	-.286	.064
	dlqi6	.279	.076	13.540	1	.000	.130	.428
	dlqi7	.012	.065	.034	1	.853	-.116	.140
	dlqi8	.119	.093	1.628	1	.202	-.064	.302
	dlqi9	.140	.083	2.869	1	.090	-.022	.302
	dlqi10	.269	.077	12.149	1	.000	.118	.420

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.170+(Z2*0.680)+(AA2*0.034)+(AB2*0.179)+(AC2*0.067)+(AD2*-0.111)+(AE2*0.279)+(AH2*0.012)+(AI2*0.119)+(AJ2*0.140)+(AK2*0.269)+(E2*0.025)+(F2*0.132)))

P(Y=2) =(1/(1+EXP(-6.005+(Z2*0.680)+(AA2*0.034)+(AB2*0.179)+(AC2*0.067)+(AD2*-0.111)+(AE2*0.279)+(AH2*0.012)+(AI2*0.119)+(AJ2*0.140)+(AK2*0.269)+(E2*0.025)+(F2*0.132))))-BB2

P(Y=3)=1-BC2-BB2

Self-care

Parameter Estimates

	Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound

Threshold	[eq5dselfcar = 1]	4.834	.353	187.256	1	.000	4.142	5.526
	[eq5dselfcar = 2]	9.464	.683	192.179	1	.000	8.126	10.802
Location	age	.031	.005	37.573	1	.000	.021	.041
	sex	-.204	.166	1.514	1	.219	-.530	.121
	dlqi1	.226	.101	5.012	1	.025	.028	.425
	dlqi2	.126	.106	1.400	1	.237	-.082	.334
	dlqi3	.165	.114	2.094	1	.148	-.059	.389
	dlqi4	.143	.098	2.121	1	.145	-.050	.336
	dlqi5	-.009	.125	.005	1	.945	-.254	.237
	dlqi6	.025	.097	.066	1	.798	-.166	.216
	dlqi7	.376	.085	19.642	1	.000	.210	.543
	dlqi8	-.014	.124	.013	1	.908	-.257	.228
	dlqi9	-7.042E-5	.106	.000	1	.999	-.209	.209
	dlqi10	.371	.099	14.163	1	.000	.178	.565

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.834+(Z2*0.226)+(AA2*0.126)+(AB2*0.165)+(AC2*0.143)+(AD2*-0.009)+(AE2*0.025)+(AH2*0.376)+(AI2*-0.014)+(AJ2*-0.00007042)+(AK2*0.371)+(E2*0.031)+(F2*-0.204)))

P(Y=2) =(1/(1+EXP(-9.464+(Z2*0.226)+(AA2*0.126)+(AB2*0.165)+(AC2*0.143)+(AD2*-0.009)+(AE2*0.025)+(AH2*0.376)+(AI2*-0.014)+(AJ2*-0.00007042)+(AK2*0.371)+(E2*0.031)+(F2*-0.204))))-AV2

P(Y=3) =1-AW2-AV2

Usual Activities

Parameter Estimates

	Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval

							95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.305	.241	188.290	1	.000	2.833	3.777
	[eq5dactiv = 2]	7.271	.351	429.388	1	.000	6.584	7.959
Location	age	.024	.004	44.266	1	.000	.017	.031
	sex	.176	.123	2.048	1	.152	-.065	.416
	dlqi1	.196	.074	7.016	1	.008	.051	.342
	dlqi2	-.116	.083	1.975	1	.160	-.278	.046
	dlqi3	.319	.089	13.005	1	.000	.146	.493
	dlqi4	.005	.079	.003	1	.953	-.150	.159
	dlqi5	.175	.098	3.209	1	.073	-.016	.366
	dlqi6	.173	.078	4.856	1	.028	.019	.327
	dlqi7	.330	.068	23.274	1	.000	.196	.464
	dlqi8	-.100	.101	.977	1	.323	-.297	.098
	dlqi9	.139	.087	2.558	1	.110	-.031	.309
	dlqi10	.300	.081	13.660	1	.000	.141	.459

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.305+(Z2*0.196)+(AA2*-0.116)+(AB2*0.319)+(AC2*0.005)+(AD2*0.175)+(AE2*0.173)+(AH2*0.330)+(AI2*-0.100)+(AJ2*0.139)+(AK2*0.300)+(E2*0.024)+(F2*0.176)))

P(Y=2) =(1/(1+EXP(-7.271+(Z2*0.196)+(AA2*-0.116)+(AB2*0.319)+(AC2*0.005)+(AD2*0.175)+(AE2*0.173)+(AH2*0.330)+(AI2*-0.100)+(AJ2*0.139)+(AK2*0.300)+(E2*0.024)+(F2*0.176))))-AY2

P(Y=3) =1-AZ2-AY2

External validation: Split Half Cross Validation (Set Five)

Anxiety / Depression

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	1.387	.179	59.830	1	.000	1.035	1.738
	[eq5danxdep = 2]	4.595	.223	424.408	1	.000	4.158	5.032
Location	age	.002	.003	.505	1	.477	-.004	.008
	sex	.384	.103	13.953	1	.000	.182	.585
	dlqi1	.022	.062	.122	1	.727	-.100	.143
	dlqi2	.378	.068	30.812	1	.000	.245	.512
	dlqi3	.036	.078	.217	1	.642	-.116	.189
	dlqi4	-.037	.067	.306	1	.580	-.168	.094
	dlqi5	.340	.086	15.594	1	.000	.171	.508
	dlqi6	-.062	.072	.758	1	.384	-.203	.078
	dlqi7	.171	.062	7.502	1	.006	.049	.293
	dlqi8	.010	.090	.012	1	.912	-.167	.187
	dlqi9	.202	.076	7.104	1	.008	.053	.350
	dlqi10	.137	.072	3.652	1	.056	-.004	.278

Link function: Logit.

P(Y=1) =1/(1+EXP(-1.387+(Z2*0.022)+(AA2*0.378)+(AB2*0.036)+(AC2*-0.037)+(AD2*0.340)+(AE2*-0.062)+(AH2*0.171)+(AI2*0.010)+(AJ2*0.202)+(AK2*0.137)+(E2*0.002)+(F2*0.384)))

P(Y=2) =(1/(1+EXP(-4.595+(Z2*0.022)+(AA2*0.378)+(AB2*0.036)+(AC2*-0.037)+(AD2*0.340)+(AE2*-0.062)+(AH2*0.171)+(AI2*0.010)+(AJ2*0.202)+(AK2*0.137)+(E2*0.002)+(F2*0.384))))-BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	4.702	.277	288.493	1	.000	4.159	5.244
	[eq5dmob = 2]	9.682	.515	353.660	1	.000	8.673	10.691
Location	age	.055	.004	179.198	1	.000	.047	.063
	sex	-.045	.127	.125	1	.724	-.295	.205
	dlqi1	.000	.078	.000	1	.999	-.152	.152
	dlqi2	.132	.088	2.257	1	.133	-.040	.303
	dlqi3	.164	.094	3.026	1	.082	-.021	.349
	dlqi4	.048	.081	.348	1	.555	-.111	.207
	dlqi5	.231	.108	4.567	1	.033	.019	.442
	dlqi6	.172	.083	4.266	1	.039	.009	.335
	dlqi7	.141	.077	3.389	1	.066	-.009	.291
	dlqi8	-.004	.109	.001	1	.969	-.217	.209
	dlqi9	-.228	.093	5.986	1	.014	-.410	-.045
	dlqi10	.324	.086	14.191	1	.000	.155	.492

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.702+(Z2*0.000)+(AA2*0.132)+(AB2*0.164)+(AC2*-0.048)+(AD2*0.231)+(AE2*0.172)+(AH2*0.141)+(AI2*-0.004)+(AJ2*-0.228)+(AK2*0.324)+(E2*0.055)+(F2*-0.045)))

P(Y=2) =(1/(1+EXP(-9.682+(Z2*0.000)+(AA2*0.132)+(AB2*0.164)+(AC2*-0.048)+(AD2*0.231)+(AE2*0.172)+(AH2*0.141)+(AI2*-0.004)+(AJ2*-

0.228)+(AK2*0.324)+(E2*0.055)+(F2*-0.045))))-AS2

P(Y=3)=1-AT2-AS2

Pain

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.348	.188	155.582	1	.000	1.979	2.717
	[eq5dpain = 2]	6.034	.248	590.123	1	.000	5.547	6.521
Location	age	.027	.003	79.835	1	.000	.021	.033
	sex	.211	.103	4.197	1	.040	.009	.412
	dlqi1	.664	.065	104.380	1	.000	.537	.792
	dlqi2	.146	.070	4.335	1	.037	.009	.283
	dlqi3	.137	.081	2.896	1	.089	-.021	.296
	dlqi4	.134	.069	3.757	1	.053	-.001	.269
	dlqi5	-.184	.089	4.264	1	.039	-.358	-.009
	dlqi6	.322	.075	18.517	1	.000	.175	.469
	dlqi7	-.116	.065	3.158	1	.076	-.243	.012
	dlqi8	.101	.093	1.163	1	.281	-.082	.283
	dlqi9	.152	.078	3.813	1	.051	-.001	.305
	dlqi10	.235	.074	10.059	1	.002	.090	.380

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.348+(Z2*0.664)+(AA2*0.146)+(AB2*0.137)+(AC2*0.134)+(AD2*-0.184)+(AE2*0.322)+(AH2*-0.116)+(AI2*0.101)+(AJ2*0.152)+(AK2*0.235)+(E2*0.027)+(F2*0.211)))

P(Y=2) =(1/(1+EXP(-6.034+(Z2*0.664)+(AA2*0.146)+(AB2*0.137)+(AC2*0.134)+(AD2*-0.184)+(AE2*0.322)+(AH2*-0.116)+(AI2*0.101)+(AJ2*0.152)+(AK2*0.235)+(E2*0.027)+(F2*0.211))))-BB2

P(Y=3)=1-BC2-BB2

Self-care

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	5.185	.366	200.578	1	.000	4.467	5.902
	[eq5dselfcar = 2]	9.722	.693	196.758	1	.000	8.363	11.080
Location	age	.037	.005	48.169	1	.000	.026	.047
	sex	-.147	.171	.743	1	.389	-.481	.187
	dlqi1	.158	.102	2.423	1	.120	-.041	.358
	dlqi2	.204	.114	3.217	1	.073	-.019	.428
	dlqi3	.134	.116	1.335	1	.248	-.094	.362
	dlqi4	-.013	.099	.016	1	.898	-.207	.181
	dlqi5	.140	.133	1.100	1	.294	-.122	.402
	dlqi6	.048	.098	.239	1	.625	-.144	.239
	dlqi7	.200	.091	4.858	1	.028	.022	.377
	dlqi8	.031	.127	.059	1	.807	-.218	.279
	dlqi9	-.149	.106	1.952	1	.162	-.357	.060
	dlqi10	.553	.101	30.225	1	.000	.356	.751

Link function: Logit.

P(Y=1) =1/(1+EXP(-5.185+(Z2*0.158)+(AA2*0.204)+(AB2*0.134)+(AC2*-0.013)+(AD2*0.140)+(AE2*0.048)+(AH2*0.200)+(AI2*0.031)+(AJ2*-0.149)+(AK2*0.553)+(E2*0.037)+(F2*-0.147)))

P(Y=2) =(1/(1+EXP(-9.722+(Z2*0.158)+(AA2*0.204)+(AB2*0.134)+(AC2*-0.013)+(AD2*0.140)+(AE2*0.048)+(AH2*0.200)+(AI2*0.031)+(AJ2*-0.149)+(AK2*0.553)+(E2*0.037)+(F2*-0.147))))-AV2

P(Y=3) =1-AW2-AV2

Usual Activities

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.606	.244	218.673	1	.000	3.128	4.084
	[eq5dactiv = 2]	7.393	.341	469.685	1	.000	6.725	8.062
Location	age	.028	.004	59.109	1	.000	.021	.035
	sex	.126	.124	1.034	1	.309	-.117	.370
	dlqi1	.197	.073	7.233	1	.007	.053	.341
	dlqi2	-.040	.084	.222	1	.638	-.205	.125
	dlqi3	.318	.086	13.571	1	.000	.149	.487
	dlqi4	.103	.075	1.856	1	.173	-.045	.250
	dlqi5	.228	.098	5.404	1	.020	.036	.421
	dlqi6	.197	.077	6.574	1	.010	.046	.348
	dlqi7	.231	.070	11.012	1	.001	.095	.368
	dlqi8	-.111	.101	1.195	1	.274	-.309	.088
	dlqi9	.069	.084	.675	1	.411	-.096	.234

dlqi10	.288	.079	13.191	1	.000	.133	.443

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.606+(Z2*0.197)+(AA2*-0.040)+(AB2*0.318)+(AC2*0.103)+(AD2*0.228)+(AE2*0.197)+(AH2*0.231)+(AI2*-0.111)+(AJ2*0.069)+(AK2*0.288)+(E2*0.028)+(F2*0.126)))

P(Y=2) =(1/(1+EXP(-7.393+(Z2*0.197)+(AA2*-0.040)+(AB2*0.318)+(AC2*0.103)+(AD2*0.228)+(AE2*0.197)+(AH2*0.231)+(AI2*-0.111)+(AJ2*0.069)+(AK2*0.288)+(E2*0.028)+(F2*0.126))))-AY2

P(Y=3) =1-AZ2-AY2

External validation: Split Half Cross Validation (Set Six)

Anxiety / Depression

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	1.574	.180	76.432	1	.000	1.221	1.927
	[eq5danxdep = 2]	4.700	.224	441.781	1	.000	4.261	5.138
Location	age	.006	.003	4.400	1	.036	.000	.012
	sex	.410	.102	16.172	1	.000	.210	.609
	dlqi1	.065	.061	1.130	1	.288	-.055	.186
	dlqi2	.356	.067	28.411	1	.000	.225	.487
	dlqi3	.096	.081	1.387	1	.239	-.064	.255
	dlqi4	-.071	.070	1.011	1	.315	-.209	.067
	dlqi5	.108	.086	1.575	1	.210	-.061	.278
	dlqi6	-.105	.074	2.020	1	.155	-.249	.040

	dlqi7	.241	.062	14.816	1	.000	.118	.363
	dlqi8	.119	.089	1.791	1	.181	-.055	.294
	dlqi9	.217	.078	7.647	1	.006	.063	.371
	dlqi10	.214	.075	8.213	1	.004	.068	.360

Link function: Logit.

P(Y=1) =1/(1+EXP(-1.574+(Z2*0.065)+(AA2*0.356)+(AB2*0.096)+(AC2*-0.071)+(AD2*0.108)+(AE2*-0.105)+(AH2*0.241)+(AI2*0.119)+(AJ2*0.217)+(AK2*0.214)+(E2*0.006)+(F2*0.410)))

P(Y=2) =(1/(1+EXP(-4.700+(Z2*0.065)+(AA2*0.356)+(AB2*0.096)+(AC2*-0.071)+(AD2*0.108)+(AE2*-0.105)+(AH2*0.241)+(AI2*0.119)+(AJ2*0.217)+(AK2*0.214)+(E2*0.006)+(F2*0.410))))-BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	4.723	.275	294.632	1	.000	4.184	5.262
	[eq5dmob = 2]	10.034	.586	293.102	1	.000	8.885	11.182
Location	age	.054	.004	174.899	1	.000	.046	.062
	sex	.165	.127	1.706	1	.191	-.083	.413
	dlqi1	.134	.077	3.024	1	.082	-.017	.285
	dlqi2	-.024	.089	.070	1	.791	-.198	.150
	dlqi3	.002	.098	.000	1	.986	-.191	.195

dlqi4	.235	.085	7.730	1	.005	.069	.401
dlqi5	.167	.106	2.501	1	.114	-.040	.375
dlqi6	.103	.086	1.430	1	.232	-.066	.273
dlqi7	.189	.076	6.254	1	.012	.041	.338
dlqi8	.070	.109	.407	1	.523	-.144	.283
dlqi9	-.103	.096	1.136	1	.286	-.291	.086
dlqi10	.202	.089	5.166	1	.023	.028	.377

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.723+(Z2*0.134)+(AA2*-0.024)+(AB2*0.002)+(AC2*0.235)+(AD2*0.167)+(AE2*0.103)+(AH2*0.189)+(AI2*0.070)+(AJ2*-0.103)+(AK2*0.202)+(E2*0.054)+(F2*0.165)))

P(Y=2) =(1/(1+EXP(-10.034+(Z2*0.134)+(AA2*-0.024)+(AB2*0.002)+(AC2*0.235)+(AD2*0.167)+(AE2*0.103)+(AH2*0.189)+(AI2*0.070)+(AJ2*-0.103)+(AK2*0.202)+(E2*0.054)+(F2*0.165))))-AS2

P(Y=3)=1-AT2-AS2

Pain

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.398	.189	160.448	1	.000	2.027	2.769
	[eq5dpain = 2]	6.138	.252	592.377	1	.000	5.644	6.632
Location	age	.028	.003	85.881	1	.000	.022	.034
	sex	.171	.103	2.762	1	.097	-.031	.373
	dlqi1	.682	.065	108.482	1	.000	.553	.810
	dlqi2	-.014	.070	.041	1	.840	-.151	.123
	dlqi3	.133	.085	2.481	1	.115	-.033	.300
	dlqi4	.178	.073	5.865	1	.015	.034	.322
	dlqi5	-.049	.090	.295	1	.587	-.226	.128
	dlqi6	.208	.077	7.395	1	.007	.058	.358
	dlqi7	-.074	.065	1.264	1	.261	-.202	.055
	dlqi8	.159	.093	2.924	1	.087	-.023	.342
	dlqi9	.193	.082	5.560	1	.018	.033	.354
	dlqi10	.276	.078	12.507	1	.000	.123	.429

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.398+(Z2*0.682)+(AA2*-0.014)+(AB2*0.133)+(AC2*0.178)+(AD2*-0.049)+(AE2*0.208)+(AH2*-0.074)+(AI2*0.159)+(AJ2*0.193)+(AK2*0.276)+(E2*0.028)+(F2*0.171)))

P(Y=2) =(1/(1+EXP(-6.138+(Z2*0.682)+(AA2*-0.014)+(AB2*0.133)+(AC2*0.178)+(AD2*-0.049)+(AE2*0.208)+(AH2*-0.074)+(AI2*0.159)+(AJ2*0.193)+(AK2*0.276)+(E2*0.028)+(F2*0.171))))-BB2

P(Y=3) =1-BC2-BB2

Self-care

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	5.045	.363	193.393	1	.000	4.334	5.756
	[eq5dselfcar = 2]	9.013	.584	238.315	1	.000	7.868	10.157
Location	age	.037	.005	48.399	1	.000	.027	.047
	sex	-.250	.171	2.130	1	.144	-.586	.086
	dlqi1	.202	.104	3.801	1	.051	-.001	.406
	dlqi2	-.004	.117	.001	1	.970	-.234	.225
	dlqi3	.235	.122	3.683	1	.055	-.005	.474
	dlqi4	.082	.107	.584	1	.445	-.128	.292
	dlqi5	.147	.136	1.170	1	.279	-.119	.413
	dlqi6	.015	.104	.020	1	.888	-.189	.218
	dlqi7	.167	.091	3.379	1	.066	-.011	.345
	dlqi8	-.029	.131	.047	1	.828	-.286	.229
	dlqi9	-.059	.113	.272	1	.602	-.281	.163
	dlqi10	.519	.105	24.613	1	.000	.314	.724

Link function: Logit.

P(Y=1) =1/(1+EXP(-5.045+(Z2*0.202)+(AA2*-0.004)+(AB2*0.235)+(AC2*0.082)+(AD2*0.147)+(AE2*0.015)+(AH2*0.167)+(AI2*-0.029)+(AJ2*-0.059)+(AK2*0.519)+(E2*0.037)+(F2*-0.250)))

P(Y=2) =(1/(1+EXP(-9.013 +(Z2*0.202)+(AA2*-0.004)+(AB2*0.235)+(AC2*0.082)+(AD2*0.147)+(AE2*0.015)+(AH2*0.167)+(AI2*-0.029)+(AJ2*-0.059)+(AK2*0.519)+(E2*0.037)+(F2*-0.250))))-AV2

P(Y=3) =1-AW2-AV2

Usual Activities

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.547	.243	213.713	1	.000	3.071	4.023
	[eq5dactiv = 2]	7.089	.331	457.674	1	.000	6.440	7.739
Location	age	.029	.004	60.190	1	.000	.022	.036
	sex	.002	.124	.000	1	.985	-.240	.244
	dlqi1	.159	.074	4.655	1	.031	.015	.304
	dlqi2	-.036	.084	.180	1	.671	-.201	.129
	dlqi3	.204	.091	5.049	1	.025	.026	.382
	dlqi4	.163	.079	4.199	1	.040	.007	.318
	dlqi5	.179	.099	3.296	1	.069	-.014	.373
	dlqi6	.192	.079	5.884	1	.015	.037	.348
	dlqi7	.315	.069	20.608	1	.000	.179	.451
	dlqi8	-.097	.101	.907	1	.341	-.296	.102
	dlqi9	.118	.087	1.827	1	.177	-.053	.289
	dlqi10	.256	.082	9.659	1	.002	.094	.417

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.547+(Z2*0.159)+(AA2*-0.036)+(AB2*0.204)+(AC2*0.163)+(AD2*0.179)+(AE2*0.192)+(AH2*0.315)+(AI2*-0.097)+(AJ2*0.118)+(AK2*0.256)+(E2*0.029)+(F2*0.002)))

P(Y=2) =(1/(1+EXP(-7.089+(Z2*0.159)+(AA2*-0.036)+(AB2*0.204)+(AC2*0.163)+(AD2*0.179)+(AE2*0.192)+(AH2*0.315)+(AI2*-0.097)+(AJ2*0.118)+(AK2*0.256)+(E2*0.029)+(F2*0.002))))-AY2

P(Y=3) =1-AZ2-AY2

External validation: Split Half Cross Validation (Set Seven)

Anxiety / Depression

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	1.404	.180	60.878	1	.000	1.051	1.756
	[eq5danxdep = 2]	4.587	.224	420.659	1	.000	4.149	5.026
Location	age	.002	.003	.279	1	.598	-.004	.007
	sex	.346	.103	11.240	1	.001	.144	.549
	dlqi1	.094	.061	2.335	1	.126	-.026	.214
	dlqi2	.399	.067	35.431	1	.000	.268	.530
	dlqi3	.064	.079	.665	1	.415	-.090	.219
	dlqi4	-.050	.068	.536	1	.464	-.184	.084
	dlqi5	.182	.084	4.749	1	.029	.018	.346

	dlqi6	-.089	.071	1.558	1	.212	-.228	.051
	dlqi7	.183	.061	8.874	1	.003	.063	.303
	dlqi8	.007	.092	.006	1	.936	-.173	.187
	dlqi9	.267	.076	12.274	1	.000	.118	.416
	dlqi10	.172	.072	5.689	1	.017	.031	.314

Link function: Logit.

P(Y=1) =1/(1+EXP(-1.404+(Z2*0.094)+(AA2*0.399)+(AB2*0.064)+(AC2*-0.050)+(AD2*0.182)+(AE2*-0.089)+(AH2*0.183)+(AI2*0.007)+(AJ2*0.267)+(AK2*0.172)+(E2*0.002)+(F2*0.346)))

P(Y=2) =(1/(1+EXP(-4.587+(Z2*0.094)+(AA2*0.399)+(AB2*0.064)+(AC2*-0.050)+(AD2*0.182)+(AE2*-0.089)+(AH2*0.183)+(AI2*0.007)+(AJ2*0.267)+(AK2*0.172)+(E2*0.002)+(F2*0.346))))-BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	4.723	.275	294.632	1	.000	4.184	5.262
	[eq5dmob = 2]	10.034	.586	293.102	1	.000	8.885	11.182
Location	age	.054	.004	174.899	1	.000	.046	.062
	sex	.165	.127	1.706	1	.191	-.083	.413
	dlqi1	.134	.077	3.024	1	.082	-.017	.285
	dlqi2	-.024	.089	.070	1	.791	-.198	.150

dlqi3	.002	.098	.000	1	.986	-.191	.195
dlqi4	.235	.085	7.730	1	.005	.069	.401
dlqi5	.167	.106	2.501	1	.114	-.040	.375
dlqi6	.103	.086	1.430	1	.232	-.066	.273
dlqi7	.189	.076	6.254	1	.012	.041	.338
dlqi8	.070	.109	.407	1	.523	-.144	.283
dlqi9	-.103	.096	1.136	1	.286	-.291	.086
dlqi10	.202	.089	5.166	1	.023	.028	.377

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.723+(Z2*0.134)+(AA2*-0.024)+(AB2*0.002)+(AC2*0.235)+(AD2*0.167)+(AE2*0.103)+(AH2*0.189)+(AI2*0.070)+(AJ2*-0.103)+(AK2*0.202)+(E2*0.054)+(F2*0.165)))

P(Y=2) =(1/(1+EXP(-10.034+(Z2*0.134)+(AA2*-0.024)+(AB2*0.002)+(AC2*0.235)+(AD2*0.167)+(AE2*0.103)+(AH2*0.189)+(AI2*0.070)+(AJ2*-0.103)+(AK2*0.202)+(E2*0.054)+(F2*0.165))))-AS2

P(Y=3) =1-AT2-AS2

Pain

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.008	.186	116.047	1	.000	1.643	2.373
	[eq5dpain = 2]	5.888	.250	553.714	1	.000	5.397	6.378
Location	age	.019	.003	42.835	1	.000	.014	.025
	sex	.161	.104	2.413	1	.120	-.042	.365
	dlqi1	.671	.065	106.660	1	.000	.543	.798
	dlqi2	.014	.069	.038	1	.846	-.123	.150
	dlqi3	.128	.083	2.372	1	.124	-.035	.290
	dlqi4	.054	.071	.566	1	.452	-.086	.193
	dlqi5	-.010	.088	.013	1	.909	-.182	.162
	dlqi6	.267	.075	12.692	1	.000	.120	.414
	dlqi7	-.074	.064	1.319	1	.251	-.200	.052
	dlqi8	.144	.096	2.233	1	.135	-.045	.332
	dlqi9	.104	.080	1.683	1	.194	-.053	.260
	dlqi10	.390	.076	25.980	1	.000	.240	.540

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.008+(Z2*0.671)+(AA2*0.014)+(AB2*0.128)+(AC2*0.054)+(AD2*-0.010)+(AE2*0.267)+(AH2*-0.074)+(AI2*0.144)+(AJ2*0.104)+(AK2*0.390)+(E2*0.019)+(F2*0.161)))

P(Y=2) =(1/(1+EXP(-5.888+(Z2*0.671)+(AA2*0.014)+(AB2*0.128)+(AC2*0.054)+(AD2*-0.010)+(AE2*0.267)+(AH2*-0.074)+(AI2*0.144)+(AJ2*0.104)+(AK2*0.390)+(E2*0.019)+(F2*0.161))))-BB2

P(Y=3) =1-BC2-BB2

Self-care

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	4.718	.361	170.365	1	.000	4.010	5.427
	[eq5dselfcar = 2]	8.858	.625	201.167	1	.000	7.634	10.082
Location	age	.029	.005	30.773	1	.000	.019	.039
	sex	-.116	.175	.439	1	.508	-.460	.228
	dlqi1	.173	.105	2.699	1	.100	-.033	.379
	dlqi2	-.089	.117	.578	1	.447	-.319	.140
	dlqi3	.208	.122	2.900	1	.089	-.031	.448
	dlqi4	.000	.105	.000	1	.997	-.206	.205
	dlqi5	.294	.135	4.727	1	.030	.029	.559
	dlqi6	-.120	.103	1.362	1	.243	-.321	.081
	dlqi7	.109	.092	1.425	1	.233	-.070	.289
	dlqi8	.034	.135	.064	1	.800	-.230	.298
	dlqi9	-.062	.110	.312	1	.577	-.278	.155

	dlqi10	.674	.103	43.249	1	.000	.473	.876

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.718+(Z2*0.173)+(AA2*-0.089)+(AB2*0.208)+(AC2*0.000)+(AD2*0.294)+(AE2*-0.120)+(AH2*0.109)+(AI2*0.034)+(AJ2*-0.062)+(AK2*0.674)+(E2*0.029)+(F2*-0.116)))

P(Y=2) =(1/(1+EXP(-8.858+(Z2*0.173)+(AA2*-0.089)+(AB2*0.208)+(AC2*0.000)+(AD2*0.294)+(AE2*-0.120)+(AH2*0.109)+(AI2*0.034)+(AJ2*-0.062)+(AK2*0.674)+(E2*0.029)+(F2*-0.116))))-AV2

P(Y=3) =1-AW2-AV2

Usual Activities

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.568	.242	217.585	1	.000	3.094	4.042
	[eq5dactiv = 2]	7.211	.333	469.683	1	.000	6.559	7.864
Location	age	.025	.004	48.353	1	.000	.018	.032
	sex	.262	.125	4.433	1	.035	.018	.506

dlqi1	.309	.072	18.315	1	.000	.168	.451
dlqi2	-.134	.083	2.615	1	.106	-.297	.029
dlqi3	.339	.086	15.385	1	.000	.170	.509
dlqi4	.046	.077	.362	1	.548	-.104	.197
dlqi5	.299	.095	9.965	1	.002	.113	.485
dlqi6	.093	.076	1.472	1	.225	-.057	.243
dlqi7	.284	.068	17.532	1	.000	.151	.417
dlqi8	-.027	.102	.068	1	.794	-.226	.173
dlqi9	.052	.084	.376	1	.540	-.113	.217
dlqi10	.207	.079	6.855	1	.009	.052	.362

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.568+(Z2*0.309)+(AA2*-0.134)+(AB2*0.339)+(AC2*0.046)+(AD2*0.299)+(AE2*0.093)+(AH2*0.284)+(AI2*-0.027)+(AJ2*0.052)+(AK2*0.207)+(E2*0.025)+(F2*0.262)))

P(Y=2) =(1/(1+EXP(-7.211+(Z2*0.309)+(AA2*-0.134)+(AB2*0.339)+(AC2*0.046)+(AD2*0.299)+(AE2*0.093)+(AH2*0.284)+(AI2*-0.027)+(AJ2*0.052)+(AK2*0.207)+(E2*0.025)+(F2*0.262))))-AY2

P(Y=3) =1-AZ2-AY2

External validation: Split Half Cross Validation (Set Eight)

Anxiety / Depression

Parameter Estimates

	Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval

							Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	1.574	.180	76.432	1	.000	1.221	1.927
	[eq5danxdep = 2]	4.700	.224	441.781	1	.000	4.261	5.138
Location	age	.006	.003	4.400	1	.036	.000	.012
	sex	.410	.102	16.172	1	.000	.210	.609
	dlqi1	.065	.061	1.130	1	.288	-.055	.186
	dlqi2	.356	.067	28.411	1	.000	.225	.487
	dlqi3	.096	.081	1.387	1	.239	-.064	.255
	dlqi4	-.071	.070	1.011	1	.315	-.209	.067
	dlqi5	.108	.086	1.575	1	.210	-.061	.278
	dlqi6	-.105	.074	2.020	1	.155	-.249	.040
	dlqi7	.241	.062	14.816	1	.000	.118	.363
	dlqi8	.119	.089	1.791	1	.181	-.055	.294
	dlqi9	.217	.078	7.647	1	.006	.063	.371
	dlqi10	.214	.075	8.213	1	.004	.068	.360

Link function: Logit.

P(Y=1) =1/(1+EXP(-1.574+(Z2*0.065)+(AA2*0.356)+(AB2*0.096)+(AC2*-0.071)+(AD2*0.108)+(AE2*-0.105)+(AH2*0.241)+(AI2*0.119)+(AJ2*0.217)+(AK2*0.214)+(E2*0.006)+(F2*0.410)))

P(Y=2) =(1/(1+EXP(-4.700+(Z2*0.065)+(AA2*0.356)+(AB2*0.096)+(AC2*-0.071)+(AD2*0.108)+(AE2*-0.105)+(AH2*0.241)+(AI2*0.119)+(AJ2*0.217)+(AK2*0.214)+(E2*0.006)+(F2*0.410))))-BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	4.723	.275	294.632	1	.000	4.184	5.262
	[eq5dmob = 2]	10.034	.586	293.102	1	.000	8.885	11.182
Location	age	.054	.004	174.899	1	.000	.046	.062
	sex	.165	.127	1.706	1	.191	-.083	.413
	dlqi1	.134	.077	3.024	1	.082	-.017	.285
	dlqi2	-.024	.089	.070	1	.791	-.198	.150
	dlqi3	.002	.098	.000	1	.986	-.191	.195
	dlqi4	.235	.085	7.730	1	.005	.069	.401
	dlqi5	.167	.106	2.501	1	.114	-.040	.375
	dlqi6	.103	.086	1.430	1	.232	-.066	.273
	dlqi7	.189	.076	6.254	1	.012	.041	.338
	dlqi8	.070	.109	.407	1	.523	-.144	.283
	dlqi9	-.103	.096	1.136	1	.286	-.291	.086
	dlqi10	.202	.089	5.166	1	.023	.028	.377

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.723+(Z2*0.134)+(AA2*-0.024)+(AB2*0.002)+(AC2*0.235)+(AD2*0.167)+(AE2*0.103)+(AH2*0.189)+(AI2*0.070)+(AJ2*-0.103)+(AK2*0.202)+(E2*0.054)+(F2*0.165)))

P(Y=2) =(1/(1+EXP(-10.034+(Z2*0.134)+(AA2*-0.024)+(AB2*0.002)+(AC2*0.235)+(AD2*0.167)+(AE2*0.103)+(AH2*0.189)+(AI2*0.070)+(AJ2*-0.103)+(AK2*0.202)+(E2*0.054)+(F2*0.165))))-AS2

P(Y=3) =1-AT2-AS2

Pain

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.398	.189	160.448	1	.000	2.027	2.769
	[eq5dpain = 2]	6.138	.252	592.377	1	.000	5.644	6.632
Location	age	.028	.003	85.881	1	.000	.022	.034
	sex	.171	.103	2.762	1	.097	-.031	.373
	dlqi1	.682	.065	108.482	1	.000	.553	.810
	dlqi2	-.014	.070	.041	1	.840	-.151	.123
	dlqi3	.133	.085	2.481	1	.115	-.033	.300
	dlqi4	.178	.073	5.865	1	.015	.034	.322
	dlqi5	-.049	.090	.295	1	.587	-.226	.128
	dlqi6	.208	.077	7.395	1	.007	.058	.358

dlqi7	-.074	.065	1.264	1	.261	-.202	.055
dlqi8	.159	.093	2.924	1	.087	-.023	.342
dlqi9	.193	.082	5.560	1	.018	.033	.354
dlqi10	.276	.078	12.507	1	.000	.123	.429

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.398+(Z2*0.682)+(AA2*-0.014)+(AB2*0.133)+(AC2*0.178)+(AD2*-0.049)+(AE2*0.208)+(AH2*-0.074)+(AI2*0.159)+(AJ2*0.193)+(AK2*0.276)+(E2*0.028)+(F2*0.171)))

P(Y=2) =(1/(1+EXP(-6.138+(Z2*0.682)+(AA2*-0.014)+(AB2*0.133)+(AC2*0.178)+(AD2*-0.049)+(AE2*0.208)+(AH2*-0.074)+(AI2*0.159)+(AJ2*0.193)+(AK2*0.276)+(E2*0.028)+(F2*0.171))))-BB2

P(Y=3) =1-BC2-BB2

Self-care

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	5.045	.363	193.393	1	.000	4.334	5.756
	[eq5dselfcar = 2]	9.013	.584	238.315	1	.000	7.868	10.157
Location	age	.037	.005	48.399	1	.000	.027	.047
	sex	-.250	.171	2.130	1	.144	-.586	.086
	dlqi1	.202	.104	3.801	1	.051	-.001	.406
	dlqi2	-.004	.117	.001	1	.970	-.234	.225

	dlqi3	.235	.122	3.683	1	.055	-.005	.474
	dlqi4	.082	.107	.584	1	.445	-.128	.292
	dlqi5	.147	.136	1.170	1	.279	-.119	.413
	dlqi6	.015	.104	.020	1	.888	-.189	.218
	dlqi7	.167	.091	3.379	1	.066	-.011	.345
	dlqi8	-.029	.131	.047	1	.828	-.286	.229
	dlqi9	-.059	.113	.272	1	.602	-.281	.163
	dlqi10	.519	.105	24.613	1	.000	.314	.724

Link function: Logit.

P(Y=1) =1/(1+EXP(-5.045+(Z2*0.202)+(AA2*-0.004)+(AB2*0.235)+(AC2*0.082)+(AD2*0.147)+(AE2*0.015)+(AH2*0.167)+(AI2*-0.029)+(AJ2*-0.059)+(AK2*0.519)+(E2*0.037)+(F2*-0.250)))

P(Y=2) =(1/(1+EXP(-9.013+(Z2*0.202)+(AA2*-0.004)+(AB2*0.235)+(AC2*0.082)+(AD2*0.147)+(AE2*0.015)+(AH2*0.167)+(AI2*-0.029)+(AJ2*-0.059)+(AK2*0.519)+(E2*0.037)+(F2*-0.250))))-AV2

P(Y=3) =1-AW2-AV2

Usual Activities

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.547	.243	213.713	1	.000	3.071	4.023
	[eq5dactiv = 2]	7.089	.331	457.674	1	.000	6.440	7.739
Location	age	.029	.004	60.190	1	.000	.022	.036
	sex	.002	.124	.000	1	.985	-.240	.244

dlqi1	.159	.074	4.655	1	.031	.015	.304
dlqi2	-.036	.084	.180	1	.671	-.201	.129
dlqi3	.204	.091	5.049	1	.025	.026	.382
dlqi4	.163	.079	4.199	1	.040	.007	.318
dlqi5	.179	.099	3.296	1	.069	-.014	.373
dlqi6	.192	.079	5.884	1	.015	.037	.348
dlqi7	.315	.069	20.608	1	.000	.179	.451
dlqi8	-.097	.101	.907	1	.341	-.296	.102
dlqi9	.118	.087	1.827	1	.177	-.053	.289
dlqi10	.256	.082	9.659	1	.002	.094	.417

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.547+(Z2*0.159)+(AA2*-0.036)+(AB2*0.204)+(AC2*0.163)+(AD2*0.179)+(AE2*0.192)+(AH2*0.315)+(AI2*-0.097)+(AJ2*0.118)+(AK2*0.256)+(E2*0.029)+(F2*0.002)))

P(Y=2) =(1/(1+EXP(-7.089+(Z2*0.159)+(AA2*-0.036)+(AB2*0.204)+(AC2*0.163)+(AD2*0.179)+(AE2*0.192)+(AH2*0.315)+(AI2*-0.097)+(AJ2*0.118)+(AK2*0.256)+(E2*0.029)+(F2*0.002))))-AY2

P(Y=3) =1-AZ2-AY2

External validation: Split Half Cross Validation (Set Nine)

Anxiety / Depression

Parameter Estimates

	Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound

Threshold	[eq5danxdep = 1]	1.439	.178	65.546	1	.000	1.090	1.787
	[eq5danxdep = 2]	4.682	.225	432.369	1	.000	4.240	5.123
Location	age	.001	.003	.186	1	.666	-.005	.007
	sex	.413	.104	15.859	1	.000	.210	.617
	dlqi1	.061	.063	.954	1	.329	-.062	.185
	dlqi2	.330	.068	23.805	1	.000	.198	.463
	dlqi3	.132	.082	2.606	1	.106	-.028	.291
	dlqi4	-.025	.068	.139	1	.710	-.158	.107
	dlqi5	.253	.088	8.300	1	.004	.081	.426
	dlqi6	-.067	.074	.825	1	.364	-.211	.077
	dlqi7	.111	.062	3.180	1	.075	-.011	.232
	dlqi8	.132	.090	2.147	1	.143	-.045	.309
	dlqi9	.160	.075	4.572	1	.032	.013	.307
	dlqi10	.146	.074	3.922	1	.048	.001	.290

Link function: Logit.

P(Y=1) =1/(1+EXP(-1.439+(Z2*0.061)+(AA2*0.330)+(AB2*0.132)+(AC2*-0.025)+(AD2*0.253)+(AE2*-0.067)+(AH2*0.111)+(AI2*0.132)+(AJ2*0.160)+(AK2*0.146)+(E2*0.001)+(F2*0.413)))

P(Y=2) =(1/(1+EXP(-4.682+(Z2*0.061)+(AA2*0.330)+(AB2*0.132)+(AC2*-0.025)+(AD2*0.253)+(AE2*-0.067)+(AH2*0.111)+(AI2*0.132)+(AJ2*0.160)+(AK2*0.146)+(E2*0.001)+(F2*0.413))))-BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	4.665	.271	296.752	1	.000	4.135	5.196
	[eq5dmob = 2]	10.248	.647	250.947	1	.000	8.980	11.516
Location	age	.053	.004	171.124	1	.000	.045	.061
	sex	.029	.128	.051	1	.822	-.222	.280
	dlqi1	.178	.079	5.155	1	.023	.024	.332
	dlqi2	.010	.089	.012	1	.911	-.165	.185
	dlqi3	.245	.098	6.221	1	.013	.053	.438
	dlqi4	.133	.083	2.559	1	.110	-.030	.296
	dlqi5	.108	.109	.975	1	.323	-.106	.322
	dlqi6	.117	.086	1.844	1	.175	-.052	.286
	dlqi7	.144	.077	3.477	1	.062	-.007	.295
	dlqi8	.097	.110	.782	1	.376	-.118	.312
	dlqi9	-.108	.092	1.402	1	.236	-.288	.071
	dlqi10	.107	.088	1.493	1	.222	-.065	.279

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.665+(Z2*0.178)+(AA2*0.010)+(AB2*0.245)+(AC2*0.133)+(AD2*0.108)+(AE2*0.117)+(AH2*0.144)+(AI2*0.097)+(AJ2*-0.108)+(AK2*0.107)+(E2*0.053)+(F2*0.029)))

P(Y=2) =(1/(1+EXP(-10.248+(Z2*0.178)+(AA2*0.010)+(AB2*0.245)+(AC2*0.133)+(AD2*0.108)+(AE2*0.117)+(AH2*0.144)+(AI2*0.097)+(AJ2*-0.108)+(AK2*0.107)+(E2*0.053)+(F2*0.029))))-AS2

P(Y=3) =1-AT2-AS2

Pain

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.230	.185	144.853	1	.000	1.867	2.593
	[eq5dpain = 2]	6.100	.252	586.632	1	.000	5.607	6.594
Location	age	.025	.003	65.886	1	.000	.019	.030
	sex	.223	.104	4.604	1	.032	.019	.426
	dlqi1	.696	.066	109.926	1	.000	.566	.826
	dlqi2	-.010	.071	.022	1	.882	-.149	.128
	dlqi3	.223	.085	6.810	1	.009	.055	.390
	dlqi4	.128	.070	3.314	1	.069	-.010	.266
	dlqi5	-.136	.092	2.165	1	.141	-.317	.045
	dlqi6	.347	.078	19.960	1	.000	.195	.499
	dlqi7	-.110	.065	2.864	1	.091	-.238	.017

	dlqi8	.213	.094	5.086	1	.024	.028	.398
	dlqi9	.125	.078	2.568	1	.109	-.028	.278
	dlqi10	.211	.077	7.614	1	.006	.061	.362

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.230+(Z2*0.696)+(AA2*-0.010)+(AB2*0.223)+(AC2*0.128)+(AD2*-0.136)+(AE2*0.347)+(AH2*-0.110)+(AI2*0.213)+(AJ2*0.125)+(AK2*0.211)+(E2*0.025)+(F2*0.223)))

P(Y=2) =(1/(1+EXP(-6.100+(Z2*0.696)+(AA2*-0.010)+(AB2*0.223)+(AC2*0.128)+(AD2*-0.136)+(AE2*0.347)+(AH2*-0.110)+(AI2*0.213)+(AJ2*0.125)+(AK2*0.211)+(E2*0.025)+(F2*0.223))))-BB2

P(Y=3) =1-BC2-BB2

Self-care

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	4.912	.363	183.098	1	.000	4.201	5.624
	[eq5dselfcar = 2]	8.814	.585	226.938	1	.000	7.667	9.961
Location	age	.034	.005	39.953	1	.000	.024	.045
	sex	-.220	.177	1.539	1	.215	-.567	.127
	dlqi1	.137	.109	1.583	1	.208	-.076	.351
	dlqi2	-.073	.122	.355	1	.551	-.311	.166
	dlqi3	.416	.128	10.538	1	.001	.165	.668
	dlqi4	-.057	.109	.271	1	.603	-.270	.157
	dlqi5	.208	.148	1.986	1	.159	-.082	.498

dlqi6	-.015	.108	.020	1	.888	-.228	.197
dlqi7	.068	.096	.504	1	.478	-.120	.256
dlqi8	-.059	.137	.186	1	.666	-.327	.209
dlqi9	.040	.109	.137	1	.711	-.173	.254
dlqi10	.605	.106	32.684	1	.000	.398	.812

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.912+(Z2*0.137)+(AA2*-0.073)+(AB2*0.416)+(AC2*-0.057)+(AD2*0.208)+(AE2*-0.015)+(AH2*0.068)+(AI2*-0.059)+(AJ2*0.040)+(AK2*0.605)+(E2*0.034)+(F2*-0.220)))

P(Y=2) =(1/(1+EXP(-8.814+(Z2*0.137)+(AA2*-0.073)+(AB2*0.416)+(AC2*-0.057)+(AD2*0.208)+(AE2*-0.015)+(AH2*0.068)+(AI2*-0.059)+(AJ2*0.040)+(AK2*0.605)+(E2*0.034)+(F2*-0.220))))-AV2

P(Y=3) =1-AW2-AV2

Usual Activities

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.776	.244	239.349	1	.000	3.298	4.255
	[eq5dactiv = 2]	7.262	.327	492.384	1	.000	6.621	7.903
Location	age	.030	.004	67.733	1	.000	.023	.038
	sex	.088	.125	.499	1	.480	-.157	.334
	dlqi1	.351	.075	21.907	1	.000	.204	.498
	dlqi2	-.127	.086	2.220	1	.136	-.295	.040
	dlqi3	.395	.091	18.766	1	.000	.216	.574

dlqi4	.101	.078	1.686	1	.194	-.051	.254
dlqi5	.242	.101	5.792	1	.016	.045	.440
dlqi6	.263	.079	10.971	1	.001	.107	.418
dlqi7	.228	.070	10.566	1	.001	.090	.365
dlqi8	-.055	.102	.291	1	.589	-.256	.145
dlqi9	.007	.084	.007	1	.934	-.158	.172
dlqi10	.111	.082	1.826	1	.177	-.050	.272

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.776+(Z2*0.351)+(AA2*-0.127)+(AB2*0.395)+(AC2*0.101)+(AD2*0.242)+(AE2*0.263)+(AH2*0.228)+(AI2*-0.055)+(AJ2*0.007)+(AK2*0.111)+(E2*0.030)+(F2*0.088)))

P(Y=2) =(1/(1+EXP(-7.262+(Z2*0.351)+(AA2*-0.127)+(AB2*0.395)+(AC2*0.101)+(AD2*0.242)+(AE2*0.263)+(AH2*0.228)+(AI2*-0.055)+(AJ2*0.007)+(AK2*0.111)+(E2*0.030)+(F2*0.088))))-AY2

P(Y=3) =1-AZ2-AY2

External validation: Split Half Cross Validation (Set Ten)

Anxiety / Depression

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	1.526	.183	69.881	1	.000	1.168	1.883
	[eq5danxdep = 2]	4.972	.236	442.786	1	.000	4.509	5.435
Location	age	.003	.003	1.066	1	.302	-.003	.009

sex	.526	.105	25.086	1	.000	.320	.732
dlqi1	.046	.064	.529	1	.467	-.079	.171
dlqi2	.381	.067	32.218	1	.000	.249	.513
dlqi3	.198	.085	5.430	1	.020	.031	.364
dlqi4	-.175	.071	6.063	1	.014	-.314	-.036
dlqi5	.053	.089	.357	1	.550	-.121	.228
dlqi6	-.075	.075	1.004	1	.316	-.223	.072
dlqi7	.193	.063	9.453	1	.002	.070	.316
dlqi8	.230	.091	6.471	1	.011	.053	.408
dlqi9	.193	.079	5.961	1	.015	.038	.348
dlqi10	.182	.076	5.698	1	.017	.033	.332

Link function: Logit.

P(Y=1) =1/(1+EXP(-1.526+(Z2*0.046)+(AA2*0.381)+(AB2*0.198)+(AC2*-0.175)+(AD2*0.053)+(AE2*-0.075)+(AH2*0.193)+(AI2*0.230)+(AJ2*0.193)+(AK2*0.182)+(E2*0.003)+(F2*0.526)))

P(Y=2) =(1/(1+EXP(-4.972+(Z2*0.046)+(AA2*0.381)+(AB2*0.198)+(AC2*-0.175)+(AD2*0.053)+(AE2*-0.075)+(AH2*0.193)+(AI2*0.230)+(AJ2*0.193)+(AK2*0.182)+(E2*0.003)+(F2*0.526))))-BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	4.355	.264	271.662	1	.000	3.837	4.873

	[eq5dmob = 2]	9.447	.534	312.638	1	.000	8.400	10.494
Location	age	.048	.004	150.566	1	.000	.041	.056
	sex	.125	.126	.982	1	.322	-.122	.373
	dlqi1	.175	.078	5.028	1	.025	.022	.329
	dlqi2	-.116	.087	1.755	1	.185	-.287	.055
	dlqi3	.262	.099	6.966	1	.008	.067	.457
	dlqi4	.111	.085	1.703	1	.192	-.056	.277
	dlqi5	.001	.106	.000	1	.992	-.206	.209
	dlqi6	.056	.087	.407	1	.523	-.115	.227
	dlqi7	.355	.074	23.151	1	.000	.210	.500
	dlqi8	-.030	.108	.076	1	.782	-.242	.182
	dlqi9	.035	.092	.148	1	.700	-.145	.216
	dlqi10	.149	.088	2.903	1	.088	-.022	.321

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.355+(Z2*0.175)+(AA2*-0.116)+(AB2*0.262)+(AC2*0.111)+(AD2*0.001)+(AE2*0.056)+(AH2*0.355)+(AI2*-0.030)+(AJ2*0.035)+(AK2*0.149)+(E2*0.048)+(F2*0.125)))

P(Y=2) =(1/(1+EXP(-9.447+(Z2*0.175)+(AA2*-0.116)+(AB2*0.262)+(AC2*0.111)+(AD2*0.001)+(AE2*0.056)+(AH2*0.355)+(AI2*-0.030)+(AJ2*0.035)+(AK2*0.149)+(E2*0.048)+(F2*0.125))))-AS2

P(Y=3) =1-AT2-AS2

Pain

Parameter Estimates

	Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval

							95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.051	.188	119.311	1	.000	1.683	2.419
	[eq5dpain = 2]	6.118	.259	559.986	1	.000	5.611	6.625
Location	age	.022	.003	53.365	1	.000	.016	.028
	sex	.146	.105	1.934	1	.164	-.060	.351
	dlqi1	.704	.067	109.071	1	.000	.572	.836
	dlqi2	-.122	.070	3.014	1	.083	-.259	.016
	dlqi3	.281	.089	9.985	1	.002	.107	.456
	dlqi4	.055	.073	.572	1	.450	-.088	.199
	dlqi5	-.060	.093	.411	1	.521	-.242	.123
	dlqi6	.307	.079	15.167	1	.000	.152	.461
	dlqi7	.017	.065	.069	1	.792	-.111	.145
	dlqi8	.235	.095	6.105	1	.013	.049	.421
	dlqi9	.091	.082	1.219	1	.270	-.071	.253
	dlqi10	.266	.080	10.982	1	.001	.109	.423

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.051+(Z2*0.704)+(AA2*-0.122)+(AB2*0.281)+(AC2*0.055)+(AD2*-0.060)+(AE2*0.307)+(AH2*0.017)+(AI2*0.235)+(AJ2*0.091)+(AK2*0.266)+(E2*0.022)+(F2*0.146)))

P(Y=2) =(1/(1+EXP(-6.118+(Z2*0.704)+(AA2*-0.122)+(AB2*0.281)+(AC2*0.055)+(AD2*-0.060)+(AE2*0.307)+(AH2*0.017)+(AI2*0.235)+(AJ2*0.091)+(AK2*0.266)+(E2*0.022)+(F2*0.146))))-BB2

P(Y=3) =1-BC2-BB2

Self-care

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	4.565	.350	170.277	1	.000	3.880	5.251
	[eq5dselfcar = 2]	8.569	.574	222.515	1	.000	7.443	9.695
Location	age	.029	.005	30.466	1	.000	.019	.039
	sex	-.312	.173	3.236	1	.072	-.652	.028
	dlqi1	.211	.107	3.931	1	.047	.002	.420
	dlqi2	-.116	.113	1.052	1	.305	-.338	.106
	dlqi3	.448	.126	12.677	1	.000	.201	.694
	dlqi4	.140	.107	1.693	1	.193	-.071	.350
	dlqi5	-.023	.137	.028	1	.867	-.291	.245
	dlqi6	-.051	.106	.229	1	.633	-.258	.157
	dlqi7	.266	.089	8.829	1	.003	.090	.441
	dlqi8	-.064	.132	.236	1	.627	-.323	.195
	dlqi9	.150	.108	1.915	1	.166	-.062	.362
	dlqi10	.405	.104	15.308	1	.000	.202	.608

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.565+(Z2*0.211)+(AA2*-0.116)+(AB2*0.448)+(AC2*0.140)+(AD2*-0.023)+(AE2*-0.051)+(AH2*0.266)+(AI2*-0.064)+(AJ2*0.150)+(AK2*0.405)+(E2*0.029)+(F2*-0.312)))

P(Y=2) =(1/(1+EXP(-8.569+(Z2*0.211)+(AA2*-0.116)+(AB2*0.448)+(AC2*0.140)+(AD2*-0.023)+(AE2*-0.051)+(AH2*0.266)+(AI2*-0.064)+(AJ2*0.150)+(AK2*0.405)+(E2*0.029)+(F2*-0.312))))-AV2

P(Y=3) =1-AW2-AV2

Usual Activities

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.486	.240	210.232	1	.000	3.015	3.957
	[eq5dactiv = 2]	7.095	.330	460.840	1	.000	6.447	7.743
Location	age	.026	.004	52.543	1	.000	.019	.034
	sex	.133	.125	1.148	1	.284	-.111	.378
	dlqi1	.341	.075	20.559	1	.000	.194	.488
	dlqi2	-.190	.083	5.173	1	.023	-.353	-.026
	dlqi3	.391	.093	17.586	1	.000	.208	.574
	dlqi4	.001	.081	.000	1	.994	-.158	.159
	dlqi5	.186	.100	3.490	1	.062	-.009	.381
	dlqi6	.238	.080	8.779	1	.003	.081	.396
	dlqi7	.328	.069	22.865	1	.000	.194	.463
	dlqi8	-.049	.102	.235	1	.628	-.249	.150
	dlqi9	.058	.086	.457	1	.499	-.111	.228
	dlqi10	.130	.083	2.428	1	.119	-.034	.294

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.486+(Z2*0.341)+(AA2*-0.190)+(AB2*0.391)+(AC2*0.001)+(AD2*0.186)+(AE2*0.238)+(AH2*0.328)+(AI2*-0.049)+(AJ2*0.058)+(AK2*0.130)+(E2*0.026)+(F2*0.133)))

P(Y=2) =(1/(1+EXP(-7.095+(Z2*0.341)+(AA2*-0.190)+(AB2*0.391)+(AC2*0.001)+(AD2*0.186)+(AE2*0.238)+(AH2*0.328)+(AI2*-0.049)+(AJ2*0.058)+(AK2*0.130)+(E2*0.026)+(F2*0.133))))-AY2

P(Y=3) =1-AZ2-AY2

Appendix XXVII: Guide to using the fitted Ordinal Logistic Regression model to predict utility values from predicted EQ-5D domain scores derived from DLQI item scores

The purpose of this appendix is to provide a practical guide to other researchers to use the model described in this paper. It is assumed that the researcher has a data set of DLQI values (each with 10 individual question scores), as well as age and sex data, from a population of subjects, and that the researcher wishes to create predicted utility values from predicted EQ-5D individual domain scores for that population.

The coefficients that are used in the fitted model are given in Table 3. Consider initially the EQ-5D domain 'Mobility' (column 2 of Table 3 gives the coefficients).

Step 1

All ten DLQI items, the patient's age (years) and the patient's sex (male = 0, female = 1) are contained in each of the 5 models. For mobility, for example, for each subject we first calculate the latent variable (from Table 3, column 2):

$$b_1x_1 + b_2x_2 + \cdots + b_mx_m$$

(where the *b's* are the coefficients and the *x's* are the indicator variables relating to the DLQI items, age and sex)

Suppose for this subject (male, aged 37) the observed DLQI item scores are respectively 1 (item 1), 1 (item 2), 0 (item 3), 1 (item 4), 2 (item 5), 1 (item 6), 3 (item 7), 0 (item 8), 1 (item 9) and 2 (item 10). Taking values from Table 3, the latent variable value is then:

(37 x 0.051) + (0 x 0.046) + (1 x 0.087) + (1 x 0.013) + (0 x 0.209) + (1 x 0.071) + (2 x 0.113) + (1 x 0.116) + (3 x 0.251) + (0 x -0.008) + (1 x -0.094) + (2 x 0.233) = 3.525

Step 2

The probability that this subject falls into category 1 (denoted $P(Y = 1)$) of the EQ-5D domain for 'Mobility' is:

$$P(Y = 1) = \frac{1}{1 + e^{(-(4.500)+3.525)}} = 0.726$$

Note that 4.500 here is the a_1 threshold for mobility in Table 3. The probability that this subject falls into either category 1 or 2 of the EQ-5D domain for 'Mobility' is then:

$$P(Y = 1) + P(Y = 2) = \frac{1}{1 + e^{(-(9.506)+3.525)}} = 0.997$$

Here 9.506 is the a_2 threshold for mobility and it follows by subtraction of $P(Y = 1)$ from $P(Y = 1) + P(Y = 2)$ that $P(Y = 2) = 0.271$. Finally, since the probability values for $Y = 1, Y = 2\ and\ Y = 3$, sum to 1, $P(Y = 3) = 1 - 0.997 = 0.003$

Step 3

Repeat this calculation giving $P(Y = 1), P(Y = 2)\ and\ P(Y = 3)$ for each subject and then use Monte Carlo simulation to assign an outcome for the 'Mobility' domain based on the calculated probabilities.

Step 4

Repeat for each of the five EQ-5D domains.

Step 5

With predicted scores for all five domains now obtained for all patients, cross-check with country-specific TTO value sets (available upon request from http://www.euroqol.org) to derive utility values. For larger datasets, SPSS syntaxes are also available from http://www.euroqol.org. Utility values for the entire dataset may then be averaged to provide an overall reflection of the dataset's generic health state.

An Excel spreadsheet is available from the corresponding author (Dr Faraz Ali, alifm@cardiff.ac.uk) to be used to make the calculations in **Steps 1-4**.

Appendix XXVIII: Psoriasis-only estimates

$$P(Y = 1) = \frac{1}{1 + e^{(-a_1 + b_1 x_1 + b_2 x_2 + \cdots + b_m x_m)}}$$

$$P(Y = 2) = \frac{1}{1 + e^{(-a_2 + b_1 x_1 + b_2 x_2 + \cdots + b_m x_m)}} - P(Y = 1)$$

$$P(Y = 3) = 1 - P(Y = 2) - P(Y = 1)$$

Anxiety / Depression

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	1.273	.375	11.501	1	.001	.537	2.008
	[eq5danxdep = 2]	4.318	.433	99.377	1	.000	3.469	5.167
Location	dlqi1	.157	.116	1.842	1	.175	-.070	.385
	dlqi2	.315	.130	5.932	1	.015	.062	.569
	dlqi3	.102	.147	.483	1	.487	-.186	.390
	dlqi4	.121	.125	.939	1	.333	-.124	.366
	dlqi5	.210	.170	1.524	1	.217	-.123	.543

dlqi6	.130	.126	1.055	1	.304	-.118	.377
dlqi7	.061	.121	.253	1	.615	-.176	.298
dlqi8	.284	.151	3.549	1	.060	-.011	.579
dlqi9	-.053	.128	.173	1	.678	-.305	.198
dlqi10	-.097	.124	.609	1	.435	-.341	.147
age	.003	.006	.228	1	.633	-.009	.016
sex	.317	.191	2.742	1	.098	-.058	.691

Link function: Logit.

P(Y=1) =1/(1+EXP(-1.273+(Z2*0.157)+(AA2*0.315)+(AB2*0.102)+(AC2*0.121)+(AD2*0.210)+(AE2*0.130)+(AH2*0.061)+(AI2*0.284)+(AJ2*-0.053)+(AK2*-0.097)+(E2*0.003)+(F2*0.317)))

P(Y=2) =(1/(1+EXP(-4.318+(Z2*0.157)+(AA2*0.315)+(AB2*0.102)+(AC2*0.121)+(AD2*0.210)+(AE2*0.130)+(AH2*0.061)+(AI2*0.284)+(AJ2*-0.053)+(AK2*-0.097)+(E2*0.003)+(F2*0.317))))-BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	3.983	.504	62.351	1	.000	2.995	4.972
	[eq5dmob = 2]	8.487	.804	111.377	1	.000	6.911	10.064

Location	dlqi1	.153	.139	1.216	1	.270	-.119	.426
	dlqi2	.065	.160	.168	1	.682	-.248	.379
	dlqi3	.319	.168	3.585	1	.058	-.011	.648
	dlqi4	-.008	.149	.003	1	.959	-.300	.285
	dlqi5	.167	.202	.683	1	.409	-.229	.563
	dlqi6	.030	.143	.045	1	.832	-.250	.311
	dlqi7	.218	.140	2.422	1	.120	-.056	.492
	dlqi8	.236	.173	1.864	1	.172	-.103	.575
	dlqi9	-.373	.153	5.982	1	.014	-.673	-.074
	dlqi10	-.037	.147	.065	1	.799	-.325	.250
	age	.046	.008	33.205	1	.000	.030	.061
	sex	-.182	.229	.635	1	.425	-.630	.266

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.983+(Z2*0.153)+(AA2*0.065)+(AB2*0.319)+(AC2*-0.008)+(AD2*0.167)+(AE2*0.030)+(AH2*0.218)+(AI2*0.236)+(AJ2*-0.373)+(AK2*-0.037)+(E2*0.046)+(F2*-0.182)))

P(Y=2) =(1/(1+EXP(-8.487+(Z2*0.153)+(AA2*0.065)+(AB2*0.319)+(AC2*-0.008)+(AD2*0.167)+(AE2*0.030)+(AH2*0.218)+(AI2*0.236)+(AJ2*-0.373)+(AK2*-0.037)+(E2*0.046)+(F2*-0.182))))-AS2

P(Y=3)=1-AT2-AS2

Pain

Parameter Estimates

	Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval

							Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.360	.401	34.556	1	.000	1.573	3.146
	[eq5dpain = 2]	6.354	.521	148.609	1	.000	5.332	7.375
Location	dlqi1	.881	.131	45.100	1	.000	.624	1.138
	dlqi2	.118	.136	.751	1	.386	-.149	.385
	dlqi3	.401	.159	6.322	1	.012	.088	.713
	dlqi4	-.086	.133	.420	1	.517	-.346	.174
	dlqi5	-.243	.181	1.797	1	.180	-.598	.112
	dlqi6	.372	.138	7.296	1	.007	.102	.642
	dlqi7	-.166	.129	1.638	1	.201	-.420	.088
	dlqi8	.134	.160	.706	1	.401	-.179	.447
	dlqi9	.255	.138	3.392	1	.066	-.016	.526
	dlqi10	.086	.131	.432	1	.511	-.171	.344
	age	.029	.007	17.767	1	.000	.015	.042
	sex	.275	.199	1.907	1	.167	-.115	.665

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.360+(Z2*0.881)+(AA2*0.118)+(AB2*0.401)+(AC2*-0.086)+(AD2*-0.243)+(AE2*0.372)+(AH2*-0.166)+(AI2*0.134)+(AJ2*0.255)+(AK2*0.086)+(E2*0.029)+(F2*0.275)))

P(Y=2) =(1/(1+EXP(-6.354+(Z2*0.881)+(AA2*0.118)+(AB2*0.401)+(AC2*-0.086)+(AD2*-0.243)+(AE2*0.372)+(AH2*-0.166)+(AI2*0.134)+(AJ2*0.255)+(AK2*0.086)+(E2*0.029)+(F2*0.275))))-BB2

P(Y=3)=1-BC2-BB2

Self-care

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	5.727	.741	59.708	1	.000	4.274	7.179
Location	dlqi1	.566	.190	8.878	1	.003	.194	.938
	dlqi2	.135	.210	.415	1	.519	-.276	.546
	dlqi3	.120	.207	.336	1	.562	-.286	.527
	dlqi4	-.003	.186	.000	1	.987	-.367	.361
	dlqi5	.291	.251	1.349	1	.245	-.200	.782
	dlqi6	-.196	.175	1.254	1	.263	-.538	.147
	dlqi7	.364	.166	4.846	1	.028	.040	.689
	dlqi8	-.123	.202	.375	1	.540	-.519	.272
	dlqi9	-.078	.175	.200	1	.655	-.422	.265
	dlqi10	.478	.182	6.908	1	.009	.122	.835
	age	.037	.011	11.888	1	.001	.016	.058
	sex	-.231	.305	.573	1	.449	-.830	.367

Link function: Logit.

P(Y=1) =1/(1+EXP(-5.727+(Z2*0.566)+(AA2*0.135)+(AB2*0.120)+(AC2*-0.003)+(AD2*0.291)+(AE2*-0.196)+(AH2*0.364)+(AI2*-0.123)+(AJ2*-0.078)+(AK2*0.478)+(E2*0.037)+(F2*-0.231)))

P(Y=2) =1-AV2

Usual Activities

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.316	.470	49.784	1	.000	2.395	4.238
	[eq5dactiv = 2]	7.256	.641	128.314	1	.000	6.001	8.512
Location	dlqi1	.338	.132	6.507	1	.011	.078	.597
	dlqi2	.025	.149	.028	1	.867	-.268	.318
	dlqi3	.250	.159	2.488	1	.115	-.061	.561
	dlqi4	-.105	.142	.550	1	.458	-.382	.172
	dlqi5	-.015	.188	.007	1	.934	-.385	.354
	dlqi6	.239	.136	3.085	1	.079	-.028	.507
	dlqi7	.362	.131	7.625	1	.006	.105	.619
	dlqi8	.211	.162	1.697	1	.193	-.107	.529
	dlqi9	-.203	.142	2.045	1	.153	-.481	.075
	dlqi10	.102	.138	.552	1	.458	-.168	.373
	age	.025	.007	10.931	1	.001	.010	.039
	sex	.355	.218	2.637	1	.104	-.073	.782

Link function: Logit.

P(Y=1) =1/(1+EXP(-3.316+(Z2*0.338)+(AA2*0.025)+(AB2*0.250)+(AC2*-0.105)+(AD2*-0.015)+(AE2*0.239)+(AH2*0.362)+(AI2*0.211)+(AJ2*-0.203)+(AK2*0.102)+(E2*0.025)+(F2*0.355)))

P(Y=2) =(1/(1+EXP(-7.256+(Z2*0.338)+(AA2*0.025)+(AB2*0.250)+(AC2*-0.105)+(AD2*-0.015)+(AE2*0.239)+(AH2*0.362)+(AI2*0.211)+(AJ2*-0.203)+(AK2*0.102)+(E2*0.025)+(F2*0.355))))-AY2

P(Y=3) =1-AZ2-AY2

Appendix XXIX: Italy-derived estimates

$$P(Y = 1) = \frac{1}{1 + e^{(-a_1 + b_1 x_1 + b_2 x_2 + \cdots + b_m x_m)}}$$

$$P(Y = 2) = \frac{1}{1 + e^{(-a_2 + b_1 x_1 + b_2 x_2 + \cdots + b_m x_m)}} - P(Y = 1)$$

$$P(Y = 3) = 1 - P(Y = 2) - P(Y = 1)$$

Anxiety / Depression

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5danxdep = 1]	2.343	.339	47.855	1	.000	1.679	3.007
	[eq5danxdep = 2]	5.517	.423	169.813	1	.000	4.688	6.347
Location	age	.022	.006	15.071	1	.000	.011	.033
	sex	.418	.188	4.966	1	.026	.050	.785
	dlqi1	.056	.124	.202	1	.653	-.187	.299
	dlqi2	.431	.140	9.551	1	.002	.158	.705
	dlqi3	.308	.153	4.065	1	.044	.009	.607

dlqi4	.026	.141	.033	1	.855	-.251	.302
dlqi5	.420	.157	7.199	1	.007	.113	.727
dlqi6	-.018	.135	.019	1	.892	-.283	.246
dlqi7	.116	.146	.628	1	.428	-.171	.403
dlqi8	.096	.154	.393	1	.530	-.205	.397
dlqi9	.164	.120	1.862	1	.172	-.071	.399
dlqi10	.003	.121	.000	1	.983	-.234	.239

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.343+(Z2*0.056)+(AA2*0.431)+(AB2*0.308)+(AC2*0.026)+(AD2*0.420)+(AE2*-0.018)+(AH2*0.116)+(AI2*0.096)+(AJ2*0.164)+(AK2*0.003)+(E2*0.022)+(F2*0.418)))

P(Y=2) =(1/(1+EXP(-5.517+(Z2*0.056)+(AA2*0.431)+(AB2*0.308)+(AC2*0.026)+(AD2*0.420)+(AE2*-0.018)+(AH2*0.116)+(AI2*0.096)+(AJ2*0.164)+(AK2*0.003)+(E2*0.022)+(F2*0.418)))) -BE2

P(Y=3) =1-BF2-BE2

Mobility

Parameter Estimates

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	[eq5dmob = 1]	4.500	.190	561.161	1	.000	4.128	4.873
	[eq5dmob = 2]	9.506	.368	667.648	1	.000	8.785	10.227

Location	dlqi1	.087	.055	2.529	1	.112	-.020	.195
	dlqi2	.013	.061	.048	1	.827	-.107	.133
	dlqi3	.209	.068	9.468	1	.002	.076	.342
	dlqi4	.071	.058	1.486	1	.223	-.043	.185
	dlqi5	.113	.075	2.283	1	.131	-.034	.260
	dlqi6	.116	.060	3.799	1	.051	-.001	.233
	dlqi7	.251	.053	22.845	1	.000	.148	.354
	dlqi8	-.008	.076	.010	1	.921	-.157	.142
	dlqi9	-.094	.065	2.097	1	.148	-.222	.033
	dlqi10	.233	.061	14.671	1	.000	.114	.353
	age	.051	.003	330.114	1	.000	.046	.057
	sex	.046	.089	.268	1	.605	-.128	.220

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.500+(Z2*0.087)+(AA2*0.013)+(AB2*0.209)+(AC2*0.071)+(AD2*0.113)+(AE2*0.116)+(AH2*0.251)+(AI2*-0.008)+(AJ2*-0.094)+(AK2*0.233)+(E2*0.051)+(F2*0.046)))

P(Y=2) =(1/(1+EXP(-9.506+(Z2*0.087)+(AA2*0.013)+(AB2*0.209)+(AC2*0.071)+(AD2*0.113)+(AE2*0.116)+(AH2*0.251)+(AI2*-0.008)+(AJ2*-0.094)+(AK2*0.233)+(E2*0.051)+(F2*0.046))))-AS2

P(Y=3) =1-AT2-AS2

Pain

Parameter Estimates

	Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval

							Lower Bound	Upper Bound
Threshold	[eq5dpain = 1]	2.165	.345	39.466	1	.000	1.490	2.840
	[eq5dpain = 2]	6.401	.477	179.949	1	.000	5.466	7.337
Location	age	.024	.006	16.735	1	.000	.013	.036
	sex	-.141	.195	.523	1	.470	-.523	.241
	dlqi1	.845	.138	37.549	1	.000	.575	1.116
	dlqi2	.247	.147	2.822	1	.093	-.041	.535
	dlqi3	.480	.165	8.441	1	.004	.156	.804
	dlqi4	.083	.150	.311	1	.577	-.210	.377
	dlqi5	-.154	.166	.867	1	.352	-.479	.170
	dlqi6	.140	.145	.936	1	.333	-.144	.424
	dlqi7	.199	.157	1.612	1	.204	-.108	.507
	dlqi8	.253	.166	2.334	1	.127	-.072	.577
	dlqi9	-.020	.128	.024	1	.877	-.271	.232
	dlqi10	.348	.130	7.102	1	.008	.092	.603

Link function: Logit.

P(Y=1) =1/(1+EXP(-2.165+(Z2*0.845)+(AA2*0.247)+(AB2*0.480)+(AC2*0.083)+(AD2*-0.154)+(AE2*0.140)+(AH2*0.199)+(AI2*0.253)+(AJ2*-0.020)+(AK2*0.348)+(E2*0.024)+(F2*-0.141)))

P(Y=2) =(1/(1+EXP(-6.401+(Z2*0.845)+(AA2*0.247)+(AB2*0.480)+(AC2*0.083)+(AD2*-0.154)+(AE2*0.140)+(AH2*0.199)+(AI2*0.253)+(AJ2*-0.020)+(AK2*0.348)+(E2*0.024)+(F2*-0.141))))-BB2

P(Y=3) =1-BC2-BB2

Self-care

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dselfcar = 1]	4.635	.535	75.073	1	.000	3.586	5.683
	[eq5dselfcar = 2]	8.633	.828	108.732	1	.000	7.010	10.255
Location	age	.044	.008	29.807	1	.000	.028	.060
	sex	-.091	.258	.125	1	.723	-.596	.414
	dlqi1	.147	.169	.754	1	.385	-.184	.478
	dlqi2	.386	.193	3.986	1	.046	.007	.765
	dlqi3	.263	.203	1.681	1	.195	-.135	.661
	dlqi4	.024	.187	.016	1	.900	-.343	.391
	dlqi5	.133	.210	.404	1	.525	-.278	.544
	dlqi6	-.205	.177	1.330	1	.249	-.552	.143
	dlqi7	.286	.181	2.478	1	.115	-.070	.641
	dlqi8	-.059	.202	.086	1	.770	-.455	.337
	dlqi9	-.390	.164	5.635	1	.018	-.711	-.068
	dlqi10	.340	.159	4.566	1	.033	.028	.651

Link function: Logit.

P(Y=1) =1/(1+EXP(-4.635+(Z2*0.147)+(AA2*0.386)+(AB2*0.263)+(AC2*0.024)+(AD2*0.133)+(AE2*-0.205)+(AH2*0.286)+(AI2*-0.059)+(AJ2*-0.390)+(AK2*0.340)+(E2*0.044)+(F2*-0.091)))

P(Y=2) =(1/(1+EXP(-8.633+(Z2*0.147)+(AA2*0.386)+(AB2*0.263)+(AC2*0.024)+(AD2*0.133)+(AE2*-0.205)+(AH2*0.286)+(AI2*-0.059)+(AJ2*-

0.390)+(AK2*0.340)+(E2*0.044)+(F2*-0.091)))) -AV2

P(Y=3) =1-AW2-AV2

Usual Activities

Parameter Estimates

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
Threshold	[eq5dactiv = 1]	3.580	.430	69.213	1	.000	2.736	4.423
	[eq5dactiv = 2]	7.106	.594	143.051	1	.000	5.941	8.270
Location	age	.036	.007	27.737	1	.000	.022	.049
	sex	.098	.221	.198	1	.656	-.334	.531
	dlqi1	.052	.147	.125	1	.723	-.235	.339
	dlqi2	.044	.165	.072	1	.788	-.280	.368
	dlqi3	.361	.170	4.497	1	.034	.027	.695
	dlqi4	-.107	.164	.423	1	.515	-.428	.214
	dlqi5	.289	.178	2.652	1	.103	-.059	.637
	dlqi6	.132	.150	.776	1	.378	-.162	.427
	dlqi7	.241	.161	2.230	1	.135	-.075	.557
	dlqi8	-.244	.178	1.883	1	.170	-.592	.105
	dlqi9	.083	.136	.371	1	.542	-.183	.349
	dlqi10	.160	.138	1.353	1	.245	-.110	.430

Link function: Logit.

$P(Y=1)$ =1/(1+EXP(-3.580+(Z2*0.052)+(AA2*0.044)+(AB2*0.361)+(AC2*-0.107)+(AD2*0.289)+(AE2*0.132)+(AH2*0.241)+(AI2*-0.244)+(AJ2*0.083)+(AK2*0.160)+(E2*0.036)+(F2*0.098)))

$P(Y=2)$ =(1/(1+EXP(-7.106+(Z2*0.052)+(AA2*0.044)+(AB2*0.361)+(AC2*-0.107)+(AD2*0.289)+(AE2*0.132)+(AH2*0.241)+(AI2*-0.244)+(AJ2*0.083)+(AK2*0.160)+(E2*0.036)+(F2*0.098))))-AY2

P(Y=3) =1-AZ2-AY2

Appendix XXX: Permission for image use from Rendon and Schäkel (2019) publication

From: **Dr. Constanze Schelhorn | MDPI** constanze.schelhorn@mdpi.com
Subject: Re: Fwd: Permission
Date: 4 August 2020 at 10:55
To: Faraz Ali farazali@icloud.com
Cc: unai Vicario vicario@mdpi.com

Dear Faraz,

For all articles published in MDPI journals, copyright is retained by the authors. Articles are licensed under an open access Creative Commons CC BY 4.0 license, meaning that anyone may download and read the paper for free. In addition, the article may be reused and quoted provided that the original published version is cited. These conditions allow for maximum use and exposure of the work, while ensuring that the authors receive proper credit. You may reuse the Figures provided you're citing the source correctly.

Kind regards,

Constanze

On 04-Aug-20 11:14 AM, Faraz Ali wrote:

> Dear Constanze
>
> Please find the original email attached.
>
> Best wishes,
>
> Faraz
>
> Begin forwarded message:
>
> > *From:* Faraz Ali <farazali@icloud.com>
> > *Date:* 3 August 2020 at 17:07:47 BST
> > *To:* vicario@mdpi.com
> > *Subject:* *Permission*
> >
> > Dear Sir / Madam,
> >
> > I am a student at Cardiff University and I am writing to you to seek permission to reproduce the following images (details below) for inclusion within my PhD thesis on Psoriasis and Quality of Life which, once completed, will be accessible worldwide through ORCA <http://orca.cf.ac.uk/>.
> >
> > Rendon, A. and Schäkel, K. 2019. Psoriasis pathogenesis and treatment. /International journal of molecular sciences/ 20(6), p. 1475.
> >
> > Images:
> >
> >
> > Best wishes,
> > Faraz

--
Constanze Schelhorn, Ph.D.
MDPI
Barcelona Office
Av. Madrid, 95, 5º-3,08028 Barcelona, Spain
Tel. +34 93 639 7662
www.mdpi.com

Appendix XXXI: Permission for image use from Menter et al. (2008a) publication

Thank you for your order with ightsLink / Elsevier

no-reply@copyright.com <no-reply@copyright.com>
Thu 16/07/2020 22:33
To: Faraz Ali <AliFM@cardiff.ac.uk>

Header

Thank you for your order!

Dear Dr. Faraz Ali,

Thank you for placing your order through Copyright Clearance Center's RightsLink® service.

Order Summary

Licensee:	Dr. Faraz Ali
Order Date:	Jul 16, 2020
Order Number:	4870981407234
Publication:	Journal of the American Academy of Dermatology
Title:	Guidelines of care for the management of psoriasis and psoriatic arthritis Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics
Type of Use:	reuse in a thesis/dissertation
Order Total:	0.00 GBP

View or print complete details of your order and the publisher's terms and conditions.

Sincerely,

Copyright Clearance Center

Tel: +1-855-239-3415 / +1-978-646-2777
customercare@copyright.com
https://myaccount.copyright.com