Medication Adherence in Clinical Research and Associated Methodological Challenges

A thesis submitted for the degree of

Doctor of Philosophy (Ph.D.)

by

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Declaration and Statements

DECLARATION

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

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This thesis is being submitted in partial fulfillment of the requirements for the degree of PhD

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It can scarcely be denied that the supreme goal of all theory is to make the irreducible basic elements as simple and as few as possible without having to surrender the adequate representation of a single datum of experience.

— Albert Einstein, 1933 (the likely origin of the famous and aptly paraphrased maxim “Everything should be made as simple as possible, but not simpler.”)

Acknowledgements

I would like to use this section to express my gratitude to everyone who has either directly or indirectly helped me throughout my PhD. This work would not have been possible without the support of these individuals.

First and foremost, I would like to thank my supervisors, Professor Kerry Hood and Dr Daniel Farewell, for their continuous support throughout this process. While I registered as a PhD student in July 2013, I first began exploring ideas for doing a PhD with Kerry and Daniel during the latter part of 2010. We have experienced both the highs of success as well as the lows of setbacks during this time, and while ultimately the submission of my thesis is down to my own persistence, I truly appreciate their persistence with me.

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keeled over and died from hypothermia!) Her friendship is truly valued, and this section would be incomplete without it being mentioned.

Work carried out for this thesis has resulted in the submission of four papers, and publication of three (one is still under review at the time of writing). I am grateful to my co-authors for helping to shape my thinking, refine my work, and engaging me in lively discussion about some of my ideas. In addition to my supervisors, these co-authors are: Professor Christopher Butler, Dr Angela Casbard, Professor Samuel Coenen, Dr Nick Francis, Professor Herman Goossens, Dr Anthony Barney Hawthorne, Dr Lucy Brookes-Howell, Dr Chris Hurt, Professor Peter Barrett-Lee, Professor Paul Little, Mr Mark Mullee, Dr Nick Murray, Professor Christopher Probert, Ms Rachel Stenson, Dr Beth Stuart, and Professor Theo Verheij.

My wife Vicky and daughters Ava and Phoebe were a constant source of inspiration throughout my PhD. As a learning disability nurse, Vic has helped keep my focus on doing research that has practical real-world benefit. She has been very understanding of the long hours and late nights, and supportive when I've lacked headspace or had doubts. Being a dad to Ava and Phoebe is what I take most pride in, and I hope that this work can be a source of inspiration to them. It may take them a few years to understand that I'm not a proper doctor, though I'm sure in the meantime they will enjoy the endless games of doctors we play together with someone who is actually called Dr Gillespie. I need to express how lucky I am to have Vic, Ava, and Phoebe in my life, and how thankful I am for them putting up with me.

Another special mention goes to my mum. Her caring nature, courage, and strong work ethic are traits I can only aspire to. She has supported me so well and has always willed me to achieve my potential, while ensuring I remain grounded. Thank you, mum.

Finally, I would like to dedicate this work to Robert Healan and my Dad Norman; the two people who occupy most of my counterfactual thoughts. I hope they would be proud of me.

Preface

I have written this thesis as a staff candidate while working full-time in the South East Wales Trials Unit (SEWTU). My original intention was to accumulate a sufficient number of publications around the theme of medication adherence, with a specific focus on methodological challenges, and submit for a PhD by published works. However, I registered to submit via the normal thesis route, assuming I could switch pathway later down the line (thus reaping the benefits that being a student brings for as long as possible), only to find out that this was something against regulations. Thus, following my first year, I had published one paper, was well on my way to publishing another, but found myself at risk of lacking a coherent thesis. I took stock, planned thesis chapters that coherently linked the work in my planned papers, and while I continued to write papers as a priority over my thesis during my second year, I had a much better understanding of how it would all fit together.

During this whole process, I did not stray from who I was as a researcher; an applied statistician with a passion for high quality evidence using the best available research methods, and a desire to communicate directly with end users.

As an applied researcher working in a clinical trials unit, I saw (and continue to see) a lot of methods and techniques recommended out of convenience and tradition, rather than the most rigorous, cutting edge methods that could be used in a given situation. In my opinion, this is often due to time constraints – to take a technique that has had its theoretical principles documented in a technical journal and translate that into an approach that can be feasibly applied, reported, and communicated during the analysis and reporting phase of a trial can take time that an applied researcher may not have. It is my intention that this thesis, and the publications that are produced from it, will aid the applied researcher to readily adopt the findings and recommendations from this work.

Why write a thesis on the subject of medication adherence?

In short, I like to tackle problems that are both challenging and yield solutions that are of practical use. I have worked on a variety of studies during almost a decade working in SEWTU. Early on, I developed a keen interest in missing data and bias arising from nonresponse. To me, medication adherence is a missing data problem and more. Measuring adherence presents a challenge in itself – I was fortunate to work on a trial early in my career where medication adherence was measured in a variety of ways. It was the first time I really had to think about some fundamental issues around this topic – "What if participants don't take their medication as prescribed?" "What is the best way of measuring whether or not they are?" "Should several measures be used, and if so, what if they don't agree?" The consequences of poor adherence also fascinated me early on. One of the clinical areas in which I specialise is infections treated in primary care; an area within which antibiotic prescribing is rife and the consequences of antibiotic resistance are a real concern. There is a strong drive to reduce antibiotic use, particularly for self-limiting infections. However, the theoretical relationship between poor use of antibiotics and antibiotic resistance is an area that is, I believe, underappreciated. Through the dissemination of the work presented throughout this thesis, particularly through an international network of primary care infections researchers (the General Practitioners' Research in Infections Network, or GRIN), I have raised the profile of the problem of adherence to antibiotic treatment, and have engaged leading clinicians in discussion around this topic.

Being awarded with a PhD will allow me to progress onto the next stage of my career, which will focus on me developing as an independent researcher. I intend to take the work I have carried out here and apply for funding to conduct high quality research, addressing questions of importance to clinicians treating patients, policy makers deciding on the value of medication, and applied researchers looking to use the most appropriate methods to answer their questions.

- David Gillespie, Cardiff 2016

Table of Contents

List of Tables and Figures

List of Tables in Chapters 1 to 7

List of Figures in Chapters 1 to 7

Summary

Poor adherence to medication wastes resources and can lead to reduced exposure to and effectiveness of pharmacological treatments. Poor adherence to medication in clinical research can dilute treatment effects, obscuring the true benefits that medication can provide. The study of medication adherence comprises significant methodological challenges.

The aim of my thesis was to investigate several methodological challenges encountered when studying medication adherence in clinical research using data from five clinical studies.

Several methods for measuring adherence were compared using both correlation and agreement approaches. I proposed extensions to data visualisation techniques for comparing agreement. As an alternative to reporting summary measures, I explored the use of advanced modelling techniques to model adherence data collected via electronic monitors. I also moved beyond comparisons of measures and investigated approaches for predicting disagreement and calibration techniques.

I investigated various methods for modelling the determinants of adherence, considering determinants according to type of measure used, type of condition being studied, different study designs, and different conceptualisations of adherence. I explored, quantitatively, the extent to which the treating clinician influenced whether a patient adhered to their treatment.

I also established the feasibility of calculating randomisation-based efficacy estimators in randomised controlled trials with non-adherence, scrutinising the implementation of these approaches during placebo-controlled trials and non-inferiority trials involving two active treatments.

My findings emphasise the need for considering the impact of medication adherence when designing a study, rather than leaving it as an afterthought, as it would appear to be much of the time. Such considerations include selecting an appropriate mode (or modes) of medication adherence ascertainment, agreeing adherence definitions of interest, measuring variables that are likely to be associated with adherence, and, particularly for trials, determining whether it is feasible to adjust findings for non-adherence while maintaining a comparison of groups as randomised.

Glossary of Abbreviations

AACTG: Adult Aids Clinical Trials Group	**ICC:** Intracluster Correlation Coefficient
AAS: Antidepressant Adherence Scale	**ICH:** International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ADHD: Attention Deficit Hyperactivity Disorder	**IQR:** Inter-Quartile Range
AED: Anti-Epileptic Drug	**ITT:** Intention-To-Treat
AIC: Akaike's Information Criterion	**IV:** Instrumental Variable
AMSTAR: Assessing the Methodological Quality of Systematic Reviews (checklist)	**IZA:** Intravenous Zoledronic Acid
ART: Anti-Retroviral Therapy	**JAMA:** Journal of the American Medical Association
BC: Before Christ	**MARS:** Medication Adherence Rating Scale
BD: Twice daily	**MASRI:** Medication Adherence Self-Report Inventory
BMC: BioMed Central	**MEMS:** Medication Event Monitoring System

BMI: Body Mass Index	**MMAS:** Morisky Medication Adherence Scale
BMJ: British Medical Journal	**MPR:** Medication Possession Ratio
BMQ: Brief Medication Questionnaire	**NEJM:** New England Journal of Medicine
BNF: British National Formulary	**NHS:** National Health Service
BPI: Brief Pain Inventory	**NICE:** National Institute for Clinical Excellence
CACE: Complier Average Causal Effect	**OD:** Once daily
CA-LRTI: Community-Acquired Lower Respiratory Tract Infection	**OIA:** Oral Ibandronic Acid
CI: Confidence Interval	**OR:** Odds Ratio
CODA: The Colitis Once Daily Asacol study	**PP:** Per-Protocol
CONSORT: Consolidated Standards of Reporting Trials	**QALY:** Quality-Adjusted Life Year
COPD: Chronic Obstructive Pulmonary Disease	**RBEE:** Randomisation-Based Efficacy Estimator
CRF: Case Report Form	**RCT:** Randomised Controlled Trial
DAG: Directed Acyclic Graph	**SD:** Standard Deviation

DAI: Drug Attitude Inventory	**SMM:** Structural Mean Model
DDD: Defined Daily Dose	**SRE:** Skeletal Related Event
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core version	**TDS:** Three times daily
ESAC: European Surveillance of Antimicrobial Consumption Network	**UC:** Ulcerative Colitis
ESPACOMP: European Society for Patient Adherence, Compliance, and Persistence	**UK:** United Kingdom
GLMM: Generalised Linear Mixed Model	**US:** United States (of America)
GP: General Practitioner	**WHO:** World Health Organisation
GRACE: Genomics to combat Resistance against Antibiotics in Community-acquired lower respiratory tract infection in Europe	**WP:** Work Package
HIV: Human Immunodeficiency Virus	**ZICE:** The Zoledronate versus Ibandronate Comparative Evaluation
HR: Hazard Ratio	

CHAPTER 1: Background

1.1 The importance of medication adherence

The consumption of medication has long been recognised as a topic of great importance, concern, and complexity. (Osterberg and Blaschke, 2005)

It is an issue that was recognised by Hippocrates during the 4th century B.C., when he remarked "Keep a watch...on the faults of the patients, which often make them lie about the taking of things prescribed. For through not taking disagreeable drinks, purgative or other, they sometimes die."

The phenomena has even been documented in religious texts. In one of the first stories in the Old Testament, God commanded Adam and Eve not to eat from the tree of knowledge of good and evil, for if they did they would most certainly die. However, despite this warning, they still ate from the tree. Relating this to the consumption of medication, this illustrates how we (as human beings) are susceptible to making decisions that are clearly irrational – such as avoiding taking medication that we have been prescribed, even when this medicine has demonstrable therapeutic benefits.

More recently, a report published by the World Health Organization indicated that adherence (which they define as the extent to which a person's behaviour corresponds with agreed recommendations from a health care provider) to long-term therapies is around 50% in developed countries and much lower in developing countries, where health resources may be scarce, and access to health care may not be universal. (Sabaté, 2003) The report also suggested that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments", and that adherence is a multifaceted problem, with patients requiring support and not blame. These aspects demonstrate the importance that is placed on this topic and development of the field.

Poor adherence to medication can lead to reduced exposure to and effectiveness of pharmacological treatments. The often quoted observation from US surgeon general C. Everett Koop that "drugs don't work in patients who don't take them" highlights this issue succinctly. The clinical impact of poor adherence varies depending on the extent to which the medicine was not taken as recommended, the condition for which the medicine was prescribed, and the therapeutic window (or forgivingness) of the medicine.

For example, early discontinuation and non-adherence to adjuvant hormonal therapy has been associated with increased mortality in women with breast cancer. (Hershman et al., 2011) With cancer being a common and severe life threatening condition, it often comes as a shock to both the public and healthcare professionals alike that non-adherence is an issue for patients with this condition. However, as remarked at an international conference on patient adherence, compliance, and persistence by a presenter who herself lives with chronic myeloid leukaemia "This is cancer. Of course my patient is taking their medicine!" is often a misled assumption. (Pelouchova, 2015)

For patients with the human immunodeficiency virus (HIV), high levels of adherence to antiretroviral therapy (e.g. ≥95%) plays a critical role in the long-term suppression of viral load. (Paterson et al., 2000) Sub-optimal levels of adherence are associated with the development of resistance, which not only affects the therapeutic nature of treatment in the individual, but can also be transmitted to others. (Wainberg and Friedland, 1998) Non-adherence is also associated with an increased risk of the virus progressing to aids and also mortality. (Bangsberg et al., 2001)

The consequences of non-adherence to anti-epileptic drugs (AEDs) in people with epilepsy are variable. While in some individuals the impact can be to increase seizure frequency, (Cramer et al., 2002) with the effects immediate in some instances, there are individuals who do not adhere to AEDs and experience no apparent ill effects and also some who adhere perfectly but continue to have an increase in seizure frequency. (Shope et al., 1988)

Moving to more acute conditions, poor adherence to antibiotics, that are appropriately prescribed for common infections in primary care, has the potential to reduce their effectiveness (e.g. delay recovery, increase the risk of complications, recurrence, re-consultations). (Daschner and Marget, 1975) There is also the theoretical possibility that poor adherence to antibiotics could result in infecting bacteria being exposed to sub-optimal levels of treatment; creating an environment that promotes antibiotic resistance. (Vrijens and Urquhart, 2005)

While the link between poor medication adherence and clinical outcomes has been disputed, what cannot be disputed is the cost associated with poor adherence. In 2010, a report published evaluating the scale, causes, and costs of wasted medicine found that the gross annual cost of NHS primary and community care prescription medicines wastage in England was approximately £300 million per annum. (Trueman et al., 2010) Combined with the cost borne out of medication adherence-related hospital admissions, (McDonnell and Jacobs, 2002) it is evident that improper use of medication places a substantial financial burden on healthcare systems.

1.2 Medication adherence in clinical research

In clinical research, non-adherence to medication can reduce the perceived impact of treatments. For example, in a two-arm randomised placebo-controlled trial, treatment effects estimated by comparing outcomes in each of the arms using the intention-to-treat principle (the gold standard principle for comparing outcomes in randomised controlled trials) will provide a diluted estimate of the true effect of treatment in the presence of non-adherence. (Hernán and Hernández-Díaz, 2012) While this estimate will still provide useful insight into the effectiveness of treatment at a population level, it does not help the individual who might be interested in knowing the likely effects they will have, good or bad, should they take their medicine as prescribed.

Medication non-adherence during the early phase drug trials, where the goal is to demonstrate the efficacy of a therapy, has the potential to adversely impact on the drug development process,

and consequentially could mean that some medicines that truly are efficacious are not taken forward to later phases and given regulatory approval. (McCann et al., 2015)

The impact of non-adherence to treatment also impacts more than the interpretation of the statistical analysis of trial outcomes. It is common for trials to include a health economic component, usually to demonstrate that a treatment is not only effective, but is also cost effective (that is, the health expected to be gained from a treatment exceeds the health likely to be forfeited through the movement of resources of other health service activities). (Drummond et al., 2015) In the UK, the National Institute for Clinical Excellence (NICE) threshold for cost effectiveness is up to £30,000 per quality-adjusted life year (QALY), which is a measure of health that combined length and quality of life. (NICE, 2012) Non-adherence to treatments in clinical research has the potential to move a treatment from being cost-effective, and therefore recommended by NICE, to not being cost-effective and not recommended. (Brilleman et al., 2016) This has a direct impact on the care that a patient can receive in the National Health Service (NHS), and therefore demonstrates the importance of the study of medication adherence in clinical research.

Interventions aimed at improving adherence to medication is an area of clinical research in itself. There exists a plethora of interventions, based on various health and psychological models of behaviour change, that have been trialled. (Nieuwlaat et al., 2014) While some have been shown to be successful in improving adherence to medication, the majority to date have failed to demonstrate that this improvement led to a clinically important improvement in clinical outcomes.

1.3 Methodological challenges in medication adherence

The study of medication adherence comprises significant methodological challenges.

Obtaining an accurate measurement of whether an individual has taken their medication as prescribed is difficult. (Farmer, 1999) Several types of measures are commonplace in research (for example, self-report, tablet counts, blood monitoring, and electronic monitoring), but all are indirect, relying on assumptions of varying strength and plausibility. These measures also vary in the quality and wealth of data they can provide, and also the extent to which they can be subject to bias. (Norell, 1981, Cramer and Mattson, 1991, Matsui et al., 1994, Vitolins et al., 2000)

Variation in the literature regarding the quantification and conceptualisation of adherence has led to confusion, ambiguity, and inconsistent reporting. (Lehane and McCarthy, 2009) While definitions have evolved over time (e.g. from compliance to adherence, concordance, and persistence), these terms continue to be broad in scope. More recent developments have moved towards defining separate elements of adherence (i.e. initiation, implementation, and persistence) that are thought to describe the processes involved in medication taking, treating the term "adherence" as an overarching term. (Vrijens et al., 2012)

Understanding the types of patients and circumstances that heighten the risk of poor adherence to medicine can help when it comes to the development of effective interventions, but determining these is not a straightforward task. (Vermeire et al., 2001) The determinants of poor adherence to medication can be multifaceted, and not purely related to the characteristics of the individual who was prescribed the medicine. Therefore, complex statistical analysis using detailed data sources are required in order to accurately quantify these influences.

Randomised controlled trials that are subject to treatment non-adherence tend to provide adjusted estimates of treatment efficacy (the effect of taking treatment as prescribed) alongside their standard estimate based on the intention-to-treat principle. (Montori and Guyatt, 2001) However, traditional approaches to estimating treatment efficacy make implicit assumptions (for example, no unmeasured confounding) that are unlikely to be plausible in practice. (Altman, 1990) Methods of analysis that are more nuanced, and importantly that respect the random

allocation of patients, can be used, but to date have largely been restricted to technical journals and seldom used in applied clinical research. The practicalities of their implementation remain uncertain.

1.4 Aim of thesis

The aim of this thesis is to investigate various methodological challenges that are encountered when studying medication adherence in clinical research, generating new evidence that will advance the field, and indicating areas in which further developments are warranted.

1.5 Thesis synopsis

The remainder of this thesis will be structured as follows. Chapter 2 will summarise and appraise the published literature on specific methodological issues of medication adherence in clinical research. Chapter 3 will provide a description of the data sources used throughout the findings chapters of the thesis. Chapter 4 will compare different types of measures of medication adherence, their correlation and agreement with one another, and methods for combining or calibrating an estimate of medication adherence in the presence of multiple types of disagreeing estimates. Chapter 5 will focus on investigating the determinants of medication adherence for a variety of conditions, including both long-term chronic conditions and short-term acute conditions. This chapter will also explore the impact of different types of measures, and different conceptualisations of medication adherence on the determinants that are found. Chapter 6 will look at how causal treatment effects can be derived from randomised controlled trials in the presence of non-adherence to medication. The concept of randomisation-based efficacy estimators will be introduced, and the feasibility of their implementation on real data and for different trial designs will be examined. Finally, Chapter 7 will summarise the key findings and novel contributions from the thesis, and propose directions of future research in this field.

CHAPTER 2: Summary and Appraisal of Key Literature on the Methodological Issues of Medication Adherence in Clinical Research

2.1 Introduction

Understanding the key gaps in knowledge that exist in this field, and the opportunities that exist for novel contribution, requires an understanding and appraisal of relevant literature. Therefore, the purpose of this Chapter is to summarise and appraise the published literature on several methodological issues related to medication adherence in clinical research. The topics of focus will be

1. The measurement of medication adherence;
2. Understanding risk factors for non-adherence to medication;
3. Adjusting findings of randomised controlled trials for medication non-adherence using randomisation-based efficacy estimators.

2.2 Type of literature review

The purpose of these literature reviews is to provide the reader with a broad overview of the topics of focus throughout my thesis. Due to their often narrow focus and resource intensity, it is not practical to carry out a systematic review of the literature. A rapid review process was therefore undertaken. This is a streamlined approach for synthesising evidence in a timely manner, and is well suited for reviewing topics that are broad in scope. (Khangura et al., 2012) To assess how far my literature review deviates from a high quality systematic review, the AMSTAR checklist will be completed and the scores reported. (Shea et al., 2007) I will also highlight where these reviews may appear deficient, according to this checklist, highlighting the likely implications of these deficiencies, and draw conclusions appropriately.

2.3 Search strategies

Search strategies were created for each topic, with each search initiated in Ovid Medline using several terms related to medication (medicine, medication, drug, or medicinal), and adherence (adherence, compliance, concordance, persistence, initiation, implementation, or discontinuation). From this point, strategies diverged, with Topic 1 aiming to capture common methods for measuring adherence (electronic monitoring, tablet count, pill count, or self-report) and narrowing the focus down to papers that were interested in comparing measures if possible (comparison, agreement, correlation, calibration, or adjustment). Topic 2 considered several terms similar to "risk factor" (factors, determinants, or predictors), and aimed to cover both long-term/chronic and short-term/acute medical conditions (long term condition, long term illness, chronic condition, chronic illness, short term condition, short term illness, acute condition, or acute illness). Finally, the primary aim of Topic 3 was to capture randomised controlled trials of medicinal products that had been published, where findings were adjusted for non-adherence using randomisation-based efficacy estimators. Therefore, a wide range of terms were used to capture this (causal inference, principal stratification, structural mean model, randomisation based efficacy estimator, instrumental variable, instrumental variables, complier average causal effect, complier-average causal effect, CACE, SMM, randomisation-based efficacy estimator, adherence-adjusted, or RBEE). The purpose of this review was to give an overview of the extent to which these methods are being used in practice, rather than describe methods that have been proposed in the statistical literature. Finally, an additional search was undertaken, specifically looking at all randomised controlled trials of medicinal products that have been published since the beginning of 2015 in the highly-ranked medical journals (specifically, The Lancet, The British Medical Journal, The New England Journal of Medicine, and The Journal of the American Medical Association). The purpose of this search was to identify whether these papers referred to medication adherence, and if so, whether/how they described methods for its measurement

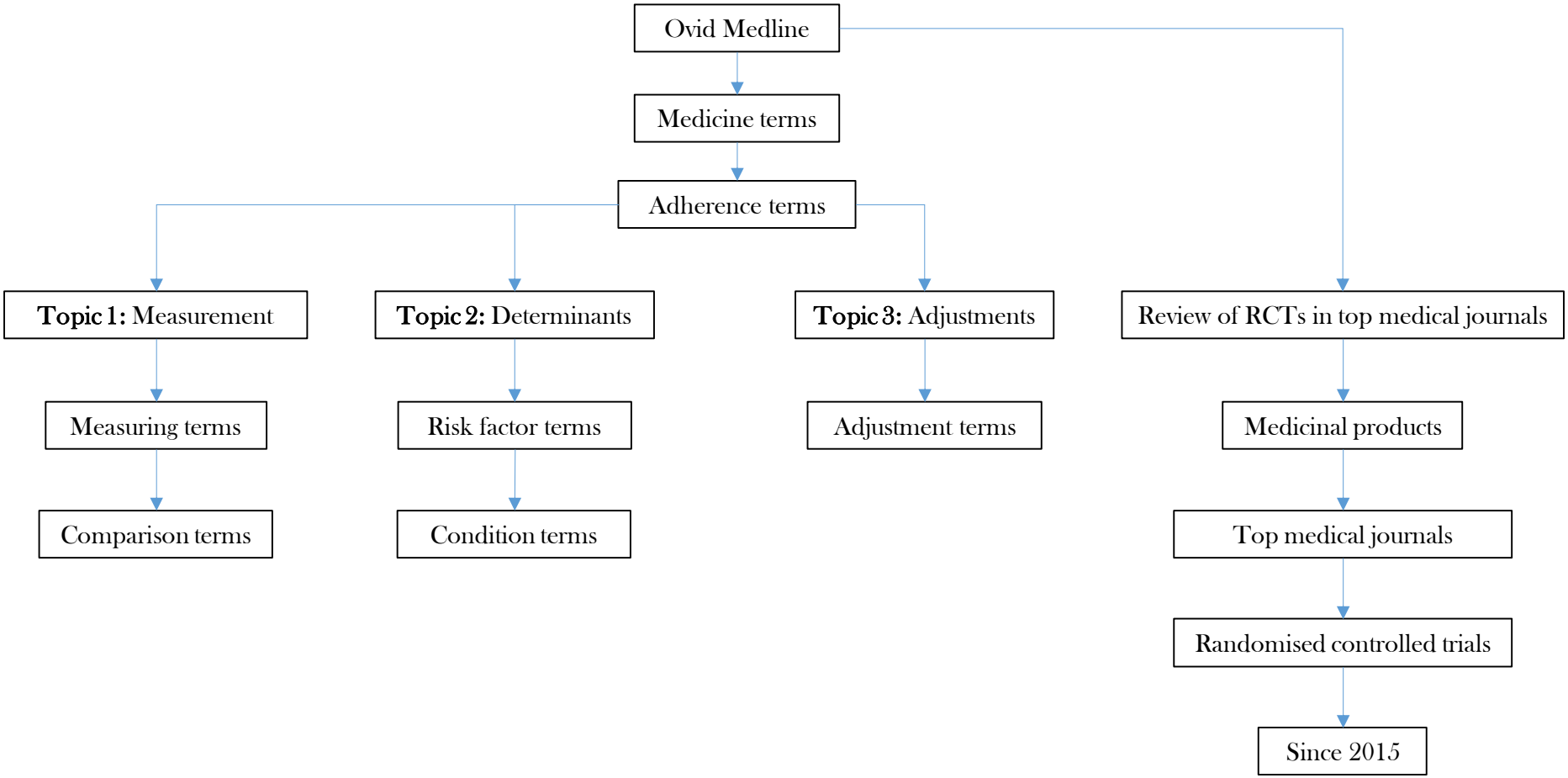
and whether/how it was modelled/adjusted for. Phase I clinical trials were excluded, as adherence to medication would be directly observed in all of these and therefore unlikely to be reported.

All strategies also limited findings to studies published on humans and written in English.

Abstracts were initially screened for duplicates. As the purpose of the review was to obtain a broad view of the literature, rather than ensure that every paper was reviewed, papers were reviewed for relevance in blocks of ten until no new themes were found within an entire block. Abstracts were reviewed in alphabetical order (with respect to the lead author). The purpose of this was to not focus on reviewing papers from any particular time point (and risk obtaining a biased view of the literature), and thus be more likely to obtain a broader view of the literature (that is, both past and present methods and techniques).

To ensure that no key literature was missed using this approach, the search was re-run with a list of key authors that have published important works on medication adherence (Bangsberg, Claxton, DiMatteo, Farmer, Horne, Hughes, Kane, Kardas, Osterberg, Pechere, Sabate, Urquhart, Vermeire, Vrijens, or Weinman). A review of other work published by these authors in the field of medication adherence was also undertaken, to ensure that any key literature not covered by these searches were read (Figure 2.1).

Figure 2.1: Flow diagram outlining search strategies*



*Searches for Topics 1 to 3 were re-run with the list of key authors specified. For this search, all abstracts were reviewed.

2.4 Topic 1: The Measurement of Medication Adherence

2.4.1 Search Results

The initial search was conducted on 19/04/2016 and yielded 195 papers, six of which were duplicates (Table 2.1). From the 189 unique papers that were identified, no new themes emerged after reviewing 60. In total, 43 papers were deemed relevant, with the remaining 17 not relevant for this review. The search was re-run with the names of key authors included. Nine paper were identified. However, four had already been reviewed, and one was deemed not relevant for the review. Therefore, this search yielded an additional four relevant papers. Following the review of full texts of all 47 papers, two papers were excluded for not being relevant, on closer inspection. The section of the Chapter therefore relates to the review of 45 papers (Figure 2.2).

2.4.2 Findings

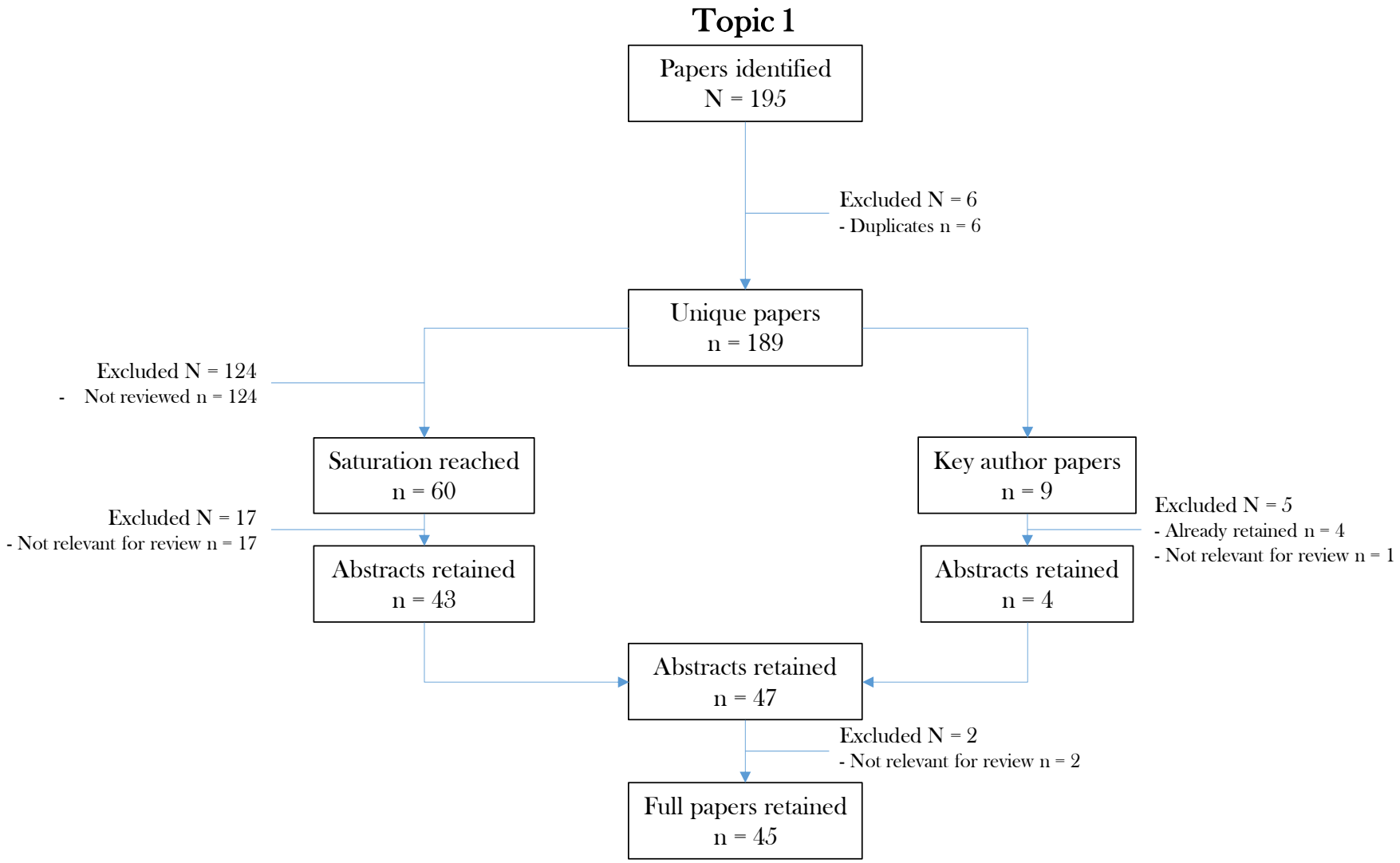
2.4.2.1 Clinical conditions

The papers found cover a wide range of conditions, including those focused on the respiratory tract (e.g. asthma, cystic fibrosis), (Berg et al., 1998, Butz et al., 2005, Daniels et al., 2011, Casey et al., 2012) long-term physical conditions such as HIV, (Dlamini et al, 2009, Haberer et al., 2011, Buscher et al., 2015) cancer, (Escalada and Griffiths, 2006) type 2 diabetes, (Farmer et al., 2006, Bogner et al., 2013) and hypertension, (Choo et al., 1999, El Zubier, 2000, Horne et al., 2010) and mental illnesses such as depression (Gabriel and Violato, 2010, De las Cuevas et al., 2014) and schizophrenia. (Garavan et al., 1998, Frangou et al., 2005, Byerly et al., 2007, Brain et al., 2014) There were also studies included in this review looking at adherence to treatment in substance abusers (e.g. alcohol, ecstasy, speed, and heroin). (Digiusto et al., 1996, Cooper et al., 2000, Feinn et al., 2003)

Table 2.1: Findings from the initial search for Topic 1

#	Searches (conducted on 19/04/2016)	Results
1	(MEDICINE or MEDICATION or DRUG or MEDICINAL).ab.	992741
2	(ADHERENCE or COMPLIANCE or CONCORDANCE or PERSISTENCE or INITIATION or IMPLEMENTATION or DISCONTINUATION).ab.	504576
3	1 and 2	67965
4	(ELECTRONIC MONITORING or TABLET COUNT or PILL COUNT or SELF REPORT).ab.	32363
5	3 and 4	1246
6	(COMPARISON or AGREEMENT or CORRELATION or CALIBRATION or ADJUSTMENT).ab.	1254070
7	5 and 6	199
8	limit 7 to (English language and humans)	195

Figure 2.2: Diagram illustrating the flow of papers from identification to review (Topic 1)



2.4.2.2 Types of measures

A variety of different methods for measuring adherence to medication were found. Indirect accounts of medication use/adherence were often used in the papers reviewed, rather than direct (observed) measures. These tended to be reported by the patient themselves (self-report), (Garber et al., 2004, Jerant et al., 2008, Brask-Lindermann et al., 2011) but in some instances were reported by some form of carer and/or a healthcare professional (proxy-report). (Cassidy et al., 2010, Daniels et al., 2011) There are several reasons one may choose to measure adherence via proxy report rather than self-report, including attempts to assess the quality of treatment administration (if the recipient requires correct technique to take the medicine), reduction of reporting bias (though this could still be present in some proxy-reports), and convenience (for example, if the proxy is responsible for administering medication). The mode of data capture also varied between studies, including completion via prospective self-completed diaries, (Anastasio et al., 1994) and other means such as face-to-face (Garavan et al., 1998) and retrospective telephone administered interviews. (Choo et al., 1999) For these subjective measures, the mode of data capture and also nature of data capture (prospective versus retrospective) can impact on the level and extent of response bias, and should be considered in full by the investigator prior to implementation. (Hood et al., 2012) Some papers also reported on the use of validated scales to obtain self/proxy-reported adherence, including scales that could be used across conditions, such as the Morisky Medication Adherence Scale (MMAS), (Morisky et al., 1986, Butler et al., 2004, Elm et al., 2007, Ayoade and Oladipo, 2012, De las Cuevas et al, 2014) the Medication Adherence Rating Scale (MARS), (Horne and Weinman, 1999, Farmer et al., 2006, Horne et al., 2010, Mahler et al., 2010) the Medication Adherence Self-Report Inventory (MASRI), (Walsh et al., 2002, Andy et al., 2015) the Drug Attitude Inventory (DAI), (Hogan et al., 1983, Dolder et al., 2004) and the Brief Medication Questionnaire (BMQ). (Svarstad et al., 1999, Choo et al., 1999) Condition-specific measures were also used, such as the Adult Aids Clinical Trials Group (AACTG) 4-day self-report measure of missed doses (de Klerk

et al., 1999, Chesney et al., 2000, Buscher et al., 2011) and the Antidepressant Adherence Scale (AAS). (Gabriel and Violato, 2010) Validated, or standardised scales give the advantage of having existing evidence demonstrating the extent to which the scale measures what it is intended to measure (validity), can yield consistent responses (reliability), and can discriminate between different types of subjects (sensitivity). Without previous investigation of these areas, ad-hoc questions risk producing data that are useless (e.g. not sensitive and cannot distinguish between people who do and do not adhere, or changes in adherence over time) or worse misleading (because the scales measure something different than what was intended). (Streiner and Norman, 2014) Pill counts also commonly featured in the papers reviewed. (Almeida et al., 2014, Banek et al., 2014, Baxi et al., 2015) While the majority of pill counts were scheduled (e.g. occurring clinic visits or other known time points), (Elzubier et al., 2000, Feinn et al., 2003, Elm et al., 2007, Brain et al., 2014) some papers reported the collection of pill count data during unannounced home visits. (Haberer et al., 2011) The purpose of the latter being to reduce the risk of pill dumping (removing pills from containers without consuming them with the intention of appearing more adherent to treatment) and/or white coat adherence (increasing medication usage as the time to a scheduled visit neared to appear more adherent) (Rudd et al, 1989, Bangsberg et al., 2000) and thus improve the validity of the measure. Indeed, Haberer et al, reported better agreement between electronic monitoring and unannounced pill counts compared to scheduled pill counts. In some of the papers reviewed, biological assays were used as a means of monitoring medication use. (Digiusto et al., 1996, Cooper et al., 2000, Banek et al., 2014, Baxi et al., 2015) Various types of samples were used to obtain measure of medication use, including samples obtained from blood, urine, and hair. The advantage of these are that they can measure the concentration of drug within an individual's body. However, they are resource intensive, invasive, and similar to pill counts, where these are scheduled, patients may take medication as prescribed a few days prior (where they had not been doing so previously).

In other words, while they can be viewed as a direct measure, in practice they remain indirect in all but short-term treatments. Pharmacy refill records were also reported in some papers. (Choo et al., 1999, Esposito et al., 2008, Clifford et al., 2014) These are records collected routinely by pharmacists which provide an account of a prescription being collected. While there are a number of advantages to using pharmacy refill data to monitor adherence (non-invasive, participant not overtly aware they are being monitored, etc.), due to the data used during this thesis, they will not be considered in any great detail. Electronic monitors were a frequently utilised means of obtaining medication adherence data in the papers reviewed. (Chui et al., 2003, Boland et al., 2014) The types of monitors varied, depending on the way in which the medication was delivered. Examples include the Medication Event Monitoring System (MEMS), (Escalada et al., 2006, Buscher et al., 2011, Baxi et al., 2015) that records the date and time of each bottle cap opening, a similar micro-switch device housed inside an inhaler, (Berg et al., 1998) and electronic nebulizer monitors, that record the date, time, and duration of each nebulizer use event. (Butz et al., 2005) Electronic monitors do not rely on patients consciously reporting their medication use, and can provide rich detail on patterns in adherence. However, their expense (relative to other types of measures) can make them infeasible. The knowledge that a patient's medication taking habits are constantly monitored can also risk influencing adherence itself. Where electronic monitoring is commonplace, this is not a problem. However, when an intervention to improve adherence is being trialled, and adherence is being monitored electronically, it may be difficult to disentangle intervention effects from the effect of the electronic monitor due to this reactivity (French and Sutton, 2010, McCambridge et al., 2011). Nevertheless, electronic monitors are widely regarded as the best measure of adherence in clinical research, with a key study by Sutton et al., (2014) finding that while electronic containers may lead to small increases in adherence, this is outweighed by their advantages. Figure 2.3

illustrates the different types and subtypes of measures described in this section, as well as summaries reported in the literature.

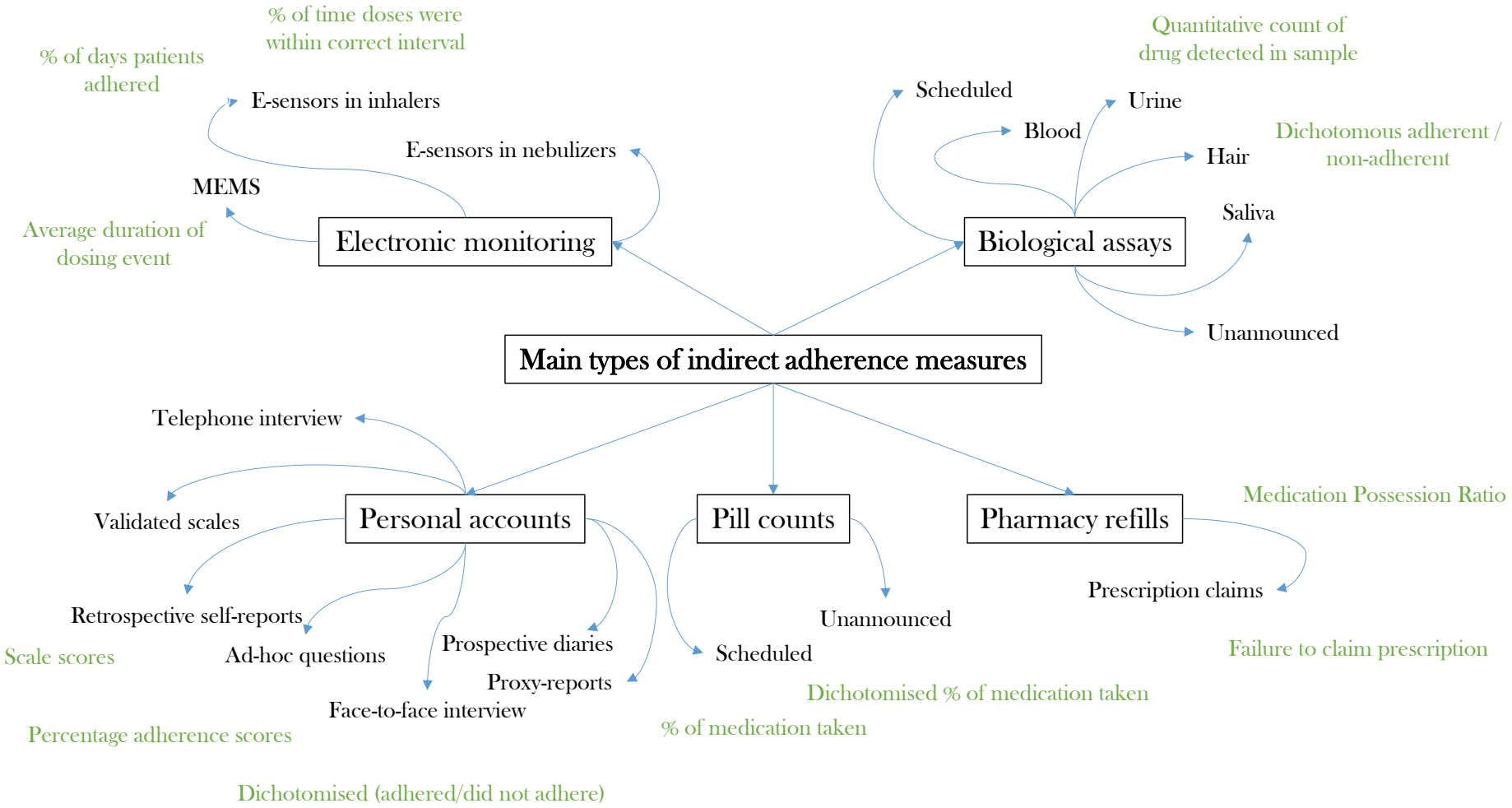
2.4.2.3 Quantification of adherence

A range of approaches were used to quantify adherence, both between and within the different types of measures described previously. For validated scales, scores or categories were computed using the items suggested by the scale developers. (Dlamini et al., 2009, Buscher et al., 2011) These, along with un-validated accounts, were often dichotomised into "adhered to medication regimen" / "did not adhere to medication regimen". (Elzubier et al., 2000, Dorz et al., 2003, DiMatteo et al., 2004, De las Cuevas et al., 2014) While a categorisation such as this may appear more intuitive for a clinical or patient audience, and for defining populations it is sometimes needed (for example, when defining an analysis population in a randomised controlled trial), dichotomising ordinal or continuous variables results in a loss of information for often very little gain. (Senn, 2005) The gain is even smaller if the categorisation is not based on strong evidence of a clear dichotomy at the chosen threshold (i.e. the threshold has been arbitrarily chosen, or chosen based on weak evidence), as participants categorised as 'not adhering' might have taken enough of the treatment for a therapeutic benefit. Indeed, these categorisations varied across studies in a fairly arbitrary fashion, with some studies using a cut-off at 100%, (Almeida et al., 2014) and others using cut-offs ranging from 70% upwards. (Bogner et al., 2013, Brain et al., 2014)

Adherence measured using pill counts tended to calculate the difference between the number of pills given and the number returned, expressing it as a percentage of the number of pills given. (Horne et al., 2010, Haberer et al., 2011) This can provide a measure of consumption within a defined period, but gives little understanding of patterns in adherence within the period (other than when adherence is 0 or 100%). Calculations from biological assays were based on either the amount of drug detected in the sample, or a categorisation of this that indicated whether the

amount of drug detected was consistent with someone adhering to their prescribed regimen. (Cooper et al., 2000, Brain et al., 2014) Note the latter summary has similar issues to dichotomisation elsewhere in that information is lost and may be an overly simplistic representation of adherence. (Farmer, 1999) Where adherence data were obtained via pharmacy refill records, the Medication Possession Ratio (MPR) was the popular metric of choice. The MPR counts the number of days of medication supplied within a time interval and divides this by the time interval, with a ratio calculated provided there is at least one refill/repeat prescription. (Steiner and Prochazka, 1997, Steiner et al., 1998) Electronic monitors that record the date and time of a dosing event have an advantage of providing data on adherence in multiple ways. Indeed, from the papers reviewed, data collected via electronic monitors were used to create adherence metrics based on the percentage of days that patients adhered to their treatment (e.g. had at least the required number of dosing events corresponding to their prescribed regimen), (Brain et al., 2014) the amount of times that doses were within a defined time interval, (Boland et al., 2014) and the average duration of each dosing event (e.g. average length of time that a nebulizer was in use during a dosing event). (Butz et al., 2005)

Figure 2.3: Diagram of the different types of indirect adherence measures described during this literature review (with summary measures in green)



Knowledge of the treatment being investigated can influence the recommended metric of interest. For treatments where time between consumption is vital for achieving or maintaining efficacy (or minimising toxicity), analysis based on time intervals is important. Conversely, where comparisons are being made between two treatments that are taken a different number of times a day, data regarding frequency of openings is important (Figure 2.3).

2.4.2.4 Comparing different types of measures - correlation

One of the key aims of this review was to summarise literature that reports comparisons of different methods for measuring adherence. Broadly speaking, the literature reviewed reported comparisons between methods in two ways – correlation and agreement. The strength of correlation between different types of methods was wide ranging. Strong relationships were found in some studies comparing self-report to pill counts, (Feinn et al., 2003, Almeida et al., 2014) and biological assays to electronic monitoring, (Baxi et al., 2015) but correlations that were weak to moderate were also found. (Elm et al., 2007 Esposito et al., 2008, Buscher et al., 2011) For example, one study found a moderate correlation between self-reported adherence and pill count-derived adherence that weakened over time. (Andy et al., 2015) This could reflect the fact that self-report adherence measures aim to measure adherence to treatment (both in terms of consumption but also tendencies to consume correct doses at the correct times), whereas pill counts are only able to provide a measure of consumption within a defined period. It would therefore follow that strength of association between these two types of measures would weaken as the observation period widened. Another study of inhaled medications compared different adherence metrics derived from electronic monitors to those derived from self-reported diaries found that while a moderate correlation was found when using frequency data (percentage of days with correct administrations), there was considerably weaker correlation when comparing diaries to metrics based on the number of puffs. (Berg et al., 1998) The latter metric yielded a lower adherence rating when based on electronic monitors compared to self-reported data (i.e. according to self-reports, patients thought they were adhering better than the electronic monitors

suggested). This study highlights the advantages of having automated date and time data, as this was combined in an algorithm, with the number of puffs at each dosing event, to determine the level of adherence of a given patient. Achieving the same detail via self-reported data would rely on patients actively recording the date, time, and number of puffs (potentially the time of each puff) at each dosing event. This is unlikely to be sustainable in patients on an indefinite basis, or even research participants (particularly where a long-term condition is of interest).

2.4.2.5 Comparing different types of methods - agreement

Assessing the correlation between two methods can only indicate the strength of the relationship between them. It cannot provide an accurate indication of the level of agreement between the two methods (for example, it is mathematically possible for two methods that are strongly correlated to have poor agreement), which is an important estimand for understanding the reliability or bias of a particular method. The papers in this review estimated agreement using a diverse range of methods. The observed percentage of agreement was often reported. (Cooper et al., 2000, Banek et al., 2014) This was usually accompanied by Cohen's Kappa, which takes into account chance-agreement for categorical variables, (Digiusto et al., 1996) or the intra-class correlation coefficient, if a quantitative measurement of adherence was used. (Cassidy et al., 2010) Some papers reported on the sensitivity and specificity of a particular method, where the performance of a particular method (often self-report) was compared to a gold/reference standard (often electronic monitoring). (de Klerk et al., 1999) This method relies on a categorical definition of adherence, and assumes that the reference standard reflects the true nature of adherence. While these approaches can describe the amount of agreement present between two types of measures, and to some extent the direction of disagreement (e.g. more adherent people according to one approach), they cannot provide information about the extent of disagreement. This might be important, as two measures may disagree by a negligible amount, or disagreement may be sensitive to how adherence thresholds were chosen (if a continuous measure was available but subsequently categorised). Another method for assessing agreement, less frequently reported

in the literature reviewed, was Bland-Altman plots and limits of agreement. These involve plotting the average and paired-difference across two types of measures that produce quantitative summaries of adherence. This plot is then used to compare methods and detect systematic disagreement (bias) between them. For example, one study used a Bland-Altman plot to assess the agreement between self-report and electronic monitoring in the use of nebulizers, demonstrating that self-reports consistently overestimated use of nebulizers, when compared to electronic monitoring. (Daniels et al., 2011) Similarly, another study found that electronic monitoring and unannounced pill counts yielded lower adherence compared to carer-reported adherence and scheduled pill counts. (Haberer et al., 2011)

2.4.2.6 Calibration and other approaches

On comparing methods, be that via correlation or agreement, the natural progression might be to use this information in an attempt at deriving a more accurate estimate of medication adherence. The majority of methods, indeed every method described in this review, provide an indirect measure of medication adherence, relying on assumptions in order for their data to be used as means for quantifying medicine use. Using information from multiple indirect sources to acquire an improved estimate (and hence understanding) of medication would therefore seem important. Despite this, there appear to have been few attempts at using the information obtained in this way. One study explicitly did this by creating a consensus definition of adherence based on pill counts along with patient, clinician, and family accounts of medication use. (Cassidy et al., 2010) However, it is not clear how this consensus was arrived at, only that all individual measures correlated very highly with the consensus measure (as would be expected). Another study, that used electronic monitors to study adherence to medication given on a multiple doses per-day regimen, added in questions at follow-up visits that took account of multiple doses being removed during a single dosing event, stating that this information was then used to add dosing events as appropriate. (Byerly et al., 2007) However, further detail of this process was lacking. This approach is likely to be unreliable, unless these questions were asked frequently and specific

questions were asked (rather than a general question, such as "how often did you remove more than one dose at a time?"). Nevertheless, this was an attempt at creating a calibrated adherence measure, using multiple sources of data. Finally, one study from those reviewed, that reported the concordance between urinalysis and self-reported drug use by applicants for methadone maintenance, conducted an analysis that looked at predictors of misreporting drug use. (Digiusto et al., 1996) The analyses yielded no strong associations. However, this is type of analysis appears to be seldom reported, and may be useful when it comes to informing the reliability of reported levels of adherence provided by individuals within a study, or potentially when it comes to selecting a suitable method/s for measuring adherence across an entire study (that is, by considering the typical characteristics of the population of interest in relation to known factors that influence misreporting of treatment adherence).

2.4.2.7 Summary (Topic 1)

The review of these papers highlighted both gaps in the literature, and areas in which knowledge and understanding could be further strengthened by the work presented in this thesis. The majority of papers focused on adherence to medication prescribed for long-term conditions. The measurement of adherence to medication prescribed for short-term illnesses appears to be a less well researched area. However, non-adherence to these medicines could impact on clinical outcomes, potentially leading to complications that have long-lasting consequences. This is an area that therefore warrants further investigation. As previously reported, electronic monitors used to measure medication adherence have the advantage of providing accounts of dosing frequency, timing, and in some instances duration. However, despite there being many studies reporting their use, simple summary measures of adherence (e.g. an average adherence score / dichotomous indicator averaged across an entire observation period) appear to be the popular means of reporting these data. It is my intention to move beyond that during this thesis and provide more accurate accounts of adherence, as measured by electronic monitoring, and demonstrate how these data can be used to demonstrate the evolution of adherence over time.

The investigation of agreement between adherence measures was reported in several studies. However, most used dichotomous definition of adherence based on an arbitrary cut-off. Bland-Altman plots were infrequently used, and this thesis will explore their use further. Agreement between adherence measures should never be an end in itself, however. This thesis will therefore explore means for estimating risk factors for disagreement between adherence measures, and consider different ways in which measures can be combined in order to create a calibrated measure that, ideally, provides a more accurate reflection of how well an individual has adhered to their prescribed medication regimen.

2.5 Topic 2: Understanding Risk Factors for Non-Adherence to Medication

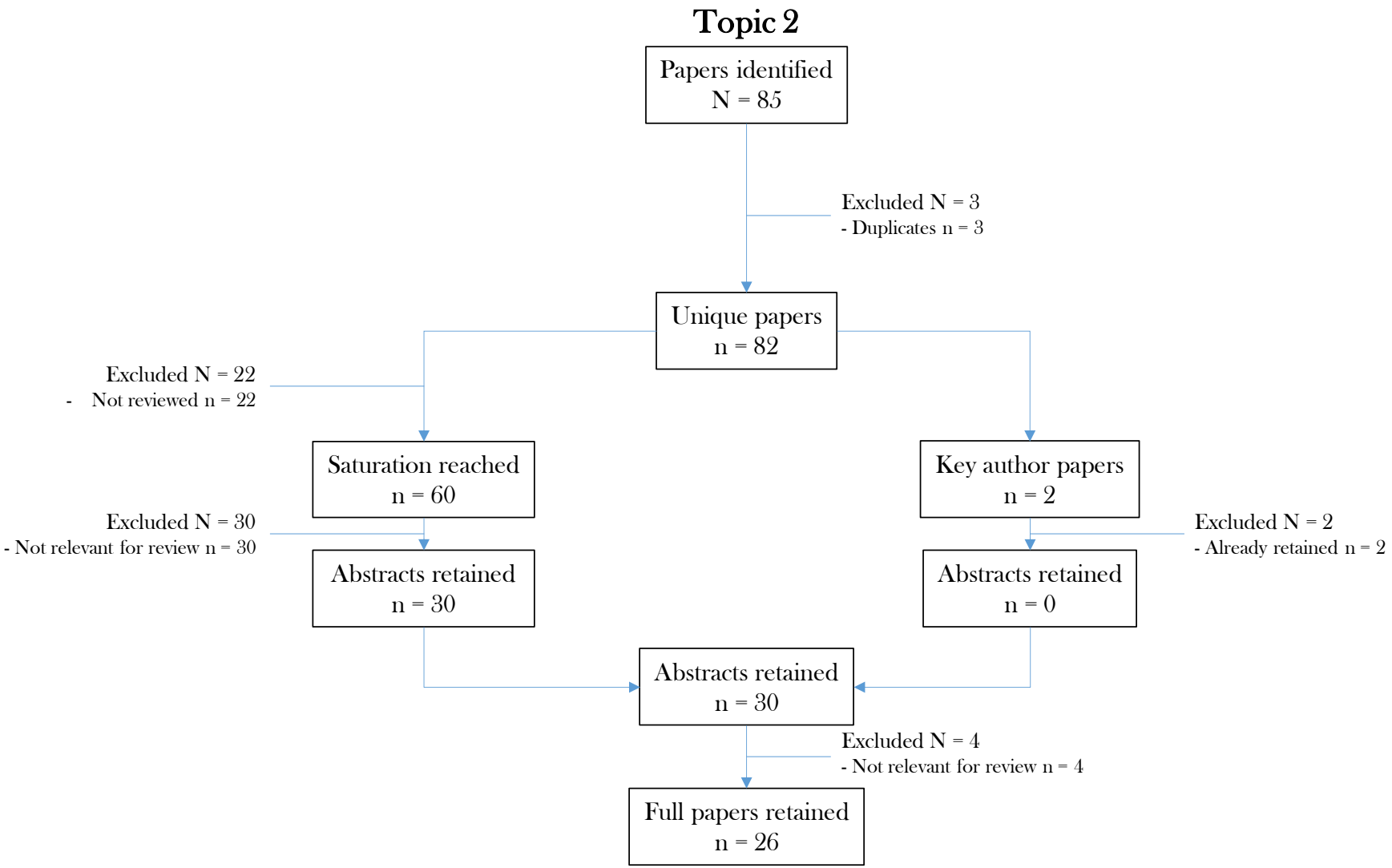
2.5.1 Search Results

The initial search, performed on 19/04/2016, yielded 85 papers (Table 2.2). Three duplicates were removed, leaving 82 unique papers. Similar to Topic 1, no new themes emerged after reviewing 60 papers. In total, 30 papers were deemed relevant, with the remaining 30 not relevant for this review. The search was re-run with the names of key authors included. Two papers were identified. However, both had already been identified in the initial search. Therefore, this approach yielded no additional papers. On further review of the full texts, four papers were subsequently excluded due to their irrelevance for this review. This section therefore relates to the review of 26 papers (Figure 2.4).

Table 2.2: Findings from the initial search for Topic 2

#	Searches (conducted on 19/04/2016)	Results
1	(MEDICINE or MEDICATION or DRUG or MEDICINAL).ab.	992741
2	(ADHERENCE or COMPLIANCE or CONCORDANCE or PERSISTENCE or INITIATION or IMPLEMENTATION or DISCONTINUATION).ab.	504576
3	1 and 2	67965
4	(RISK FACTORS or DETERMINANTS or PREDICTORS or FACTORS).ab.	1381410
5	3 and 4	11798
6	(LONG TERM CONDITION or LONG TERM ILLNESS or CHRONIC CONDITION or CHRONIC ILLNESS or SHORT TERM CONDITION or SHORT TERM ILLNESS or ACUTE CONDITION or ACUTE ILLNESS).ab.	12851
7	5 and 6	87
8	limit 7 to (English language and humans)	85

Figure 2.4: Diagram illustrating the flow of papers from identification to review (Topic 2)



2.5.2 Findings

2.5.2.1 Clinical conditions

In the same way as Topic 1, the papers found for this review covered a wide range of clinical conditions. The majority focused on long-term or chronic conditions (e.g. HIV, ADHD, and bipolar disorder), (Berk et al., 2004, Harvey et al., 2008, Coletti et al., 2012, Mackey et al., 2012) with some papers focusing on risk factors of non-adherence medicines in general, but in a specific population (e.g. the elderly). (Henriques et al., 2012, Dharmapuri et al., 2015)

2.5.2.2 Approaches used to study risk factors

The papers reviewed used both quantitative and qualitative means of studying risk factors for non-adherence. Those that used quantitative means tended to report their findings on the basis of regression analyses. (Bagchi et al., 2007, Dean et al., 2011, Gadkari et al., 2012) This is a useful approach for measuring the strength of association that these risk factors may have on adherence, and how this association is influenced by other factors. Univariable analyses were also reported in some papers, though these lack the advantage of being able to be adjusted for any confounding relationships that may exist. (Dalbeth et al., 2011, Lin et al., 2014) One paper used a stated-preference approach to quantify how certain attributes of medication affected the adherence to these treatments. (Johnson et al., 2007) This approach is a systematic method for understanding preferences through structured trade-offs. (Thurstone, 1927, Louviere et al., 2000) Relevant medication attributes were identified using existing literature (for example, frequency of mania episode), with participants asked to choose between a series of medicines that had varying levels of these attributes (for example, less than once a year; 1-3 times a year; 4-6 times a year; more than 6 times a year), as well as being asked to compare their current medication with hypothetical medication (again, with varying levels of the identified attributes). This approach has the key advantage of data being cheap and quick to collect (compared to, for example, a cohort study investigating risk factors of adherence to a treatment being taken long-term). However, as with all stated-preference approaches, it has the disadvantage of yielding data

related to decisions and trade-offs for hypothetical scenarios, rather than observed behaviour. There is therefore the risk of a lack of external validity. Nevertheless, identifying risk factors for non-adherence naturally leads to the development of interventions to improve adherence. These risk factors (stated or revealed) will thus be validated externally through this process. Qualitative methods that were used to study risk factors for non-adherence included interviews, focus groups, and narrative commentaries on existing literature. (Kjellgren et al., 2004, Li et al., 2007, Chen et al., 2014) Each of these methods have their benefits, with interviews being particularly useful in situations where the issue of non-adherence for a certain medication, or indeed, the condition for which the medication is treating, is of a sensitive nature. Interviews are also a valuable method for seeking detailed opinions/perspectives on topics from individuals. For example, a study exploring the factors facilitating and challenging access and adherence to antiretroviral therapy (ART) interviewed patients to explore this topic in depth and found risk factors that would be difficult to quantify (for example, loss of earnings due to side effects making them too ill to work, and the desire to see their children finish school, rather than leave small orphans). (Grant et al., 2008) Focus groups allow for the appraisal of multiple perspectives on a topic in an interactive group setting, and the acceptance and challenge around ideas that are put forward can be documented more easily than from interviews. An example of this is seen in a study investigating patient-provider perceptions on engagement of HIV care in Argentina. In this study, both patients and providers considered a strong therapeutic alliance as vital to achieving treatment adherence. (Bofill et al., 2014) However, while providers suggested that poor communication skills and a passive attitude on behalf of the patient were factors influencing adherence, perceiving non-adherence as a patient failure, patients expressed frustration over the lack of shared responsibility between patient and provider for achieving adequate adherence levels. Narrative reviews of the literature are useful when studies have been conducted, and the harmony and dissonance of the risk factors identified across studies is required. One such review, investigating

the influences of adherence to paediatric asthma treatment, found a variety of different risk factors associated with adherence to asthma treatment that were consistent across studies, if of varying strength. (Drotar and Bonner, 2009) Some inconsistent findings were also reported, with factors positively associated with adherence in some studies, and negatively associated in others. (Nischal et al., 2005, Browne and Merighi, 2010) This could reflect differences in the characteristics of the samples considered (different cultures or ethnicities, different treatments, patients from different socio-economic backgrounds, etc.)

2.5.2.3 Risk factors

The risk factors that were found varied across, and even sometimes within, the various clinical conditions in which this work has been studied. Factors that were found fairly consistently across studies as associated with improved adherence were age (older people are more likely to adhere to treatment than younger people), (Horne and Weinman, 1999, Grant et al., 2004) social support (for example, being married, having medication administered by a carer), (Berk et al., 2004, Browne and Merighi, 2010) therapeutic alliance (the relationship the patient has with their healthcare provider), (Lin et al., 1995, Nischal et al., 2005, Bofill et al., 2014) improvements in health literacy, (Henriques et al., 2012) and educational level. (Kalkan et al., 2013) Factors found that were negatively associated with adherence include side effects, (Chesney, 2003) the complexity of the regimen, (Beni, 2011) both in terms frequency of treatment and additional instructions given with the treatment (e.g. daily fluid restrictions in the use of oral medications for haemodialysis patients), (Browne and Merighi, 2010) pill burden in general (e.g. polypharmacy), (Chen et al., 2014) and the stigma of the illness for which the medication was prescribed. (Bofill et al., 2014) Other factors associated include race and access to healthcare. (Nischal et al., 2005, Bagchi et al., 2007) In addition to the risk factors identified, there is a wealth of literature suggesting that adherence to medication can be characterised and predicted by behavioural models, with several health psychology theories used to describe this phenomenon

(e.g. social cognitive theory, self-regulatory theory). (Munro et al., 2007, Holmes et al., 2014, Patton et al., 2016)

These factors show that the ability to take medication as prescribed is a complex phenomenon that may rely on a variety of interacting aspects. Nevertheless, many of these factors are likely to be modifiable or amenable to targeted interventions.

2.5.2.4 Summary

The key gaps and deficiencies identified in the literature during this review can be divided into three areas – the conditions in which this work mainly resides; the method of calculation primarily used when looking at risk factors of adherence; and the research methods used to explore some of the factors related to medication adherence. Papers reviewed for this Topic focused on long-term and chronic conditions. While they were not an exhaustive list of publications that investigate risk factors of medication adherence, they nevertheless indicate a lack of research on adherence to treatments for short-term acute conditions, such as antibiotics to treat uncomplicated respiratory tract infections. This is an area that requires investigation, and a comparison of the determinants of adherence to those reported in the literature on long-term conditions may be of interest. As was also reported for Topic 1, the majority of papers conceptualised adherence as a single, all-encompassing and dichotomous trait. Rarely was a quantitative measure of adherence used or an attempt made to investigate risk factors related to any separate element of adherence (e.g. initiation, implementation, or persistence). Investigating risk factors of a quantitative measure or by using different elements of adherence, means the data are likely to be better used, as there is generally a reduction in information and statistical power when a continuous / quantitative variable is dichotomised. Investigating elements of adherence separately also allows for the possibility that there may be different mechanisms influencing whether a person initiates, the extent to which they implement their medication correctly, and the length of time they persist with their treatment. (Vrijens et al., 2012) These matters will be

explored in this thesis. Finally, while qualitative research methods can provide information that is often difficult to capture quantitatively, their findings are generally viewed as hypothesis generating, rather than hypothesis confirming. Indeed, there appears to be a lack of quantitative evidence regarding some of the on the barriers and facilitators of medication adherence reported in abundance throughout the qualitative studies – particularly those related to healthcare provider (e.g., therapeutic alliance) and healthcare system (e.g. ease of access to healthcare). Some of these factors will be explored quantitatively during this thesis.

2.6 Topic 3: Adjusting Findings of Randomised Controlled Trials for Medication Non-Adherence: The Use of Randomisation-Based Efficacy Estimators

2.6.1 Search Results

The initial search, performed on 18/04/2016, yielded 32 papers (Table 2.3). Two duplicates were removed, leaving 30 unique papers. Due to the low number of papers, all abstracts were reviewed. One paper was retained, with the other 29 excluded for a variety of reasons (study protocol, n = 2; not a trial of a medication, n = 20; trial did not adjust findings for adherence using a randomisation-respecting approach; n = 7) (Figure 2.5).

2.6.2 Findings

The search led to the retention of one paper. This reported a randomised controlled trial comparing the efficacy of two different antidepressants. (Wiles et al., 2014) In this paper, a structural mean modelling approach was used to generate adherence-adjusted estimates of the efficacy of one antidepressant compared to another, while maintaining a comparison of groups as randomised. The paper highlights, during its discussion section, the appropriateness of these methods for non-inferiority trials.

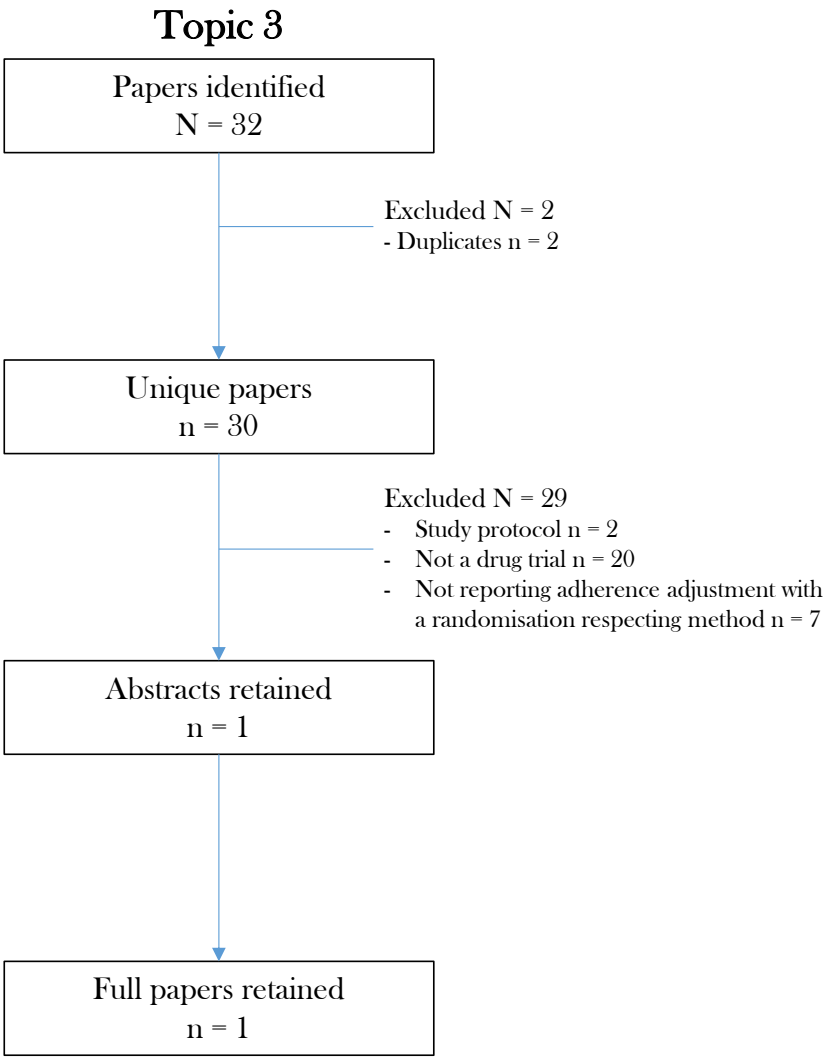
The implication from this review is clear: there are few randomised controlled trials of medicinal products that are adjusting for treatment adherence using randomisation-based efficacy estimators. There is a need to investigate the implementation of these approaches using real datasets. There is also a specific need to investigate how these approaches can be used for non-inferiority trials.

An additional review was undertaken that relaxed the focus on papers describing randomised controlled trials of medicinal products, therefore allowing trials of other interventions to be considered. This search yielded 34 unique papers from 45 papers initially found, which were reduced to 11 following an assessment of the full papers. These studies reported a variety of interventions, including music education (Cogo-Moreira et al., 2013), exercise (Mock et al., 2005, Jago et al., 2006, Tilbrook et al., 2014), family training programmes (Stanger et al., 2011, Kogan et al., 2016), housing-based interventions (Osypuk et al., 2012, Nguyen et al., 2013), and psychological interventions (Dunn et al., 2003, Knox et al., 2014, Picardi et al., 2016). These papers all used an instrumental variables approach, primarily using the term "complier average causal effect". That these analytical approaches are more frequently used in trials of complex interventions is surprising, given some of the assumptions required (to be described in Chapter 6).

Table 2.3: Findings from the initial search for Topic 3

#	Searches (conducted on 18/04/2016)	Results
1	(MEDICINE or MEDICATION or DRUG or MEDICINAL).ab.	1048176
2	(ADHERENCE or COMPLIANCE or CONCORDANCE or PERSISTENCE or INITIATION or IMPLEMENTATION or DISCONTINUATION).ab.	534564
3	1 and 2	72854
4	(CAUSAL INFERENCE or PRINCIPAL STRATIFICATION or STRUCTURAL MEAN MODEL or RANDOMISATION BASED EFFICACY ESTIMATOR or INSTRUMENTAL VARIABLE or INSTRUMENTAL VARIABLES or COMPLIER AVERAGE CAUSAL EFFECT or COMPLIER-AVERAGE CAUSAL EFFECT or CACE or SMM or RANDOMISATION-BASED EFFICACY ESTIMATOR or ADHERENCE-ADJUSTED or RBEE or STRUCTURAL or RANDOMIZATION-BASED EFFICACY ESTIMATOR or RANDOMIZATION BASED EFFICACY ESTIMATOR).af.	487509
5	3 and 4	1126
6	limit 5 to (English language and humans and randomized controlled trial)	32

Figure 2.5: Diagram illustrating the flow of papers from identification to review (Topic 3)



2.7 Review of Top Medical Journals

2.7.1 Search Results

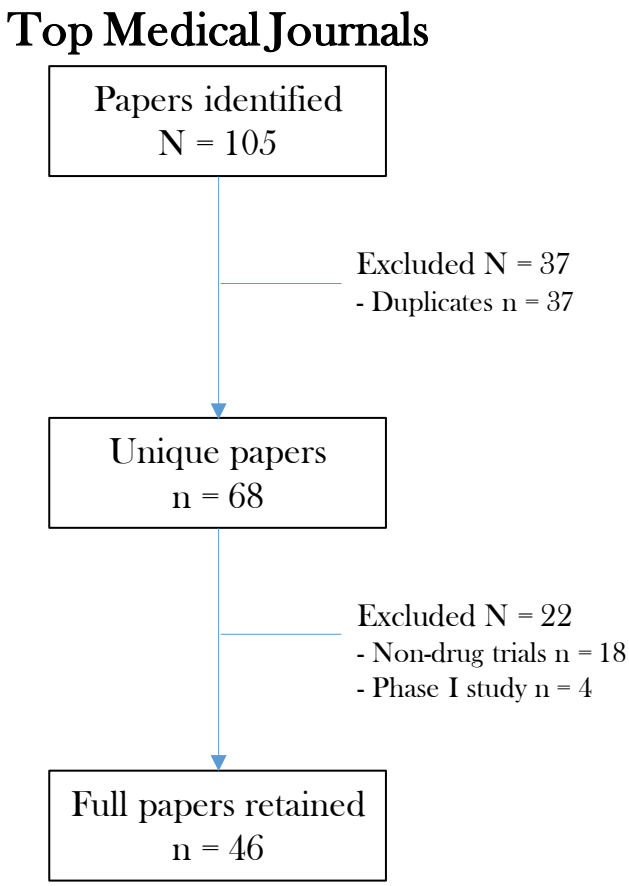
Given the single paper retained for the previous topic, a review of all randomised controlled trials of medicinal products, published in top medical journals within the past year, provides an additional exploration of the extent that randomised controlled trials (and indeed, those published in high ranking medical journals) are using these cutting-edge techniques.

A total of 105 papers were identified using the search strategy above, which was run on 18/04/2016 (Table 2.4). Once duplicates were identified and removed, 68 papers remained. An additional 22 papers were excluded, with 18 describing non-drug trials (either trials of surgical or behavioural interventions), and four describing Phase I dose-escalation studies. There were therefore 46 unique and relevant papers included in this section of the review (Figure 2.6).

Table 2.4: Findings from the initial search for the review of top medical journals

#	Searches (conducted on 18/04/2016)	Results
1	(MEDICINE or MEDICATION or DRUG or MEDICINAL).ab.	1048176
2	limit 1 to (english language and humans and yr="2015")	51544
3	(The Lancet or The British Medical Journal or The Journal of the American Medical Association or The New England Journal of Medicine or Lancet or NEJM or BMJ or JAMA or British Medical Journal or The BMJ).jn.	398974
4	1 and 2 and 3	264
5	limit 4 to randomized controlled trial	105

Figure 2.6: Diagram illustrating the flow of papers from identification to review (Top Medical Journals)



2.7.2 Findings

From the 46 full papers retained, 18 were from The Lancet, 17 from The New England Journal of Medicine, nine from The Journal of the American Medical Association, and two from The British Medical Journal.

2.7.2.1 Papers that mention medication adherence

Seven papers made no mention of medication adherence in relation to their trial. (Kereiakes et al., 2015, Ruff et al., 2015) There was no consistent reason why adherence was not mentioned in these papers. For some, treatment was administered directly by a healthcare professional, (Langendonk et al., 2015, Rahman et al., 2015, Saver et al., 2015) and it might have been assumed (or implied) that all participants therefore received their randomised treatment. Other

paper described trials of conditions such as glaucoma and hypertension, conditions for which medication adherence is a highly discussed topic, and also for which treatments have to be taken long-term and self-administered. (Garway-Heath et al., 2015, Williams et al., 2015)

2.7.2.2 Description of type of measures

For the remaining 39 that mentioned medication adherence, 24 papers did not explicitly state how it was measured. (Robert et al., 2015, Scott et al., 2015) While the majority of these went on to report adherence levels, or report some adherence-adjusted trial analysis, two of these papers did not. (Hézode et al., 2015, Kuyken et al., 2015) The remaining 22 papers either reported adherence without adjusting any analysis for it (Cannon et al., 2015, Postow et al., 2015, Robert et al., 2015, Wyles et al., 2015) or performed some form of adjusted analysis. Fifteen papers reported how medication adherence was ascertained, doing so in a variety of ways including direct observations (Desai et al., 2015, Krug et al., 2015), self-reports either via diaries (Leder et al., 2015) or at follow-up visits, (Azizi et al., 2015, Kastelien et al., 2015, Khanna et al., 2015, Tshefu et al., 2015), pill counts, (Gagyor et al., 2015, Marrazzo et al., 2015) electronic monitoring, (Donny et al., 2015), pharmacy records, (Wechsler et al., 2015), biological samples, (Dawson et al., 2015) or using multiple types of measures (Smith et al., 2015)

2.7.2.3 Use of adjusted analysis

Twenty-four papers reported statistical analysis that adjusted for non-adherence in some way. The terminology used varied substantially between papers, with seven referring to their analysis as a "safety" analysis, where six of these excluded participants who had not initiated treatment (Dawson et al., 2015, DeVincenzo et al., 2015, Gerding et al., 2015, Gheorghiade et al., 2015, Grainger et al., 2015, Robert et al., 2015), and the remaining using their safety analysis to analyse participants in the groups corresponding to the treatment received (regardless of the treatment to which they were randomised). (Swain et al., 2015) Other studies reported an "efficacy" analysis that excluded participants who did not initiate treatment (Davies et al., 2015, Kastelein et al.,

2015, Raal et al., 2015, Raal et al., 2015) or a "modified intention to treat" analysis. (Gaudet et al., 2015, Sax et al., 2015, Wainwright et al., 2015, Zinman et al., 2015) For two studies, no specific terminology was used, but the primary analysis excluded participants who did not initiate treatment. (Bachelez et al., 2015, Bakris et al., 2015) A "per-protocol" analysis was reported in four of the studies, all of which defined their own adherence populations. (Desai et al., 2015, Gnat et al., 2015, Lee et al., 2015, Tshefu et al., 2015) Two papers reported "intention-to-treat" analyses that excluded participants who did not receive the intervention. (Cung et al., 2015, Scott et al., 2015) All of the above analyses make post-randomisation exclusions or adjustments. As I will describe in Chapter 6, this risks inducing selection bias unless it is plausible that those excluded or switched are equivalent to those who remain. One paper from the 46 reviewed (2.2%) adjusted trial findings for non-adherence using a randomisation-respecting approach. (Schlumberger et al., 2015) This paper used a rank-preserving structural accelerated failure time model to account for treatment switches in a time-to-event analysis. This paper was not found in the search in Topic 3.

While this paper described treatment switching that followed processes in the study protocol, and was investigator-led (rather than non-adherence in terms of participants not receiving their allocated treatment as intended), it did include a randomisation-respecting analytical approach used to circumvent selection bias through departures from randomised treatment. The key term used in this paper was "crossover bias". To ensure that key papers were not missed during topic 3, I re-ran the search and included this term. Eleven papers were found. However, all but one described investigator-led treatment switching. The one paper that was investigating non-adherence, (Kubo et al., 2015) did so using the same rank-preserving structural accelerated failure time model as Schlumberger et al.

2.7.2.4 Summary

This search of all randomised controlled trials of medicinal intervention published in top medical journals in the past year demonstrates a lack of consistency with regards to the extent to which descriptions of medication adherence are given. Analytical approaches either did not account for non-adherence or were not randomisation respecting in 98% of papers reviewed, and in those that did account for non-adherence there was a lack of consistency around the description of this analysis. The one paper that used a randomisation-respecting approach to adjust for departures from randomisation treatment was not strictly accounting for non-adherence, but rather protocol-approved treatment switching that was instigated by the clinical team. In summary, This search, as well as that carried out in the previous section (Topic 3), demonstrate that for randomised controlled trials of medicinal products, randomisation-based efficacy estimators are a rare feature. More work is needed to investigate the implementation and presentation of these analytical approaches to medical researchers.

2.8 AMSTAR checklist scores and implications

Using the AMSTAR checklist to score these reviews, scores of 5/11 were obtained (where 11 was deemed a systematic review of the highest methodological quality). The key areas where these rapid reviews were negatively marked were:

- No duplicate study entry or extraction: no resource was available to have duplicate study entry or data extraction for any of the reviews;
- Comprehensive literature search was not performed (i.e. only one database): while this is the case, recent work by Hartling et al., 2016 has demonstrated that the vast majority of relevant studies appear within a limited number of databases, and restricting the number looked at rarely altered conclusions or resulted in systematic bias;

- List of excluded studies were not included: while this is also the case, reasons for excluding studies were documented throughout.

Two items were deemed not applicable, as they appeared focused on a systematic review asking a clinical question, rather than methodological literature reviews (assessments of publication bias and conflicts of interest).

Despite this, the literature reviews provide a broad overview of the methodological areas, key authors were identified *a priori*, with searches re-run to screen for their works, and to ensure key papers were not missed during Topic 3, I re-ran the search using a term newly discovered during my review of randomised controlled trials from top medical journals.

2.9 Summary

These literature reviews have identified some key gaps and deficiencies that will be explored during this thesis:

- Adherence to treatments for short-term or acute conditions appears to be an under researched area, with literature tending to focus on long-term conditions. During my thesis, I intend to explore both, and particularly will aim to see how certain paradigms that have been developed for long-term conditions fit with short-term conditions.

- Electronic monitoring is a popular method for obtaining data on medication adherence. Despite this, there seems to be an overreliance on simple summary measure. I plan to use advanced statistical modelling techniques to exploit the richness of data obtained from electronic monitors.

- Bland-Altman plots and limits of agreement are seldom used to assess agreement between different types of adherence measures. I will investigate their use, as well as the use of other agreement techniques and plotting methods during this thesis.

- Approaches for determining risk factors for disagreement between measures will be considered throughout this thesis, as will methods for deriving calibrated measure of adherence when multiple sources are available

- Determining risk factors for non-adherence will be considered for both short and long-term conditions. The value of separating adherence out into different processes (rather than modelling it as a single summary measure) will be explored.

- Modelling approaches that aim to quantify the extent of therapeutic alliance, or influence that clinicians have on a patient's adherence, will be investigated.

- The implementation of randomisation-based efficacy estimators to adjust randomised controlled trials will be investigated. This work will consider these approaches for both placebo-controlled superiority trials and non-inferiority trials with two active treatments. The uses and limitations of these approaches using real world data, as well as effective ways of communicating the approaches and their findings, will be of primary focus.

The following Chapter will describe the data used to address the abovementioned gaps and deficiencies.

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CHAPTER 3: Description of Data Sources

3.1 Introduction

The aim of this thesis is to investigate various methodological challenges that are encountered when studying medication adherence in clinical research. It therefore follows from this aim that data from real clinical research will form the basis of the illustration of these challenges. Datasets from five clinical studies, three of which are from the same research project, will be used throughout this thesis. It is my intention to exemplify and discuss some of the methodological challenges that are common when studying medication adherence and how they differ for various study designs, for example randomised controlled trials and observational studies, and for different clinical conditions, for example short-term or acute conditions and long-term or chronic conditions.

The remainder of this Chapter will provide an introduction to the different research projects and datasets used throughout this thesis. An outline of the studies will be given, the method/s used to record adherence to study medication will be described, and the contribution that the dataset makes to the thesis will be specified.

3.2 GRACE

Acute lower respiratory tract infection (LRTI) is a short-term, largely self-limiting condition that accounts for approximately one fifth of all consultations in primary care. (Currie et al., 2014) The majority of patients who consult with this condition are prescribed antibiotics, though the appropriateness of these prescriptions is often questionable. (Butler et al., 2009) Use (and overuse) of antibiotics has been shown to be associated with the development of antibiotic resistance, (Goossens et al., 2005, Costelloe et al., 2010) the consequences of which involve widespread deaths from common infections and minor illness that were previously treatable. (World Health Organization, 2014) However, adherence to antibiotics in primary care is often

poor. (Kardas et al., 2005, Francis et al., 2012) Poor adherence to antibiotics, in those who are prescribed, them wastes healthcare resources, could negatively impact on clinical outcomes (e.g. slow recovery or increase the risk of complications), and for those in whom they are needed could also result in the infecting bacteria being exposed to suboptimal levels of antibiotic; creating an environment that promotes antibiotic resistance. (Vrijens and Urquhart, 2005)

Genomics to combat Resistance against Antibiotics in Community-acquired LRTI (CA-LRTI) in Europe (GRACE) was a European Union Framework Programme 6 funded network of excellence. The project aimed to combat resistance to antibiotics in CA-LRTI by integrating and co-ordinating the activities of clinicians and scientists from 15 European countries (Figure 3.1).

Figure 3.1: Map of Europe indicating primary care networks involved in the GRACE project

The project was divided into several work packages (WPs), with three of these containing clinical studies. These studies are described in chronological order below. For completeness, Table 3.1 briefly outlines the 12 different WPs included in the project.

Table 3.1: Outline of GRACE work packages

Work package	Purpose
1	Project management
2	Manage data and outputs from all work packages
3	i.) Develop novel rapid genome-based diagnostic tests for the detection of pathogens; ii.) Establish a European repository of specimens and strains linked to a database including microbial and patient information
4	i.) Undertake a large-scale genome wide screen for human susceptibility genes affecting severe CA-LRTI; ii.) Use human genomic data to devise the potential genetic risk profile; iii.) Determine whether the human genetic risk factors identified in GRACE interact with each other or with key microbial genetic or other environmental risk factor
5	Develop and test novel molecular techniques based on amplification-based detection assays
6	i.) Correlate antibiotic resistance, virulence characteristics and pneumococcal genotype to severity of CA-LRTI; ii.) Perform comparative pneumococcal genomics with micro-array technology
7	i.) Investigate the distribution, transmission and evolution of antibiotic resistance; ii.) Assess risk factors for infection with resistant H. influenza;

Work package	Purpose
	iii.) Quantify the relationship between the exposure to antibiotics and both the distribution of resistance elements and their population structure
8*	Describe current presentation, investigation, treatment and outcomes of CA-LRTI and analyse the determinants of antibiotic use in 14 primary care networks across 12 European countries, using qualitative and quantitative approaches
9*	Develop models to i.) Differentiate viral from bacterial infections; ii.) Detect patients with pneumonia; iii.) Identify patients at risk for adverse outcomes including severe and prolonged illness
10*	Develop and conduct i.) A randomised placebo-controlled double-blind trial with patients as unit of randomisation to study the clinical effectiveness of antibiotics in CA-LRTI; ii.) A randomised controlled trial with primary care clinicians' practices as unit of randomisation to study improvements of antibiotic prescribing behaviour
11	i.) Study the economics of molecular diagnostics in CA-LRTI; ii.) Model the macroeconomic impact of resistance and policies to contain it; iii.) Model the cost-effectiveness of the management strategies developed in the observational studies; iv.) Conduct economic evaluations in parallel with the intervention studies
12	Spread knowledge, raise professional and public awareness, and provide training on the containment of antimicrobial resistance in CA-LRTI

*Contained clinical studies used throughout this thesis

3.2.1 GRACE WP8 observational study

This was a prospective observational study, conducted between 2006 and 2007, that aimed to describe the presentation, management, and outcomes of patients consulting in primary care with an acute cough or signs suggestive of a LRTI. (Butler et al., 2009)

Patients were eligible for the study if they were aged 18 years or older, consulting with an illness where an acute or worsened cough was the main symptom (or their clinical presentation suggested a LRTI), had been unwell for no longer than 28 days, were consulting for the first time with their particular illness episode, were seen within normal working hours, had not previously participated in the study, were able to fill out study materials, had provided written informed consent, and were considered immunocompetent.

Recruited participants had their clinical history, presenting signs and symptoms, and management recorded on a case report form (CRF), and were then asked to complete a diary for up to 28 days. The diary contained daily information regarding the severity of symptoms and the use of medication. Adherence data were therefore obtained via self-report (Figure 3.2).

A description of the variables considered can be found in Appendix I.

Figure 3.2: Example of self-report medication use questions taken from the GRACE WP8 diary

2. Have you taken medicine for your cough during the past week? ☐ Yes ☐ No

If yes, please give the details and tick each study day you took each medicine

Name of medicine	Number of doses per day	Tick if the medicine was prescribed for you	Day						
			8	9	10	11	12	13	14
		☐							
		☐							
		☐							

The data obtained from GRACE WP8 are from an observational study. They are therefore more likely to reflect the behaviour of patients under normal circumstances. Participants in

randomised controlled trials tend to receive considerably more information about their treatment, are more closely monitored, and tend to have higher motivations for participation. Their adherence levels may therefore not reflect that which is seen in routine practice.

These data will be used to investigate the determinants of adherence to antibiotics for this condition, and will be useful in comparing adherence levels and determinants across different study types for the same condition, with observational studies likely to more closely reflect practice than randomised controlled trials.

3.2.2 GRACE WP9 observational study

Similar to WP8, GRACE WP9 was also a prospective observational study. It was conducted between 2007 and 2010, and aimed to investigate the aetiology, diagnosis, and prognosis of LRTI. (van Vugt et al., 2013) The key difference between this study and the WP8 observational study is that participants in this study provided various biological samples alongside being observed over time.

Eligibility was similar to that in GRACE WP8, with the addition of patients having not been on antibiotic treatment in the previous month and not pregnant at the point of recruitment.

Data collection methods were similar to GRACE WP8, and adherence was captured via self-report. The rationale for including these data in this thesis are therefore the same as for the previous study.

A description of the variables considered can be found in Appendix I.

While participants in GRACE WP8 and WP9 could be prescribed any treatment for their illness, the analysis in this thesis will be restricted to those that were prescribed amoxicillin for immediate use. Amoxicillin is the recommended first-line choice of antibiotic for LRTI in the European Union, and consequently the most frequently prescribed. By focussing on this

treatment, it allows for the investigation of the impact of the dose, frequency, and duration without being confounded by type of antibiotic prescribed. This thesis does not consider adherence to delayed prescriptions, focussing solely on amoxicillin prescribed for immediate use. While a delayed prescription is also a legitimate prescribing strategy, adherence under this strategy is ambiguous. Delay instructions can often be vague (for example, "here is a prescription if you get any worse"), and delayed prescriptions are often issued with the intention that the patient would never actually take their treatment. This is in contrast with a prescription issued for immediate use, where the working assumption is that the clinician intended that the treatment would be taken as prescribed.

GRACE WP10a placebo-controlled trial

The aim of GRACE WP10a was to investigate the benefits and harm of amoxicillin in acute uncomplicated community-acquired LRTI. To achieve this, a randomised placebo-controlled trial was conducted between 2007 and 2010, nested within GRACE WP9. (Little et al., 2013)

Patients were eligible to participate in the trial if they met the eligibility criteria for WP9, and in addition were not allergic to penicillin (or have a contra-indication for amoxicillin because of a major interaction with other medication), and their history/physical examination was not suggestive of community-acquired pneumonia (see Table 3.2 for a comparison of eligible criteria).

Table 3.2: Comparison of eligibility criteria for the GRACE WP8, WP9, and WP10a studies

Eligibility criteria	WP8	WP9	WP10a
Aged 18 years or over	x	x	x
An illness where an acute or worsened cough is the main or dominant symptom, or a clinical presentation suggesting LRTI, < 28 days duration	x	x	x
First consultation for this illness episode	x	x	x
Seen within normal consulting hours	x		
First time in the study	x	x	x
Able to fill out study materials	x	x	x
Written consent to participate	x	x	x
Immunocompetent	x	x	x
Not been on antibiotic treatment in previous month		x	x
Not pregnant		x	x
Allergic to penicillin or have a contra-indication for amoxicillin because of a major interaction with other medication			x
History/physical examination suggestive of community acquired pneumonia (CAP)?			x

Randomised participants received a prescription for amoxicillin, to be taken as two 500mg tablets three times a day for seven days, or a placebo identical in appearance, taste and texture. Other data collection methods were similar to GRACE WP8 and WP9.

A description of the variables considered can be found in Appendix I.

While data collection methods were mostly similar to GRACE WP8 and WP9, adherence to trial medication in WP10a was also recorded via tablet counts at the end of the study and during telephone follow-ups, with the latter generally conducted in participants who had not returned a diary (i.e. after the 28 day follow-up period).

The data from GRACE WP10a will contribute to this thesis in many ways. Capturing adherence using multiple types of measures allows for a comparison of the different types, and levels of agreement between types to be estimated. Using other information on the trial participants, variables that predict disagreement can also be investigated. The participants allocated to the amoxicillin group can be used to explore the determinants of adherence to amoxicillin. Finally, data from participants in the whole trial can also be used to investigate the use of randomisation-based efficacy estimators for adjusting trial findings for treatment non-adherence.

CODA

Ulcerative Colitis (UC) is a chronic inflammatory disease that affects the internal lining of the colonic mucosa and rectum, with patients exhibiting symptoms such as abdominal pain, blood and pus in stools, diarrhoea, fever, rectal pain and weight loss. The estimated prevalence of UC is 8 to 246 cases per 100,000 per year, and is most commonly seen in the populations of Northern Europe and North America. The disease is often relapse-remitting, with patients experiencing few or no symptoms between systematic flare ups. (Ardizzone, 2003) Coated formulations of mesalazine (Asacol®) have been demonstrated in many trials to prevent relapses in patients who have achieved remission. (Sutherland and MacDonald, 2006) Treatment is often prescribed in

divided daily doses (e.g. two or three times daily dosing schedules (BD, TDS)), (BNF Online, 2013) with adherence and treatment success suffering as a result. (Shale and Riley, 2003, D'IncÀ et al., 2008) There has thus been an increasing interest in evaluating once-daily (OD) dosing of mesalazine. (Hussain et al., 2001, Kane, 2006, Gandia et al., 2007, Flourie et al., 2013)

The Colitis Once Daily Asacol (CODA) study assessed the efficacy and safety of OD dosing with mesalazine versus TDS dosing over a 12-month period for patients in remission with UC. (Hawthorne et al., 2012) Patients were eligible to take part in the study as long as they were in remission with UC and on maintenance therapy with mesalazine, sulfasalazine, olsalazine, or balsalazide for at least 4 weeks, but who had had at least one relapse within the previous two years. Patients had to be aged over 18, if female to be taking adequate contraception (if otherwise able to conceive), and able to give informed consent. Patients were excluded if they had Crohn's disease; symptoms of active colitis; a modified Baron score at sigmoidoscopy of 2 or 3; used enema or suppository therapy for UC in the past 4 weeks; had started or altered the dose of azathioprine or 6-mercaptopurine in the past 3 months (these drugs were permitted if in stable dosage over that period of time); had intolerance to mesalazine; known HIV infection; significant renal or hepatic impairment; or other medical or psychiatric disorder (including alcohol dependence) that in the opinion of the investigator would affect participation in the study; or females if pregnant or lactating.

Randomised participants were given 800mg Asacol tablets and told to take either three tablets once daily (OD) or in three divided doses (TDS) for 12-months or until relapse (whichever came first). Participants attended trial follow-up visits at six weeks, six months, and 12 months after randomisation, or in the event of a suspected relapse. In addition, participants were also contacted via telephone at three and nine months.

A description of the variables considered can be found in Appendix II.

The study found that the OD regimen was no worse than TDS in terms of clinical relapse. Although this was attributed to better adherence among the participants allocated to the OD regimen, the main trial captured adherence using self-report and tablet counts at clinic visits, two types of measures with several known limitations. Detailed measures of adherence in this setting were also lacking from previous trials of patients in remission with UC. Foreseeing this as a problem, a sub study was run alongside the main study. The aim of this sub study was to evaluate the impact of an OD dosing regimen on treatment adherence using electronic monitors (namely, the Medication Event Monitoring System, or MEMS), a more intensive monitoring process to capture adherence than that had been used previously (Figure 3.3).

Figure 3.3: Example of a MEMS container

The data from the CODA study will contribute to this thesis in several ways. The long-term chronic condition of UC will provide a contrast to the short-term nature of acute LRTI. Adherence was captured using self-report and tablet counts during the main study, and also electronic monitoring for the substudy. Therefore a subgroup of CODA participants will have adherence measured in three different ways.

Capturing adherence using electronic monitoring allows for each dosing event to be recorded. This provides very rich data over a 12-month period, and allows for longitudinal modelling and the exploration and testing of behavioural aspects of medication taking.

The main study was also designed to assess the non-inferiority of the OD regimen over the TDS regimen on the rate of relapse over the 12-month follow-up period. The data will therefore be used to investigate different approaches to adjusting trial findings for non-adherence – particularly in the case of the CODA study exploiting the non-inferiority design, use of an active control group, and the similar nature of the treatment groups.

ZICE

Bone metastases cause major morbidity in metastatic breast cancer. The introduction of bisphosphonate therapy has led to a substantial reduction in the incidence of skeletal-related events for this clinical condition, (Wong et al., 2012) and in particular zoledronic acid, which has been shown to lower skeletal morbidity rates and risk of skeletal complications compared to standard therapies. (Rosen et al., 2003)

However, zoledronic acid is given by four weekly intravenous infusion, which may be inconvenient for patients who may not otherwise need to attend hospital. An alternative bisphosphonate, ibandronic acid, is available in both intravenous and oral formulations. Alongside the potential for reducing inconvenience, a self-administered oral therapy is likely to incur considerably less healthcare costs compared to a therapy administered via intravenous in hospital.

The Zoledronate versus Ibandronate Comparative Evaluation (ZICE) study was a randomised phase 3 trial designed to assess the noninferiority of oral ibandronic acid compared with intravenous zoledronic acid in preventing skeletal-related events in an unselected UK population of patients with breast cancer metastatic to bone. (Barrett-Lee et al., 2014)

Randomised participants were either assigned to receive intravenous zoledronic acid (4mg over a minimum of 15 minutes in at least 100mL of saline) every four weeks for 96 weeks or one 50mg tablet of ibandronic acid to be taken daily for 96 weeks. Following randomisation,

participants were assessed at three to four week intervals up to week 12, and every 12 weeks up to 96 weeks thereafter. Following week 96, participants were assessed every year up to five years post-randomisation. Adherence to study medication was noted by the treating clinician at interim and 12-weekly visits (clinician / self-report).

The primary outcome in the main ZICE study was based on the time and frequency of skeletal-related events (SREs) over the first 96 weeks post-randomisation. For illustrative purposes, this thesis will focus on a simplified version of this outcome, specifically the proportion of participants experiencing a skeletal-related event during the first 12 months of the study.

A description of the variables considered can be found in Appendix III.

The original study found that oral ibandronic acid was inferior to intravenous zoledronic acid, though side effect profiles were similar in both groups and the oral treatment was generally more convenient.

Like the CODA study, data from the ZICE study allows for the assessment of adherence to a long-term condition and was designed to assess non-inferiority. However, unlike CODA, ZICE has two very contrasting treatment arms, comparing a four-weekly intravenous therapy administered in hospital by a clinician to a daily oral therapy self-administered at home. This study will mainly be used during this thesis to investigate different approaches to adjusting trial findings for non-adherence.

Summary

This Chapter described the data sources that will be used throughout the following three Chapters, including a justification for the study, a description of the data flow, and the rationale for using these particular studies throughout this thesis. This concludes the background Chapters that have laid out the motivation of the thesis, problems that will be addressed, and data sources

that will be used. The next three Chapters will each focus on distinct methodological challenges encountered when studying medication adherence in clinical research, providing the reader with detail on the methodologies used, and using the data sources to illustrate how the proposed methods work on data from real clinical research studies.

CHAPTER 4: Measuring Medication Adherence in Clinical Research: Correlation, Agreement, and Calibration Techniques

4.1 Introduction

When clinical research involves determining the safety and efficacy of treatments intended for human use, the goal is to conduct this research as rigorously as possible, while balancing this within the confines of limited resources. In clinical research aiming to generalise findings to a real world setting, there is an additional aspiration of ensuring that considerations have been made related to the usefulness and implementation of these findings in practice (e.g. outcomes have been selected that are of importance to patients and clinicians). (Loudon et al, 2015) The study of medication adherence within clinical research does not escape these restrictions, and as such there is a reliance on methods for measuring adherence that are cheap, minimise participant burden, and can be replicated in a real world setting, if required. (Lam and Fresco, 2015) The consequence of this is that the majority of medication adherence measures used in clinical research are indirect. That is, they rely on unverifiable assumptions that vary in their degree of plausibility, depending on context, and consequently multiple modes of measurement are often used in clinical research. Gaining an understanding of different types of measures of medication adherence, their advantages and disadvantages, how to compare them (when multiple modes are available), and what to do when disagreement occurs, is therefore an area of great importance in this field.

The aims of this Chapter are to compare several methods commonly used for measuring medication adherence in clinical research, using a variety of method-comparison techniques. I will demonstrate the potential of advanced statistical modelling techniques for modelling patterns in electronically monitored medication adherence over time. Moving beyond method-comparison, I will also investigate the predictors of disagreement between medication adherence

measures, and develop calibration techniques to arrive at summary measures of medication adherence that incorporates knowledge and uncertainty from the different types of measures.

To meet these aims, this Chapter will draw on data from the CODA and GRACE WP10a studies, to highlight the differences and similarities between medication given for long-term and short-term conditions.

4.2 Methods

4.2.1 Adherence definitions, summary measures, and assumptions

As described during Chapter 3, adherence to medication during the CODA study was monitored via self-report and tablet counts at study follow-up visits, and electronically via the MEMs. Participants were asked about their adherence levels (i.e. whether or not they thought they had taken their study tablets as prescribed at least 90% of the time) and the ease of medication taking (very easy, fairly easy, fairly difficult or very difficult to remember to take their medication). These provide retrospective accounts of adherence. For analysis purposes, these reports are taken at face value (i.e. it was assumed that participants reported their levels of adherence accurately and had perfect recall in the time under consideration). Tablet counts were performed by trained research nurses at each trial follow-up visit. It was assumed that the difference between the number of tablets participants started with and the amount remaining at each follow-up visit equated to the amount taken during the time interval. For the purposes of reporting, adherence measured using tablet counts was reported as the number of tablets taken expressed as the percentage of correct number of tablets taken. The date and time of bottle cap openings were electronically recorded using the MEMS, with data uploaded onto the study database at each trial follow-up visit. Calculating adherence using the MEMS assumed that the correct number of tablets were removed and consumed each time the bottle was opened. Adherence was reported

as the percentage of days that a participant adhered to their allocated regimen (i.e. the percentage of days that a participant opened their bottle the correct number of times).

The GRACE WP10a study measured adherence to allocated medication via self-reported diaries, tablet counts, and self-reports collected over the telephone. Using their daily symptom diary, participants prospectively recorded whether or not they took their study medication on a given day, and whether they took their study medication according to the instructions. Participants for whom a diary was not returned were asked to (retrospectively) state the number of days that they took their study medication. This information was collected via telephone interviews. Participants were also instructed to return their study medication bottles, complete with any unused medication, at the end of the trial. The number of tablets returned was recorded by members of the research team. Participants were given 42 tablets in total (two 500mg tablets, to be taken three times a day for seven days).

Adherence to study medication was defined as the percentage of the correct number of tablets taken during the first seven days of the follow-up period (i.e. the period for which the medication was prescribed). For each of the three types of measures, a binary definition was also created, with a cut-off at 100% (i.e. took all prescribed tablets during the first seven days of the follow-up period).

Where participants indicated that they had taken medication on a particular day, in the absence of information to the contrary (e.g. stating that they only took one tablet three times a day instead of two tablets), to calculate adherence, an assumption was made that a participant consumed all study medication as instructed. Where medication bottles were returned, it was assumed that the difference between the number of tablets prescribed and the number returned equated to the number of tablets consumed. It was also assumed that all tablets were consumed during the first seven days of the follow-up period. Where a short questionnaire or telephone call was

conducted, it was assumed that the correct numbers of tablets were taken for the number of days medication was reportedly taken. Table 4.1 provides a summary of the types of measures used and assumptions made across the two studies.

Table 4.1: Types of medication adherence measures available across the CODA and GRACE studies

Type of measure	Data collection intensity	Measured in CODA	Measured in GRACE	Assumptions
Self-report at clinic visits	Clinic visits (6 weeks, 6 months, 12 months)	✓		Accurate reporting. Perfect recall.
Self-reported diary	Daily		✓	
Self-reported telephone	At the end of the study		✓	
Tablet counts	Clinic visits	✓	✓	All tablets not returned were consumed. Consumption was in line with prescribed regimen.
Electronic monitoring	Each dosing event	✓		Dosing event equates to correct number of tablets being consumed.

Quantitative measures are reported as means with associated standard deviations, medians, and minimum / maximum values. Binary measures are reported as frequencies and percentages.

4.2.2 Longitudinal modelling of electronic monitoring data

Using the data obtained from the MEMS caps, medication adherence was modelled over time by fitting a two-level generalised linear (logistic) mixed effects model, with daily adherence indicators nested within participants. This is an extension to the generalised linear model, (McCullagh and Nelder, 1989) and is a useful approach for modelling discrete repeated measures. (Verbeke, 2005) The general model formula is given by $y = X\beta + Z\gamma + \epsilon$, where y

is the outcome variable, X represents the predictor variables, Z represents the random effects (participants for whom multiple daily adherence indicators are available), and ε are the residuals. A logit link function ($log\left(\frac{p}{1-p}\right)$) is applied to account for the binary nature of the outcome variable. Alternatives to this approach would involve summarising adherence over the time period, or not accounting for the correlated nature of responses within individuals. For the former, information regarding the evolution of adherence over time (and behavioural patterns over time) would be lost. For the latter, assuming observations were independent would risk calculating standard errors that were artificially narrow, and hence drawing erroneous conclusions regarding the width of the confidence intervals around model estimates. For these models, a participant was assumed to have adhered to their allocated regimen on a given day if they opened their cap the required number of times (once for the OD group and three times for the TDS group). Non-linear patterns of adherence over time were accounted for using B-splines. The model also accounted for different participant adherence patterns by fitting B-spline estimates of a time-varying mean with random coefficients, thereby allowing each participant to have their own individual curve that was not restricted by the overall fixed effect curve. B-splines are piecewise polynomials with interior knots (or turning points) linking each polynomial function via a series of linear combinations. (Marsh and Cormier, 2001) An accessible mathematical formulation of B-splines has been presented previously. (Weisstein) B-splines provide a flexible and arguably more interpretable approach to accounting for non-linear effects in regression models. Alternative approaches involving making linearity assumptions or fitting polynomial functions (e.g. modelling time as a quadratic or cubic function, or using fractional polynomial functions (Royston and Altman, 1994)). However, the drawback of these is poorer model fit, implausibility of assumptions, and difficulties in interpretation. (Tilling et al., 2014) Trial arm (dosing regimen) was included in the model as an explanatory variable, in order to describe the

difference in adherence patterns between regimens. The interaction between trial arm and time was also explored, in order to assess whether adherence trajectories differed for each regimen.

To explore any potential differences in adherence during the week compared to the weekend, the above model was extended by the addition of an indicator that distinguished whether a day fell on a weekday or weekend. Its interaction with trial arm was also explored to determine whether these differences were larger for participants allocated to a particular dosing regimen. Similarly, the model was also extended to explore any potential differences in adherence at clinic visit dates (defined as the date of a scheduled clinic visit and one week either side of this date). Model fit was assessed using Akaike's Information Criterion (AIC). (Akaike, 1974) The AIC is a relative assessment of model fit (i.e. it compares the fit of a model relative to each of the other models fitted) that penalises for the number of parameters included in the model. The AIC value is calculated as $AIC = 2k - 2\ln(L)$, where k is the number of parameters and L is the maximum value of the likelihood function, and smaller AIC values reflect better model fit. Results are presented as odds ratios with associated 95% confidence intervals and p-values.

4.2.3 Comparing different types of measures

4.2.3.1 Correlation

Different types of measures were initially compared using correlational methods. Scatter plots were produced to compare different quantitative measures to each other. Each scatter plot includes a black dashed line along the line of perfect agreement (y=x). Where multiple data points overlapped (i.e. there was over-plotting), jittering and semi-transparency were used to highlight this, (Few, 2009) with these modified plots displayed beneath the original. Pearson product-moment correlation coefficients were calculated to compare the different types of measures, (Pearson, 1895) with mathematically equivalent point biserial correlation coefficients used for the binary measures. (Glass and Hopkins, 1970) To provide some qualitative

description and visualisation around the correlation coefficients, intervals suggested by Hinkle et al. with increasingly darker shades of yellow indicating stronger correlation (Table 4.2).

Table 4.2: Descriptions and visualisations of correlation coefficients*

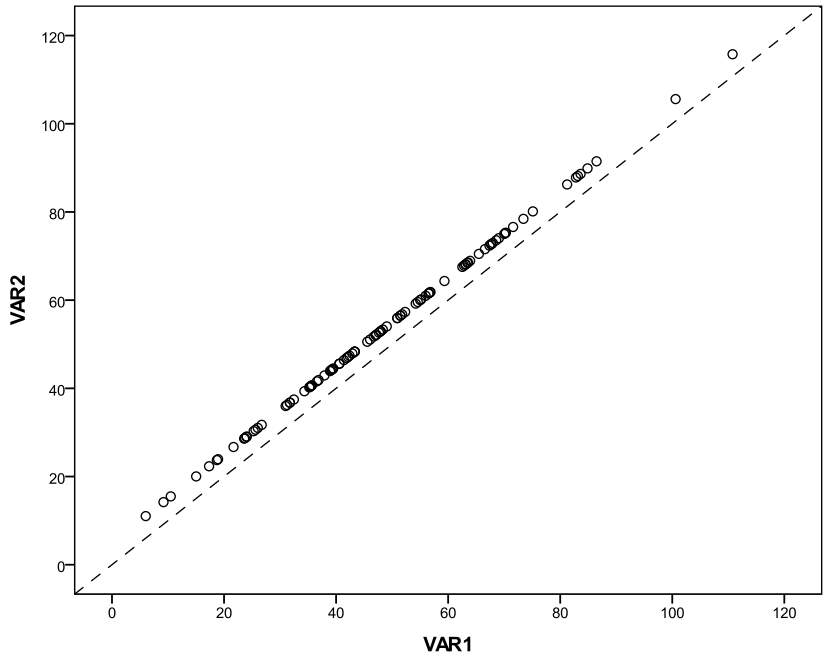
Size of Correlation	Interpretation	Colour code indication
>.90 to 1.00 or −.90 to −1.00	Very high positive or negative correlation	
>.70 to .90 or −.70 to −.90	High positive or negative correlation	
>.50 to .70 or −.50 to −.70	Moderate positive or negative correlation	
>.30 to .50 or −.30 to −.50	Low positive or negative correlation	
.00 to .30 or .00 to −.30	negligible correlation	

*Intervals and interpretation as suggested in Hinkle et al., 2003

4.2.3.2 Agreement

Correlation provides an assessment of the linear relationship between two variables. However, given the nature of the variables being compared (i.e. different ways of measuring adherence to medication), a high degree of correlation would not be surprising. What correlation cannot tell you is how well different types of measures agree. High correlation can be found between two variables without any agreement whatsoever, as demonstrated in Figure 4.1.

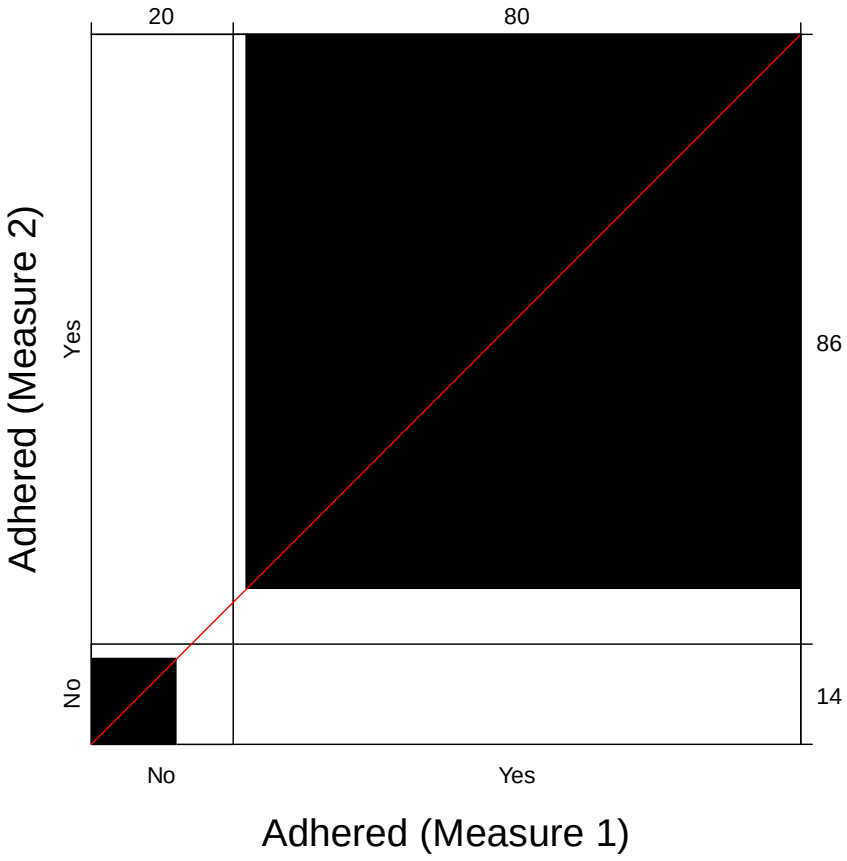
Figure 4.1: Scatter plot of two simulated variables showing perfect correlation but no agreement*



*The black dashed line represents the line of perfect agreement (i.e. y = x).

Throughout this Chapter, agreement between different types of measures is presented in several ways. For dichotomous measures of adherence, observed agreement, expressed as a percentage, will be presented (e.g. the percentage of times both measures either indicated less than 100% adherence or 100% adherence) alongside kappa statistics (a measure of inter-rater agreement for categorical items that corrects for chance agreement) (Cohen, 1960) and Bangdiwala observed agreement charts. (Bangdiwala, 1988) These charts plot observed agreement between categorical measures and provide a graphical illustration of an N x N contingency table. The white rectangles represent marginal totals, and the area shaded black within them represents the amount of observed agreement (Figure 4.2).

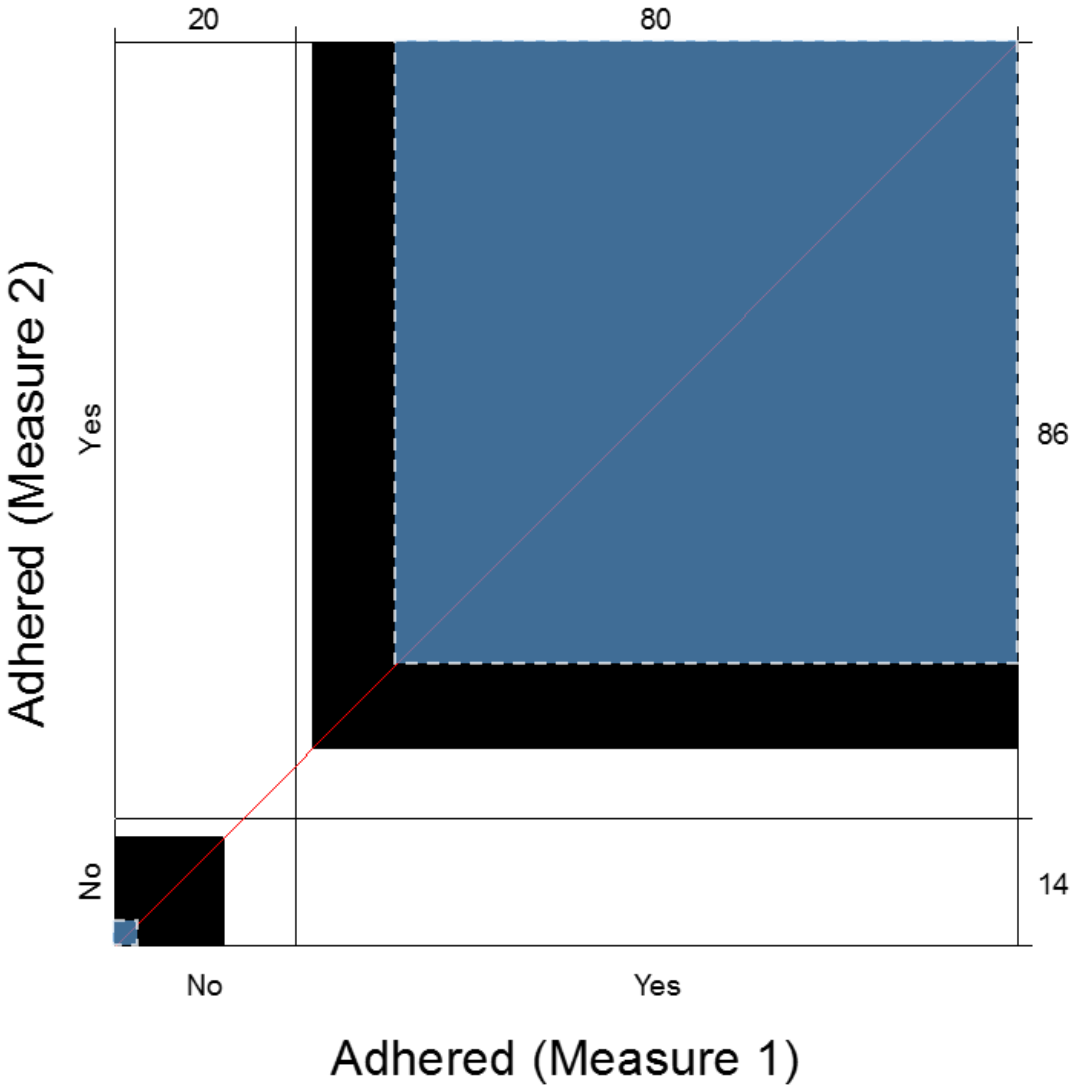
Figure 4.2: Example of a Bangdiwala observed agreement chart for two binary measures of adherence



In the paper first proposing these charts, it was acknowledged that it was not easy to visualise the kappa statistic on the chart. However, in my experience, the components that make up the kappa statistic (that is, the relative observed agreement, and the relative agreement that would be expected by chance) provide greater information than the statistic itself. I therefore propose an extension to these charts that involves overlaying the observed agreement with the expected agreement. This chart can provide additional information which would have otherwise been lacking. See Figure 4.3 for an illustration of these extended charts. In this Figure, the expected agreement (i.e. assuming that adherence for each measure is determined by chance) is represented by a blue semi-transparent square that overlays the observed agreement. The

interpretation of the black shaded region thus alters slightly, and becomes the amount of observed agreement that is in addition to that expected purely by chance.

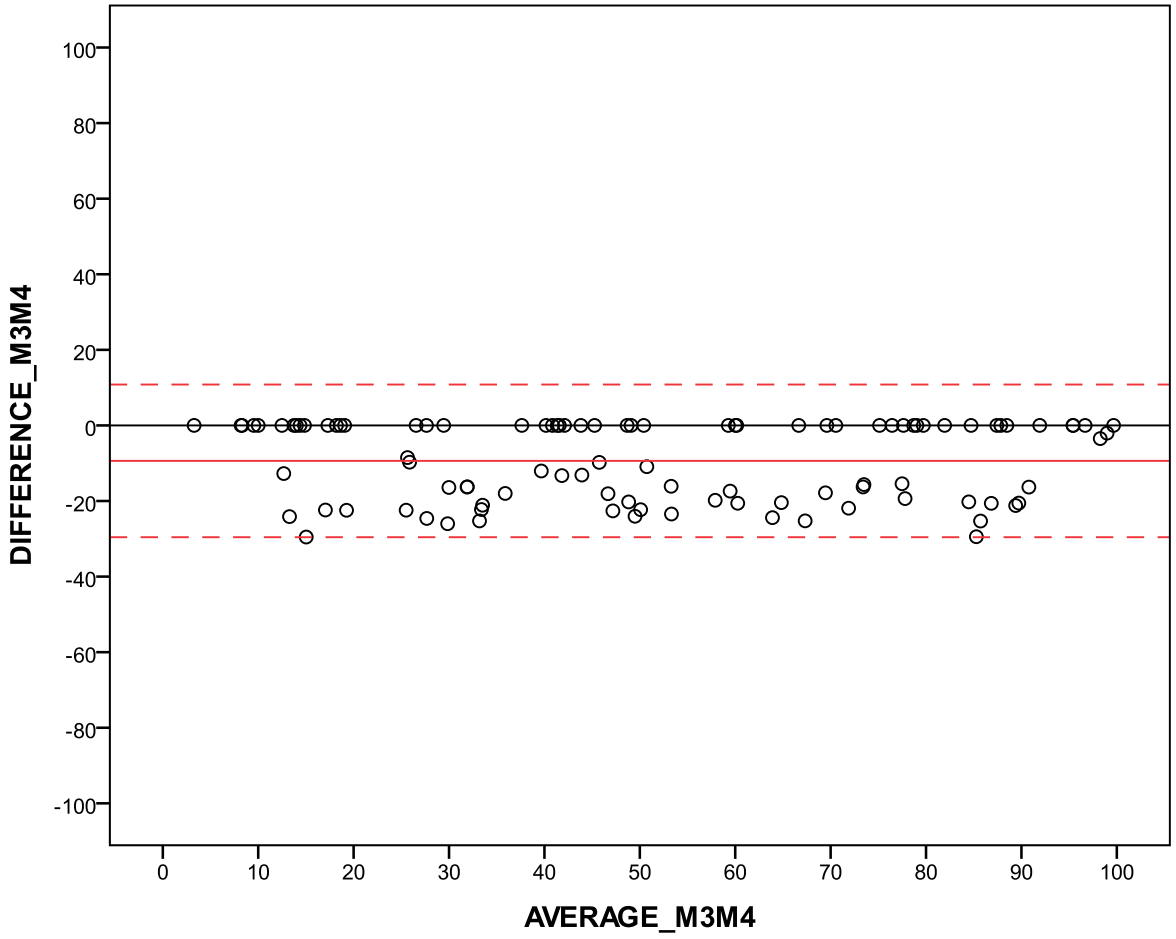
Figure 4.3: Example of an extended Bangdiwala agreement chart for two binary measures of adherence (with chance agreement also illustrated)



For continuous or interval measures, Bland-Altman plots will be presented. (Bland and Altman, 1986) These plot the average of two types of measure against the difference. Perfect agreement would be illustrated in these plots by all data points lying along the line y = 0, with symmetric random scatter above and below the line an indication of no systematic biases in either of the measures. The mean difference is calculated, to indicate the degree of systematic bias between

the two types of measures (red solid line), with 95% limits of agreement also displayed to indicate the extent of disagreement likely to be seen for most participants (red dashed lines). See Figure 4.4 for an illustration of these plots.

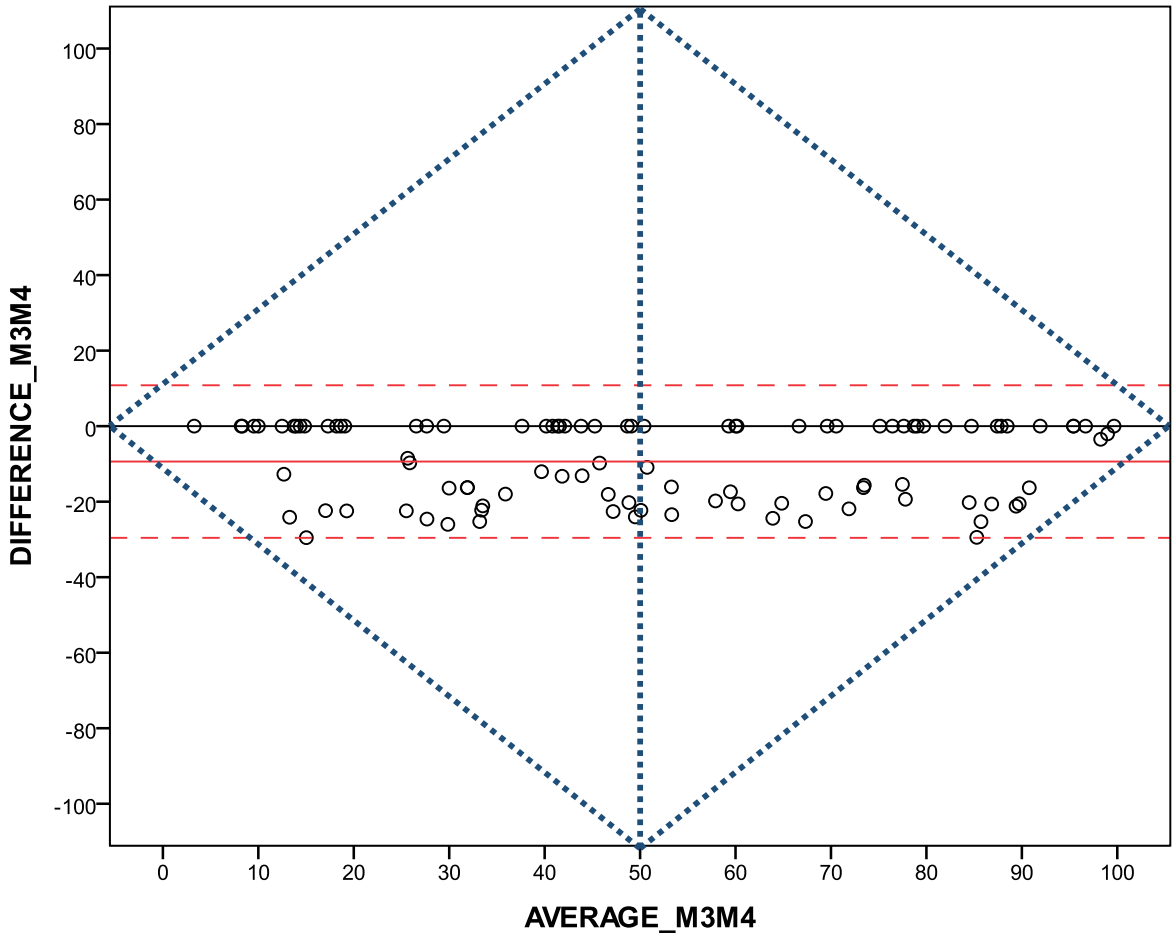
Figure 4.4: Example of a Bland-Altman plot of the comparison of adherence as measured by measure 3 (M3) and measure 4 (M4)



What is not obvious from Figure 4.4, but is clear on plots with more extreme values, is that when comparing two measures on the same scale (for example, two measures of adherence that range from 0 to 100), data points can only ever be plotted within a restricted space. For the example provided in Figure 4.4, the most extreme a data point could be is [50, +/- 100], and in general this would be $\left[\frac{max(x_i)}{2}, \pm max(x_i)\right]$, where x is the measure of interest and i=1, 2. The

relationship between the difference and the mean imposes this restriction (i.e. as the average of the two measures moves away from 1/2 of the maximum, the difference between the two measures gets smaller). This has implications for the 95% limits of agreement, and I propose an extension to these plots that involves overlaying with a diamond shape that indicates the space in which the data points can lie. An example of this is given in Figure 4.5, with the effective space being indicated with navy dashed lines.

Figure 4.5: Example of an extended Bland-Altman plot of the comparison of adherence as measured by M3 and M4 (with boundaries marked)



Measuring and examining the comparability of different types of adherence measures is a useful way of establishing the quality of the adherence data that has been collected. However, in order to maximise the benefits of collecting multiple types of adherence measures, further

investigations can be carried out to determine characteristics that predict disagreement between measures, and approaches to generate an agreed or calibrated measure of adherence. It is clear to see why calibration is worthwhile. In practice, the use of multiple types of adherence measures implies a lack of trust in any of the measures used. The aim of calibration, in this instance, is to achieve a measure of adherence that is closer to the truth (or at least has less systematic bias). Understanding the circumstances and situations that are likely to lead to greater disagreement can inform researchers (and potentially practitioners) of adherence measures that are most suited to certain populations, and whether certain populations require adherence measured via multiple methods (i.e. a risk-adapted approach to adherence monitoring).

4.2.3.4 Predictors of disagreement between different types of adherence measures

Three different approaches were taken in this thesis to investigate predictors of disagreement between different types of adherence measures. The first approach, and simplest of the three, was to treat the comparison as a dichotomous variable (disagreed / agreed) and investigate predictors of disagreement using logistic regression. The second approach was to consider the difference between types of measures and create a categorical variable that indicated whether they were the same (i.e. agreed), one was lower, or higher, investigating predictors of being lower or higher compared to being the same using multinomial logistic regression. The third approach taken was to consider the direction and extent of disagreement by treating the difference between types of measures as a continuous variable and investigating predictors using linear regression.

The GRACE WP10a data were used to investigate predictors of disagreement using the three approaches described above. Adherence according to self-report diaries and tablet counts were used, as these two types of measures were most frequently available for participants. When considering the direction and extent of disagreement, this was based on self-reported diary minus tablet count adherence data, and therefore the "lower" category, or a lower value meant that adherence data according to self-reported diaries was lower than tablet count data, and vice versa.

The clustered nature of participants within clinicians was accounted for by fitting mixed models for approaches 1 and 3 (i.e. two-level logistic and linear regression models), and by calculating cluster-robust standard errors for the multinomial logistic regression model. (Williams, 2000) The candidate variables considered for inclusion related to participant characteristics (age, gender, co-morbidities, use of chronic medication, and smoking status (never/past/current)) and characteristics about the illness with which the participant presented (presence/absence of 14 different symptoms, clinician-rated symptom severity, auscultation abnormality, and days waited prior to consulting). Variables were selected into a univariable model and retained if they were significant at the $p < 0.1$ level (it was sufficient to demonstrate an association at the $p < 0.1$ level for at least one of the lower / higher comparisons for the multinomial logistic regression model). Variables in the multivariable model that were not significant at the $p < 0.05$ level were removed sequentially, from largest to smallest p-value, until a final multivariable model was attained. Findings from the models are presented as odds ratios / relative risk ratios / mean differences, for approaches 1, 2, and 3 respectively, with associated 95% confidence intervals and *p*-values.

4.2.3.5 Calibrating adherence

Where multiple types of methods are used to measure adherence, and there are discrepancies between them, several approaches could be taken to adjust or agree upon a measure that takes into account these discrepancies. The GRACE WP10a data were used throughout this section. The approaches considered in this Chapter are described below:

4.2.3.5.1 Range calibration

This approach is based on taking the minimum or maximum adherence measure across several types of measures. There are several advantages to using an approach such as this. It is easy to understand and communicate, it allows for calibration based on more than two methods of measurement, and while taking the minimum could be viewed as conservative, also reporting the maximum gives a likely range of the level of adherence in a given sample.

4.2.3.5.2 Hierarchy calibration

Calibrating adherence based on a hierarchy involves making a judgement by ranking your methods from most to least reliable, and basing your measure on the most reliable method you have available. In a similar way to the range calibration, this is easy to understand and communicate and calibration can be based on more than two methods of measurement. However, the judgement is, to some extent, subjective (though can be based on previous evidence and the plausibility of the assumptions each method makes), and can vary depending on the context (e.g. the medication and regimen under investigation, the population of interest, etc.) Using the GRACE WP10a data, the ordering of the hierarchy was:

1. Adherence based on tablet count data
2. Adherence based on self-reported diary data
3. Adherence based on self-reported telephone data

4.2.3.5.3 Calibration based on classification

The final calibration approach presented in this thesis is an adaptation of a technique developed by Dukic et al. The original technique used biological assays to measure cotinine, a metabolite of nicotine, to calibrate self-reported measures of smoking in pregnant women. While a more direct adaptation of this technique would rely on biological assays, the general approach can be adapted for other methods of medication adherence measurement. The calibration approach, based on having two types of measures, is as follows:

1. Declare one type of measure as the reference standard (the measure that will be used to calibrate) and one as the comparator (the measure that will be calibrated). Using the GRACE WP10a data, tablet count data were used to calibrate self-reported diary data. Tablet count data were used as the reference standard. While adherence according to

self-reported diary allowed for an assessment of whether a participant took their medication on a given day, it had to be assumed that if they stated they had taken it, they had also taken the correct number of tablets. Calibrating by tablet count data therefore provided a way of correcting for instances where this assumption may not have been true.

2. Calculate adherence according to each measure and compare them
3. Classify individuals into groups based on the above comparison and some sensibly chosen cut-offs:
    a. Extreme over-reporter
    b. Over-reporter
    c. Accurate reporter
    d. Under-reporter
    e. Extreme under-reporter

Participants were classified as "accurate reporters" if there was perfect agreement between self-reported diary and tablet count adherence data (i.e. zero difference). A cut-off of 1/7 was used to distinguish between over/under-reporters and extreme over/under-reporters. This cut-off was chosen as it reflected a discrepancy equivalent to an entire days' worth of medication. Participants were given 42 tablets, to be taken as two tablets, three times a day for seven days. Adherence was expressed as a percentage and 6/42 expressed as a percentage is 1/7. Over/under-reporters were classified so if the discrepancy between self-reported diary and tablet count adherence was up to 1/7 percentage points (inclusive), with extreme classifications given when the discrepancy exceeded this cut-off.

4. Calculate the mean in each of the above groups

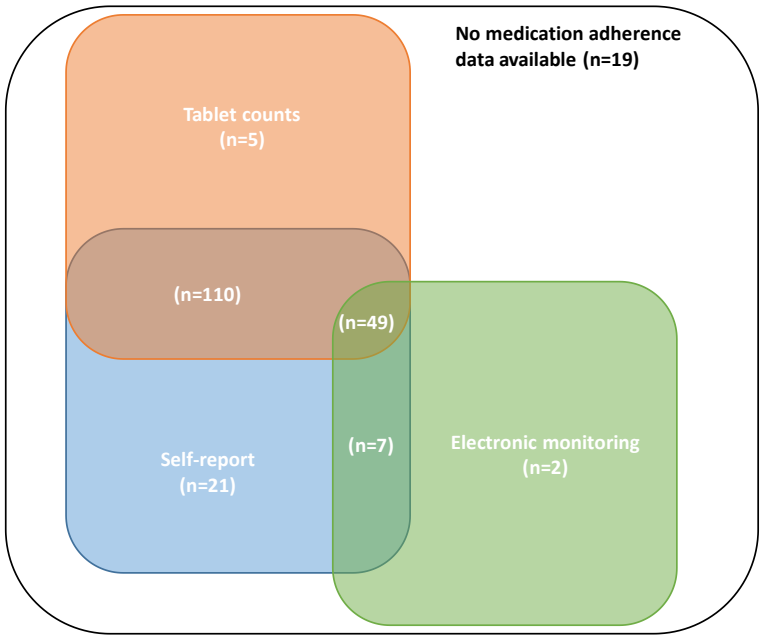
5. Use these means and the group to which an individual belongs and calibrate their adherence measure

4.3 Results

4.3.1 Available data

A total of 213 participants were recruited into the main CODA study, with 61 of these also included in the sub-study that involved the use of electronic monitoring of medication use. Self-reported adherence data were available for 187 participants (87.8%), with 164 having tablet count data (77.0%). Of those included in the sub-study, 58 had valid electronic monitoring data (95.1%). Electronic monitoring data was therefore available for 27.2% of all participants in the CODA study. Nineteen participants had no data collected that could be used to assess adherence to medication (8.9%). All three types of measures were available for 49 participants (23.0%). Participants infrequently only had one type of measure available (21 had self-report only (9.9%), five had tablet count only (2.3%), and two had electronic monitoring data only (0.9%)). The most frequent combination seem in this study was the collection of valid self-report and tablet count data (110 participants (51.6%)) (Figure 4.6).

Figure 4.6: Availability of the different types of medication adherence measures for participants in the CODA study



The GRACE WP10a study included 2061 participants in total, with self-reported adherence data, collected via a self-completed diary, available for 1675 participants, tablet count data available for 1266, and self-reported telephone data for 129. Adherence data of at least one type were available for 1854 participants (90.0% of those included in the study). Multiple types of measures were available for the majority of participants (1214, or 58.9%), with the majority of these involving the availability of both self-reported diary and tablet count data. Self-reported telephone data was generally collected in circumstances where diaries were not returned, hence the low number of participants with both diary and telephone data available (Figure 4.7). The small number of participants with both self-reported diaries and telephone adherence measures (and all three measures) represents those who were telephoned for their information (as they had not returned their diary), and then the research team subsequently receiving their diary.

Figure 4.7: Availability of the different types of medication adherence measures for participants in the GRACE WP10a study

4.3.2 Summary measures of adherence

In the CODA study, 170 participants stated that they had taken their medication as prescribed (at least 90% of the time), when asked at the end of the study (90.9%). According to tablet counts, 154 participants had consumed at least 75% of the medication that was prescribed for them (93.9%), with 19 consuming all medication that was prescribed for them (11.6%), and a mean percentage of medication that was consumed of 92.7% (SD: 11.7). Thirteen participants consumed more than 100% of medication than they should have, according to tablet counts. This relates to participants who exited the study before the 12-month period (due to withdrawal or relapse), but returned fewer tablets than they should have. On average, the percentage of days that participants adhered to their regimen, according to electronic monitoring data, was 73.7% (SD: 30.2), however the distribution of these data was considerably more skewed than the tablet

count data (Table 4.3). The majority of participants adhered to their treatment regimen on at least 75% of days (37 participants, or 63.8%), with no participants adhering on 100% of days.

Table 4.3: Summary statistics of medication adherence data in the CODA study

Type of measure	Summary measure	N (%)	Mean (SD)	Median (Min, Max)
Self-report (n=187)	Taken their study tablets as prescribed at least 90% of the time	170 (90.9)		
Tablet count (n=164)	Consumed at least 75% of tablets that they should have	154 (93.9)		
	Consumed (at least) 100% of tablets that they should have*	19 (11.6)		
	Percentage of tablets consumed		92.7 (11.7)	96.2 (42.2,133.3)
Electronic monitoring (n=58)	Adhered to their regimen at least 75% of the time	37 (63.8)		
	Adhered to their regimen 100% of the time	0 (0.0)		
	Percentage of days that they adhered to their regimen		73.7 (30.2)	89.2 (0.0,99.39)

*The number of tablets returned by some participants implied they consumed more than 100% of the number of tablets they should have consumed.

For participants in the GRACE WP10a study, 100% adherence was observed in 1342 participants based on self-reported diary data (80.1%), 934 based on tablet count data (73.8%), and 88 based on self-reported telephone data (68.2%). The mean adherence score was 91.2 based on self-reported diary data (SD: 22.0), 88.5 based on tablet count data (SD: 25.4), and 77.5 based on self-reported telephone data (SD: 36.9). Due to adherence generally being high, and bounded at 100%, the distributions of adherence scores were highly skewed to the left for all measures (Table 4.4).

Table 4.4: Summary statistics of medication adherence data in the GRACE WP10a study

Type of measure	Summary measure	n (%)	Mean (SD)	Median (Min, Max)
Self-reported diary (n=1675)	100% adherence	1342 (80.1)		
	Adherence score		91.2 (22.0)	100.0 (0.0,100.0)
Tablet count (n=1266)	100% adherence	934 (73.8)		
	Adherence score		88.5 (25.4)	100.0 (0.0,100.0)
Self-reported telephone (n=129)	100% adherence	88 (68.2)		
	Adherence score		77.5 (36.9)	100.0 (0.0,100.0)

4.3.3 Longitudinal modelling of electronic monitoring data (CODA)

Electronic monitoring data were available for 14,863 days nested within 58 participants. As demonstrated by Figure 4.8 and Table 4.5, there was a small but statistically discernible decrease in medication adherence over time. In Figure 4.8, the bold black lines represent the overall estimated adherence probabilities derived from the fixed effects of the GLMM, with the greyed area representing the 95% confidence bands around these probabilities. All other curves are estimated individual adherence probabilities, derived from the random effects of the GLMM, for each participant in the study. Colour-coded indicators are attached to each individual curve to represent days that a participant adhered to or did not adhere to their medication (blue and red respectively). There were two instances of individuals having MEMS caps that malfunctioned for a small period during the study, with no data collected during this time. These periods are marked as grey on the corresponding individual curves. There was an initial decrease in adherence followed by a period of stabilisation, with some further reduction in adherence towards the end of the study. There was a marked difference between the two dosing regimens

(OR for TDS compared to OD regimen 0.03, 95% CI: 0.01 to 0.08, $p < 0.001$). As is also evident, there was considerably more variation in individual adherence patterns over time for TDS participants than for OD participants. There was no evidence of an interaction between dosing regimen and time (all p-values ≥ 0.1), indicating that while medication adherence was generally higher for participants allocated to the OD regimen, the adherence in both groups decreased over time at a similar rate.

As demonstrated by Figure 4.9, medication adherence was generally lower on weekends than it was on weekdays, with the difference larger for participants allocated to the TDS dosing regimen than for those allocated to OD. While the absolute difference was small, there was a statistically discernible difference in adherence on weekdays compared with adherence at weekends, with odds of being adherent 47% higher on weekdays compared to weekends (OR for weekday 1.47, 95% CI: 1.31 to 1.65, $p < 0.001$) (Table 4.5). There was no evidence of an interaction between time of the week and dosing regimen ($p = 0.111$), indicating that while the difference was descriptively more pronounced for participants allocated to the TDS regimen, this difference was not statistically discernible at the 5% level.

Similarly, there was a small but discernible difference between adherence around (i.e. a week either side of) clinic visit times and non-clinic visit times, with the odds of being adherent around clinic visit times 43% higher compared to non-clinic visit times (OR for clinic visit times 1.43, 95% CI: 1.18 to 1.72, $p < 0.001$). The interaction between time of visit and dosing regimen was not discernible at the 5% level ($p = 0.429$) (Figure 4.10, Table 4.5).

Table 4.5: Estimated daily adherence over time from a two-level generalised linear mixed model with time modelled as a cubic B-spline (based on 14,863 days nested within 58 participants)

Variable	Adherence over time and differences between dosing regimen		Differences in adherence during weekdays		Differences in adherence at clinic visit times	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Intercept	121.49 (56.78 - 259.93)	<0.001	94.65 (43.95 - 203.84)	<0.001	113.67 (53.36 - 242.17)	<0.001
Day	0.07 (0.02 - 0.26)	<0.001	0.07 (0.02 - 0.26)	<0.001	0.07 (0.02 - 0.27)	<0.001
Day^2	1.08 (0.46 - 2.52)	0.857	1.09 (0.46 - 2.54)	0.851	1.09 (0.47 - 2.54)	0.843
Day^3	0.14 (0.07 - 0.28)	<0.001	0.13 (0.06 - 0.28)	<0.001	0.15 (0.07 - 0.03)	<0.001
Once daily dosing regimen	Reference category for dosing regimen (trial arm)					
Three times daily dosing regimen	0.03 (0.01 - 0.08)	<0.001	0.03 (0.01 - 0.08)	<0.001	0.03 (0.01 - 0.08)	<0.001
Weekday: Yes			1.47 (1.31 - 1.65)	<0.001		
Weekday: No	Reference category for weekday indicator					
Clinic visit time: Yes					1.43 (1.18 - 1.72)	<0.001
Clinic visit time: No	Reference category for clinic visit time indicator					

Figure 4.8: Estimated medication adherence probabilities over time (using the MEMS cap data)

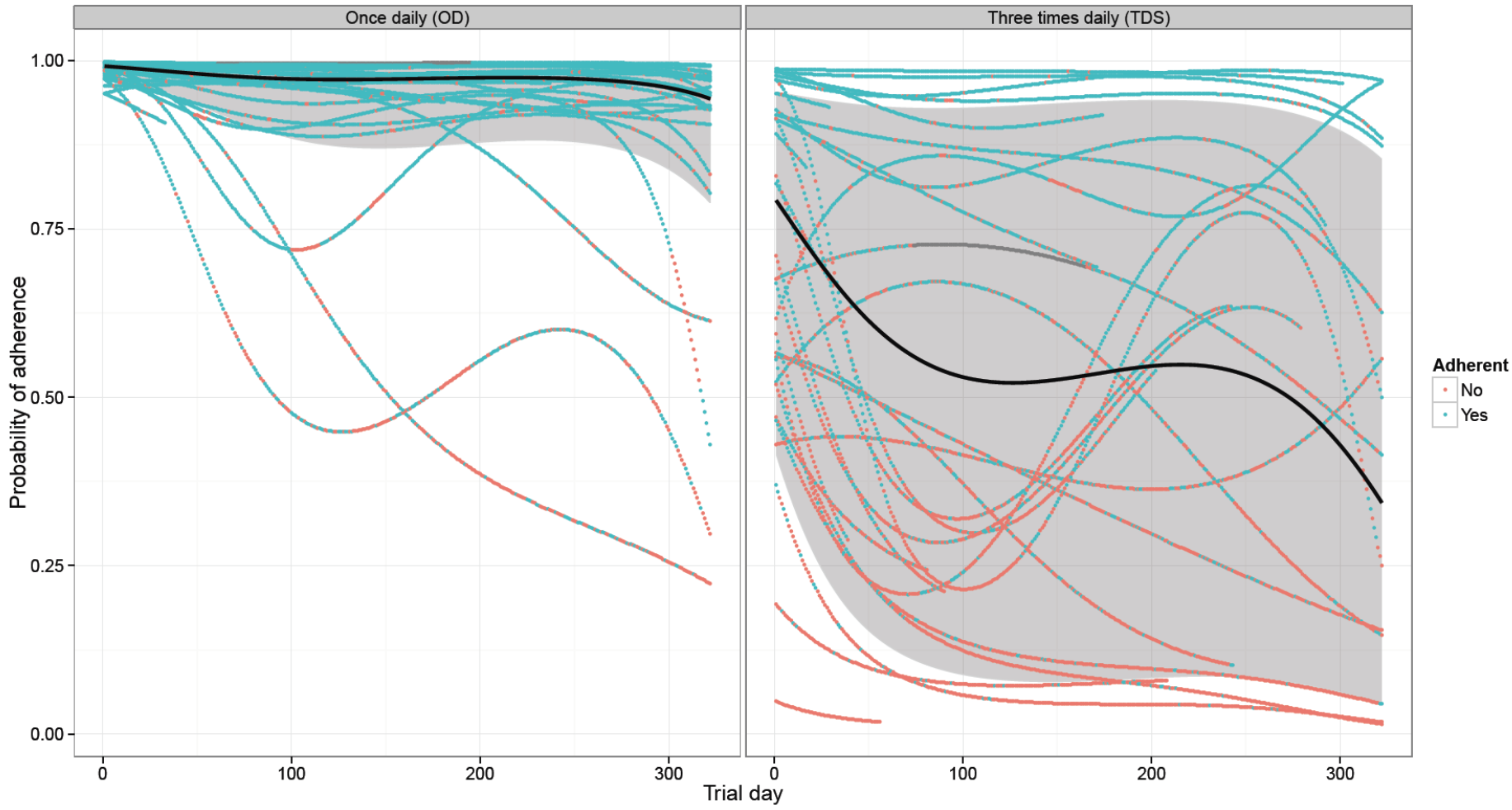
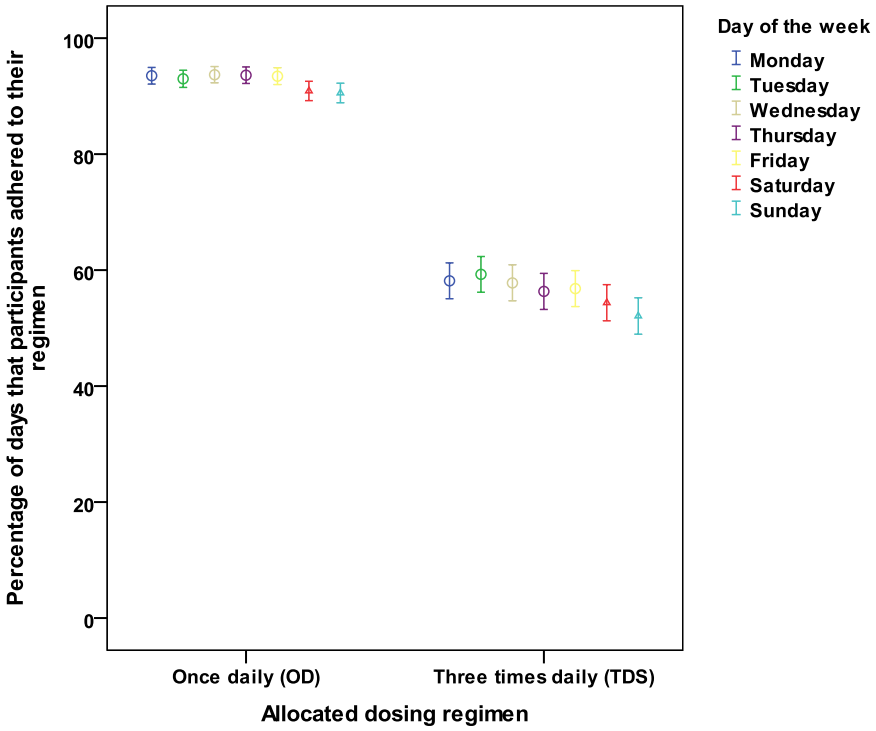
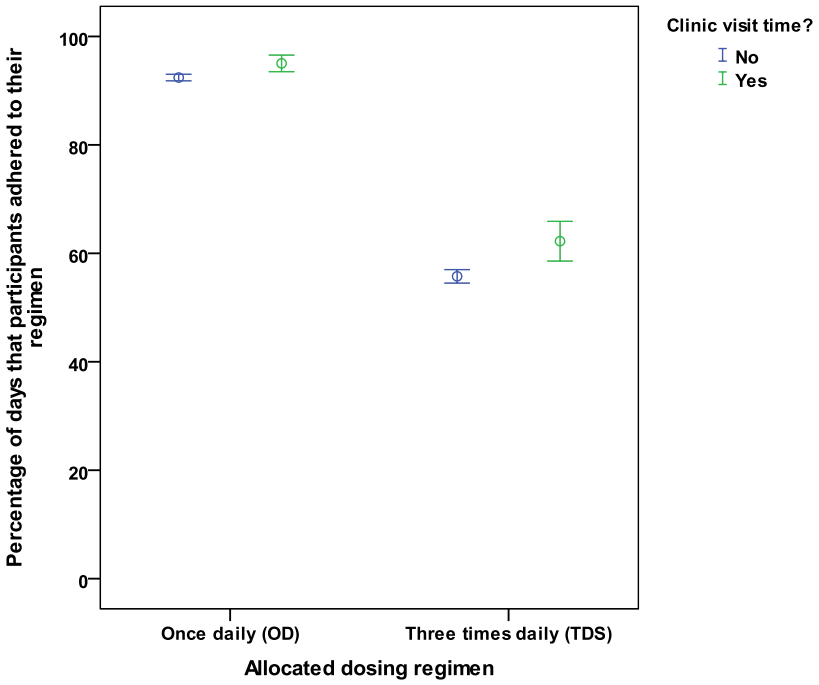


Figure 4.9: Percentage of days participants adhered to regimen for each day of the week split by allocated regimen



Figures 4.10: Percentage of days that participants adhered to regimen during clinic visit periods and non-clinic visit periods split by allocated regimen



4.3.4 Comparing different types of measures

4.3.4.1 Correlation

In the CODA study, there was negligible to low positive correlation between adherence as measured using self-report and tablet count data (correlation coefficients, ρ, ranged from 0.111 to 0.339), and low to moderate positive correlation when compared to electronic monitoring (ρ ranged from 0.465 to 0.523). The dichotomous measures of adherence based on tablet count data correlated negligibly with both dichotomous and quantitative electronic monitoring adherence measures (ρ ranged from 0.141 to 0.300). However, high positive correlation, largely driven by a clustering of points at 100%, was observed between adherence as measured quantitatively by tablet counts and dichotomous/quantitative electronic monitoring measures (ρ = 0.702 and 0.725 respectively) (Figure 4.11, Table 4.6).

Figure 4.11: Scatter plot comparing medication adherence as measured quantitatively using electronic monitoring and tablet counts (dashed line represents the line of perfect agreement)

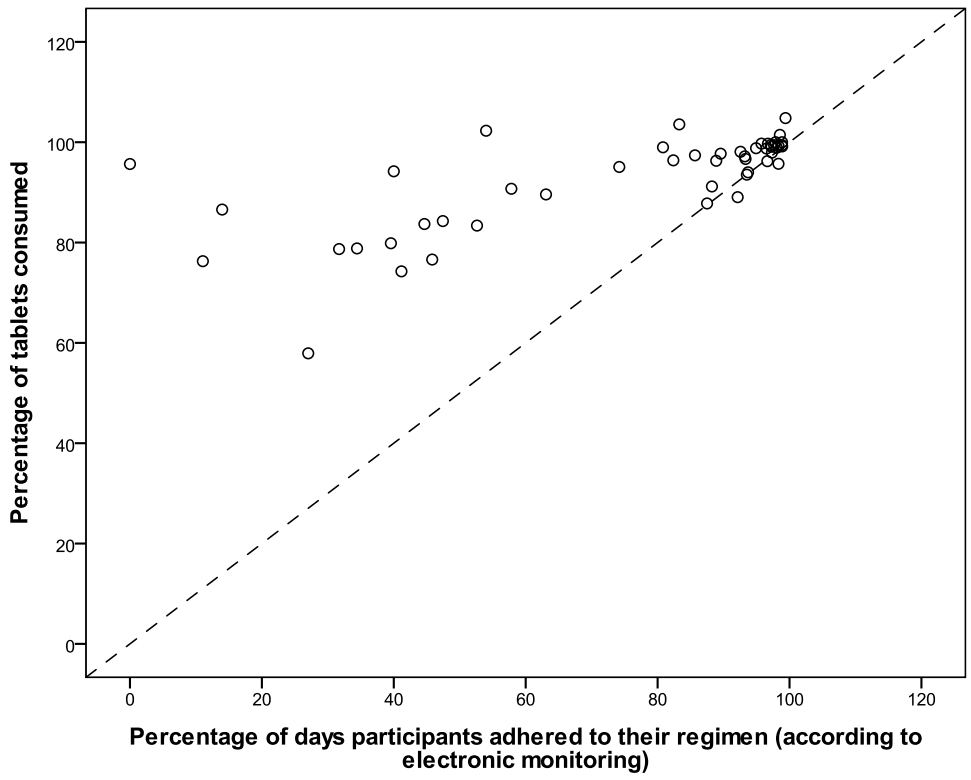


Table 4.6: Correlation coefficients for different types of adherence measures in the CODA study

			Tablet count			Electronic monitoring	
		Self-report	Consumed at least 75% of tablets that they should have	Consumed (at least) 100% of tablets that they should have	Percentage of tablets consumed	Adhered to their regimen at least 75% of the time	Percentage of days that they adhered to their regimen
	Self-report	1.000					
Tablet count	Consumed at least 75% of tablets that they should have	0.194	1.000				
	Consumed (at least) 100% of tablets that they should have	0.111	0.092	1.000			
	Percentage of tablets consumed	0.339	0.736	0.394	1.000		
Electronic monitoring	Adhered to their regimen at least 75% of the time	0.465	0.283	0.141	0.702	1.000	
	Percentage of days that they adhered to their regimen	0.523	0.300	0.179	0.725	0.901	1.000

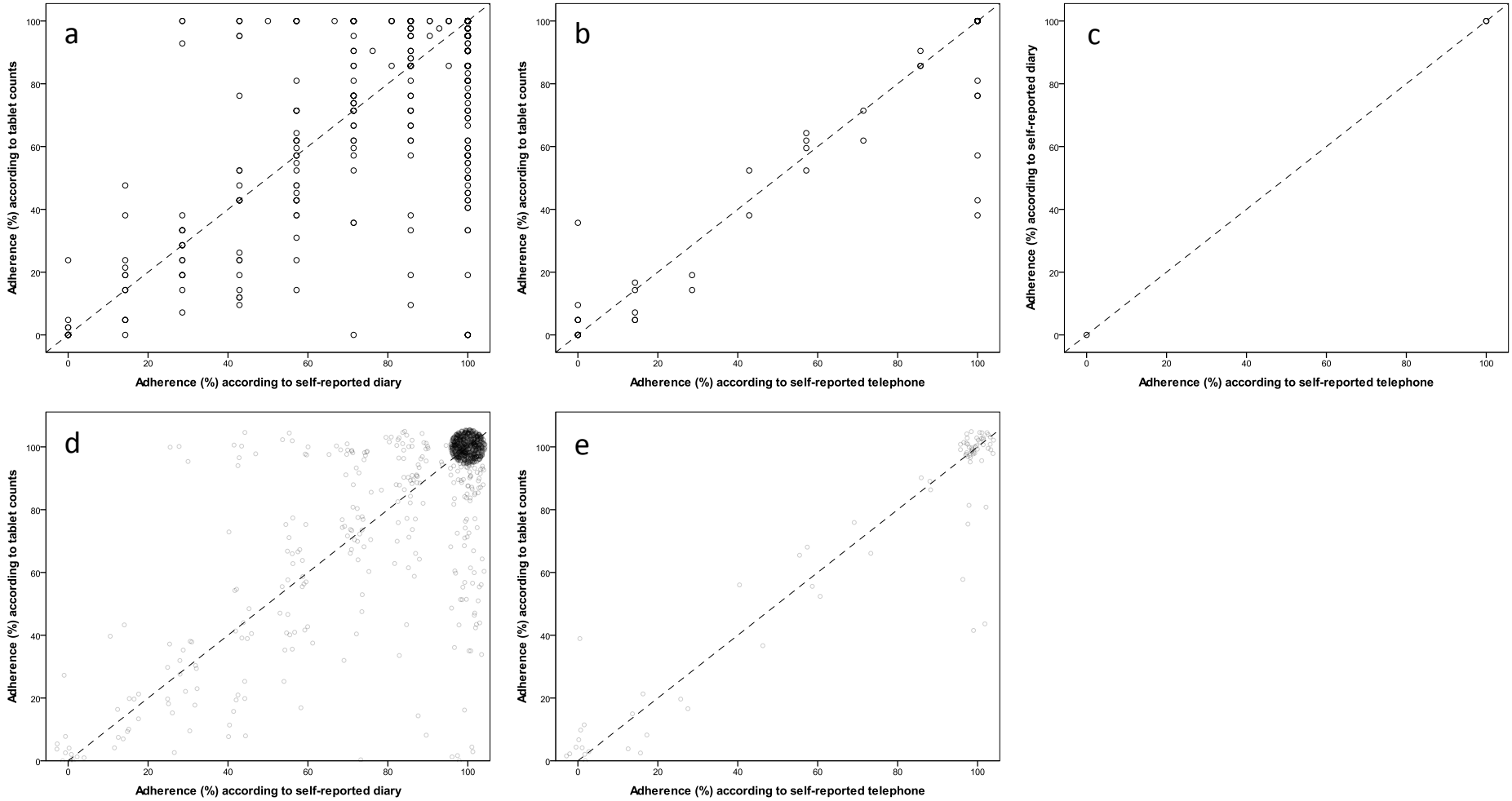
In the GRACE WP10a study, correlation between different types of adherence measures was moderate to very high (ρ ranged from 0.547 to 1). Moderate correlation was observed when comparing binary measures of adherence as measured using self-reported diaries and tablet counts to each other (ρ = 0.583) and to their quantitative equivalent (correlations between binary self-reported diary and quantitative tablet count = 0.591, and binary tablet count and quantitative self-reported diary = 0.547). All other correlation was high or very high. Table 4.7 provides correlation coefficients for all comparisons. Figures 4.12a to 4.12e illustrate the relationship between the quantitative measures of adherence. What is evident, particularly when observing Figures 4.12d and 4.12e, is that there is a high concentration of participants for whom adherence was 100% across all types of measures.

Table 4.7: Correlation coefficients for different types of adherence measures in the GRACE WP10a study

		Self-reported diary		Tablet counts		Self-reported telephone	
		Adherence score	100% adherence	Adherence score	100% adherence	Adherence score	100% adherence
Self-reported diary	Adherence score	1.000					
	100% adherence	0.803	1.000				
Tablet counts	Adherence score	0.767	0.591	1.000			
	100% adherence	0.547	0.583	0.756	1.000		
Self-reported telephone	Adherence score	1.000*	1.000*	0.949	0.752	1.000	
	100% adherence	1.000*	1.000*	0.828	0.855	0.895	1.000

*NB. These are based on three data points.

Figures 4.12a to 4.12e: Scatter plots comparing medication adherence as measured via self-reported diaries, tablet counts, and self-reported telephone (plots d and e include identical data to those in a and b respectively, with jittering and semi-transparency used to indicate the extent of over plotting)



4.3.4.2 Agreement

When comparing the observed percentage of agreement between different types of measures in the CODA study, it is clear from Table 4.8 and Figures 4.13a to 4.13f that for some comparisons there is considerable disagreement. The lowest agreement is observed when comparing across measures or within measures and using different cut-points (though the latter is not surprising). The Figures 4.13a to 4.13f illustrate that where disagreement occurred it was generally due to tablet counts suggesting higher levels of adherence compared to self-report and electronic monitoring, with self-report similarly suggesting higher levels of adherence when compared to electronic monitoring. Note the highest kappa is for the comparison between electronic monitoring and self-report, despite this not having the highest observed agreement. Figures 4.13a to 4.13f illustrate that while observed agreement may have been higher for other comparisons (e.g. 4.13a), a lot of this agreement was expected by chance. Figure 4.13c displays the greatest amount of observed agreement that is in addition to that expected by chance.

When comparing the agreement between quantitative measures of adherence via tablet counts and electronic monitoring, the absolute mean difference of -17.81 suggested that tablet counts consistently provided a higher estimate of adherence compared to electronic monitoring. Figure 4.14 illustrates the agreement between the two types of measures, and highlights that while there is a large concentration of data points around [100, 0] (fully adhered according to both types of measure), the majority of instances where disagreement occurred was for participants allocated to the TDS regimen, where there was a requirement to open the MEMs cap on three separate occasions throughout the day.

Table 4.8: Percentage of observed agreement between dichotomous measures of adherence in the CODA study (kappa in brackets)

	Self-report	Tablet count (75%)	Tablet count (100%)	Electronic monitoring (75%)
Self-report	100%			
Tablet count (75%)	88.7% (0.19)	100%		
Tablet count (100%)	20.1% (0.02)	17.7% (0.02)	100%	
Electronic monitoring (75%)	75.0% (0.36)	69.4% (0.15)	42.9% (0.07)	100%

Figures 4.13a to 4.13f: Extended observed agreement charts for dichotomous measures of adherence in the CODA study

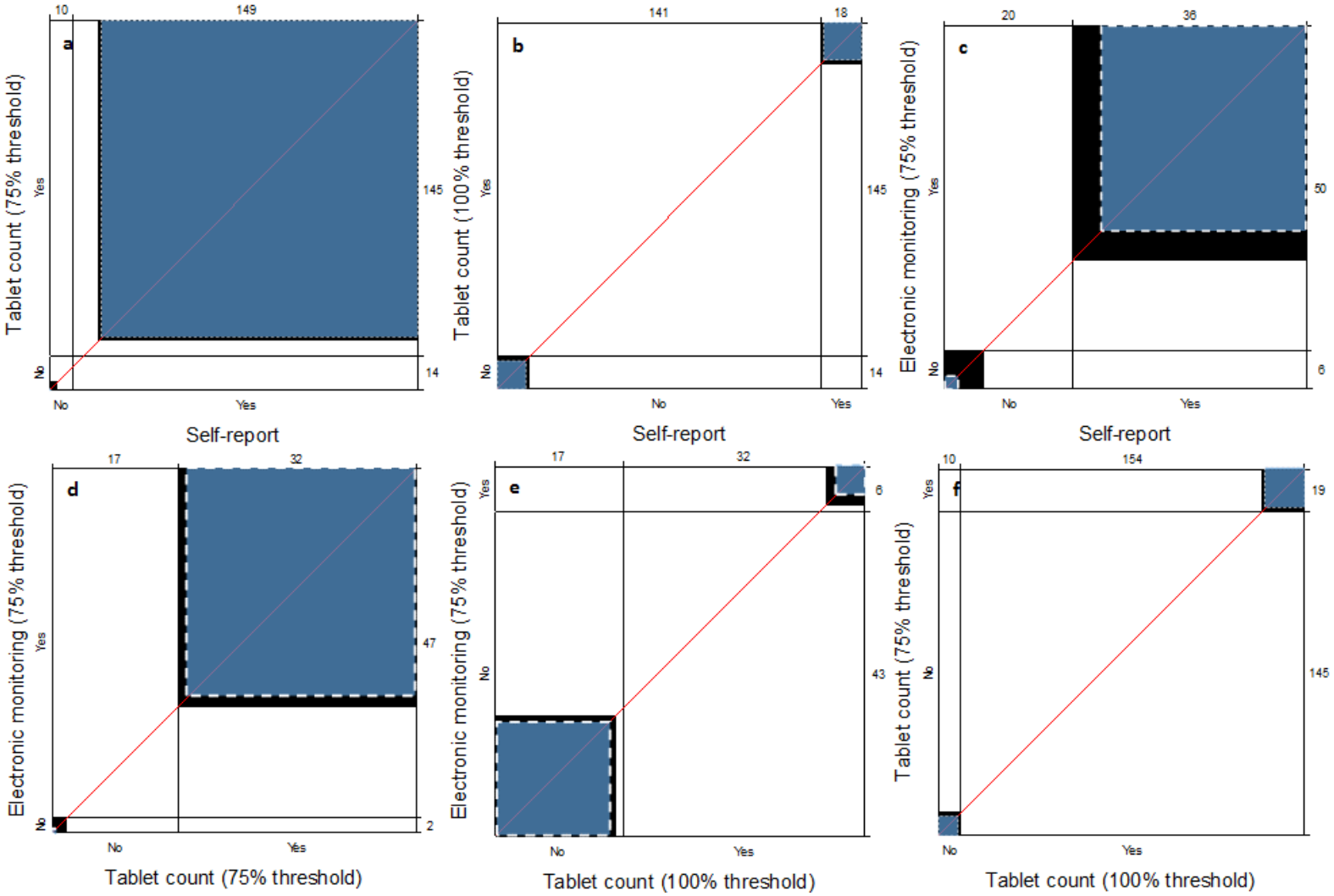
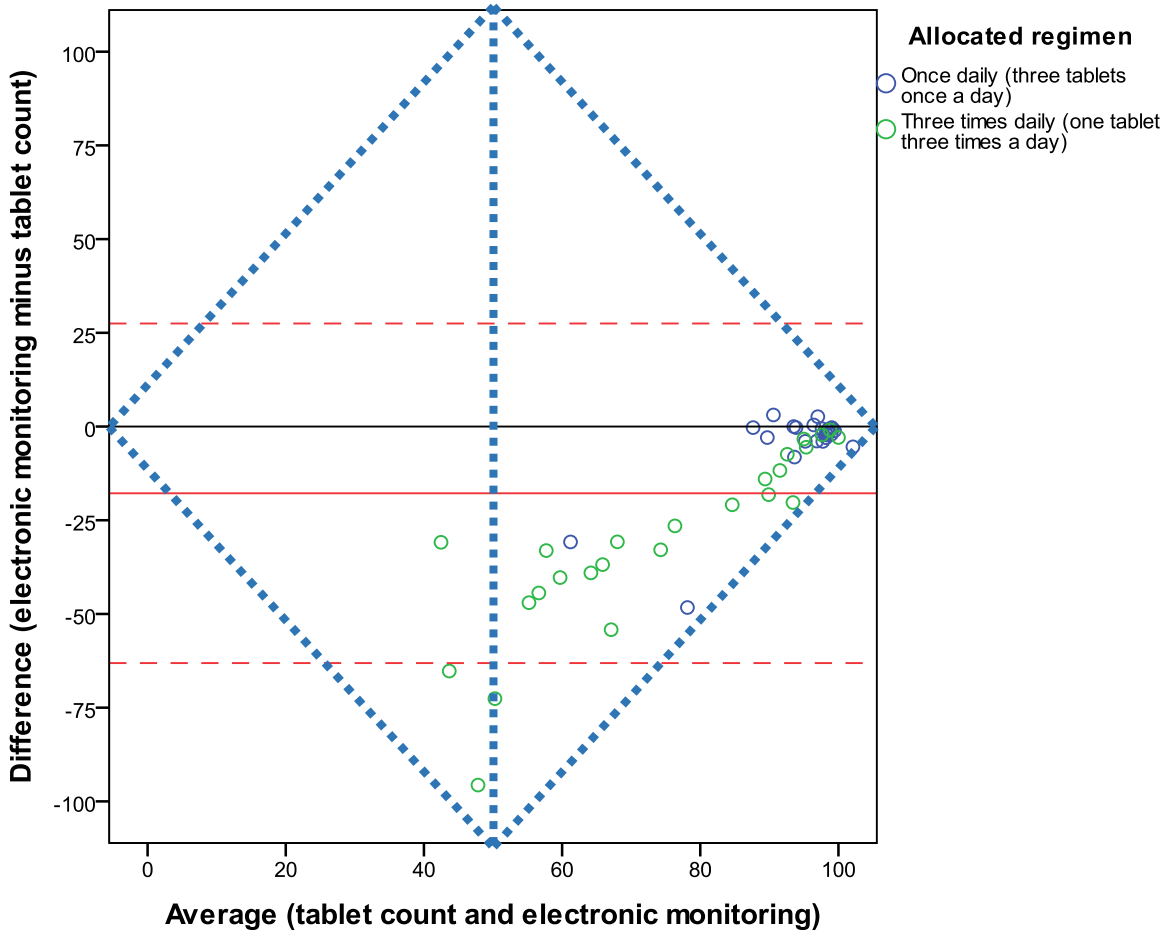


Figure 4.14: Extended Bland-Altman plot investigating the agreement between electronic monitoring and tablet count adherence measures in the CODA study*



*The black unbroken line is set at y=0 (i.e. no disagreement). The red unbroken line represents the mean difference between the two measures (i.e. the bias [-17.81]), and the red dashed lines represent the lower and upper 95% limits of agreement (-63.11 and 27.49 respectively). The blue dashed diamond represents the space in which data points can lie.

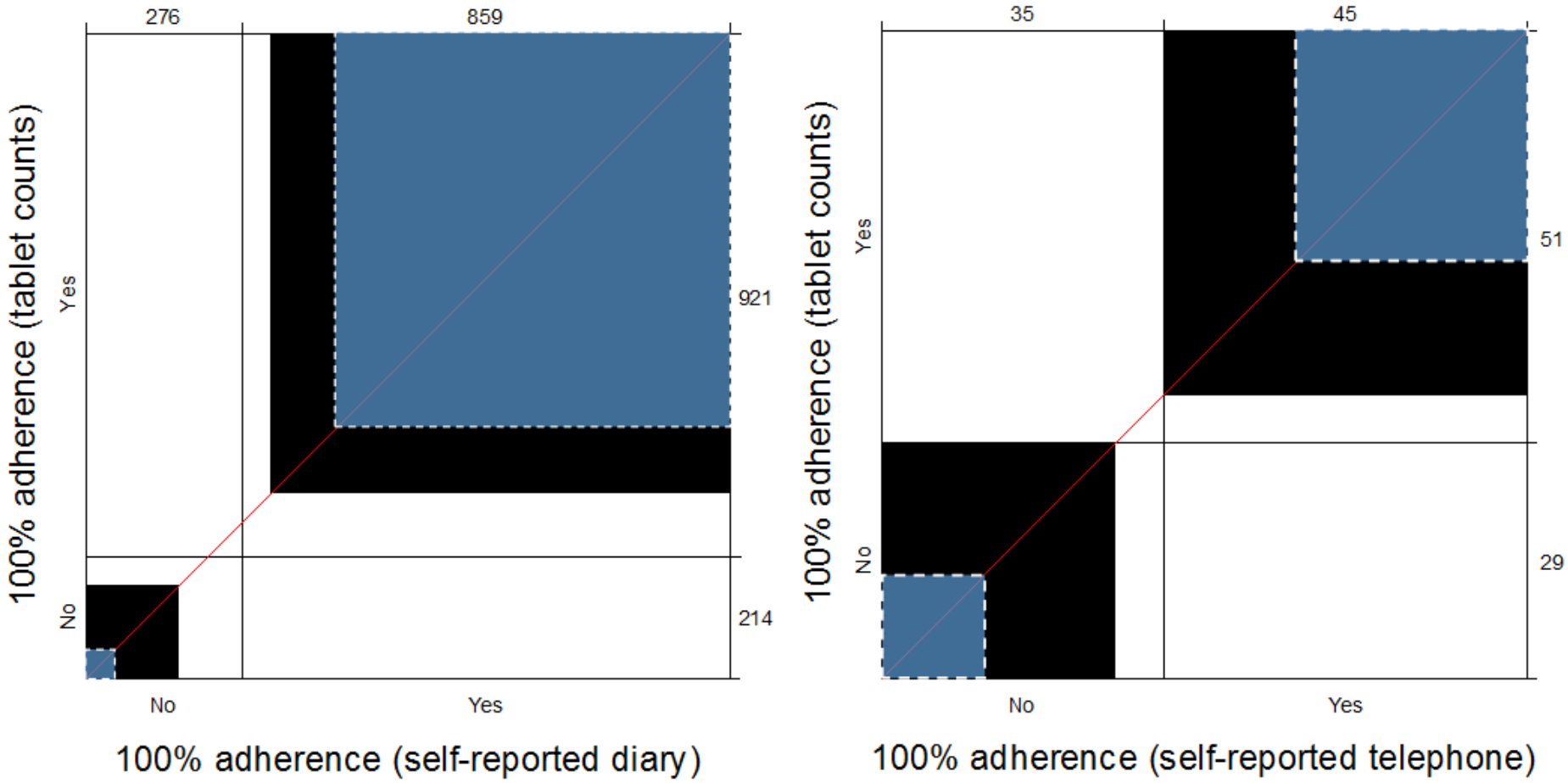
Agreement between different types of measures in the GRACE WP10a study was generally high, with the lowest percentage agreement observed when comparing binary measures of self-report diary and tablet count adherence (85.6%) (Table 4.9). Disagreement occurred most frequently between different types of measures because self-report (both diary and telephone) indicated adherence was 100% when tablet counts did not (Figures 4.15a and 4.15b).

Agreement when comparing different types of measures quantitatively was similarly high. The absolute mean difference when comparing tablet counts to self-reported diary and self-reported telephone was 1.7 and 2.6 respectively. The limits of agreement when comparing diary and tablet count adherence ranged from -26.8 (self-reported diary adherence was calculated as 26.8 percentage points lower than tablet count adherence) to 30.2 (self-reported diary adherence was calculated as 30.2 percentage points higher than tablet count adherence) and when comparing telephone and tablet count from -21.8 to 26.9. Figures 4.16a and 4.16b provide an illustration of the level of agreement between different types of measures. What is clear from these figures is that adherence was high and was generally good (most data points on both plots are clustered around the co-ordinate [100, 0], indicating full adherence and no difference between measures). For the comparison of diary to tablet count adherence, 7% of participants were outside the limits of agreement; for the comparison of telephone to tablet count adherence, 5% of participants were outside the limits of agreement.

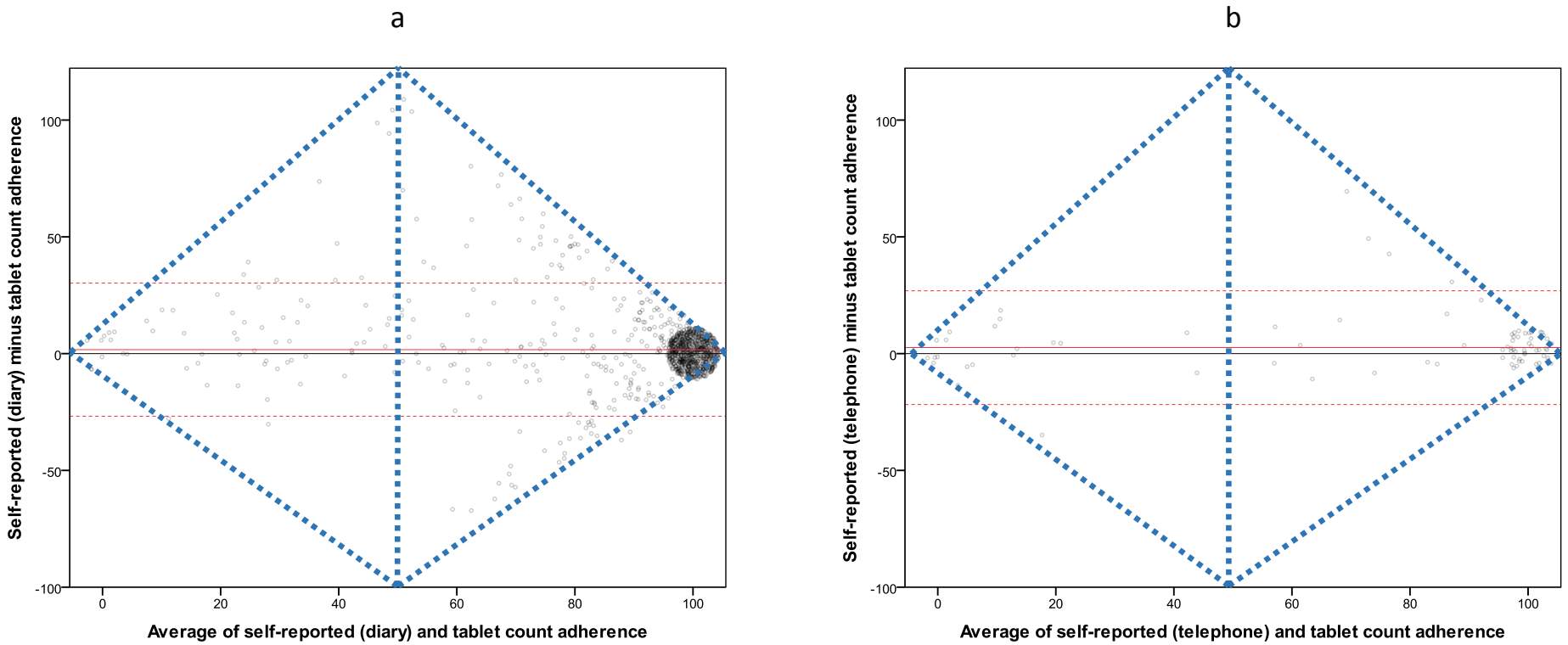
Table 4.9: Percentage of observed agreement between dichotomous measures of adherence in the GRACE WP10a study (kappa in brackets)

	Self-report diary	Tablet counts	Self-report telephone
Self-report diary	100%		
Tablet counts	85.6% (0.58)	100%	
Self-report telephone	100% (1.00)	92.5% (0.85)	100%

Figures 4.15a and 4.15b: Extended observed agreement charts for dichotomous measures of adherence in the GRACE WP10a study



Figures 4.16a and 4.16b: Extended Bland-Altman plots investigating the agreement between self-reported diary, tablet count, and self-reported telephone adherence measures in the GRACE WP10a study*



*The black unbroken line is set at y=0 (i.e. no disagreement). The red unbroken line represents the mean difference between the two measures (i.e. the bias), and the red dashed lines represent the lower and upper 95% limits of agreement. For the comparison of self-reported diary and tablet counts (4.16a), the bias was 1.7, and the 95% limits of agreement were -26.8 to 30.2. For the comparison of self-reported telephone and tablet counts (4.16b), the bias was 2.6, and the 95% limits of agreement were -21.8 to 26.9. Where data points lie outside the bounded region (blue dashed lines), this is due to the use of jittering.

4.3.4.3 Predictors of disagreement between different types of adherence measures

4.3.4.3.1 Descriptive statistics for disagreement variables

As demonstrated in the previous section, agreement between adherence as measured using self-reported diaries and tablet counts was high. Indeed, for the quantitative measure of adherence, disagreement was observed in only one-quarter of cases (Table 4.10).

Table 4.10: Observed disagreement between adherence as measured using self-reported diaries and tablet counts in the GRACE WP10a study

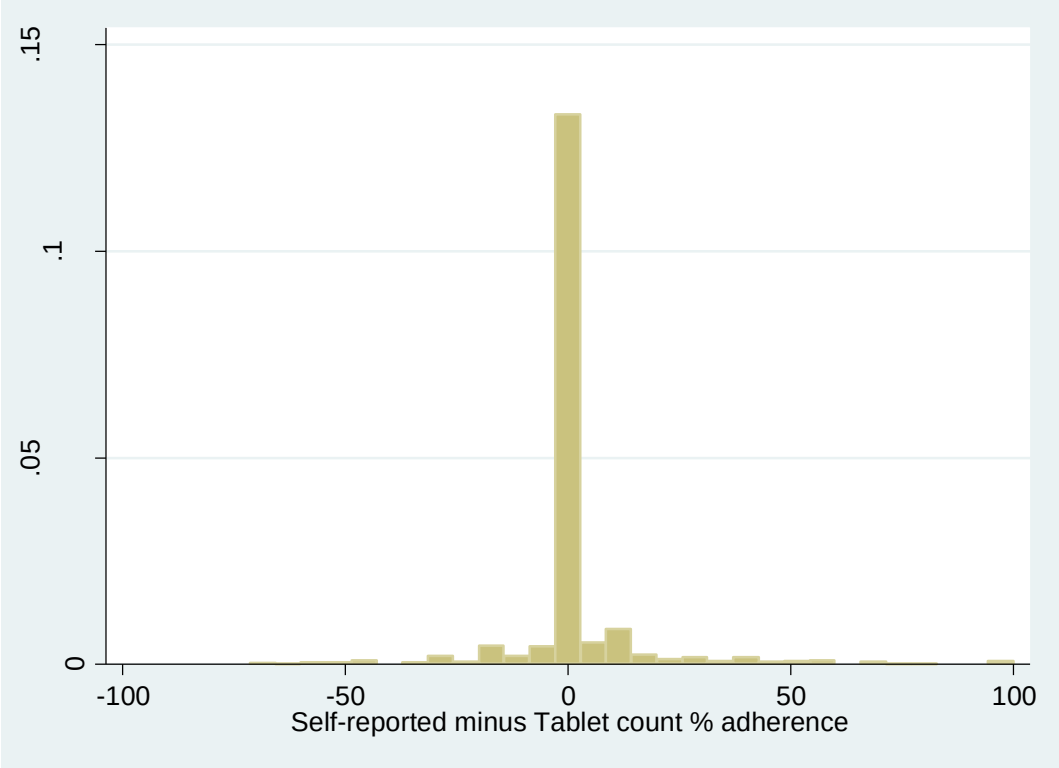
Binary Disagreement (YES/NO)	n (%)
Yes (disagree)	286 (25.2)
No (agree)	849 (74.8)
Total	1135 (100.0)

When calculating the difference between the two types of measures (self-report diary minus tablet count), Figure 4.17 demonstrates a fairly symmetric distribution around zero, with Table 4.11 revealing slightly more instances of participants providing higher measures of adherence according to self-reported diary compared to tablet counts (173, or 15.2% of participants), compared to instances where self-reported diaries were lower (113, or 10% of participants). That is, where different types of measures disagreed, self-report diaries were more likely to produce higher adherence than tablet counts.

Table 4.11: Direction of disagreement between adherence as measured using self-reported diaries and tablet counts in the GRACE WP10a study

Self-report diary versus Tablet Count (Lower / Same / Higher)	n (%)
Lower	113 (10.0)
Same	849 (74.8)
Higher	173 (15.2)
Total	1135 (100.0)

Figure 4.17: Histogram of the difference between adherence as measured using self-reported diaries and tablet counts



4.3.4.3.2 Predictors of binary disagreement

In the univariable analyses, age, gender, presenting with phlegm, feeling generally unwell, or diarrhoea, and the number of days waited prior to consulting were all associated with the two types of adherence measures disagreeing at the 10% significance level, and were therefore retained for the initial multivariable model. The final multivariable model included age, gender, presenting with phlegm, and the number of days waited prior to consulting (Table 4.12).

Table 4.12: Multivariable two-level logistic regression model of associations between participant/illness characteristics and disagreement between self-reported diary and tablet count adherence measures*

Variable	Odds ratio for disagreement	95% Confidence Interval		p-value
		Lower	Upper	
Age (decades)	0.84	0.77	0.92	<0.001
Male	Reference category			
Female	1.49	1.10	2.01	0.011
Phlegm (presenting symptom)	1.55	1.06	2.26	0.023
Waited 7 days or fewer prior to consulting	Reference category			
Waited 8 to 14 days prior to consulting	0.66	0.45	0.96	0.011
Waited 15+ days prior to consulting	0.59	0.39	0.88	
Intercept	0.49	0.27	0.91	0.024

*Based on 1133 participants nested within 183 clinicians. The clinician-level ICC was 0.09 (95% CI: 0.04 to 0.19).

As demonstrated in Table 4.12, the odds of disagreeing were lower in older participants (OR for a decade increase = 0.84, 95% CI: 0.77 to 0.92), with a mean age of 46.9 years for those whose adherence disagreed, and 51.8 years for those who agreed (SD = 16.2 and 15.9 respectively). For those who had waited longer prior to consulting, the odds of disagreeing were lower, with a dose-response relationship observed (OR for waiting 8 to 14 days compared to 7 days or fewer = 0.66, 95% CI: 0.45 to 0.96, OR for waiting 15+ days compared to 7 days or fewer = 0.59, 95% CI: 0.39 to 0.88). The odds of disagreeing were higher for females (OR = 1.49, 95% CI: 1.10 to 2.01), and for those presenting with phlegm (OR = 1.55, 95% CI: 1.06 to 2.26).

4.3.4.3.3 Predictors of the direction of disagreement

In the univariable analyses, several variables were associated with either self-report diary yielding lower adherence than tablet counts (versus the same), or higher at the 10% significance level. The

variables, age, gender, use of chronic medication, smoking status, presenting with phlegm, muscle aching, feeling generally unwell, confusion / disorientation, or diarrhoea, having an auscultation abnormality, and the number of days waited prior to consulting were associated for at least one of the directions. Only age was univariably associated in both directions (Table 4.13).

The final multivariable model included age, gender, presenting with phlegm, diarrhoea, auscultation abnormality, and number of days waited prior to consulting. An increase in age was associated with a lower risk of disagreeing in either direction (RRR for lower = 0.85, 95% CI: 0.74 to 0.98, RRR for higher = 0.85, 95% CI: 0.76 to 0.94). The risk of disagreeing in either direction was higher for participants presenting with phlegm. Being female or presenting with diarrhoea were associated with a higher risk of having an adherence score lower according to self-report diary (versus tablet count) compared to it being the same. Having an auscultation abnormality on presentation was associated with a lower risk of having an adherence score lower according to self-report diary compared to it being the same. The longer participants waited before consulting, the lower their risk of having an adherence score higher according to self-report diary compared to it being the same (Table 4.14).

Table 4.13: Univariable associations between participant and illness characteristics and the direction of disagreement

Variable	p-value (lower versus same)	p-value (higher versus same)	Retain for multivariable analysis?
Age	0.005	<0.001	Yes
Gender	0.003	0.186	Yes
Comorbidities	0.526	0.872	No
Use of chronic medication	0.485	0.047	Yes
Current smoker	0.375	0.204	No
Smoking status	0.383	0.096	Yes
Phlegm	0.159	0.084	Yes
Shortness of breath	0.261	0.464	No
Wheeze	0.398	0.840	No
Runny nose	0.275	0.714	No
Chest pain	0.880	0.401	No
Fever	0.932	0.602	No
Muscle aching	0.801	0.066	Yes
Headache	0.778	0.142	No
Disturbed sleep	0.202	0.847	No
Feeling generally unwell	0.704	0.003	Yes
Interference with normal activities	0.322	0.409	No
Confusion / disorientation	0.481	0.096	Yes
Diarrhoea	0.065	0.494	Yes
Symptom severity score	0.247	0.162	No
Auscultation abnormality	0.011	0.670	Yes
Days waited prior to consulting	0.948	0.001	Yes

Table 4.14: Multivariable multinomial logistic regression model of associations between participant/illness characteristics and the direction of disagreement between self-reported diary and tablet count adherence measures*

Model	Variable	Relative Risk Ratio	95% Confidence Interval		p-value
			Lower	Upper	
Adherence according to self-reported diary lower than tablet counts (versus same)	Age (per decade increase)	0.85	0.74	0.98	0.020
	Male	Reference category			
	Female	1.83	1.19	2.82	0.006
	Phlegm (presenting symptom)	1.67	1.04	2.68	0.032
	Diarrhoea (presenting symptom)	2.19	1.05	4.56	0.037
	Auscultation abnormality	0.56	0.35	0.89	0.015
	Waited 7 days or fewer prior to consulting	Reference category			
	Waited 8 to 14 days prior to consulting	1.03	0.61	1.75	0.940
	Waited 15+ days prior to consulting	1.10	0.66	1.83	
	Intercept	0.14	0.06	0.36	<0.001
Adherence according to self-reported diary higher than tablet counts (versus same)	Age (per decade increase)	0.85	0.76	0.94	0.003
	Male	Reference category			
	Female	1.22	0.87	1.72	0.255
	Phlegm (presenting symptom)	1.61	1.03	2.51	0.037
	Diarrhoea (presenting symptom)	1.19	0.61	2.31	0.603
	Auscultation abnormality	0.95	0.68	1.33	0.772

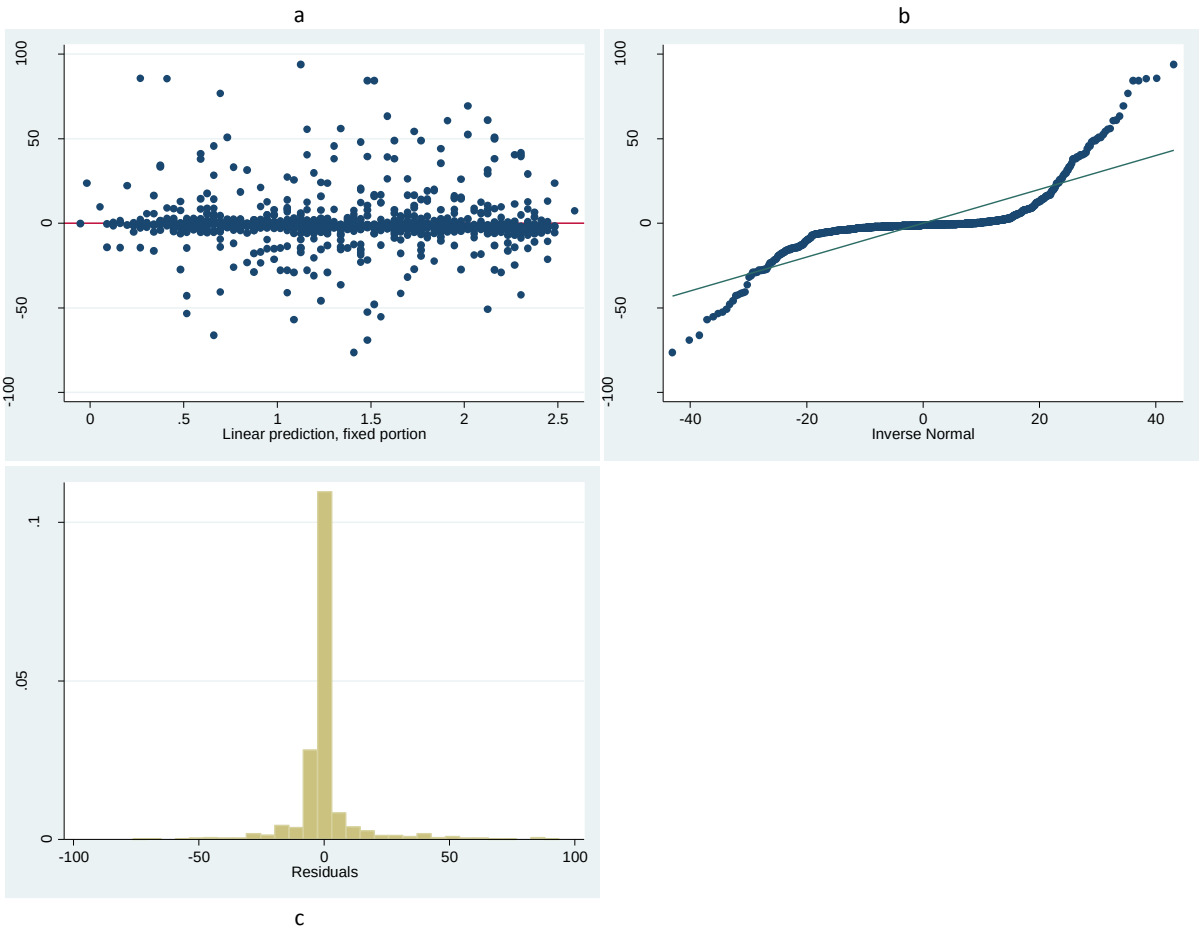
Model	Variable	Relative Risk Ratio	95% Confidence Interval		p-value
			Lower	Upper	
	Waited 7 days or fewer prior to consulting	Reference category			
	Waited 8 to 14 days prior to consulting	0.49	0.29	0.83	0.002
	Waited 15+ days prior to consulting	0.39	0.23	0.69	
	Intercept	0.38	0.18	0.80	0.011

*Based on 1128 participants. Standard errors corrected for clustering of 182 clinicians.

4.3.4.3.4 Predictors of the direction and extent of disagreement

Perhaps unsurprisingly, given the distribution of the difference between adherence as measured using self-reported diaries and tablet counts as shown in Figure 4.17, the assumptions of a linear regression were not satisfied, with the distribution of the residuals non-normal but fairly symmetric (see Figures 4.18a to 4.18c for the residual plots for the univariable model that includes age as a predictor). A linear mixed model was therefore fitted with robust standard errors to obtain accurate standard errors (and hence confidence intervals and p-values).

Figures 4.18a to 4.18c: Residual plots from linear mixed model of difference between self-report



In the univariable analyses, presenting with a headache, feeling generally unwell, the clinician-rated symptom severity score, and number of days waited prior to consulting were all associated with the difference in adherence scores at the 10% significance level. However, the variable

"Symptom severity score" was missing for 385 participants and the final multivariable model (including symptom severity) excluded all other variables. When the modelling process excluded symptom severity score, the only variable retained was days waited prior to consulting. The findings for both of these models are therefore presented separately (Table 4.15 for symptom severity score and Table 4.16 for days waited prior to consulting).

Table 4.15: Association between clinician-rated symptom severity score at baseline and differences between adherence as rated via self-reported diaries and tablet counts*

Variable	Mean difference (self-report diary minus tablet count)	95% Confidence Interval		p-value
		Lower	Upper	
Symptom severity score	0.10	0.01	0.18	0.026
Intercept	-3.54	-7.63	0.55	0.090

*Based on 750 participants within 163 clinicians

Table 4.16: Association between days waited prior to consulting and differences between adherence as rated via self-reported diaries and tablet counts*

Variable	Mean difference (self-report diary minus tablet count)	95% Confidence Interval		p-value
		Lower	Upper	
Waited 7 days or fewer prior to consulting	Reference category			
Waited 8 to 14 days prior to consulting	-2.00	-3.51	-0.48	0.003
Waited 15+ days prior to consulting	-2.66	-4.47	-0.84	
Intercept	2.29	0.96	3.62	0.001

*Based on 1134 participants within 184 clinicians

As shown in Table 4.15, for each unit increase in symptom severity score (which ranged from 0 – all 14 symptoms normal / not causing a problem, to 100 – all 14 symptoms as bad as they could be) adherence according to self-reported diaries is 0.1 percentage points higher (95% CI: 0.01 to 0.18). Table 4.16 demonstrates that for participants who waited 8 to 14 days prior to consulting, adherence according to self-reported diaries was, on average, 2 percentage points lower than

tablet counts (95% CI: 3.51 to 0.48 percentage points lower), compared to those who waited 7 days or fewer. For those who waited 15+ days, adherence was 2.66 percentage points lower than tablet counts (95% CI: 4.47 to 0.84 percentage points lower).

4.3.4.4 Calibration

The GRACE WP10a data were used to create calibrated measure of medication adherence using several methods. The summary statistics for the different types of measures are presented in Table 4.18.

4.3.4.4.1 Range

Taking the minimum/maximum value from all available types of adherence measures, adherence data in the GRACE WP10a trial were available for 1854 participants (90% of all randomised participants). The average percentage of medication taken was 87.3 when taking the minimum value (with an SD of 26.5) and 90.8 when taking the maximum (SD = 23.8).

4.3.4.4.2 Hierarchy

Of the 1854 participants with adherence data, adherence was based on tablet counts in 1266 instances (68.3%), self-reported diaries in 540 instances (29.1%), and self-reported telephone in the remaining 48 instances (2.6%). The average percentage of medication taken was 88.5 when considering a measure of adherence calibrated and based on treating different types of measures in a hierarchy (SD = 25.9).

4.3.4.4.3 Classification

As demonstrated in Figure 4.17, while agreement between self-reported diary and tablet count adherence was high, there were instances of high levels of disagreement in both directions. When comparing the two types of measures, 849 participants were classed as accurate reporters (74.8%). Over-reporting of adherence (reporting a higher level of adherence in self-reported diaries than in tablet counts) occurred for 173 participants, with 97 classified as over-reporters and 76 as

extreme over-reporters (8.5 and 6.7% of all participants for whom both types of measures were available respectively). Under-reporting occurred for 113 participants, with 73 classified as under-reporters and 40 as extreme under-reporters (6.4 and 3.5% respectively) (Table 4.17).

Table 4.17: Summary of reporter classifications and mean differences within each classification

Reporter classification	Frequency (%)	Mean difference*
Extreme over-reporter	76 (6.7)	41.1
Over-reporter	97 (8.5)	8.7
Accurate reporter	849 (74.8)	0.0
Under-reporter	73 (6.4)	-8.6
Extreme under-reporter	40 (3.5)	-36.3

*Self-reported diary minus Tablet count

When calibrating self-reported diary adherence using this classification approach, the average percentage of medication taken was 90.0 (SD = 23.2).

Table 4.18 provides summary statistics for the different types of calibrated measures.

Table 4.18: Summary statistics for different types of calibrated adherence measures

Calibrated adherence measure	n	Mean	S.D.	Median	Lower quartile	Upper quartile	Min	Max
Minimum	1854	87.3	26.5	100.0	90.5	100.0	0.0	100.0
Maximum	1854	90.8	23.8	100.0	100.0	100.0	0.0	100.0
Hierarchy	1854	88.5	25.9	100.0	100.0	100.0	0.0	100.0
Self-reported diary (calibrated)	1675	90.0	23.2	100.0	97.2	100.0	0.0	100.0

4.4 Discussion

4.4.1 Summary

In this Chapter, several types of methods for measuring adherence to medication were presented and compared. Summary statistics were presented, treating adherence as a dichotomous variable and also treating it as a continuous variable where this was possible. Moving beyond summary

measures, electronic monitoring data were used to model adherence patterns over time, considering the clustered nature of daily adherence measures within individuals, non-linear time effects, the testing of behavioural hypotheses, and visual means by which the findings can be presented. Several methods for comparing different types of measures were presented, including frequently-used correlational methods and infrequently-used agreement methods (see Chapter 2). For the latter, I proposed extensions to observed agreement plots and Bland Altman limits of agreement, which were utilised as a way of reporting agreement based on dichotomous and continuous measures of adherence respectively. The final part of the Chapter presented various methods for investigating predictors of disagreement, and several methods for calibrating adherence measures. Disagreement was considered as a dichotomous variable (disagreed / agreed), and the direction and extent of disagreement was also considered, with suitable statistical models suggested for each. Several methods for arriving at an adherence measure that takes into account numerous types of (occasionally discrepant) measures were presented, with some methods requiring fewer assumptions than others.

4.4.2 Learning points

1. Summary measures of medication adherence provide useful information about the sample from which data were collected. Continuous summary measures should be reported, where possible, as these can give a better indication of the distribution of the data (e.g. the average and variability) than can be provided by dichotomous summary measures. However, dichotomous or categorical measures presented alongside can provide complementary information, particularly if the categories have some clinically important meaning. For example, in the CODA study the average percentage of tablets consumed was 92.7, while only 11.6% of participants consumed 100% (or more) of their prescribed medication.

2. When comparing measures in the CODA (long-term medication for a chronic condition) and GRACE (short-term medication for an acute condition) studies, self-report and tablet count agreement was considerably higher in the latter. This could be related to the duration of monitoring in the CODA study, the fact that self-report data was only obtained retrospectively during clinic visits (GRACE had both prospective self-report via diaries and retrospective via telephone calls), and that clinic visits were often far apart (increasing the likelihood of recall bias).

3. Measuring adherence to medication electronically allows data to be captured at each dosing event in a passive manner (i.e. participants do not have to physically record the event, the device records it automatically). Capturing data so frequently, particularly over a long time period, provides the opportunity to explore patterns in adherence over time and enable detailed insights into patient behaviour to be gained. Mixed models are a suitable tool for the statistical analysis of these data, as they can provide estimates about the evolution of adherence over time, while accounting for the correlated nature of events within individuals. In the CODA study, mixed models were used to demonstrate that adherence to mesalazine declined over time, was more variable for participants allocated to take medication in divided doses, was better on weekdays than at weekends, and was better around clinic visit dates than non-clinic visit dates.

4. When comparing different types of measures, correlation can provide an indication of the strength of association between different types of measures. However, it is usually agreement that should be the main parameter of focus. Where adherence is only measured in a dichotomous or categorical manner, observed agreement plots provide a visual means of representing the extent of agreement between two types of measure. Extending these by also including the agreement expected by chance enhanced the amount of information that could be obtained from these plots. Bland Altman plots and

limits of agreement provide a greater level of detail regarding the extent of agreement and direction of disagreement between different types of measures. For example, in the CODA study, while high positive correlation was observed between tablet count and electronic monitoring, the Bland-Altman plot and limits of agreement suggested that this association may belie a lack of agreement, particularly for participants allocated to take their medication in divided doses. The plots were enhanced by overlaying them with the boundaries within which data points can lie. These provided a more accurate representation of the boundaries in which data can lie than that suggested by the limits of agreement.

5. Several statistical models can be used to investigate which patient and illness characteristics predict disagreement between different types of adherence measures. If the focus is purely on whether there is disagreement (regardless of direction or extent), a multivariable binary logistic regression model can be fitted. If the direction is also of interest, a multivariable multinomial logistic regression model can be fitted. If direction and extent are both of interest, a multivariable linear regression model can be fitted. Each of these approaches provides increasingly detailed insights into variables that are associated with disagreement, and these can be used to inform the selection of appropriate type/s medication adherence measures. For example, in the GRACE WP10a study, older patients were less likely to have adherence measured using self-reported diary and tablet count data that disagreed. This may indicate that an age-stratified approach to measuring adherence to medication (i.e. tailoring the type of measure, or whether multiple types are used, is dependent on the age of a participant) may prove useful in subsequent research.

6. Calibration techniques provide a means of moving beyond merely reporting the comparison of different types of measures, and onto an approach to using a more reliable

measure of adherence (relative to reliance on a single type of measure), taking into account multiple data sources. The approaches presented in this Chapter are straightforward to implement, easy to communicate, and require relatively minimal assumptions. In the GRACE WP10a study, range calibration was used to maximise the amount of adherence data available and provide bounds on the level of medication adherence during the study. Hierarchy calibration was used to similarly maximise the amount of data available, but then created an agreed measure by making assumptions about the reliability of different types of measures. Calibration by classification was then used specifically to calibrate self-reported diary data using tablet count data. While these different calibration techniques did not result in the mean adherence differing by a large amount (the mean adherence was as low as 87.3 when based on the minimum value of all available measures and was as high as 90.8 when the maximum was used), the recommended approach will depend on the purpose of your calibration. If the purpose is to use all available data and provide bounds on the extent that participants adhered to treatment (for example, in sensitivity analysis), the range approach is most suitable. However, if more formal calibration is required, whereby assumptions are required about the reliability of different sources of adherence data, a hierarchy or classification approach may be more suitable.

CHAPTER 5: Determinants of Non-adherence to Medication: A Comparison among Different Clinical Conditions and Study Designs

5.1 Introduction

As described in earlier Chapters, non-adherence to medication can have severe consequences at both an individual and societal level. There exists a plethora of research investigating the effectiveness of interventions to improve adherence to medication, (Nieuwlaat et al., 2014) though only a minority of studies have reported on interventions that successfully improve both adherence and clinical outcomes, the latter arguably being the main goal in research of this kind. Interventions with this aim are likely to be most effective if they are informed by theory and developed gradually (for example, using a framework such as that proposed for the development of complex interventions (Craig, 2008)), and one of the first steps in this process involves developing an understanding of the determinants of adherence/non-adherence itself.

The aims of this Chapter are to investigate the determinants of non-adherence to medication and to explore several methodological considerations when investigating these determinants. The methodological aspects considered in this Chapter are:

- How determinants differ depending on type of measure
- How they differ across different clinical conditions (short-term acute conditions versus long-term conditions)
- How they differ depending on the study design (observational studies versus trials)
- How different domains of adherence can be appropriately modelled
- The value of modelling adherence as distinct processes rather than as a single variable

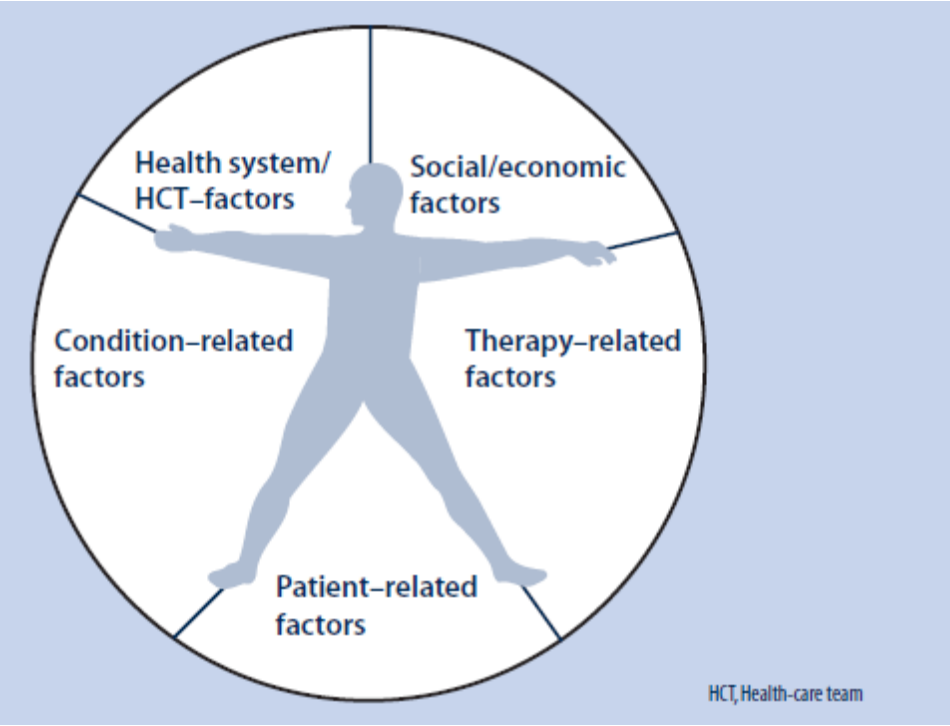
To meet these aims, this Chapter will draw on data from all studies described in Chapter 3.

5.2 Methods

5.2.1 Description of candidate determinants

The determinants of non-adherence to medication can be multifaceted. Indeed, the World Health Organisation (WHO) has identified five dimensions that all have the potential for influencing how medication is taken to treat long-term conditions, which comprise factors related to the patient, condition, therapy, social/economic, and healthcare team/system (Figure 5.1). The variables collected that were considered potentially influential on an individual's adherence to their medication (the candidate determinants) are described for each study in the following Section. All variables considered were collected (or known) prior to any medication being prescribed. This is important as it means that the variables may be modifiable or amenable to intervention, as they include details that can be known prior to commencing treatment.

Figure 5.1: The five dimensions of adherence (from Sabaté, 2003)



5.2.1.1 CODA

The candidate baseline determinants used in the CODA study included patient-related factors (age study entry (<65, ≥65), age at diagnosis (≤25, 26-45, 46-64, ≥65), gender, and smoking status (never smoker, current smoker, ex-smoker)), condition-related factors (length of remission (<12 months, ≥12 months), calprotectin concentration at study entry (<60mg/kg stool, ≥60 mg/kg stool), maximum documented extent of colitis (extensive, left-sided or sigmoid, proctitis), disease duration (≤10 years, 11 to 20 years, >20years), and endoscopy findings at study entry (normal, not normal)), a therapy-related factor (allocated regimen (once daily/three times daily)), and a social/economic factor (employment status (unemployed, employed)). No healthcare team or healthcare system factors were collected.

5.2.1.2 ZICE

The ZICE study included determinants related to patients (age at study entry, gender, Body Mass Index (BMI) at study entry), the condition (the modified Brief Pain Inventory severity score at study entry, Quality of Life (EORTC QLQ-C30 score version 3.0) at study entry, SRE within the previous three months), and therapy (previous use of bisphosphonates, treatments being received at study entry (including painkilling drugs, chemotherapy, hormone therapy, and trastuzumab), allocated treatment (oral ibandronic acid or intravenous zoledronic acid)). No social/economic, healthcare team, or healthcare system factors were collected.

5.2.1.3 GRACE

Participants in the GRACE studies had a substantial amount of data collected about them prior to receiving an allocation to or prescription of antibiotic treatment.

Patient-related determinants included age at study entry, gender, and whether the participant had a co-morbidity (at least one of the following: Chronic Obstructive Pulmonary Disease (COPD), asthma, other lung disease, heart failure, ischemic heart disease, other heart disease, or diabetes).

Condition-related determinants included presenting symptoms (cough, phlegm, shortness of breath, wheeze, coryza, fever, chest pain, muscle aching, headache, disturbed sleep, feeling

generally unwell, interference with normal activities, confusion/disorientation, and diarrhoea), clinician-rated symptom severity score (a summation of the severity of the 14 symptoms previously described scaled to range from 0 to 100, where 100 represented the maximum severity on all 14 symptoms and 0 represented no problems on any of the 14 symptoms), phlegm colour (categorised as no phlegm, normal coloured phlegm (white or clear), and discoloured phlegm (yellow, green, or bloodstained)), whether an abnormality was found when performing an auscultation examination (at least one of the following: diminished vesicular breathing, wheeze, crackles, or rhonchi), and the number of days of symptoms prior to consulting (categorised as seven days or less, eight to 14 days, or 15 days or more).

Therapy-related determinants included the dose (categorised as less than 500mg, 500mg, between 500 and 1000mg (not inclusive), and 1000mg or more), frequency (categorised as twice a day or more than twice a day), and duration (categorised as five days or less, six to seven days, or eight or more days) of the amoxicillin prescription. For the participants in the trial, this was fixed, as all participants were prescribed 1000mg of amoxicillin, three times a day for seven days.

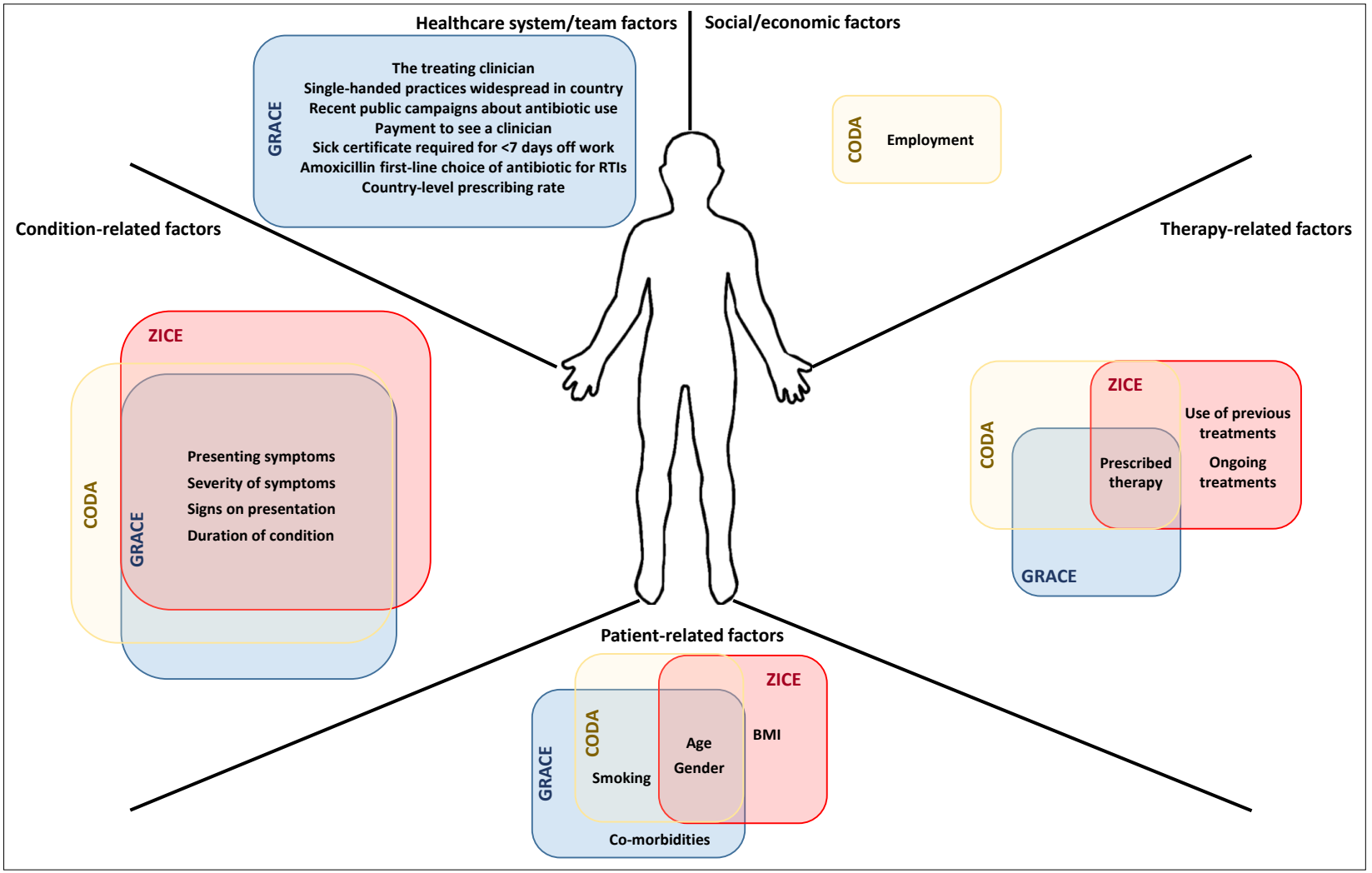
While there were no specific healthcare professional-related determinants available consistently across all three datasets, responsible clinician identifiers were available and could be used to determine whether variation in adherence could be attributed to the influence of individual clinicians.

Participants were recruited from several European countries (Belgium, England, Finland, France, Germany, Hungary, Italy, Norway, Poland, Slovakia, Slovenia, Spain, Sweden, The Netherlands, and Wales), and healthcare setting-related determinants were established from work carried out as part of the GRACE project (GRACE website. Available from: http://www.grace-lrti.org/portal/en-gb/), and subsequent surveys among clinicians from countries that were not represented in this work (France and Slovenia). These included whether single-handed (i.e. one clinician running an entire practice) practices were common (i.e. representing

at least a quarter of all practices), whether there had been public campaigns related to antibiotic use at the time the study was conducted, whether patients had to pay to see a general practitioner, whether clinicians were required to certify sickness for less than seven days of absence from work, whether amoxicillin was the first-line choice of antibiotic for a respiratory infection in primary care, and the country-level antibiotic prescribing rate. The prescribing rate was obtained from the European Surveillance of Antimicrobial Consumption Network (ESAC) antimicrobial consumption interactive database (ESAC-Net. Available from: http://tinyurl.com/zh233d3), defined as the Defined Daily Dose (DDD) per 1000 inhabitants per day, averaged across the years 2007 to 2010.

The figure below illustrates the candidate determinants available across the different domains and studies. Note the lack of social / economic factors available. While these factors were clearly not measured in as much detail as other factors were (e.g. those related to the patient or condition) in the studies considered throughout this thesis, some of the social / economic factors reported as being found to be associated with adherence in the WHO report by Sabaté (e.g. illiteracy, low level of education, unstable living conditions) may have also been key influencers for people not taking part in research (potentially an indicator of sampling bias). What is also lacking from all studies, which may have provided useful insight into how patients take their medication, are questions related to the patient's personality and beliefs about their condition and treatment. (Horne et al., 2013) As highlighted during Chapter 2, these behavioural influences (a patient-related factor) have been demonstrated to be predictive of adherence to medication.

Figure 5.2: Candidate determinants available for the CODA, ZICE, and GRACE studies



5.2.2 Definitions of adherence

5.2.2.1 Determinants of adherence depending on type of measure used

As described in Chapter 4, adherence was captured in the CODA study through self-reports, tablet counts, and electronic monitoring. In this Chapter, the determinants of adherence to treatment in the CODA study will be assessed and compared across all three types of measure in order to investigate the sensitivity of these (specifically, the ability to detect groups who adhered better/worse).

5.2.2.1.1 Self-report

At the end of the study, participants were asked "whether or not they had taken their study tablets as prescribed (e.g. at least 90% of the time)", hence participants were defined as having adhered to their treatment if they gave a response of "yes" and not adhered if "no".

5.2.2.1.2 Tablet counts

Research nurses counted the number of tablets returned at each study visit, and deducting this from the number of tablets issued determined the number consumed during the study period. Adherence to study medication in the original trial was defined as participants consuming at least 75% of their issued medication, and due to the skewed nature of the responses, this definition will also be used in this Chapter.

5.2.2.1.3 Electronic monitoring

The date and time of bottle cap openings were electronically recorded using the MEMS, with data uploaded onto the study database at each trial follow-up visit. Adherence was reported as the percentage of days that a participant adhered to their allocated regimen. Due to the skewed nature of responses, this measure also had to be dichotomised, with a 75% threshold chosen in order to be consistent with the tablet count threshold.

5.2.2.2 Adherence as a single variable or as distinct processes

Adherence may be defined as "the process by which patients take their medicine as prescribed. Traditionally, this has been represented quantitatively as a single variable (e.g. percentage of medicine taken as prescribed, a binary variable of taken as prescribed / not, etc.). However, recent work in this field encourages the use of the distinct processes involved in taking medicine; namely, initiation (the taking of the first dose), implementation (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose), and persistence or time to discontinuation (length of time between initiation and the last dose). (Vrijens et al., 2012) Each individual process may have its own determinants and influences on outcomes. Therefore, different interventions may be required to address each of the adherence processes. For the ZICE and GRACE studies, the benefits of modelling the determinants of adherence as a single variable and as distinct processes will be considered. ZICE and GRACE were considered to provide a comparison between long and short-term conditions. CODA was not considered in this section as all participants initiated treatment.

5.2.2.2.1 ZICE

Questions about adherence to study medication were asked at three initial interim visits, and then subsequently at 12-weekly visits.

Missing visit patterns were inspected, with the view to calculate adherence levels only in those with complete visit data up until the point of an event, withdrawal, death, or the end of the first 12 months.

For participants allocated to intravenous zoledronic acid, adherence was based on interim and 12-weekly visit data, as participants were required to attend to receive intravenous medication. It was assumed that participants did not adhere to study medication if they either did not attend a scheduled visit, or attended but were noted as not receiving study medication as prescribed during at least one visit. Participants in the oral ibandronic acid arm were also invited to attend

interim visits to minimise the likelihood that an increase in clinical contact in one arm could impact on trial findings. However, as it was not necessary for participants in this arm to attend visits to receive medication, and non-attendance at one or more interim visit was high, adherence to oral ibandronic acid was based on 12-weekly visit data only. It was assumed that participants did not adhere to study medication if they were noted as not receiving study medication as prescribed during at least one visit.

5.2.2.2.1.1 Combined summary measure

A single combined summary measure was created that indicated whether or not a participant took their treatment as prescribed. Based on the approach described above, a participant was considered to have adhered to their treatment if that had reported that they had taken their allocated treatment as prescribed when asked at valid clinic visits. This excludes visits that were not mandatory to attend, such as the interim visits for participants allocated to the oral ibandronic acid treatment, and visits where data were censored due to withdrawal.

5.2.2.2.1.2 Initiation

Participants were considered as having initiated their treatment if they reported, on at least one occasion/clinic visit, that they had taken their treatment.

5.2.2.2.1.3 Implementation

In those who reported initiating their treatment, participants were considered to have fully implemented their treatment if that had reported that they had taken their allocated treatment as prescribed when asked at all valid clinic visits.

5.2.2.2.1.4 Discontinuation

While I considered time from initiation to discontinuation for ZICE, I ultimately concluded it inappropriate to define with the type of measure used to capture adherence in this study.

Adherence relied on reports at clinic visits, but the interim visits (when treatment generally initiated) were not mandatory for one of the treatment arms (and these participants generally did not attend interim visits). I therefore considered it inappropriate to define time to discontinuation for this treatment group, and determinants of discontinuation will thus not be explored for this study.

5.2.2.2.2 GRACE

5.2.2.2.2.1 Combined summary measure

Using participant-completed diaries, a single summary measure was calculated, that indicated whether or not a participant took the full amount of medication they were prescribed (Yes/No).

5.2.2.2.2.2 Initiation

Participants were defined as having initiated their amoxicillin if they indicated in their diary that they took amoxicillin at least once during the 28 day follow-up period.

5.2.2.2.2.3 Implementation

In participants who initiated their amoxicillin, implementation describes the extent to which the prescription was taken as prescribed. As the focus was on amoxicillin prescribed for immediate use, for the purpose of this Chapter, it is defined as the proportion of amoxicillin reportedly taken during the prescribed period. For example, if a participant was prescribed amoxicillin for five days and only reported taking it for four days during the first five days of the follow-up period, their implementation score would be 0.8 (i.e. they initiated their amoxicillin course and took 80% of it during the prescribing period). A participant was considered to have fully implemented their amoxicillin if they reported taking it for the number of days it was prescribed for during the prescribing period.

5.2.2.2.2.4 Discontinuation

Participants were defined as having discontinued their amoxicillin prescription if they initiated their prescription and subsequently reported a full week of not taking their medicine. A gap of one week was deemed appropriate in distinguishing between patients who stopped and restarted their medicine, and those who were prescribed a new course of amoxicillin. The first day of that one-week gap was defined as the day they discontinued, and the time to discontinuation was calculated as the difference in days between the day of discontinuation and the day of initiation. For example, if a participant was prescribed a seven day course of amoxicillin for immediate use, initiated their amoxicillin on day three, and days 10 to 17 were the first full week where no amoxicillin was reportedly taken, they would be defined as having discontinued on day 10, and their time from initiation to discontinuation would be seven days (however, their implementation score would be 0.7, or 5/7).

5.2.3 Modelling

Logistic regression models of the odds of adhering to, initiating, and implementing treatment were presented as odds ratios, 95% confidence intervals, and p-values. Cox proportional hazards models of the time from initiation to discontinuation of treatment were presented as hazard ratios, 95% confidence intervals, and p-values. (Cox, 1972) Variables were entered into a univariable model and retained if they were significant at the $p < 0.1$ level. All retained variables were then entered into a multivariable model, with those that were not significant at the $p < 0.05$ level (in the multivariable model) removed sequentially, from largest to smallest p-value, until a final multivariable model was attained.

For the GRACE studies, participants recorded the use (or non-use) of amoxicillin on each study day. They also presented to clinicians within different countries. Data were available to indicate where participants presented to in terms of clinician and country. Variables pertaining to the

healthcare setting / country were also available for analysis. To investigate the proportion of variation that was attributable to differences between clinicians / countries, and hence may be potential influencers in whether someone adheres to their treatment (or initiates / implements it as intended), and also to appropriately model these determinants (i.e. calculate standard errors, and hence confidence intervals and p-values that are not artificially small), an appropriate hierarchy was selected prior to any further analysis taking place. To do this, null models were fitted with an increasing number of levels, with the AIC used to establish the best fitting model, with a smaller AIC indicating a better model fit. Some clinicians participated in more than one of the three studies, and where this was the case their identifier was linked across studies.

Data from the GRACE studies were also combined in order to increase the precision of the estimates. The study from which a participant provided data was used in all models (both univariable and multivariable), to ensure that any association was not confounded by the characteristics of participants from different studies.

5.3 Results

5.3.1 CODA

Levels of adherence based on self-report, tablet count, and electronic monitoring data were reported in Chapter 4. They are briefly reported again here for consistency throughout this Chapter and to assist with interpretation of the findings (Figure 5.3).

5.3.1.1 Determinants of adherence to mesalazine based on self-report data

When the candidate determinants were tested in univariable analysis, only the allocated regimen could be retained for further investigation (Table 5.1).

Table 5.1: Univariable analysis of determinants of adherence to mesalazine based on self-report data*

Domain	Variable	Univariable p-value	Retain for multivariable analysis
Patient-related factors	Age	0.509	No
	Gender	0.746	No
	Smoking status	0.456	No
Social / economic-related factors	Employment status	0.519	No
Condition-related factors	Length of remission	0.184	No
	Calprotectin concentration	0.575	No
	Maximum documented extent of ulcerative colitis	0.375	No
	Duration of disease	0.215	No
	Endoscopy findings	0.292	No
Therapy-related factor	Allocated regimen	0.011	Yes

*Analysis based on up to 187 participants

The odds of adhering, based on self-report data, were over five times higher for participants allocated to the once daily regimen, compared to those allocated to the three times daily regimen (Table 5.2).

Table 5.2 Logistic regression model of the odds of adhering to mesalazine based on self-report data

Domain	Variable	Odds ratio*	95% Confidence Interval	p-value
Therapy-related factor	Allocated to three times daily regimen	Reference category		
	Allocated to once daily regimen	5.25	1.46 to 18.94	0.011

*Odds for adhering to prescribed regimen, according to self-report data. Analysis is based on 187 participants.

5.3.1.2 Determinants of adherence to mesalazine based on tablet count data

No variables were found to be associated at the $p < 0.1$ level with adherence according to tablet count data (Table 5.3).

5.3.1.3 Determinants of adherence to mesalazine based on electronic monitoring data

Two variables were retained for multivariable analysis, when investigating the determinants of adherence based on electronic monitoring data – gender and allocated regimen (Table 5.4).

Both variables were also retained in the final multivariable model, which demonstrated that the odds of adhering to treatment, according to tablet count data, was 80% lower in females than in males (75% of males adhered, 50% of females adhered), and over 30 times higher for those allocated to the once daily regimen (93% of those allocated to once daily adhered compared to 37% of those allocated to three times daily), compared to those allocated to the three times daily regimen (Table 5.5).

Table 5.3: Univariable analysis of determinants of adherence to mesalazine based on tablet count data*

Domain	Variable	Univariable p-value	Retain for multivariable analysis
Patient-related factors	Age	0.637	No
	Gender	0.492	No
	Smoking status	0.135	No
Social / economic-related factors	Employment status	0.968	No
Condition-related factors	Length of remission	0.446	No
	Calprotectin concentration	0.955	No
	Maximum documented extent of ulcerative colitis	0.260	No
	Duration of disease	0.277	No
	Endoscopy findings	0.163	No
Therapy-related factors	Allocated regimen	0.467	No

*Analysis based on up to 164 participants

Figure 5.3: Levels of adherence to mesalazine by type of measure and allocated regimen

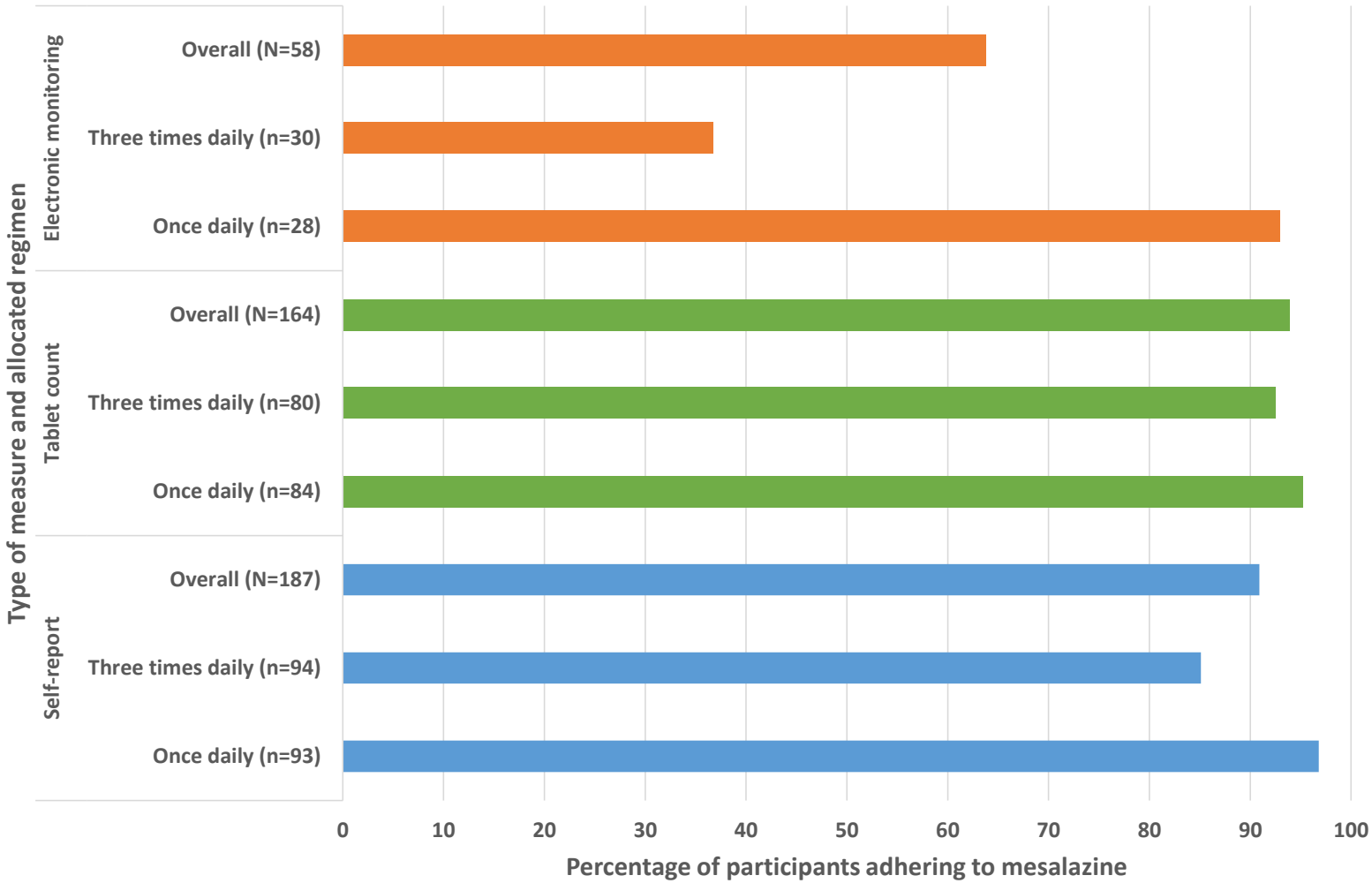


Table 5.4: Univariable analysis of determinants of adherence to mesalazine based on electronic monitoring data*

Domain	Variable	Univariable p-value	Retain for multivariable analysis
Patient-related factors	Age	0.254	No
	Gender	0.052	Yes
	Smoking status	0.764	No
Social / economic-related factors	Employment status	0.159	No
Condition-related factors	Length of remission	0.462	No
	Calprotectin concentration	0.515	No
	Maximum documented extent of ulcerative colitis	0.111	No
	Duration of disease	0.194	No
	Endoscopy findings	0.278	No
Therapy-related factors	Allocated regimen	<0.001	Yes

*Analysis based on up to 58 participants

Table 5.5: Multivariable logistic regression model of the odds of adhering to mesalazine based on electronic monitoring data

Domain	Variable	Odds ratio*	95% Confidence Interval	p-value
Patient-related factor	Male	Reference category		
	Female	0.20	0.04 to 0.89	0.035
Therapy-related factor	Allocated to three times daily regimen	Reference category		
	Allocated to once daily regimen	30.47	5.15 to 180.25	<0.001

*Odds for adhering to prescribed regimen for at least 75% of study days, according to electronic monitoring data. Analysis is based on 58 participants.

5.3.2 ZICE

5.3.2.1 Adherence measures in the ZICE trial

Overall, 66.9% of participants adhered to their treatment in the ZICE trial, based on the combined summary measure. More participants allocated to oral ibandronic acid adhered than those allocated to intravenous zoledronic acid (76.7% compared to 60.0%). Initiation was extremely high in the ZICE trial. Overall, 95.0% of participants initiated treatment. Consequently, full implementation provides similar characteristics as the combined summary measure (Table 5.6).

Table 5.6: Adherence to treatment in the ZICE trial based on a combined summary measure and separated into different elements (initiation and implementation)*

	Oral ibandronic acid	Intravenous zoledronic acid	Overall
Adhered (based on combined summary measure)	76.7 (371/484)	60.0 (408/680)	66.9 (779/1164)
Initiated treatment	95.6 (614/642)	94.4 (646/684)	95.0 (1260/1326)
Fully implemented treatment	77.9 (371/476)	63.4 (408/644)	69.6 (779/1120)

*Numbers are % (n/N)

5.3.2.2 Determinants of adherence to treatment in the ZICE trial based on a combined summary measure

Univariable analysis led to the retention of two variables: participant age and allocated treatment (Table 5.7). However, only allocated treatment was retained in the final model. The odds of adhering to treatment in the ZICE trial were 47% lower in those allocated to intravenous zoledronic acid compared to those allocated to oral ibandronic acid (95% CI: 0.42 to 0.69, $p < 0.001$).

Table 5.7: Univariable analysis of determinants of adherence to treatment in the ZICE trial*

Domain	Variable	Univariable p-value	Retain for multivariable analysis
Patient-related factors	Age	0.095	Yes
	Gender	0.642	No
	BMI	0.630	No
Condition-related factors	BPI pain severity score	0.980	No
	BPI pain interference score	0.825	No
	QLQ C30 global health	0.272	No
	QLQ C30 physical functioning	0.242	No
	QLQ C30 role functioning	0.729	No
	QLQ C30 emotional functioning	0.870	No
	QLQ C30 cognitive functioning	0.144	No
	QLQ C30 social functioning	0.721	No
	QLQ C30 fatigue symptoms	0.220	No
	QLQ C30 nausea/vomiting symptoms	0.339	No
	QLQ C30 dyspnoea symptoms	0.174	No
	QLQ C30 insomnia symptoms	0.234	No
	QLQ C30 appetite symptoms	0.875	No
	QLQ C30 constipation symptoms	0.650	No
	QLQ C30 diarrhoea symptoms	0.581	No
	QLQ C30 financial symptoms	0.744	No
	Previous SRE (last 3 months)	0.978	No
Therapy-related factors	Allocated treatment	<0.001	Yes
	Previous bisphosphonates use	0.971	No
	Recent use of pain medication	0.121	No
	Current use of chemotherapy	0.489	No
	Current use of hormone therapy	0.258	No
	Current use of trastuzumab therapy	0.352	No

*Analysis based on up to 1,164 participants

5.3.2.3 Determinants of initiation of treatment in the ZICE trial

Univariable analysis led to the retention of variables related to the condition (global health, cognitive functioning, social functioning, and fatigue symptoms) and therapy (current use of hormone therapy) (Table 5.8).

The final model found that the odds of initiating treatment in the ZICE study increased as social functioning increased (odds ratio for a unit increase = 1.01, 95% CI: 1.00 to 1.02, p = 0.029).

5.3.2.4 Determinants of implementation of treatment in the ZICE trial

Univariable analysis of the determinants of implementation of treatment in the ZICE trial led to the retention of similar variables to those retained when using the combined summary measure (participant age and allocated treatment), with the addition of another therapy-related factor (recent use of pain medication). However, only allocated treatment was retained in the final model, which demonstrated that the odds of implementing treatment in the ZICE trial was 51% lower for those allocated to intravenous zoledronic acid compared to those allocated to oral ibandronic acid (95% CI: 0.37 to 0.64, p < 0.001).

Table 5.8: Univariable analysis of determinants of initiation of treatment in the ZICE trial*

Domain	Variable	Univariable p-value	Retain for multivariable analysis
Patient-related factors	Age	0.894	No
	Gender	0.864	No
	BMI	0.884	No
Condition-related factors	BPI pain severity score	0.626	No
	BPI pain interference score	0.417	No
	QLQ global health	0.083	Yes
	QLQ physical functioning	0.600	No
	QLQ role functioning	0.737	No
	QLQ emotional functioning	0.308	No
	QLQ cognitive functioning	0.044	Yes
	QLQ social functioning	0.029	Yes
	QLQ fatigue symptoms	0.059	Yes
	QLQ nausea/vomiting symptoms	0.583	No
	QLQ dyspnoea symptoms	0.273	No
	QLQ insomnia symptoms	0.445	No
	QLQ appetite symptoms	0.164	No
	QLQ constipation symptoms	0.869	No
	QLQ diarrhoea symptoms	0.268	No

Domain	Variable	Univariable p-value	Retain for multivariable analysis
	QLQ financial symptoms	0.655	No
	Previous SRE (last 3 months)	0.226	No
Therapy-related factors	Allocated treatment	0.319	No
	Previous bisphosphonates use	0.109	No
	Recent use of pain medication	0.854	No
	Current use of chemotherapy	0.851	No
	Current use of hormone therapy	0.099	Yes
	Current use of trastuzumab therapy	0.550	No

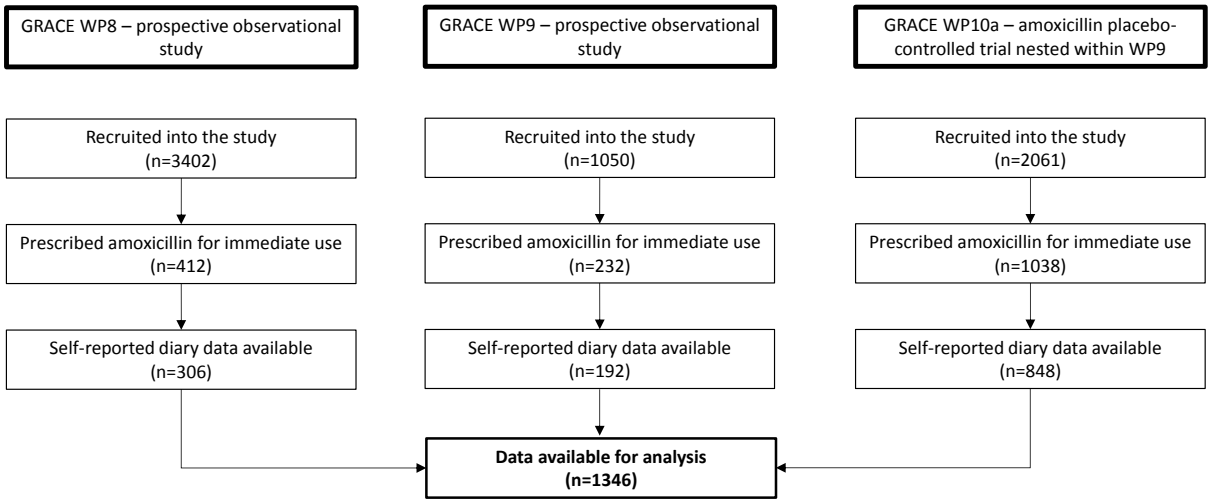
*Analysis based on up to 1,326 participants

5.3.3 GRACE

In total, data were available for 1,346 participants prescribed amoxicillin for immediate use and for whom self-reported follow-up diary data were available (WP10a, the placebo-controlled trial, n = 848; WP8, the prospective observational study, n = 306; and WP9, the observational study within which the trial was nested, n = 192).

Overall, participants were recruited by 322 clinicians who were based in 15 different countries across Europe (Figure 5.4).

Figure 5.4: Flow diagram showing data from all three GRACE studies used in this Chapter



5.3.3.1 Characteristics of participants in the GRACE studies

Participants were aged between 18 and 88 years (median 51, IQR: 38 to 62). While the age distributions in WP8 and WP10a were similar, those recruited into WP9 tended to be slightly older (median 58, IQR: 45 to 65). Overall, 540 participants were men (40.1%), and 372 participants had at least one of the listed co-morbidities (27.7%). WP9 contained a higher percentage of participants with co-morbidities (36.5%) (Table 5.9).

5.3.3.2 Illness characteristics of participants in the GRACE studies

Other than cough, which was part of the inclusion criteria for all three studies, the five most frequently reported symptoms were phlegm (81.3%), feeling generally unwell (79.8%), interference with normal activities (69.6%), disturbed sleep (64.5%), and shortness of breath (59.0%). Fever and headache were most frequently reported by participants in WP8, and coryza by participants in WP10a. Phlegm, shortness of breath, wheeze, disturbed sleep, feeling generally unwell, and diarrhoea were symptoms most frequently reported by participants in WP9 (Table 5.9).

Overall, the median clinician-rated symptom severity score at recruitment was 36 (IQR: 25 to 46), with participants from WP9 reporting the highest average symptom severity (median = 38, IQR: 26 to 48) and those from WP10a the lowest (median = 35, IQR: 25 to 46). Abnormal findings on auscultation examination were found in 652 participants (48.5%), with participants in WP10a least likely to have abnormal findings (34.3%). Discoloured phlegm was reported by 680 participants (53.2%) (Table 5.9).

Table 5.9: Participant and illness characteristics by study

Participant / illness characteristic	WP8 (n=306)	WP9 (n=192)	WP10a (n=848)	Overall (n=1346)
Age (years)*	49 (37 to 62)	58 (45 to 65)	50 (37 to 61)	51 (38 to 62)
Male†	124 (40.5)	75 (39.1)	341 (40.2)	540 (40.1)
Female†	182 (59.5)	117 (60.9)	507 (59.8)	806 (59.9)
At least one co-morbidity†	77 (25.2)	70 (36.5)	225 (26.6)	372 (27.7)
Clinician-rated symptom severity*	36 (26 to 48)	38 (26 to 48)	35 (25 to 46)	36 (25 to 46)
Phlegm	255 (83.6)	173 (90.1)	665 (78.5)	1093 (81.3)
Shortness of breath	198 (64.7)	143 (74.5)	452 (53.4)	793 (59.0)
Wheeze	175 (57.2)	125 (65.1)	344 (40.6)	644 (47.9)
Coryza	204 (66.9)	134 (69.8)	635 (75.0)	973 (72.4)
Fever	183 (59.8)	79 (41.1)	290 (34.3)	552 (41.1)
Chest pain	157 (51.3)	100 (52.1)	372 (44.0)	629 (46.8)
Muscle aching	179 (58.5)	108 (56.2)	421 (49.7)	708 (52.6)
Headache	199 (65.0)	104 (54.2)	467 (55.1)	770 (57.2)
Disturbed sleep	213 (69.8)	145 (75.9)	508 (60.0)	866 (64.5)
Feeling generally unwell	269 (88.2)	174 (90.6)	629 (74.3)	1072 (79.8)
Interference with normal activities	242 (79.3)	143 (74.5)	551 (65.1)	936 (69.6)
Confusion/disorientation	23 (7.5)	11 (5.7)	23 (2.7)	57 (4.2)

Participant / illness characteristic	WP8 (n=306)	WP9 (n=192)	WP10a (n=848)	Overall (n=1346)
Diarrhoea	23 (7.5)	19 (9.9)	53 (6.3)	95 (7.1)
Abnormal auscultation finding†‡	220 (71.9)	142 (74.3)	290 (34.3)	652 (48.5)
No phlegm†§	50 (16.5)	17 (9.1)	133 (16.9)	200 (15.6)
Normal coloured phlegm†§	71 (23.4)	60 (32.1)	268 (34.0)	399 (31.2)
Discoloured phlegm†§	182 (60.1)	110 (58.8)	388 (49.2)	680 (53.2)
Waited 7 days or fewer prior to consulting†	212 (70.4)	123 (65.4)	524 (62.7)	859 (64.8)
Waited 8 to 14 days prior to consulting†	68 (22.6)	43 (22.9)	192 (23.0)	303 (22.9)
Waited 15 days or more prior to consulting†	21 (7.0)	22 (11.7)	120 (14.4)	163 (12.3)

*Median (IQR); †n (%); ‡ At least one of the following: diminished vesicular breathing, wheeze, crackles, or rhonchi; § Normal coloured phlegm = clear or white, discoloured phlegm = yellow, green, or bloodstained.

5.3.3.3 Prescription characteristics of participants in the GRACE studies

While participants in WP10a were prescribed a fixed dose, frequency, and duration of amoxicillin, it was not fixed for participants in the other two studies. For these participants, the most frequently prescribed dose was 500mg (218, or 44.2% of all participants were prescribed this dose), with 393 instructed to take their medication three or more times a day (79.2%), and 339 prescribed a six or seven day course (68.3%). Participants in WP8 were more likely to be prescribed higher doses to be taken less frequently and for a shorter duration, than those in WP9 (Table 5.10).

5.3.3.4 Healthcare setting characteristics of participants in the GRACE studies

Of the 15 countries included, single handed practices were common in six (40.0%), campaigns around antibiotic use had recently been conducted in seven (46.7%), patients were required to pay to see a GP at the point of delivery of care in seven (46.7%), and a doctor-issued sick certificate was required for certifying people off work for less than seven days in three (20.0%). Amoxicillin was the first-line choice of antibiotic in the national guidelines of six of the countries (40.0%), and antibiotic prescribing rates ranged from 11.2 DDDs per 1000 inhabitants/day (The Netherlands) to 28.6 DDDs per 1000 inhabitants/day (France), with six countries categorised as low prescribers (The Netherlands, Sweden, Germany, Slovenia, Norway, and Hungary), five as moderate (England, Wales, Finland, Spain, and Poland), and four as high prescribers (Slovakia, Belgium, Italy, and France) (Table 5.11).

Table 5.10: Amoxicillin prescription characteristics by study

Prescription characteristic*		WP8 (n=306)	WP9 (n=192)	WP10a (n=848)	Overall (n=1346)
Dose (mg)	Less than 500	23 (12.3)	52 (17.0)	0 (0.0)	75 (5.6)
	500	99 (52.9)	119 (38.9)	0 (0.0)	218 (16.3)
	500 to 1000 (not inclusive)	8 (4.3)	34 (11.1)	0 (0.0)	42 (3.1)
	1000 or more	57 (30.5)	101 (33.0)	848 (100.0)	1006 (75.0)
Frequency (times per day)	Twice	13 (6.8)	90 (29.4)	0 (0.0)	103 (7.7)
	More than twice	177 (93.2)	216 (70.6)	848 (100.0)	1241 (92.3)
Duration (days)	5 or fewer	14 (7.3)	59 (19.3)	0 (0.0)	73 (5.4)
	6 or 7	144 (75.4)	195 (63.9)	848 (100.0)	1187 (88.3)
	8 or more	33 (17.3)	51 (16.7)	0 (0.0)	84 (6.2)

*n (%)

5.3.3.5 Adherence measures in the GRACE studies

Full adherence, based on a combined summary measure, was observed in 827 participants overall (61.5%), though varied widely between studies, from 26.7% for participants in WP9 to 87.1% for those in WP10a.

While overall a high proportion of participants initiated their amoxicillin (1057, or 78.5% of participants), this was again largely driven by the almost-complete initiation of amoxicillin seen in WP10a, the randomised placebo-controlled trial (97.6%). Initiation in participants from WP8 and WP9 were considerably lower (51.0 and 38.0% respectively). When initiation occurred, it was mostly on the day of prescription (91.5% of participants who initiated did so on day 1).

In participants who initiated amoxicillin, implementation levels were high and highly skewed across all three studies. Full implementation was achieved by 827 participants overall (78.3%),

with full implementation across studies ranging from 70.8% of participants in WP9 (51/72) to 80.0% in WP10a (662/828).

The median time from initiation to discontinuation of amoxicillin was seven days across all three studies (overall IQR: 7 to 8 days).

Table 5.11: Healthcare setting characteristics of participants in the GRACE studies*

Country	Widespread availability of single-handed practices*	Recent public campaigns around antibiotic use	Payment required to see GP	Sick certification required for less than 7 days off work	Amoxicillin first-line choice for a respiratory infection in primary care	Antibiotic prescribing rate†
Belgium	✓	✓	✓	✓	✓	27.1 (25.2 to 28.2)
England		✓			✓	17.4 (16.5 to 18.7)
Finland			✓			18.1 (17.8 to 18.5)
France	✓		✓		✓	28.6 (28.1 to 29.6)
Germany	✓				✓	14.6 (14.5 to 14.9)
Hungary			✓			15.6 (15.2 to 16.0)
Italy	✓					28.1 (27.6 to 28.7)
The Netherlands	✓	✓	✓			11.2 (11.1 to 11.4)
Norway			✓			15.5 (15.2 to 15.8)
Poland		✓		✓		21.9 (20.8 to 23.6)
Slovakia	✓	✓				23.9 (23.2 to 24.8)
Slovenia					✓	14.9 (14.3 to 15.9)

Country	Widespread availability of single-handed practices*	Recent public campaigns around antibiotic use	Payment required to see GP	Sick certification required for less than 7 days off work	Amoxicillin first-line choice for a respiratory infection in primary care	Antibiotic prescribing rate†
Spain		✓		✓		19.9 (19.7 to 20.3)
Sweden		✓	✓			14.6 (14.1 to 15.5)
Wales					✓	17.4 (16.5 to 18.7)

*Obtained from interview data as part of the GRACE project. Characteristics relate to the time at which participant data were collected.

†Obtained from the European Surveillance of Antimicrobial Consumption Network (ESAC) antimicrobial consumption interactive database (http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/esac-net-database/Pages/overview-country-consumption.aspx), and defined as the Defined Daily Dose (DDD) per 1000 inhabitants per day. Rate averaged across years 2007 to 2010 (min and max values in brackets). United Kingdom rates used for England and Wales.

5.3.3.6 Determinants of adherence to amoxicillin based on combined summary measure

As demonstrated by Table 5.12, the best fitting model according to the AIC was a three-level model with participants nested within clinicians nested within countries. All univariable and multivariable analyses will therefore be based on this. The clinician-level ICC from this initial model was 0.29, and the country-level ICC was 0.06.

Table 5.12: Hierarchy selection for a logistic regression model of adherence to amoxicillin based on a combined summary measure

Model	Description	ICCs	AIC	Decision
1	Single level	N/A	1794.938	Null model (to obtain benchmark AIC)
2	Two-level (participant within clinician)	Clinician: 0.29	1701.074	Better model fit
3	Three-level (participant within clinician within country)	Clinician: 0.29 Country: 0.06	1677.694	Better model fit

Univariable analysis led to participant age, muscle aching, phlegm colour, clinician-rated symptom severity score, duration of prescription, and being from a country where payment is required to see a GP being retained (Table 5.13).

Table 5.13: Univariable analysis of determinants of adherence to amoxicillin based on a combined summary measure*

Domain	Variable	Univariable p-value	Retain for multivariable analysis
Patient-related factors	Age	0.002	Yes
	Gender	0.135	No
	Smoking status	0.453	No
	Co-morbidities	0.227	No
Condition-related factors	Phlegm	0.271	No
	Shortness of breath	0.768	No
	Wheeze	0.611	No
	Coryza	0.582	No
	Fever	0.227	No
	Chest pain	0.478	No
	Muscle aching	0.076	Yes
	Headache	0.966	No
	Disturbed sleep	0.158	No
	Feeling generally unwell	0.666	No
	Interference with normal activities	0.374	No
	Confusion / disorientation	0.888	No
	Diarrhoea	0.883	No
	Phlegm colour	0.078	Yes
	Clinician-rated symptom severity score	0.077	Yes
	Auscultation abnormality	0.184	No
	Days waited prior to consulting	0.229	No
Therapy-related factors	Dose	0.386	No
	Frequency	0.599	No
	Duration	0.099	Yes
Healthcare setting-related factors	Single handed practices widespread	0.268	No

Domain	Variable	Univariable p-value	Retain for multivariable analysis
	Recent public campaigns on antibiotic use	0.701	No
	Payment required to see GP	0.065	Yes
	Sick certification required for missing less than 7 days of work	0.384	No
	Amoxicillin first line choice of antibiotic	0.952	No
	Country-level prescribing rate	0.545	No

*Analysis based on up to 1345 participants nested within 332 clinicians within 15 countries

The only determinant retained in the final model was participant age, with the odds of adhering to amoxicillin increasing by 15% per 10-year increase in age (Table 5.14).

The ICCs from the final model indicated that 15% of the total variation in adherence was attributable to clinicians, with 3% attributable to country differences.

Table 5.14: Three-level logistic regression model of the odds of adhering to amoxicillin based on a combined summary measure

Domain	Variable	Odds ratio*	95% Confidence Interval	p-value
Patient-related factor	Age (per decade increase)	1.15	1.05 to 1.26	0.002
N/A	Participant from WP8	Reference category		
	Participant from WP9	0.51	0.31 to 0.83	<0.001
	Participant from WP10a	7.83	5.22 to 11.74	

*Odds for fully adhering to prescribed treatment, according to self-report diary data. Analysis is based on 1345 participants nested within 332 clinicians within 15 countries.

5.3.3.7 Determinants of initiation of amoxicillin

Similar to the combined measure, the best fitting model according to the AIC incorporated clustering at both the clinician and country levels. The clinician-level ICC from this initial model was 0.28, and the country-level ICC was 0.22 (Table 5.15).

Table 5.15: Hierarchy selection for a logistic regression model of initiation of amoxicillin

Model	Description	ICCs	AIC	Decision
1	Single level	N/A	1402.192	Null model (to obtain benchmark AIC)
2	Two-level (participant within clinician)	Clinician: 0.54	1244.809	Better model fit
3	Three-level (participant within clinician within country)	Clinician: 0.28 Country: 0.22	1193.064	Better model fit

Univariable analysis led to the retention of participant age, number of days waited prior to consulting, duration of prescription, and being in a country where sick certification is required for missing less than seven days of work (Table 5.16).

Table 5.16: Univariable analysis of determinants of initiation of amoxicillin*

Domain	Variable	Univariable p-value	Retain for multivariable analysis
Patient-related factors	Age	0.095	Yes
	Gender	0.927	No
	Co-morbidities	0.327	No
Condition-related factors	Cough	0.950	No
	Phlegm	0.192	No
	Shortness of breath	0.808	No
	Wheeze	0.663	No
	Coryza	0.595	No
	Fever	0.513	No
	Chest pain	0.549	No
	Muscle aching	0.913	No
	Headache	0.100	No
	Disturbed sleep	0.413	No

Domain	Variable	Univariable p-value	Retain for multivariable analysis
	Feeling generally unwell	0.213	No
	Interference with normal activities	0.144	No
	Confusion/disorientation	0.749	No
	Diarrhoea	0.633	No
	Clinician-rated symptom severity score	0.909	No
	Phlegm colour	0.408	No
	Auscultation abnormality	0.940	No
	Number of days with illness prior to consulting	0.008	Yes
Therapy-related factors	Dose	0.459	No
	Frequency	0.776	No
	Duration	0.005	Yes
Healthcare setting-related factors	Single handed practices widespread	0.885	No
	Recent public campaigns on antibiotic use	0.325	No
	Payment required to see GP	0.810	No
	Sick certification required for missing less than 7 days of work	0.001	Yes
	Amoxicillin first line choice of antibiotic	0.740	No
	Country-level prescribing rate	0.893	No

*Analysis based on up to 1346 participants within 332 clinicians within 15 countries.

Compared to those who had waited seven days or fewer, participants who had waited 15 days or more prior to consulting had higher odds of initiating their amoxicillin (OR = 2.77, 95% CI: 1.35 to 5.67). There was some evidence that the duration of the prescription was also associated with amoxicillin initiation. Participants who were prescribed amoxicillin for eight days or more had higher odds of initiating their amoxicillin than those prescribed for five days or less, though this

was not statistically significant at the 5% level (OR = 2.29, 95% CI: 0.97 to 5.42). Participants in countries where a sick certificate was required for taking fewer than seven days off work had higher odds of initiating their amoxicillin (OR = 2.15, 95% CI: 1.27 to 3.64) (Table 5.17).

The ICC from the final multivariable model indicated that 17% of the total variation in initiation was attributable to differences between clinicians. The country-level ICC was negligible.

Table 5.17: Multivariable logistic regression model investigating the determinants of initiation of amoxicillin

Domain	Variable*	Odds ratio	95% CI		p-value
			Lower	Upper	
Condition-related factor	Waited 7 days or less prior to consulting	Reference category			
	Waited 8 to 14 days prior to consulting	1.47	0.92	2.34	0.010
	Waited 15+ days prior to consulting	2.77	1.35	5.67	
Therapy-related factor	Prescribed amoxicillin for 5 days or fewer	Reference category			
	Prescribed amoxicillin for 6 or 7 days	0.84	0.44	1.62	0.013
	Prescribed amoxicillin for 8 days or more	2.29	0.97	5.42	
Healthcare setting-related factor	Sick certification required for missing less than 7 days of work	2.15	1.27	3.64	0.004
N/A	Participant from WP8	Reference category			
	Participant from WP9	0.46	0.28	0.75	<0.001
	Participant from WP10a	56.04	27.54	114.03	

* The model is based on 1,323 participants, nested within 330 clinicians, nested within 15 countries. The AIC for the final model was 814.3369, an improvement over the AIC of the null three-level model. The ICCs from the final model were: Clinician: 0.17; Country: 0.00.

5.3.3.8 Determinants of implementation of amoxicillin

The AIC indicated that a four-level model was the best fitting for the implementation data, with days nested within participants (ICC = 0.64) within clinicians (ICC = 0.06) within countries (ICC = 0.01). This approach therefore modelled implementation as the probability of correctly implementing on a given day (Table 5.18).

Table 5.18: Hierarchy selection for a logistic regression model of implementation of amoxicillin

Model	Description	ICCs	AIC	Decision
1	Single level	N/A	3964.348	Null model (to obtain benchmark AIC)
2	Two-level (day within participant)	Participant: 0.72	3005.479	Better model fit
3	Three-level (day within participant within clinician)	Clinician: 0.07 Participant: 0.64	2996.044	Better model fit
4	Four-level (day within participant within clinician within country)	Country: 0.01 Clinician: 0.06 Participant: 0.64	2994.807	Better model fit

The univariable analysis led to the retention of several variables, with variables related to the patient (age), condition (fever, muscle aching, clinician-rated symptom severity score, and auscultation abnormality), and therapy (duration of prescription) retained for further investigation (Table 5.19).

Table 5.19: Univariable analysis of determinants of implementation of amoxicillin*

Domain	Variable	Univariable p-value	Retain for multivariable analysis
Patient-related factors	Age	0.021	Yes
	Gender	0.179	No
	Co-morbidities	0.370	No
Condition-related factors	Cough	0.970	No
	Phlegm	0.765	No
	Shortness of breath	0.947	No
	Wheeze	0.405	No
	Coryza	0.520	No

Domain	Variable	Univariable p-value	Retain for multivariable analysis
	Fever	0.094	Yes
	Chest pain	0.490	No
	Muscle aching	0.055	Yes
	Headache	0.734	No
	Disturbed sleep	0.174	No
	Feeling generally unwell	0.350	No
	Interference with normal activities	0.504	No
	Confusion/disorientation	0.818	No
	Diarrhoea	0.331	No
	Clinician-rated symptom severity score	0.086	Yes
	Phlegm colour	0.137	No
	Auscultation abnormality	0.040	Yes
	Number of days with illness prior to consulting	0.560	No
Therapy-related factors	Dose	0.369	No
	Frequency	0.585	No
	Duration	<0.001	Yes
Healthcare setting-related factors	Single handed practices widespread	0.733	No
	Recent public campaigns on antibiotic use	0.171	No
	Payment required to see GP	0.138	No
	Sick certification required for missing less than 7 days of work	0.462	No
	Amoxicillin first line choice of antibiotic	0.794	No
	Country-level prescribing rate	0.258	No

*Analysis based on up to 7,463 days within 1,057 participants within 281 clinicians within 15 countries

The final multivariable model found that the odds of implementing amoxicillin on a given day were higher among older participants (OR for a decade increase = 1.21, 95% CI: 1.03 to 1.41), and there was some evidence that it was higher for participants with abnormal auscultation findings at their index consultation, though the 95% CI included 1 (OR = 1.71, 95% CI: 1.00 to 2.91). The odds were lower for participants prescribed courses of amoxicillin lasting eight days or more (OR compared to courses lasting up to five days = 0.07, 95% CI: 0.01 to 0.42) (Table 5.20).

Sixty-two percent of the total variation in whether amoxicillin was taken on a given day was attributable to differences between participants. The clinician and country-level ICCs were both 0.04.

Table 5.20: Four-level logistic regression model investigating the determinants of implementation of amoxicillin

Variable*	Odds ratio	95% CI		p-value
		Lower	Upper	
Age (per decade increase)	1.21	1.03	1.41	0.019
Auscultation abnormality†	1.71	1.00	2.91	0.050
Prescribed amoxicillin for 5 days or less	Reference category			
Prescribed amoxicillin for 6 or 7 days	1.18	0.22	6.25	<0.001
Prescribed amoxicillin for 8 days or more	0.07	0.01	0.42	
Participant from WP8	Reference category			
Participant from WP9	1.23	0.42	3.64	0.909
Participant from WP10a	1.18	0.48	2.88	

* The model is based on 7,421 days nested within 1,054 participants, nested within 281 clinicians, nested within 15 countries. The ICCs from the final model were: Participant: 0.62; Clinician: 0.04; Country: 0.04. † At least one of the following: diminished vesicular breathing, wheeze, crackles, or rhonchi.

5.3.3.9 Determinants of time to discontinuation of amoxicillin

Attempts were made to conduct survival analyses that explicitly modelled the multilevel structure of the data (i.e. frailty models). However, these models failed to converge for the majority of candidate determinants. These analyses are therefore based on single-level Cox proportional hazards models with standard errors corrected for clustering of participants within clinicians. In addition, the final model was also fitted correcting for the clustering of participants within countries, to explore the robustness of findings to alterations in how the standard errors were corrected.

The univariable analysis led to the retention of determinants related to therapy factors (dose and duration of prescription) and healthcare setting factors (participants from countries where single handed practices were widespread and where recent public campaigns on antibiotic use had taken place) (Table 5.21).

Findings from the final multivariable model indicated that longer courses were associated with a longer time to discontinuation (HR for six to seven days compared to five days or less = 0.30, 95% CI: 0.17 to 0.55, HR for 8 days or more compared to five days or less = 0.19, 95% CI: 0.10 to 0.36). Participants from countries where single-handed practices were widespread were associated with a shorter time until discontinuation (HR = 1.15, 95% CI: 1.03 to 1.28) (Table 5.22). These results persisted when the standard errors were corrected for clustering of participants within countries (Table 5.23).

5.3.3.10 Differences across studies

As indicated by the forest plots, there was insufficient evidence to suggest that the determinants found in the models for initiation, implementation, and discontinuation differed within the individual studies (Figures 5.5, 5.6, and 5.7).

Table 5.21: Univariable analysis of determinants of time to discontinuation of amoxicillin*

Domain	Variable	Univariable p-value	Retain for multivariable analysis
Patient-related factors	Age	0.273	No
	Gender	0.331	No
	Smoking status	0.312	No
	Co-morbidities	0.189	No
Condition-related factors	Phlegm	0.389	No
	Shortness of breath	0.217	No
	Wheeze	0.198	No
	Coryza	0.972	No
	Fever	0.549	No
	Chest pain	0.859	No
	Muscle aching	0.245	No
	Headache	0.497	No
	Disturbed sleep	0.405	No
	Feeling generally unwell	0.244	No
	Interference with normal activities	0.445	No
	Confusion / disorientation	0.147	No
	Diarrhoea	0.365	No
	Phlegm colour	0.689	No
	Clinician-rated symptom severity score	0.761	No
	Auscultation abnormality	0.265	No
	Days waited prior to consulting	0.252	No
Therapy-related factors	Dose	0.017	Yes
	Frequency	0.432	No
	Duration	<0.001	Yes
Healthcare setting-related factors	Single handed practices widespread	0.051	Yes
	Recent public campaigns on antibiotic use	0.044	Yes

Domain	Variable	Univariable p-value	Retain for multivariable analysis
	Payment required to see GP	0.543	No
	Sick certification required for missing less than 7 days of work	0.286	No
	Amoxicillin first line choice of antibiotic	0.255	No
	Country-level prescribing rate	0.133	No

*Analysis based on up to 1,057 participants, with standard errors corrected for clustering of participants within 274 clinicians.

Table 5.22: Cox proportional hazards model of time from initiation to discontinuation of amoxicillin

Domain	Variable	Odds ratio*	95% Confidence Interval	p-value
Therapy-related factor	Prescribed or five days or fewer	Reference category		<0.001
	Prescribed for six to seven days	0.30	0.17 to 0.55	
	Prescribed for eight+ days	0.19	0.10 to 0.36	
Healthcare setting-related factor	Single handed practices widespread	1.15	1.03 to 1.28	0.010
N/A	Participant from WP8	Reference category		0.05
	Participant from WP9	0.77	0.56 to 1.06	
	Participant from WP10a	0.78	0.64 to 0.96	

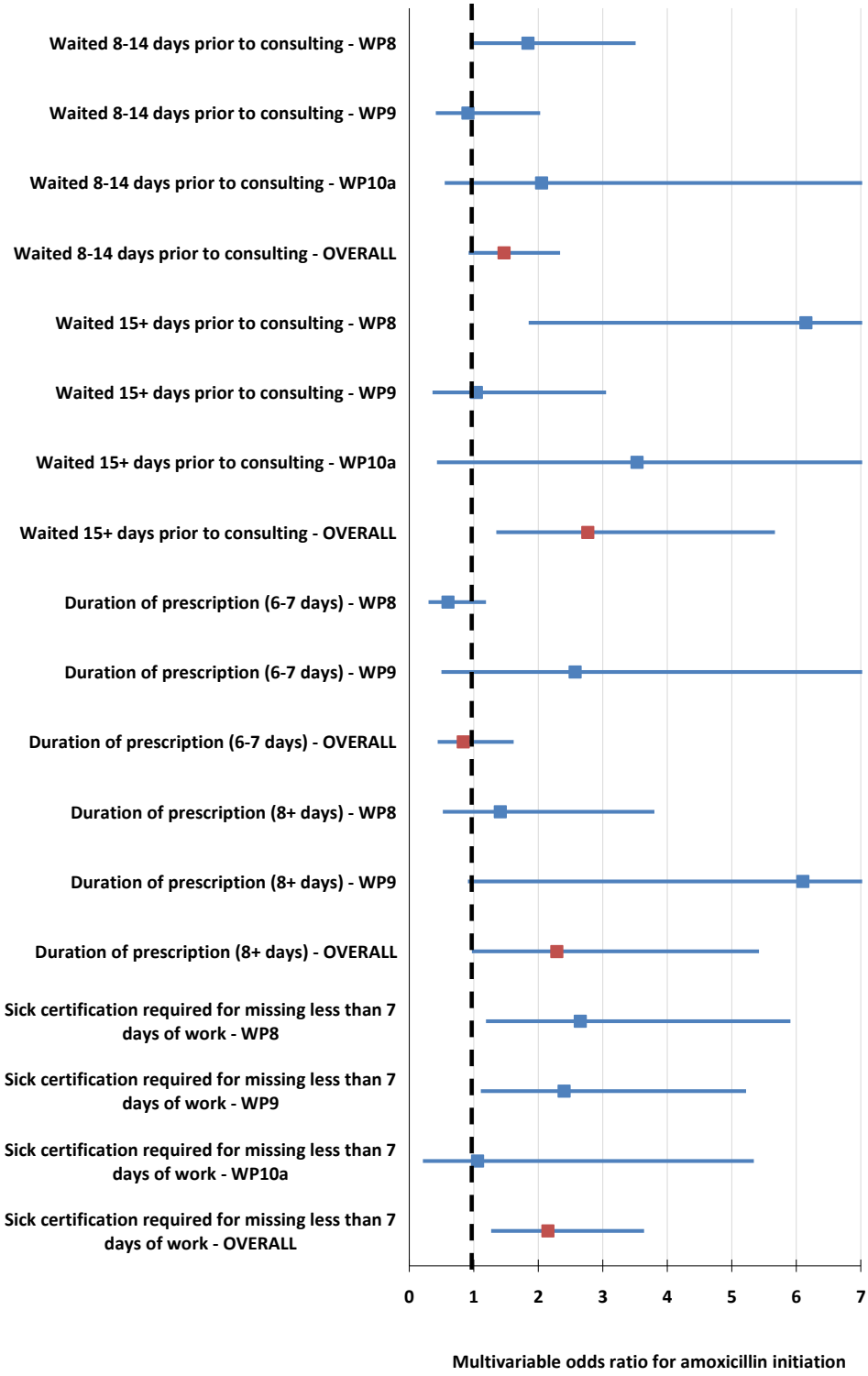
*Odds for fully adhering to prescribed treatment, according to self-report diary data. Analysis is based on 1056 participants, with confidence intervals corrected for clustering at the clinician level (274 clinicians).

Table 5.23: Cox proportional hazards model of time from initiation to discontinuation of amoxicillin

Domain	Variable	Odds ratio*	95% Confidence Interval	p-value
Therapy-related factor	Prescribed or five days or fewer	Reference category		<0.001
	Prescribed for six to seven days	0.30	0.17 to 0.55	
	Prescribed for eight+ days	0.19	0.09 to 0.42	
Healthcare setting-related factor	Single handed practices widespread	1.15	1.04 to 1.27	0.005
N/A	Participant from WP8	Reference category		0.06
	Participant from WP9	0.77	0.59 to 0.99	
	Participant from WP10a	0.78	0.62 to 0.98	

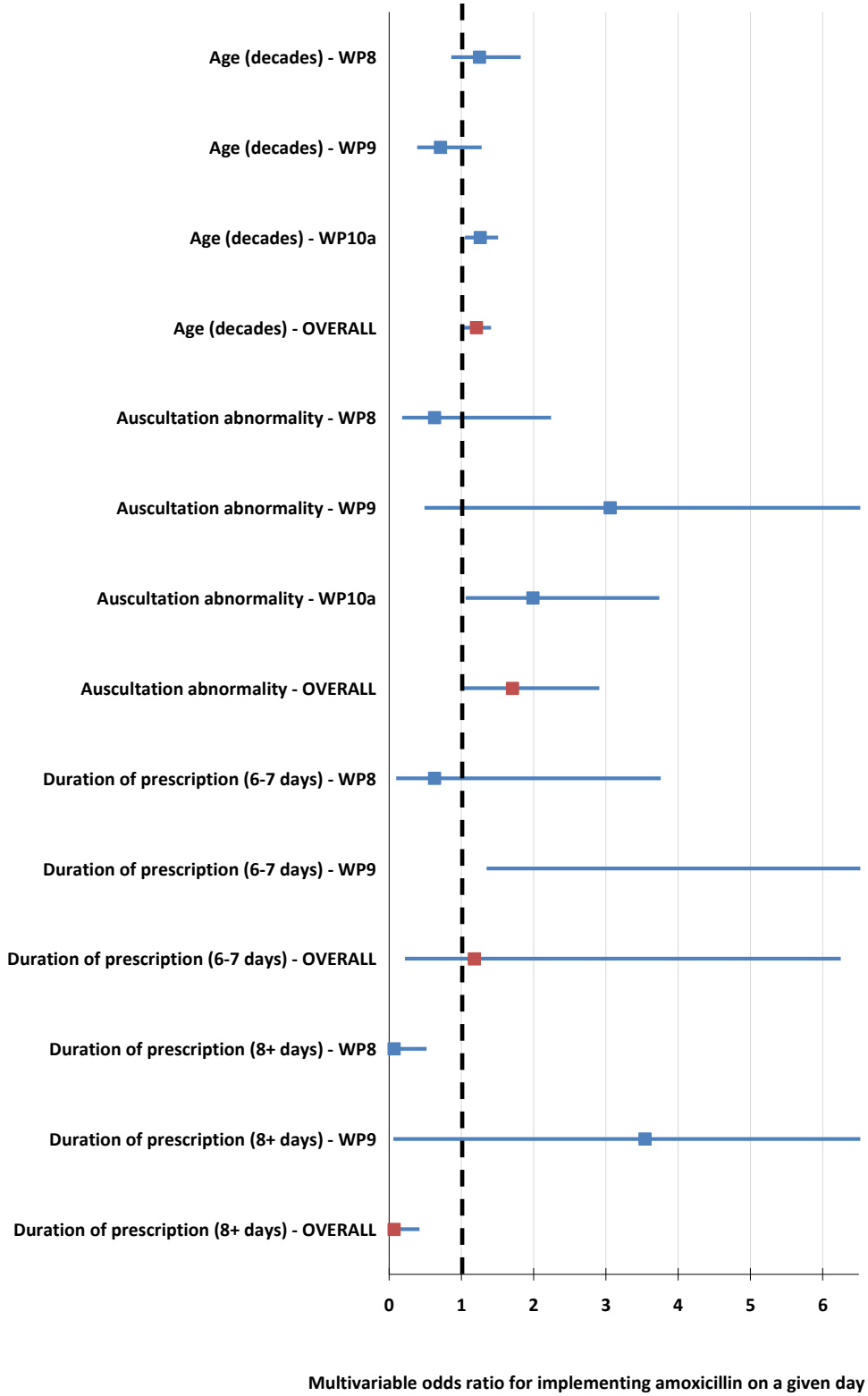
*Same model as above, but with confidence intervals corrected for clustering at the country level (15 countries).

Figure 5.5: Forest plot illustrating the odds ratios and 95% confidence intervals for the initiation model for each individual study and overall*



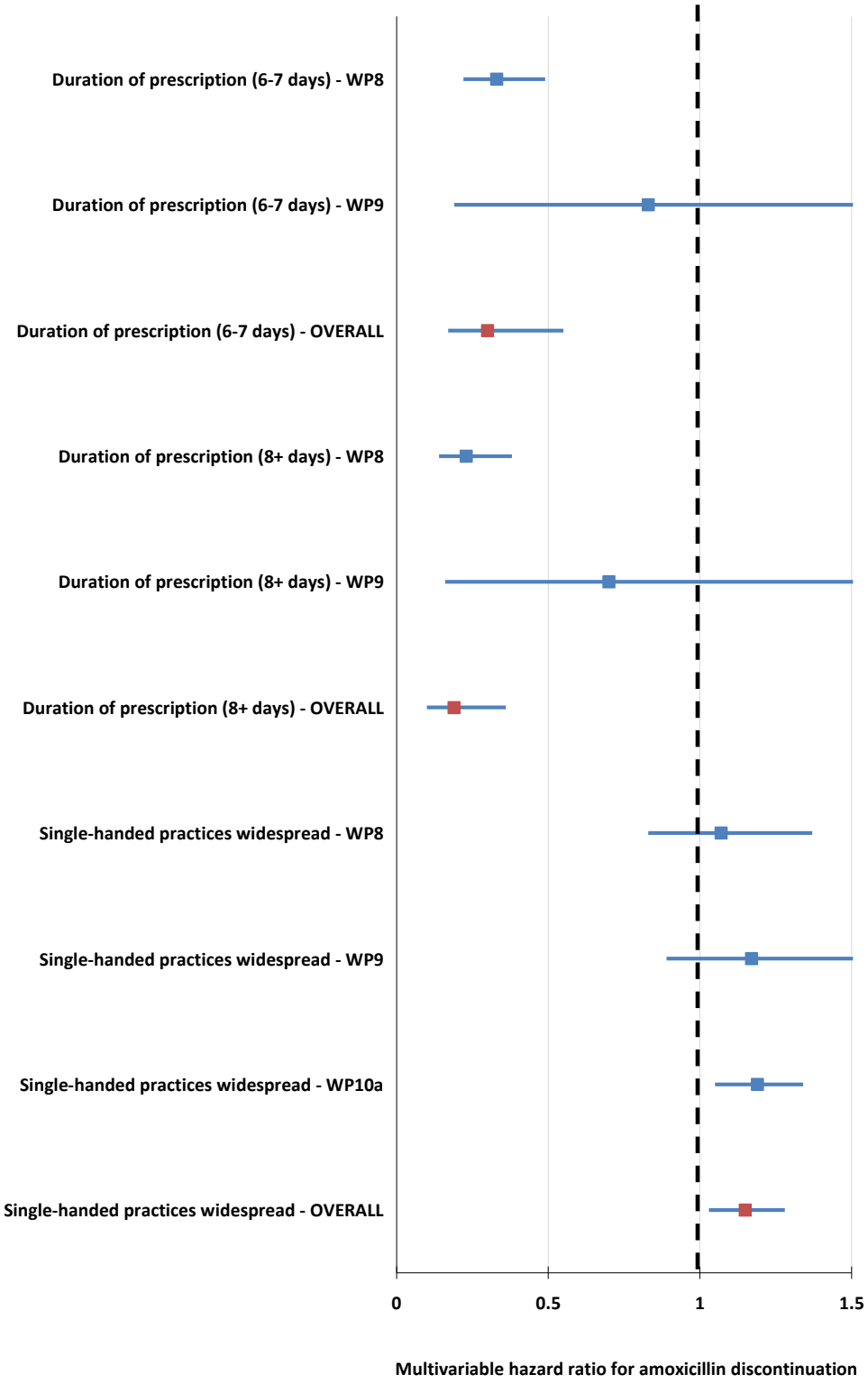
*Days waited prior to consulting compared to a reference category of 7 days or fewer. Duration of prescription variable compared to a reference category of 5 days or fewer.

Figure 5.6: Forest plot illustrating the odds ratios and 95% confidence intervals for the implementation model for each individual study and overall*



*Duration of prescription variable compared to a reference category of 5 days or fewer

Figure 5.7: Forest plot illustrating the hazard ratios and 95% confidence intervals for the discontinuation model for each individual study and overall*



*Duration of prescription variable compared to a reference category of 5 days or fewer

5.4 Discussion

5.4.1 Summary

In this Chapter, several methods for modelling the determinants of adherence to medication were investigated. Data from the CODA study were used to compare the determinants of adherence to treatment across self-report, tablet count, and electronic monitoring data. Three clinical conditions were considered. One short-term condition (lower-respiratory-tract infection), and two long-term conditions (ulcerative colitis and breast cancer with bone metastases). Data from three studies, two observational and one trial, were compared and combined in order to investigate whether (and how) determinants differed across study designs. Several domains of determinants of medication adherence were also considered throughout the Chapter. Where domains were included at a healthcare professional or healthcare setting-level, modelling approaches were considered that appropriately accounted for this. Finally, for the GRACE and ZICE studies, a comparison was made between modelling adherence as a single combined variable and modelling it based on distinct processes (e.g. initiation, implementation, and discontinuation).

5.4.2 Learning points

1. Using the CODA study to compare the determinants of adherence across different types of measures highlighted the importance of considering the uses and limitations of the choice of measure, and how that should depend on the treatment under consideration. Using the CODA data, adherence was found to be strongly associated with allocated regimen for both self-report and electronic monitoring data, but not for tablet count data. As the regimens were three tablets once daily or three tablets in divided doses (therefore both groups are required to take the same number of tablets overall), this is hardly surprising. Self-report and electronic monitoring data can inform us about patterns in adherence, from which we can infer consumption, but tablet count data can only do the

latter. While it still may be useful to record consumption using tablet count data in instances such as this, it is inadvisable for such a measure to be the *primary* adherence measure, particularly if the aim is for participants to maintain the regimen to which they were allocated.

2. The complexity of treatment was the one determinant that was consistently associated with adherence across all studies. Participants in the CODA study were less likely to adhere when allocated to take their medication in divided doses (rather than at one point during the day), those in the ZICE study were less likely to adhere when allocated to intravenous zoledronic acid that required hospital attendance to maintain (rather than daily oral medication that could be consumed at home), and those in the GRACE studies were less likely to adhere if they were prescribed long courses of amoxicillin.

3. While the previous learning point may indicate that treatments should be as simple as possible, this needs to be balanced against the consequence of non-adherence and how this may be amplified in treatments that are simplified. An example of this can be seen in the ZICE study, where despite implementation being worse for those prescribed intravenous zoledronic acid (compared to those prescribed oral ibandronic acid), the latter was still inferior to the former (as I will describe in the next Chapter).

4. While the three GRACE studies comprised two observational studies and the active arm of a double blind placebo-controlled trial, and it was found that the samples differed according to their participant, illness, and prescribing characteristics, and adherence differed between studies considerably (ranging from 27% to 87%), the *mechanisms* by which adherence / initiation / implementation / time to discontinuation occurred were generally consistent across studies. Indeed, all models controlled for study as a fixed effect, and determinants of adherence and each of the elements were found that were therefore independent of study/ study type.

5. Multilevel analysis enabled determinants related to individual characteristics (e.g. the person, their condition, their treatment) to be simultaneously account for with determinants related to healthcare professionals and healthcare settings. By appropriately accounting for the data hierarchy, correct inferences could be drawn regarding the magnitude of the influence that each determinant had. In the GRACE studies, the amount of clustering at the clinician-level was high, perhaps a quantitative indication of therapeutic alliance so often reported in qualitative research as important for achieving high levels of adherence (see Chapter 2). Prescribers, and their relationship and interaction with patients, would appear to be an important area for further investigation with regards to how this influences adherence to medication.

6. Separating out adherence into distinct processes enabled different sets of determinants to be considered. The processes are distinct, and indeed different determinants were associated with each. Such nuances would have been missed, had adherence been considered as a single variable. While the analysis of initiation and implementation were performed separately, in essence the approach taken can be viewed as a hurdle model (Mullahy, 1986), where initiation was considered first as a binary variable, and then in those who initiate, implementation was considered consequently. This approach made fuller use of the available data, and allowed for a better assessment of where the variability in the data lie. The distinction between adherence when considered as a single variable and when it was separated out into its elements was clearer for the GRACE study than it was for ZICE, as almost all participants in the ZICE study initiated treatment. Clearly, the level of adherence and each adherence element needs inspecting before determining the necessity of this approach.

7. Following from the previous point, while I could see the value of investigating the determinants of initiation and implementation of amoxicillin (that is, they are elements

that are desirable to intervene on), there was arguably less necessity in investigating the determinants of time from initiation to discontinuation (regardless of how well the amoxicillin was implemented). There needs to be a clear rationale behind the decision around which elements are of interest.

CHAPTER 6: Adjusting Findings of Randomised Controlled Trials for Medication Non-Adherence: The Use of Randomisation-Based Efficacy Estimators

6.1 Introduction

Chapters 4 and 5 of this thesis focused on the investigation of different modes of medication adherence measurement, and methods for modelling the determinants of medication non-adherence, in clinical research. While these topics are crucial in the study of medication adherence, the consumption of the majority of medicine relies on individual decision making, and inevitably non-adherence will occur, even in clinical research. When there is interest in the relationship between use of medication and clinical outcomes (e.g. use of antidepressants and incidents of self-harm, use of antibiotics and time to recovery from pneumonia, etc.), this interest generally centres on determining the causative nature of the relationship. Determining the causal nature of a treatment is not straightforward even in randomised controlled trials (RCTs), where participants are allocated to treatment groups at random, as the choice to consume the allocated treatment is unlikely to be determined at random (i.e. independent of both observed and unobserved confounders). While this is an issue for all RCTs, the problem is compounded for RCTs that are designed to evaluate whether a new treatment is equivalent to (or no worse than) an existing treatment. Traditional approaches for investigating these relationships in RCTs make implicit assumptions (e.g. medication non-adherence occurs completely at random) which are likely implausible in practice. Approaches that are randomisation-respecting exist, and are becoming increasingly popular, but are generally only reported in specialist methodological journals.

The aims of this Chapter, therefore, is to explore the use of randomisation-based efficacy estimators for adjusting findings of RCTs for medication non-adherence, and the feasibility of their implementation for different trial designs.

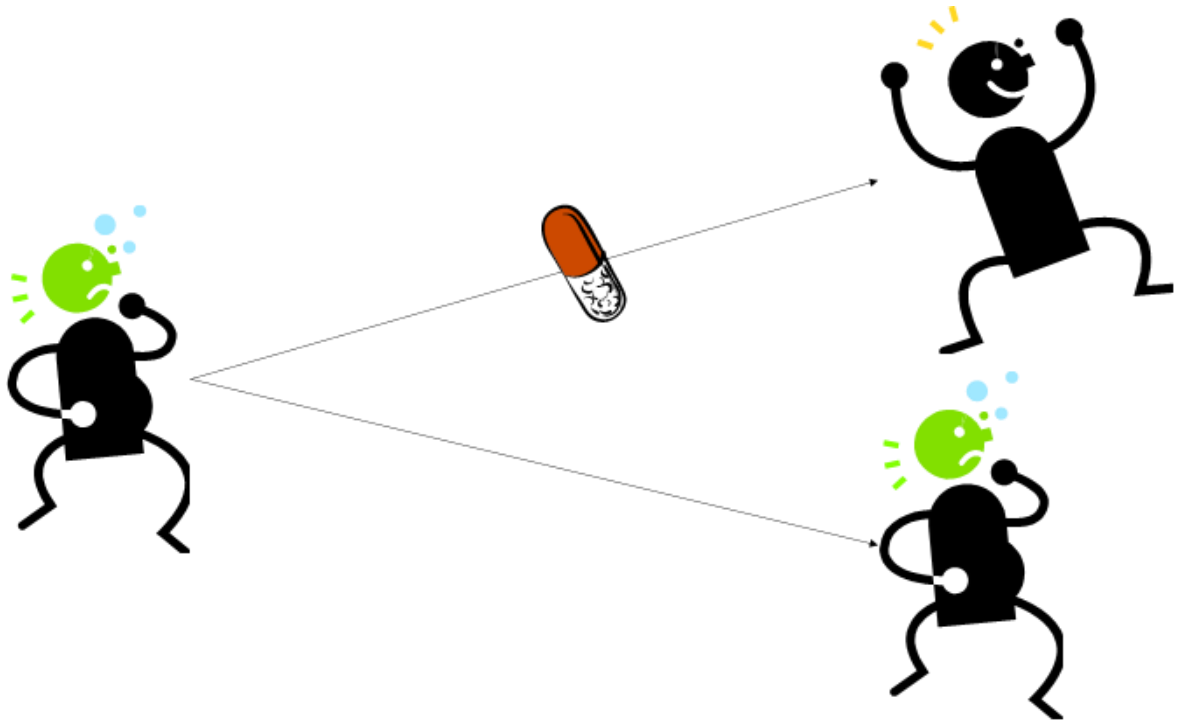
To meet these aims, this Chapter will draw on data from the GRACE WP10a, CODA, and ZICE studies.

6.2 Methods

6.2.1 Randomised Controlled Trials and their importance for inferring causal treatment effects

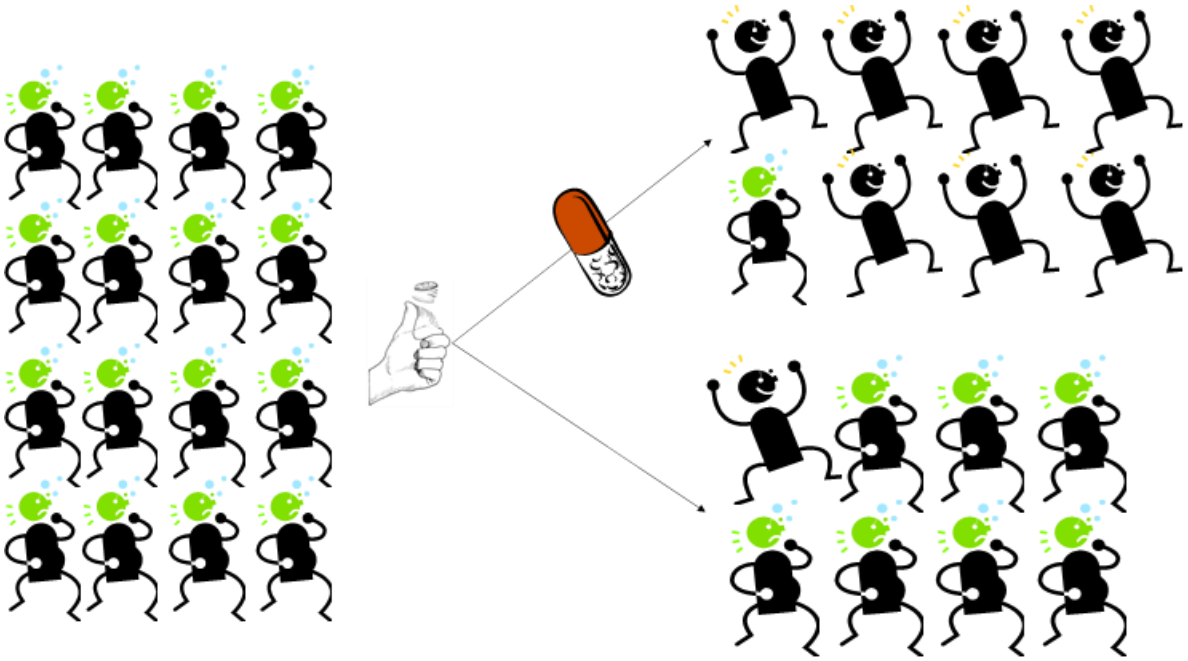
One of the key reasons we perform experiments is to determine the effect that a treatment has on some outcome of interest, that is, the causal effect. Causal effects in health sciences research are generally represented using potential outcomes or graphical models. The former relies on counterfactuals, that is, the outcome that would have happened if, contrary to the fact, the exposure of interest had been something other than what it actually was. The latter relies on fixing conditions. That is, the outcome when physically forcing an exposure on an individual. While graphical methods can be useful for displaying assumptions inherent in analytical approaches, potential outcomes have been more useful in developing these approaches. See Greenland and Brumback 2002 for a more detailed overview of different types of causal models found in health sciences research. I have chosen to describe causal effects throughout my thesis using the potential outcomes framework because the analytical techniques I implement are based on this framework. However, I also illustrate these approaches using graphical methods to give the reader a more visual interpretation. Ideally, causal effects would be measured at the level of the individual. However, without simultaneously observing the effect of both giving and not giving treatment, we will never be able to calculate a true individual-level treatment effect (Figure 6.1).

Figure 6.1: Illustration of an individual-level treatment effect



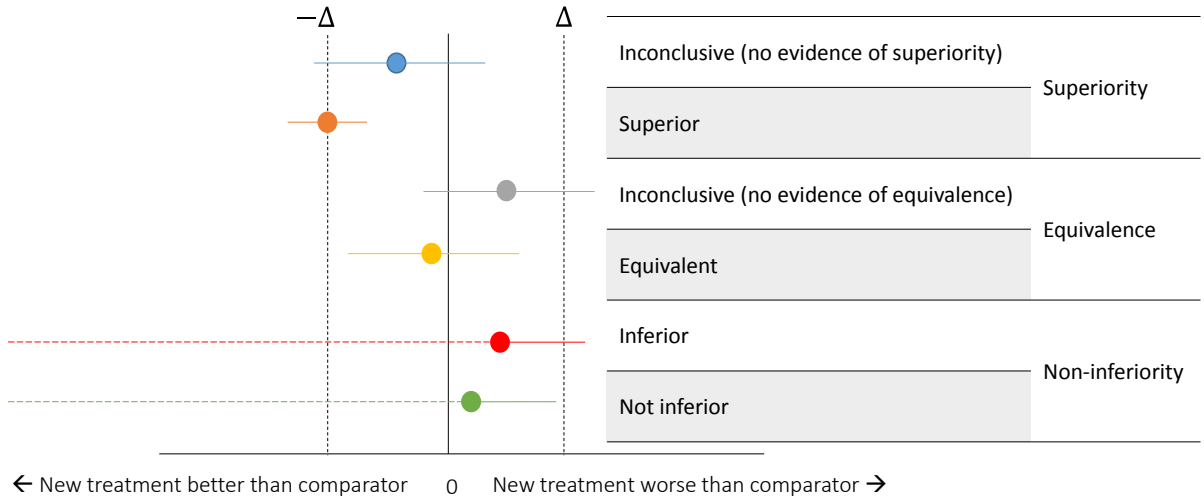
Instead of striving to directly calculate these individual-level effects, we instead calculate population-level (or average) treatment effects, where the average outcomes of individuals in the treated group are compared to those in the untreated group, and we use this calculation as an estimate for the individual-level effects. For this estimate to be valid, the choice to be in the treated / untreated group must be made at random (Figure 6.2). If the choice is not made at random, the estimate is likely to be biased unless the decision to choose one group over another (i.e. the selection mechanism) is measured and adjusted for. This is unlikely in most circumstances, where typically some variables that contribute to the selection mechanism will remain unmeasured. (Lewis, 1999)

Figure 6.2: Illustration of a population-level (average) treatment effect from a randomised experiment



RCTs involve the allocation of participants to groups at random, and hence provide unbiased estimates of the causal effect of being in one group (e.g. being given a new treatment to take), compared to another group (e.g. given a placebo to take, or given a different/standard treatment to take). These comparisons are generally then used to test hypotheses regarding the difference between groups (also known as "*superiority*") (i.e. null hypothesis, H_0, stating that the two groups are the same ($\mu_1 = \mu_2$), alternative, H_1, stating that they are different ($\mu_1 \neq \mu_2$)) (Moher et al., 2010). However, for some RCTs, the purpose of the comparison lies in testing different hypotheses, such as whether the groups are equivalent (H_0: $|\mu_1 - \mu_2| > \Delta$; H_1: $|\mu_1 - \mu_2| < \Delta$, where Δ is a margin that represents an acceptable / negligible difference), or whether one (e.g. a new treatment) is not inferior to another (e.g. an existing / standard treatment). For these *non-inferiority* trials, the hypotheses are H_0: $\mu_1 - \mu_2 > \Delta$ and H_1: $\mu_1 - \mu_2 < \Delta$ (i.e. the one-sided version of the equivalence hypotheses). Commonly, comparisons from these trial designs are also interpreted using confidence intervals (Figure 6.3). (Piaggio et al., 2006)

Figure 6.3: Confidence intervals illustrating some conclusions drawn from different study designs*



*Dashed lines indicate the limit that is not of interest extends to minus infinity.

The work presented in this Chapter will focus on two-arm RCTs, including superiority trials where one treatment is compared to a placebo control, and non-inferiority trials that compare a new treatment against an existing / standard treatment (active control).

6.2.2 Estimating treatment effectiveness in RCTs

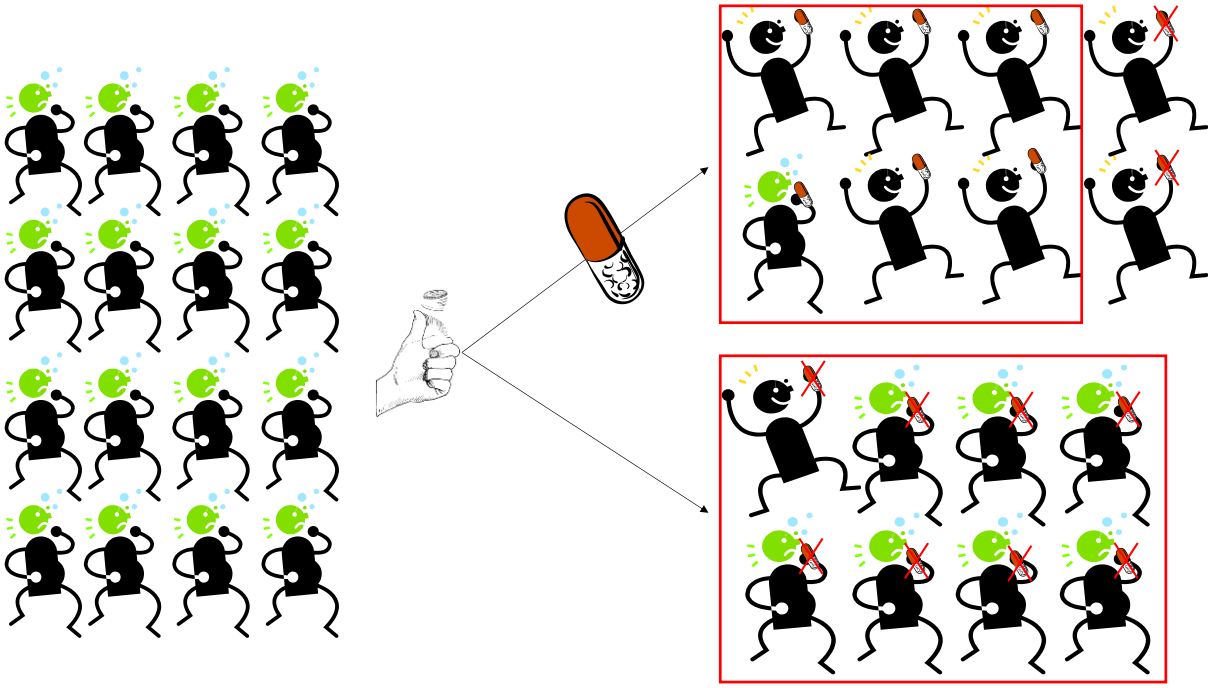
The gold standard approach to estimating treatment effectiveness in RCTs (i.e. the performance of a treatment under 'real-world' conditions (Singal et al., 2014)) is based on the Intention To Treat (ITT) principle, where participants are analysed in the groups to which they were originally randomised. (Montori and Guyatt, 2001) This approach preserves a comparison of groups as randomised, and in the presence of perfect adherence also provides an unbiased comparison of treatment efficacy (performance of the treatment under ideal circumstances), while in the presence of imperfect adherence it provides an unbiased estimate of *offering* treatment.

6.2.3 Traditional methods for estimating treatment efficacy in RCTs

As described above, under certain circumstances an ITT analysis can be used to estimate treatment efficacy in RCTs. However, non-adherence to medication is an issue that pervades many RCTs, and in the presence of non-adherence (or departures from randomised treatment), efficacy based on an ITT analysis may provide an estimate that is biased towards demonstrating no differences between treatments. While this is deemed conservative for a trial aiming to determine whether or not there is a difference between treatments (and, in conjunction with its randomisation-respecting nature, why it is considered the gold standard approach for the analysis of these designs (Moher et al., 2010)), for a non-inferiority trial this is anticonservative, as it is desirable for treatment groups to be as similar as possible. (Jones et al., 1998 and ICH Steering Committee, 1998)

The most common approach to assessing treatment efficacy in an RCT that accounts for treatment non-adherence is to conduct a per-protocol (PP) analysis. This analysis excludes participants who have not adhered to their randomised treatment (Figure 6.4). However, this approach fails to maintain a comparison of groups as randomised, and is therefore prone to selection bias (a phenomenon whereby individuals' membership in a group is not determined at random). While selection bias is thought to be minimised in trials with blinding, and modified definitions of these populations that adjust for observed confounders can be used (a confounder being a variable that is correlated with both exposure and outcome), selection bias can never be completely discounted from any analyses that make post-randomisation exclusions or manipulations. Nevertheless, PP analyses are commonly reported alongside ITT analyses in publications of RCT findings (see Chapter 2). Indeed, due to the anticonservative nature of ITT analysis in non-inferiority trials, it is recommended to conduct a PP analysis alongside an ITT analysis and only conclude non-inferiority if indicated in both analyses. (Lesaffre, 2008)

Figure 6.4: Illustration of a per-protocol analysis



To estimate treatment efficacy in RCTs, the ideal analytical method would be based on participants who received the treatment to which they were allocated, whilst maintaining a comparison of groups as randomised. This approach would avoid selection bias, while also yielding an estimate of the causal effect of receiving treatment.

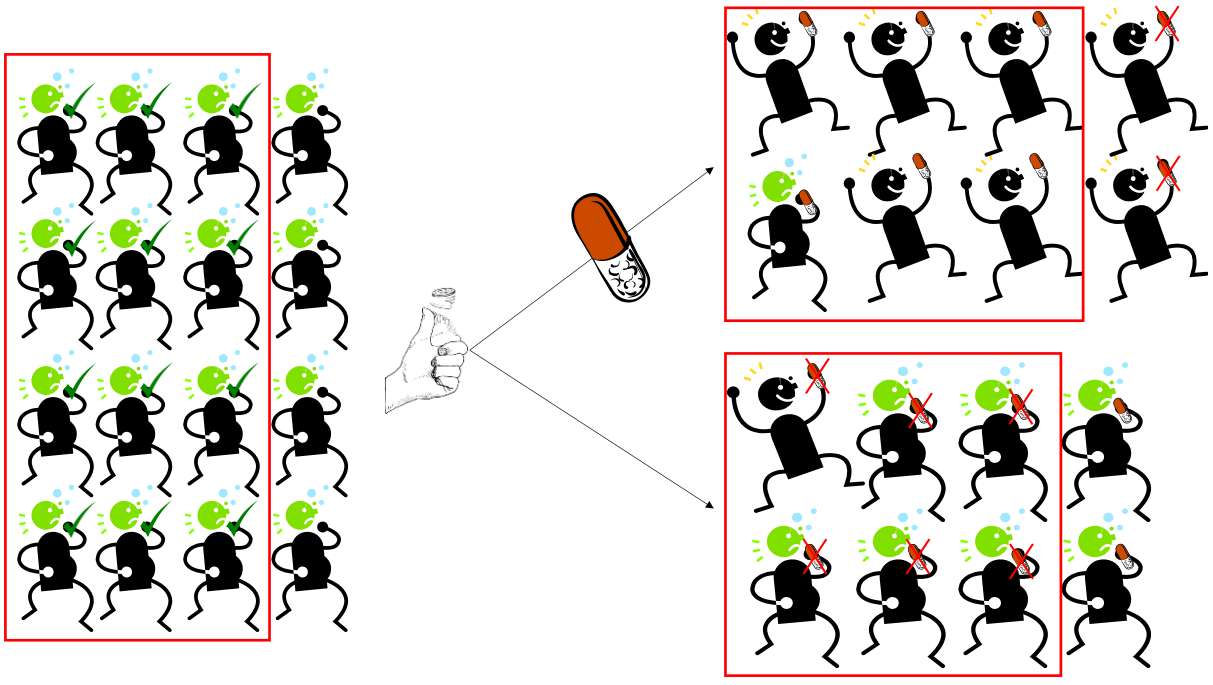
6.2.4 Randomisation-based efficacy estimators

Randomisation-based efficacy estimators (RBEEs) compare outcomes between groups of participants who were allocated to and received treatment with groups not allocated to treatment, but who would have received treatment had they been allocated to the treatment group. (White, 2005) By taking a potential outcomes framework perspective on causal modelling, and recognising that at the beginning of a trial all participants have two potential outcomes – one if they are treated and one if they are not, a RBEE relates average outcomes in treated participants to their (potentially counterfactual) outcomes that would have been observed had they received no treatment (i.e. their treatment-free outcome). (Frangakis and Rubin, 2002)

Inferring causal treatment effects from RBEEs relies on the following core assumptions (Angrist and Imbens, 1996):

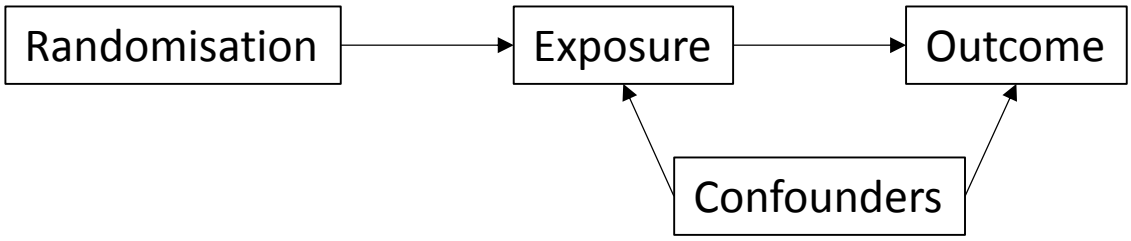
- For binary adherence (adhered / did not adhere) adherence-type is a latent trait, a baseline characteristic that is independent of randomisation. One way to think of RBEEs is as the ITT effect in the sub-group of participants who would always adhere to treatment (Figure 6.5).
- An individual's outcome is unaffected by the treatment received by another individual.
- Due to randomisation, the expected proportion of non-adherers will be the same in each group.
- In the absence of treatment, randomisation in and of itself has no effect on outcome. This assumption is often referred to as the exclusion restriction.

Figure 6.5: Illustration of randomisation-based efficacy estimator (green ticks correspond to those who would adhere to treatment if allocated to it)



By treating randomisation as an instrument (i.e. assuming that it is independent of both observed and unobserved confounders, and only effects outcome through its effect on exposure to treatment), the observed data on exposure to treatment can be used to obtain estimates of the effect of taking treatment that avoids selection bias (Figure 6.6). RBEEs can be estimated using Structural Mean Models (SMM), whereby a value of the treatment effect is found such that balance is achieved between groups on the outcome in participants who were not treated (i.e. the treatment-free outcome).

Figure 6.6: Causal Directed Acyclic Graph (DAG) illustrating the use of randomisation as an instrument to derive a randomisation-respecting estimate of treatment efficacy



6.2.4.1 RBEEs in active control trials

The methodological approach described above relies on a comparison between an active treatment and no treatment (or placebo). In trials comparing two active treatments, a common feature of non-inferiority trials, there is no observed outcome on which to base the potential outcome in the untreated/treatment-free group, and therefore the method cannot readily be applied.

Following Fischer et al. (2011), for a two-arm trial where n participants are allocated to one of two active treatments, we can define the structural mean models for treatments A and B as:

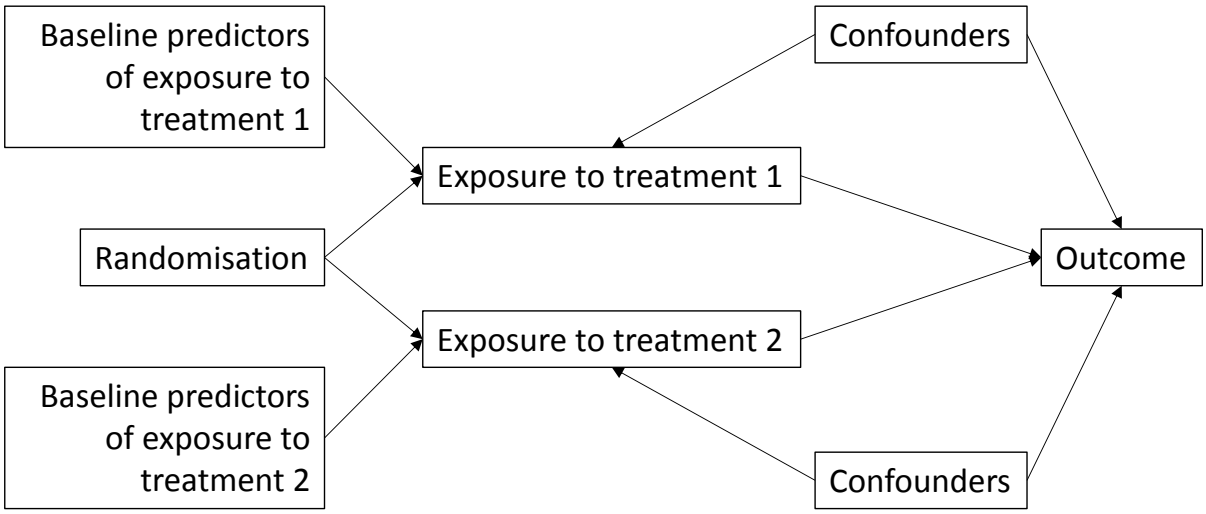
$$E\left[Y_i^A - \gamma^A\left(C_i^A, X_i; \Psi^A\right) | C_i^A, X_i\right] = E\left[Y_i^0 | C_i^A, X_i\right] \text{ and}$$

$$E\left[Y_i^B - \gamma^B\left(C_i^B, X_i; \Psi^B\right) | C_i^B, X_i\right] = E\left[Y_i^0 | C_i^B, X_i\right],$$

where $i = 1, \ldots, n$, ${Y_i}^A, {Y_i}^B$ are (potential) outcomes under assignment to A or B respectively, ${Y_i}^0$ is the potential treatment-free outcome, ${C_i}^A, {C_i}^B$ are (potential) vectors of treatment adherence summaries observed under assignment to A or B respectively, X_i is a vector of baseline covariates, ${R_i}^A, {R_i}^B$ are randomisation indicators with value 1 when a participants is allocated to A (B, respectively) and 0 otherwise (and where the observed outcome, $Y_i = {Y_i}^A {R_i}^A + {Y_i}^B {R_i}^B$), and assumes that the average effects of allocation to A and B are known functions γ^A and γ^B of adherence, baseline characteristics and unknown parameter vectors Ψ^A or Ψ^B, respectively. (Goetghebeur and Lapp, 1997) The exclusion restrictions $\gamma^A(0, X_i; \Psi^A) = 0$ and $\gamma^B(0, X_i; \Psi^B) = 0$ state that if no active treatment is received, the expected outcome equals the expected treatment-free outcome. However, as the distribution of the potential treatment-free outcome is not observed for trials with two active treatments, this estimator is not directly applicable.

One approach that attempts to address this issue is based on identifying baseline covariates that are differentially associated with exposure to treatment (or treatment adherence) for each of the treatments. The method enables distinct causal estimators to be derived, from which a contrast can be made (the contrast between the two treatments generally being of primary interest). These baseline covariates must also be independent of outcome, therefore allowing separate sets of instruments to be derived for each treatment and a potential treatment-free response to be estimated (Figure 6.7).

Figure 6.7: Causal DAG illustrating the IV approach to deriving randomisation-respecting treatment efficacy with two active treatments



When the main interest is in comparing the use (efficacy) of two active treatments, identifying distinct causal parameters that can then be contrasted is of greatest interest. However, in practice it is not always possible to identify baseline covariates that differentially predict treatment adherence while remaining independent of outcome. When this is the case, it is still possible to derive the following:

- An estimate of treatment efficacy in the subpopulation who would always adhere to their allocated treatment at a fixed level (that is, if we were to intervene and fix adherence levels the same in both treatment arms)

- Estimates of treatment efficacy at varying levels of adherence (by performing a series of sensitivity analyses that involves varying adherence parameters)

- An estimate of treatment efficacy at varying levels of exposure to the experimental treatment compared to being assigned to the standard treatment, regardless of adherence levels in this group (by fitting standard structural mean models and treating the standard treatment as the treatment-free/placebo group)

6.2.5 Modelling RBEEs in a two-arm placebo-controlled superiority trial

Data from the GRACE WP10a trial was used to produce adherence-adjusted estimates of the benefits and harms of amoxicillin for adults consulting in primary care with an acute uncomplicated LRTI, whilst preserving a comparison of groups as randomised.

As reported in previous Chapters, adherence was measured in three ways during this trial: using self-reported diaries, via tablet counts, and over the telephone (usually for participants who did not return a diary). In Chapter 4 it was shown that while agreement between different types of measures was generally good, some discrepancies did occur. During this Chapter, where multiple types of measure are available, the minimum reported adherence value was used for analysis. Randomised participants were prescribed 42 tablets. Adherence to study medication was defined as the percentage of the correct number of tablets taken during the first seven days of the follow-up period (i.e. the period for which the medication was prescribed). Three binary definitions of adherence were also constructed in order to provide sensitivity analyses around the continuous/quantitative definition. The three binary definitions were full (100%) adherence versus not full adherence, at least the equivalent of a five-day course (approx. 71.4%) versus less and at least one tablet versus no tablets (i.e. initiated/did not initiate).

To demonstrate the benefits and harms of taking amoxicillin in this population, the analysis focused on the following three clinical outcomes. The first was the mean clinician-rated symptom severity between days two and four after initial presentation. The second was the development of new or worsening symptoms, defined as returning to the clinician with new or worsening symptoms, new signs or an illness requiring admission to hospital within the four week follow-up period. The third outcome was the presence of any non-respiratory symptoms (diarrhoea, skin rash or vomiting) during the four week follow-up period. These specific symptoms were recorded as they are known side effects of amoxicillin. The first two outcomes were used to demonstrate

the clinical benefits of amoxicillin for patients with an acute uncomplicated LRTI in primary care, with the third used to demonstrate harms.

Two-stage instrumental variables regression was used to fit SMMs to the above outcomes. (Fischer-Lapp and Goetghebeur, 1999) This procedure involved regressing the exposure variable onto the instrument/s during the first stage, saving the predicted values from this regression, and then, in the second stage, regressing the outcome onto the predicted values. A correction is made during the second stage in order to obtain correct standard errors. The between-group mean difference in symptom severity on days two to four was estimated using a two-stage least squares instrumental variables regression model. To compare the odds of developing new or worsening symptoms and reporting any non-respiratory symptoms, a generalised linear (double logistic) SMM was estimated via a generalised method of moments procedure. The double logistic SMM involves an additional stage, whereby the association between outcome (development of new or worsening symptoms or reporting of side effects), trial arm and adherence was modelled first, with estimates from this model used in the SMM in order to obtain correct standard errors (and hence correct 95% confidence intervals). (Vansteelandt and Goetghebeur, 2003) As the main adherence measure is on a scale ranging from 0 to 100 (i.e. the percentage of the correct number of tablets taken during the first seven days of the follow-up period), the coefficient from the SMMs are interpreted as the effect per percentage point increase in adherence. These effects are then multiplied by 100 to give an interpretation for those who completely adhere to study medication. See Box 6.1 for an outline and further description of the syntax used for these models.

6.2.6 Modelling RBEEs in non-inferiority trials with two active treatments

Data from the CODA and ZICE trials were used to illustrate how RBEEs can be fitted for non-inferiority trials with two active treatments, including their utility and limitations. These trials

differed in terms of the nature of the interventions being compared, with CODA comparing the same treatment prescribed with different regimens, and ZICE comparing two different treatments with different modes of administration. These examples, while contrasting, are typical of the types of non-inferiority trials conducted, and will therefore provide useful insight into the methods proposed.

As described in Chapter 5, adherence to study medication in the original CODA trial analysis was defined as participants consuming at least 75% of their issued medication. This definition will also be used for the analysis presented in this Chapter. For the ZICE trial, adherence will be based on the combined summary measure, also described in Chapter 5.

For the CODA trial, the outcome of interest was the proportion of participants relapsing during the 12 month study period. The OD regimen was considered to be non-inferior to the TDS regimen as long as the lower bound of the 95% confidence interval of the difference in the proportion of participants in each arm relapsing (OD minus TDS) did not include minus 0.1 (i.e. the difference in the proportion of participants relapsing, between participants allocated to OD compared to those allocated to TDS, had to be less than 10 percentage points). For the ZICE trial, the outcome of interest for this analysis was the proportion of participants experiencing a skeletal-related event (SRE) during the first 12 months of the study. This is a simplified version of the primary outcome from the main trial analysis (which was based on the time and frequency of SREs and analysed using an Andersen-Gill model (Andersen and Gill, 1982)), and used for illustration purposes only. There was therefore no pre-specified non-inferiority margin for this outcome.

Deriving distinct causal estimators for each treatment arm relied on identifying baseline variables that predicted adherence to treatment differently in each arm, whilst not predicting clinical outcome (that is, they are used as instruments for the separate treatments). Determining these predictors involved two main steps. First, multivariable logistic regression was used to determine

the factors that predicted clinical outcome. Variables that were identified univariably at the 20% significance level were entered into the multivariable model, with backward selection used to retain variables independently associated at the 10% significance level. Following this, multivariable logistic regression was used, with the binary adherence variable as the outcome of interest. Predictors of adherence were entered one-by-one into a regression model that included trial arm, and interaction between candidate predictor and trial arm, and the predictors of clinical outcome that were identified during the previous step. Any variables that were associated with adherence at the 20% significance level, as either a main effect or as an interaction with trial arm, were retained in the multivariable regression model. Predictors that remained associated at the 10% significance level were then retained in the final regression model.

For the CODA trial, the candidate baseline predictors used in the outcome and adherence models were age (<65, ≥65), age at diagnosis (≤25, 26-45, 46-64, ≥65), gender, length of remission (<12 months, ≥12 months), calprotectin concentration (<60mg/kg stool, ≥60 mg/kg stool), smoking status (never smoker, current smoker, ex-smoker), employment status (unemployed, employed), maximum documented extent of colitis (extensive, left-sided or sigmoid, proctitis), disease duration (≤10 years, 11 to 20 years, >20years), number of relapses during the past two years (1, 2, 3, ≥4), and endoscopy findings (normal, not normal).

For the ZICE trial, the candidate predictors were age, gender, Body Mass Index (BMI), the modified Brief Pain Inventory severity score, Quality of Life (EORTC QLQ-C30 score version 3.0 (Fayers et al., 2001)), SRE within the previous three months, previous use of bisphosphonates, treatments being received (including painkilling drugs, chemotherapy, hormone therapy, and trastuzumab).

The SMM models were fitted using a two-stage least squares instrumental variables regression approach. Using this procedure, the trial arm (the instrument), predictors of outcome, and differential predictors of adherence were used to estimate values of the adherence variables in

the first stage. These values were then regressed onto the outcome in the second stage. The Huber-White robust standard error, with additional correction for small-samples, was used in order to make correct inferences about the differences in proportions. (Cheung, 2007) Box 6.2 provides sample syntax using Stata.

Box 6.1: Stata syntax for the structural mean models used for RBEEs in the GRACE WP10a trial

Structural mean model for the between-group difference in the mean clinician-rated symptom severity between days two and four after initial presentation using two-stage least squares instrumental variables regression

ivregress 2sls y c (x=z)

In the syntax above, y = outcome, c = covariate, x = exposure, and z = randomisation indicator

Generalised linear (double logistic) structural mean model for the between-group ratio of the odds of developing new or worsening symptoms and reporting any non-respiratory symptoms using generalised method of moments

logit y x z

matrix from = e(b)

predict xblog, xb

gmm (invlogit(xblog - x{psi})-ey0), instruments(z)*

matrix from = (from, e(b))

gmm (y - invlogit({xb: x z} + {b0})) (invlogit({xb:} + {b0} - x{psi}) - ey0), instruments(1:x z) instruments(2:z) winitial(unadjusted, independent) from(from)*

lincom[psi]_cons, eform

estat overid

In the syntax above, y = outcome, x = exposure, z = randomisation indicator, ey0 = mean exposure-free potential outcome (to stabilise the model, this has been fixed as the proportion of people with positive outcomes in the control group. It can however be directly estimated from the model). This model requires an additional stage (an associational model) because collapsing the logistic SMM over observed exposure (z) depends on the distribution of z. It is therefore not possible to derive causal odds ratios in a single stage. The stages are first run individually to obtain initial values for the joint estimation. The stages are then run jointly to produce standard errors that correctly incorporate the error from the first stage of the model.

Box 6.2: Stata syntax for modelling RBEEs in the CODA and ZICE trials

Structural mean model for the between-group difference in proportion of participants relapsing during the 12-month follow-up period using two-stage least squares instrumental variables regression

ivregress 2sls y (x=z), vce(robust)

In the syntax above, y = outcome, x = exposure, and z = randomisation indicator. The use of the robust standard error is indicated by vce(robust).

Structural mean model for the between-group difference in proportion of participants experiencing a skeletal-related event during the first 12 months of the study using two-stage least squares instrumental variables regression

ivregress 2sls y c1 c2 (x1 x0 = z c1 z*c1 c2 z*c2), vce(robust)

lincom[<<Experimental treatment arm effect>> - <<Standard treatment arm effect>>]

In the syntax above, y = outcome, c1 = predictors of outcome, c2 = predictors of adherence, x1 = exposure in the experimental arm, x2 = exposure in the standard arm, and z = randomisation indicator. An interaction is denoted by a *. The use of the robust standard error is indicated by vce(robust). The lincom command allows for a linear comparison between two estimates from a previously run model.

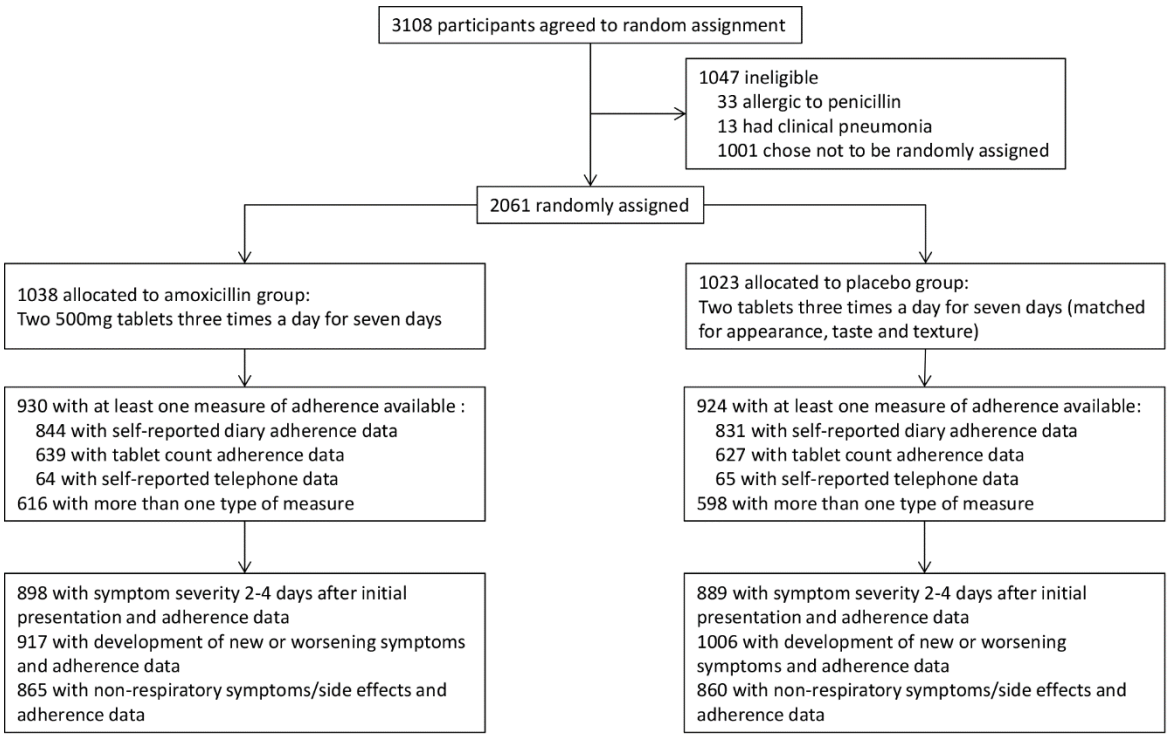
For the CODA trial, the adherence indicator was one variable that was 1 if the participant was allocated to the OD arm (experimental intervention) and adhered, 0 if they were allocated to the OD arm and did not adhere, and also 0 if they were allocated to the TDS arm (standard care). For the ZICE trial, as distinct causal parameters were identifiable, each arm had its own variable to denote adherence. This variable was 1 if the participant was allocated to the arm and adhered, 0 if they were allocated to the arm and did not adhere, and 0 if they were allocated to the other arm.

6.3 Results

6.3.1 RBEEs in superiority trials: analysis of the GRACE WP10a trial

2061 participants were recruited and randomised to either the amoxicillin group (1038) or placebo (1023) (Figure 6.8). The groups were well matched on baseline characteristics (Table 6.1).

Figure 6.8: CONSORT flow diagram for participants in the GRACE WP10a trial



As reported in Chapter 4, adherence data were available for 1854 participants (90.0% of all randomised participants), and the majority of participants had multiple types of measure recorded (1214, or 58.9% of all randomised). Taking the minimum value, when more than one type of adherence measure was available, adherence to study medication was similar between trial arms and relatively high and negatively skewed overall (Table 6.2). Translating adherence from a percentage score into an equivalent number of days of amoxicillin consumed (assuming 42 tablets were prescribed and six tablets were meant to be taken per day for seven days, so one day equals 100*[6/42] = 14.3%) Figure 6.9 illustrates the high percentage of participants who fully

adhered to study medication (72.3%), took at least five days' worth of medication (84.5%), and initiated medication (96.2%).

Table 6.1: Baseline characteristics of GRACE WP10a trial participants

Baseline characteristic	Amoxicillin	Placebo
Women	624/1038 (60.1%)	600/1023 (58.7%)
Age (years)	48.6 (16.7)	49.3 (16.4)
Non-smoker (past or present)	477/1037 (46.0%)	483/1022 (47.3%)
Illness duration before index consultation (days)	9.5 (8.0)	9.3 (7.2)
Respiratory rate (breaths per minute)	16.9 (3.3)	16.9 (3.3)
Body temperature (°C)	36.7 (3.3)	36.8 (3.3)
Lung disease*	163/1037 (15.7%)	147/1023 (14.4%)
Mean severity score (all symptoms)†	2.1 (0.5)	2.1 (0.5)
Mean severity score (cough)†	3.1 (0.7)	3.2 (0.7)
Sputum production	814/1036 (78.6%)	824/1021 (80.7%)
Discoloured sputum‡	481/968 (49.7%)	468/957 (48.9%)

Data are n/N (%) or mean (SD). *Chronic obstructive pulmonary disease or asthma. †Severity of symptoms: 1=no problem; 2=mild problem; 3=moderate problem; 4=severe problem. ‡Green, yellow or blood-stained.

Table 6.2: Levels of adherence to study medication used for statistical analyses (with the minimum value reported when participants had more than one type of measure)

	Amoxicillin (n = 930)	Placebo (n = 924)	Overall (n = 1854)
Mean (SD)	88.0 (25.8)	86.6 (27.2)	87.3 (26.5)
Median (IQR)	100.0 (95.2 to 100.0)	100.0 (85.7 to 100)	100.0 (90.5 to 100.0)
Min to Max	0.0 to 100.0	0.0 to 100.0	0.0 to 100.0

Figure 6.9: Proportion of participants at each adherence level (with the minimum value reported when participants had more than one type of measure)

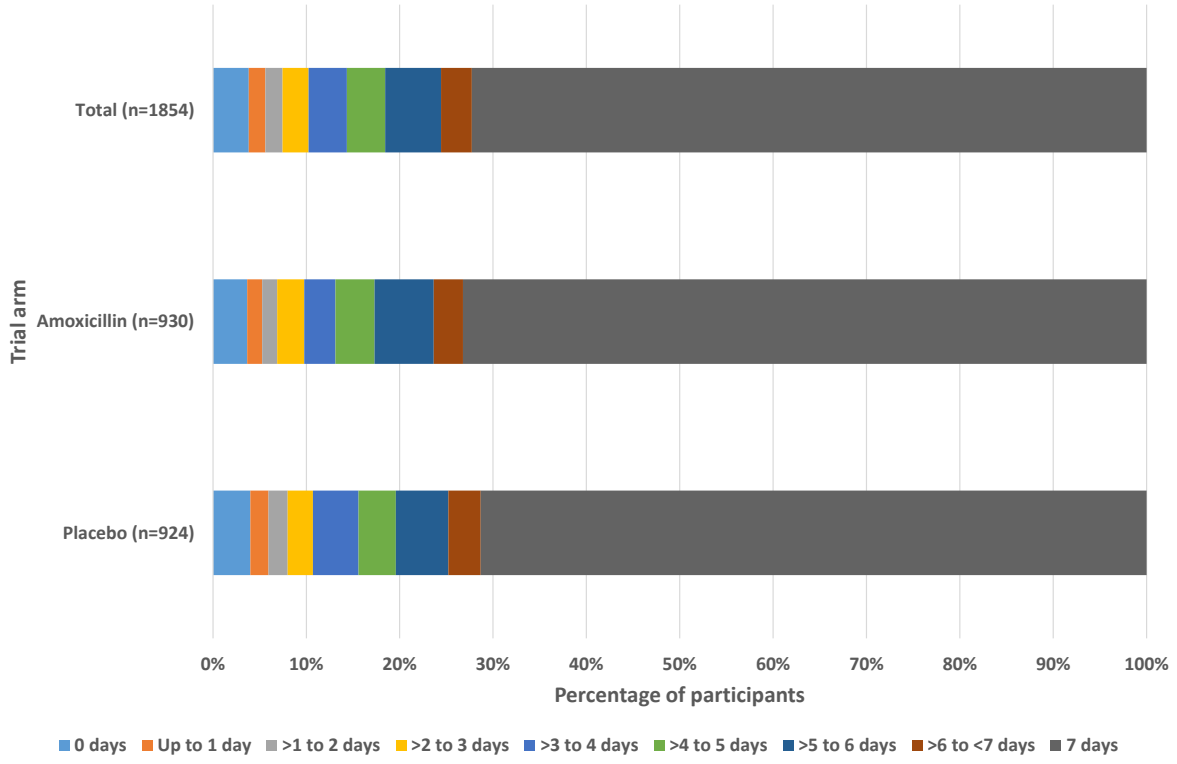


Table 6.3 provides descriptive statistics for each of the three clinical outcomes. As reported in the original paper, the adjusted between-group mean difference in symptom severity score on days two to four was slightly lower in the amoxicillin group than the placebo group (adjusted mean difference of -0.07, 95% C.I. -0.15 to 0.01). Being allocated to the amoxicillin arm (i.e.

being prescribed amoxicillin) was associated with decreased odds of developing new or worsening symptoms in the four weeks post-randomisation follow-up period. The odds of developing new or worsening symptoms were 21% lower for participants who were prescribed amoxicillin than for those prescribed a matched placebo (OR = 0.79, 95% C.I. 0.63 to 0.99). When the effectiveness analyses were only performed on participants for whom both outcome and adherence data were available, there was a 19% decrease in the odds of developing new or worsening symptoms in participants prescribed amoxicillin (OR = 0.81, 95% C.I. 0.64 to 1.03). Being prescribed amoxicillin was associated with a 28% increase in the odds of reporting non-respiratory symptoms (side effects) in the four weeks post-randomisation (OR = 1.28, 95% C.I. 1.03 to 1.59).

Table 6.3: Descriptive statistics of the three outcome measures

Outcome	Amoxicillin	Placebo
Mean symptom severity between days 2 and 4 post-randomisation*	1.6 (0.8)	1.7 (0.8)
Development of new or worsening symptoms in the 4 weeks post-randomisation	162/1021 (15.9)	194/1006 (19.3)
Reported non-respiratory symptoms/side effects in the 4 weeks post-randomisation	249/867 (28.7)	206/860 (24.0)

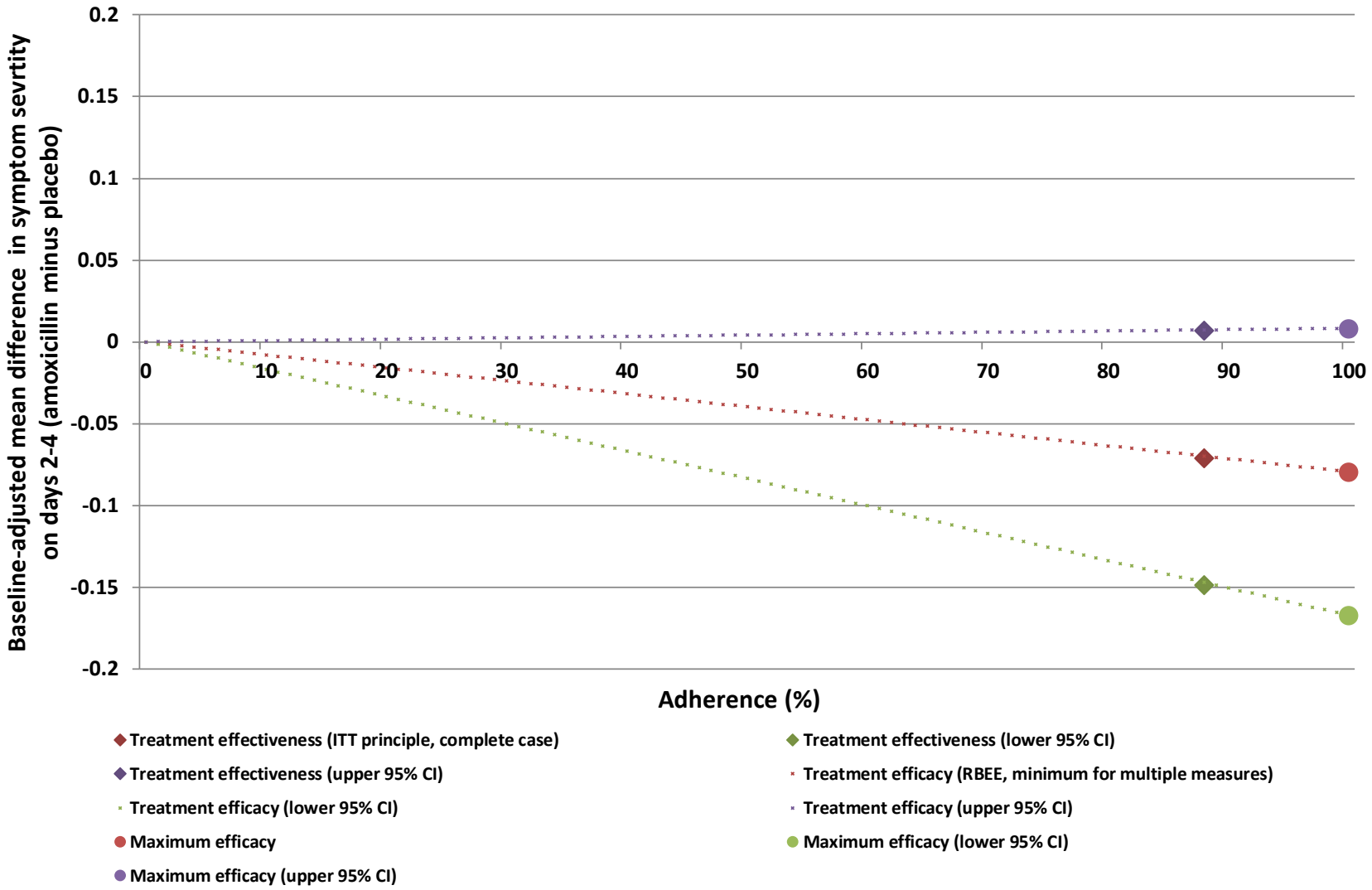
Data are n/N (%) or Mean (SD). * Each symptom was scored from 0 to 6 (0=no problem, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad, 6=as bad as it could be).

Adjusting for adherence using the SMM, the between-group mean difference in symptom severity score for participants who complete their course of amoxicillin increased by a small amount, compared to the ITT estimate (mean difference for 100% adherence -0.08, 95% C.I. -0.17 to 0.01). For the symptom severity outcome, Figure 6.10 provides a graphical illustration of the SMM and how it relates to the original effectiveness analysis. The treatment efficacy when adherence is 0% is 0 (an illustration of the exclusion restriction), the ITT (effectiveness) is

illustrated by the diamonds (positioned at an adherence level of 88% - the patient-average), and the maximum efficacy when adherence is 100% (circles).

The odds of developing new or worsening symptoms remained lower in participants who took their full course of amoxicillin (OR for 100% adherence to amoxicillin = 0.81, 95% C.I. 0.66 to 0.98). A small increase in the odds of reporting non-respiratory symptoms was found when adjusting for adherence (OR for 100% adherence = 1.32, 95% C.I. 1.12 to 1.57) (Table 6.4).

Figure 6.10: Graphical illustration of the effectiveness and efficacy of amoxicillin on mean symptom severity on days two to four



Refitting the above efficacy analyses with binary definitions of adherence, the results remained largely similar and did not alter the conclusions drawn by either the efficacy or indeed the effectiveness analyses. The most extreme definition of adherence (full vs. not) yielded the largest between group differences and the least extreme (at least one tablet vs. none) yielded the smallest (Table 6.5).

Table 6.4: Comparison of effectiveness and efficacy of amoxicillin for acute uncomplicated LRTI in primary care

Outcome	Effectiveness*	Effectiveness for whom adherence data were also available†	Efficacy per 10% increase in adherence†	Maximum efficacy (100% adherence)†
Adjusted between-group mean difference in symptom severity between days 2 and 4 post-randomisation	-0.07 (-0.15 to 0.01)	-0.07 (-0.15 to 0.01)	-0.008 (-0.017 to 0.001)	-0.08 (-0.17 to 0.01)
Odds ratio for developing new or worsening symptoms in the 4 weeks post-randomisation	0.79 (0.63 to 0.99)	0.81 (0.64 to 1.03)	0.978 (0.960 to 0.998)	0.81 (0.66 to 0.98)
Odds ratio for reporting non-respiratory symptoms/side effects in the 4 weeks post-randomisation	1.28 (1.03 to 1.59)	1.28 (1.04 to 1.59)	1.028 (1.011 to 1.046)	1.32 (1.12 to 1.57)

* Analysis based on 1789, 2027 and 1727 participants for the symptom severity, new symptoms and side effect outcomes respectively. † Analysis based on 1787, 1923 and 1725 participants for the symptom severity, new symptoms and side effect outcomes respectively.

Table 6.5: Efficacy analyses with binary definitions of adherence (for sensitivity)

Outcome	Efficacy with binary definition of adherence (full vs. not full)	Efficacy with binary definition of adherence (at least five day course vs. less than five day course)	Efficacy with binary definition of adherence (at least one tablet vs. no tablets)
Adjusted between-group mean difference in symptom severity between days 2 and 4 post-randomisation	-0.10 (-0.20 to 0.01)	-0.08 (-0.18 to 0.01)	-0.07 (-0.15 to 0.01)
Odds ratio for developing new or worsening symptoms in the 4 weeks post-randomisation	0.78 (0.62 to 0.98)	0.80 (0.65 to 0.98)	0.82 (0.69 to 0.98)
Odds ratio for reporting non-respiratory symptoms/side effects in the 4 weeks post-randomisation	1.43 (1.15 to 1.79)	1.35 (1.26 to 1.62)	1.29 (1.11 to 1.50)

When the data used to estimate adherence are missing, there may remain some residual bias in these efficacy analyses. To understand how severe this bias could be (particularly, how low the odds ratio for new or worsening symptoms could be), further sensitivity analyses were conducted. Table 6.6 provides the findings of these additional sensitivity analyses where participants with missing adherence data are assumed to have not taken any study medication (i.e. their adherence level is 0%). The findings demonstrate that making this most extreme assumption about missing adherence data did not alter the clinical conclusions that were drawn from the analyses.

Table 6.6: Efficacy analysis with missing adherence data imputed as 0%

Outcome	Effectiveness*	Effectiveness for whom adherence data were also available†	Efficacy per 10% increase in adherence†	Maximum efficacy (100% adherence)†	Efficacy per 10% increase in adherence*§	Maximum efficacy (100% adherence)*§
Adjusted between-group mean difference in symptom severity between days 2 and 4 post-randomisation	-0.07 (-0.15 to 0.01)	-0.07 (-0.15 to 0.01)	-0.008 (-0.017 to 0.001)	-0.08 (-0.17 to 0.01)	-0.008 (-0.017 to 0.001)	-0.08 (-0.17 to 0.01)
Odds ratio for developing new or worsening symptoms in the 4 weeks post-randomisation	0.79 (0.63 to 0.99)	0.81 (0.64 to 1.03)	0.978 (0.960 to 0.998)	0.81 (0.66 to 0.98)	0.973 (0.954 to 0.994)	0.76 (0.62 to 0.94)
Odds ratio for reporting non-respiratory symptoms/side effects in the 4 weeks post-randomisation	1.28 (1.03 to 1.59)	1.28 (1.04 to 1.59)	1.028 (1.011 to 1.046)	1.32 (1.12 to 1.57)	1.028 (1.011 to 1.046)	1.32 (1.11 to 1.56)

*Analysis based on 1789, 2027 and 1727 participants for the symptom severity, new symptoms and side effect outcomes respectively. † Analysis based on 1787, 1923 and 1725 participants for the symptom severity, new symptoms and side effect outcomes respectively. § Assuming those participants with missing adherence data did not take any medication (i.e. their adherence level is 0%).

6.3.2 RBEEs in non-inferiority / active control trials

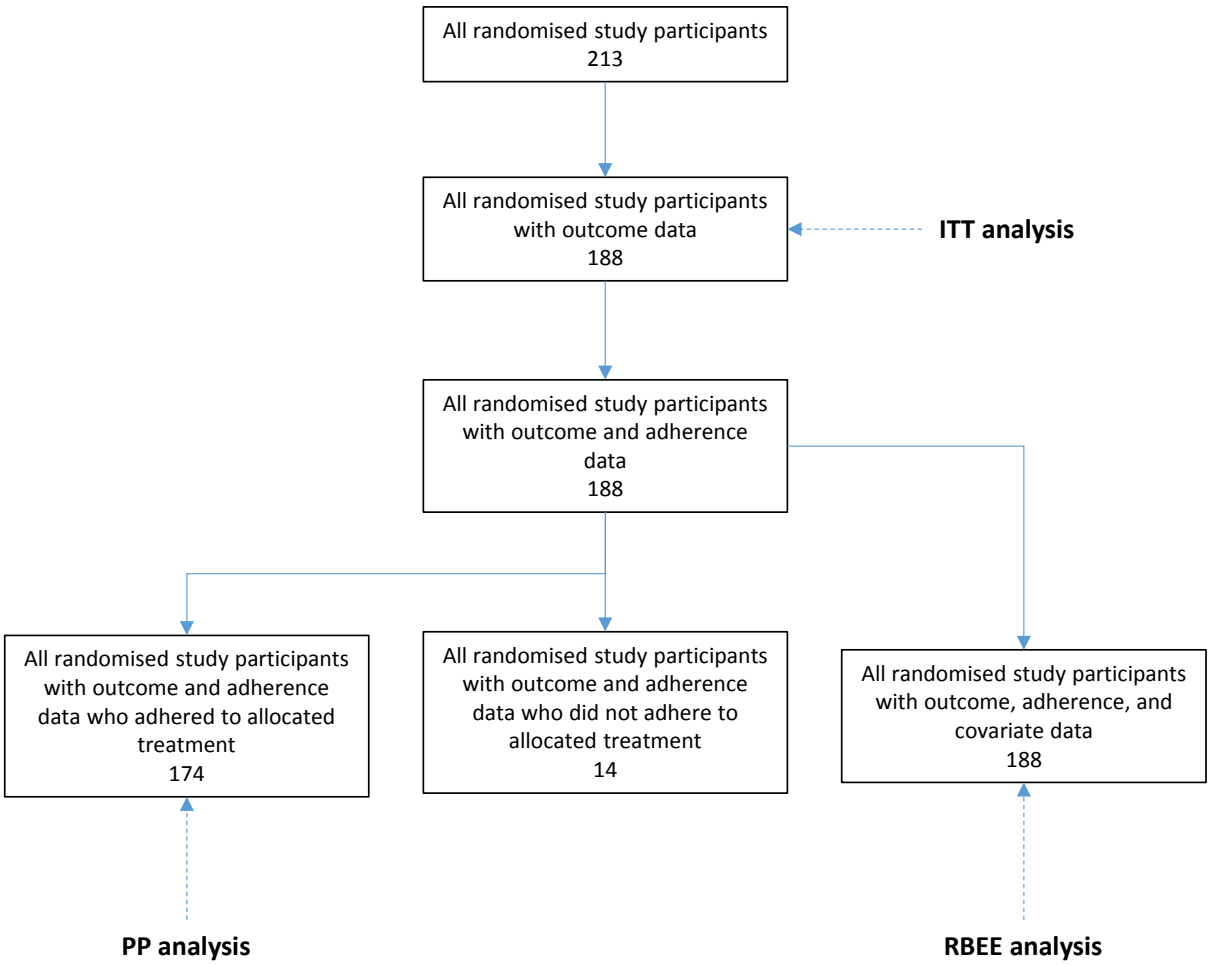
6.3.2.1 Analysis of the CODA trial

The analysis using data from the CODA trial was based on 188 randomised participants with outcome data.

In total, 174 participants adhered to their study medication (92.6%), with these making up the per-protocol population (Figure 6.11). The percentage of participants adhering to study medication was higher in those randomised to the intervention arm compared to the active control arm (95.7% and 89.4% respectively).

Overall, 56 participants relapsed within the 12 month follow-up period (29.8% of all participants). The percentage of participants who relapsed was lower in the intervention arm compared to the active control arm (24.5% and 35.1% respectively). The main trial analysis based on complete cases demonstrated that the relapse rate was 10.6 percentage points higher in those randomised to the TDS arm compared to in the OD (95% confidence interval (CI): -2.5 to 23.8 percentage points). As the lower limit of the 95% CI did not include -10%, and this was also found in the PP analysis, the findings confirmed the non-inferiority of the OD regimen compared to the TDS regimen.

Figure 6.11: Flow diagram describing data available for each type of analysis in the CODA trial



Predictors of relapse were age (participants aged 65 or older had decreased odds of relapsing during the follow-up period), length of remission (participants in remission for at least 12 months had decreased odds of relapsing during the follow-up period), and endoscopy findings at baseline (participants with non-normal endoscopy findings at baseline had increased odds of relapsing during the follow-up period) (Table 6.7).

When conditioning on the predictors of relapse, smoking status at baseline was the only variable that remained independently associated with participants adhering to their study medication at the 10% significance level (Table 6.8). Compared to non-smokers, the odds of participants adhering to their study medication was higher in those who were ex-smokers.

However, smoking status did not differentially predict adherence across the two arms (i.e. the interaction between smoking status and trial arm was not statistically significant).

Table 6.7: Multivariable determinants of relapse in the CODA trial (odds of relapsing during the 12 follow-up period)

Variable	Adjusted odds ratio	95% Confidence Interval		p-value
		Lower	Upper	
Age at baseline (≥65 compared to <65 years)	0.30	0.10	0.88	0.028
Length of remission (≥12 compared to <12 months)	0.34	0.14	0.81	0.014
Endoscopy findings at baseline (non-normal compared to normal)	4.14	2.04	8.39	<0.001

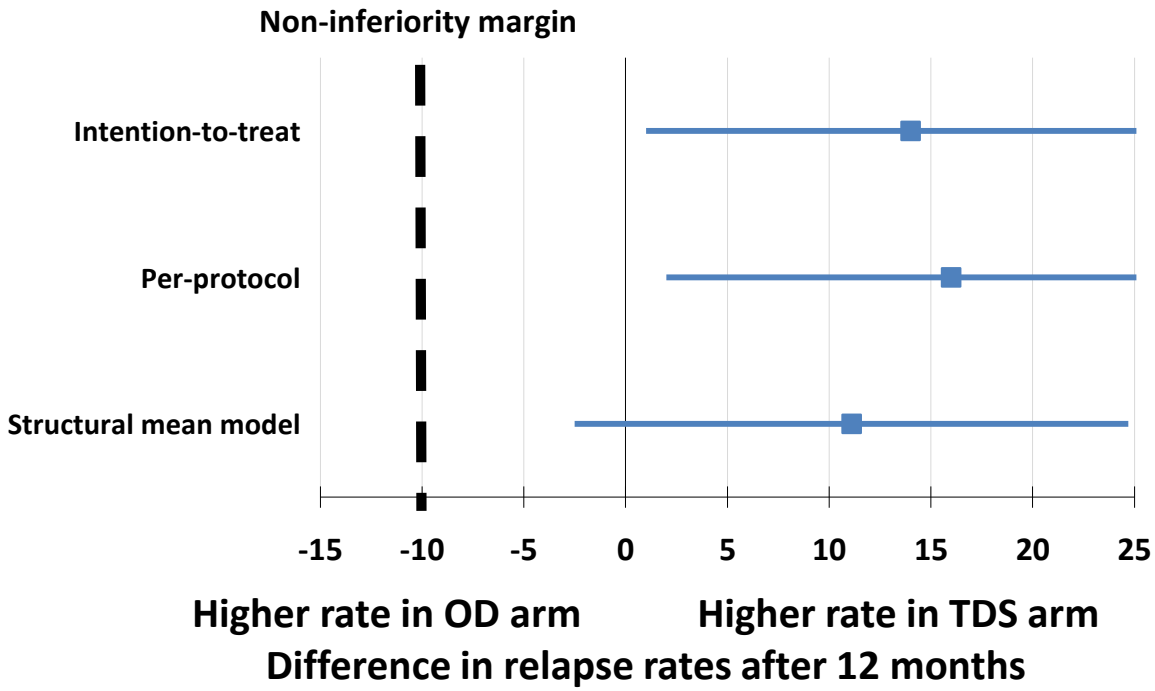
It was not possible to derive two distinct causal parameters based on observed data, as there were no baseline variables differentially associated with adherence for each of the arms. Given that the definition of adherence was binary, the only sensible analysis was to consider the standard treatment (active control) as the "placebo" group and use standard SMM methods.

The SMM analysis found that after adjusting for adherence, the relapse rate was 11.1 percentage points higher in those randomised to intervention. The 95% CI did not contain -10% (95% CI: -2.5 to 24.7 percentage points), and non-inferiority could be confirmed based on this analysis (Figure 6.12).

Table 6.8: Multivariable determinants of adhering to medication in the CODA trial

Purpose	Variable	Adjusted odds ratio	95% Confidence Interval		p-value
			Lower	Upper	
Associated with disease status at 12 months (relapsed/still in remission)	Intervention (OD arm compared to TDS arm)	2.61	0.75	9.03	0.131
	Age at baseline (≥65 years compared to <65 years)	2.42	0.27	21.70	0.430
	Length of remission (≥12 months compared to <12 months)	1.05	0.29	3.75	0.940
	Endoscopy findings at baseline (non-normal compared to normal)	0.31	0.10	1.01	0.053
Associated with adherence to study medication	Smoking status at baseline (current smoker compared to non-smoker)	1.31	0.25	6.79	0.076
	Smoking status at baseline (ex-smoker compared to non-smoker)	11.46	1.40	94.01	

Figure 6.12: Forest plot of the difference in relapse rates in the CODA trial for various analysis sets

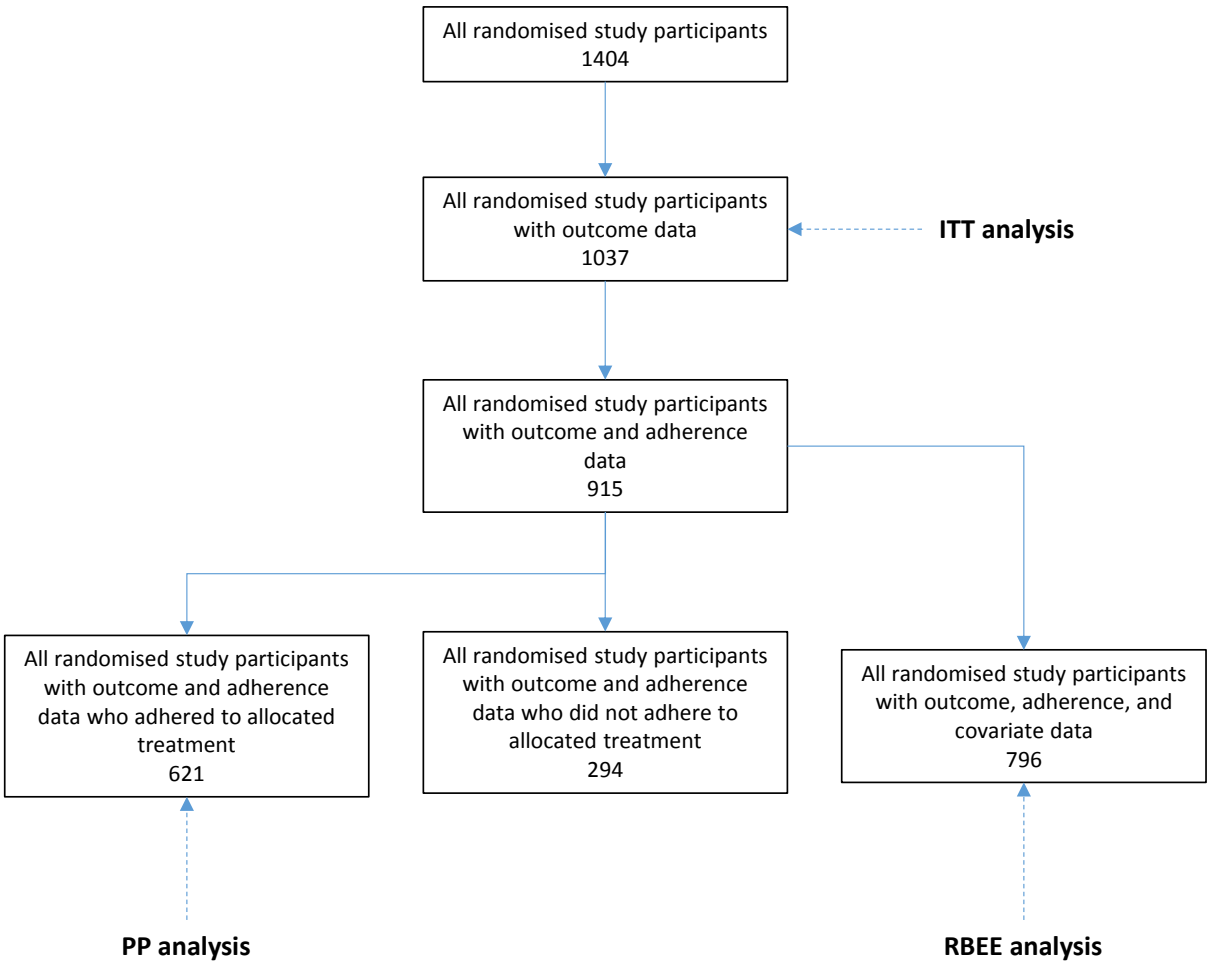


6.3.2.2 Analysis of the ZICE trial

The analysis is based on 1037 randomised participants with SRE data. In total, 621 of 915 participants with adherence data adhered to their study medication (67.9%), with these making up the per-protocol population. The percentage of participants adhering to study medication was higher in those randomised to the OIA arm compared to the IZA arm (77.4% and 60.7% respectively). Baseline covariate data were available for 796 participants. This made up the SMM population (Figure 6.13).

Overall, 382 participants experienced an SRE within the 12 month follow-up period (36.8% of all participants). The percentage of participants who experienced an SRE was higher in the OIA arm compared to the IZA arm (38.3% and 35.4% respectively). The trial analysis based on complete cases (and the full study period) demonstrated that the SRE rate was 3.0 percentage points higher in those randomised to the OIA arm compared to in the IZA (95% confidence interval (CI): -2.9 to 8.8 percentage points) and concluded that OIA was inferior to IZA.

Figure 6.13: Flow diagram describing data available for each type of analysis in the ZICE trial



The odds of experiencing an SRE within the first 12 months of the study were higher in participants with higher BMI scores, in participants who had poor role functioning, worse nausea/vomiting symptoms, had experienced an SRE in the three months prior to the study, or had recently used pain medication. The odds of experiencing an SRE within the first 12 months of the study were lower in females than in males, in participants with higher overall general health, and in participants with increasing dyspnoea (Table 6.9).

Table 6.9: Multivariable determinants of outcome in the ZICE trial (odds of experiencing a skeletal-related event during the first 12 months)

Variable	Adjusted odds ratio	95% Confidence Interval		p-value
		Lower	Upper	
Gender (female compared to male)	0.23	0.06	0.88	0.032
18.5kg/m^2 < BMI ≤ 25kg/m^2 (normal/healthy weight) compared to ≤ 18.5kg/m^2 (underweight)	6.16	0.75	50.65	<0.001
25kg/m^2 < BMI ≤ 30kg/m^2 (overweight) compared to ≤ 18.5kg/m^2 (underweight)	6.85	0.84	56.13	
30kg/m^2 < BMI ≤ 35kg/m^2 (moderately obese) compared to ≤ 18.5kg/m^2 (underweight)	13.17	1.59	108.81	
35kg/m^2 < BMI ≤ 40kg/m^2 (severely obese) compared to ≤ 18.5kg/m^2 (underweight)	6.99	0.81	60.39	
BMI > 40kg/m^2 (very severely obese) compared to ≤ 18.5kg/m^2 (underweight)	13.11	1.44	119.65	
QLQ-C30 global health domain (per unit increase)	0.98	0.98	0.99	0.001
QLQ-C30 role functioning domain (per unit increase)	1.01	1.00	1.02	0.005
QLQ-C30 nausea / vomiting domain (per unit increase)	1.01	1.01	1.02	<0.001
QLQ-C30 dyspnoea domain (per unit increase)	0.99	0.99	1.00	0.056
SRE within the three months prior to baseline compared to no SRE within three months prior to baseline	1.56	1.14	2.13	0.006
Recent use of pain medication at baseline compared to no recent use of pain medication	1.63	1.08	2.46	0.019

After conditioning on the above, both cognitive functioning and use of chemotherapy were independently associated with adhering to study medication differently in the two arms (Table 6.10). The results from the model suggest that the odds of adhering to study medication are:

- Higher for participants allocated to the OIA arm, with the lowest levels of cognitive functioning, and not undergoing chemotherapy at baseline
- Higher as cognitive functioning increases for participants allocated to the IZA arm
- Lower as cognitive functioning increases for participants allocated to the OIA arm
- Higher for participants undergoing chemotherapy at baseline and allocated to the IZA arm
- Lower for participants undergoing chemotherapy at baseline and allocated to the OIA arm

Distinct causal parameters could be estimated using the ZICE data, and therefore the difference between the two arms could be calculated. After adjusting for treatment adherence, the proportion with SRE in the first 12 months was no different in either of the arms (difference in proportions 0.0, 95% CI: -13.9 to 13.8 percentage points). While the point estimate from the SMM was closer to no difference, the width of the confidence interval was wide and crossed any non-inferiority margin that could be justified (Figure 6.14).

As for the analysis of the GRACE WP10a trial, missing data posed a potential problem in deriving RBEEs for the ZICE trial. Applying a basic imputation method meant that the predictors originally found were no longer statistically significant. The SMM method could therefore not be applied as it had been originally. Another approach I explored involved restricting the ITT and PP analysis to those who also feature in the SMM analysis. However, this changed the point estimates as well as widening the confidence intervals slightly (Figure 6.15).

Table 6.10: Multivariable determinants of adhering to medication in the ZICE trial

Purpose	Variable	Adjusted odds ratio	95% Confidence Interval		p-value
			Lower	Upper	
Associated with the development of a SRE within 12 months	Gender (female compared to male)	1.29	0.36	4.55	0.697
	18.5kg/m^2 < BMI ≤ 25kg/m^2 (normal/healthy weight) compared to ≤ 18.5kg/m^2 (underweight)	2.19	0.74	6.47	<0.001
	25kg/m^2 < BMI ≤ 30kg/m^2 (overweight) compared to ≤ 18.5kg/m^2 (underweight)	2.05	0.70	6.00	
	30kg/m^2 < BMI ≤ 35kg/m^2 (moderately obese) compared to ≤ 18.5kg/m^2 (underweight)	2.35	0.79	7.03	
	35kg/m^2 < BMI ≤ 40kg/m^2 (severely obese) compared to ≤ 18.5kg/m^2 (underweight)	3.07	0.95	9.95	
	BMI > 40kg/m^2 (very severely obese) compared to ≤ 18.5kg/m^2 (underweight)	3.90	1.06	14.31	
	QLQ-C30 global health domain (per unit increase)	1.00	1.00	1.01	0.358
	QLQ-C30 role functioning domain (per unit increase)	1.00	1.00	1.01	0.300
	QLQ-C30 nausea / vomiting domain (per unit increase)	1.01	1.01	1.02	0.000
	QLQ-C30 dyspnoea domain (per unit increase)	1.00	0.99	1.00	0.547
	SRE within the three months prior to baseline compared to no SRE within three months prior to baseline	1.07	0.79	1.46	0.660
	Recent use of pain medication at baseline compared to no recent use of pain medication	0.65	0.45	0.94	0.021
Differentially associated with	Oral ibandronic acid arm (main effect)	5.77	2.05	16.26	0.001
	QLQ-C30 cognitive functioning (main effect)	1.01	1.00	1.02	0.005

Purpose	Variable	Adjusted odds ratio	95% Confidence Interval		p-value
			Lower	Upper	
adherence by trial arm	Oral ibandronic acid arm * QLQ-C30 cognitive functioning (interaction)	0.99	0.98	1.00	0.061
	Use of chemotherapy at baseline (main effect)	2.12	1.28	3.53	0.004
	Oral ibandronic acid arm * Use of chemotherapy at baseline (interaction)	0.47	0.22	1.02	0.057

Figure 6.14: Forest plot of the difference in the proportion with SRE in the first 12 months in the ZICE trial for various analysis sets

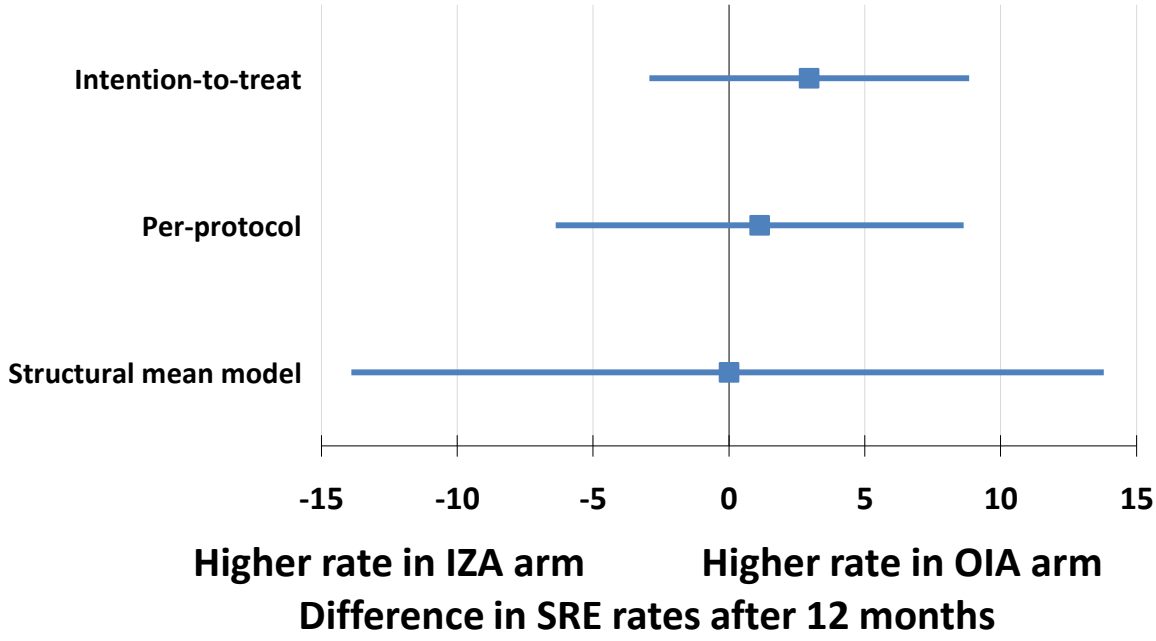
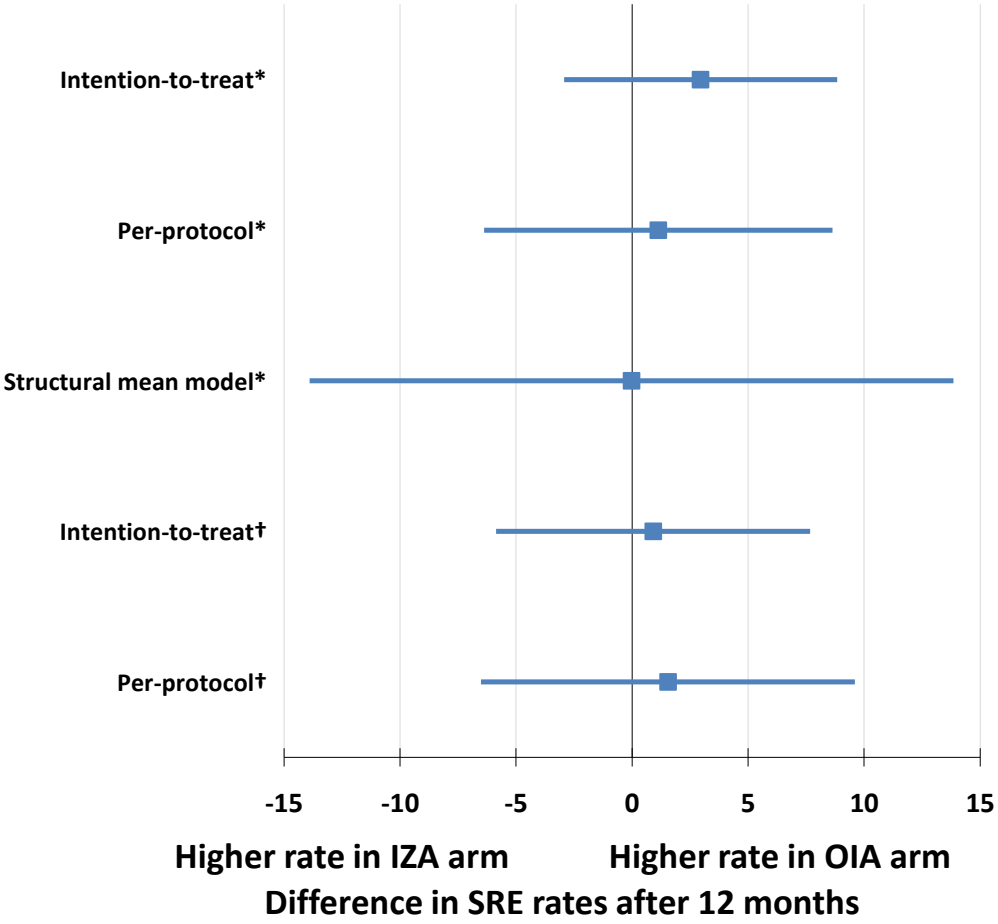


Figure 6.15 Impact of missing data on the interpretation of the SMM analysis



*Intention-to-treat n = 1037; Per-protocol n = 621; Structural mean model n = 796
†Analysis performed in participants who were included in the structural mean model analysis. Intention-to-treat n = 796; Per-protocol n = 536.

6.4 Discussion

6.4.1 Summary

In this Chapter, the feasibility of implementing RBEEs to adjust findings of RCTs for medication non-adherence was explored using data from three clinical trials. Several design considerations were investigated, including whether the trial was designed to investigate the superiority or non-inferiority of one treatment to a comparator, whether a placebo or active treatment was used as a comparator, and what the comparison of interest was (e.g. difference in means, difference in proportions, odds ratio). Sensitivity analyses were also conducted to examine the robustness of the methods under a various assumptions, including assumptions related to missing adherence and outcome data.

6.4.2 Learning points

1. Clinically:

    a. The findings from the GRACE WP10a trial suggest that taking amoxicillin improved (i.e. further reduced) symptom severity on days 2-4 (compared to the effect of it merely being prescribed, regardless of the extent to which participants adhered to treatment), further decreased the odds of developing new or worsening symptoms, and further increased the odds of reporting side effects. Nevertheless, due to the high levels of adherence to study medication, the findings of the original effectiveness analyses were reasonably robust to departures from randomised treatment.

    b. In the CODA trial, it was not possible to derive distinct estimators, and standard SMM methods were applied instead, treating the active control arm in the same way that a placebo arm would be treated. This analysis was consistent with the ITT and PP findings (i.e. there was evidence to suggest that OD was not inferior to TDS in terms of preventing relapse). The

reasons for this are likely threefold: (1) a limited set of baseline predictors that were not selected with the different treatment regimens in mind; (2) a small sample size, limiting the probability of detecting differences where they exist (i.e. power); (3) the lack of an adherence measure on all participants that adequately captured patterns in adherence, rather than just overall consumption. As the two treatments being compared were identical, and the only difference was their prescribed regimen, it would be difficult to find discernible differences between arms (as already indicated during Chapters 4 and 5).

c. In the ZICE trial, it was possible to derive distinct estimators, and when comparing the arms the point estimate implied no difference in SRE rates between the arms, but the confidence intervals were considerably wider than the intention-to-treat and per-protocol analyses.

2. Methodologically, the use of SMMs to adjust trial findings for non-adherence is attractive, as it allows for a comparison of groups that is independent of measured and unmeasured confounders. It is also straightforward to apply these techniques with minimal programming skills, and I have created a graph to depict a linear SMM – something that illustrates the technique, its assumptions, and how the efficacy estimate relates to effectiveness. However, for these approaches to be valid, they rely on the key assumption that for participants who were categorised as non-adherers, merely being allocated to receive treatment had no effect on outcome (the so-called 'exclusion restriction'). While this was likely to be a valid assumption for the GRACE WP10a trial, as participants and clinicians were blinded to allocation, this is less likely to be valid for non-blinded studies (for example, a two-arm randomised controlled trial of a weight loss intervention (versus no intervention), where participants are aware that the focus is on bodyweight).

3. Treating adherence as a continuous measure in the GRACE WP10a trial (and generally) made the exclusion restriction more plausible, as the lowest level of adherence could be defined as receiving no treatment, a level at which being allocated to either treatment group should really have no effect on outcome. However, this approach made the additional assumption that the effect of receiving an increasing amount of treatment on outcome increased linearly, which for a trial involving medication is unlikely to be true. Sensitivity analyses were conducted using various binary definitions of adherence, ranging from one or more tablets (versus no tablets) to full course (versus less than full course). While the former increased the plausibility of the exclusion restriction, the estimated treatment efficacy was too conservative. The latter analysis combined participants who would have taken 99% of their medication with participants who would have taken no medication and considered them all as not adhering (and therefore assumed they would have received no benefit from being allocated to the amoxicillin arm). This clearly violated the exclusion restriction. However, the findings from the sensitivity analyses largely agreed with the main findings (where adherence was measured continuously), adding further strength to the conclusions drawn in this Chapter. Similar issues were present in the CODA and ZICE trials.

4. While these methods are particularly desirable for NI trials, as neither of ITT or PP analysis provide both a conservative and unbiased comparison of treatments, this work highlights the increase in variance when fitting these models, something that can only be reduced when the models include strong predictors of adherence and outcome. Use of the method is more accurate in terms of reducing selection bias, but the reduced precision necessitates the collection of relevant and complete baseline variables. To do this, the research team must have a good understanding of the predictors of outcome, and also the barriers and facilitators to adhering to

the randomised treatments. Studies with feasibility or pilot stages could explore these aspects, as well as how best to capture this data, before progressing onto more definitive studies. The significance thresholds for inclusion of variables in this paper were higher than current practice. Future studies that collect strong baseline predictors of adherence need not use such high significance levels.

5. By modelling the determinants of differential adherence in the different treatment arms, researchers will also gain an understanding of the circumstances under which the treatments will be better received by patients, and therefore more likely to work. For example, in the ZICE study, we were able to demonstrate that for participants allocated to the intravenous zoledronic acid arm, adherence was higher for patients with higher cognitive function and for those receiving chemotherapy at baseline, whereas for those allocated to the oral ibandronic acid arm adherence was lower for patients with lower cognitive function and for those receiving chemotherapy at baseline. One explanation for this could be that patients with low cognitive function could have their medicines dispensed by a care giver, which is likely to reduce forgetfulness and increase adherence. Patients receiving chemotherapy at baseline will be attending hospital regularly for these visits, and the delivery of IZA often coincided with other hospital visits for cancer therapy, thereby increasing their chances of receiving IZA treatment. The implications of this, regardless of the comparative efficacy of the treatments themselves, could be that IZA should be offered to those undergoing additional cancer treatments (or any other treatments that require regular hospital visits). OIA could be offered along with an additional intervention to increase adherence (e.g. a reminder or monitoring system), or in instances where patients were not in control of their own medication dispensing (e.g. elderly nursing home residents).

6. Despite the fact that incomplete outcome and adherence data were minimal, their impact on findings remains unknown. However, for the GRACE WP10a trial, as the condition under investigation is generally self-limiting, and outcome data included worsening of illness (a composite outcome collected from medical notes that included hospitalisation), we do not believe that the small amount of missing data would have severely impacted on the findings or conclusions drawn from this study. Indeed, the further sensitivity analyses conducted, where missing data were taken into account, demonstrated that clinical conclusions remained largely unaltered, even when taking an extreme assumption about missing adherence data. Similarly for the ZICE trial, an assessment of the impact of missing data on the interpretation of the SMM analysis was performed as a sensitivity analysis with conclusions remaining largely the same.

CHAPTER 7: Discussion

7.1 Summary and interpretation of findings

The aim of this thesis was to investigate various methodological challenges encountered when studying medication adherence in clinical research, generating new evidence that would advance the field, and indicating areas in which further developments are warranted.

During my literature review in Chapter 2, I identified gaps and deficiencies in knowledge pertaining to the measurement of medication adherence, modelling of electronic monitoring data over time, considerations when multiple types of measure are used (and disagree), approaches to modelling determinants of medication adherence, and the feasibility of implementing randomisation-based efficacy estimators in randomised trials with non-adherence.

I explored these areas using data from three studies, described in detail in Chapter 3. These studies were chosen as they encompassed contrasting clinical conditions (ranging from short to long-term conditions), study designs (randomised controlled trials and observational studies), had multiple types of measures (self-report, tablet counts, electronic monitoring), and the randomised controlled trials varied in their comparators (placebo, same drug but different regimen, and different drug and different route of administration). Substantive, as opposed to synthetic data were used, as the new evidence generated would be of clinical relevance, and it was my intention to demonstrate the utility and limitations that can be encountered when investigating these methods in practice.

In Chapter 4, I compared several types of methods used to measure adherence to medication in clinical research, using a variety of correlational and agreement approaches. I explored the use of advanced modelling techniques to maximise the utility of electronic monitoring data collected over a 12-month time period. I also considered other ways in which studies could make use of adherence data when captured via multiple routes, namely

the development of prediction models for disagreement, and several approaches to creating a calibrated adherence measure. I used generalised linear mixed models, accounting for the correlated nature of repeated observations within individuals, and modelled non-linear time effects using splines, to investigate patterns in adherence over time using electronic monitoring data. This made better use of the data, compared to summarising adherence over the study period, as it enabled differences between and within individuals to be described, and allowed behavioural patterns to be investigated (e.g. white coat adherence and different patterns during the week compared to at weekends). I found that, according to electronic monitors, patients on more complex dosing regimens adhered less well, and were considerably more variable, than those on simpler regimens. Nevertheless, for both regimens, adherence decreased over time similarly (on average). This may reflect treatment fatigue (patients struggling to maintain the constant routine of taking medication over a long time period) or perhaps treatment optimisation (patients developing an understanding on what works for them in terms of how they take their medication). There was evidence to suggest adherence improved around clinic visit dates, a hypothesised indicator of white coat adherence. In addition, there was evidence to suggest that adherence was worse on weekends than on weekdays. This comparison was chosen as, for the majority of people, routines tend to be different during weekdays than during weekends, largely down to patterns in work (e.g. the Monday to Friday 9-5 routine). It was therefore suggested that this break in routine may impact on levels of adherence. This was also found in the seminal paper by Vrijens et al., 2008. The absence of differential effects by regimen for these two behavioural patterns adds weight to these being naturally occurring behaviours, rather than artefacts of the regimen a person was on.

I found that, like other method comparison research, correlations can provide misleading evidence of the performance of two measures that aim to measure the same phenomena. Analytical approaches for measuring agreement exist, and depending on whether

adherence can be summarised as a binary or continuous scale different approaches can provide information on the extent and nature of disagreement. Where agreement was a focal point in the previously identified literature, most relied on taking an arbitrary cut-off of adherence and reporting kappa statistics. My thesis aimed to move beyond that, providing visual and quantitative representations of agreement, using both binary and continuous measures. Bangdiwala observed agreement plots provided this for binary adherence measures. I considered ways of enhancing these plots, for example by overlaying them with reference lines to indicate agreement that would be expected by chance (akin to a visual representation of a kappa statistics). Bland-Altman plots and limits of agreement in particular can provide a wealth of information about the level of agreement between two types of adherence measures, provided they can both be summarised on a continuous scale. I identified a nuance with the Bland-Altman approach that, to my knowledge, has not been remarked upon previously. When plotted on its full scale (i.e. both axes spanning the entire range of possible values), the data points are bounded within a restricted space. For example, when comparing two measures, both on a scale from 0 to 100, they can be as extreme as [50, -100], but nothing beyond this (e.g. they cannot be [60, -100] or [20, 100]). This may have implications for the 95% confidence intervals and limits of agreement around the bias (e.g. it may be more appropriate to fit non-linear confidence intervals or limits of agreement to these data). Clinically, I found that when comparing adherence as measured via tablet counts and electronic monitoring, disagreement largely occurred for participants on the three times daily dosing regimen, with adherence consistently higher when measured by tablet counts than when measured by electronic monitoring. There is a wealth of literature devoted to describing the biases that may occur from measuring medication adherence using tablet counts (e.g. so-called "pill dumping"). However, the fact that this disagreement is overwhelmingly seen in patients on the three times daily regimen is intriguing. One plausible explanation for this finding is that patients opened their

container once and took all three tablets out (for example, so they did not have to carry the medication bottle with them throughout the day). If this were true, it would highlight a deficiency in the use of electronic monitoring for patients on complex regimens, on the grounds of both validity and acceptability. In practice, using several types of adherence measures implies a lack of trust of any one type of measure.

While the vast majority of work to date correlates or assesses agreement between the different measures, I felt it was important to exploit this even further, and explore different ways of predicting disagreement and deriving calibrated adherence measures. I used several regression models to investigate predictors of disagreement. Each model provided different information (predicting agreement or disagreement, direction of disagreement, and direction and extent of disagreement), and while different contexts could mean any of the models could be beneficial, in the context used in this thesis, I found that while certain variables predicted disagreement and the direction of disagreement, the extent of disagreement (and arguably the importance of the disagreement) was minimal. A description of the predictors of disagreement will be described in more detail later on in the Chapter. The different calibration approaches I explored made only minor differences to reported summary measures of adherence. However, this will not be the case in all instances. Using a calibrated adherence measure allows a researcher to maximise the amount of adherence data available and/or report a measure that has some correction for potential misreporting, depending on the approach used and purposes of using the adherence estimate.

In Chapter *5*, I investigated various methods for modelling the determinants of adherence. The determinants of adherence were compared across different types of methods used to measure adherence within the same study, different clinical conditions (acute lower-respiratory-tract infection, ulcerative colitis, and breast cancer with bone metastases), different study designs (observational study and RCT), and using different

conceptualisations of adherence (a single summary measure or as distinct processes). I found that different types of adherence measures can have an influence on the determinants that can be found. This strengthens the importance of considering appropriate adherence measures prior to conducting a study. For example, in a trial of two different dosing regimens (but where participants in both groups were expected to consume the same quantity of tablets), tablet count data will provide a measure of consumption, but will not be able to provide particularly sensitive data on patterns of adherence. This work has led me to consider adherence more in line with the general framework around the development and validation of outcome measures. This is something I will write about in more detail later on in this Chapter.

The complexity of the treatment was one determinant that was consistently associated with adherence across all clinical conditions. Other determinants found to be associated with adherence, but not consistently across conditions, were age, gender, social functioning (the ability to interact with others in a normal way in society), days waited prior to consulting, clinical signs (both for the acute condition), as well as some country or structural determinants (countries in which a sick certification is required for missing fewer than seven days of work or in which single-handed practices (i.e. one clinician treating all patients) were widespread). Through the use of multilevel analysis, I was also able to quantify the extent to which the treating clinician influenced whether a patient adhered to their treatment. This is a determinant of medication adherence often reported in the literature, but only using qualitative data. The approach I have taken is novel and important, as it goes further than an acknowledgement that clinicians can influence medication taking behaviour and provides estimates of the extent to which they do influence this behaviour. I also demonstrated that separating adherence out into distinct processes is not only useful when summarising the extent to which patients took their medicine, but also for investigating the

determinants of adherence. Indeed, I found different determinants for each of the processes. I will provide further detail of the implications of this later in this Chapter.

While initiation and implementation are vital processes for all medication taking (both short and long-term treatments), my investigations left me unconvinced of the necessity of investigating the determinants of time from initiation to discontinuation for short-term conditions. This is not necessarily a process that would become a target for improvements, particularly for treatments such as antibiotics where sub-optimal implementation, for a prolonged period of time, could heighten the risk of carrying antibiotic resistant organisms. Despite this, depending on the type of adherence measure available, time from initiation to discontinuation may be the only metric that can be reliably estimated. Determinants were grouped into five dimensions, following the framework laid out in Sabaté, 2003. What became clear when looking at the variables available in my datasets, and grouping them into these dimensions, was that while factors related to patients, conditions, and therapies were often available, factors related to social/economic or healthcare professionals/systems were rarely present. This may be due to a perception that they are likely to be less associated with clinical outcomes than other dimensions and due to a balance between measuring everything that is of interest and minimising response burden. Nevertheless, where a treatment is efficacious, poor adherence will have an impact on clinical outcomes (adherence is clearly on the causal pathway to clinical outcome), so a consideration of variables to collect that are related to both adherence and outcomes is needed. I make recommendations based on this at the end of this Chapter.

An interesting observation is that there was considerable overlap when comparing the determinants of adherence in Chapter 5 and the determinants of disagreement between different types of adherence measures in Chapter 4 (Table 7.1). The three determinants that were found to be associated in both Chapters all went in the same direction. That is, participants were more likely to provide adherence measures that agreed and more likely

to adhere to their treatment. This may be suggestive of a link between the two, though whether this link is purely a function of the measures (high adherence is high adherence, no matter how it is measured) or whether this could be linked to any behavioural theories (e.g. participants who adhere poorly may be found to be more likely to provide measures that disagree due to the inherent social desirability of being seen to be someone adhering to their treatment), is an area that requires further investigation.

Table 7.1: Overlap between determinants of adherence and determinants of disagreement between different types of adherence measures for participants in the GRACE studies

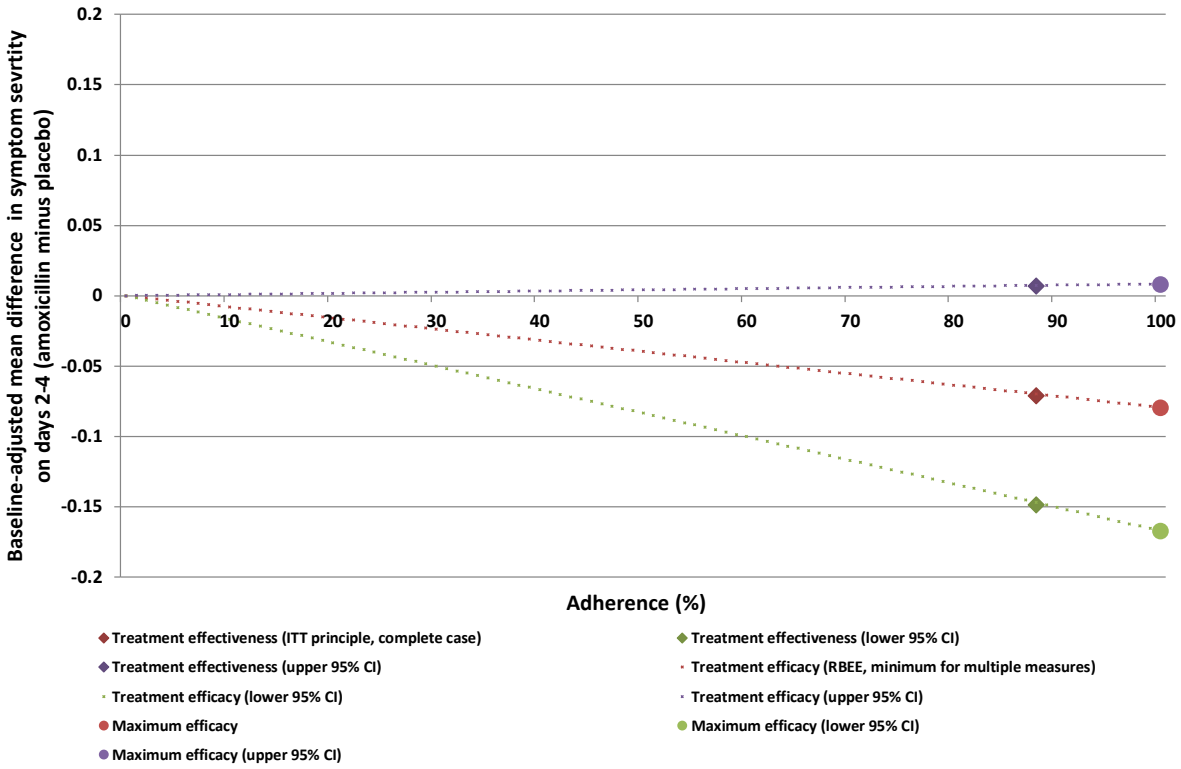
Determinant	Agreement between types of adherence measures	Adherence
Age	Older participants more likely to agree	Older participants more likely to adhere
Auscultation abnormality	Those with an auscultation abnormality more likely to agree	Those with an auscultation abnormality more likely to adhere
Days waited prior to consulting	The longer participants waited prior to consulting, the more likely they were to agree	The longer participants waited prior to consulting, the more likely they were to adhere

Finally, during Chapter 6, I established the feasibility of calculating randomisation-based efficacy estimators in RCTs with non-adherence, scrutinising the implementation of these approaches under a variety of circumstances commonly encountered in RCTs. The specific circumstances I considered were where binary and/or continuous measures of adherence are available, where binary and/or continuous outcome variables are of interest, where outcome data are missing, and where the trial compares two active treatments. It is rare to see these analytical approaches described outside of methodological journal articles, and it was my intention to explore their use in practice and indicate considerations that are important in the design, conduct, analysis, and reporting of RCTs in which non-adherence is likely. I found that the techniques can be readily applied in most instances using standard statistical software, and minimal programming. However, while randomisation-based

efficacy estimators are an attractive prospect, in terms of their ability to eliminate selection bias, this generally comes at a cost of increased variance (i.e. less precision around estimates), and additional assumptions that may not always be possible to satisfy. For example, one of the core assumptions (the exclusion restriction), relies on there being no benefit gained from being allocated to receive treatment for non-adherers. When adherence is all-or-nothing (e.g. a single tablet), this assumption is rather plausible. However, when adherence is not all-or-nothing (e.g. two tablets, three times a day, for seven days), how you summarise the measure of adherence influences the plausibility of this assumption. Taking a cut-off at 100% for example (i.e. all medication consumed as prescribed), makes the assumption that anyone who would adhere less than this (anywhere between no medication consumed to 99% of medication consumed accurately) would receive no benefit from being allocated to receive treatment. Options I explored to circumvent this issue involved creating different cut-offs (initiated treatment versus not; adhered for the first five days versus not) and treating adherence as a continuous measure, the latter of which relied on the additional assumption that the effect of treatment was linearly related to the level of adherence, an assumption that is also unlikely to be plausible, given that log dose-response curves are generally sigmoidal.

I constructed a graph of a randomisation-based efficacy estimator that used a continuous adherence measure, illustrating the increasing efficacy as adherence increased, and how these estimates related to the original effectiveness estimates. Under the assumption of linearity, this is a valuable way of presenting the findings from this analysis, as it shows the exclusion restriction assumption clearly (at the co-ordinate [0, 0]), the increase in efficacy as adherence increases, the effectiveness estimate (at the level of adherence achieved during the trial), and the potential effect of treatment in those who fully adhered (Figure 7.1).

Figure 7.1: Graphical illustration of the effectiveness and efficacy of amoxicillin on mean symptom severity on days two to four



I made a case for randomisation-based efficacy estimators to be used when analysing non-inferiority trials. However, these trials generally involve the comparison of two active treatments, and thus the derivation of these estimators relies on identifying pre-randomisation variables that are differentially associated with adherence to the different treatments, while remaining independent of outcome. For the data available and used in my thesis, I found I was unable to identify such variables in one study, and while I identified some in another study, they were rather weak which meant it was difficult to draw any conclusions based on the confidence intervals (though the impact the adjustment had on the point estimate was still of use). Nevertheless, by modelling the differential determinants of adherence for each of the treatment groups, I was able to provide some indication of the types of patients who may benefit differently from the different treatments (e.g. the convenience of giving intravenous medication to someone already attending hospital for

another reason). In addition, I considered the impact of missing adherence data on these analytical methods, conducting several sensitivity analyses to explore the impact of varying assumptions regarding missing mechanisms on the findings.

7.2 Novel aspects of this work

The work presented in this thesis is both clinically and methodologically novel. Methodologically, I have demonstrated an approach to modelling and graphically illustrating electronic monitoring data of daily medication adherence that is innovative. Certainly, plotting the predicted probability of adherence curves for each individual and overlaying this with their raw data is something rather unique. When investigating agreement, I have considered a useful extension to the Bangdiwala observer agreement plots by overlaying these with reference domains that indicate chance agreement. I have identified bounded regions within the Bland-Altman plots that may have implications for how confidence intervals and limits of agreement are constructed in future method comparison studies. I have produced a graphical illustration of the randomisation-based efficacy estimator, when adherence is treated as a continuous measure. This is a convenient way of illustrating a concept that is difficult to grasp for both applied researchers and clinicians alike. I have also implemented randomisation-based efficacy estimators in non-inferiority trials, critically considering the uses and limitations of these methods on real world data. To date, this is something that has only been considered in theory, so the work presented in this thesis is the first of its kind.

Clinically, I have reported on the first study to electronically monitor medication adherence in adults in remission with ulcerative colitis. Adherence is a major concern for this condition, hence the move to evaluating simplified dosing regimens. By modelling adherence in patients over time and considering behaviour patterns of non-adherence, this study provided significant advances in this clinical area. I have also conducted the first study

that separately investigated the determinants of initiation, implementation, and discontinuation of antibiotic treatment. Within this work, I have also provided estimates of variation in initiation and implementation that is attributable to differences between clinicians (and countries / healthcare settings). That is, a quantitative (rather than qualitative) estimate of the amount influence clinicians / healthcare settings have on an individual's propensity to initiate treatment or implement their treatment correctly on a given day. This work is not only of clinical importance, but also provides a framework for future studies aiming to measure this quantitatively.

The findings presented in Chapters 4, 5, and 6 of this thesis have formed the basis of four publications, each of which have been published in peer-reviewed journals (Inflammatory Bowel Diseases, BMJ Open, BMC Trials, and Patient Preference and Adherence). This adds further strength to this body of work, demonstrating that the contributions I have made are of importance and value to the scientific community. See Appendix IV for the papers, as well as a diagram illustrating how they link to Chapters 4, 5, and 6. In addition, I have presented work related to my PhD at various national and international conferences, in order to increase awareness of the medication adherence field more generally (but specifically the methodological challenges herein). See Appendix V for more details. Alongside this, I have also discussed and piloted some of these ideas with colleagues in the Centre for Trials Research. The feedback I have received to date has been positive, with the figures seen as useful visualisations of either complex or abstract methodological topics. For example, the variability displayed by the spaghetti plot (Figure 4.8 in Section 4.3.3) was something not immediately apparent when reading the parameter estimates from the preceding Table (Table 4.5). This plot therefore enhanced the understanding of the findings from merely a difference between regimens for the fixed effects (averaged across participants) to also a higher degree of variability for participants allocated to the TDS

regimen, something that would be an important consideration for a prescriber / healthcare professional.

7.3 Limitations

While I discussed the rationale for using real world data earlier in this Chapter, there are some limitations to taking this approach. Being limited by the sample size of the original study meant that extra care was required when interpreting a lack of evidence of any association examined. This could indeed imply there was no (or limited) association, or could be due to a lack of power to detect an association. As the data used throughout this thesis came from previously conducted studies, I had no influence on the variables that were collected, or types of adherence measures used, at the time I began my studies. There are several examples of these limitations.

In the CODA study, an OD regimen was compared against a TDS regimen, with the TDS regimen chosen as the comparator, as it was deemed the most logical way to divide 3 tablets over the course of the day and is still used by a substantial number of gastroenterologists. (Sandborn et al., 2010) Although there is evidence of medication adherence issues for TDS regimens, less pronounced differences have been shown when comparing OD regimens with BD regimens. (Eisen et al., 1990)

In the GRACE studies, the analysis of determinants focused on adherence to amoxicillin prescriptions for immediate use only. While this reduces the potential number of participants (other antibiotics were prescribed and delayed prescriptions were given in the included observational studies), it allowed for the investigation of the impact of the dose, frequency, and duration without being confounded by type of antibiotic prescribed. Since Amoxicillin is the most commonly prescribed and recommended antibiotic for acute respiratory infections across Europe, (Butler et al., 2009, Wood et al., 2011) the results retain wide applicability. Advice regarding delayed prescriptions, while also recommended

for this condition, (Francis et al., 2012) are often vague (for example, "here is a prescription if you get any worse"), and may have been issued with the intention that the patient would never actually take antibiotic treatment. The work presented in this thesis assumes that amoxicillin was prescribed for immediate use by a clinician with the intention that it would be taken as prescribed.

I used a simplified version of the original primary outcome in the ZICE study in order to illustrate the use of randomisation-based efficacy estimators in non-inferiority trials. One consequence of this is that while a non-inferiority margin was defined for the original primary outcome, one was not defined for the simplified version. While this could have limited the interpretation of this analysis, the confidence intervals were too wide for any NI margin to be justified, even post hoc (given that the original trial analysis suggested inferiority, this was a simplified outcome that would have had lower power than a recurrent event outcome, and the confidence interval of the SMM analysis was over twice as wide as the ITT and PP analyses).

In terms of the types of adherence measures that were used, although self-reports are simple, cheap, and convenient to implement, particularly when regular follow-up visits are scheduled and the study runs over a long time period, recall is not always perfect, and participants are not always accurate. A participant who forgot to take his medication may have had no conscious recollection that he forgot his medication. (Cramer and Spilker, 1991) The use of a validated questionnaire to capture self-reported adherence may have also provided a greater level of understanding of the circumstances around any non-adherence (e.g. intentional or unintentional) than the self-report questions that were asked in these studies. (Horne and Weinman, 2002) In the GRACE studies, adherence was primarily measured using prospective self-report diaries. While this type of measure remains prone to similar biases, collecting these data prospectively and frequently may improve recall biases and hence be an improvement over retrospectively collected self-

report data with a longer recall period (Lu et al., 2008) where unintentional non-adherence is an issue. However, questions in the diary only asked about daily use of treatment. We have therefore had to assume that if a participant reported that they consumed amoxicillin on a given day, they consumed the correct number of doses and these doses were spread evenly throughout the day – an assumption that could have been checked with a measure such as electronic monitoring. Similarly, adherence measured through tablet counts is simple, cheap, and convenient. However, mistakes in counting, intentional increases in medication around follow-up visits (so-called "white coat" adherence), and intentional tablet misrepresentation (e.g., by not bringing all medication to follow-up visits) (Vermeire et al., 2001) may have distorted the true number of tablets taken. There may have been social desirability factors that influenced participants to intentionally misrepresent their level of adherence. (Farmer, 1999) Electronically monitored adherence yields data that have a high level of granularity, though it remains difficult to determine whether the correct numbers of tablets are removed and ingested at each dosing event. (Kenna et al., 2005) Coupled with the increased bulk of the bottle (compared to a standard bottle), there remains disadvantages to their implementation, particularly for patients taking several doses of medication a day. Variables that might have been important to capture were omitted from the studies considered. For example, social / economic determinants were missing from most of the studies, as were structural determinants. No study collected data on medication/illness concerns, beliefs, or preferences prior to being prescribed medication. This has been shown to be a powerful predictor of intentional non-adherence. (Horne and Weinman, 1999, Benedetti et al., 2011) Without simulated data, and hence knowledge about the truth (in our case, the real adherence level of a participant), it is difficult to assess the performance of some of the methods used during the thesis. Finally, use of real world data means that it is difficult to generalise some of these findings beyond the clinical setting in which the studies were conducted, or indeed specific type of measure that was used (e.g.

it would be difficult to extrapolate the findings based on prospective self-report diaries to other forms of self-report, such as retrospective validates self-report questionnaires). However, while this is true for the specific clinical findings (for example: prospective self-report diaries and tablet count adherence data had high levels of agreement, clinicians accounted for approximately 20% of the total variation in whether a patient initiated their amoxicillin, fully adhering to a seven-day prescription of amoxicillin lowers your odds of developing new or worsening symptoms within four weeks, but increases your odds of reporting non-respiratory symptoms also), the general principles that I have discussed in detail throughout this Chapter can be generalised.

Throughout my thesis, multivariable regression models have been built using a single standardised approach. That is, first by considering candidate predictors and whether they had a sound basis for consideration, second by screening chosen variables in univariable analyses, and then, depending on the outcome of these, building a multivariable model using a backward selection process. While this approach is criticised for overfitting (that is, yielding estimates that do not reflect the overall population), there is no universally agreed approach to selecting variables in a multivariable regression model. The rationale behind the approach I have taken is that I wanted to develop simple models, with unnecessary predictors removed, in order to reduce the risk of finding spurious relationships to random error. Other approaches exist for selecting variables (e.g. forward selection, ridge regression, lasso, etc.). However, when developing these models, the purpose was to develop a set of predictors that succinctly described the relationship they had with the outcome of interest (usually a measure of adherence), rather than to compare the performance of different variable selection methods. Overfitting is an ever-present concern when developing and generalising the findings from a model beyond the data in which it was developed. The associations found in the models developed throughout my thesis

require further understanding (and validating on external data). This is something I also indicate in the next section.

7.4 Comparisons to existing literature

Levels of medication adherence in the CODA study were generally high, as found in other trials measuring adherence in UC. (Farup et al., 2001, Prantera et al., 2005) Indeed, adherence levels were higher than those reported in prospective community-based studies of patients with UC, (Kane et al., 2001) which is to be expected given both the increased motivation and monitoring generally seen in participants in clinical trials. Similarly, adherence to amoxicillin in the GRACE trial was considerably higher than that reported in the GRACE observational studies, despite the participants recruited into the trial appearing reasonably similar to those recruited into the aforementioned observational study in terms of their baseline characteristics. (Butler et al., 2009, Francis et al., 2012)

The finding in the CODA study that adherence deteriorated over the 12-month study period is also consistent with previous literature. Indeed, a study conducted in Canada found a 1-year persistence rate of 50% for people diagnosed with UC, (Lachaine et al., 2013) with another study conducted in the USA finding that 55% of participants continued to take their UC medication. (Kane et al., 2009)

Instances of poor agreement between the adherence measures, with more traditional methods providing higher estimates than those provided by the MEMS, particularly when adherence was poor, is consistent with the findings of a study conducted in young patients with inflammatory bowel disease. (Greenley et al., 2012) This pattern has also been found in other settings. (Daniels et al., 2011)

An inverse relationship between the complexity of a dosing regimen and the adherence has long been established. (Cockburn et al., 1987, Claxton et al., 2001, Pechère et al., 2007, D'inca et al., 2008, Saini et al., 2009, Llor et al., 2009) However, the less frequent dosing

of intravenous bisphosphonates (compared to a daily oral regimen) has previously been cited as contributing to improved levels of adherence. (Conte and Guarneri, 2004)

Females having lower odds of adhering to maintenance treatment for ulcerative colitis concurs with the findings of Lachine et al., 2014, but other studies have found the opposite relationship. (Kane et al., 2001)

Approaches for adjusting treatment effects for non-adherence while preserving randomisation have been in existence for approximately 20 years. (Angrist et al., 1996) However, they have largely been consigned to specialist methodological journals, rarely used in practice and when used, generally focussed on non-pharmacological treatments. (Dunn et al., 2003)

A recently published paper investigating the comparative efficacy of two different antidepressants was the first to demonstrate the practical implementation of the SMM approach as outlined by Fischer et al. (Wiles et al., 2014) One other study has reportedly implemented this approach on a non-inferiority trial. (Taylor et al,. 2012) However, as this was a placebo-controlled trial, and the paper detail of the approach was lacking, it was unclear whether they applied standard SMM methodology or the extended work described by Fischer et al.

7.5 Methodological and clinical implications

There are several implications arising from this work, primarily for researchers and applied statisticians working in clinical areas, but also for healthcare professionals who monitor medication adherence in their patients.

We, as researchers, should always strive to use the data we have collected to its maximum potential. Often in research, we are too quick to take a set of data and summarise it as a single value that, on the surface, has face value, but when considered more critically does

not provide much useful information. This point is exemplified in two places in my thesis. First, where I took adherence collected via electronic monitors in participants over a 12-month period and modelled daily adherence within individuals. This allowed me to describe adherence patterns over time, variation between and within individuals, and explore behavioural patterns. Had I combined these data into a single summary measure, none of this would have been possible. Second, where I investigated the determinants of different elements of adherence (i.e. initiation, implementation, and discontinuation). Traditional approaches to investigating factors associated with adherence/non-adherence involved regressing onto a single summary measure (e.g. adhered/did not adhere, an adherence 'score'). By investigating factors for different adherence processes, I was able to uncover certain characteristics that were more associated with these different processes (e.g. initiation but not implementation, or vice versa). This again is something that would have (and indeed was) missed when condensing adherence into a single summary measure.

In terms of implications for healthcare professionals, these findings indicate that for patients on long-term treatments adherence may decline over time, and behaviour may change around clinic visit dates/during breaks in an individual's normal routine. The former point requires further exploration into why this is occurring. As discussed earlier in this Chapter, this could be down to treatment fatigue or treatment optimisation. It should be acknowledged that patient behaviour may change around clinic visits (both before and afterwards), and this should be taken into account if monitoring adherence. Gaining an understanding of an individual's daily routine, how much it varies day-to-day, and whether it is generally consistent or there are distinct disruptions (such as at weekends) would seem important when it comes to understanding how to integrate medication into an individual's life. Where disruptions in routine are present, alternative strategies may be required, and these should be devised in advance of commencing treatment.

The work presented in Chapters 4 and 5 has led me to conclude that when considering methods for measuring medication adherence in clinical research, this should be approached in a way analogous to the selection of appropriate outcome measures. There needs to be an understanding of the phenomena that is of importance. This will be context-specific. For example, when interest lies in the extent to which patients take their medication as prescribed, and two different dosing regimens are compared (where the same amount of medication is consumed, but the regimen differs), using tablet counts as your primary means of describing medication adherence would not be recommended. Electronic monitoring is better suited for this purpose, as dose patterns and timings can be collected. For this reason, it is a more valid means of measuring adherence in this situation. This does not mean that tablet count data should be discarded however, even in the scenario described. Assessing agreement between tablet counts and electronic monitoring during Chapter 4, I suggested that for patients on complex dosing regimens, electronic monitoring may not necessarily be an acceptable or reliable way of measuring adherence. Tablet count data could provide a useful reliability check in this instance. The ability for a measure to detect change (i.e. responsiveness), is a related and another desirable property of an adherence measure. During Chapter 5 I demonstrated that adherence as measured using self-reported data and electronic monitors were able to distinguish between regimens, whereas tablet counts were not. In addition, understanding the types of people or circumstances that are likely to result in disagreement between measures could aid in choosing appropriate adherence measures in future research, or even tailoring types of adherence measures (certain types or single/multiple types for certain individuals).

It is difficult to interpret the determinants found during Chapter 5, and further work would still be required prior to implementing any interventions to improve adherence in reaction to these determinants. That said, the general lack of consistency across setting would imply that adherence to treatment is context-specific, and this context is likely to entail the types

of patients being treated and types of treatment being given. The types of determinants found to be associated with adherence suggest, however, that addressing cultural perceptions of illness and medication taking behaviour could be a pathway to improving adherence. The therapeutic alliance between treating clinician and patient is acknowledged as vital for achieving good clinical outcomes, and this would indeed appear to be the case if they influence the extent to which a patient takes their medication as prescribed. Different determinants were associated with different adherence processes. The implication of this is that depending on where the adherence problem lies for a specific condition (i.e. people are not initiating, or are initiating but not implementing correctly, or initiation is sufficient to achieve positive clinical outcomes, or what matters most is the length of time you're on treatment, regardless of how well you take it, so time to discontinuation is important) the intervention to improve this (with the ultimate goal of improving clinical outcomes), may differ.

The drawbacks of using randomisation-based efficacy estimators in RCTs with non-adherence can be largely addressed by ensuring studies are designed to appropriately answer the question of treatment efficacy from the start. Retrofitting randomisation-based efficacy estimators to studies is fraught with compromises that are likely to lead to imprecise estimates and/or the employment of questionable assumptions that are difficult to verify. Considering the use of these analytical approaches from the outset requires building non-adherence into the sample size calculation, thinking about how adherence will be defined, the type or types of measures that will be used, and ensuring that variables that are likely to be associated with adherence (in both arms, if there are two active treatments) are collected. When determining the type of measure (or measures) to monitor adherence, the findings and implications from the work I carried out during Chapter 4 will be particularly relevant. The dimensions described in Chapter 5 can be used as a framework for deciding on important variables to measure for this work.

The increase in variance that is observed when fitting randomisation-based efficacy estimators might be seen unacceptable when the key question of interest is related to the effectiveness (or population-level) effect of treatment. However, this increase in variance represents real uncertainty, and therefore where the question of treatment efficacy is of interest, this needs considering during the design phase. A simple sample size adjustment would inflate for the reciprocal of the proportion of participants estimated to adhere to treatment, but may also increase the effect size, as there would be an expectation that an efficacy effect (effect in participants who take their treatment) would be larger than an effectiveness effect (effect in participants regardless of whether or not they take treatment).

Finally, a theme running throughout my work has been that adherence is more difficult for patients on complex treatments. The natural reaction to this is to simplify treatments. For example, prescribe treatment for a shorter duration, have patients take all medication at one point during a day, or let patients have treatments they can take at home rather than having to travel to hospital for each dose. While to a large degree I agree with this idea, what is often overlooked is the consequence of non-adherence and how this can be exacerbated for patients on simple regimens (compared to them being on more complex regimens). For example, one of the studies I focused on during my thesis comprised two groups of patients: both groups were prescribed three tablets a day, but one group were told to take all three tablets at the same time and the other were told to take the tablets in three divided doses throughout the day. An individual was defined as having not adhered to their regimen on a given day if they did not take the correct number of doses. An individual in one group could be described as not adhering to their regimen even if they took two out of the three tablets, whereas if an individual in the other group did not adhere this was because they took no tablets on that day. For individuals on a treatment for a long time period, several instances of non-adherence could amount to a considerable lack of treatment in one group and could potentially be quite clinically harmful, whereas an

individual could be perceived to be as non-adherent to a more complex regimen, but at a reduced risk of harm due to them still consuming some medication. This insight leads to the implication that it is not as straightforward as simplifying treatment regimens in all circumstances. There will be instances where complex regimens remain the only safe option while non-adherence is still a possibility.

7.6 Further areas for research

There are various strands of work that can be taken forward, following the work presented in my thesis. These are summarised below:

1. Joint modelling of electronic monitoring data and pharmacology data (e.g. data from pharmacokinetic / pharmacodynamic studies): By combining these rich data sources, models could be developed that described patterns in adherence, and how they related to treatment response. These models could then be used to refine medication use (for example, they could be used to determine the number of doses a patient could safely miss, and this could be built into their prescribing strategy to minimise side effects caused by taking medication for a prolonged duration). One area in which this may be important is in the prescribing of antibiotics, as the risk that poor adherence poses is not just clinical failure, but also development of antibiotic resistant organisms, and this would be a concern at a society-level (rather than purely a problem for the individual).

2. Calibration techniques: Extensions could be made to the hierarchy calibration technique I explored during Chapter 4. This technique could be improved by accounting for the different variances associated with the different types of measures considered, or even the number of measures considered. More complex calibration techniques, for example using latent variable approaches (e.g. structural equation modelling), are also worthy of further investigation. The use of nested study designs

for informing calibrated measures may be provide an efficient way of carrying out research in this area. Another approach to calibrating could also be to use one measure that captures overall consumption (e.g. tablet counts), use another that captures patterns (e.g. prospective self-report diaries or electronic monitoring) and calibrate the patterned data with the overall consumption data.

3. Further exploration of the limits of agreement and confidence intervals around them are needed for bounded measures such as the ones encountered when measuring adherence.

4. Development of a model that incorporates all adherence processes without amalgamating them as a single summary measure: This is the natural progression from separating the elements out, and attempts I have made at combining them (for example, using hurdle models). The utility of such a model, however, will depend on the approach or approaches used to monitor adherence.

5. Further extensions to randomisation-based efficacy estimators: deficiencies in the application of these approaches on real datasets has been described throughout my thesis. Methodological work in this area that would be of immediate practical importance, focuses on the extension of these techniques to more complex outcomes (for example, recurrent events that are usually modelled using the Anderson-Gill Cox regression model), empirical guidance on situations when assuming a linear relationship between adherence and treatment effect or the exclusion restriction is most appropriate, and, following on from this, methods to account for non-linear relationships between adherence and treatment effects.

6. Finally, the development of standardised approaches when a key goal of research is to study medication adherence. The work presented throughout my thesis, but particularly in Chapters 5 and 6, highlight the need for the development of core

measure sets for research where adherence is the focus. These sets may be generic, condition-specific, perhaps only separate for short and long-term treatments, but would contain guidance on items that are vitally important to collect when medication adherence is a focus (primary or key secondary) during a study. This might lead to a requirement to collect more data in a study, something that on the surface may seem to conflict with other initiatives (such as Trial Forge (Treweek et al., 2015)), however for studies that plan to focus on medication adherence, this additional data will be important.

7.7 Concluding remarks

I have investigated various methodological challenges that are encountered when studying medication adherence in clinical research. The new evidence I have generated will advance the field, and I have indicated areas in which further developments are warranted.

It is my hope that this work and recommendations herein will be seized upon by applied medical researchers, and that moving forward medication adherence will be a key consideration during the design, conduct, analysis, and reporting of all research where the use of medication is being investigated.

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Appendices

Appendix I – Description of variables collected as part of the GRACE studies

I. GRACE WP8 CRF

CRF
COUGH / CHEST INFECTION STUDY

Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe

Registration details
Please enter on GRACE platform on day of recruitment

Patient study number ☐☐☐☐

Patient's gender ☐ Male ☐ Female

Patient's date of birth ☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)

Date of patient inclusion ☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)

Name of clinician _____

Clinician study number ☐☐☐

Patient identifiers and contact details
NOT to be entered on GRACE platform

First name _____ Telephone number _____

Last name _____ Mobile telephone number _____

Address _____ Email address _____

_____

WP8 CRF 2.1 20060822

Patient study number

A Patient eligibility? (Exclude if answer NO to any of the following questions):

1.	Aged 18 years and over?	☐ Yes ☐ No
2.	An illness where a acute or worsened cough is the main or dominant symptom, or a clinical presentation suggesting LRTI, ≤ 28 days duration?	☐ Yes ☐ No
3.	First consultation for this illness episode?	☐ Yes ☐ No
4.	Seen within normal consulting hours?	☐ Yes ☐ No
5.	First time in this study?	☐ Yes ☐ No
6.	Ability to fill out study materials?	☐ Yes ☐ No
7.	Written consent to participate?	☐ Yes ☐ No
8.	Immunocompetent?	☐ Yes ☐ No

B. Which of the following is the patient presenting now?

Symptom	Present		Severity			
			No problem	*Mild problem*	*Moderate problem*	*Severe problem*
1. Cough	☐ Yes	☐ No	☐	☐	☐	☐
2. Phlegm production	☐ Yes	☐ No	☐	☐	☐	☐
3. Shortness of breath	☐ Yes	☐ No	☐	☐	☐	☐
4. Wheeze	☐ Yes	☐ No	☐	☐	☐	☐
5. Coryza (blocked/runny nose)	☐ Yes	☐ No	☐	☐	☐	☐
6. Fever during this illness	☐ Yes	☐ No	☐	☐	☐	☐
7. Chest pain	☐ Yes	☐ No	☐	☐	☐	☐
8. Muscle aching	☐ Yes	☐ No	☐	☐	☐	☐
9. Headache	☐ Yes	☐ No	☐	☐	☐	☐
10. Disturbed sleep	☐ Yes	☐ No	☐	☐	☐	☐
11. Feeling generally unwell	☐ Yes	☐ No	☐	☐	☐	☐
12. Interference in normal activities	☐ Yes	☐ No	☐	☐	☐	☐
13. Confusion/disorientation	☐ Yes	☐ No	☐	☐	☐	☐
14. Diarrhoea	☐ Yes	☐ No	☐	☐	☐	☐

15. If producing phlegm, what colour? ☐ Clear ☐ White ☐ Yellow ☐ Green ☐ Bloodstained

C Oral temperature (compulsory)

1. Temperature
(use TempaDot disposable thermometer included in pack) ☐☐.☐ °C
2. Would you **normally** have taken the temperature for **this** patient? ☐ Yes ☐ No

D Please record the examination you did for this patient

	Performed?		Findings:		
1. Auscultation	☐ Yes	☐ No	Diminished vesicular breathing	☐ Yes	☐ No
			Wheeze	☐ Yes	☐ No
			Crackles	☐ Yes	☐ No
			Rhonchi	☐ Yes	☐ No
2. Blood Pressure	☐ Yes	☐ No	Systolic ☐☐☐	Diastolic ☐☐☐	
3. Pulse rate	☐ Yes	☐ No	☐☐ beats per minute		
4. Respiratory rate	☐ Yes	☐ No	☐☐ breaths per minute		
5. Pulse oximitery	☐ Yes	☐ No	☐☐ % saturation		
6. Peak flow	☐ Yes	☐ No	☐☐ litres per minute		

E What is your working diagnosis?

1. Please state diagnosis _____

F Perception of treating clinician (tick the box that best describes your response to each statement)

	Strongly agree:	*Agree*	*Neither agree nor disagree*	*Disagree*	*Strongly disagree*
1. "This patient wanted me to prescribe antibiotics for them"	☐	☐	☐	☐	☐
2. "This patient was satisfied with the consultation"	☐	☐	☐	☐	☐
3. "Antibiotics will help this patient get better quicker"	☐	☐	☐	☐	☐

G Management

1. Referral

- ☐ No
- ☐ Same day emergency assessment at hospital
- ☐ Routine specialist out-patient hospital appointment
- ☐ Other: please state _____

2. **Antibiotic** treatment ☐ Yes ☐ No

If **Yes, state details**

Generic name	Dose per unit	Times per day	Duration: days
_____	_____	☐☐	☐☐

If antibiotics prescribed, did you advise **delay** ☐ Yes ☐ No

If yes, number of days: ☐☐

3. Did you **prescribe** any **other treatment** for this cough? ☐ Yes ☐ No

If Yes, state **name** of additional medication below	Dose per unit	Times per day	Duration: days
1. _____	_____	☐☐	☐☐
2. _____	_____	☐☐	☐☐
3. _____	_____	☐☐	☐☐

4. Did you make any **follow-up** arrangements?

- ☐ No
- ☐ See anytime if worse
- ☐ See in one week
- ☐ See in two weeks
- ☐ Other: state _____

5. Did you give any **advice** about **over the counter** medication?

- ☐ No
- ☐ Paracetamol
- ☐ NSAIDS
- ☐ Cough mixture
- ☐ Other: state _____

6. Did you give any advice about staying off work?
   - ☐ No
   - ☐ ≤ 7 days
   - ☐ ≤ 14 days
   - ☐ ≥ 15 days
   - ☐ Other: state _____

7. Did you issue a sick certificate?
   - ☐ No
   - ☐ ≤ 7 days
   - ☐ ≤ 14 days
   - ☐ ≥ 15 days

   Reason/diagnosis _____

8. Where was the patient seen by treating clinician?
   - ☐ Surgery/office
   - ☐ Patient's private home
   - ☐ Nursing home or residential institution

H. Comorbidity: tick if present

1. Chronic Obstructive Pulmonary Disease (COPD)	☐ Yes	☐ No
2. Asthma	☐ Yes	☐ No
3. Other lung disease	☐ Yes	☐ No
4. Heart failure	☐ Yes	☐ No
5. Ischemic heart disease	☐ Yes	☐ No
6. Other heart disease (e.g. valvular lesions, cardiomypoathy etc)	☐ Yes	☐ No
7. Diabetes	☐ Yes	☐ No

8. Please give details of any other relevant medical history:

_____

I. Is the patient on any of the following regular medications?

1. Inhaled bronchodilators	☐ Yes	☐ No
2. Inhaled steroids	☐ Yes	☐ No
3. Oral steriods	☐ Yes	☐ No
4. Oral agents for diabetes	☐ Yes	☐ No
5. Insulin	☐ Yes	☐ No
6. Antihypertensives	☐ Yes	☐ No
7. Non steroidal anti inflammatories (oral)	☐ Yes	☐ No

J. Investigations ordered for this illness

1. Full Blood Count (FBC)	☐ Yes	☐ No
2. C-reactive protein (CRP)	☐ Yes	☐ No
3. Erythrocyte sedimentation rate (ESR)	☐ Yes	☐ No
4. Procalcitonin	☐ Yes	☐ No
5. Urea or Createnine	☐ Yes	☐ No
6. Electrolytes	☐ Yes	☐ No
7. Chest x-ray	☐ Yes	☐ No
8. Blood for serology	☐ Yes	☐ No
9. Sputum for culture	☐ Yes	☐ No
10. Nose or throat swabs	☐ Yes	☐ No
11. Spirometry	☐ Yes	☐ No
12. Other: please state	_____	

II. GRACE WP8 Diary

DIARY
COUGH / CHEST INFECTION STUDY

Genomics to combat Resistance against
Antibiotics in Community-acquired LRTI in Europe

Patient study number	☐☐☐☐☐☐
Date of patient consultation	☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)
Clinician study number	☐☐☐

A. General questions part 1

Please tell us about yourself

1. What is your date of birth? *Day* ☐☐ - *Month* ☐☐ - *Year* ☐☐☐☐

2. What is your gender:
☐ Male
☐ Female

3. How many people live in your household, including you? ☐☐

4. Are there dependant children living in your household?
☐ Yes
☐ No

If yes, how many dependant children live in you household aged:
3 years or less ☐☐
4 - 18 years ☐☐

5. What is your current occupation? (please tick one box):
☐ High level executive, major professional
☐ Administrative personnel, minor Professional, owner of small business
☐ Sales, technician, farmer
☐ Skilled manual employee
☐ Unskilled employee
☐ Student
☐ Homemaker
☐ Unemployed
☐ Disabled
☐ Retired

6. If you work outside the home, do you work:
☐ Full time
☐ Part time

7. How many years were you in full time school from age 6 years? ☐☐

8. What is your highest educational level? (please tick one box)
☐ University (completed)
☐ University (uncompleted)
☐ Professional training (completed)
☐ Professional training (uncompleted)
☐ High school (completed)
☐ High school (uncompleted)
☐ Never attended high school

9. Have you received any further training since leaving full time education:
☐ Yes
☐ No

If yes, please specify: _____

10. Do you have any long-term illness, health problem, or handicap which limits your daily activities or the work you can do? (Please include any problems that are due to old age) ☐ Yes ☐ No

If yes, please specify: _____

11. Have you ever had hay fever or eczema? ☐ Yes ☐ No

12. Has any person in your family (parent, grandparents, sisters, brothers or your children) had asthma? ☐ Yes ☐ No

13. How many times have you had a cough lasting more than a week in last 12 months? ☐☐

14. Other than with the cough / chest infection you have at the moment, have you in the last 12 months

a. Had wheezing or whistling in your chest? ☐ Yes ☐ No

b. Woken up with a feeling of tightness in your chest? ☐ Yes ☐ No

c. Woken by an attack of coughing? ☐ Yes ☐ No

15. Do you smoke? ☐ Yes ☐ No ☐ Occasionally

a. **If you smoke**, what do you smoke? ☐ Cigarettes ☐ Rolled tobacco ☐ Pipe ☐ Sigares / cigarillos

How many years have you smoked **in total**? ☐☐ years

If you smoke daily, how many do you smoke, on average, per day? ☐☐

If you smoke occasionally, how many do you smoke, on average, per week? ☐☐

b. **If No (you don't smoke now)**, have you ever smoked? ☐ Yes ☐ No

If Yes, what did you use to smoke? ☐ Cigarettes ☐ Rolled tobacco ☐ Pipe ☐ Sigares / cigarillos

For how many years in total did you smoke? ☐☐ years

How many did you use to smoke per day on average? ☐☐ per day

When did you give up? ☐☐ years ago, or ☐☐ months ago, or ☐☐ days ago

Questions about your cough

16. How many days were you unwell before you saw your GP or nurse for *this* cough? ☐☐ days

17. Did you treat this cough with any over the counter medications?
☐ Yes
☐ No

If Yes, please give the details of what you took:

Name of over the counter medicine	Number of days you took the medicine

18. Have you taken any other remedies for this cough?
☐ Yes
☐ No

If yes, please specify: _____

*Now we ask that you think back to the moment **before** you saw your GP or nurse.*

19. Were you *expecting* your GP or nurse to prescribe antibiotics?
☐ Yes
☐ No

20. Were you *hoping* that your GP or nurse would prescribe antibiotics?
☐ Yes
☐ No

21. Did you *ask* your GP or nurse for antibiotics?
☐ Yes
☐ No

22. How satisfied are you with your visit to your GP or nurse today? (please tick one box)
☐ Very satisfied
☐ Satisfied
☐ Neither satisfied nor dissatisfied
☐ Dissatisfied
☐ Very dissatisfied

23. What was the *main* reason for you to visit your GP or nurse today? Please tick *one* box only
☐ You worried about a more serious condition
☐ A friend or family member made you go
☐ To get antibiotic treatment for the cough
☐ To get other treatment for the cough
☐ To get a sick note / certificate

24. Did problems with any of the following *usual daily activities* cause you to visit your GP/nurse today? Please tick the most important (one) box only
☐ Problems with work/college because of this illness
☐ Problems with doing usual daily activities, because of this illness
☐ Problems with relaxation or sport because of this illness
☐ Problems with sleeping because of this illness
☐ No problem with daily activities

By ticking one box for each of the items below, please indicate which statement best describes your own health state today

25. Mobility

- ☐ I have no problems in walking about
- ☐ I have some problems in walking about
- ☐ I am confined to bed

26. 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

27. 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

28. Pain or discomfort

- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

29. Anxiety or depression

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

SYMPTOMS FOR EACH DAY
Please start today - the day you have seen your GP or nurse. This is day 1.

For each day, please give every symptom a score from 0 to 6 until you score 0 for all symptoms, or until it is day 28.

Then answer the General Questions Part 2, and post the diary back to us. If you continue to have symptoms, please continue for 28 days.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

EXAMPLE: For a cough that is 'as bad as it' could be for the first 2 days then gradually starts to improve but is still present on day 7, and phlegm which is 'very bad' on day 1 but improves quickly and is completely gone by day 5, and no other symptoms.

Symptoms	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Cough	6	6	5	4	4	4	3
Phlegm	5	3	3	1	0	0	0
Shortness of breath	0	0	0	0	0	0	0
Wheeze	0	0	0	0	0	0	0
Blocked/runny nose	0	0	0	0	0	0	0
Chest pain	0	0	0	0	0	0	0
Fever (high temperature)	0	0	0	0	0	0	0
Muscle aching	0	0	0	0	0	0	0
Headache	0	0	0	0	0	0	0
Disturbed sleep	0	0	0	0	0	0	0
Feeling generally unwell	0	0	0	0	0	0	0
Interference with normal activities/ work	0	0	0	0	0	0	0
Interference with social activities	0	0	0	0	0	0	0

WEEK 1

For each day, please give every symptom a score from 0 to 6. If you score 0 for all symptoms, complete the weekly questions for week 1 and go to the General Questions Part 2.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Symptoms	Day 1*	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7**
Cough							
Phlegm							
Shortness of breath							
Wheeze							
Blocked/runny nose							
Chest pain							
Fever (high temperature)							
Muscle aching							
Headache							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities/ work							
Interference with social activities							

* Please note, day 1 is the day that you saw your GP or nurse, not the first day of this illness.
** Please answer the weekly questions for week 1 and continue until you score '0' for all symptoms, or it is day 28

Weekly questions, week 1

1. How many days in the past week have you been unable to work or attend college? ☐☐ days

2. Have you taken medicine for your cough during the past week? ☐ Yes ☐ No

If yes, please give the details and tick each study day you took each medicine

Name of medicine	Number of doses per day	Tick if the medicine was prescribed for you	Day						
			1	2	3	4	5	6	7
		☐							
		☐							
		☐							

By ticking one box for each of the items below, please indicate which statement best describes your own health state today

3. **Mobility**
   - ☐ I have no problems in walking about
   - ☐ I have some problems in walking about
   - ☐ I am confined to bed

4. **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

5. **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

6. **Pain or discomfort**
   - ☐ I have no pain or discomfort
   - ☐ I have moderate pain or discomfort
   - ☐ I have extreme pain or discomfort

7. **Anxiety or depression**
   - ☐ I am not anxious or depressed
   - ☐ I am moderately anxious or depressed
   - ☐ I am extremely anxious or depressed

WEEK 2

For each day, please give every symptom a score from 0 to 6. If you score 0 for all symptoms, complete the weekly questions for week 2 and go to the General Questions Part 2.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Symptoms	Day 8*	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14**
Cough							
Phlegm							
Shortness of breath							
Wheeze							
Blocked/runny nose							
Chest pain							
Fever (high temperature)							
Muscle aching							
Headache							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities/ work							
Interference with social activities							

* Please note, day 8 is one week after you saw your GP or nurse.
** Please answer the weekly questions for week 2 and continue until you score '0' for all symptoms, or it is day 28

Weekly questions, week 2

1. How many days in the past week have you been unable to work or attend college? ☐☐ days

2. Have you taken medicine for your cough during the past week? ☐ Yes ☐ No

If yes, please give the details and tick each study day you took each medicine

Name of medicine	Number of doses per day	Tick if the medicine was prescribed for you	Day						
			8	9	10	11	12	13	14
		☐							
		☐							
		☐							

By ticking one box for each of the items below, please indicate which statement best describes your own health state today

3. **Mobility**
   - ☐ I have no problems in walking about
   - ☐ I have some problems in walking about
   - ☐ I am confined to bed

4. **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

5. **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

6. **Pain or discomfort**
   - ☐ I have no pain or discomfort
   - ☐ I have moderate pain or discomfort
   - ☐ I have extreme pain or discomfort

7. **Anxiety or depression**
   - ☐ I am not anxious or depressed
   - ☐ I am moderately anxious or depressed
   - ☐ I am extremely anxious or depressed

WEEK 3

For each day, please give every symptom a score from 0 to 6. If you score 0 for all symptoms, complete the weekly questions for week 3 and go to the General Questions Part 2.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Symptoms	Day 15*	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21**
Cough							
Phlegm							
Shortness of breath							
Wheeze							
Blocked/runny nose							
Chest pain							
Fever (high temperature)							
Muscle aching							
Headache							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities/ work							
Interference with social activities							

* Please note, day 15 is two weeks after you saw your GP or nurse.
** Please answer the weekly questions for week 3 and continue until you score '0' for all symptoms, or it is day 28

Weekly questions, week 3

1. How many days in the past week have you been unable to work or attend college? ☐☐ days

2. Have you taken medicine for your cough during the past week? ☐ Yes ☐ No

If yes, please give the details and tick each study day you took each medicine

Name of medicine	Number of doses per day	Tick if the medicine was prescribed for you	Day						
			15	16	17	18	19	20	21
		☐							
		☐							
		☐							

By ticking one box for each of the items below, please indicate which statement best describes your own health state today

3. **Mobility**
   - ☐ I have no problems in walking about
   - ☐ I have some problems in walking about
   - ☐ I am confined to bed

4. **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

5. **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

6. **Pain or discomfort**
   - ☐ I have no pain or discomfort
   - ☐ I have moderate pain or discomfort
   - ☐ I have extreme pain or discomfort

7. **Anxiety or depression**
   - ☐ I am not anxious or depressed
   - ☐ I am moderately anxious or depressed
   - ☐ I am extremely anxious or depressed

WEEK 4

For each day, please give every symptom a score from 0 to 6. If you score 0 for all symptoms, complete the weekly questions for week 4 and go to the General Questions Part 2.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Symptoms	Day 22*	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28**
Cough							
Phlegm							
Shortness of breath							
Wheeze							
Blocked/runny nose							
Chest pain							
Fever (high temperature)							
Muscle aching							
Headache							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities/ work							
Interference with social activities							

* Please note, day 22 is three weeks after you saw your GP or nurse.
** Please answer the weekly questions for week 4.

Weekly questions, week 4

1. How many days in the past week have you been unable to work or attend college? ☐☐ days

2. Have you taken medicine for your cough during the past week? ☐ Yes ☐ No

If yes, please give the details and tick each study day you took each medicine

Name of medicine	Number of doses per day	Tick if the medicine was prescribed for you	Day						
			22	23	24	25	26	27	28
		☐							
		☐							
		☐							

By ticking one box for each of the items below, please indicate which statement best describes your own health state today

3. **Mobility**
   - ☐ I have no problems in walking about
   - ☐ I have some problems in walking about
   - ☐ I am confined to bed

4. **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

5. **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

6. **Pain or discomfort**
   - ☐ I have no pain or discomfort
   - ☐ I have moderate pain or discomfort
   - ☐ I have extreme pain or discomfort

7. **Anxiety or depression**
   - ☐ I am not anxious or depressed
   - ☐ I am moderately anxious or depressed
   - ☐ I am extremely anxious or depressed

B. General question part 2

Please answer these question if you have scored '0' for all daily symptoms, or it is day 28

1. Overall, on what day did you feel recovered?
   The day you started this dairy was day 1.
   Please state the **number of the day you felt recovered:**
   Day number ☐☐

2. Since your visit to your GP on day 1,
   were you admitted to hospital for this illness?
   ☐ Yes
   ☐ No

   If yes, how many nights did you spend in the hospital? ☐☐ nights

3. Since your visit to your GP/nurse on day 1, have you **visited** any of the following about this illness?

a. GP in usual working hours	☐ Yes ☐ No	If yes, how many times?	☐☐
b. Nurse in usual working hours	☐ Yes ☐ No	If yes, how many times?	☐☐
c. Hospital emergency department	☐ Yes ☐ No	If yes, how many times?	☐☐
d. Out of hours GP service	☐ Yes ☐ No	If yes, how many times?	☐☐
e. Pharmacist	☐ Yes ☐ No	If yes, how many times?	☐☐
f. Walk in centre	☐ Yes ☐ No	If yes, how many times?	☐☐
g. Specialist	☐ Yes ☐ No	If yes, how many times?	☐☐
h. Other	☐ Yes ☐ No	If yes, how many times?	☐☐
		If yes, please specify	_____

4. Since your visit to your GP/nurse on day 1, have you **contacted** *(but not visited)* any of the following about this illness? (please tick box and specify how many times you contacted this service)

a. GP in usual working hours	☐ Yes ☐ No	If yes, how many times?	☐☐
b. Nurse in usual working hours	☐ Yes ☐ No	If yes, how many times?	☐☐
c. GP out of hours service	☐ Yes ☐ No	If yes, how many times?	☐☐
d. NHS Direct	☐ Yes ☐ No	If yes, how many times?	☐☐
e. Pharmacist	☐ Yes ☐ No	If yes, how many times?	☐☐
f. Walk in centre	☐ Yes ☐ No	If yes, how many times?	☐☐
g. Other	☐ Yes ☐ No	If yes, how many times? If yes, please specify _____	☐☐

5. Since your visit to your GP/nurse on day 1, have you had a chest X-Ray? ☐ Yes ☐ No

6. For each of the statements below, please tick the box that best describes your view

	Strongly agree:	*Agree*	*Neither agree nor disagree*	*Disagree*	*Strongly disagree*
a. "I believe that most coughs lasting more than just a few days should be treated with antibiotics"	☐	☐	☐	☐	☐
b. "Antibiotics can harm people who take them"	☐	☐	☐	☐	☐
c. "Using antibiotics too often makes it harder to treat infections"	☐	☐	☐	☐	☐

III. GRACE WP9 and WP10a CRF

CRF
GRACE diagnosis and treatment study 1

Patient study number

A. Patient eligibility? (Exclude if answer NO to any of the following questions):

1. Aged 18 years to 60 years or 60 years and over? ☐ Yes ☐ No
2. An illness where an acute or worsened cough is the main or dominant symptom, or a clinical presentation suggesting LRTI, ≤ 28 days duration? ☐ Yes ☐ No
3. First consultation for this illness episode? ☐ Yes ☐ No
4. Not been included earlier in the current GRACE trial, either as a case or a control patient? ☐ Yes ☐ No
5. Ability to fill out study materials? ☐ Yes ☐ No
6. Written consent to participate? ☐ Yes ☐ No
7. Immunocompetent? ☐ Yes ☐ No
8. Not been on antibiotic treatment in previous month? ☐ Yes ☐ No
9. Not Pregnant? ☐ Yes ☐ No

Exclude for WP10 if answer YES to any of the following questions:

10. Allergic to penicillin or have a contra-indication for amoxicillin because of a major interaction with other medication ☐ Yes ☐ No
11. History/physical examination suggestive of community acquired pneumonia (CAP)? ☐ Yes ☐ No

B. PLEASE ASK PATIENT IF EACH OF THE FOLLOWING SYMPTOMS ARE PRESENT AND THEIR RATING OF THE SEVERITY OF THE PROBLEM

Symptom	Present		Severity			
			No problem	*Mild problem*	*Moderate problem*	*Severe problem*
1. Cough	☐ Yes	☐ No	☐	☐	☐	☐
2. Phlegm production	☐ Yes	☐ No	☐	☐	☐	☐
3. Shortness of breath	☐ Yes	☐ No	☐	☐	☐	☐
4. Wheeze	☐ Yes	☐ No	☐	☐	☐	☐
5. Coryza (blocked/runny nose)	☐ Yes	☐ No	☐	☐	☐	☐
6. Fever	☐ Yes	☐ No	☐	☐	☐	☐
7. Chest pain	☐ Yes	☐ No	☐	☐	☐	☐
8. Muscle aching	☐ Yes	☐ No	☐	☐	☐	☐
9. Headache	☐ Yes	☐ No	☐	☐	☐	☐
10. Disturbed sleep	☐ Yes	☐ No	☐	☐	☐	☐
11. Feeling generally unwell	☐ Yes	☐ No	☐	☐	☐	☐
12. Interference in normal activities	☐ Yes	☐ No	☐	☐	☐	☐
13. Confusion/disorientation	☐ Yes	☐ No	☐	☐	☐	☐
14. Diarrhoea	☐ Yes	☐ No	☐	☐	☐	☐

15. If producing phlegm, what colour? ☐ Clear ☐ White ☐ Yellow ☐ Green ☐ Bloodstained

C. **Prior duration of symptoms:** Duration of prior illness ☐☐ days Duration of prior cough ☐☐ days

D **Please record your findings regarding the following examinations (all compulsory)**

		Findings:
1. Normal consciousness?		☐ Yes ☐ No
2. General toxicity?		☐ Yes ☐ No
3. Auscultation	Diminished vesicular breathing	☐ Yes ☐ No
	Wheeze	☐ Yes ☐ No
	Crackles	☐ Yes ☐ No
	Rhonchi	☐ Yes ☐ No
4. Pulse rate		☐☐☐ beats per minute
5. Respiratory rate		☐☐ breaths per minute
6. Prolonged expiration?		☐ Yes ☐ No
7. Blood Pressure	Systolic	☐☐☐ Diastolic ☐☐☐
8. Oral temperature (use TempaDot disposable thermometer included in pack)		☐☐.☐ °C

9. **What is your working diagnosis?**

Please state diagnosis _____

E **Management**

1. Did you **prescribe any medication (apart from the study medication)** for this illness ☐ Yes ☐ No

If Yes, state **name of** (additional) medication below	Dose per unit	Times per day	Duration: days
1. _____	_____	☐☐	☐☐
2. _____	_____	☐☐	☐☐
3. _____	_____	☐☐	☐☐

2. Where was the patient seen by treating clinician?
   - ☐ Surgery/office
   - ☐ Patient's private home
   - ☐ Nursing home or residential institution

F. Other history: Tick if present

1. Chronic Obstructive Pulmonary Disease (COPD)	☐ Yes	☐ No
2. Asthma	☐ Yes	☐ No
3. Other lung disease (e.g. fibrosis, bronchiectatis etc)	☐ Yes	☐ No
4. Heart failure	☐ Yes	☐ No
5. Ischemic heart disease	☐ Yes	☐ No
6. Other heart disease (e.g. valvular lesions, cardiomyopathy etc)	☐ Yes	☐ No
7. Diabetes	☐ Yes	☐ No
8. Previous hospitalisation for respiratory illness	☐ Yes	☐ No
9. Antibiotic treatment in previous six months	☐ Yes	☐ No
10. Allergic disease (hay fever, urticaria, or history of allergic reaction)	☐ Yes	☐ No

11. Please give details of any other relevant medical history:

_____

G. Ethnic background ☐ Caucasian ☐ Asian ☐ African ☐ Other _____

H1. Smoking ☐ Never ☐ Past ☐ Current

If past or current: **H2.** How many per day normally? ☐☐

H3. How many years? ☐☐

I. Is the patient on any of the following regular medications?

1. Inhaled bronchodilators	☐ Yes	☐ No
2. Inhaled steroids	☐ Yes	☐ No
3. Oral steroids	☐ Yes	☐ No
4. Oral agents for diabetes	☐ Yes	☐ No
5. Insulin	☐ Yes	☐ No
6. Antihypertensives/diuretics	☐ Yes	☐ No
7. Non steroidal anti inflammatories (oral)	☐ Yes	☐ No
8. Benzodiazepines/antidepressants	☐ Yes	☐ No
9. Did the patient get an influenza vaccination this fall or winter?	☐ Yes	☐ No

IV: GRACE WP9 and WP10a Diary

DIARY
Diagnosis and treatment study

Genomics to combat Resistance against
Antibiotics in Community-acquired LRTI in Europe

Patient study number	
Date of patient consultation	☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)
Clinician study number	☐☐☐

A. General questions part 1

Please tell us about yourself

1. What is your date of birth? *Day* ☐☐ - *Month* ☐☐ - *Year* ☐☐☐☐

2. What is your gender:
   ☐ Male
   ☐ Female

3. Do you have any long-term illness, health problem, or handicap which limits your daily activities or the work you can do?
   (Please include any problems that are due to old age)
   ☐ Yes
   ☐ No
   If yes, please specify: _____

4. Have you ever had hay fever or eczema?
   ☐ Yes
   ☐ No

5. Has any person in your family (parent, grandparents, sisters, brothers or your children) had asthma?
   ☐ Yes
   ☐ No

6. How many times have you had a cough lasting more than a week in last 12 months? ☐☐

7. Other than with the cough / chest infection you have at the moment, have you in the last 12 months
   a. Had wheezing or whistling in your chest? ☐ Yes ☐ No
   b. Woken up with a feeling of tightness in your chest? ☐ Yes ☐ No
   c. Been woken by an attack of coughing? ☐ Yes ☐ No

   Please tick Yes or No for all 3 questions above.

8. **Do you smoke?**
   ☐ Yes
   ☐ No
   ☐ Occasionally

   a. If **Yes** or **Occasionally:**

   How many years have you smoked for **in total**? ☐☐ years

   If you smoke daily, how many do you smoke, on average, per day? ☐☐

   If you smoke occasionally, how many do you smoke, on average, per week? ☐☐

b. If **No** (you don't smoke now), have you ever smoked? ☐ Yes ☐ No

If **Yes**

For how many years in total did you smoke? ☐☐ years

How many did you use to smoke per day on average? ☐☐ per day

When did you give up smoking? ☐☐ years ago, or ☐☐ months ago, or ☐☐ days ago

Questions about your cough / chest infection

9. How many days were you unwell before you saw your GP or nurse for *this* illness? ☐☐ days

10. Did you treat this cough with any over the counter medications before going to your GP? ☐ Yes ☐ No

If **Yes**, please give the details of what you took:

Name of over the counter medicine	Number of days you took the medicine

11. Have you taken any other remedies for this illness before going to your GP? ☐ Yes ☐ No

If yes, please specify remedy: _____

By ticking one box for each of the items below, please indicate which statement best describes your own health state today

12. Mobility

- ☐ I have no problems in walking about
- ☐ I have some problems in walking about
- ☐ I am confined to bed

13. 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

14. 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

15. Pain or discomfort

- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

16. Anxiety or depression

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

SYMPTOMS FOR EACH DAY
Please start today - the day you have seen your GP or nurse. This is day 1.

For each day, please give every symptom a score from 0 to 6 until you score 0 for all symptoms, or until it is day 28.

Then answer the General Questions Part 2, and post the diary back to us. If you continue to have symptoms, please continue for 28 days.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

EXAMPLE: For a cough that is 'as bad as it could be' for the first 2 days then gradually starts to improve but is still present on day 7, and phlegm which is 'very bad' on day 1 but improves quickly and is completely gone by day 5, and no other symptoms.

Symptoms	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Cough	6	6	5	4	4	4	3
Phlegm	5	3	3	1	0	0	0
Shortness of breath	0	0	0	0	0	0	0
Wheeze	0	0	0	0	0	0	0
Blocked / runny nose	0	0	0	0	0	0	0
Chest pain	0	0	0	0	0	0	0
Fever (high temperature)	0	0	0	0	0	0	0
Muscle aching	0	0	0	0	0	0	0
Headache	0	0	0	0	0	0	0
Disturbed sleep	0	0	0	0	0	0	0
Feeling generally unwell	0	0	0	0	0	0	0
Interference with normal activities / work	0	0	0	0	0	0	0
Taken your study medication?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

WEEK 1

For each day, please give every symptom a score from 0 to 6. If you score 0 for all symptoms, complete the weekly questions for week 1 and go to the General Questions Part 2.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Symptoms	Day 1*	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7**
Cough							
Phlegm							
Shortness of breath							
Wheeze							
Blocked/runny nose							
Chest pain							
Fever (high temperature)							
Muscle aching							
Headache							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities/ work							
Interference with social activities							
Taken your study medication?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

* Please note, day 1 is the day that you saw your GP or nurse, not the first day of this illness.
** Please answer the weekly questions for week 1 and continue until you score '0' for all symptoms, or it is day 28

ATTENTION: Always complete the **Weekly questions** on the next pages. If all symptoms are scored '0', you can finish your diary by filling out the **General Questions Part 2** on page 17.

Weekly questions, week 1

1. How many days in the past week have you been unable to work or attend college?
(please answer 'not applicable' if you do not work or attend college: if you work or attend college but have not missed any days, please put zero)

☐☐ days

☐ Not applicable

2. Have you taken medicine, *other then the study medication*, for your cough / chest infection during the past week? (including increased dosage of your inhalation medication)

☐ Yes

☐ No

If yes, please give the details and tick each study day you took each medicine

Name of medicine	Number of doses per day	Tick if the medicine was prescribed for you	Day						
			1	2	3	4	5	6	7
		☐							
		☐							
		☐							
		☐							
		☐							

By ticking <u>one</u> box for each of the items below, please indicate which statement best describes your own health state <u>today</u>

3. **Mobility**
   - ☐ I have no problems in walking about
   - ☐ I have some problems in walking about
   - ☐ I am confined to bed

4. **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

5. **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

6. **Pain or discomfort**
   - ☐ I have no pain or discomfort
   - ☐ I have moderate pain or discomfort
   - ☐ I have extreme pain or discomfort

7. **Anxiety or depression**
   - ☐ I am not anxious or depressed
   - ☐ I am moderately anxious or depressed
   - ☐ I am extremely anxious or depressed

Potential side effects of medication

8. Did you have diarrhoea in the last week?

☐ Yes **If yes, please specify** _____
☐ No

9. Did you have nausea in the last week?

☐ Yes **If yes, please specify** _____
☐ No

10. Did you have a skin rash in the last week?

☐ Yes **If yes, please specify** _____
☐ No

Study medication

11. Did you take your study medication according to the instructions?

☐ Yes **If no, please explain** _____
☐ No

ATTENTION: If all symptoms are scored '0' (see page 7), you can finish your diary by filling out the **General Questions Part 2** on page 17. If not, please continue on next page.

WEEK 2

For each day, please give every symptom a score from 0 to 6. If you score 0 for all symptoms, complete the weekly questions for week 2 and go to the General Questions Part 2.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Symptoms	Day 8*	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14**
Cough							
Phlegm							
Shortness of breath							
Wheeze							
Blocked/runny nose							
Chest pain							
Fever (high temperature)							
Muscle aching							
Headache							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities/ work							
Interference with social activities							
Taken your study medication?	☐ Yes ☐ No	/	/	/	/	/	/

* Please note, day 8 is one week after you saw your GP or nurse.
** Please answer the weekly questions for week 2 and continue until you score '0' for all symptoms, or it is day 28

ATTENTION: Always complete the **Weekly questions** on the next pages. If all symptoms are scored '0', you can finish your diary by filling out the **General Questions Part 2** on page 17.

Weekly questions, week 2

1. How many days in the past week have you been unable to work or attend college? *(please answer 'not applicable' if you do not work or attend college: if you work or attend college but have not missed any days, please put zero)*

☐☐ days

☐ Not applicable

2. Have you taken medicine, *other then the study medication*, for your cough / chest infection during the past week? (including increased dosage of your inhalation medication)

☐ Yes

☐ No

If yes, please give the details and tick each study day you took each medicine

Name of medicine	Number of doses per day	Tick if the medicine was prescribed for you	Day						
			8	9	10	11	12	13	14
		☐							
		☐							
		☐							
		☐							
		☐							

By ticking <u>one</u> box for each of the items below, please indicate which statement best describes your own health state <u>today</u>

3. **Mobility**
   - ☐ I have no problems in walking about
   - ☐ I have some problems in walking about
   - ☐ I am confined to bed

4. **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

5. **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

6. **Pain or discomfort**
   - ☐ I have no pain or discomfort
   - ☐ I have moderate pain or discomfort
   - ☐ I have extreme pain or discomfort

7. **Anxiety or depression**
   - ☐ I am not anxious or depressed
   - ☐ I am moderately anxious or depressed
   - ☐ I am extremely anxious or depressed

Potential side effects of medication

8. Did you have diarrhoea in the last week?

☐ Yes **If yes**, please specify _____
☐ No

9. Did you have nausea in the last week?

☐ Yes **If yes**, please specify _____
☐ No

10. Did you have a skin rash in the last week?

☐ Yes **If yes**, please specify _____
☐ No

Study medication

11. Did you take your study medication according to the instructions?

☐ Yes **If no**, please explain _____
☐ No

ATTENTION: If all symptoms are scored '0' (see page 10), you can finish your diary by filling out the **General Questions Part 2** on page 17. If not, please continue on next page.

WEEK 3

For each day, please give every symptom a score from 0 to 6. If you score 0 for all symptoms, complete the weekly questions for week 3 and go to the General Questions Part 2.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Symptoms	Day 15*	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21**
Cough							
Phlegm							
Shortness of breath							
Wheeze							
Blocked/runny nose							
Chest pain							
Fever (high temperature)							
Muscle aching							
Headache							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities/ work							
Interference with social activities							

* Please note, day 15 is two weeks after you saw your GP or nurse.
** Please answer the weekly questions for week 3 and continue until you score '0' for all symptoms, or it is day 28

ATTENTION: Always complete the **Weekly questions** on the next pages. If all symptoms are scored '0', you can finish your diary by filling out the **General Questions Part 2** on page 17.

Weekly questions, week 3

1. How many days in the past week have you been unable to work or attend college? *(please answer 'not applicable' if you do not work or attend college: if you work or attend college but have not missed any days, please put zero)*

☐☐ days

☐ Not applicable

2. Have you taken medicine for your cough / chest infection during the past week? (including increased dosage of your inhalation medication)

☐ Yes
☐ No

If yes, please give the details and tick each study day you took each medicine

Name of medicine	Number of doses per day	Tick if the medicine was prescribed for you	Day						
			15	16	17	18	19	20	21
		☐							
		☐							
		☐							
		☐							
		☐							

By ticking <u>one</u> box for each of the items below, please indicate which statement best describes your own health state <u>today</u>

3. **Mobility**
   - ☐ I have no problems in walking about
   - ☐ I have some problems in walking about
   - ☐ I am confined to bed

4. **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

5. **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

6. **Pain or discomfort**
   - ☐ I have no pain or discomfort
   - ☐ I have moderate pain or discomfort
   - ☐ I have extreme pain or discomfort

7. **Anxiety or depression**
   - ☐ I am not anxious or depressed
   - ☐ I am moderately anxious or depressed
   - ☐ I am extremely anxious or depressed

ATTENTION: If all symptoms are scored '0' (see page 13), you can finish your diary by filling out the **General Questions Part 2** on page 17. If not, please continue on next page.

WEEK 4

For each day, please give every symptom a score from 0 to 6. If you score 0 for all symptoms, complete the weekly questions for week 4 and go to the General Questions Part 2.

SCORE	Severity of symptom
0	Normal/not affected
1	Very little problem
2	Slight problem
3	Moderately bad
4	Bad
5	Very bad
6	As bad as it could be

Symptoms	Day 22*	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28**
Cough							
Phlegm							
Shortness of breath							
Wheeze							
Blocked/runny nose							
Chest pain							
Fever (high temperature)							
Muscle aching							
Headache							
Disturbed sleep							
Feeling generally unwell							
Interference with normal activities/ work							
Interference with social activities							

* Please note, day 22 is three weeks after you saw your GP or nurse.

ATTENTION: Always complete the **Weekly questions** on the next pages. If all symptoms are scored '0', you can finish your diary by filling out the **General Questions Part 2** on page 17.

Weekly questions, week 4

1. How many days in the past week have you been unable to work or attend college? *(please answer 'not applicable' if you do not work or attend college: if you work or attend college but have not missed any days, please put zero)*

☐☐ days

☐ Not applicable

2. Have you taken medicine for your cough / chest infection during the past week? (including increased dosage of your inhalation medication)

☐ Yes
☐ No

If yes, please give the details and tick each study day you took each medicine

Name of medicine	Number of doses per day	Tick if the medicine was prescribed for you	Day						
			22	23	24	25	26	27	28
		☐							
		☐							
		☐							
		☐							
		☐							

By ticking one box for each of the items below, please indicate which statement best describes your own health state today

3. **Mobility**
   - ☐ I have no problems in walking about
   - ☐ I have some problems in walking about
   - ☐ I am confined to bed

4. **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

5. **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

6. **Pain or discomfort**
   - ☐ I have no pain or discomfort
   - ☐ I have moderate pain or discomfort
   - ☐ I have extreme pain or discomfort

7. **Anxiety or depression**
   - ☐ I am not anxious or depressed
   - ☐ I am moderately anxious or depressed
   - ☐ I am extremely anxious or depressed

B. General question part 2

Please answer these questions if you have scored '0' for all daily symptoms, or it is day 28

1. Overall, on what day did you feel recovered? The day you started this diary was day 1. Please state the **number of the day that you felt recovered** (If you are not yet recovered, please answer not applicable).

Day number ☐☐

☐ Not applicable

2. Since your visit to your GP/nurse on day 1, have you been admitted to hospital for this illness? ☐ Yes ☐ No

If yes,

Date of admission: ☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)

Date of of discharge: ☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)

3. Since your visit to your GP/nurse on day 1, have you **visited** any of the following about this illness?

a. GP in usual working hours

☐ Yes ☐ No

If yes, how many times? ☐☐

If yes, date(s) of your visit(s)

☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)

☐☐ - ☐☐ - ☐☐☐☐

b. Nurse in usual working hours

☐ Yes ☐ No

If yes, how many times? ☐☐

If yes, date(s) of your visit(s)

☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)

☐☐ - ☐☐ - ☐☐☐☐

c. Hospital emergency department

☐ Yes ☐ No

If yes, how many times? ☐☐

If yes, date(s) of your visit(s)

☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)

☐☐ - ☐☐ - ☐☐☐☐

d. Out of hours GP service

☐ Yes ☐ No

If yes, how many times? ☐☐

If yes, date(s) of your visit(s)

☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)

☐☐ - ☐☐ - ☐☐☐☐

e. Pharmacist without a prescripton from your GP

☐ Yes
☐ No

If yes, how many times? ☐☐

If yes, date(s) of your visit(s)

☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)

☐☐ - ☐☐ - ☐☐☐☐

f. Walk in Centre

☐ Yes
☐ No

If yes, how many times? ☐☐

If yes, date(s) of your visit(s)

☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)

☐☐ - ☐☐ - ☐☐☐☐

g. Specialist

☐ Yes
☐ No

If yes, how many times? ☐☐

If yes, date(s) of your visit(s)

☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)

☐☐ - ☐☐ - ☐☐☐☐

h. Other

☐ Yes
☐ No

If yes, how many times? ☐☐

If yes, please specify _____

_____

4. Since your visit to your GP/nurse on day 1, have you **contacted (but not visited)** any of the following about this illness? (please tick box and specify how many times you contacted this service)

a. GP in usual working hours	☐ Yes ☐ No	If yes, how many times?	☐☐
b. Nurse in usual working hours	☐ Yes ☐ No	If yes, how many times?	☐☐
c. GP out of hours service	☐ Yes ☐ No	If yes, how many times?	☐☐
d. NHS Direct	☐ Yes ☐ No	If yes, how many times?	☐☐
e. Pharmacist	☐ Yes ☐ No	If yes, how many times?	☐☐
f. Walk in centre	☐ Yes ☐ No	If yes, how many times?	☐☐
g. Specialist	☐ Yes ☐ No	If yes, how many times?	☐☐
h. Other	☐ Yes ☐ No	If yes, how many times?	☐☐
		If yes, please specify	_____

Appendix II – Description of variables collected as part of the CODA study

CODA Study

Colitis: Once Daily Asacol

A Randomized, Multicentre, Parallel Group Single-Blind Study to Assess the Efficacy and Safety of Dosing Mesalazine 800mg Tablets (Asacol®) at 2.4g Once Daily versus Divided Doses Three Times Daily for 12 months in the Maintenance of Remission of Ulcerative Colitis

Case Report Form

CONTENTS

Section **Page**

SCREENING ASSESSMENT: Visit date: __ __ /__ __ __/ __ __ __ __
d d m m m y y y y

NOTE: You can combine screening and baseline visits. Take U&E, CRP and test urine immediately – once results are confirmed to be within normal range, patient can be randomised
Procedures to be carried out at this visit:
• Consent *To be obtained prior to undertaking any study procedure*
• Demographics, disease history & disease assessment
• Rigid or flexible sigmoidoscopy (biopsy not required)
• Concomitant medication
• Blood for U & E, CRP
• Urine dipstick
• Inclusion & exclusion criteria
• Document details of visit in medical notes

1 Patient details:

1.1 Date of Birth: __ __ /__ __ __/ __ __ __ __
d d m m m y y y y

1.2 Sex: Male ☐ Female ☐

2 Disease history:

2.1 Date UC diagnosed: __ __ __/ __ __ __ __

m m m y y y y

2.2 Maximum Documented Extent of UC:

Extensive ☐ Left-sided or sigmoid ☐ Proctitis ☐

3 Relapse history:

Patient must be in remission, and have had a relapse in the past two years - Relapse definition: symptoms of colitis requiring treatment

3.1 When did the patient finish treatment for the last episode of active colitis?

__ __ /__ __ __/ __ __ __ __

d d m m m y y y y

3.2 How many relapses has the patient had in the past two years? ___ ___

4 Which 5-ASA containing drug is currently being used:

This will be stopped when trial medication is started

Drug name	Dose	Frequency	Route	Date started (year only)

5 Other Current Drug Therapy for Ulcerative Colitis:

Complete medication documentation on page 30

6 Blood and urine sample:

Take blood for urea & electrolytes and CRP, carry out dipstick urinalysis (send blood to local lab & use local dipsticks). Record results on laboratory samples page 32

7 Other Medical Conditions:

Condition *Tick either active or inactive for each condition*	**Currently active**	**Inactive**

7.1 Has the patient had appendicectomy?

Yes ☐ No ☐ Don't know ☐

8 Usual Stool Frequency:

8.1 What is the normal stool frequency for this patient when in remission?

_____ stools / day

9 Current disease status:

Perform sigmoidoscopy – no biopsy required

10 Mayo Clinic Score:

Score symptoms according to the past 3 days	**Subscore**
Stool frequency 0=Normal no. of stools for this subject 1= 1-2 stools/day more than normal 2= 3-4 stools/day more than normal 3= ≥5 stools/day more than normal	
Rectal bleeding 0= No blood seen 1= Streaks of blood with <50% of stools 2= Obvious blood seen with ≥50% of stools 3= Blood alone passed	
Physician's global assessment 0= Normal (ie inactive) 1= Mild disease 2= Moderate disease 3= Severe disease	
Findings on Sigmoidoscopy * 0= Normal 1= Mild disease (erythema, decreased vascular pattern, mild friability). No contact bleeding. 2= Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3= Severe disease (spontaneous bleeding, ulceration)	
Total score	

* For this trial the sigmoidoscopic score will be equivalent to the modified Baron score: - i.e. contact bleeding will be classed as grade 2 and spontaneous bleeding as grade 3

CODA Study Colitis: Once Daily Asacol **SCREENING**

Patient initials __ __ __ Randomisation No. __ __ __ __

11 Inclusion Criteria *Tick to confirm the following applies to the patient:-*	**Tick**
Diagnosis of ulcerative colitis confirmed histologically in the past	
Colitis in clinical remission for 4 weeks or longer	
Has undergone rigid or flexible sigmoidoscopy at this visit showing mucosal appearance of grade 0 or 1 (modified Baron score)	
Has had symptomatic relapse of UC within past 2 years	
Has a current Mayo score of ≤ 2	
Currently taking mesalazine, sulphasalazine, balsalazide, olsalazine or other drug containing 5-aminosalicylic acid, for 4 weeks or longer	
Aged over 18	
If female, must be (as documented in patient notes): ▪ postmenopausal (at least 1 year without spontaneous menses), or ▪ surgically sterile (tubal ligation or hysterectomy at least 6 months prior to enrolment), or ▪ using acceptable contraception (e.g., oral, intramuscular, or implanted hormonal contraception) at least 3 months prior to enrolment, or ▪ have a sexual partner with non-reversed vasectomy (with confirmed azoospermia), or ▪ be using 1 barrier method (e.g., condom, diaphragm, spermicide, or intra-uterine device)	
Has given written informed consent	

12 Exclusion Criteria *Tick to confirm there is no evidence of :-*	**Tick**
Crohn's disease	
Symptoms of active colitis	
Modified Baron sigmoidoscopy score of 2 or 3	
Use of oral, enema, intravenous or suppository preparations of corticosteroids, oral or intravenous ciclosporin, mesalazine enemas or suppositories within the past four weeks.	
Altered dose or commencement of azathioprine or 6-mercaptopurine within the past three months, (these drugs permitted in stable dose during the study).	
Intolerance to Asacol 400 mg or mesalazine.	
Women who are pregnant or lactating.	
Known HIV infection	
Known hepatic disease with significant elevation of liver enzymes (more than twice upper limit of normal)	
Renal impairment (creatinine above local reference range), or with positive urine dipstick test to blood or protein	
Other serious medical or psychiatric illness that in the opinion of the investigator would possibly compromise the study	

Problem alcohol excess or drug abuse that in the opinion of the investigator would possibly compromise the study	

This patients fits the study criteria and is suitable for inclusion Yes ☐ No ☐

If no, please retain screening documents

Signature: _____ Date __ __ /__ __ __/ __ __ __ __

d d m m m y y y y

Name:

(*in capitals)* _____ Designation_____

CODA Study Colitis: Once Daily Asacol **SCREENING**

Patient initials __ __ __ Randomisation No. __ __ __ __

Screening checklist

Have the following been completed?	**Tick**
Consent	
Sigmoidoscopy	
Blood for U & E, CRP	
Urine dipstick	
Record concomitant medication	
Document visit in medical notes	
Arrange baseline visit *(must be within 10 days of screening)*: date: __ __/__ __ __/__ __ __ __ d d m m m y y y y *or* complete baseline visit today if blood and urine results are available to confirm eligibility	

CODA Study Colitis: Once Daily Asacol **BASELINE**

Patient initials __ __ __ Randomisation No. __ __ __ __

BASELINE ASSESSMENT:

Visit date: __ __ /__ __ __/ __ __ __ __

d d m m m y y y y

Procedures to be carried out at this visit:
• Randomisation
• Dispense medication
• Faecal calprotectin
• Other medical history
• Document details of visit in medical notes
• Fax Clinical Trial Coordinator to inform of recruitment
• Send GP letter

1 Extra-intestinal Complications (current or previous) *Tick all that apply*	**Tick**
Arthritis (swollen or deformed joints)	
Arthralgia	
Sacro-iliitis	
Ankylosing spondylitis	
Pyoderma gangrenosum	

Erythema nodosum	
Aphthous ulcers or stomatitis	
Primary sclerosing cholangitis	
Auto-immune hepatitis	
Uveitis or iritis	
None of the above	

2 Smoking status:

2.1 Is the patient a current smoker? Yes ☐ No ☐ *(If no go to part 2.5)*

2.2 Does the patient smoke daily ☐ occasionally ☐

2.3 Does the patient smoke: cigarettes ☐ pipe ☐ cigars ☐

2.4 How many per day: <10 ☐ ≥10 ☐ ounces tobacco ☐

2.5 Is the patient an ex-smoker? Yes ☐ No ☐ *(If no go to part 2.7)*

2.6 Date gave up __ __ __ __

y y y y

2.7 Do you use nicotine in any other form (e.g. chewing gum, patches)? Yes ☐ No ☐

If yes, please specify _____

3 Ethnicity:

White ☐ African or Afrocaribbean ☐

South Asian (Indian subcontinent) ☐ Other (give detail): _____

4 Employment ***please tick all that apply***	**Tick**
Full-time education	

Part-time education	
Full-time employment	
Part-time employment	
Homemaker or not in paid employment	
Unemployed or seeking work	
Not working due to disability	
Retired	

5 Faecal calprotectin:

Collect stool sample for faecal calprotectin as per instructions on enclosed sheet

5.1 Was the stool sample obtained: at this visit ☐ *or* pot given to patient ☐

6 Study medication:

Complete prescription for study medication. Remind patient not to open a new bottle of medication until the opened one is empty and to return unused medication and empty bottles at next visit.

Obtain randomisation number from pharmacy, once the patient has collected their trial medication.

CODA Study Colitis: Once Daily Asacol **BASELINE**

Patient initials __ __ __ Randomisation No. __ __ __ __

Baseline checklist

Have the following been completed?	**Tick**
Randomisation - *Pharmacy will assign the randomisation number. You need to obtain the number from pharmacy (or the patient) to complete the CRF and calprotectin sample documents*	
Dispense medication	
Faecal calprotectin sample	
Document details of visit in medical notes	
Give patient trial card	
Write to GP – trial participation	
Fax Clinical Trial Coordinator to inform of recruitment	
Arrange next visit *(6 weeks +/-1 week)* date __ __/__ __ __/__ __ __ __ d d m m m y y y y	
Remind patient to bring remaining study medication & empty bottles to next visit	

WEEK 6 ASSESSMENT:

Visit date: __ __ /__ __ __/ __ __ __ __

d d m m m y y y y

Procedures to be carried out at this visit:
• Tablet count & give tablets back to patient
• Disease assessment
• Concomitant medication
• Blood for U & E, CRP
• Urine dipstick
• Record any adverse events
• Document details of visit in medical notes

1 Disease status:

1.1 Has the patient received treatment for a flare up of ulcerative colitis?

Yes ☐ No ☐

Note: It is a violation of the protocol for patients to receive treatment for flare up whilst in the study. If patient has received treatment for UC flare up withdraw them from trial and complete relapse assessment – page 26. Do not complete any further questions for this visit.

1.2 Bowel frequency *(past 3 days)* ___ / day

1.3 Rectal bleeding *(past 3 days)* None ☐

Streaks of blood with <50% of stools ☐

Obvious blood with ≥50% of stools ☐

Blood alone passed ☐

1.4 Is it possible that the patient has relapsed? Yes ☐ No ☐

If yes, do not complete any further questions for this visit. Complete relapse assessment page 26 and withdraw from study if relapse confirmed

2 Trial medication:

Remind patient not to open a new bottle of medication until the opened one is empty and to return unused medication and empty bottles at next visit

2.1 Record how many trial tablets are left in the medication pack: _____
There are 180 tablets in an unopened bottle.

2.2 According to the patient have they taken their study tablets as prescribed?

Yes *(≥ 90% of the time)* ☐ No *(< 90% of the time)* ☐

2.3 According to the patient how easy was it remembering to take the trial tablets:

Very easy ☐ Fairly easy ☐ Fairly difficult ☐ Very difficult ☐

3 Concomitant medication:

3.1 Have there been any changes in medication?

Yes ☐ No ☐

Record any changes on the changes to concomitant medication page 31

4 Adverse events:

4.1 Has the patient experienced any adverse events since the last visit?

Yes ☐ No ☐

If yes, complete adverse events page 33

5 Blood and urine sample:

Take blood for urea & electrolytes and CRP, carry out dipstick urinalysis (send blood to local lab & use local dipsticks). Record results on laboratory samples page 32

CODA Study Colitis: Once Daily Asacol **WEEK 6**

Patient initials __ __ __ Randomisation No. __ __ __ __

Week 6 Checklist

Have the following been completed?	**Tick**
Tablet count & give tablets back to patient	
Changes to medication check	
Symptom assessment	
Blood for U & E, CRP	
Urine dipstick	
Record any adverse events	
Remind patient to bring remaining study medication & empty bottles to next visit	
Document visit in medical notes	
Date in diary for 3 month telephone contact: __ __/__ __ __/__ __ __ __ d d m m m y y y y	
Arrange 6 month visit (max 6 months/- 2 weeks): date: __ __/__ __ __/__ __ __ __ d d m m m y y y y	

THREE MONTH TEL. CONTACT: Contact date: __ __/__ __ __/__ __ __ __

d d m m m y y y y

1 Disease status:

1.1 Has the patient received treatment for a flare up of ulcerative colitis?

Yes ☐ No ☐

Note: It is a violation of the protocol for patients to receive treatment for flare up whilst in the study. If patient has received treatment for UC flare up withdraw them from trial & arrange relapse assessment visit as soon as possible. Do not complete any further questions for this visit.

1.2 Bowel frequency *(past 3 days)* ___ / day

1.3 Rectal bleeding *(past 3 days)* None ☐

Streaks of blood with <50% of stools ☐

Obvious blood with ≥50% of stools ☐

Blood alone passed ☐

1.4 Is possible that the patient has relapsed? Yes ☐ No ☐

If yes, arrange relapse assessment visit as soon as possible

2 Trial medication:

2.1 According to the patient have they taken their study tablets as prescribed?

Yes *(≥ 90% of the time)* ☐ No *(< 90% of the time)* ☐

2.2 According to the patient how easy was it remembering to take the trial tablets:

Very easy ☐ Fairly easy ☐ Fairly difficult ☐ Very difficult ☐

3 Concomitant medication:

3.1 Have there been any changes in medication?

Yes ☐ No ☐

Record any changes on the changes to concomitant medication page 31

4 Adverse events:

4.1 Has the patient experienced any adverse events since the last visit?

Yes ☐ No ☐

If yes, complete adverse events page 33

Confirm date of next visit and remind patient to bring remaining study medication with them.

SIX MONTH ASSESSMENT:

Visit date: __ __ /__ __ __/ __ __ __ __

d d m m m y y y y

Procedures to be carried out at this visit:
• Tablet count & return empty bottles and unused tablets to pharmacy
• Dispense medication
• Disease assessment
• Concomitant medication
• Blood for U & E, CRP
• Urine dipstick
• Record any adverse events
• Document details of visit in medical notes

1 Disease status:

1.1 Has the patient received treatment for a flare up of ulcerative colitis?

Yes ☐ No ☐

Note: It is a violation of the protocol for patients to receive treatment for flare up whilst in the study. If patient has received treatment for UC flare up withdraw them from trial and complete relapse assessment – page 26. Do not complete any further questions for this visit.

1.2 Bowel frequency *(past 3 days)* ___ / day

1.3 Rectal bleeding *(past 3 days)* None ☐

Streaks of blood with <50% of stools ☐

Obvious blood with ≥50% of stools ☐

Blood alone passed ☐

1.4 Is it possible that the patient has relapsed? Yes ☐ No ☐

If yes, do not complete any further questions for this visit. Complete relapse assessment pages 26 and withdraw from study if relapse confirmed

2 Trial medication:

Complete prescription for study medication. Remind patient not to open a new bottle of medication until the opened one is empty and to return unused medication and empty bottles at next visit

2.1 Record how many trial tablets are left in the medication pack: _____
There are 180 tablets in an unopened bottle

2.2 According to the patient have they taken their study tablets as prescribed?

Yes *(≥ 90% of the time)* ☐ No *(< 90% of the time)* ☐

2.3 According to the patient how easy was it remembering to take the trial tablets:

Very easy ☐ Fairly easy ☐ Fairly difficult ☐ Very difficult ☐

3 Concomitant medication:

3.1 Have there been any changes in medication?

Yes ☐ No ☐

Record any changes on the changes to concomitant medication page 31

4 Adverse events:

4.1 Has the patient experienced any adverse events since the last visit?

Yes ☐ No ☐

If yes, complete adverse events page 33

5 Blood and urine sample:

Take blood for urea & electrolytes and CRP, carry out dipstick urinalysis (send blood to local lab & use local dipsticks). Record results on laboratory samples page 31

CODA Study Colitis: Once Daily Asacol **6 MONTH**

Patient initials __ __ __ Randomisation No. __ __ __ __

Six month checklist

Have the following been completed?	**Tick**
Tablet count & return unused tablets and empty bottles to pharmacy	
Changes to medication check	
Symptom assessment	
Blood for U & E, CRP	
Urine dipstick	
Record any adverse events	
Prescribe study medication	
Remind patient to bring remaining study medication & empty bottles to next visit	
Document visit in medical notes	
Date in diary for 9 month telephone contact: __ __/__ __ __/__ __ __ __ d d m m m y y y y	
Arrange 12 month visit (max 12 months/- 2 weeks): date: __ __/__ __ __/__ __ __ __ d d m m m y y y y *Sigmoidoscopy required at 12 month visit*	

NINE MONTH TEL. CONTACT: Contact date: __ __/__ __ __/__ __ __ __

d d m m m y y y y

1 Disease status:

1.1 Has the patient received treatment for a flare up of ulcerative colitis?

Yes ☐ No ☐

Note: It is a violation of the protocol for patients to receive treatment for flare up whilst in the study. If patient has received treatment for UC flare up withdraw them from trial & arrange relapse assessment visit as soon as possible. Do not complete any further questions for this visit.

1.2 Bowel frequency *(past 3 days)* ___ / day

1.3 Rectal bleeding *(past 3 days)* None ☐

Streaks of blood with <50% of stools ☐

Obvious blood with ≥50% of stools ☐

Blood alone passed ☐

1.4 Is possible that the patient has relapsed? Yes ☐ No ☐

If yes, arrange relapse assessment visit as soon as possible

2 Trial medication:

2.1 According to the patient have they taken their study tablets as prescribed?

Yes *(≥ 90% of the time)* ☐ No *(< 90% of the time)* ☐

2.2 According to the patient how easy was it remembering to take the trial tablets:

Very easy ☐ Fairly easy ☐ Fairly difficult ☐ Very difficult ☐

3 Concomitant medication:

3.1 Have there been any changes in medication?

Yes ☐ No ☐

Record any changes on the changes to concomitant medication page 31

4 Adverse events:

4.1 Has the patient experienced any adverse events since the last visit?

Yes ☐ No ☐

If yes, complete adverse events page 33

Confirm date of next visit and remind patient to bring remaining study medication with them.

TWELVE MONTH ASSESSMENT: Visit date: __ __ /__ __ __/ __ __ __ __

d d m m m y y y y

Procedures to be carried out at this visit:
• Tablet count and stop study drug – return unused medication and empty bottles to pharmacy
• Rigid or flexible sigmoidoscopy (biopsy not required)
• Disease assessment
• Concomitant medication
• Blood for U & E, CRP
• Urine dipstick
• Record any adverse events
• Prescription for future treatment
• Write to GP – trial completion
• Document details of visit in medical notes
• Arrange routine hospital follow up
• Thank patient for participating

1 Disease status:

1.1 Has the patient received treatment for a flare up of ulcerative colitis?

Yes ☐ No ☐

Note: It is a violation of the protocol for patients to receive treatment for flare up whilst in the study. If patient has received treatment for UC flare up withdraw them from trial and complete relapse assessment – page 26. Do not complete any further questions for this visit.

1.2 Bowel frequency *(past 3 days)* ___ / day

1.3 Rectal bleeding *(past 3 days)* None ☐

Streaks of blood with <50% of stools ☐

Obvious blood with ≥50% of stools ☐

Blood alone passed ☐

1.4 Is possible that the patient has relapsed? Yes ☐ No ☐

If yes, do not complete any further questions for this visit. Complete relapse assessment pages 26 and withdraw from study if relapse confirmed

1.5 **Mayo Clinic Score**

Score symptoms according to the past 3 days	**Subscore**
Stool frequency 0=Normal no. of stools for this subject 1= 1-2 stools/day more than normal 2= 3-4 stools/day more than normal 3= ≥5 stools/day more than normal	
Rectal bleeding 0= No blood seen 1= Streaks of blood with <50% of stools 2= Obvious blood seen with ≥50% of stools 3= Blood alone passed	
Physician's global assessment 0= Normal (ie inactive) 1= Mild disease 2= Moderate disease 3= Severe disease	
Findings on Sigmoidoscopy * 0= Normal 1= Mild disease (erythema, decreased vascular pattern, mild friability). No contact bleeding 2= Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3= Severe disease (spontaneous bleeding, ulceration)	

* ***For this trial the sigmoidoscopic score will be equivalent to the modified Baron score: - i.e. contact bleeding will be classed as grade 2 and spontaneous bleeding as grade 3***

2 Trial medication:

2.1 Record how many trial tablets are left in the medication pack: _____
There are 180 tablets in an unopened bottle

2.2 According to the patient have they taken their study tablets as prescribed?

Yes *(≥ 90% of the time)* ☐ No *(< 90% of the time)* ☐

2.3 According to the patient how easy was it remembering to take the trial tablets:

Very easy ☐ Fairly easy ☐ Fairly difficult ☐ Very difficult ☐

3 Concomitant medication:

3.1 Have there been any changes in medication?

Yes ☐ No ☐

Record any changes on the changes to concomitant medication page 31

4 Adverse events:

4.1 Has the patient experienced any adverse events since the last visit?

Yes ☐ No ☐

If yes, complete adverse events page 33

6 Blood and urine sample:

Take blood for urea & electrolytes and CRP, carry out dipstick urinalysis (send blood to local lab & use local dipsticks). Record results on laboratory samples page 32

7 Trial completion:

Date patient completed trial treatment: __ __/__ __ __/ __ __ __ __
d d m m m y y y y

Complete end of study form page 29

CODA Study Colitis: Once Daily Asacol **12 MONTH**

Patient initials __ __ __ Randomisation No. __ __ __ __

Twelve month checklist

Have the following been completed?	**Tick**
Tablet count & return unused medication and empty bottles to pharmacy	
Changes to medication check	
Symptom assessment	
Sigmoidoscopy	
Blood for U & E, CRP	
Urinalysis	
Record any adverse events	
Complete end of study form	
Discuss dose of mesalazine to be used by patient and prescribe if required	
Document details of visit in medical notes	
Thank patient for participation in study	
Write to GP – trial completion	
Arrange routine hospital follow up	

This patient has completed the study according to the protocol & remained in remission

Signature: _____ Date __ __ /__ __ __/ __ __ __ __

d d m m m y y y y

Name:

(*in capitals)* _____ Designation_____

UNSCHEDULED ASSESSMENT:

Visit date: __ __ /__ __ __/ __ __ __ __
d d m m m y y y y

Procedures to be carried out at this visit:
• Tablet count
• Disease assessment
• Concomitant medication
• Record any adverse events
• Document details of visit in medical notes

1 Reason for visit:

NOTE:
a) If the reason for this visit is suspected relapse do not complete these pages, go to relapse assessment page 26
b) If unscheduled visit falls within time window of routine visits, do not complete these pages, complete relevant visit pages

1.1 State reason for visit: _____

2 Disease status:

2.1 Bowel frequency *(past 3 days)* ___ / day

2.2 Rectal bleeding *(past 3 days)* None ☐

Streaks of blood with <50% of stools ☐

Obvious blood with ≥50% of stools ☐

Blood alone passed ☐

2.3 Is the patient still in remission? Yes ☐ No ☐

If no, do not complete any further questions for this visit. Complete relapse assessment page 26 and withdraw from study if relapse confirmed

3 Trial medication:

Remind patient not to open a new bottle of medication until the opened one is empty and to return unused medication and empty bottles at next visit

3.1 Record how many trial tablets are left in the medication pack: _____
There are 180 tablets in an unopened bottle

3.2 According to the patient have they taken their study tablets as prescribed?

Yes *(≥ 90% of the time)* ☐ No *(< 90% of the time)* ☐

3.3 According to the patient how easy was it remembering to take the trial tablets:

Very easy ☐ Fairly easy ☐ Fairly difficult ☐ Very difficult ☐

4 Concomitant medication:

4.1 Have there been any changes in medication?

Yes ☐ No ☐

Record any changes on the changes to concomitant medication page 31

5 Adverse events:

5.1 Has the patient experienced any adverse events since the last visit?

Yes ☐ No ☐

If yes, complete adverse events page 33

CODA Study Colitis: Once Daily Asacol **UNSCHEDULED**

Patient initials __ __ __ Randomisation No. __ __ __ __

Unscheduled checklist

Have the following been completed?	**Tick**
Tablet count	
Changes to medication check	
Symptom assessment	
Record any adverse events	
Document details of visit in medical notes	
Continue trial and arrange next visit date: __ __/__ __ __/__ __ __ __ d d m m m y y y y	

RELAPSE ASSESSMENT **DATE:** __ __ /__ __ __/ __ __ __ __

d d m m m y y y y

1 Disease status:

1.1 Has the patient received treatment for flare up of UC?

Yes ☐ No ☐ *if no, go to part 1.3*

1.2 If yes, what date did the treatment for flare up start?

__ __ /__ __ __/ __ __ __ __ *go to part 3*

d d m m m y y y y

Note: It is a violation of the protocol for patients to receive treatment for flare up whilst in the study. If patient has received treatment for UC flare up withdraw them from trial.

1.3 Has the patient got symptoms of active disease?

Symptoms of relapse are defined as:

- *Bloody diarrhoea or rectal bleeding lasting 3 days or more*
- *Non-bloody diarrhoea or increase in stool frequency lasting 3 days or more*
- *Other symptoms the patient associates with relapse of his/her ulcerative colitis*

Yes ☐ No ☐ *If no, go to section 3 - patient continues in trial.*

1.4 Perform sigmoidoscopy

Date of sigmoidoscopy: __ __ /__ __ __/ __ __ __ __

d d m m m y y y y

1.5 **Mayo Clinic Score**

Score symptoms according to the past 3 days	**Subscore**
Stool frequency 0=Normal no. of stools for this subject 1= 1-2 stools/day more than normal 2= 3-4 stools/day more than normal 3= ≥5 stools/day more than normal	
Rectal bleeding 0= No blood seen 1= Streaks of blood with <50% of stools 2= Obvious blood seen with ≥50% of stools 3= Blood alone passed	
Physician's global assessment 0= Normal (ie inactive) 1= Mild disease 2= Moderate disease 3= Severe disease	
Findings on Sigmoidoscopy * 0= Normal 1= Mild disease (erythema, decreased vascular pattern, mild friability).No contact bleeding 2= Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3= Severe disease (spontaneous bleeding, ulceration)	

* ***For this trial the sigmoidoscopic score will be equivalent to the modified Baron score: - i.e. contact bleeding will be classed as grade 2 and spontaneous bleeding as grade 3***

1.6 In the opinion of the investigator has the patient relapsed?
Relapse is defined as symptoms of active disease with grade 2 or 3 changes on sigmoidoscopy

Yes ☐ No ☐

3 Trial medication:

3.1 Record how many trial tablets are left in the medication pack: _____
There are 180 tablets in an unopened bottle

3.2 According to the patient have they taken their study tablets as prescribed?

Yes *(≥ 90% of the time)* ☐ No *(< 90% of the time)* ☐

3.3 According to the patient how easy was it remembering to take the trial tablets:

Very easy ☐ Fairly easy ☐ Fairly difficult ☐ Very difficult ☐

4 Concomitant medication:

4.1 Have there been any changes in medication? *Include any treatment for flare up*

Yes ☐ No ☐

Record any changes on the changes to concomitant medication page 31

5 Adverse events:

5.1 Has the patient experienced any adverse events since the last visit?

Yes ☐ No ☐

If yes, complete adverse events page 33

6 Blood and urine sample:

Take blood for urea & electrolytes and CRP, carry out dipstick urinalysis (send blood to local lab & use local dipsticks). Record results on laboratory samples page 32

If patient has relapsed or started treatment for a flare up complete end of study form on page 29. Patient is withdrawn from the study and offered routine treatment for relapse.

Relapse assessment checklist

Have the following been completed?	**Tick**
Tablet count	
Changes to medication check	
Symptom assessment and Mayo clinic score *Not required if patient has already started treatment for flare up*	
Sigmoidoscopy *Not required if patient has already started treatment for flare up*	
Blood for U & E, CRP	
Urine dipstick	
Record any adverse events	
Document details of visit in medical notes	

If relapse confirmed:

- Withdraw patient from study
  (complete end of study page 29)

- Discuss further treatment and prescribe if required

- Thank patient for participation in study

- Write to GP – re: withdrawal

- Arrange routine hospital follow up

If no relapse:

- Confirm date of next visit:
  __ __/__ __ __/__ __ __ __
  d d m m m y y y y

END OF STUDY:

1 What date did the patient stop taking trial treatment: __ __ /__ __ __/ __ __ __ __
d d m m m y y y y

2 Did the patient complete the 12 month trial period in remission:

Yes ☐ No ☐

If yes go to part 4

3 Withdrawal:

3.1 Was the patient withdrawn from the study during the trial period?

Yes ☐ No ☐

3.2 What was the principal reason for withdrawal from trial treatment?

Relapse of colitis ☐

Drug side-effects ☐

Patient preference ☐

Other ☐ please state: _____

4 Signature: _____ Date __ __ /__ __ __/ __ __ __ __
d d m m m y y y y

Name:

(*in capitals)* _____ Designation_____

Please ensure that data entered into CRF is complete and accurate. Remove the top copy of each page and post a complete copy of the CRF to the Trial Co-ordinator.

All pages must be sent even if data has not been entered on them.

Concomitant medication at start of trial

Drug treatment for ulcerative colitis

Name	**Dose & route**	**Frequency & time of day taken**	**Start date – *only required if started in last 3 months (dd/mmm/yyyy)***

Other Current Drug Therapy

Name	**Dose**	**Frequency & time of day taken**	**Route**

CODA Study Colitis: Once Daily Asacol **CONCOMITANT MEDICATION**

Patient initials __ __ __ Randomisation No. __ __ __ __

CODA Study Colitis: Once Daily Asacol **MEDICATION CHANGES**

Patient initials __ __ __ Randomisation No. __ __ __ __

Changes to Concomitant Medication during trial (including study drug if stopped)

Drug	**Date of change** *(dd/mmm/yyyy)*	**Dose & route**	**Frequency & time of day taken**	**Date stopped -** *leave blank if ongoing*

CODA Study Colitis: Once Daily Asacol **LAB RESULTS**

Patient initials __ __ __ Randomisation No. __ __ __ __

Laboratory Results

Please enter normal range for your laboratory

	Normal range	Screening	6 weeks	6 months	12 months	Unscheduled
Visit date						
Urea						
Creatinine						
Sodium						
Potassium						
CRP						
Urine protein (dipstick)						
Urine blood (dipstick)						

Record urinalysis results as: nil; trace; +1; +2; +3 etc.

Adverse events

DEFINITIONS:

Adverse event:

Any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with this treatment. This includes "any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study drug". This may include, for example, a cold, or an accident.

Serious adverse event:

Any untoward medical occurrence or effect that at any dose:

- results in death
- is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Note: Do not record Serious Adverse Events on this page. Complete SAE form on page 36

Detail all adverse events here. This includes drug side-effects and deterioration of UC or UC-related symptoms, whether or not they are drug related.

Date started: _ _/ _ _ _/ _ _ _ _ Date resolved: _ _/ _ _ _/ _ _ _ _

Describe adverse event: _____

* Please give details

Severity: Action taken:

□ Mild □ None

□ Moderate □ Symptomatic therapy*

□ Severe □ Study medication dose changed*

□ Study medication permanently discontinued

□ Pat

(co

□Oth

Change in Severity:

Additional Notes:

Adverse events

Detail all adverse events here. This includes drug side-effects and deterioration of UC or UC-related symptoms, whether or not they are drug related.

Date started: _ _/ _ _ _/ _ _ _ _ Date resolved: _ _/ _ _ _/ _ _ _ _

Describe adverse event: _____

* Please give details

Severity: Action taken:

☐ Mild ☐ None

☐ Moderate ☐ Symptomatic therapy*

☐ Severe ☐ Study medication dose changed*

☐ Study medication permanently discontinued

☐ Patient hospitalized or hospitalization prolonged

(complete SAE form)

☐ Other action*

Change in Severity:

Additional Notes:

Date started: _ _/ _ _ _/ _ _ _ _ Date resolved: _ _/ _ _ _/ _ _ _ _

Describe adverse event: _____

* Please give details

Severity: Action taken:

☐ Mild ☐ None

☐ Moderate ☐ Symptomatic therapy*

☐ Severe ☐ Study medication dose changed*

☐ Study medication permanently discontinued

☐ Patient hospitalized or hospitalization prolonged

(complete SAE form)

☐ Other action*

Change in Severity:

Additional Notes:

Adverse events

Detail all adverse events here. This includes drug side-effects and deterioration of UC or UC-related symptoms, whether or not they are drug related.

Date started: _ _/ _ _ _/ _ _ _ _ Date resolved: _ _/ _ _ _/ _ _ _ _

Describe adverse event: _____

* Please give details

Severity: Action taken:

☐ Mild ☐ None

☐ Moderate ☐ Symptomatic therapy*

☐ Severe ☐ Study medication dose changed*

☐ Study medication permanently discontinued

☐ Patient hospitalized or hospitalization prolonged

(complete SAE form)

☐ Other action*

Change in Severity:

Additional Notes:

Date started: _ _/ _ _ _/ _ _ _ _ Date resolved: _ _/ _ _ _/ _ _ _ _

Describe adverse event: _____

* Please give details

Severity: Action taken:

☐ Mild ☐ None

☐ Moderate ☐ Symptomatic therapy*

☐ Severe ☐ Study medication dose changed*

☐ Study medication permanently discontinued

☐ Patient hospitalized or hospitalization prolonged

(complete SAE form)

☐ Other action*

Change in Severity:

Additional Notes:

SERIOUS ADVERSE EVENT

☐	An event that resulted in death	☐	An event that has prolonged hospitalisation
☐	An event that is life-threatening	☐	An event that results in persistent or significant disability or incapacity
☐	An event that requires hospitalisation	☐	An event that is a congenital anomaly or birth defect

Person reporting Adverse Event

Name: …… Telephone: ……..

Account of Adverse Event:

Start Date:

End Date:

Action Taken:

	None	* Provide further details of action here, including any additional medication or altered dose levels:
	Symptomatic treatment*	
	Asacol dose altered*	
	Asacol discontinued	
	Hospitalisation	
	Other*	

Outcome

	Resolved
	Ongoing
	Permanent Residual Effect
	Death

Relationship of the event to Asacol treatment

	None: clearly due to other causes (clinical state, environment, other medication)
	Unlikely: no temporal relationship to treatment, not an anticipated response to Asacol, more likely to be caused by patient's clinical state or other medication
	Possible: temporal relationship to Asacol treatment, may be an anticipated response to Asacol but may be caused by clinical state or other medication
	Probably: temporal relationship to Asacol treatment, an anticipated response to Asacol, not reasonably explained by clinical state or other medication
	Definite: an anticipated response to Asacol that stops on withdrawal of Asacol and restarts on reintroduction, not explained by other factors.

Serious adverse event events must be reported to the Trial Co-ordinator at the University Hospital of Wales within 24 hours. Please complete this page with all available details and fax to 029 20742108

Appendix III – Description of variables collected as part of the ZICE study

Registration:

doreg	Registration Date
rptini	Patient Initials
rdob	Date of Birth
rpatid	Patient Trial No

Screening:

ptini	Patient Initials
dob	Date of Birth
patid	Patient Trial No
doinf	Date of Informed Consent
dovis	Date of Visit
dovis	Date of Visit
sex	Gender
wt	Weight
ht	Height
secog	ECOG
screat	Serum Creatinine
doscrt	Date of Sample
doscrt	Date of Sample
ecreat	Estd Creatinine Clearance
doecrt	Date of Sample
doecrt	Date of Sample
albu	Albumin
doalbu	Date of Sample
doalbu	Date of Sample
corcal	Corrected Calcium
docrcl	Date of Sample
docrcl	Date of Sample
serbil	Serum Bilirubin
dosrbl	Date of Sample
dosrbl	Date of Sample
ast	AST
astlvl	AST Level
doast	Date of Sample
doast	Date of Sample
alt	ALT

altlvl	ALT Level
doalt	Date of Sample
doalt	Date of Sample
qlq	Quality of life
reqlq	Reason
bpi	BPI
rebpi	Reason
bis	Any Bisphosphonate treatment prior to Rando?
dobis	Last dose date
dobis	Last dose date

Randomisation:

dor	Randomisation Date
centno	Centre No
hosp	Hospital
ptini	Patient Initials
dob	Date of Birth
hosno	Hospital Number
chemo	Chemotherapy
hormone	Hormone Therapy
sre	SRE
ageok	Over 18 years
mets	Newly Dignosed with Mets
dodiag	Diagnosis Date
diatime	Time since diagnosis (days) *[Derived]*
suit	Suitable for Bisphosphonate treatment
clindec	Clinician decision to treat with bisphosphonates
dodec	Date of clinical decision
isoscn	ISO scan conducted?
doiso	ISO Scan date
isotime	ISO Time (days) *[Derived]*
inf	Informed Consent obtained?
ecogok	ECOG 0,1 or 2
mcntnv	Central Nervous System Mets
dent	Current active Dental problems
jaw	Planned dental or Jaw Surgery
peptic	Peptic Ulcer
preg	Pregnant or Lactating
ckgult	Cockcroft-Gault
astalt	AST or ALT Levels
pbis	Previous Bisphosphonate Treatment
dopbis	Prev. Bis treatment ending date

dopbis	Prev. Bis treatment ending date
pbistime	Prv.Bis.treatment ending time (days) *[Derived]*
uncomp	Unable to comply with instructions to study med
hypbis	Hypersensitivity to bisphosphonates
patid	Patient Trial No
treat	Treatment allocated

Baseline and disease history:

patid	Patient Trial No	
dobrst	Date of diagnosis of Breast Cancer	
dobrst	Date of diagnosis of Breast Cancer	
dobrst	Date of diagnosis of Breast Cancer	
erstat	ER Status	
prstat	PR Status	
herstat	HER-2 Status	
menstat	Current menstrual status	
ajchmo	Adjuvant chemotherapy	
ajendo	Adjuvant endocrine therapy	
ajtras	Adjuvant Trastuzumab	
locrec	Local recurrence	
recsite	If Yes, first site	
recspec	Specify	
dorec	Date of diagnosis	
pmets	Previous history of mets	
dopmet	Date of Diagnosis	
dopmet	Date of Diagnosis	
frsite	First Site(s)	*[Repeated]*
othsite	Specify	*[Repeated]*
metcur	Current Bone Mets	*[Repeated]*
metoth	Specify	*[Repeated]*
bassre	Any SRE(s) in previous 3 months	
radpln	Previous or planned radiotherapy for bone mets	
ortsur	Orthopaedic surgery for bone mets	
symfrac	Symptomatic vertebral fracture	
patfrac	Pathological non-vertebral fracture	
spicom	Spinal cord compression	
hyper	Hypercalcaemia	
dothxy	Date of Thoracic Spine Xray	

dothxy	Date of Thoracic Spine Xray	
thles	Mets lesion in Thoracic Spine	
thtype	Type of Lesion in Thoracic Spine	
thfrac	Fracture/Vertabal collapse visible -Thoracic Spine	
dolmxy	Date of Lumbar spine Xray	
dolmxy	Date of Lumbar spine Xray	
lumles	Mets lesion - Lumbar spine	
lumtype	Type of Lesion in Lumbar Spine	
lumfrac	Fracture/Vertabal collapse visible -Lumbar Spine	
radioot	Other - specify	*[Repeated]*
doot	Date of Xray	*[Repeated]*
doot	Date of Xray	*[Repeated]*
otles	Mets lesion	*[Repeated]*
ottype	Type of Lesion	*[Repeated]*
othfrac	Fracture/Vertabal collapse visible	*[Repeated]*
pain	Painkilling Drugs	
drug	Drug Name (painkiller)	*[Repeated]*
cat	Category (Painkiller)	*[Repeated]*
lstday	No of days in last 7	*[Repeated]*
bchmo	Chemotherapy	
bchspc	Specify	
dobchm	Start Date	
bhorm	Hormone Therapy	
bhrmspc	Specify	
dobhorm	Start Date	
btrast	Trastuzumab	
btstspc	Specify	
dobtrst	Start Date	
bother	Other	
bothspc	Specify	
doboth	Start Date	

otdrug	Patient on any other medication inc antiemetics	
bdrug	Drug Name	*[Repeated]*
dobdrug	Start Date	*[Repeated]*

Interims:

patid	Patient Trial No	
attend	Did patient attend	
doyvis	Visit date	
donvis	Date last known to be alive	
revis	Reason for not attending	
revis	Reason for not attending	
visoth	other	
dosttrt	Medication start date	
dosttrt	Medication start date	
bpi	BPI been completed	
rebpi	No, reason	
sched	Study Medication administered as prescribed	
resched	Reason if no	
schedot	Specify	
iban	Ibandronate only patient tablet amount	
pain	Any Painkilling Drugs taken in last 7 days	
drug	*Drug Name (painkiller)*	*[Repeated]*
cat	Category (Painkiller)	*[Repeated]*
lstday	No of days in last 7	*[Repeated]*
bis	Any Bisphosphonates been given since last visit	
bisnme	BIS drug Name	*[Repeated]*
cont	Continuing	*[Repeated]*
dostrt	start date	*[Repeated]*
dostp	stop date	*[Repeated]*
vits	Vitamin D and Calcium	
medchg	Has there been any other changes to medications	
mednme	Other medication drug name	*[Repeated]*
medcat	Category	*[Repeated]*
dostmed	Start date	*[Repeated]*
medcont	Continuing	*[Repeated]*

dospmed	Stop date	*[Repeated]*
sre	Any SRE's since last visit	
bscan	Any bone scans or X rays performed	
srerel	Related to SRE's	
srerel	Related to SRE's	
screat	Serum Creatinine	
doscrt	Date of Sample	
doscrt	Date of Sample	
wt	Weight	
ecreat	Estd Creatinine Clearance	
conhlh	Patient Consultations since last visit	
hthpro	Health Provider	*[Repeated]*
locat	Home or Surgery	*[Repeated]*
visnum	Number of visits	*[Repeated]*
rehvis	Reason for visit	*[Repeated]*
travel	How did they travel to clinic	
accomp	Who accompanied patient	
tmeoff	Involve time of work	
cost	Cost of visit	
dist	Mileage/Distance	
dent	Current active Dental problems	
otprob	Other problems (toxicity)	
toxic	Toxicity	*[Repeated]*
toxgrd	Toxicity Grade	*[Repeated]*
toxot	Toxicity other	*[Repeated]*

12 weekly assessments:

ptini	Patient Initials
dob	Date of Birth
patid	Patient Trial No
attend	Did patient attend
doyvis	Visit date
donvis	Date last known to be alive
ecog	ECOG
revis	Reason for not attending
visoth	other
sched	Study Medication administered as prescribed
resched	Reason if no
schedot	Specify
iban	Ibandronate only patient tablet amount
qlbp	Qual of life and BPI Questionnaire been completed
reqlbp	Reason if no
pain	Painkilling Drugs in the past 7 days
drug	Drug Name (painkiller) *[Repeated]*
cat	Category (Painkiller) *[Repeated]*
lstday	No of days in last 7 *[Repeated]*
bis	Any Bisphosphonates other than study drug been given since last visit
bisnme	BIS drug Name *[Repeated]*
cont	Continuing *[Repeated]*
dostrt	start date *[Repeated]*
dostp	stop date *[Repeated]*
vits	Vitamin D and Calcium been taken
medchg	Has there been any other changes to medications
mednme	Other medication drug name *[Repeated]*
medcat	Category *[Repeated]*
dostmed	Start date *[Repeated]*
medcont	Continuing *[Repeated]*

dospmed	Stop date	*[Repeated]*
sre	Any SRE's since last visit	
bscan	Any bone scans or X rays performed	
srerel	Related to SRE's	
screat	Serum Creatinine	
doscrt	Date of Sample	
doscrt	Date of Sample	
wt	Weight	
ecreat	Estd Creatinine Clearance	
conhlh	Patient Consultations since last visit	
hthpro	Health Provider	*[Repeated]*
locat	Home or Surgery	*[Repeated]*
visnum	Number of visits	*[Repeated]*
rehvis	Reason for visit	*[Repeated]*
travel	How did they travel to clinic	
accomp	Who accompanied patient	
tmeoff	Involve time of work	
cost	Cost of visit	
dist	Mileage/Distance	
dent	Current active Dental problems	
otprob	Other problems (toxicity)	
toxic	Toxicity	*[Repeated]*
toxgrd	Toxicity Grade	*[Repeated]*
toxot	Toxicity other	*[Repeated]*

Annual follow-up:

ptini	Patient Initials
dob	Date of Birth
patid	Patient Trial No
point	Follow up time point
doass	Date of Assessment
fustat	Status
dostat	Date last known to be alive
osteo	Osteonecrosis of the Jaw
doosteo	Date of diagnosis

Withdrawal

ptini	Patient Initials
dob	Date of Birth
patid	Patient Trial No
rewith	Level of withdrawal
dowith	Date of withdrawal
intol	Intolerance to treatment
patcho	Patient choice
clidec	Clinicians Decision
nocomp	Non Compliance
withot	other, specify

SRE:

ptini	Patient Initials	
dob	Date of Birth	
patid	Patient Trial No	
dosre	Date of visit	
fracnum	Fractures since last visit	
sreste	Site	*[Repeated]*
sreoth	Specify	*[Repeated]*
doid	Date Identified	*[Repeated]*
disrel	Disease related/traumatic	*[Repeated]*
sresym	Symptomatic/asymptomatic	*[Repeated]*
xrysre	Radiotherapy since last visit	
xryste	Site	*[Repeated]*
xryoth	Specify	*[Repeated]*
doxry	Start Date	*[Repeated]*
hypmal	Hypercalcemia of Malignancy	
srco	value	*[Repeated]*
dosrco	Onset Date	*[Repeated]*
ortsurg	Orthopaedic surgery since last visit	
ortste	Site	*[Repeated]*
ortoth	Specify	*[Repeated]*
doort	Date of surgery	*[Repeated]*
spi	Spinal Cord compression since last visit	
spilvl	Level	*[Repeated]*
desrel	Disease related/traumatic	*[Repeated]*
dospi	Date of diagnosis	*[Repeated]*
spimtd	Method	*[Repeated]*
spioth	Specify	*[Repeated]*

SAE:

ptini	Patient Initials	
dob	Date of Birth	
patid	Patient Trial No	
dorep	Report date	
reptyp	Report Type	
sex	Sex	
saeser	Why was the event serious	
saedes	Description of SAE	
saenme	SAE Name (CTACE)	*[Repeated]*
saegrd	Grade (CTCAE)	*[Repeated]*
dosae	Onset Date	*[Repeated]*
dspsae	Resolved Date	*[Repeated]*
saestat	SAE Status	*[Repeated]*
saerel	SAE Relationship	*[Repeated]*
saeexp	Expectedness	*[Repeated]*
saetrt	Trial Drug	
dose	Total Daily Dose	
dodose	Start date	
condse	Ongoing Therapy	
dostdse	End date	
actn	Action taken	
clin	Reporting Clinicians Name	
clintl	Contact Telephone No.	
doclin	Date completed	

End of treatment:

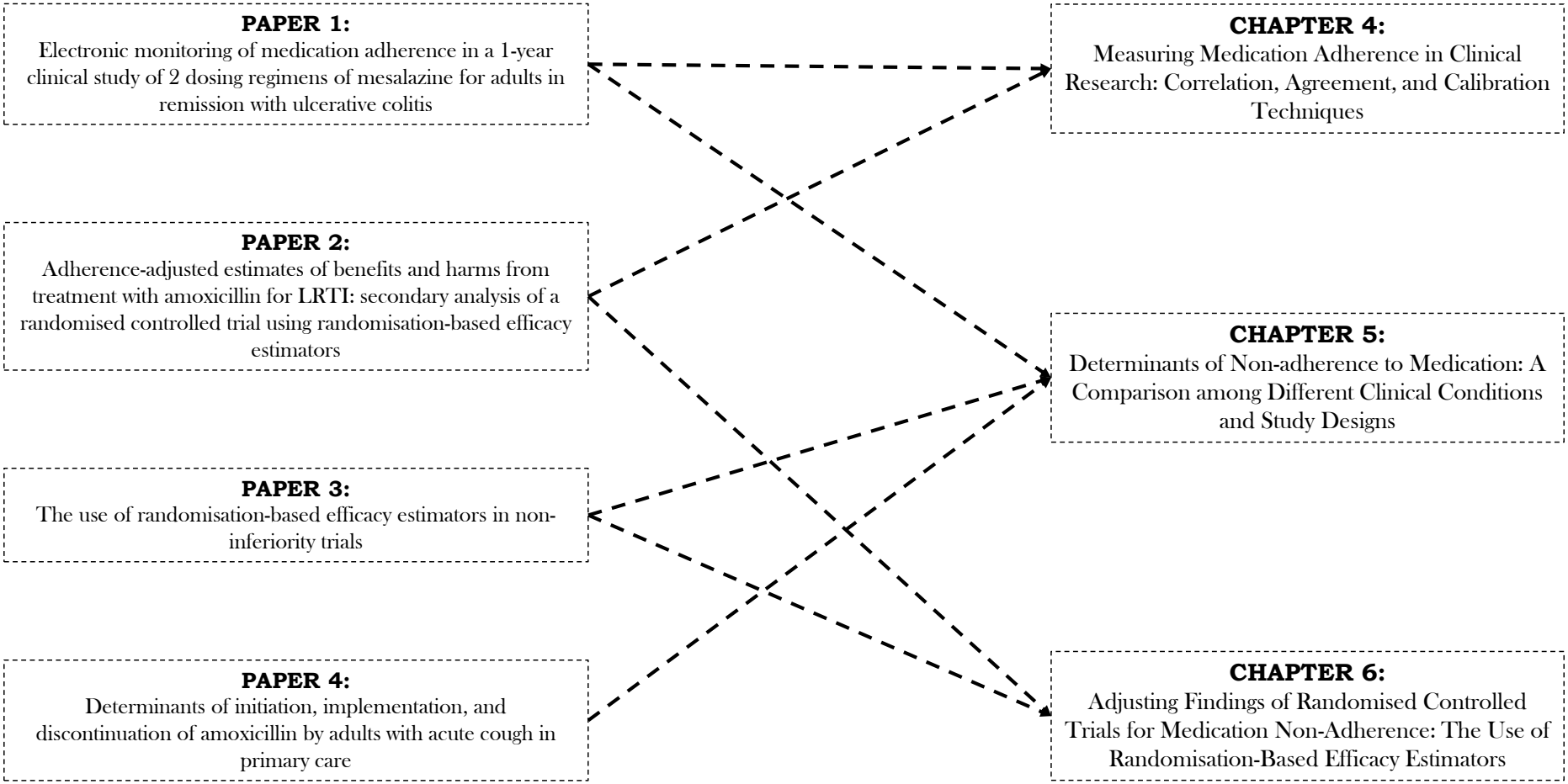
patid	Patient Trial No	
dob	Date of Birth	
ptini	Patient Initials	
doass	Date of Assessment	
ht	Height	
dothxy	Date of Thoracic Spine Xray	
thles	Mets lesion in Thoracic Spine	
thtype	Type of Lesion in Thoracic Spine	
thfrac	Fracture/Vertabal collapse visible -Thoracic Spine	
dolmxy	Date of Lumbar spine Xray	
lumles	Mets lesion - Lumbar spine	
lumtype	Type of Lesion in Lumbar Spine	
lumfrac	Fracture/Vertabal collapse visible -Lumbar Spine	
radioot	Other - specify	*[Repeated]*
doot	Date of Xray	*[Repeated]*
otles	Mets lesion	*[Repeated]*
ottype	Type of Lesion other	*[Repeated]*
othfrac	Fracture/Vertabal collapse visible	*[Repeated]*

Death:

ptini	Patient Initials
dob	Date of Birth
patid	Patient Trial No
dod	Date of death
cause	Primary Cause of death
cseoth	Specify

Appendix IV – Papers published from work carried out as part of my thesis

I: Diagram illustrating papers and how the work within them links to thesis chapters



Electronic Monitoring of Medication Adherence in a 1-year Clinical Study of 2 Dosing Regimens of Mesalazine for Adults in Remission with Ulcerative Colitis

David Gillespie, BSc, Kerenza Hood, PhD,* Daniel Farewell, PhD,† Rachel Stenson, MSc,‡ Christopher Probert, MD,§ and A. Barney Hawthorne, DM¶*

Background: Adherence to medication is an issue of great importance for patients with ulcerative colitis. Once daily mesalazine seems to be no worse than divided doses in preventing relapse in remitting patients. Although this has been attributed to improved adherence, detailed measures of adherence have been lacking from previous studies.

Methods: A 1-year substudy was conducted alongside a trial that compared 2 different dosing regimens (once daily versus three times daily) of mesalazine for patients in remission with ulcerative colitis. Participants in the substudy had their adherence monitored electronically using the medication event monitoring system, self-report, and tablet counts. We compared measures, determined factors associated with adherence and associations between adherence and relapse, modeled adherence over time, and explored behavioral aspects.

Results: We included 58 participants. Adherence was high across all measures (89.3% self-report, 96.7% tablet counts, and 89.2% medication event monitoring system). Agreement between the measures was poor at times. Adherence according to the medication event monitoring system best distinguished between the participants who relapsed (71.4%) and those who remained in remission (93.4%), although this difference was not statistically discernible at the 5% level. Adherence deteriorated over the study period, with three times daily participants generally less adherent than once-daily participants (odds ratio, 0.03; 95% confidence interval, 0.01–0.08). Adherence was higher on weekdays (odds ratio, 1.47; 95% confidence interval, 1.31–1.65) and around clinic visit dates (odds ratio, 1.43; 95% confidence interval, 1.18–1.72).

Conclusions: Simple dosing regimens are preferable to multiple daily dosing regimens. Electronic monitoring of adherence should be used more often in clinical studies. Self-reported adherence and tablet counts may underestimate adherence. Adherence declined over time, and adherence was generally lower and more varied for those allocated to the three times daily regimen.

(Inflamm Bowel Dis 2014;20:82–91)

Key Words: medication adherence, ulcerative colitis, MEMS, mesalazine, clinical trial

Adherence to medication has long been recognized as a topic of great importance, concern, and complexity, particularly for patients with long-term chronic conditions.[1] Poor adherence to medication has been demonstrated to be associated with reduced effectiveness of pharmacological treatments. In some areas, poor adherence has been shown to lead to the development of more severe life-threatening illnesses.[2,3] In addition to being a major public health concern, poor adherence to medication places a substantial financial burden on healthcare systems, both through the prescription of medication that is not taken and through medication adherence-related hospital admissions.[3–7]

Coated formulations of mesalazine (Asacol) have been demonstrated in many trials to prevent relapses in patients who have achieved remission of ulcerative colitis (UC).[8,9] Treatment is often prescribed in divided daily doses (e.g., two or three times daily dosing schedules [TDS]),[10] with adherence and treatment success suffering as a result.[11,12] There has been an increasing interest in evaluating once-daily (OD) dosing of mesalazine.[3,13–15]

The Colitis Once-Daily Asacol study assessed the efficacy and safety of OD dosing with mesalazine versus TDS dosing over a 12-month period for patients in remission with UC. The study

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found that the OD regimen was no worse than TDS in terms of clinical relapse.[16] Although this was attributed to better adherence, the measures used (self-report and tablet counts at clinic visits) have several known limitations,[17] with detailed measures of adherence lacking from both the main trial and from previous studies in the UC field. Foreseeing this as a problem, a substudy was run alongside the main study. The aim of the substudy was to evaluate the impact of OD dosing on treatment adherence, using a more intensive monitoring process to capture adherence than that had been used previously. Using this substudy, the aim of this article was to investigate the use of the electronic monitoring device for assessing medication adherence, comparing this method with those used in the main trial, and exploring patterns in adherence over time.

MATERIALS AND METHODS

Study Design

The original study was an investigator-blind multicenter randomized trial comparing OD Asacol given as three 800 mg tablets (OD group), with one 800 mg Asacol tablet given TDS as a maintenance therapy over a 12-month period or until relapse of UC. Participants attended trial follow-up visits at 6 weeks, 6 months, and 12 months after randomization, or in the event of a suspected relapse. In addition, participants were also contacted through telephone at 3 and 9 months. A subgroup of participants was invited to participate in a substudy, with a separate consent process, where they were given a bottle cap that recorded the date and time of bottle openings throughout the study. Details of the randomization and data collection methods are described elsewhere.[16] Further analyses were undertaken on this subgroup of participants to explore our study questions.

Participants

Participants were recruited into the main trial with UC in remission on maintenance therapy with mesalazine, sulfasalazine, olsalazine, or balsalazide for at least 4 weeks, but who had experienced at least 1 relapse within the previous 2 years. Participants had to be aged older than 18 years, if female to be taking adequate contraception, and able to give informed consent. Participants were excluded if they had Crohn's disease, symptoms of active colitis, a modified Baron score at sigmoidoscopy of 2 or 3, used enema or suppository therapy for UC in the past 4 weeks, had started or altered the dose of azathioprine or 6-mercaptopurine in the past 3 months, had intolerance to mesalazine, known HIV infection, significant renal or hepatic impairment, or other medical or psychiatric disorder that in the opinion of the investigator would affect participation in the study, or women if pregnant or lactating. Further participant details are described elsewhere.[16] Five of the 32 centers that recruited participants into the main trial were also asked to recruit participants into the substudy.

Measures of Medication Adherence

Medication adherence was monitored through self-report and tablet counts at the trial follow-up visits (6 weeks, 6 months, and 12 months postrandomization, or at point of relapse) and electronically via the medication event monitoring system (MEMS). These methods will now be discussed in turn.

Self-report

Participants were asked about their perceived adherence levels (i.e., whether or not they had taken their study tablets as prescribed at least 90% of the time), and the ease of medication taking (very easy, fairly easy, fairly difficult, or very difficult to remember to take their medication). For analysis purposes, we assumed that participants reported their levels of adherence honestly and had perfect recall in the time under consideration.

Tablet Count

Tablet counts were performed by trained research nurses at each trial follow-up visit. We assumed that the difference between the number of tablets participants started with and the amount remaining at each follow-up visit equated to the amount taken during the time interval. For the purposes of reporting, adherence measured using tablet counts was reported as the number of tablets taken expressed as the percentage of correct number of tablets taken. Tablet counts provide a measure of consumption over a defined period rather than adherence patterns over a defined period.

Electronic Monitoring

The date and time of bottle cap openings were electronically recorded using the MEMS, with data uploaded onto the study database at each trial follow-up visit. Use of the MEMS assumes that the correct number of tablets is removed and consumed each time the bottle is opened. Adherence was reported as the percentage of days that a participant was adherent (i.e., the percentage of days that a participant opened their bottle the correct number of times).

Statistical Methods

Medication adherence measures were reported as detailed above and compared using nonparametric methods, correlation coefficients, and scatter plots. For the comparison between tablet count and MEMS adherence, a Bland–Altman plot was constructed to illustrate the level of agreement between the 2 measures,[18] where perfect agreement would be illustrated by all data points lying along the line $y = 0$, with symmetric random scatter above and below the line an indication of no systematic biases in either of the measures.

Factors associated with varying levels of medication adherence and the association between medication adherence and clinical relapse were determined using appropriate statistical models.

Using the data obtained from the MEMS caps, medication adherence was modeled over time by fitting a 2-level generalized linear (logistic) mixed-effects model, with daily adherence indicators nested within participants. A participant was assumed to be adherent on a given day if they opened their cap the required number of times (once for the OD group and 3 times for the TDS group). Nonlinear patterns of adherence over time were accounted for using B-splines.[19] The model also accounted for different

participant adherence patterns by fitting B-spline estimates of a time-varying mean with random coefficients, thereby allowing each participant to have their own individual curve that was not restricted by the overall fixed effect curve. Trial arm (dosing regimen) was included in the model as an explanatory variable to describe the difference in adherence patterns between the regimens. The interaction between trial arm and time was also explored.

To explore any potential differences in adherence during the week compared with the weekend, the above model was extended by the addition of an indicator that distinguished whether a day fell on a weekday or weekend. Its interaction with trial arm was also explored to determine whether these differences were larger for participants allocated to a particular dosing regimen. Similarly, the model was also extended to explore any potential differences in adherence at clinic visit dates (defined as the date of a scheduled clinic visit and 1 week either side of this date). Model fit was assessed using Akaike's Information Criterion.[20] Results are presented as odds ratios (OR) with associated 95% confidence intervals (CIs) and *P* values.

The term "statistically discernible" will be used in place of "statistically significant" throughout the article, as the authors believe it is a more meaningful descriptor of the results arising from hypothesis testing.

Data management and descriptive statistics were performed using IBM SPSS Statistics[20,21] with the generalized linear mixed-effect modeling implemented in R.[22,23]

ETHICAL CONSIDERATIONS

Ethical approval was received for this study (REC reference number: 05/Q2502/156). Written informed consent was obtained from each participant. The study was registered at ClinicalTrials.gov (NCT00708656).

Role of Funding Source

The funding sources had no roles in data collection, analysis, or interpretation; report writing; or submission. D. Gillespie had full access to all the data in the study and takes responsibility for the integrity and the accuracy of the data analysis. All authors had responsibility for the final decision to submit for publication.

Role of Study Sponsor

Cardiff and Vale University Health Board, as trial sponsor was responsible for the scientific quality of the study, monitoring, and management to ensure quality and accuracy of the data, and the safety and well-being of participants.

RESULTS

Participants

In total, 579 participants were assessed for eligibility in the main Colitis Once-Daily Asacol trial, with a total of 213 randomized from 32 centers. Of these participants, 71 from 5 centers were approached to take part in the substudy. Ten participants declined to take part, with the most common reason for nonparticipation being the unwillingness to carry around the MEMS bottles during the daytime (e.g., because of work commitments). Three participants did not provide any MEMS cap data because of faulty caps, leaving 58 participants who took part in the substudy and provided data. Participants were approximately equally split between the trial arms (Fig. 1). The average age at study entry was 49.4 years (standard deviation, 15.72 years) and 55.2% were male. Overall, 29.8% of participants had extensive colitis, 50.9% left-sided colitis or proctosigmoiditis, and 19.9% had proctitis at study entry. The percentage of participants who classified themselves as current smokers was 10.3%, 44.8% classified themselves as nonsmokers with the remaining 44.8% ex-smokers. The median duration of remission before study entry was 6 months (interquartile range [IQR], 3.0–12.0 months) (Table 1). Participants were mostly representative of those in the main trial.[16]

Medication Adherence

Self-reported adherence data was available for 56 participants (96.6% of all sub-study participants). At the final follow-up visit (12 months or relapse if before 12 months), 50 participants believed that they had taken their medication at least 90% of the time throughout the study period (89.3%). The remaining 6 stated that they had taken their medication <90% of the time. In total, 45 of the 50 participants who reported being adherent found it fairly or very easy to remember to take their medication (90.0%). Of the 6 participants who reported not being adherent, 5 stated that they found it difficult (fairly or very) to remember to take their medication. Figure, Supplemental Digital Content 1, http://links.lww.com/IBD/A379, describes self-reported adherence longitudinally (at each of the follow-up visits). Adherence data based on tablet counts was available for 49 participants (84.5% of all sub-study participants). The median percentage of correct number of tablets taken, conducted at the final follow-up visit, was 96.7% (IQR, 89.0%–99.2%). The median percentage of adherent days, collected using the MEMS, was 89.2% (IQR, 52.3%–96.7%).

Comparison of Measures

Participants who reported that they had taken their medication as prescribed had a median percentage of correct number of tablets taken, according to tablet counts, of 97.6% (IQR, 92.3%–99.4%). Similarly, their median percentage of adherent days according to the MEMS was 92.9% (IQR, 63.1%–97.3%). Those that believed that their adherence was <90% had considerably lower median adherence levels according to these 2 measures, with tablet count median 76.6% (IQR, 74.3%–83.4%) and MEMS median 34.1% (IQR, 14.0%–45.8%). Both differences were statistically discernible, with both $P \leq 0.001$.

Adherence measured by tablet counts was strongly correlated with adherence measured by the MEMS, with a coefficient of 0.756 (Fig. 2). Although this suggests a strong relationship between the 2 measures, Figure 3 demonstrates that there is a distinct lack of agreement between the 2, with adherence measured

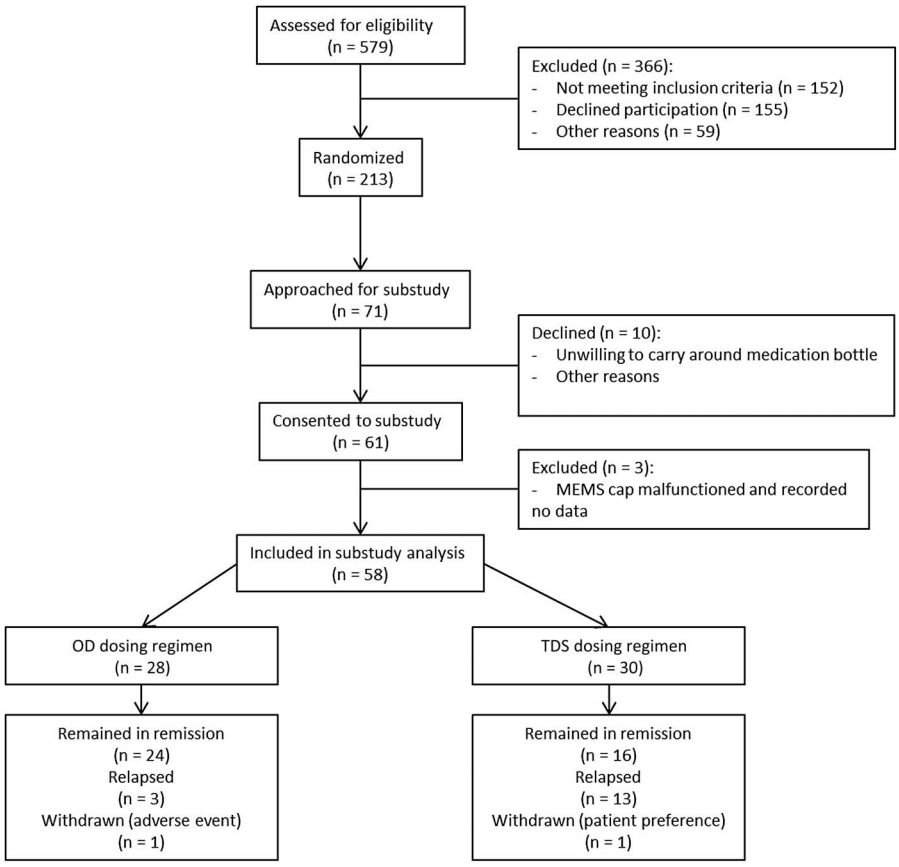

FIGURE 1. Participant flow diagram.

using the MEMS consistently lower than adherence measured using tablet counts, particularly for participants with low levels of adherence.

Factors Associated with Medication Adherence

We found no statistically discernible associations between medication adherence and demographic variables (age, gender, smoking, or employment status). The trial arm (i.e., prescribed dosing regimen) that participants were randomly assigned to was the only variable that was consistently different for the 3 adherence measures. Of the participants randomized to OD, 26/27 (96.3%) described themselves as at least 90% adherent compared with 24/29 (82.8%) randomized to TDS. By tablet counts, the median percentage of correct number of tablets taken for OD participants was 98.9% (IQR, 94.8%–99.6%) compared with 94.2% for TDS participants (IQR, 83.4%–97.4%). MEMS cap data show that the median percentage of adherent days for OD participants was 96.6% (IQR, 92.7%–98.0%) compared with 54.9% for TDS participants (IQR, 34.4%–85.7%). The differences observed for the tablet count and MEMS adherence measures were statistically discernible ($P = 0.005$ and $P < 0.001$, respectively), whereas the self-report adherence measure was not (P value based on the exact test was 0.195), although there were only a few participants who described themselves as <90% adherent (Table 2).

Medication Adherence and Relapse

In total, 16 participants included in the substudy relapsed during the study period (27.6%). The median number of days that relapsing participants were in the study was 216.5 (IQR, 65.5–262.0).

All 16 participants who relapsed described themselves as at least 90% adherent, whereas 85.0% of participants who remained in remission described themselves as at least 90% adherent (34/40).

The median percentage of correct number of tablets taken for participants who relapsed was 96.0% (IQR, 83.7–97.4) compared with a median percentage of 97.7% for those who remained in remission (IQR, 89.3–99.4).

According to the MEMS, the median percentage of adherent days for participants who relapsed was 71.4% (IQR, 39.8–93.0) compared with a median percentage of 93.4% for those who remained in remission (IQR, 60.5–97.3).

The association between medication adherence and clinical relapse was not statistically discernible at the 5% level for any of the adherence measures.

TABLE 1. Participant Characteristics at Study Entry

Variable	Substudy Participants (n = 58)
Age at study entry*	49.4 (15.72)
Gender (male)†	32 (55.2)
Maximum documented extent of UC	
Extensive†	17 (29.8)
Left-sided or sigmoid†	29 (50.9)
Proctitis†	11 (19.9)
Smoking status	
Nonsmoker†	26 (44.8)
Current smoker†	6 (10.3)
Ex-smoker†	26 (44.8)
Employment status	
In full-time employment†	32 (55.2)
Not in full-time employment†	26 (44.8)
Disease duration, yrs‡	6.0 (2.0–12.0)
Number of relapses in past 2 years‡	1.0 (1.0–2.0)
Duration of remission, mo‡	6.0 (3.0–12.0)
Calprotectin concentration, mg/kg stool‡	46.3 (19.5–112.3)
Baseline sigmoidoscopy score	
Normal†	42 (72.4)
Not normal†	16 (27.6)

*Mean (standard deviation).
†Number (%).
‡Median (IQR).

Medication Adherence over Study Period

There was a small but statistically discernible decrease in medication adherence over time. As illustrated by Figure 4, there is an initial decrease in adherence followed by a period of stabilization, with some further reduction in adherence towards the end of the study. There was a marked difference between the 2 dosing regimens (OR for TDS regimen, 0.03; 95% CI, 0.01–0.08; $P < 0.001$). As is also evident in Figure 4, there was considerably more variation in individual adherence patterns over time for TDS participants than for OD participants. There was no discernible interaction between dosing regimen and time (all $P \geq 0.124$), indicating that although medication adherence was generally higher for participants allocated to the OD regimen, the adherence in both the groups decreased over time at a similar rate.

Behavioral Aspects of Medication Adherence

Comparison Between Weekday and Weekend Medication Adherence

As demonstrated by Figure 5, medication adherence was generally lower on weekends than it was on weekdays, with the difference larger for participants allocated to the TDS dosing regimen than for those allocated to OD. There was a small but statistically discernible difference in adherence on weekdays compared with adherence at weekends, with odds of being adherent 47% higher on weekdays compared with weekends (OR for weekday, 1.47; 95% CI, 1.31–1.65; $P < 0.001$). The interaction between time of the week and dosing regimen was not discernible at the 5% level ($P = 0.111$).

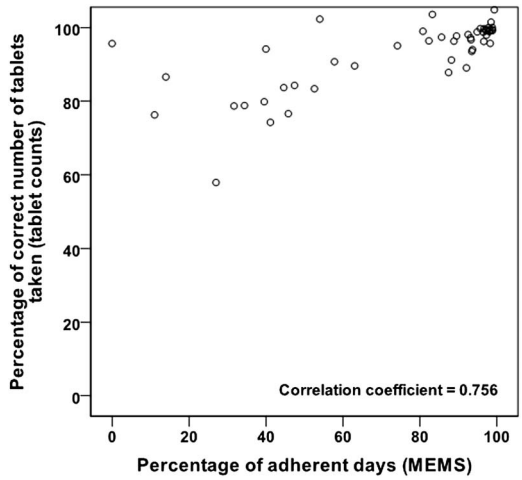

FIGURE 2. Scatter plot comparing tablet counts to MEMS adherence. One participant had a reported tablet count adherence level of 244% and were adherent for 40% of the days that they were participating in the trial (according to the MEMS). This was viewed as an outlier, and the participant had their tablet count recoded assuming that they did not return an unopened pack of 180 tablets (reducing their tablet count adherence to 94.2%). This increased the size of the correlation coefficient from 0.681 to 0.756. Removing the outlier entirely increased the coefficient to 0.757.

Medication Adherence Around Clinic Visit Dates

Similarly, there was a small but discernible difference between adherence around clinic visit times and nonclinic visit times, with the odds of being adherent around clinic visit times 43% higher compared with nonclinic visit times (OR for clinic visit times, 1.43; 95% CI, 1.18–1.72; $P < 0.001$). The interaction between time of visit and dosing regimen was not discernible at the 5% level ($P = 0.429$).

DISCUSSION

Summary of Key Findings

This study found that medication adherence, as measured by self-report, tablet counts, and the MEMS, was generally high. Although self-reported adherence produced estimates consistent with the other 2 measures, there were noticeable disparities, particularly between tablet counts and the MEMS. The MEMS provided estimates of adherence lower than those provided by tablet counts. Although the relationship between MEMS adherence and relapse was not statistically discernible at the 5% level, compared with the other measures it best distinguished between

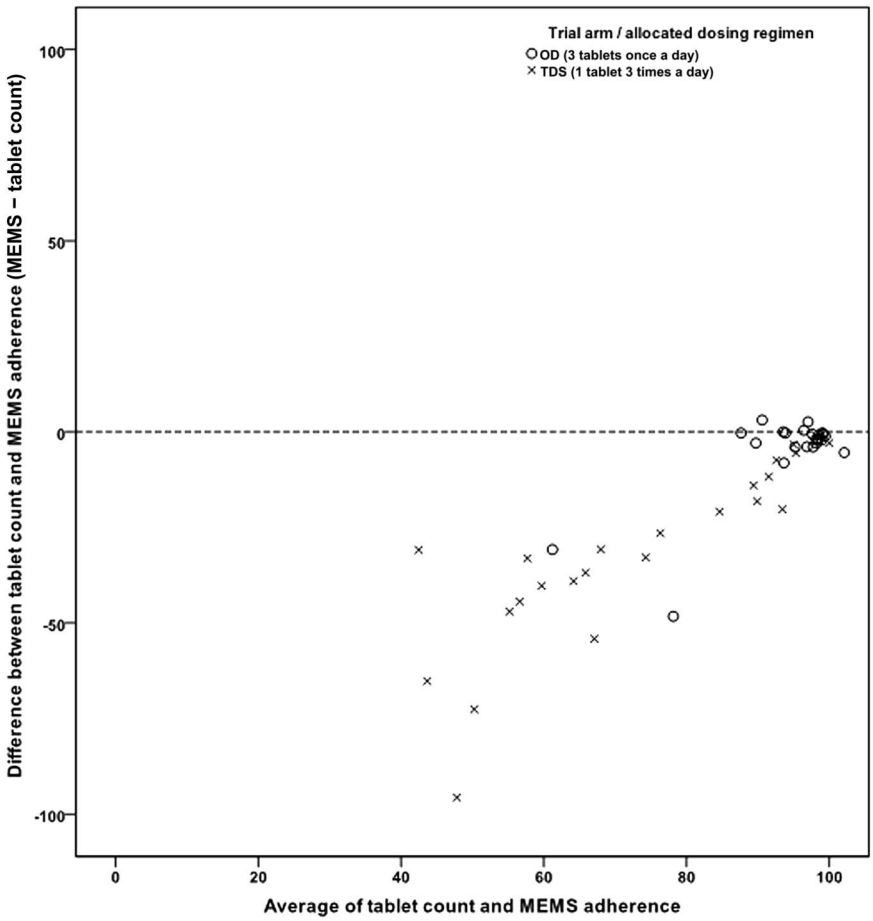

FIGURE 3. Bland-Altman plot comparing the agreement between tablet counts and MEMS adherence.

the participants who relapsed and those who remained in remission, suggesting that this may be the most useful method for measuring medication adherence in clinical studies of patients with long-term chronic conditions. There was a small but statistically discernible decrease in medication adherence over the 12-month study period, and while adherence levels were largely influenced by the dosing regimen to which participants were randomized, there was no evidence of different rates of decreases for these regimens. Finally, adherence to medication was slightly better on weekdays than it was at weekends and slightly better around clinic visit times than at other times.

Strengths and Limitations

This is the first study to electronically monitor medication adherence in adults in remission with UC. Participants were monitored for up to 12 months (or until point of relapse), which allowed for both a rich description of adherence over a long time period and for the exploration of various behavioral aspects of medication adherence. However, although the study collected and analyzed adherence data for almost 15,000 participant days, this only equated to a total of 58 participants. Therefore, there is substantial uncertainty around some of the estimates.

Adherence was measured over the study period using self-report, tablet counts, and electronic measures. This allowed for a direct comparison of measures within the same individuals, and enabled a greater understanding of the utility of each of the measures. However, all adherence measures used in the study were indirect, relying on various assumptions that were difficult to test. Although measuring adherence using self-reports was simple, cheap, and convenient to implement, particularly in the case of our study, as regular follow-up visits were a necessary feature, recall is not always perfect, and participants are not always accurate. A participant who forgot to take his medication may have had no conscious recollection that he forgot his medication.[24] The use of a validated questionnaire to capture self-reported adherence may have also provided a greater level of understanding than the self-report questions that were asked in this study.[25] Adherence measured through tablet counts was similarly simple, cheap, and convenient. However, mistakes in counting, intentional increases in medication around follow-up visits (so-called "white coat" adherence), and intentional tablet misrepresentation (e.g., by not bringing all medication to follow-up visits)[1] may have distorted the true number of tablets taken. There may have been social desirability factors that influenced participants to intentionally misrepresent their

TABLE 2. Factors Associated with Medication Adherence Across all 3 Measures

Variable	Medication Adherence According To:						
	Self-report: Yes (n = 50)	Self-report: No (n = 6)	*P*	Tablet Counts (n = 49)	*P*	MEMS (n = 58)	*P*
Age at baseline*	52.0 (39–60)	50.0 (32.0–57.0)	0.853	0.20	0.169	0.14	0.284
Gender†							
Male	28 (56.0)	2 (33.3)	0.401	97.4 (92.4–99.3)	0.252	92.4 (77.5–96.7)	0.217
Female	22 (44.0)	4 (66.7)		94.9 (84.3–99.1)		72.7 (44.6–97.2)	
Maximum documented extent of UC†‡							
Extensive	13 (26.0)	2 (40.0)	0.280	95.7 (85.1–98.7)	0.254	89.6 (41.2–95.8)	0.142
Left-sided or sigmoid	28 (56.0)	1 (20.0)		98.0 (94.0–99.2)		93.2 (80.8–97.3)	
Proctitis	9 (18.0)	2 (40.0)		92.4 (77.7–97.9)		57.1 (42.9–92.3)	
Smoking status†							
Nonsmoker	23 (46.0)	3 (50.0)	0.664	96.4 (90.2–99.1)	0.971	93.3 (54.0–96.7)	0.710
Current smoker	6 (12.0)	0 (0.0)		96.2 (94.2–98.9)		70.2 (40.0–96.6)	
Ex-smoker	21 (42.0)	3 (50.0)		97.4 (83.4–99.4)		88.7 (52.3–97.2)	
Employment status†							
In full-time employment	28 (56.0)	3 (50.0)	1.000	96.7 (91.6–99.0)	0.809	93.3 (57.7–97.3)	0.325
Not in full-time employment	22 (44.0)	3 (50.0)		96.0 (84.3–99.2)		84.5 (47.4–95.8)	
Disease duration, yrs*	17.0 (5.0–21.0)	5.5 (2.0–10.0)	0.108	0.001	0.992	−0.18	0.177
Number of relapses in the past 2 years*	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.892	−0.02	0.914	0.11	0.393
Duration of remission, mo*	6.5 (3.0–13.0)	5.0 (3.0–11.0)	0.690	0.08	0.571	−0.09	0.487
Calprotectin concentration, mg/kg stool*	40.6 (19.5–106.6)	97.8 (19.5–199.0)	0.451	−0.10	0.498	−0.03	0.819
Baseline sigmoidoscopy†							
Normal	35 (70.0)	5 (83.3)	0.662	95.7 (86.6–99.2)	0.318	90.3 (45.8–96.7)	0.281
Not normal	15 (30.0)	1 (16.7)		97.7 (95.6–99.1)		89.2 (77.5–98.3)	
Allocated dosing regimen (trial arm)†							
OD regimen	26 (52.0)	1 (16.7)	0.195	98.9 (94.8–99.6)	0.005	96.6 (92.7–98.0)	<0.001
TDS regimen	24 (48.0)	5 (83.3)		94.2 (83.4–97.4)		54.9 (34.4–85.7)	

*Median (IQR) for self-report, Spearman's correlation coefficient for tablet counts and MEMS.
†Number (%) for self-report, median (IQR) for tablet counts and MEMS.
‡There was 1 missing value of maximum documented extent of UC.

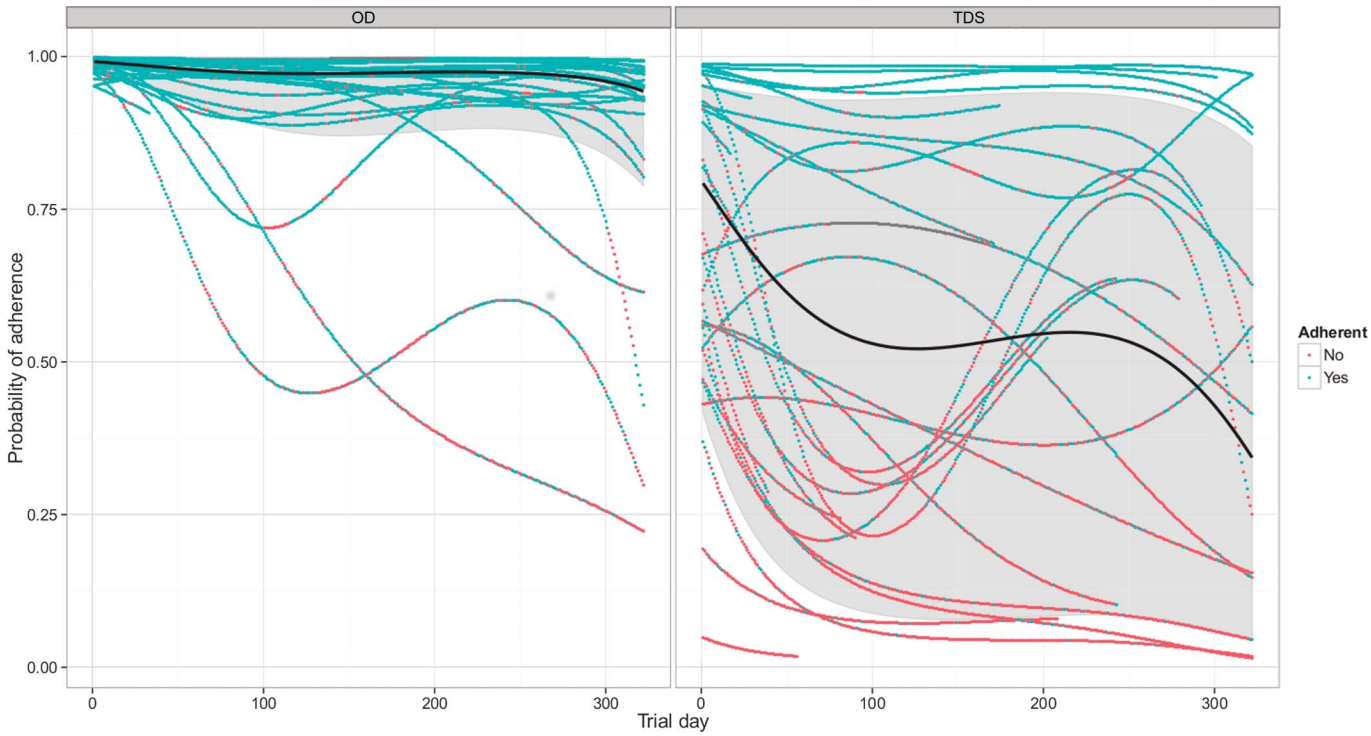

FIGURE 4. Estimated medication adherence probabilities over time (using the MEMS cap data). The bold black lines represent the overall estimated adherence probabilities derived from the fixed effects of the Generalized Linear Mixed-effects Mode, with the grayed area representing the 95% confidence bands around these probabilities. All other curves are estimated individual adherence probabilities, derived from the random effects of the Generalized Linear Mixed-effects Mode, for each participant in the study. Color-coded indicators are attached to each individual curve to represent days that a participant adhered to or did not adhere to their medication (blue and red, respectively). There were 2 instances of individuals having MEMS caps that malfunctioned for a small period during the study, with no data collected during this time. These periods are marked as gray on the corresponding individual curves.

level of adherence.[26] The use of an electronic monitoring device such as the MEMS was deemed advantageous, as it could provide detailed insights into patterns of adherence over an entire study period. Consequently, it is viewed by some to be the current gold standard for measuring medication adherence.[27] However, with this additional level of detail comes an increase in cost. It was also difficult to determine whether the correct numbers of tablets were removed (and ingested) at each dosing event.[17] In addition, the MEMS cap is bulky, and significantly disadvantages patients obliged to carry a large bottle and cap with them during the day, if on a TDS dosing regimen.

The study compared an OD regimen against a TDS regimen, with the TDS regimen chosen as the comparator, as it was deemed the most logical way to divide 3 tablets over the course of the day and is still used by a substantial number of gastroenterologists.[28] Although there is evidence of medication adherence issues for TDS regimens, less pronounced differences have been shown when comparing OD regimens with BD regimens.[29]

Comparisons with Other Studies

Levels of medication adherence in our study were generally high, as found in other trials measuring adherence in UC.[30,31] Our study found medication adherence levels higher than those reported in prospective community-based studies of patients with UC,[32] which is to be expected given both the increased motivation and monitoring generally seen in participants in clinical trials.

The finding of occasional poor agreement between the adherence measures, with more traditional methods providing higher estimates than those provided by the MEMS, particularly when adherence was poor, is consistent with the findings of a study conducted in young patients with inflammatory bowel disease.[33]

An inverse relationship between the complexity of a dosing regimen and the adherence has long been established.[27,34] Our findings are consistent with this work and, given the association seen in previous work between the levels of adherence and adverse clinical outcomes,[35,36] support the use of a OD dosing regimen.

The finding that adherence deteriorated over the 12-month study period is also consistent with previous literature. Indeed, a recent study conducted in Canada found a 1-year persistence rate $<50\%$ for people diagnosed with UC,[37] with an older study conducted in the USA finding that 55% of participants continued to take their UC medication.[38] The finding also coincides with those reported for other chronic conditions.[39]

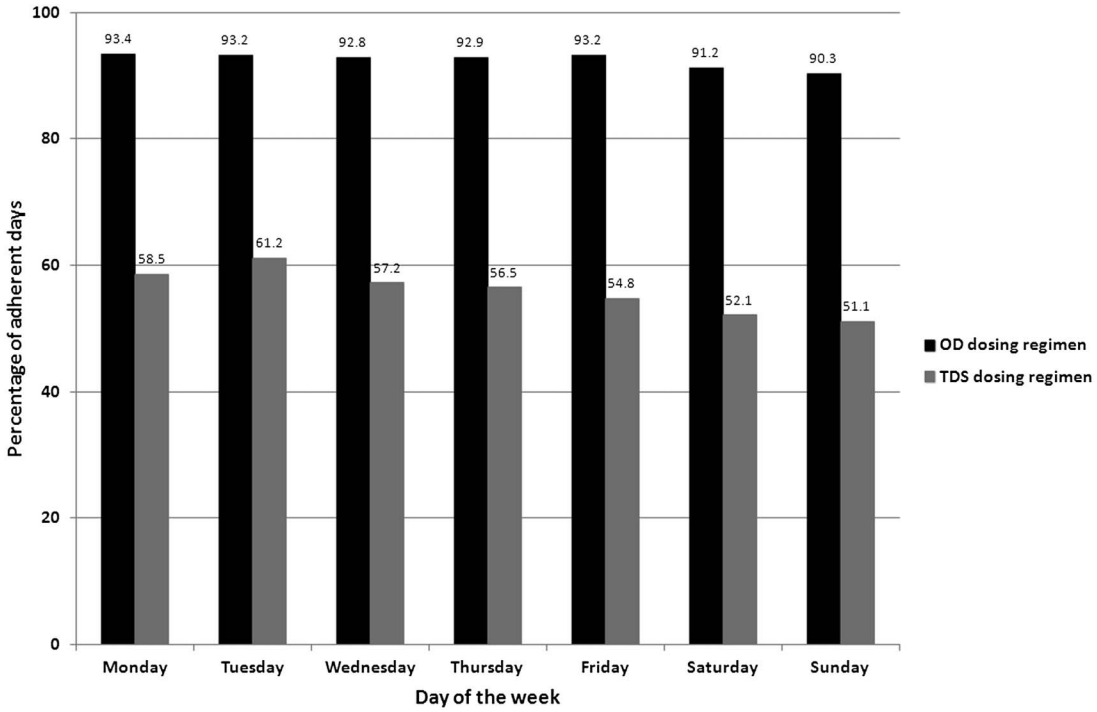

FIGURE 5. Comparison of percentage of adherent days by day of the week (using the MEMS cap data).

White-coat adherence is a phenomenon that has been previously documented, with 2 recent studies of chronic conditions in particular demonstrating improved adherence around clinic visit dates.[40,41] The finding that adherence is better during weekdays is comparable to the findings of a study of antipsychotic medication adherence in people with schizophrenia, which found that dose omissions were more likely to occur on weekends.[42]

Interpretation and Implications

This study has demonstrated that ongoing electronic monitoring of medication adherence in clinical research provides a level of information that is not possible with standard methods. It is likely that self-reported adherence and tablet counts may significantly underestimate adherence.

For patients with chronic conditions, required to take long-term medication, simple single dosing regimens are preferable over more complex ones. Therefore, in clinical studies involving patients with long-term chronic conditions, researchers should strongly consider collecting medication adherence data electronically, particularly where patients are given complex dosing regimens to follow. There was a general decline in medication adherence over time. Further research is needed to develop and evaluate interventions aimed at improving adherence to medication for long-term chronic conditions.

ACKNOWLEDGMENTS

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BMJ Open

Adherence-adjusted estimates of benefits and harms from treatment with amoxicillin for LRTI: secondary analysis of a 12-country randomised placebo-controlled trial using randomisation-based efficacy estimators

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ABSTRACT

Objectives: Estimate the efficacy of amoxicillin for acute uncomplicated lower-respiratory-tract infection (LRTI) in primary care and demonstrate the use of randomisation-based efficacy estimators.

Design: Secondary analysis of a two-arm individually-randomised placebo-controlled trial.

Setting: Primary care practices in 12 European countries.

Participants: Patients aged 18 or older consulting with an acute LRTI in whom pneumonia was not suspected by the clinician.

Interventions: Amoxicillin (two 500 mg tablets three times a day for 7 days) or matched placebo.

Main outcome measures: Clinician-rated symptom severity between days 2–4; new/worsening symptoms and presence of side effects at 4-weeks. Adherence was captured using self-report and tablet counts.

Results: 2061 participants were randomised to the amoxicillin or placebo group. On average, 88% of the prescribed amoxicillin was taken. The original analysis demonstrated small increases in both benefits and harms from amoxicillin. Minor improvements in the benefits of amoxicillin were observed when an adjustments for adherence were made (mean difference in symptom severity −0.08, 95% CI −0.17 to 0.01, OR for new/worsening symptoms 0.81, 95% CI 0.66 to 0.98) as well as minor increases in harms (OR for side effects 1.32, 95% CI 1.12 to 1.57).

Conclusions: Adherence to amoxicillin was high, and the findings from the original analysis were robust to non-adherence. Participants consulting to primary care with an acute uncomplicated LRTI can on average expect minor improvements in outcome from taking amoxicillin. However, they are also at an increased risk of experiencing side effects.

Trial registration numbers: Eudract-CT 2007-001586-15 and ISRCTN52261229.

The trial was registered at EudraCT in 2007 due to an administrative misunderstanding that EudraCT was a suitable registry—which it was not in 2007, but has become since. On discovery of this error, the trial was also registered at ISRCTN (January 2009). Trial procedures did not change between the two registrations.

Strengths and limitations of this study

- This is the largest randomised placebo-controlled trial evaluating amoxicillin for acute, uncomplicated lower-respiratory-tract infection in primary care to date.
- Consideration of the benefits and harms of amoxicillin allowed for a balanced assessment of this treatment.
- Multiple types of adherence measures meant that agreement between measures could be assessed.
- As is often the case in research, indirect measures of medication adherence were collected. These rely heavily on their inherent assumptions (eg, accurate patient recall, returning of all unused medication). Direct measures (eg, direct observation) are preferable, but often not feasible in practice.
- Structural mean models enabled an adjustment for treatment non-adherence while maintaining a comparison of groups as randomised.

INTRODUCTION

Acute uncomplicated lower-respiratory-tract infection (LRTI) is one of the most common reasons for patients consulting in primary care.[1 2] Antibiotics are prescribed to the majority of consulting patients, with amoxicillin being the most common across Europe.[3] Evidence for the benefits and harms of antibiotic treatment has been unclear, primarily

due to underpowered and inappropriately designed studies.[4] With antibiotic resistance becoming a growing problem worldwide, the need for clear evidence for the benefits and harms of antibiotics for this condition has never been more of a priority.[5 6]

A recently published trial of amoxicillin for acute uncomplicated LRTI in primary care concluded that amoxicillin provides little clinical benefit and causes slight harms.[7] The findings of this trial were based on a comparison of participants in the arm to which they were originally randomised (ie, using the intention to treat (ITT) principle). While an ITT analysis is an important part of the analysis of any trial, as it reflects the design of the trial and uses randomisation to avoid selection bias,[8] this approach does not take into account deviations that occur following randomisation, such as lack of adherence to treatment.

Adherence to antibiotic treatment in primary care is poor.[9] Less than 60% of patients prescribed an antibiotic for an acute cough/LRTI in primary care initiated their treatment, and less than half took the full course.[10] Poor levels of adherence to antibiotics wastes healthcare resources, could negatively impact on clinical outcomes and could increase the selective pressures for antibiotic resistance. When issues with adherence are present in a trial, analysis based on the ITT principle underestimates treatment effects, and can only provide an unbiased estimate of the effect of prescribing treatment (effectiveness), rather than the effect of treatment itself (efficacy).[11]

Two traditional approaches to estimating treatment efficacy include per-protocol analysis, where participants who do not adhere to their allocated treatment are excluded from analyses, and on-treatment analysis, where participants are analysed in the group corresponding to the treatment they took (regardless of the group they were allocated to).[12] Both methods make the implicit assumption that the groups of participants are equivalent with respect to observed and unobserved variables, something that is implausible in practice.[13] Approaches to estimating efficacy without making this key assumption exist, and are becoming increasingly popular.[14 15] However, these approaches are generally reported in specialist methodological journals, rather than the general medical literature and as such there still remains a reliance on more traditional and arguably inadequate methods.

The aim of this paper is to use the data set from the largest placebo-controlled trial of amoxicillin for acute uncomplicated LRTI in primary care to produce adherence-adjusted estimates of the benefits and harms from amoxicillin for adults consulting in primary care with an acute uncomplicated LRTI, while preserving a comparison of groups as randomised.

METHODS

Study design and participants

A two-arm individually-randomised placebo-controlled trial was conducted between November 2007 and April 2010. Patients were recruited consecutively from primary care practices from 12 European countries (Belgium, England, France, Germany, Italy, the Netherlands, Poland, Slovakia, Slovenia, Spain, Sweden and Wales).

The trial has previously been described in detail elsewhere.[7] A brief description about recruitment, randomisation, blinding, the interventions, data collection and follow-up are given below. Further analyses were performed in order to investigate our study question.

Recruitment, randomisation, blinding and interventions

Participants were eligible for inclusion if they were aged 18 years or older and consulting for the first time with either an acute cough (≤28 days' duration) as their main symptom, for which non-infective diagnoses were judged very unlikely, or an illness in which cough was not the most prominent symptom but the clinician thought acute LRTI the most probable diagnosis.

Participants were deemed ineligible if their initial diagnosis was community-acquired pneumonia (ie, complicated LRTI) on the basis of focal chest signs (focal crepitations, bronchial breathing) and systemic features (high fever, vomiting, severe diarrhoea). Participants were also ineligible if their working diagnosis was cough of a non-infective cause (eg, pulmonary embolus, left ventricular failure, oesophageal reflux, allergy), they had used antibiotics in the previous month, were unable to provide informed consent or complete the diary (eg, they had dementia, psychosis or severe depression), were pregnant, allergic to penicillin or had immunological deficiencies.

Participants were allocated to groups on a 1:1 basis using block randomisation. As this was a double-blinded trial, clinicians and participants were blinded to the randomisation sequence and allocation. All outcome data were also collected without prior knowledge of the group to which participants were allocated.

Randomised participants received a prescription for amoxicillin, to be taken as two 500 mg tablets three times a day for 7 days, or a placebo identical in appearance, taste and texture.

Data collection and participant follow-up

Consenting participants had their comorbidities, clinical signs and symptoms recorded by the recruiting clinician.

Following recruitment, consent and randomisation, participants were given a daily symptom diary to complete for up to 28 days. The diary recorded the duration and severity of 12 symptoms (cough, phlegm, shortness of breath, wheeze, blocked or runny nose, chest pain, muscle aches, headaches, disturbed sleep, general feeling of being unwell, fever and interference with normal activities). Severity was scored on a scale from 0 to 6 (0=no problem, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad, 6=as bad as it could be). Patients also recorded non-respiratory symptoms, such as diarrhoea, skin rash and vomiting.

Members of the research team telephoned participants after 4 days to offer support and answer questions about the completion of the diary. If the diary was not returned after 4 weeks, brief information was collected about symptom duration and severity. This information was collected with either a short questionnaire or a standardised telephone call.

Measures of adherence

Using their daily symptom diary, participants recorded whether or not they took their study medication on a given day, and whether they took their study medication according to the instructions. Where it was indicated that participants did not take their study medication according to the instructions, space was given to provide more detail. Participants for whom a diary was not returned were asked to state the number of days that they took their study medication. This information was collected using the short questionnaire/telephone call described in the previous section. Participants were also instructed to return their study medication bottles, complete with any unused medication, at the end of the trial. The number of tablets returned was recorded by members of the research team.

Randomised participants were prescribed 42 tablets. Adherence to study medication was defined as the percentage of the correct number of tablets taken during the first 7 days of the follow-up period (ie, the period for which the medication was prescribed). Three binary definitions of adherence were also constructed in order to provide sensitivity analyses around the continuous definition. The three binary definitions were full (100%) adherence versus not full adherence, at least the equivalent of a 5-day course (approximately 71.4%) versus less and at least one tablet versus no tablets.

Where participants indicated that they had taken medication on a particular day, in the absence of information to the contrary (eg, stating that they only took one tablet three times a day instead of two tablets), the assumption was made that a participant consumed all study medication as instructed. Where medication bottles were returned, it was assumed that the difference between the number of tablets prescribed and the number returned equated to the number of tablets consumed. We also assumed that all tablets were consumed during the first 7 days of the follow-up period. Where a short questionnaire or telephone call was conducted, it was assumed that the correct numbers of tablets were taken for the number of days medication was reportedly taken.

Where multiple types of adherence measures were available for a participant the agreement between measures, and the assumptions inherent in our definition of adherence, were investigated.

Outcomes

To demonstrate the benefits and harms of amoxicillin in this population, and to illustrate the use of randomisation-based efficacy estimators, the paper concentrates on three of the outcomes described in the original paper. The first was the mean clinician-rated symptom severity between days 2 and 4 after initial presentation. The second outcome was the development of new or worsening symptoms, defined as returning to the clinician with new or worsening symptoms, new signs or an illness requiring admission to hospital within the 4-week follow-up period. The third outcome was the presence of any non-respiratory symptoms (diarrhoea, skin rash or vomiting) during the 4-week follow-up period. These specific symptoms were recorded as they are known side effects of amoxicillin. The first two outcomes were used to demonstrate the clinical benefits of amoxicillin for patients with an acute uncomplicated LRTI in primary care, with the third used to demonstrate harms. The decision to exclude the outcome "time to resolution of moderately bad symptoms" from the analysis was made for two reasons. First, in order to reduce the number of assumptions made when deriving the definition of adherence (we have not made any assumptions about adherence on individual days, but would have to make this additional assumption to perform analysis on this outcome). The second reason was that standard techniques for adjusting time-to-event outcomes for non-adherence rely on fitting an accelerated failure time model. The original outcome was analysed using a Cox proportional hazards model, and therefore the outcome would initially require reanalysing using an accelerated failure time model before an adjustment could be made. As the results from this analysis cannot be directly compared with the findings from the main paper, the decision to exclude this outcome from consideration was made.

Statistical analysis

Participants and their adherence to study medication were described using means (SDs), medians (IQRs) and percentages as appropriate.

Participants for whom more than one measure of adherence was available had their agreement between measures compared using Bland and Altman limits of agreement.[16] Bland and Altman plots are presented with jittering and semitransparency to highlight overlapping data points. Where multiple types of adherence measures were reported and there was disagreement between values, the minimum value was used for analysis.

The between-group mean difference in symptom severity on days 2 to 4 postrandomisation was estimated using linear regression. The mean clinician-rated symptom severity at baseline was controlled for as a covariate. The between-group odds of developing new or worsening symptoms and of reporting any non-respiratory symptoms in the 4 weeks following randomisation were compared using logistic regression without covariates. These analyses included participants on an intention-to-treat basis. That is, they did not adjust for deviations following randomisation. The analyses

therefore provide an estimate of the effectiveness of amoxicillin for patients with an acute uncomplicated LRTI in primary care, and as an estimate of efficacy, are viewed as being biased towards the null.

To determine efficacy in a way that preserves randomisation (ie, provides a comparison of groups ie, independent of observed and, importantly, unobserved confounders), and is not biased towards the null, structural mean models (SMM) were used to compare the between-group differences in the aforementioned outcomes. By recognising that at the beginning of a trial, all participants have two potential outcomes—one if they are treated and one if they are not, a SMM relates a treated participant's observed outcome to their potentially counterfactual outcome that would have been observed had they received no treatment. Standard approaches to fitting a SMM rely on using observed levels of exposure, and treating randomisation as an instrument (ie, assuming that it is independent of both observed and unobserved confounders and only effects outcome through its effect on exposure). Estimation procedures therefore rely on finding a value of the treatment effect such that balance is achieved between groups on the outcome (or potential outcome) in participants who were not treated. The between-group mean difference in symptom severity on days 2 to 4 was estimated using a two-stage least squares instrumental variables regression model.[17] To compare the odds of developing new or worsening symptoms and reporting any non-respiratory symptoms, a generalised linear (double logistic) SMM was estimated via a generalised method of moments procedure.[18] The double logistic SMM involved a two-step process whereby the association between outcome (development of new or worsening symptoms or reporting of side effects), trial arm and adherence was modelled first, with estimates from this model used in the SMM in order to obtain correct SEs (and hence correct 95% CIs). For more information on the use of randomisation-based efficacy estimators and their core assumptions, including the Stata syntax used to implement the SMMs, please see the online supplementary appendices 1 and 2.

Results from the linear regression model are presented as adjusted mean differences with associated 95% CIs. Results from the logistic regression models are presented as ORs with associated 95% CIs. For the SMM (double logistic SMM), results are presented as both the adjusted mean difference (OR) per % increase in adherence and per 100% adherence, the latter of which can be interpreted as the maximum possible efficacy.

Additional analyses using the three binary definitions of adherence were performed to investigate the sensitivity of the main efficacy analyses to departures from the assumed linear relationship between adherence and outcome.

Data management and descriptive statistics were performed using IBM SPSS Statistics V.20.[19] All other analyses were performed using Stata V.13.[20]

RESULTS

Participants

In total, 2061 participants were recruited and randomised to either the amoxicillin group (1038) or placebo (1023; figure 1). The groups were well matched on baseline characteristics (table 1).

Adherence to study medication

Adherence data were available for 1854 participants (90% of all randomised participants). The majority of participants had multiple types of measure recorded (1214, or 58.9% of all randomised; figure 2).

Adherence to study medication was similar between trial arms and relatively high overall. Average levels of adherence were highest for responses obtained from self-reported diaries and lowest for responses from self-reported telephone. Adherence data were highly skewed for all three measures and spanned the entire range of possible responses (table 2).

Agreement between adherence measures

Where multiple types of adherence measures were available, self-reports (diary and telephone formats) provided slightly higher estimates of adherence on average compared to tablet counts (mean differences of 1.7 and 2.6 percentage points, respectively). The limits of agreement when comparing diary and tablet count adherence ranged from −26.8 (self-reported diary adherence was calculated as 26.8 percentage points lower than tablet count adherence) to 30.2 (self-reported diary adherence was calculated as 30.2 percentage points higher than tablet count adherence) and when comparing telephone and tablet count from −21.8 to 26.9 (table 3). Figure 3A, B provide an illustration of the level of agreement between different types of measures. What is clear from these figures is that adherence was high and was generally good (most data points on both plots are clustered around the coordinate (100, 0), indicating full adherence and no difference between measures). For the comparison of diary to tablet count adherence, 7% of participants were outside the limits of agreement; for the comparison of telephone to tablet count adherence, 5% of participants were outside the limits of agreement.

Taking the minimum reported adherence value (where multiple values were reported), adherence to study medication remained high and negatively skewed (table 4 and figure 4).

Outcomes

Table 5 provides descriptive statistics for each of the three clinical outcomes.

Effectiveness

Table 6 compares the effectiveness and efficacy of amoxicillin with respect to the various outcomes below.

As reported in the original paper, the adjusted between-group mean difference in symptom severity score on days 2 to 4 was slightly lower in the amoxicillin

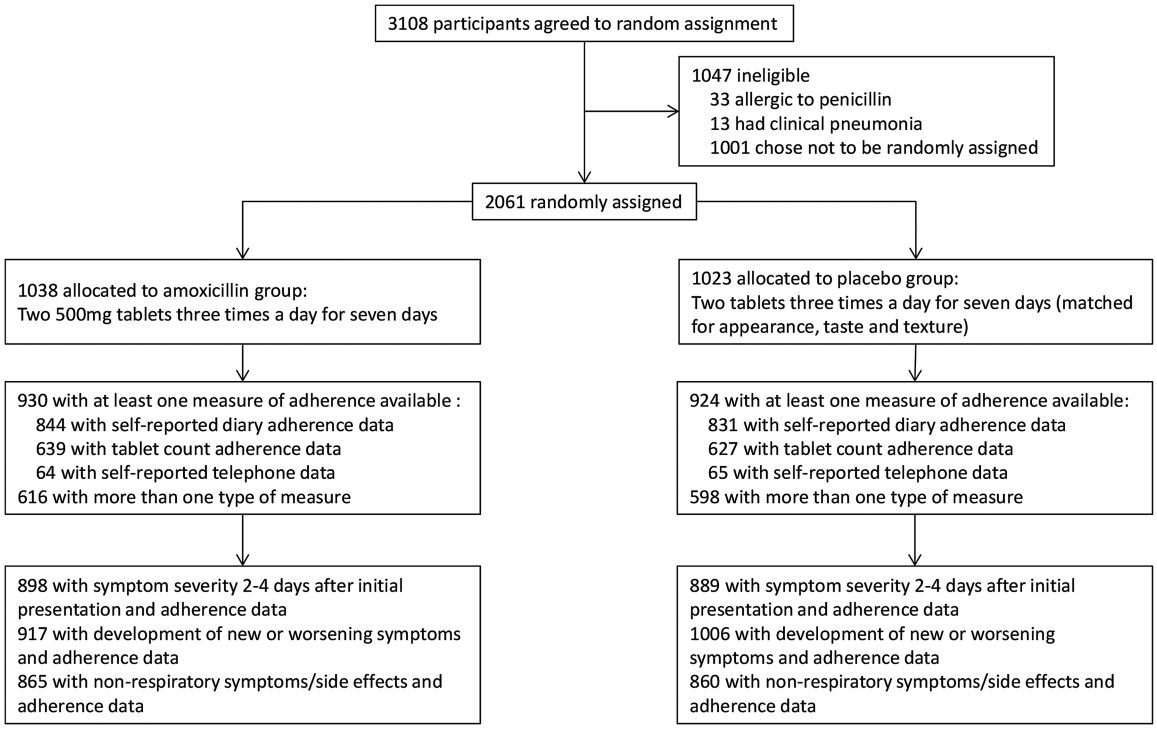

Figure 1 CONSORT flow diagram.

group than the placebo group (adjusted mean difference of −0.07, 95% CI −0.15 to 0.01).

Being allocated to the amoxicillin arm (ie, being prescribed amoxicillin) was associated with decreased odds of developing new or worsening symptoms in the 4 weeks postrandomisation follow-up period. The odds of developing new or worsening symptoms were 21% lower for participants who were prescribed amoxicillin than for those prescribed a matched placebo (OR=0.79, 95% CI 0.63 to 0.99). When the effectiveness analyses were only performed on participants for whom outcome and adherence data were available, there was a 19% decrease in the odds of developing new or worsening symptoms in participants prescribed amoxicillin (OR=0.81, 95% CI 0.64 to 1.03).

Being prescribed amoxicillin was associated with a 28% increase in the odds of reporting non-respiratory symptoms (side effects) in the 4 weeks postrandomisation (OR=1.28, 95% CI 1.03 to 1.59).

Efficacy

Adjusting for adherence using the SMM, a small increase in the between-group mean difference in symptom severity score for participants who complete their course of amoxicillin was found (−0.08, 95% CI −0.17 to 0.01).

Table 1 Baseline characteristics of trial participants

Baseline characteristic	Amoxicillin	Placebo
Women	624/1038 (60.1%)	600/1023 (58.7%)
Age (years)	48.6 (16.7)	49.3 (16.4)
Non-smoker (past or present)	477/1037 (46.0%)	483/1022 (47.3%)
Illness duration before index consultation (days)	9.5 (8.0)	9.3 (7.2)
Respiratory rate (breaths per minute)	16.9 (3.3)	16.9 (3.3)
Body temperature (°C)	36.7 (3.3)	36.8 (3.3)
Lung disease*	163/1037 (15.7%)	147/1023 (14.4%)
Mean severity score (all symptoms)†	2.1 (0.5)	2.1 (0.5)
Mean severity score (cough)†	3.1 (0.7)	3.2 (0.7)
Sputum production	814/1036 (78.6%)	824/1021 (80.7%)
Discoloured sputum‡	481/968 (49.7%)	468/957 (48.9%)

Data are n/N (%) or mean (SD).
*Chronic obstructive pulmonary disease or asthma.
†Severity of symptoms: 1=no problem; 2=mild problem; 3=moderate problem; 4=severe problem.
‡Green, yellow or blood stained.

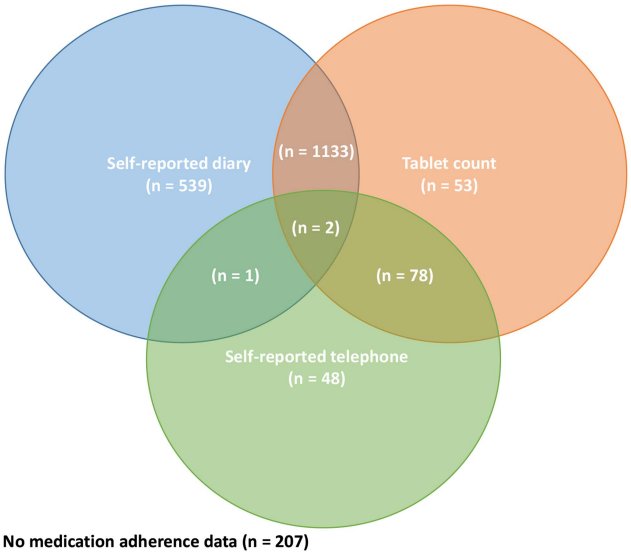

Figure 2 Availability of different types of adherence data for all 2061 randomised participants.

Figure 5 provides an illustration of the effectiveness and efficacy of amoxicillin for the above outcome. The treatment efficacy when adherence is 0% is 0, the ITT (effectiveness) is illustrated by the diamonds (positioned at an adherence level of 88%—the patient-average), and the maximum efficacy when adherence is 100%.

The odds of developing new or worsening symptoms remained lower in participants who took their full course of amoxicillin (OR for 100% adherence to amoxicillin=0.81, 95% CI 0.66 to 0.98).

A small increase in the odds of reporting non-respiratory symptoms was found when adjusting for adherence (OR for 100% adherence=1.32, 95% CI 1.12 to 1.57).

Sensitivity analyses

Refitting the above efficacy analyses with binary definitions of adherence, the results remained largely similar and did not alter the conclusions drawn by either the efficacy or indeed the effectiveness analyses. The most extreme definition of adherence (full vs not) yielded the largest between group differences and the least extreme (at least one tablet vs none) yielded the smallest (table 7).

DISCUSSION

Principal findings

In this 12-country randomised placebo-controlled trial of amoxicillin for acute uncomplicated LRTI in primary care, reported levels of adherence to study medication was very high. Prescribing amoxicillin in this setting was shown to have modest improvements in symptom severity on days 2–4, and a decrease in the odds of developing new or worsening symptoms in the 4 weeks following index consultation. However, this has to be balanced with the odds of reporting non-respiratory symptoms (side effects) in the 4 weeks following index consultation, which also increased. Adjusting these findings for

Table 2 Levels of adherence to study medication across all types of measures

	Amoxicillin			Placebo			Overall		
	Mean (SD)	Median (IQR)	Minimum–maximum	Mean (SD)	Median (IQR)	Minimum–maximum	Mean (SD)	Median (IQR)	Minimum–maximum
Self-reported diary (n=1675)	91.6 (21.8)	100.0 (100.0–100.0)	0.0–100.0	90.8 (22.3)	100.0 (100.0–100.0)	0.0–100.0	91.2 (22.0)	100.0 (100.0–100.0)	0.0–100.0
Self-reported telephone (n=129)	80.4 (36.0)	100.0 (78.6–100.0)	0.0–100.0	74.7 (37.9)	100.0 (42.9–100.0)	0.0–100.0	77.5 (36.9)	100.0 (57.1–100.0)	0.0–100.0
Tablet count (n=1266)	90.0 (23.8)	100.0 (100.0–100.0)	0.0–100.0	87.0 (26.9)	100.0 (90.5–100.0)	0.0–100.0	88.5 (25.4)	100.0 (95.2–100.0)	0.0–100.0

Table 3 Difference between adherence measures and limits of agreement

Difference between adherence measures	Self-reported diary adherence minus tablet count adherence (n=1135)	Self-reported telephone adherence minus tablet count adherence (n=80)
Mean	1.7	2.6
SD	14.5	12.4
Lower 95% limit of agreement	−26.8	−21.8
Upper 95% limit of agreement	30.2	26.9

adherence, the effect of taking amoxicillin in this setting largely agreed with the effect of prescribing described above. Given the high level of adherence reported in the trial, the adjustments made were minor, though in the expected direction. Compared to the effect of prescribing amoxicillin (ie, including participants who may take their medication to a varying degree), taking amoxicillin was shown to further improve symptom severity on days 2–4, further decrease the odds of developing new or worsening symptoms and further increase the odds of reporting side effects.

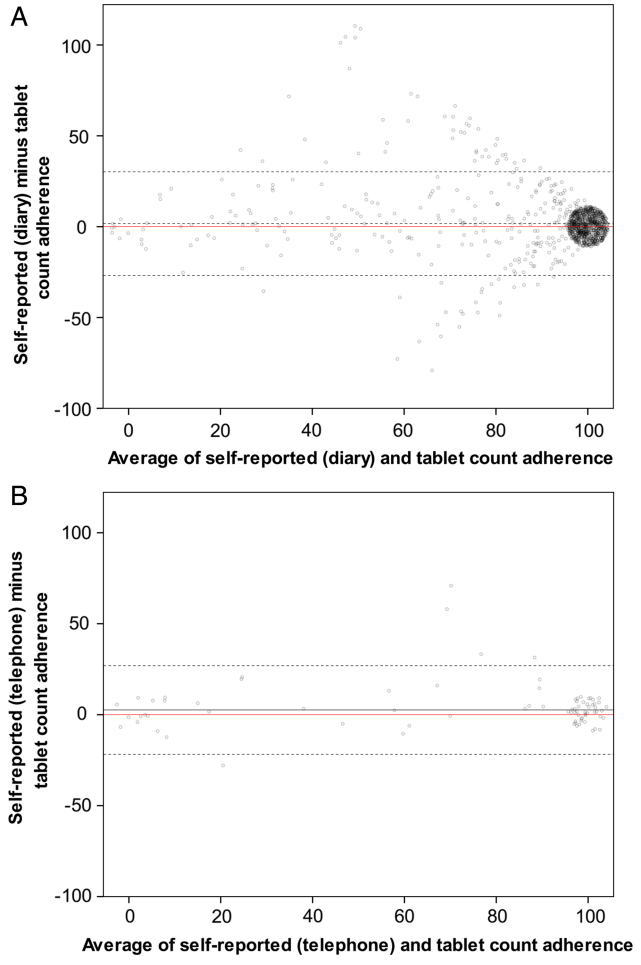

Figure 3 (A and B) Bland and Altman plots illustrating the agreement between the self-reported (diary (A) and telephone (B)) and tablet count adherence measures. Red solid line represents perfect agreement between measures. Black solid line represents the mean difference (bias) between measures. Black dashed lines are the 95% limits of agreement. Where data points took the same value (ie, when more than one participant had both the same average and difference in adherence), semitransparency and jittering effects were applied to provide an illustration of the number of overlapping data points. There were a large number of data points at (100, 0), and this is illustrated by the large cluster of jittered points around this coordinate.

Strengths and weaknesses

To date, this remains the largest randomised placebo-controlled trial evaluating amoxicillin for acute, uncomplicated LRTI in primary care. By maintaining a broad inclusion criteria, recruiting across a range of different countries, and recruiting participants similar in nature to previously conducted observational studies in this setting,[3] the findings of this study are likely to be widely applicable.

This paper demonstrated that the findings of main effectiveness analysis were robust to non-adherence to treatment, and did so using a method of analysis that was not prone to the usual selection biases that arise when ITT findings are adjusted for treatment adherence traditionally (eg, per-protocol analysis).

By considering the benefits and harms, the study provided a comprehensive account of the consequences of taking amoxicillin for an acute uncomplicated LRTI in primary care.

Adherence to medication was assessed using self-report and tablet count data, and while both only provided indirect measures of medication adherence, relying heavily on various assumptions (eg, accurate participant recall, returning of all unused medication), both measures were often available for the same individual, allowing for the assessment of agreement between measures. Agreement was good, with adherence calculated as 100% for both measures for the majority of participants.

The use of SMMs to adjust trial findings for non-adherence was attractive as it allowed for a comparison of groups that was independent of measured and unmeasured confounders. However, for this comparison to be valid, it relied on the key assumption that for participants who were categorised as non-adherers, merely being allocated to receive treatment had no effect on outcome (the so-called exclusion restriction).[21] While this was likely to be a valid assumption for this study, as participants and clinicians were blinded to allocation, this is less likely to be valid for non-blinded studies.

Table 4 Levels of adherence to study medication used for statistical analyses (with the minimum value reported when participants had more than one type of measure)

	Amoxicillin (n=930)	Placebo (n=924)	Overall (n=1854)
Mean (SD)	88.0 (25.8)	86.6 (27.2)	87.3 (26.5)
Median (IQR)	100.0 (95.2–100.0)	100.0 (85.7–100)	100.0 (90.5–100.0)
Minimum–maximum	0.0–100.0	0.0–100.0	0.0–100.0

Defining adherence as a continuous measure made the exclusion restriction more plausible, as the lowest level of adherence could be defined as receiving no treatment, a level at which being allocated to either treatment group should really have no effect on outcome. However, this approach made the additional assumption that the effect of receiving an increasing amount of treatment on outcome increased linearly,[22] which for a trial involving medication is unlikely to be true. Sensitivity analyses were conducted using various binary definitions of adherence, ranging from one or more tablets (vs no tablets) to full course (vs less than full course). While the former increased the plausibility of the exclusion restriction, the estimated treatment efficacy was too conservative. The latter analysis combined participants who would have taken 99% of their medication with participants who would have taken no medication and considered them all as not adhering (and therefore assumed they would have received no benefit from being allocated to the amoxicillin arm). This clearly violated the exclusion restriction. However, the findings from the sensitivity analyses largely agreed with the main findings (where adherence was measured continuously), adding further strength to the conclusions of the paper.

Despite the fact that incomplete outcome and adherence data were minimal, their impact on findings remains unknown. However, as the condition under investigation is generally self-limiting, and outcome data included worsening of illness (a composite outcome collected from medical notes that included hospitalisation), we do not believe that the small amount of missing data would have severely impacted on the findings or conclusions drawn from this study. Indeed, sensitivity analyses demonstrate that clinical conclusions remain largely unaltered even when taking an extreme assumption about missing adherence data (see online supplementary appendix 3 for further details).

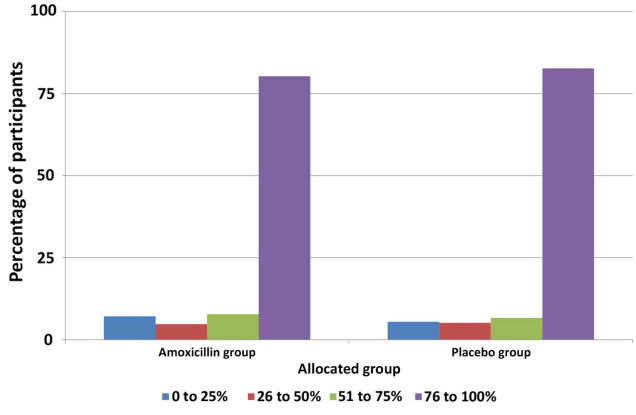

Figure 4 Proportion of participants at each adherence level (with the minimum value reported when participants had more than one type of measure).

Comparison to existing literature

The findings from this study concur with those reported in the main findings paper,[7] both of which are consistent with a recently published Cochrane review of antibiotics for acute bronchitis.[3]

Adherence to amoxicillin in this study was considerably higher than that reported in an observational study of antibiotics for adults with acute cough/LRTI in primary care.[10] However, the participants recruited into this trial were similar to those recruited into the aforementioned observational study in terms of their baseline characteristics.[3]

Approaches for adjusting treatment effects for non-adherence while preserving randomisation have been in existence for approximately 20 years.[21] However, they have largely been consigned to specialist methodological journals, rarely used in practice and when used, generally focussed on non-pharmacological treatments.[23] A recent publication using the same SMM approach as this paper on a clinical trial involving patients with depression demonstrates further that these methods are becoming more mainstream and should be reported alongside standard ITT estimates of treatment effectiveness, when there is also interest in knowing the efficacy of treatment.[24]

Implications

The slight benefits gained from taking amoxicillin in adults consulting to primary care with acute uncomplicated LRTI must be balanced against the slight harms that amoxicillin causes in terms of side effects, as well as the associated contribution to antibiotic resistance.

While estimating the effectiveness of treatment using the ITT principle remains the gold standard in clinical trials, an ITT analysis only tells us the population-average effect that prescribing treatment has. The analysis therefore provides the answer to a question that is of primary interest to clinicians and policymakers ("What are the effects when this drug is prescribed?"). However, to a patient, the analysis may not be as informative ("What are the effects when I take this drug as prescribed?"). Some of these prescriptions will not be taken in their entirety, others not at all. In general, an ITT analysis does not estimate how good the medication is at treating the illness

Table 5 Descriptive statistics of the three outcome measures

Outcome	Amoxicillin	Placebo
Mean symptom severity between days 2 and 4 postrandomisation*	1.6 (0.8)	1.7 (0.8)
Development of new or worsening symptoms in the 4 weeks postrandomisation	162/1021 (15.9)	194/1006 (19.3)
Reported non-respiratory symptoms/side effects in the 4 weeks postrandomisation	249/867 (28.7)	206/860 (24.0)

Data are n/N (%) or mean (SD).
*Each symptom was scored from 0–6 (0=no problem, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad, 6=as bad as it could be).

Table 6 Comparison of effectiveness and efficacy of amoxicillin for acute uncomplicated LRTI in primary care

Outcome	Effectiveness*	Effectiveness for whom adherence data were also available†	Efficacy per 10% increase in adherence†	Maximum efficacy (100% adherence)†
Adjusted between-group mean difference in symptom severity between days 2 and 4 postrandomisation	−0.07 (−0.15 to 0.01)	−0.07 (−0.15 to 0.01)	−0.008 (−0.017 to 0.001)	−0.08 (−0.17 to 0.01)
OR for developing new or worsening symptoms in the 4 weeks postrandomisation	0.79 (0.63 to 0.99)	0.81 (0.64 to 1.03)	0.978 (0.960 to 0.998)	0.81 (0.66 to 0.98)
OR for reporting non-respiratory symptoms/side effects in the 4 weeks postrandomisation	1.28 (1.03 to 1.59)	1.28 (1.04 to 1.59)	1.028 (1.011 to 1.046)	1.32 (1.12 to 1.57)

*Analysis based on 1789, 2027 and 1727 participants for the symptom severity, new symptoms and side effect outcomes, respectively.
†Analysis based on 1787, 1923 and 1725 participants for the symptom severity, new symptoms and side effect outcomes, respectively.
LRTI, lower-respiratory-tract infection.

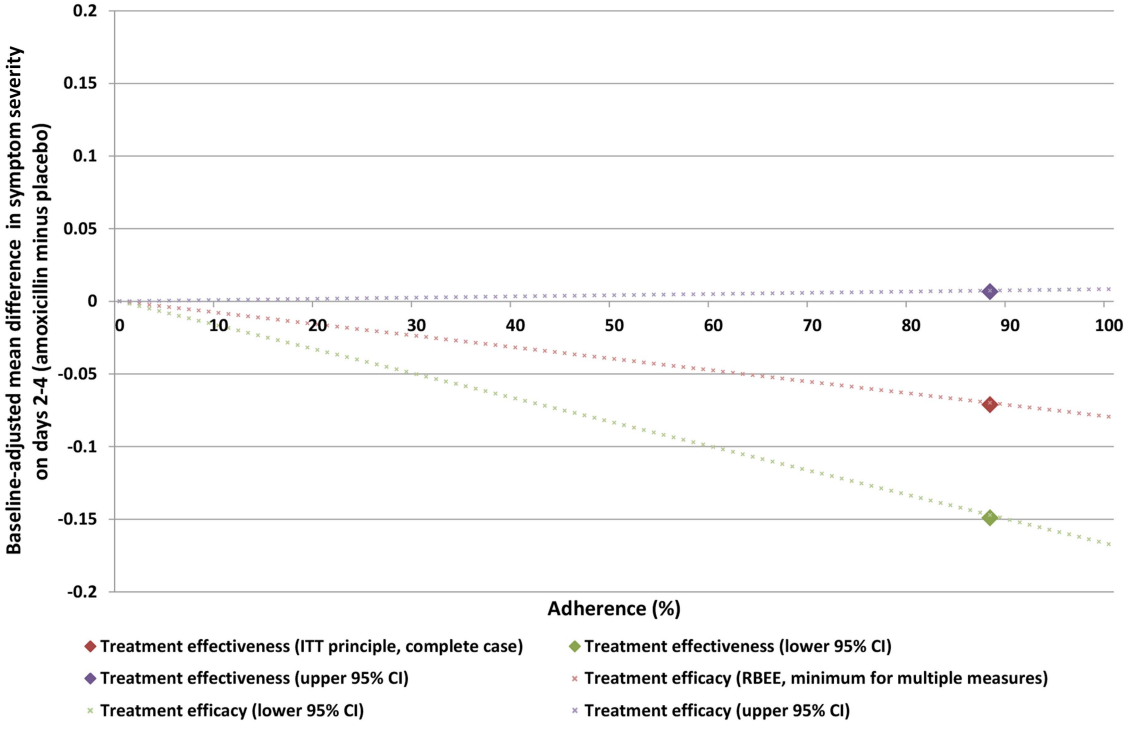

Figure 5 Graphical illustration of the effectiveness and efficacy of amoxicillin on mean symptom severity on days 2–4.

Table 7 Efficacy analyses with binary definitions of adherence (for sensitivity)

Outcome	Efficacy with binary definition of adherence (full vs not full)	Efficacy with binary definition of adherence (at least five day course vs less than five day course)	Efficacy with binary definition of adherence (at least one tablet vs no tablets)
Adjusted between-group mean difference in symptom severity between days 2 and 4 postrandomisation	−0.10 (−0.20 to 0.01)	−0.08 (−0.18 to 0.01)	−0.07 (−0.15 to 0.01)
OR for developing new or worsening symptoms in the 4 weeks postrandomisation	0.78 (0.62 to 0.98)	0.80 (0.65 to 0.98)	0.82 (0.69 to 0.98)
OR for reporting non-respiratory symptoms/side effects in the 4 weeks postrandomisation	1.43 (1.15 to 1.79)	1.35 (1.26 to 1.62)	1.29 (1.11 to 1.50)

under consideration. Adjusting for adherence does allow for the estimation of this. If an ITT analysis shows little evidence of benefit, but an adherence-adjusted analysis demonstrates benefit, then the attention of policymakers should turn to ensuring that patients take their treatment properly. Estimating efficacy can provide additional insight into the potential benefit from treatment, and can indicate whether additional resources need to be allocated to the improvement of adherence to medication for specific conditions.

As was seen in this paper, if an ITT analysis finds little evidence of any benefit, and these conclusions are not affected by an adherence-adjusted analysis, it can be concluded that the intervention does not work in practice or principle.

Estimating efficacy in clinical trials while preserving the random allocation of participants to treatment groups is vital for inferring causal treatment effects. Standard software is available for implementing methods such as the SMM, and should become more widely used and reported in the medical literature.

Future research

While the main findings paper reported that a subgroup of older participants (aged 60 years or older) received no differential effect of treatment, investigating the efficacy of amoxicillin in this subgroup may be beneficial.

The SMM as presented in this paper relies on the assumption of a linear relationship between adherence (dose) and treatment efficacy. The incorporation of non-linear dose–response relationships into SMMs may increase the applicability of these methods in clinical trials, and is something that needs further attention.

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Ethics approval Ethical approval for the UK was granted by Southampton and South West Hampshire Local Research Ethics Committee (B) (ref. 07/H0504/104). Competent authority approval for the UK was granted by the Medicines and Healthcare Products Regulatory Agency. The research sites outside of the UK also obtained ethical and competent authority approval from their local organisations. Patients who fulfilled the inclusion criteria were given written and verbal information on the study and asked for informed consent.

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BMJ Open

Adherence-adjusted estimates of benefits and harms from treatment with amoxicillin for LRTI: secondary analysis of a 12-country randomised placebo-controlled trial using randomisation-based efficacy estimators

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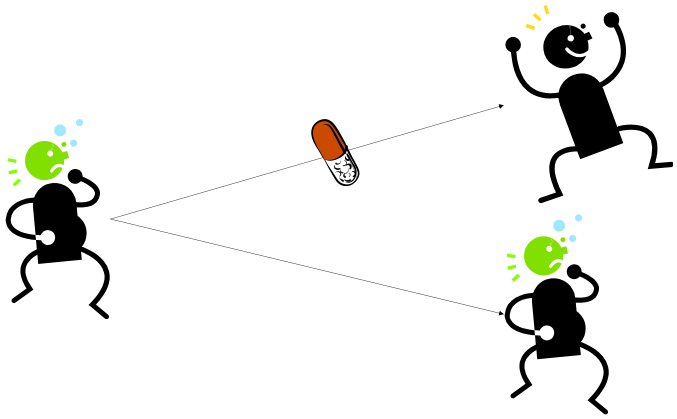
Appendices

Appendix 1. Summary of concepts and motivation for randomisation-based efficacy estimators

1. The importance of randomisation when inferring causal treatment effects

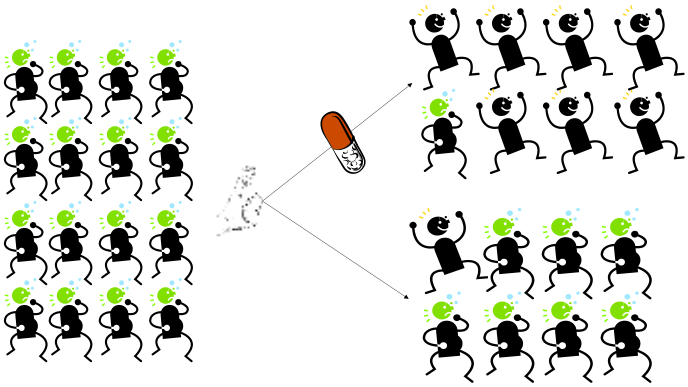
- One of the key reasons we perform experiments is to determine the effect that a treatment has on some outcome of interest – the causal effect.
- In general, we would like to infer these causal effects to the level of individuals. However, without simultaneously observing the effect of both giving and not giving treatment, we will never be able to calculate a true individual-level treatment effect.

Figure 1: Illustration of an individual-level treatment effect



- Instead, we calculate population-level (or average) treatment effects, where the average outcomes of individuals in the treated group are compared to those in the untreated group and we use this calculation as an estimate for the individual-level effects (that we only ever partially observe).
- For this estimate to be valid, the choice to be in the treated / untreated group must be made at random.
    - If the choice is not made at random, the estimate is likely to be biased unless the decision to choose one group over the other (i.e. the selection mechanism) is fully measured and adjusted for. However, this is very unlikely to be the case in practice, where typically some variables that contribute to the selection mechanism are likely to remain unmeasured.

Figure 2: Illustration of a population-level (average) treatment effect from a randomised experiment



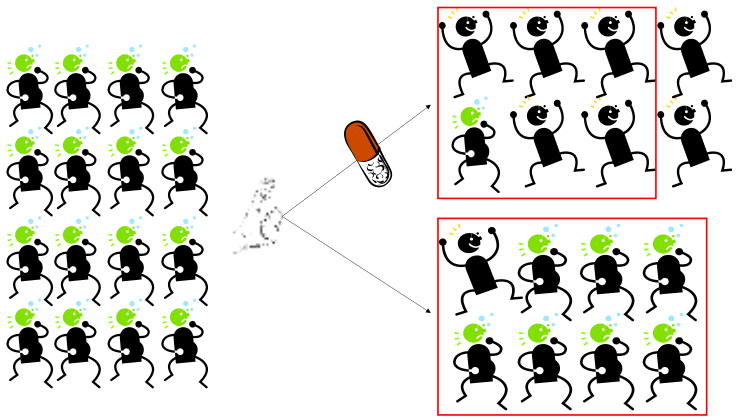
2. What does an Intention to Treat (ITT) analysis allow and what does it not allow?

- ITT analysis allows for a comparison of groups as randomised, independent of both observed and (most importantly) *unobserved* confounders. It reflects the design of the trial and uses randomisation to avoid selection bias. To preserve randomisation, deviations following randomisation (such as lack of adherence to allocated treatment) are not adjusted for.
- When all participants receive their allocated medication as intended, an ITT analysis provides an unbiased estimate of the effect of both prescribing and taking treatment.
- When some participants do not receive their treatment as intended, an ITT analysis can only be guaranteed to provide an unbiased estimate of the effect of prescribing treatment.

3. What is a per-protocol analysis and why is it usually inappropriate to perform in an RCT?

- A per-protocol analysis generally only includes participants who followed study protocol as intended. Examples of protocol deviations could be:
    - Participant was incorrectly randomised
    - Being in the treatment arm and not taking treatment
    - Being in the control arm and taking treatment
    - Not providing follow-up data
- A per-protocol analysis makes the assumption that analysed participants are equivalent to excluded participants (i.e. that the choice to deviate from protocol is made completely at random, or, if there is a selection mechanism, that it has been fully measured and adjusted for).
- However, these exclusions occur post-randomisation, and as illustrated in Point 1, selection mechanisms that are not based on randomisation are likely to yield biased estimates of treatment effects. Therefore using a per-protocol population to estimate treatment effects in RCTs should usually be avoided.

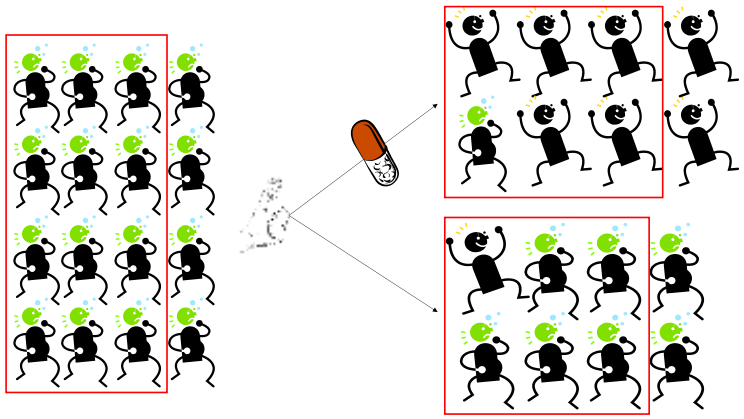
Figure 3: Illustration of per protocol analysis



4. What are randomisation-based efficacy estimators and why are they generally a better approach?

- Randomisation-based efficacy estimators (RBEE) compare the effect of treatment in those who were allocated to and adhered to treatment with those allocated to control who would have adhered to treatment (if allocated to the treatment arm).
- Dependent on data type, there are many ways of calculating a RBEE, but most methods rely on the following core assumptions:
    1. Participants' adherence/compliance-type is a latent trait, a baseline characteristic that is independent of randomisation. One way to think of RBEEs is as the ITT effect in the sub-group of participants who would always adhere to treatment.
    2. Due to randomisation, the proportion of participants classed as non-adherers will be the same in each group.
    3. In the absence of treatment, randomisation in and of itself has no effect on outcome.
- By making these assumptions, observed adherence data can be used to classify individuals and obtain estimates of the effect of receiving treatment on outcome that are not prone to the selection bias commonly seen in traditional efficacy analyses.
- While a binary definition of adherence is often used, this can either make the third core assumption implausible (by including participants in the non-adherent group that may have received some treatment and may therefore benefit from it) or involve a restrictive definition of adherence (e.g. took at least one tablet).
- A continuous definition of adherence makes this third assumption plausible, as zero can represent those who received no treatment. However, the use of a continuous definition implies the additional assumption of a linear relationship between adherence and treatment effect, which is likely to have varying degrees of plausibility depending on setting.

Figure 4: Illustration of randomisation-based efficacy estimator



Appendix 2: Stata syntax for the structural mean models

Structural mean model for "mean clinician-rated symptom severity between days two and four after initial presentation" outcome using two-stage least squares instrumental variables regression

```
ivregress 2sls y c (x=z)
```

In the syntax above, y = outcome, c = covariate, x = exposure, and z = randomisation indicator

Generalised linear (double logistic) structural mean model for "development of new or worsening symptoms" and "presence of any non-respiratory symptoms" outcomes using generalised method of moments

```
logit y x z

matrix from = e(b)

predict xblog, xb

gmm (invlogit(xblog - x*{psi})-ey0), instruments(z)

matrix from = (from, e(b))

gmm (y - invlogit({xb: x z} + {b0})) (invlogit({xb:} + {b0} - x*{psi}) - ey0), instruments(1:x z)
instruments(2:z) winitial(unadjusted, independent) from(from)

lincom[psi]_cons, eform

estat overid
```

In the syntax above, y = outcome, x = exposure, z = randomisation indicator, ey0 = mean exposure-free potential outcome (to stabilise the model, this has been fixed as the proportion of people with positive outcomes in the control group. It can however be directly estimated from the model). This model requires an additional stage (an associational model) because collapsing the logistic SMM over observed exposure (z) depends on the distribution of z. It is therefore not possible to derive causal odds ratios in a single stage. The stages are first run individually to obtain initial values for the joint estimation. The stages are then run jointly to produce standard errors that correctly incorporate the error from the first stage of the model.

Appendix 3: Additional sensitivity analysis with missing adherence data imputed

The aim of this paper was to demonstrate how randomisation-based efficacy estimators can be used to produce unbiased adherence-adjusted estimates of benefits and harms from treatment with amoxicillin for patients consulting with an LRTI. The main effectiveness findings (reference 7 in the main manuscript) were used as the reference results. However, two participants did not have adherence data available for the symptom severity between days 2 and 4 post-randomisation and non-respiratory symptoms/side effects in the 4 weeks post-randomisation outcomes. A total of 104 participants did not have adherence data available for the new or worsening symptoms in the 4 weeks post-randomisation outcome. While the two former outcomes were collected via symptom diaries, the latter was collected from patient notes, and was consequently available for more participants. Table 2 in the manuscript suggests that the level of adherence in participants without self-reported diary or tablet count data was considerably lower (self-reported telephone data was primarily collected in those who did not return diaries). In the presence of missing adherence data, there may remain some residual bias. To understand how severe this bias could be (particularly, how low the odds ratio for new or worsening symptoms could be), Table 9 provides the findings of additional sensitivity analyses where participants with missing adherence data are assumed to have not taken any study medication (i.e. their adherence level is 0%). The findings demonstrate that making this most extreme assumption about missing adherence data did not alter the clinical conclusions that were drawn from the analyses.

Table 9: Efficacy analysis with missing adherence data imputed as 0%

Outcome	**Effectiveness***	**Effectiveness for whom adherence data were also available[†]**	**Efficacy per 10% increase in adherence[†]**	**Maximum efficacy (100% adherence)[†]**	**Efficacy per 10% increase in adherence*[§]**	**Maximum efficacy (100% adherence)*[§]**
Adjusted between-group mean difference in symptom severity between days 2 and 4 post-randomisation	-0.07 (-0.15 to 0.01)	-0.07 (-0.15 to 0.01)	-0.008 (-0.017 to 0.001)	-0.08 (-0.17 to 0.01)	-0.008 (-0.017 to 0.001)	-0.08 (-0.17 to 0.01)
Odds ratio for developing new or worsening symptoms in the 4 weeks post-randomisation	0.79 (0.63 to 0.99)	0.81 (0.64 to 1.03)	0.978 (0.960 to 0.998)	0.81 (0.66 to 0.98)	0.973 (0.954 to 0.994)	0.76 (0.62 to 0.94)
Odds ratio for reporting non-respiratory symptoms/side effects in the 4 weeks post-randomisation	1.28 (1.03 to 1.59)	1.28 (1.04 to 1.59)	1.028 (1.011 to 1.046)	1.32 (1.12 to 1.57)	1.028 (1.011 to 1.046)	1.32 (1.11 to 1.56)

* Analysis based on 1789, 2027 and 1727 participants for the symptom severity, new symptoms and side effect outcomes respectively. † Analysis based on 1787, 1923 and 1725 participants for the symptom severity, new symptoms and side effect outcomes respectively. § Assuming those participants with missing adherence data did not take any medication (i.e. their adherence level is 0%).

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Trials

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The use of randomisation-based efficacy estimators in non-inferiority trials

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Abstract

Background: In a non-inferiority (NI) trial, analysis based on the intention-to-treat (ITT) principle is anti-conservative, so current guidelines recommend analysing on a per-protocol (PP) population in addition. However, PP analysis relies on the often implausible assumption of no confounders. Randomisation-based efficacy estimators (RBEEs) allow for treatment non-adherence while maintaining a comparison of randomised groups. Fischer et al. have developed an approach for estimating RBEEs in randomised trials with two active treatments, a common feature of NI trials. The aim of this paper was to demonstrate the use of RBEEs in NI trials using this approach, and to appraise the feasibility of these estimators as the primary analysis in NI trials.

Methods: Two NI trials were used. One comparing two different dosing regimens for the maintenance of remission in people with ulcerative colitis (CODA), and the other comparing an orally administered treatment to an intravenously administered treatment in preventing skeletal-related events in patients with bone metastases from breast cancer (ZICE). Variables that predicted adherence in each of the trial arms, and were also independent of outcome, were sought in each of the studies. Structural mean models (SMMs) were fitted that conditioned on these variables, and the point estimates and confidence intervals compared to that found in the corresponding ITT and PP analyses.

Results: In the CODA study, no variables were found that differentially predicted treatment adherence while remaining independent of outcome. The SMM, using standard methodology, moved the point estimate closer to 0 (no difference between arms) compared to the ITT and PP analyses, but the confidence interval was still within the NI margin, indicating that the conclusions drawn would remain the same. In the ZICE study, cognitive functioning as measured by the corresponding domain of the QLQ-C30, and use of chemotherapy at baseline were both differentially associated with adherence while remaining independent of outcome. However, while the SMM again moved the point estimate closer to 0, the confidence interval was wide, overlapping with any NI margin that could be justified.

Conclusion: Deriving RBEEs in NI trials with two active treatments can provide a randomisation-respecting estimate of treatment efficacy that accounts for treatment adherence, is straightforward to implement, but requires thorough planning during the design stage of the study to ensure that strong baseline predictors of treatment are captured. Extension of the approach to handle nonlinear outcome variables is also required.

Trial registration: The CODA study: ClinicalTrials.gov, identifier: NCT00708656. Registered on 8 April 2008. The ZICE study trial: ClinicalTrials.gov, identifier: NCT00326820. Registered on 16 May 2006.

Keywords: Treatment non-adherence, Non-inferiority, Efficacy, Intention-to-treat, Per-protocol, Structural mean models

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Background

In the majority of randomised controlled trials (RCTs), the primary goal is to investigate the superiority of one treatment over another [1]. However, in some instances, it can be sufficient to demonstrate that a treatment is no worse than another on some outcome of interest. This is particularly true where a standard treatment is already in place (a so-called 'active control'), and the new treatment could offer substantial benefits on non-primary outcomes such as reduce side effects, reduced costs, simpler dosing regimen, etc. This is the purpose of a non-inferiority (NI) trial, where the aim is to demonstrate that a new treatment is no worse than a standard treatment by more than an acceptable amount [2].

The 'gold standard' approach to analysis in a superiority trial is based on the intention-to-treat (ITT) principle, where participants are analysed in the groups to which they were originally randomised [3]. This approach is favoured as it preserves randomisation and, in the case of departures from randomised treatment, makes treatment groups appear more similar; therefore, producing a conservative estimate of treatment effect. However, in a NI trial it is desirable for treatment groups to be as similar as possible, and therefore an ITT analysis is viewed as anti-conservative in this situation [4, 5]. Current recommendations are that a per-protocol (PP) analysis should be conducted alongside an ITT analysis for NI trials [6]. A PP analysis excludes participants with departures from randomised treatment, but assumes that the group of participants who are excluded are similar to those who are included on both observed and unobserved variables; an assumption that is usually deemed implausible [7]. The ideal analytical method would be based on participants who received the treatment to which they were allocated, while maintaining a comparison of groups as randomised (and thus not prone to the selection biases that are common with a PP analysis).

Randomisation-based efficacy estimators (RBEEs), such as Structural Mean Models (SMMs), compare the effect of treatment in the group of participants who were allocated to and adhered to treatment with the group allocated to receive control (or standard treatment) but who *would have* adhered to treatment (had they been allocated to the treatment group) [8]. The approach allows for treatment non-adherence [9] while maintaining a comparison of randomised groups. Fischer et al. have developed an approach for estimating treatment efficacy in randomised trials with two active treatments, a common feature of NI trials [10].

The aim of this paper is to demonstrate the use of RBEEs in NI trials using the methods outlined by Fischer et al., and to appraise the feasibility of these estimators as the primary analysis in NI trials. A brief introduction to randomisation-based efficacy estimators will be given in 'Methods section', specifically where the estimators are used in trials with two active interventions. This section will also highlight general steps to fitting these models using standard statistical software, before concluding with a description of the studies used as examples in this paper. 'Results section' will present worked examples using data from the studies described in 'Methods section', while 'Discussion section' will summarise the work of the previous sections and highlight the implications of using these methods in practice.

Methods

Traditional approaches to deriving efficacy in RCTs

An ITT analysis is used to determine treatment effectiveness in RCTs [11, 12]. Under certain circumstances (e.g. all participants receive all of the treatment to which they were randomised), an ITT analysis can also be used to estimate treatment efficacy. However, in the presence of non-adherence, or departures from randomised treatment, the most common approach to assessing treatment efficacy in an RCT is to conduct a PP analysis. This analysis excludes participants who are determined to have not adhered to their randomised treatment. However, it fails to maintain a comparison of groups as randomised, and is therefore prone to selection bias [11]. While selection bias is thought to be minimised in trials with blinding, and modified definitions of these populations that adjust for observed confounders can be used, selection bias can never be completely discounted from any analyses that make postrandomisation exclusions or manipulations.

Structural Mean Models to derive randomisation-based efficacy estimators

By recognising that at the beginning of a trial all participants have two potential outcomes – one if they are treated and one if they are not, a SMM relates a treated participant's observed outcome to their (potentially counterfactual) outcome that would have been observed had they received no treatment [13]. Standard approaches to fitting a SMM rely on using observed exposure, treating randomisation as an instrument (i.e. assuming that it is independent of both observed and unobserved confounders and only effects outcome through its effect on exposure), and finding a value of the treatment effect such that balance is achieved between groups on the outcome in participants who were not treated [14].

By doing this it becomes possible to derive an estimate of treatment efficacy (the effect that *receiving* treatment has on outcome) that is not prone to the usual selection biases usually found in traditional methods (Fig. 1).

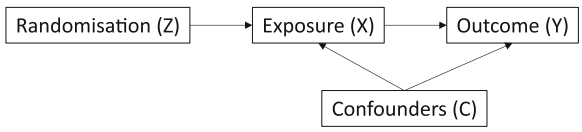

Fig. 1 Causal Directed Acyclic Graph (DAG) illustrating using randomisation as an instrument to derive a randomisation-based efficacy estimate

SMMs with two active treatments

Conventional SMM methodology is based on trials comparing an active treatment to no treatment (or a placebo). However, in non-inferiority trials it is common to just compare two active treatments – one experimental and one standard. This complicates matters, as without a no-treatment group there is no observed outcome on which to base the potential outcome in the untreated, and therefore the method described above cannot be readily applied.

By identifying baseline covariates that are differentially associated with treatment adherence for each of the treatments, the methodology developed by Fischer et al. allows for the estimation of two distinct causal parameters, from which a contrast can then be made. Identifying baseline covariates that are differentially associated with treatment adherence for each of the treatments, but independent of outcome, allows separate sets of instruments to be derived for each treatment, and allows a potential treatment-free response to be estimated [10].

If suitable baseline covariates are not identified, two distinct causal parameters cannot be estimated. Despite this, a linear contrast can still be made and the following approaches can be taken:

- Fix adherence levels as the same in both arms, and estimate the treatment efficacy in the subpopulation that would always adhere to their treatment at that given level
- Perform sensitivity analyses that vary adherence parameters to explore the impact that differential adherence levels has on outcomes
- Use standard SMM methods and consider the standard treatment as the 'placebo' group. This will allow for the comparison of average outcomes at varying levels of the experimental treatment to the average outcome if assigned to the standard treatment (regardless of adherence levels to that standard treatment)

Example studies

Two non-inferiority trials, whose data were available to the authors, were used to illustrate the proposed methods and its uses and limitations. Beyond the availability of data, the two studies described below were chosen as they were both two-arm non-inferiority trials, with two active treatments involving patients with long-term conditions whose medication use was monitored throughout the trial. The trials differ in terms of the nature of the interventions being compared, with Colitis Once Daily Asacol (CODA) comparing the same treatment prescribed with different regimens, and Zoledronate versus Ibandronate Comparative Evaluation (ZICE) comparing two different treatments with different modes of administration. These examples, while contrasting, are typical of the types of non-inferiority trials conducted and will, therefore, provide useful insight into the methods proposed.

The Colitis Once Daily Asacol (CODA) trial

The CODA trial was designed to assess the efficacy and safety of once daily dosing (OD) versus three times daily dosing (TDS) of mesalazine over a 12-month period for patients in remission with ulcerative colitis. The study concluded that the OD regimen was no worse than (non-inferior to) the TDS regimen in terms of clinical relapse using both an ITT and a PP analysis [15]. Research nurses counted the number of tablets returned at each study visit, and deducting this from the number of tablets issued determined the number consumed during the study period. Adherence to study medication in the original trial was defined as participants consuming at least 75% of their issued medication. A subset of participants also had their medication adherence recorded using the Medication Event Monitoring System (MEMS), an electronic monitor that records the date and time of each bottle cap opening. This substudy demonstrated that adherence to study medication was generally lower and more varied for participants allocated to the TDS regimen. However, as this type of measure was not used for all trial participants, it will not be considered further in this paper [16].

The Zoledronate versus Ibandronate Comparative Evaluation (ZICE) trial

The ZICE trial was designed to assess whether orally administered ibandronic acid (OIA) was non-inferior to intravenously administered zoledronic acid (IZA) in preventing skeletal-related events (SREs) in patients with bone metastases from breast cancer. The study concluded that orally administered ibandronic acid was inferior to intravenously administered zoledronic acid in both ITT and PP populations [17].

Adherence to study medication was noted by the treating clinician at interim and 12-weekly visits. Participants were defined as having adhered to their allocated treatment if the clinician recorded that study medication had been administered as prescribed during all scheduled visits. See Additional file 1 for more detail.

Statistical methods

Outcomes

For the CODA trial, the outcome of interest was the proportion of participants relapsing during the 12-month study period. The OD regimen was considered to be non-inferior to the TDS regimen as long as the lower bound of the 95% confidence interval of the difference in the proportion of participants in each arm relapsing (OD minus TDS) did not include −0.1.

For the ZICE trial, the outcome of interest for this paper was the proportion of participants experiencing a SRE during the first 12 months of the study. This is a simplified version of the primary outcome from the main paper (time and frequency of SREs), and used for illustration purposes only. There was, therefore, no pre-specified non-inferiority margin for this outcome.

Modelling approach

Determining baseline covariates that differentially predict adherence Deriving distinct causal estimators for each treatment arm relied on identifying baseline variables that predicted adherence to treatment differently in each arm, while not predicting clinical outcome. Determining these predictors involved two main steps. First, multivariable logistic regression was used to determine the factors that predicted clinical outcome. Variables that were identified univariably at the 20% significance level were entered into the multivariable model, with backward selection used to retain variables independently associated at the 10% significance level. Following this, multivariable logistic regression was used, with the binary adherence variable as the outcome. Predictors of adherence were entered one-by-one into a regression model that included trial arm, and interaction between candidate predictor and trial arm, and the predictors of clinical outcome that were identified during the previous step. Any variables that were associated with adherence at the 20% significance level, as either a main effect or as an interaction with trial arm, were retained in the multivariable regression model. Predictors that remained associated at the 10% significance level were then retained in the final regression model.

For the CODA trial, the candidate baseline predictors used in the outcome and adherence models were age (<65, ≥65 years), age at diagnosis (≤25, 26–45, 46–64, ≥65 years), gender, length of remission (<12 months, ≥12 months), calprotectin concentration (<60 mg/kg stool, ≥60 mg/kg stool), smoking status (never smoker, current smoker, ex-smoker), employment status (unemployed, employed), maximum documented extent of colitis (extensive, left-sided or sigmoid, proctitis), disease duration (≤10 years, 11 to 20 years, >20 years), number of relapses during the past 2 years (1, 2, 3, ≥4), and endoscopy findings (normal, not normal).

For the ZICE trial, the predictors were age, gender, Body Mass Index (BMI), the modified Brief Pain Inventory severity score, quality of life (EORTC QLQ-C30 score version 3.0), SRE within the previous 3 months, previous use of bisphosphonates, treatments being received (including painkilling drugs, chemotherapy, hormone therapy, and trastuzumab).

Variables that were included in the models were checked for notable deviations from linearity. While the relationship between age and outcome in the CODA trial was considered non-linear, this was not the case for the ZICE trial. A cut-off of 65 years was chosen to distinguish between elderly/non-elderly participants (see http://www.who.int/healthinfo/survey/ageingdefnolder/en/).

Fitting the structural mean model The SMM models were fitted using a two-stage, least squares, instrumental variables regression approach. Using this procedure, the trial arm (the instrument), predictors of outcome, and differential predictors of adherence were used to estimate values of the adherence variables in the first stage. These values were then regressed onto the outcome in the second stage. These regressions were fitted simultaneously in order to avoid standard errors that were artificially large. The Huber-White robust standard error, with additional correction for small samples, was used in order to make correct inferences about the differences in proportions [18]. Table 1 provides sample syntax using Stata (v13.0).

Table 1 Sample Stata (v13.0) syntax of the structural mean models described in 'Methods section' and fitted in 'Results section'

The Colitis Once Daily Asacol (CODA) trial
ivregress 2sls < <Outcome> > (<<Adherence indicator> > = < <Trial arm indicator>>), vce(robust)
The Zoledronate versus Ibandronate Comparative Evaluation (ZICE) trial
ivregress 2sls < <Outcome> > <<Predictors of outcome> > <<Predictors of adherence> > (<<Adherence in experimental arm> > <<Adherence in standard treatment arm> > = < <Trial arm indicator> > <<Predictors of outcome> > <<Trial arm * Predictors of outcome interactions> > <<Predictors of adherence> > <<Trial arm * Predictors of adherence interaction>>), vce(robust)
lincom[<<Experimental treatment arm effect> > - < <Standard treatment arm effect>>]
For the CODA trial, the adherence indicator was one variable that was 1 if the participant was allocated to the OD arm (experimental intervention) and adhered, 0 if they were allocated to the OD arm and did not adhere, and also 0 if they were allocated to the TDS arm (standard care).
For the ZICE trial, as distinct causal parameters were identifiable, each arm had its own variable to denote adherence. This variable was 1 if the participant was allocated to the arm and adhered, 0 if they were allocated to the arm and did not adhere, and 0 if they were allocated to the other arm.

OD once daily, *TDS* three times daily

Results

The CODA trial

The analysis is based on 188 randomised participants with outcome data. In total, 174 participants adhered to their study medication (92.6%), with these making up the PP population (Fig. 2). The percentage of participants adhering to study medication was higher in those randomised to the intervention arm compared to the active control arm (95.7% and 89.4%, respectively).

Overall, 56 participants relapsed within the 12-month follow-up period (29.8% of all participants). The percentage of participants who relapsed was lower in the intervention arm compared to the active control arm (24.5% and 35.1%, respectively). The main trial analysis based on complete cases demonstrated that the relapse rate was 10.6 percentage points higher in those randomised to the TDS arm compared to in the OD (95% confidence interval (CI): −2.5 to 23.8 percentage points). As the lower limit of the 95% CI did not include −10%, and this was also confirmed in the PP analysis, the findings confirmed the non-inferiority of the OD regimen compared to the TDS regimen.

Predictors of outcome

Predictors of relapse were age (participants aged 65 years or older had decreased odds of relapsing during the follow-up period), length of remission (participants in remission for at least 12 months had decreased odds of relapsing during the follow-up period), and endoscopy findings at baseline (participants with non-normal endoscopy findings at baseline had increased odds of relapsing during the follow-up period) (Table 2).

Predictors of adherence

When conditioning on the above variables, smoking status at baseline was the only variable that remained independently associated with participants adhering to their study medication at the 10% significance level (Table 3). Compared to non-smokers, the odds of participants adhering to their study medication was higher in those who were ex-smokers. However, smoking status did not differentially predict adherence across the two arms (i.e. the interaction between smoking status and trial arm was not statistically significant).

Structural mean model

It was not possible to derive two distinct causal parameters based on observed data, as there were no baseline variables differentially associated with adherence for each of the arms. Given that the definition of adherence was binary, the only sensible analysis was to consider the standard treatment (active control) as the 'placebo' group and use standard SMM methods.

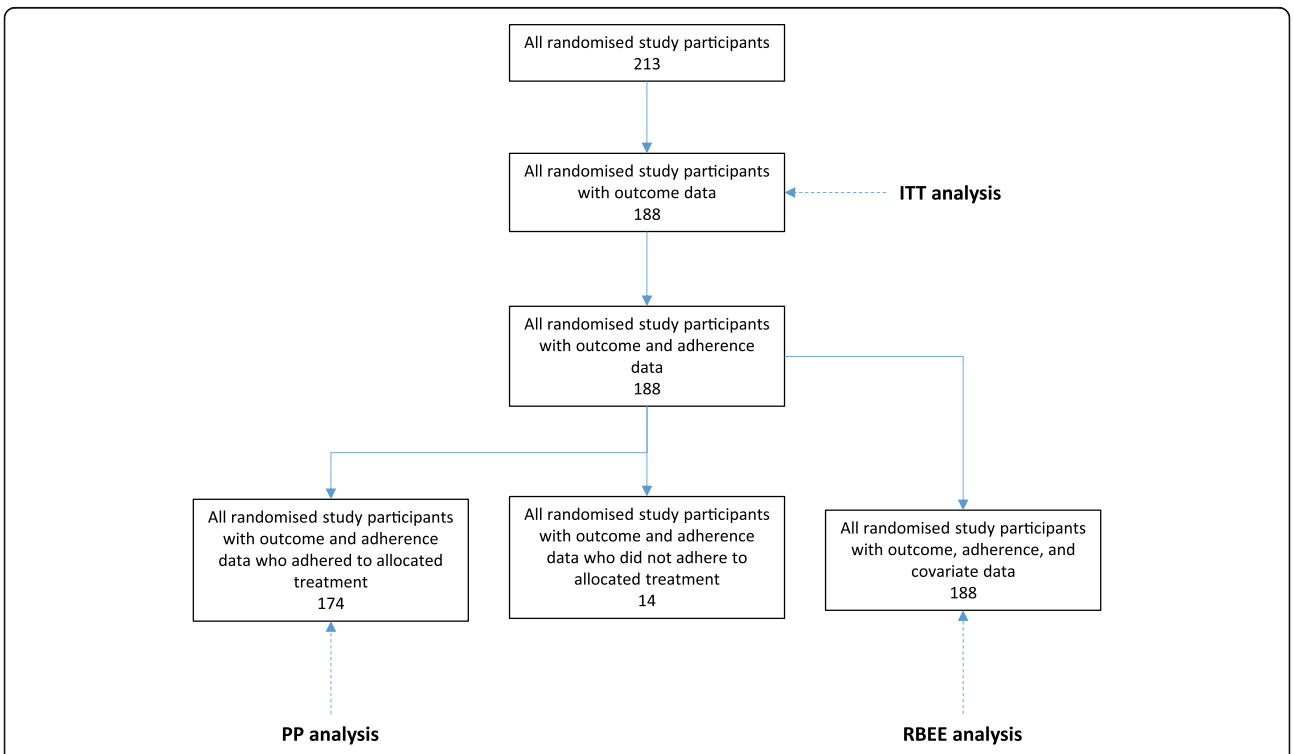

Fig. 2 Flow diagram describing data available for each type of analysis in the Colitis Once Daily Asacol (CODA) trial

Table 2 Multivariable determinants of outcome in the Colitis Once Daily Asacol (CODA) trial (odds of relapsing during the 12-month follow-up period)

Variable	Adjusted odds ratio	95% Confidence interval		*p* value
		Lower	Upper	
Age at baseline (≥65 compared to <65 years)	0.30	0.10	0.88	0.028
Length of remission (≥12 compared to <12 months)	0.34	0.14	0.81	0.014
Endoscopy findings at baseline (non-normal compared to normal)	4.14	2.04	8.39	<0.001

The SMM analysis found that after adjusting for adherence, the relapse rate was 11.1 percentage points higher in those randomised to intervention. The 95% CI did not contain −10% (95% CI −2.5 to 24.7 percentage points), and non-inferiority could be confirmed based on this analysis (Fig. 3).

The ZICE trial

The analysis is based on 1037 randomised participants with outcome data. In total, 621 of 915 participants with adherence data adhered to their study medication (67.9%), with these making up the PP population. The percentage of participants adhering to study medication was higher in those randomised to the OIA arm compared to the IZA arm (77.4% and 60.7%, respectively). Baseline covariate data were available for 796 participants. This made up the SMM population (Fig. 4).

Overall, 382 participants experienced an SRE within the 12-month follow-up period (36.8% of all participants). The percentage of participants who experienced an SRE was higher in the OIA arm compared to the IZA arm (38.3% and 35.4%, respectively). The trial analysis based on complete cases demonstrated that the SRE rate was 3.0 percentage points higher in those randomised to the OIA arm compared to in the IZA (95% confidence interval (CI) −2.9 to 8.8 percentage points) and concluded that OIA was inferior to IZA.

Predictors of outcome

The odds of experiencing an SRE within the first 12 months of the study were higher in participants with higher BMI scores, in participants who had poor role functioning, worse nausea/vomiting symptoms, had experienced an SRE in the 3 months prior to the study, or had recently used pain medication. The odds of experiencing an SRE within the first 12 months of the study were lower in women than in men, in participants with higher overall general health, and in participants with increasing dyspnoea (Table 4).

Predictors of adherence

After conditioning on the above, both cognitive functioning and use of chemotherapy were independently associated with adhering to study medication differently in the two arms (Table 5). The results from the model suggest that the odds of adhering to study medication are:

- Higher for participants allocated to the OIA arm, with the lowest levels of cognitive functioning, and not undergoing chemotherapy at baseline
- Higher as cognitive functioning increases for participants allocated to the IZA arm
- Lower as cognitive functioning increases for participants allocated to the OIA arm
- Higher for participants undergoing chemotherapy at baseline and allocated to the IZA arm
- Lower for participants undergoing chemotherapy at baseline and allocated to the OIA arm
- *BMI* Body Mass Index, IZA Intravenously administered zoledronic acid, *OIA* Orally administered ibandronic acid OIA, *QLQ-C30* EORTC QLQ-C30 score version 3.0, *SRE* Skeletal-related event,

Table 3 Multivariable determinants of adhering to medication in the Colitis Once Daily Asacol (CODA) trial

Purpose	Variable	Adjusted odds ratio	95% Confidence interval		*p* value
			Lower	Upper	
Associated with disease status at 12 months (relapsed/still in remission)	Intervention (OD arm compared to TDS arm)	2.61	0.75	9.03	0.131
	Age at baseline (≥65 years compared to <65 years)	2.42	0.27	21.70	0.430
	Length of remission (≥12 months compared to <12 months)	1.05	0.29	3.75	0.940
	Endoscopy findings at baseline (non-normal compared to normal)	0.31	0.10	1.01	0.053
Associated with adherence to study medication	Smoking status at baseline (current smoker compared to non-smoker)	1.31	0.25	6.79	0.076
	Smoking status at baseline (ex-smoker compared to non-smoker)	11.46	1.40	94.01	

OD once daily, *TDS* three times daily

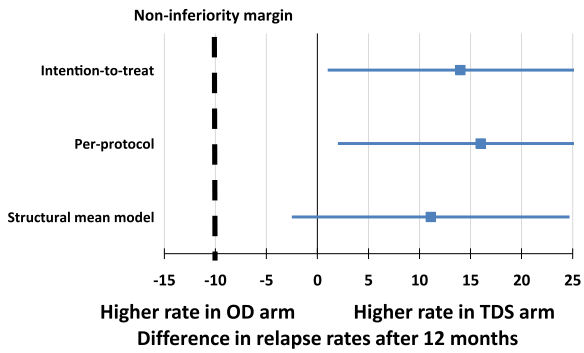

Fig. 3 Forest plot of the difference in relapse rates in the Colitis Once Daily Asacol (CODA) trial for various analysis sets

Structural mean model

Distinct causal parameters could be estimated using the ZICE data, and therefore the difference between the two arms could be calculated. After adjusting for treatment adherence, the proportion with SRE in the first 12 months was no different in either of the arms (difference in proportions 0.0, 95% CI −13.9 to 13.8 percentage points). While the point estimate from the SMM was closer to no difference, the width of the confidence interval contains any non-inferiority margin that could be justified (Fig. 5).

Discussion

Summary of paper

This paper investigated the use of randomisation-based efficacy estimators in non-inferiority trials. Structural mean models were fitted using a method proposed by Fischer et al., where baseline variables that predicted adherence differentially were sought to derive causal estimators in each treatment arm. This method was applied to two datasets from clinical trials involving patients in remission with ulcerative colitis (CODA) and breast cancer with bone metastases (ZICE) using standard statistical software. In the CODA trial, it was not possible to derive distinct estimators, and standard SMM methods were applied instead, treating the active control arm in the same way that a placebo arm would be treated. This analysis was consistent with the ITT and PP findings (i.e. there was evidence to suggest that OD was not inferior to TDS in terms of preventing relapse). In the ZICE trial it was possible to derive distinct estimators, and when comparing the arms the point estimate implied no difference in SRE rates between the arms, but the confidence intervals were considerably wider than the ITT and PP analyses.

Strengths and weaknesses of the approach

To our knowledge, this is the first paper to demonstrate the potential use of randomisation-based efficacy

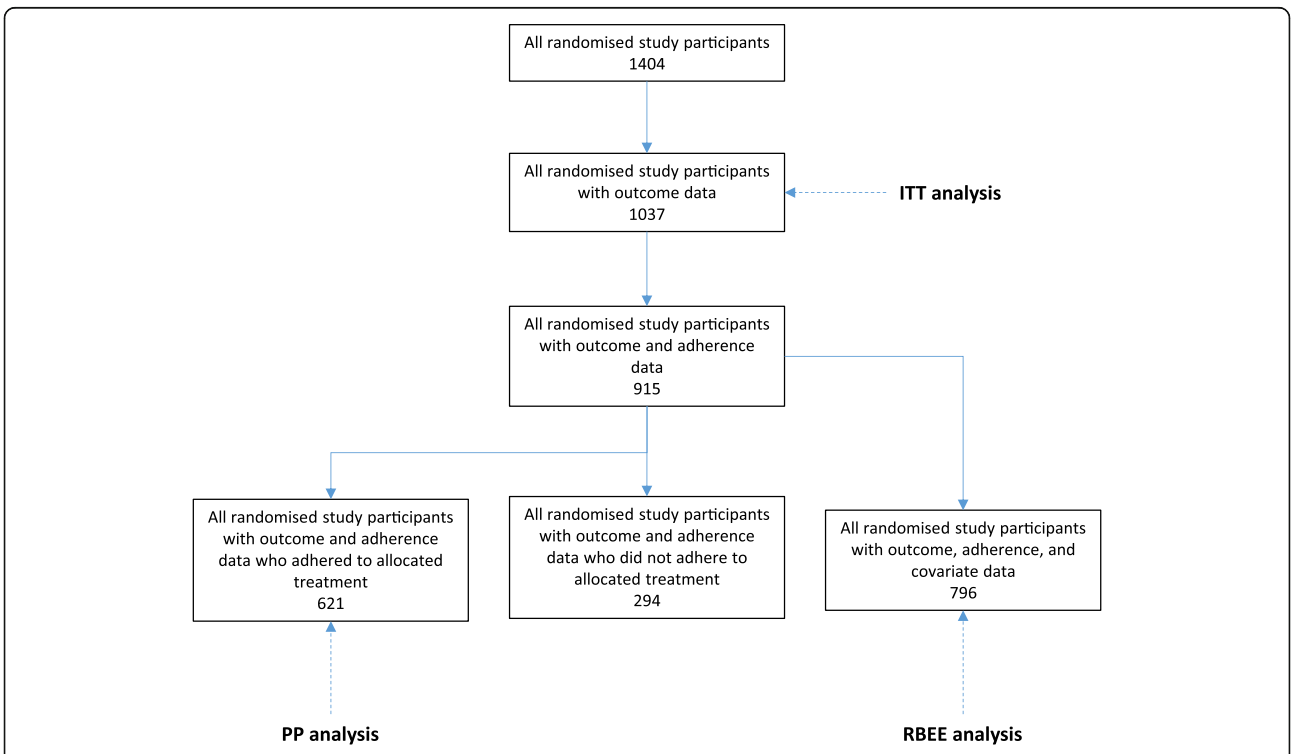

Fig. 4 Flow diagram describing data available for each type of analysis in the Zoledronate versus Ibandronate Comparative Evaluation (ZICE) trial

Table 4 Multivariable determinants of outcome in the Zoledronate versus Ibandronate Comparative Evaluation (ZICE) trial (odds of experiencing a skeletal-related event during the first 12 months)

Variable	Adjusted odds ratio	95% Confidence interval		*p* value
		Lower	Upper	
Gender (female compared to male)	0.23	0.06	0.88	0.032
18.5 kg/m^2 < BMI ≤ 25 kg/m^2 (normal/healthy weight) compared to ≤ 18.5 kg/m^2 (underweight)	6.16	0.75	50.65	<0.001
25 kg/m^2 < BMI ≤ 30 kg/m^2 (overweight) compared to ≤ 18.5 kg/m^2 (underweight)	6.85	0.84	56.13	
30 kg/m^2 < BMI ≤ 35 kg/m^2 (moderately obese) compared to ≤ 18.5 kg/m^2 (underweight)	13.17	1.59	108.81	
35 kg/m^2 < BMI ≤ 40 kg/m^2 (severely obese) compared to ≤ 18.5 kg/m^2 (underweight)	6.99	0.81	60.39	
BMI > 40 kg/m^2 (very severely obese) compared to ≤ 18.5 kg/m^2 (underweight)	13.11	1.44	119.65	
QLQ-C30 global health domain (per unit increase)	0.98	0.98	0.99	0.001
QLQ-C30 role functioning domain (per unit increase)	1.01	1.00	1.02	0.005
QLQ-C30 nausea / vomiting domain (per unit increase)	1.01	1.01	1.02	<0.001
QLQ-C30 dyspnoea domain (per unit increase)	0.99	0.99	1.00	0.056
SRE within the three months prior to baseline compared to no SRE within three months prior to baseline	1.56	1.14	2.13	0.006
Recent use of pain medication at baseline compared to no recent use of pain medication	1.63	1.08	2.46	0.019

Table 5 Multivariable determinants of adhering to medication in the Zoledronate versus Ibandronate Comparative Evaluation (ZICE) trial

Purpose	Variable	Adjusted odds ratio	95% confidence interval		*p* value
			Lower	Upper	
Associated with the development of a SRE within 12 months	Gender (female compared to male)	1.29	0.36	4.55	0.697
	18.5 kg/m^2 < BMI ≤ 25 kg/m^2 (normal/healthy weight) compared to ≤ 18.5 kg/m^2 (underweight)	2.19	0.74	6.47	<0.001
	25 kg/m^2 < BMI ≤ 30 kg/m^2 (overweight) compared to ≤ 18.5 kg/m^2 (underweight)	2.05	0.70	6.00	
	30 kg/m^2 < BMI ≤ 35 kg/m^2 (moderately obese) compared to ≤ 18.5 kg/m^2 (underweight)	2.35	0.79	7.03	
	35 kg/m^2 < BMI ≤ 40 kg/m^2 (severely obese) compared to ≤ 18.5 kg/m^2 (underweight)	3.07	0.95	9.95	
	BMI > 40 kg/m^2 (very severely obese) compared to ≤ 18.5 kg/m^2 (underweight)	3.90	1.06	14.31	
	QLQ-C30 global health domain (per unit increase)	1.00	1.00	1.01	0.358
	QLQ-C30 role functioning domain (per unit increase)	1.00	1.00	1.01	0.300
	QLQ-C30 nausea/vomiting domain (per unit increase)	1.01	1.01	1.02	0.000
	QLQ-C30 dyspnoea domain (per unit increase)	1.00	0.99	1.00	0.547
	SRE within the 3 months prior to baseline compared to no SRE within 3 months prior to baseline	1.07	0.79	1.46	0.660
	Recent use of pain medication at baseline compared to no recent use of pain medication	0.65	0.45	0.94	0.021
Differentially associated with adherence by trial arm	Orally administered ibandronic acid arm (main effect)	5.77	2.05	16.26	0.001
	QLQ-C30 cognitive functioning (main effect)	1.01	1.00	1.02	0.005
	Orally administered ibandronic acid arm x QLQ-C30 cognitive functioning (interaction)	0.99	0.98	1.00	0.061
	Use of chemotherapy at baseline (main effect)	2.12	1.28	3.53	0.004
	Orally administered ibandronic acid arm x Use of chemotherapy at baseline (interaction)	0.47	0.22	1.02	0.057

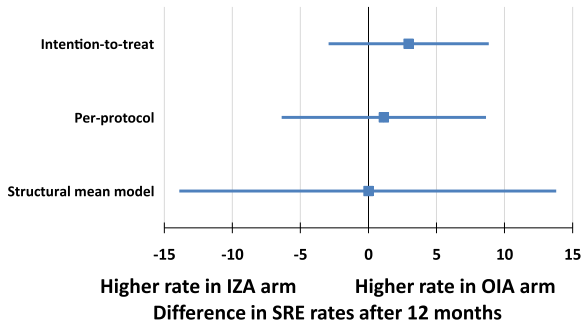

Fig. 5 Forest plot of the difference in the proportion with skeletal-related event (SRE) in the first 12 months in the Zoledronate versus Ibandronate Comparative Evaluation (ZICE) trial for various analysis sets

estimators as a primary analysis in non-inferiority trials. Data from two non-inferiority trials were used, and the strengths and limitations of RBEEs and SMMs using the method proposed by Fischer et al. when applied to real-world data were established.

Both studies captured adherence to treatment differently. In the CODA trial, adherence was captured using tablet counts and in the ZICE trial adherence was captured using self-report and hospital attendance data. These methods have been demonstrated to overestimate adherence in certain circumstances, [19–21] but they are methods that are cheap and easy to apply in large-scale randomised controlled trials, so are likely to reflect the type of data obtained in other settings (as opposed to more direct methods or electronic monitoring).

The ZICE trial used a simplified version of the original primary outcome in order to illustrate the use of these methods. One consequence of this is that while a non-inferiority margin was defined for the original primary outcome, one was not defined for the simplified version. While this could have limited the interpretation of this analysis, the confidence intervals were too wide for any NI margin to be justified, even post hoc (given that the original trial analysis suggested inferiority, this was a simplified outcome that would have had lower power than a recurrent event outcome, and the confidence interval of the SMM analysis was over twice as wide as the ITT and PP analyses).

Both studies took adherence as a quantitative measure and dichotomised it. While this was necessary for defining the analysis set, it was an approach that meant a loss of information with regards to the extent to which participants adhered to treatment. Using a binary definition of adherence (≥75%/<75% for the CODA trial and full versus not full for the ZICE trial) meant that the exclusion restriction was less likely to be plausible [14]. However, choosing an arbitrary lower threshold would have yielded estimates that were difficult to interpret, and treating adherence as a quantitative measure would have meant the additional assumption of a linear relationship between treatment adherence and treatment effect [22].

Participants with missing outcome or adherence data may have induced some selection bias in the findings presented. However, adjustments for missing data (e.g. with multiple imputation) tend to be used as secondary/sensitivity analysis in trials [23], and the purpose of this paper was to demonstrate the use of RBEEs as the main analysis in NI trials. An assessment of the impact of missing data on the interpretation of the SMM analysis can be seen in Additional file 1. Additionally, other variables that were not recorded in sufficient detail that may have influenced adherence to trial treatments, clinical outcomes, and/or dropout include the use of rescue medication and other medication that was added to a patient's treatment plan part way through the study.

It was also decided to present an approach that could be adopted more readily, hence the use of modified least squares (MLS) for a binary outcome, rather than deriving estimates using a generalised method of moments approach [24].

Comparisons to existing trials literature

A recently published paper investigating the comparative efficacy of two different antidepressants was the first to demonstrate the practical implementation of the SMM approach as outlined by Fischer et al. [25]. However, this approach is particularly appropriate for non-inferiority trials (as indicated in the abovementioned paper), and thus our publication complements this work by implementing this SMM approach in two non-inferiority trials. One other study has reportedly implemented this approach on a non-inferiority trial [26]. However, as this was a placebo-controlled trial, and the paper detail of the approach was lacking, it was unclear whether they applied standard SMM methodology or the extended work described by Fischer et al. Therefore, to our knowledge, this is the first publication to demonstrate how this approach works in practice for non-inferiority trials with two active interventions.

Implications for researchers

Structural mean models could replace traditional efficacy analyses that are often reported alongside an ITT analysis in non-inferiority trials. However, this paper highlights the increase in variance experienced when fitting these models, something that can only be reduced when the models include strong predictors of adherence and outcome. Use of the method is more accurate in terms of reducing selection bias, but is likely to be less precise, and increases the importance of collecting relevant and complete baseline variables. To do this, the research team must have a good understanding of the predictors of outcome, and also the barriers/facilitators to adhering

to the randomised treatments. Studies with feasibility/pilot stages could explore these aspects, as well as how best to capture this data, before progressing onto more definitive studies. The significance thresholds for inclusion of variables in this paper were higher than current practice. Future studies that collect strong baseline predictors of adherence need not use such high significance levels.

Estimating efficacy in randomised trials is valuable, as it answers a more patient-centred question than can be answered by an estimate of effectiveness. That is, "*what is the effect if I take this treatment?*", rather than the more health care professional-centred question "*what is the effect if I offer this treatment?*" Both questions are useful, but for a patient trying to understand the effect of a treatment, the more pertinent of the two questions relates to efficacy rather than effectiveness.

By modelling the determinants of differential adherence in the different treatment arms, researchers will also gain an understanding of the circumstances under which the treatments will be better received by patients and, therefore, more likely to work. For example, in the ZICE study, we were able to demonstrate that for participants allocated to the intravenously administered zoledronic acid arm, adherence was higher for patients with higher cognitive function and for those receiving chemotherapy at baseline. Whereas for those allocated to the orally administered ibandronic acid arm adherence was lower for patients with lower cognitive function and for those receiving chemotherapy at baseline. One explanation for this could be that patients with low cognitive function could have their medicines dispensed by a care giver, which is likely to reduce forgetfulness and increase adherence. Patients receiving chemotherapy at baseline will be attending hospital regularly for these visits, and the delivery of IZA often coincided with other hospital visits for cancer therapy, thereby increasing their chances of receiving IZA treatment. The implications of this, regardless of the comparative efficacy of the treatments themselves, could be that IZA should be offered to those undergoing additional cancer treatments (or any other treatments that require regular hospital visits). OIA could be offered along with an additional intervention to increase adherence (e.g. a reminder or monitoring system), or in instances where patients were not in control of their own medication dispensing (e.g. elderly residents of nursing homes).

Potential extensions and future work

By extending this methodology to allow for different types of outcome (e.g. binary, count, survival), this approach could be more widely used. For example, the primary analysis in the ZICE trial was based on an Anderson-Gill model (survival model with recurrent events) [27].

While not as necessary here, as a binary definition of treatment receipt is required to define an analysis set, methods of RBEEs that allow for non-linear relationships between an increase in adherence and treatment effects would be useful for capturing the complexity of some dose-response relationships more accurately.

Finally, further work is needed in order to incorporate necessary adjustments into sample size calculations for the design of trials that wish to use these methods as more than an exploratory analysis. Adjustments will likely depend on the proportion of non-adherence, as well as the number and strength of baseline predictors/instruments that are likely to be identified.

Conclusions

In NI trials, RBEEs can provide a randomisation-respecting estimate of treatment efficacy that accounts for treatment adherence, addressing the deficiencies of both ITT and PP analysis for this study design. For NI trials involving two active treatments, RBEEs can also be modelled, remain straightforward to implement using standard statistical software, but require thorough planning during the design stage of the study to ensure that strong baseline predictors of treatment are captured.

Additional file

Additional file 1: Data assumptions made for the ZICE trial. Descriptions of how the adherence and outcome data were derived for the ZICE study. Sensitivity analysis exploring the impact of missing data on the interpretation of the SMM analysis in the ZICE trial. (DOCX 20 kb)

Abbreviations

BMI: Body Mass Index; CODA: Colitis Once Daily Asacol; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire developed for Cancer Patients; ITT: Intention-to-treat; IZA: Intravenously administered zoledronic acid; MEMS: Medication Event Monitoring System; NI: Non-inferiority; OD: Once daily; OIA: Orally administered ibandronic acid; PP: Per-protocol; RBEE: Randomisation-based efficacy estimator; RCT: Randomised controlled trial; SMM: Structural Mean Model; SRE: Skeletal-related event; TDS: Three times daily; ZICE: Zoledronate versus Ibandronate Comparative Evaluation

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Availability of data and materials

No additional data available.

Authors' contributions
DG performed all statistical analysis and drafted the manuscript. DF and KH commented on early drafts of the manuscript. PB-L, AC, ABH, CH, NM, CP, and RS were investigators on the original studies and commented on draft versions of the manuscript. All authors read and approved the final version of the manuscript.

Authors' information
No additional information provided.

Competing interests
AB Hawthorne has received payment from Warner Chilcott Pharmaceuticals Ltd. for participation in advisory panels. C Probert has received research support, hospitality, and speakers fees from Warner Chilcott Pharmaceuticals Ltd. All other authors have no conflicts of interest to disclose.

Consent for publication
Not applicable.

Ethics approval and consent to participate
For the CODA study, ethical approval was received for this study by the Leicestershire, Northamptonshire and Rutland Research Ethics Committee 2 (REC reference number: 05/Q2502/156). Written informed consent was obtained from each participant. For the ZICE study, all patients gave written informed consent before study entry and the trial protocol was approved by the UK Medicines and Health-care products Regulatory Agency and a Multi-Centre Research Ethics Committee (MREC for Wales ref: 05/MRE09/57).

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Additional material:

1. Full description of determining medication adherence in the ZICE study

Questions about adherence to study medication were asked at three initial interim visits, and then subsequently at 12-weekly visits.

Missing visit patterns were inspected, with the view to calculate adherence levels only in those with complete visit data up until the point of an event, withdrawal, death, or the end of the first 12 months.

For participants allocated to intravenous zoledronic acid:

- Adherence to intravenous zoledronic acid was based on interim and 12-weekly visit data, as participants were required to attend to receive intravenous medication. It was assumed that participants did not adhere to study medication if they either did not attend a scheduled visit, or attended but were noted as not receiving study medication as prescribed during at least one visit.

For participants allocated to oral ibandronic acid:

- Interim visits were primarily arranged so that participants allocated to intravenous zoledronic acid could receive their medication. Participants in the oral ibandronic acid arm were also invited to attend interim visits to minimise the likelihood that an increase in clinical contact in one arm could impact on trial findings. However, as it was not necessary for participants in this arm to attend visits to receive medication, and non-attendance at one or more interim visit was high, adherence to oral ibandronic acid was based on 12-weekly visit data only. It was assumed that participants did not adhere to study medication if they were noted as not receiving study medication as prescribed during at least one visit.

Adherence data were available for 1164 participants.

2. Full description of determining outcome (a skeletal-related event within the first 12 months) in the ZICE study

The outcome used for the ZICE study in this paper is the occurrence of a skeletal-related event (SRE) by the end of the 12 month post-randomisation follow-up period. Based on the available data (up to the end of the trial), participants were classed as one of the following:

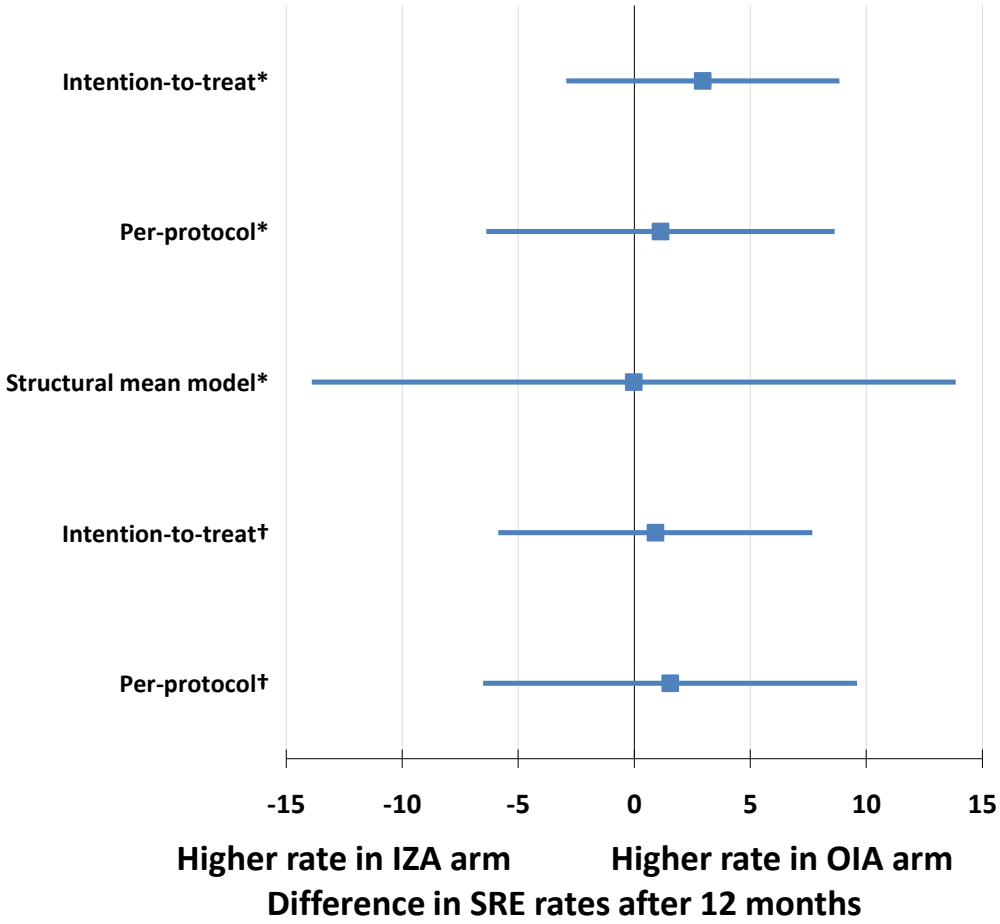
- Reported an SRE within the first 12 months (YES)
- Reported an SRE after the first 12 months (NO)
- Alive at the end of the follow up period, no SRE reported (NO)
- Died after the end of the 12 month follow-up period, did not report an SRE in the first 12 months (NO)
- Died before the end of the 12 month follow-up period, no SRE reported (MISSING)
- Withdrew after the end of the 12 month follow-up period, did not report an SRE in the first 12 months (NO)
- Withdrew before the end of the 12 month follow-up period, no SRE reported (MISSING)

SRE outcome data were available for 1037 participants.

3. Impact of missing data on the interpretation of the SMM analysis

Applying a basic imputation method meant that the predictors I had originally found were no longer statistically significant. I was therefore unable to apply the SMM method as I had originally. Another approach I took, was to restrict the ITT and PP analysis to those who also feature in the SMM analysis. However, this changes the point estimates as well as widening the confidence intervals slightly (Additional Figure 1).

Additional Figure 1: Impact of missing data on the interpretation of the SMM analysis



*Intention-to-treat n = 1037; Per-protocol n = 621; Structural mean model n = 796

†Analysis performed in participants who were included in the structural mean model analysis. Intention-to-treat n = 796; Per-protocol n = 536

Patient Preference and Adherence

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ORIGINAL RESEARCH

Determinants of initiation, implementation, and discontinuation of amoxicillin by adults with acute cough in primary care

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Aim: To investigate the determinants of adherence to amoxicillin in patients with acute lower respiratory tract infection.

Materials and methods: Three European data sets were used. Adherence data were collected using self-reported diaries. Candidate determinants included factors relating to patient, condition, therapy, health care system/provider, and the study in which the patient participated. Logistic and Cox regression models were used to investigate the determinants of initiation, implementation, and discontinuation of amoxicillin.

Results: Although initiation differed across samples, implementation and discontinuation were similar. Determinants of initiation were days waited before consulting, duration of prescription, and being in a country where a doctor-issued sick certificate is required for being off work for <7 days. Implementation was higher for older participants or those with abnormal auscultation. Implementation was lower for those prescribed longer courses of amoxicillin (≥8 days). Time from initiation to discontinuation was longer for longer prescriptions and shorter for those from countries where single-handed practices were widespread.

Conclusion: Nonadherence to amoxicillin was largely driven by noninitiation. Differing sets of determinants were found for initiation, implementation, and discontinuation. There is a need to further understand the reasons for these determinants, the impact of poor adherence to antibiotics on outcomes, and to develop interventions to improve antibiotic use when prescribed.

Keywords: adherence, antibiotics, general practice, determinants

Introduction

Lower respiratory tract infections (LRTIs), characterized by acute cough, account for approximately one-fifth of all consultations in primary care, and the majority of patients who consult are prescribed antibiotics.[1,2] However, adherence to antibiotics in primary care is often poor.[3,4] This wastes health care resources,[5,6] could negatively impact on clinical outcomes,[7] and could result in infecting bacteria being exposed to sub-optimal levels of treatment; creating an environment that promotes antibiotic resistance.[8]

With concerns growing about the consequences of increasing levels of antimicrobial resistance,[9] interventions that effectively promote the appropriate use of antibiotics are important. Although most antibiotic stewardship programs have focused on reducing antibiotic use,[10,11] less attention has been paid to ensuring that antibiotics are appropriately used when prescribed. Interventions for improving adherence are likely to be most effective if they are informed by an understanding of the determinants of sub-optimal adherence. These determinants may operate on multiple levels to impact

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on whether a patient adheres to a prescribed treatment, and therefore large, detailed data sets are required to accurately quantify these influences.

Adherence may be defined as "the process by which patients take their medicine as prescribed".[12] Traditionally, this has been represented quantitatively as a single variable (eg, percentage of medicine taken as prescribed and a binary taken as prescribed or not). However, recent work in this field encourages the use of the distinct processes involved in taking medicine, namely, initiation, implementation, and discontinuation.[13] Each individual process may have its own determinants and influences on outcomes. Therefore, different interventions may be required to address each of the adherence processes.

In this paper, we aim to investigate the determinants of initiation, implementation, and discontinuation of amoxicillin by adults consulting with an acute LRTI in European primary care.

Materials and methods

Studies, patients, settings, and inclusion criteria for analysis

Data were used from three studies conducted as part of the Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe (GRACE) Network of Excellence research program.[14] All three studies recruited adult patients aged ≥18 years consulting with an acute LRTI/cough in primary care and are described in detail elsewhere. In brief, Study 1 was a prospective cohort study conducted in 13 European countries between 2006 and 2007;[1] Study 2 was an observational study on the etiology, diagnosis, and prognosis of LRTI conducted in 12 European countries between 2007 and 2010;[15] and Study 3 was a placebo-controlled trial of amoxicillin nested within Study 2.[16] Following an initial consultation with a clinician, participants in all three studies were given a diary that recorded symptoms, medication use, and health care contacts. Participants were asked to complete their diary for 28 days. All three studies collected data using similar case report forms (CRFs) and patient diaries. Study participants were included in analysis if they were prescribed amoxicillin for immediate use at their initial consultation (defined as being prescribed amoxicillin and not advised to delay, as recorded on the CRF) and it was possible to ascertain adherence measures using self-reported diary data. The present study focuses on the use of amoxicillin only, as this is the recommended first-line antibiotic for LRTI in the European Union.[17] In Studies 1 and 2, participants who were prescribed antibiotics other than amoxicillin were excluded. In Study 3 (the trial), amoxicillin was the only antibiotic prescribed.

Definition of adherence elements

Initiation

Participants were defined as having initiated their amoxicillin if they indicated in their diary that they took amoxicillin at least once during the 28 day follow-up period.

Implementation

In participants who initiated their amoxicillin, implementation describes the extent to which the prescription was taken as prescribed among those who initiated their amoxicillin. For the purpose of this paper, it is defined as the proportion of amoxicillin reportedly taken during the prescribed period. For example, if a participant was prescribed amoxicillin for 5 days and only reported taking it for 4 days during the first 5 days of the follow-up period, their implementation score would be 0.8 (ie, they initiated their amoxicillin course and took 80% of it during the prescribing period).

Discontinuation

Participants were defined as having discontinued their amoxicillin prescription if they initiated their prescription and subsequently reported a full week of not taking their medicine. A gap of 1 week was deemed appropriate in distinguishing between patients who stopped and restarted their medicine and those who were prescribed a new course of amoxicillin. The first day of that 1-week gap was defined as the day they discontinued, and the time to discontinuation was calculated as the difference in days between the day of discontinuation and the day of initiation. For example, if a participant was prescribed a 7-day course of amoxicillin, initiated their amoxicillin on day 3, and days 10–17 were the first full week where no amoxicillin was reportedly taken, they would be defined as having discontinued on day 10, and their time from initiation to discontinuation would be 7 days.

Candidate determinants

Determinants related to the patient, illness, prescription, and health care setting were investigated. A full description of the candidate determinants is given in the online supplementary materials.

Statistical analysis

Descriptive statistics were reported as numbers and percentages, means and standard deviations (SDs), or medians and interquartile ranges (IQRs), as appropriate.

Findings in all descriptive tables are presented both overall and separately for each study.

A three-level logistic regression model was fitted to investigate the determinants of initiation, with participants nested within clinicians nested within countries.

To investigate the determinants of implementation, a multilevel logistic regression model was fitted to participants who had initiated amoxicillin. The model allowed for clustering at four levels, specifically, days nested within participants nested within clinicians nested within countries. This approach, therefore, modeled implementation as the probability of correctly implementing on a given day.

A Cox proportional hazards model[18] was fitted to investigate the determinants of time from initiation to discontinuation. The standard errors from this model were corrected for the clustering of participants within clinicians.

Throughout, results are presented in terms of odds ratios (ORs), hazard ratios (HRs), and associated 95% confidence intervals (CIs), as appropriate. Variables were entered into a univariable model and retained if they were significant at the $P<0.1$ level. Variables in the multivariable model that were not significant at the $P<0.05$ level were removed sequentially, from largest to smallest P-value, until a final multivariable model was attained. The study from which a participant provided data was used in all models (both univariable and multivariable) to ensure that any association was not confounded by the characteristics of participants from different studies.

For initiation and implementation, the clinician and country-level intracluster correlation coefficients (ICCs) were calculated to demonstrate the proportion of variation in initiation/implementation that was attributable to differences between clinicians and countries. Some clinicians participated in more than one of the three studies, and where this was the case their identifier was linked across studies.

Data management and descriptive statistics were conducted using Statistical Package for the Social Sciences, version 20 (IBM Corporation, Armonk, NY, USA).[19] All other analyses used Stata version 13.[20]

Ethical approval

The original studies were approved by ethics committees in all participating countries. The work carried out in this paper remains sufficiently within the remit of those original approvals.

Results

Descriptive statistics

Number of participants, clinicians, and primary care networks

In total, data were available for 1,346 participants prescribed amoxicillin for immediate use and for whom self-reported follow-up diary data were available (Study 3, the placebo-controlled trial, n=848; Study 1, the prospective observational study, n=306; and Study 2, the observational study within which the trial was nested, n=192).

Overall, participants were recruited by 322 clinicians who were based in 15 different countries across Europe (Figure 1).

Participant characteristics

Participants were aged between 18 and 88 years (median 51, IQR: 38–62). Although the age distributions in Studies 1 and 3 were similar, those recruited into Study 2 tended to be slightly

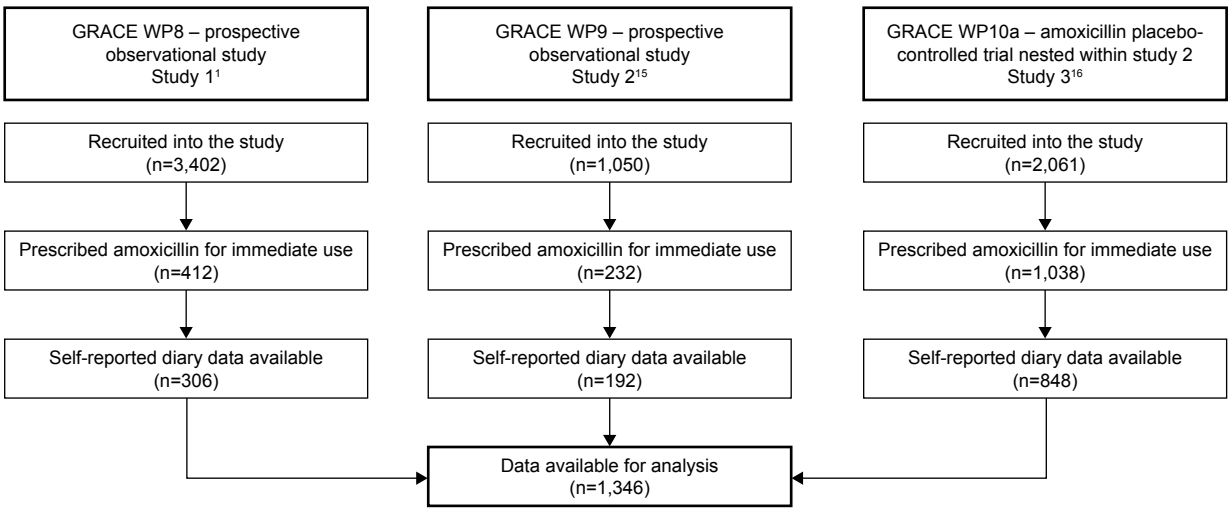

Figure 1 Study flow diagram.
Abbreviations: GRACE, Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe; LRTI, lower respiratory tract infection.

older (median 58, IQR: 45–65). Overall, 540 participants were men (40.1%) and 372 participants had at least one of the listed co-morbidities (27.7%). Study 2 contained a higher percentage of participants with co-morbidities (36.5%; Table 1).

Illness characteristics

Other than cough, which was part of the inclusion criteria for all three studies, the five most frequently reported symptoms were phlegm (81.3%), feeling generally unwell (79.8%), interference with normal activities (69.6%), disturbed sleep (64.5%), and shortness of breath (59.0%). Fever and headache were most frequently reported by participants in Study 1 and coryza by participants in Study 3. Phlegm, shortness of breath, wheeze, disturbed sleep, feeling generally unwell, and diarrhea were the symptoms most frequently reported by participants in Study 2 (Table 1).

Overall, the median clinician-rated symptom severity score at recruitment was 36 (IQR: 25–46), with participants from Study 2 reporting the highest average symptom severity (median =38, IQR: 26–48) and those from Study 3 the lowest (median =35, IQR: 25–46). Abnormal findings on auscultation examination were found in 652 participants (48.5%), with participants in Study 3 least likely to have abnormal findings (34.3%). Discolored phlegm was reported by 680 participants (53.2%; Table 1).

Prescription characteristics

Although participants in Study 3 were prescribed a fixed dose, frequency, and duration of amoxicillin, it was not fixed for participants in the other two studies. For these participants, the most frequently prescribed dose was 500 mg (218, or 44.2% of all participants were prescribed this dose), with 393 instructed to take their medication three or more times a day (79.2%), and 339 prescribed a 6- or 7-day course (68.3%). Participants in Study 1 were more likely to be prescribed higher doses to be taken less frequently and for a shorter duration, than those in Study 2 (Table 2).

Healthcare setting characteristics

Of the 15 countries included, single-handed practices were common in six (40.0%), campaigns around antibiotic use had recently been conducted in seven (46.7%), patients were required to pay to see a general practitioner at the point of delivery of care in seven (46.7%), and a doctor-issued sick certificate was required for certifying people off work

Table 1 Participant and illness characteristics by study

Participant/illness characteristics	Study 1 (n=306)	Study 2 (n=192)	Study 3 (n=848)	Overall (n=1,346)
Age[a]	49 (37–62)	58 (45–65)	50 (37–61)	51 (38–62)
Male[b]	124 (40.5)	75 (39.1)	341 (40.2)	540 (40.1)
Female[b]	182 (59.5)	117 (60.9)	507 (59.8)	806 (59.9)
At least one co-morbidity[b]	77 (25.2)	70 (36.5)	225 (26.6)	372 (27.7)
Clinician-rated symptom severity[a]	36 (26–48)	38 (26–48)	35 (25–46)	36 (25–46)
Phlegm[b]	255 (83.6)	173 (90.1)	665 (78.5)	1,093 (81.3)
Shortness of breath[b]	198 (64.7)	143 (74.5)	452 (53.4)	793 (59.0)
Wheeze[b]	175 (57.2)	125 (65.1)	344 (40.6)	644 (47.9)
Coryza[b]	204 (66.9)	134 (69.8)	635 (75.0)	973 (72.4)
Fever[b]	183 (59.8)	79 (41.1)	290 (34.3)	552 (41.1)
Chest pain[b]	157 (51.3)	100 (52.1)	372 (44.0)	629 (46.8)
Muscle aching[b]	179 (58.5)	108 (56.2)	421 (49.7)	708 (52.6)
Headache[b]	199 (65.0)	104 (54.2)	467 (55.1)	770 (57.2)
Disturbed sleep[b]	213 (69.8)	145 (75.9)	508 (60.0)	866 (64.5)
Feeling generally unwell[b]	269 (88.2)	174 (90.6)	629 (74.3)	1,072 (79.8)
Interference with normal activities[b]	242 (79.3)	143 (74.5)	551 (65.1)	936 (69.6)
Confusion/disorientation[b]	23 (7.5)	11 (5.7)	23 (2.7)	57 (4.2)
Diarrhea[b]	23 (7.5)	19 (9.9)	53 (6.3)	95 (7.1)
Abnormal auscultation finding[b,c]	220 (71.9)	142 (74.3)	290 (34.3)	652 (48.5)
No phlegm[b,d]	50 (16.5)	17 (9.1)	133 (16.9)	200 (15.6)
Normal colored phlegm[b,d]	71 (23.4)	60 (32.1)	268 (34.0)	399 (31.2)
Discolored phlegm[b,d]	182 (60.1)	110 (58.8)	388 (49.2)	680 (53.2)
Waited 7 days or fewer prior to consulting[b]	212 (70.4)	123 (65.4)	524 (62.7)	859 (64.8)
Waited 8–14 days prior to consulting[b]	68 (22.6)	43 (22.9)	192 (23.0)	303 (22.9)
Waited 15 days or more prior to consulting[b]	21 (7.0)	22 (11.7)	120 (14.4)	163 (12.3)

Notes: [a]Median (IQR). [b]n (%). [c]At least one of the following: diminished vesicular breathing, wheeze, crackles, or rhonchi. [d]Normal colored phlegm = clear or white, discolored phlegm = yellow, green, or bloodstained. Study 1: prospective cohort study conducted in 13 European countries between 2006 and 2007.[1] Study 2: observational study on the etiology, diagnosis, and prognosis of LRTI conducted in 12 European countries between 2007 and 2010.[15] Study 3: placebo-controlled trial of amoxicillin nested within Study 2.[16]
Abbreviations: IQR, interquartile range; LRTI, lower respiratory tract infection.

Table 2 Amoxicillin prescription characteristics by study

Prescription characteristic	Study 1 (n=306)	Study 2 (n=192)	Study 3 (n=848)	Overall (n=1,346)
Dose (mg)				
<500	23 (12.3)	52 (17.0)	0 (0.0)	75 (5.6)
500	99 (52.9)	119 (38.9)	0 (0.0)	218 (16.3)
≥500 to <1,000 (not inclusive)	8 (4.3)	34 (11.1)	0 (0.0)	42 (3.1)
≥1,000	57 (30.5)	101 (33.0)	848 (100.0)	1,006 (75.0)
Frequency (times per day)				
Twice	13 (6.8)	90 (29.4)	0 (0.0)	103 (7.7)
More than twice	177 (93.2)	216 (70.6)	848 (100.0)	1,241 (92.3)
Duration (days)				
≤5	14 (7.3)	59 (19.3)	0 (0.0)	73 (5.4)
6 or 7	144 (75.4)	195 (63.9)	848 (100.0)	1,187 (88.3)
≥8	33 (17.3)	51 (16.7)	0 (0.0)	84 (6.2)

Notes: Data presented as n (%). Study 1: prospective cohort study conducted in 13 European countries between 2006 and 2007.[1] Study 2: observational study on the etiology, diagnosis, and prognosis of lower respiratory tract infection conducted in 12 European countries between 2007 and 2010.[15] Study 3: placebo-controlled trial of amoxicillin nested within Study 2.[16]

for <7 days in three (20.0%). Amoxicillin was the first-line choice of antibiotic in the national guidelines of six of the countries (40.0%), and antibiotic prescribing rates ranged from 11.2 defined daily doses per 1,000 inhabitants/day (the Netherlands) to 28.6 defined daily doses per 1,000 inhabitants/day (France), with six countries categorized as low prescribers (the Netherlands, Sweden, Germany, Slovenia, Norway, and Hungary), five as moderate (England, Wales, Finland, Spain, and Poland), and four as high prescribers (Slovakia, Belgium, Italy, and France) (Table 3).

Analysis

Initiation

While overall, a high proportion of participants initiated their amoxicillin (1,057 or 78.5% of participants), this was largely driven by the almost-complete initiation of amoxicillin seen in Study 3 (97.6%). Initiation in participants from Study 1 and Study 2 was considerably lower (51.0% and 38.0%, respectively). When initiation occurred, it was mostly on the day of prescription (91.5% of participants who initiated did so on day 1).

Compared to those who had waited ≤7 days, participants who had waited ≥15 days prior to consulting had higher odds of initiating their amoxicillin (OR =2.77, 95% CI: 1.35–5.67). There was some evidence that the duration of the prescription was also associated with amoxicillin initiation. Participants who were prescribed amoxicillin for ≥8 days had higher odds of initiating their amoxicillin than those prescribed for ≤5 days, although this was not statistically significant at the 5% level (OR =2.29, 95% CI: 0.97–5.42). Participants in countries where a sick certificate was required for taking <7 days off work had higher odds of initiating their amoxicillin (OR =2.15, 95% CI: 1.27–3.64) (Table 4).

The ICC from the final multivariable model indicated that 17% of the total variation in initiation was attributable to differences between clinicians. The country-level ICC was negligible.

Table 3 Health care setting characteristics

Country	Widespread availability of single-handed practices[a]	Recent public campaigns around antibiotic use[a]	Payment required to see general practitioner[a]	Sick certification required for less than 7 days off work[a]	Amoxicillin first-line choice for a respiratory infection in primary care[a]	Antibiotic prescribing rate[b]
Belgium	✓	✓	✓	✓	✓	27.1 (25.2–28.2)
England		✓			✓	17.4 (16.5–18.7)
Finland			✓			18.1 (17.8–18.5)
France	✓		✓		✓	28.6 (28.1–29.6)
Germany	✓				✓	14.6 (14.5–14.9)
Hungary			✓			15.6 (15.2–16.0)
Italy	✓					28.1 (27.6–28.7)
the Netherlands	✓	✓	✓			11.2 (11.1–11.4)
Norway			✓			15.5 (15.2–15.8)
Poland		✓		✓		21.9 (20.8–23.6)
Slovakia	✓	✓				23.9 (23.2–24.8)
Slovenia					✓	14.9 (14.3–15.9)
Spain		✓		✓		19.9 (19.7–20.3)
Sweden		✓	✓			14.6 (14.1–15.5)
Wales					✓	17.4 (16.5–18.7)

Notes: [a]Obtained from interview data as part of the GRACE project.[14] [b]Obtained from the *Antimicrobial consumption interactive database (ESAC-Net)*,[30] and defined as the defined daily dose per 1,000 inhabitants per day. Rate averaged across years 2007–2010 (min and max values in brackets). United Kingdom rates used for England and Wales.
Abbreviations: GRACE, Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe; LRTI, lower respiratory tract infection; max, maximum; min, minimum.

Table 4 Three-level multivariable logistic regression model investigating the determinants of the initiation of amoxicillin

Variables[a]	Odds ratio	95% CI		*P*-value
		Lower	Upper	
Waited ≤7 days prior to consulting	Reference category			
Waited 8–14 days prior to consulting	1.47	0.92	2.34	0.010
Waited 15+ days prior to consulting	2.77	1.35	5.67	
Prescribed amoxicillin for ≤5 days	Reference category			
Prescribed amoxicillin for 6 or 7 days	0.84	0.44	1.62	0.013
Prescribed amoxicillin for 8≥ days	2.29	0.97	5.42	
Sick certification required for missing <7 days of work	2.15	1.27	3.64	0.004
Participant from Study 1	Reference category			
Participant from Study 2	0.46	0.28	0.75	<0.001
Participant from Study 3	56.04	27.54	114.03	

Notes: [a]The model is based on 1,323 participants, nested within 330 clinicians, nested within 15 countries. The intracluster correlation coefficients from the final model were: clinician: 0.17; country: 0.00. Study 1: prospective cohort study conducted in 13 European countries between 2006 and 2007.[1] Study 2: observational study on the etiology, diagnosis, and prognosis of LRTI conducted in 12 European countries between 2007 and 2010.[15] Study 3: placebo-controlled trial of amoxicillin nested within Study 2.
Abbreviations: CI, confidence interval; LRTI, lower respiratory tract infection.

Implementation

In participants who initiated amoxicillin, implementation levels were high and highly skewed across all three studies. Full implementation was achieved by 827 participants overall (78.3%), with full implementation across studies ranging from 70.8% of participants in Study 2 (51/72) to 80.0% in Study 3 (662/828) (Figure 2).

The odds of implementing amoxicillin on a given day were higher among older participants (OR for a decade increase =1.21, 95% CI: 1.03–1.41), and there was some evidence that it was higher for participants with abnormal auscultation findings at their index consultation, although the 95% CI included 1 (OR =1.71, 95% CI: 1.00–2.91). The odds were lower for participants prescribed courses of amoxicillin lasting ≥8 days (OR compared to courses lasting up to 5 days =0.07, 95% CI: 0.01–0.42) (Table 5).

Sixty-two percent of the total variation in whether amoxicillin was taken on a given day was attributable to differences between participants. The clinician and country-level ICCs were both 0.04.

Discontinuation

The median time from initiation to discontinuation of amoxicillin was 7 days across all three studies (overall IQR: 7–8 days).

Longer courses were associated with a longer time to discontinuation (HR for 6–7 days compared with ≤5 days =0.30, 95% CI: 0.17–0.55, HR for ≥8 days compared with ≤5 days =0.19, 95% CI: 0.10–0.36). Participants from countries where single-handed practices were widespread were associated with a shorter time until discontinuation (HR =1.15, 95% CI: 1.03–1.28). The findings persisted when the standard errors were corrected for clustering of participants within countries.

Differences across studies

As indicated by the forest plots presented in the online supplementary materials, there was insufficient evidence to suggest that the determinants found in the models for initiation, implementation, and discontinuation differed within the individual studies.

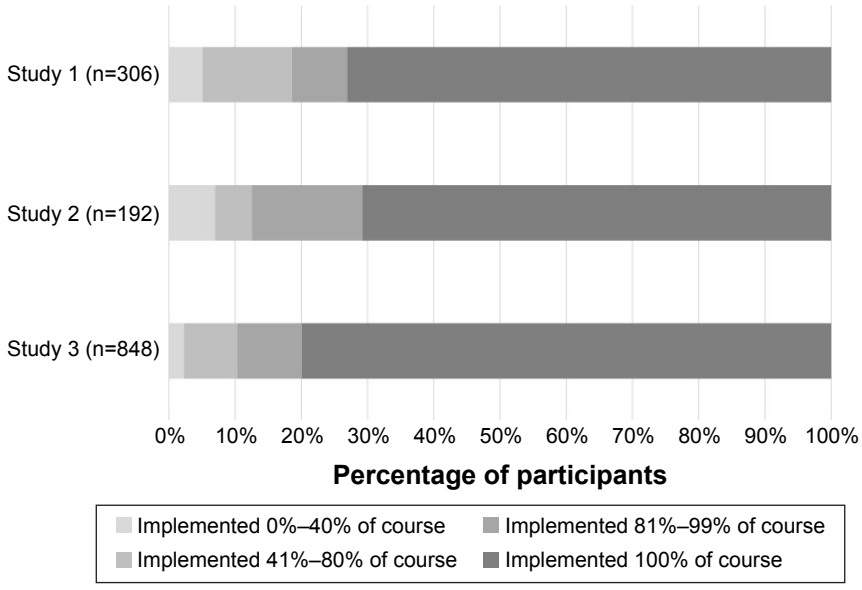

Figure 2 Implementation of amoxicillin by study.
Notes: Study 1: prospective cohort study conducted in 13 European countries between 2006 and 2007.[1] Study 2: observational study on the etiology, diagnosis, and prognosis of lower respiratory tract infection conducted in 12 European countries between 2007 and 2010.[15] Study 3: placebo-controlled trial of amoxicillin nested within Study 2.[16]

Table 5 Four-level logistic regression model investigating the determinants of the implementation of amoxicillin

Variables[a]	Odds ratio	95% CI		*P*-value
		Lower	Upper	
Age (per decade increase)	1.21	1.03	1.41	0.019
Auscultation abnormality[b]	1.71	1.00	2.91	0.050
Prescribed amoxicillin for ≤5 days	Reference category			
Prescribed amoxicillin for 6 or 7 days	1.18	0.22	6.25	<0.001
Prescribed amoxicillin for ≥8 days	0.07	0.01	0.42	
Participant from Study 1	Reference category			
Participant from Study 2	1.23	0.42	3.64	0.909
Participant from Study 3	1.18	0.48	2.88	

Notes: [a]The model is based on 7,421 days nested within 1,054 participants, nested within 281 clinicians, nested within 15 countries. The intracluster correlation coefficients from the final model were: participant: 0.62; clinician: 0.04; country: 0.04. [b]At least one of the following: diminished vesicular breathing, wheeze, crackles, or rhonchi.
Abbreviation: CI, confidence interval.

Discussion

Summary of key findings

In this pooled analysis of three European studies of amoxicillin treatment for LRTI in primary care, participants who had waited longer before consulting or were prescribed a longer course of amoxicillin were more likely to initiate their course. In those who did initiate amoxicillin, older participants, or those with abnormal chest findings were more likely to implement their amoxicillin correctly on a given day. Participants were less likely to correctly implement their amoxicillin on a given day if they were prescribed a longer course. A considerable amount of variation in initiation and implementation was attributable to differences between clinicians, and the odds of initiation were higher in countries where sick certificates were required for being absent from work for <7 days. Course length (time from initiation to discontinuation) was longer in countries where single-handed practices were common.

Strengths and limitations

This is the first study to separately investigate the determinants of initiation, implementation, and discontinuation of antibiotic treatment and builds on previous work where we have described initiation, partial, and full adherence to antibiotics prescribed in primary care.[3] In that study, we found that the odds of fully adhering to treatment was positively associated with the duration of symptoms prior to consulting, negatively associated with the duration of prescribed treatment, and varied according to antibiotic class.

This analysis used a large amount of prospective primary care data from patients in diverse settings in Europe, using similar data collection methods and with similar inclusion criteria. The determinants of nonadherence to medication can be multifaceted.[9] Four of the five World Health Organization-defined dimensions were investigated, and it was possible to assess the clustering of initiation and implementation behavior by clinician, which gave an indication of the influence of clinician attributes on patients' antibiotic treatment adherence. Characteristics of the countries from which patients were recruited were obtained and investigated, rather than estimating the differences between the countries themselves. This provided more useful information, as the goal of this study was to investigate determinants as a platform for intervening in the process, rather than simply to describe variation by country.

Our findings are consistent with previous studies of adherence to antibiotic treatment and other treatments alike.[21–25]

Separating out adherence into distinct processes enabled different sets of determinants to be considered. The processes are distinct, and indeed different determinants were associated with each. Had adherence been considered as a single variable, such nuances would have been missed. This approach made fuller use of the available data.

The analysis in this paper focuses on adherence to amoxicillin prescriptions for immediate use only. Although this reduces the potential number of participants (other antibiotics were prescribed and delayed prescriptions were given in the included observational studies), it allowed for the investigation of the impact of the dose, frequency, and duration without being confounded by the type of antibiotic prescribed. As amoxicillin is the most commonly prescribed and recommended antibiotic for acute respiratory infections across Europe,[1,17] the results retain wide applicability. Advice regarding delayed prescriptions, while also recommended for this condition,[26] are often vague (eg, here is a prescription if you get any worse), and may have been issued with the intention that the patient would never actually take antibiotic treatment. The work presented in this paper assumes that amoxicillin was prescribed for immediate use by a clinician with the intention that it would be taken as prescribed.

Our estimation of initiation, implementation, and discontinuation is based on data obtained from self-reported diaries. Although this type of measure is prone to bias,[27,28] by having a daily entry, these biases are likely to be minimized. This method is also generally more feasible on larger populations, compared to more precise measures (eg, electronic monitoring) and provides more informative data than tablet counts, which can only provide an overall measure of consumption. However, questions in the diary only asked about daily the use of treatment. We have, therefore, had to assume that if

a participant reported that they consumed amoxicillin on a given day, they consumed the correct number of doses and these doses were spread evenly throughout the day – an assumption that could have been checked with a measure, such as electronic monitoring.

To reduce any biases that may arise, from comparing adherence to medication in observational studies and trials, all analyses controlled for the study from which a patient participated.

Implications

Clinicians may be able to improve adherence to prescribed antibiotics, especially in those most likely to benefit from antibiotic treatment, by considering which patients are unlikely to start or incorrectly implement their prescription.

There are no obvious, evidence-based, reasons for variation in adherence related to the determinants we identified. There is a need to further understand the reasons for these determinants and to develop interventions to improve antibiotic use in this setting. However, the determinants that were found associated with initiation and implementation (particularly days with symptoms prior to consulting and auscultation findings) may imply that an intervention that addresses patients' perceptions about their illness might help improve adherence. Given the degree of clustering of initiation and implementation at the level of the responsible clinician, an intervention that was delivered by clinicians would seem most likely to be effective.

Given the theorized association between sub-optimal exposure to antibiotics and the development of antibiotic resistance, time from initiation to discontinuation (regardless of how correctly the medicine was implemented) does not seem to be a priority target for intervention. Although it is an element that has value in other areas (eg, medicines to be taken long term and for which there may not be a defined end date), its value for antibiotics for acute conditions is questionable.

Selection of resistance may already occur after the first dose of an antibiotic, and therefore initiation of antibiotic treatment may be the main driver of antibiotic resistance, not necessarily implementation or discontinuation.[29] Nonadherence was driven by noninitiation. Different determinants were found for each adherence element.

Future research

Future work should focus on establishing whether there is a causal relationship between noninitiation, poor implementation, and clinical outcomes (eg, patient recovery, hospitalizations, re-consultations, and short- and long-term carriage of antibiotic-resistant organisms). Should a link be established, the findings reported in this paper could inform the development of an intervention that improves initiation and implementation, and in turn improves clinical outcomes for patients with acute respiratory infections in primary care.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Description of candidate determinants

Patient-related determinants included age, gender, and whether the participant had a co-morbidity (at least one of the following: Chronic Obstructive Pulmonary Disease (COPD), asthma, other lung disease, heart failure, ischemic heart disease, other heart disease, or diabetes).

Illness-related determinants included presenting symptoms (cough, phlegm, shortness of breath, wheeze, coryza, fever, chest pain, muscle aching, headache, disturbed sleep, feeling generally unwell, interference with normal activities, confusion/disorientation, and diarrhoea), clinician-rated symptom severity score (a summation of the severity of the 14 symptoms previously described scaled to range from 0 to 100, where 100 represented the maximum severity on all 14 symptoms and 0 represented no problems on any of the 14 symptoms), phlegm colour (categorised as no phlegm, normal coloured phlegm (white or clear), and discoloured phlegm (yellow, green, or bloodstained)), whether an abnormality was found when performing an auscultation examination (at least one of the following: diminished vesicular breathing, wheeze, crackles, or rhonchi), and the number of days of symptoms prior to consulting (categorised as seven days or less, eight to 14 days, or 15 days or more).

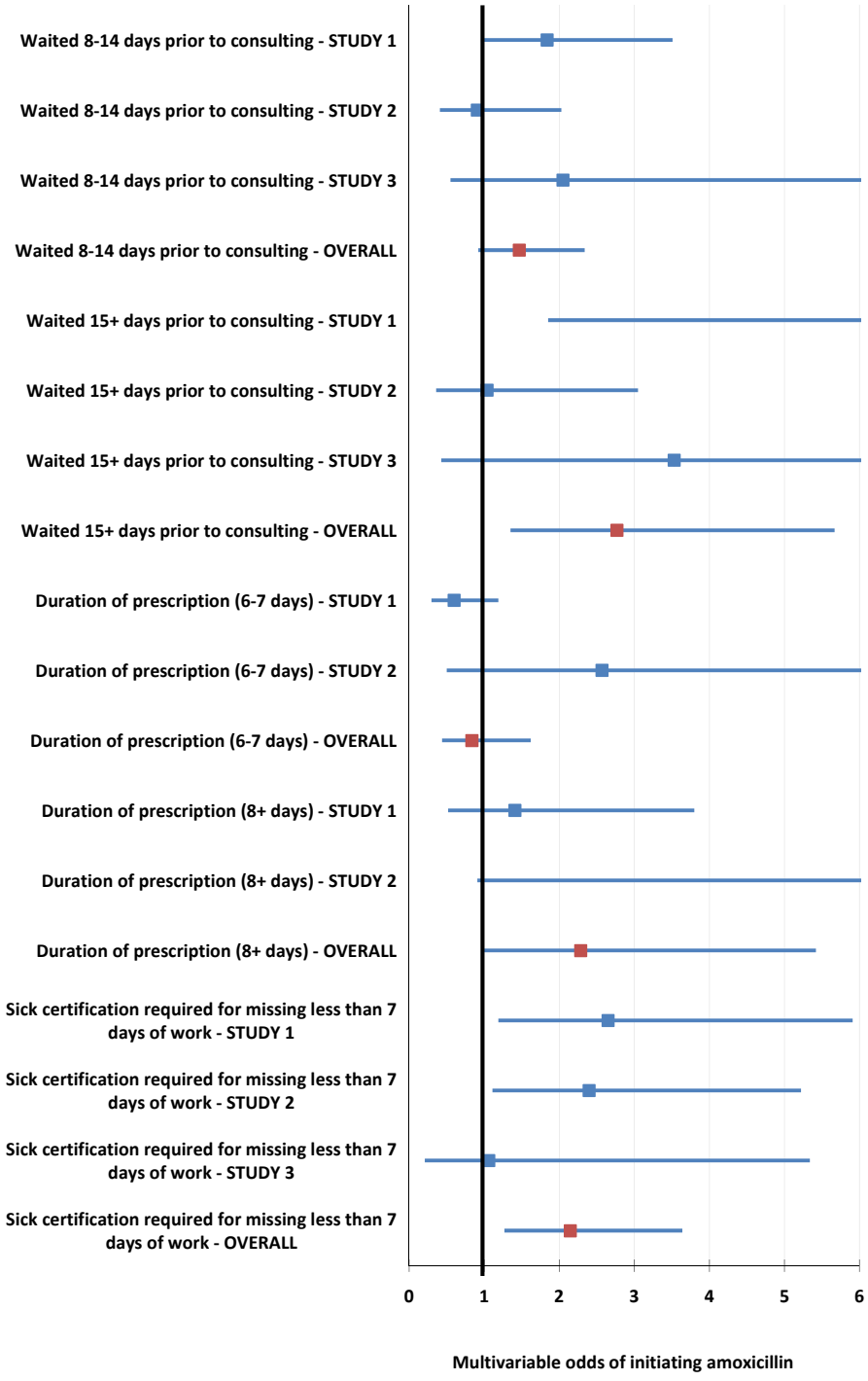
Prescription-related determinants included the dose (categorised as less than 500mg, 500mg, between 500 and 1000mg (not inclusive), and 1000mg or more), frequency (categorised as twice a day or more than twice a day), and duration (categorised as five days or less, six to seven days, or eight or more days) of the amoxicillin prescription. For the participants in study 3 (i.e. the placebo-controlled trial), this was fixed, as all participants were prescribed 1000mg of amoxicillin, three times a day for seven days.

While there were no specific healthcare professional-related determinants available consistently across all three datasets, responsible clinician identifiers were available and could be used to determine whether variation in adherence could be attributed to the influence of individual clinicians.

Participants were recruited from several European countries (Belgium, England, Finland, France, Germany, Hungary, Italy, Norway, Poland, Slovakia, Slovenia, Spain, Sweden, The Netherlands, and Wales), and healthcare setting-related determinants were established from work carried out as part of the GRACE project (GRACE website. Available from: http://www.grace-lrti.org/portal/en-gb/), and subsequent surveys among clinicians from countries that were not represented in this work. These included whether single-handed practices were common (e.g. representing at least a quarter of all practices), whether there had been public campaigns related to antibiotic use, whether patients had to pay to see a general practitioner, whether clinicians were required to certify sickness for less than seven days of absence from work, whether amoxicillin was the first-line choice of antibiotic for a respiratory infection in primary care, and the country-level antibiotic prescribing rate. The prescribing rate was obtained from the European Surveillance of Antimicrobial Consumption Network (ESAC) antimicrobial consumption interactive database (ESAC-Net. Available from: http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/esac-net-database/Pages/overview-country-consumption.aspx.), defined as the Defined Daily Dose (DDD) per 1000 inhabitants per day, averaged across the years 2007 to 2010.

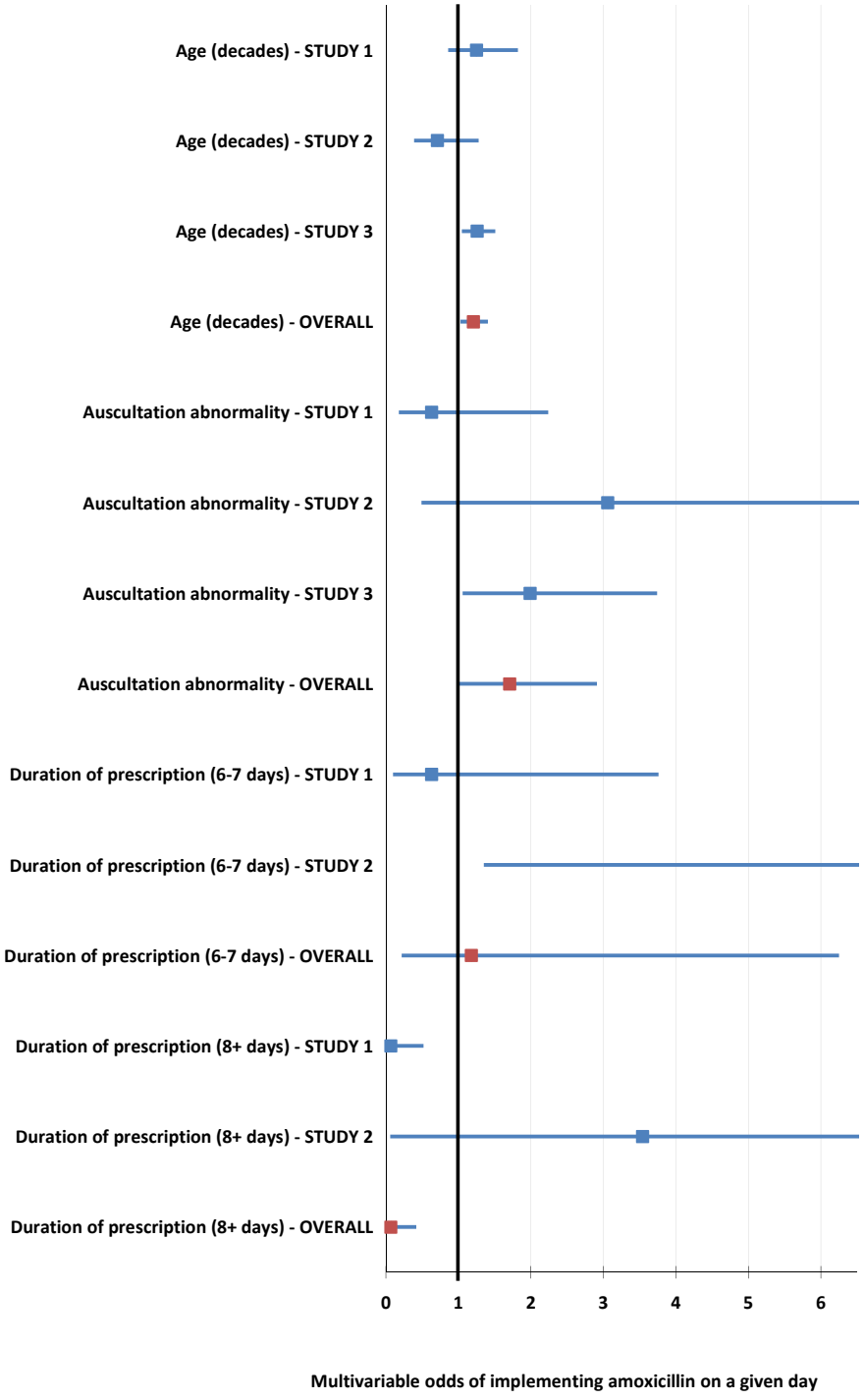
Finally, the study in which the patient participated was evaluated as a potential determinant in all analyses.

*Forest plot illustrating the odds ratios and 95% confidence intervals for the initiation model for each individual study and overall**



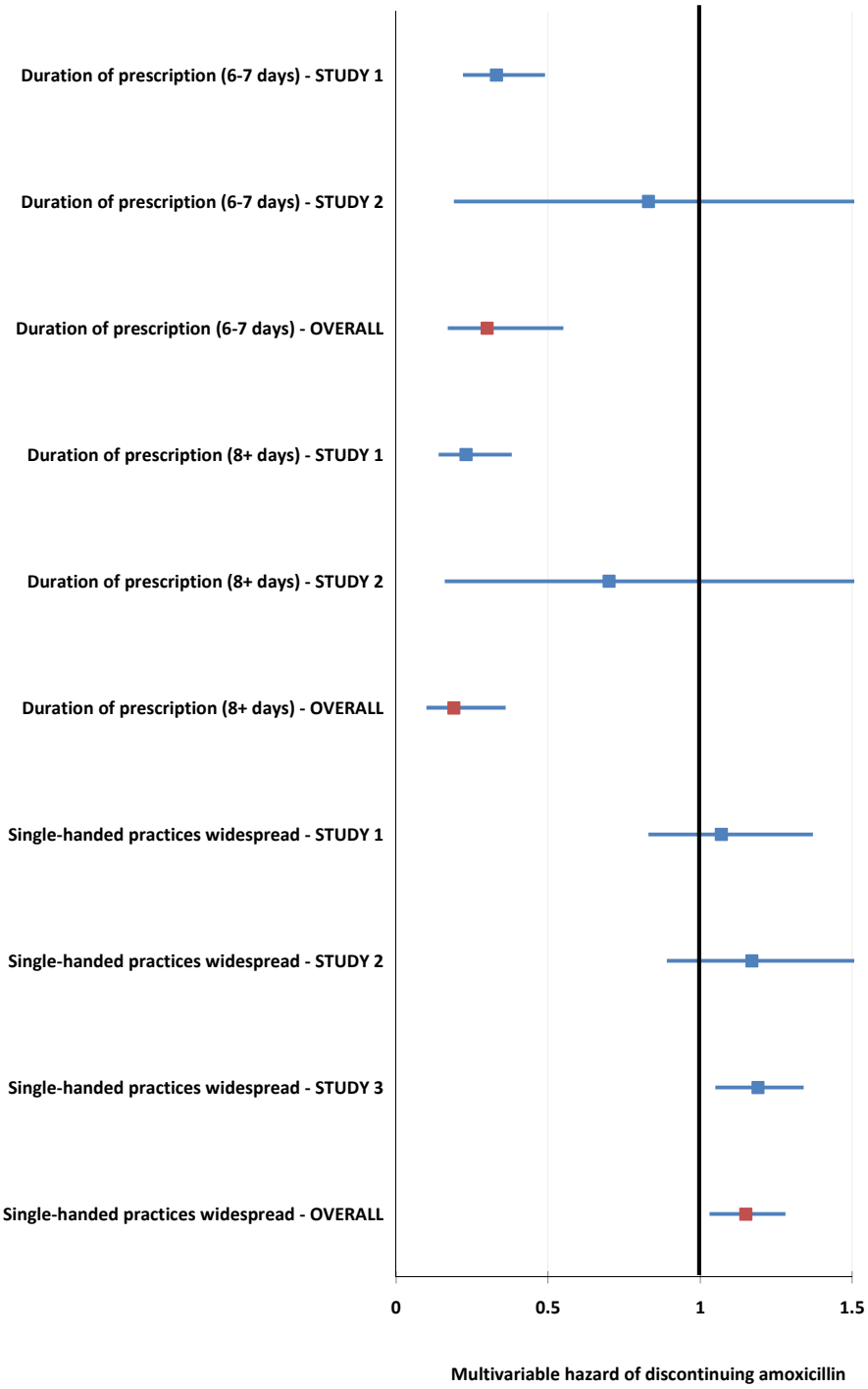
*Days waited prior to consulting compared to a reference category of 7 days or less. Duration of prescription variable compared to a reference category of 5 days or less.

*Forest plot illustrating the odds ratios and 95% confidence intervals for the implementation model for each individual study and overall**



*Duration of prescription variable compared to a reference category of 5 days or less

*Forest plot illustrating the hazard ratios and 95% confidence intervals for the discontinuation model for each individual study and overall**



*Duration of prescription variable compared to a reference category of 5 days or less

Appendix V – List of conference presentations given as part of my thesis

Title	Format	Conference	Date
Medication adherence for long term chronic conditions: results from a 12 month trial of patients in remission with Ulcerative Colitis	Oral	Young Statisticians' Meeting (YSM), London	July 2013
Determining the Efficacy of Amoxicillin for Acute Uncomplicated Lower-Respiratory-Tract Infection in Primary Care	Oral	General Practitioners' Research in Infections Network (GRIN) annual meeting, Nice	October 2013
1. Efficacy of amoxicillin for acute uncomplicated lower-respiratory-tract infection in primary care: findings from a 12-country randomised placebo-controlled trial 2. Factors associated with adherence to prescribed antibiotics: a comparison of findings from an observational study and a randomised clinical trial	1. Elevator pitch 2. Poster	South West Society for Academic Primary Care (SWSAPC) annual meeting, Bristol	March 2014
Factors associated with adherence to prescribed antibiotics: a comparison of findings from an observational study and a randomised clinical trial	Oral	GRIN annual meeting, Antwerp	October 2014
Adherence to antibiotics in primary care and the impact of non-adherence on clinical outcomes	Oral	Postgraduate Research Day, Cardiff	December 2014
Adherence-Adjusted Estimates Of Benefits And Harms From Treatment With Amoxicillin For LRTI: Secondary Analysis Of A 12-Country Randomised Placebo-Controlled Trial Using Randomisation-Based Efficacy Estimators	Poster	Society for Clinical Trials annual meeting, Washington DC	May 2015
Determinants of initiation, implementation, and completion of amoxicillin for adults with an acute cough in primary care: pooled analysis of three international datasets	Oral	GRIN annual meeting, Galway	October 2015
Determinants of initiation, implementation, and completion of amoxicillin for adults with an acute cough in primary care: pooled analysis of three international datasets	Oral	European Society for Patient Adherence, Compliance, and Persistence (ESPACOMP) annual meeting, Prague	November 2015

The use of randomisation-based efficacy estimators in non-inferiority trials	Poster	International Clinical Trials Methodology Conference bi-annual meeting, Glasgow	November 2015