Investigation of pain and discomfort associated with anti-VEGF injections

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Declaration

This thesis is the result of my own independent work, except where otherwise stated, and the views expressed are my own. Other sources are acknowledged by explicit references. The thesis has not been edited by a third party beyond what is permitted by Cardiff University's Use of Third Party Editors by Research Degree Students Procedure.

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Summary

Intravitreal injection of anti-vascular endothelial growth factors (VEGF) is the only current treatment for neovascular age-related macular Degeneration (AMD) but necessitates ongoing patient adherence with recuring injections to be effective. Furthermore, AMD itself poses a significant social and economic burden, as the population ages. Patient experience is one of the central pillars of the patient journey. Ocular pain is arguably one of the most common outcomes that affects the patient experience during intravitreal injections, with post-injection experiences and patient adherence to treatment remaining relatively underexplored. Thus, improving the understanding of factors associated with pain and using this to inform pain management strategies in ophthalmic care can drive quality improvement to enhance the patient experience.

The aim of the work presented in this thesis was to describe the experiences of patients undergoing anti-VEGF injections associated with pain and the impact on patient adherence and wellbeing, and to explore the factors that contribute to pain.

An exploratory sequential mixed methods study was undertaken involving semi-structured face-to-face interviews (n=14 individuals with neovascular AMD, n=7 healthcare practitioners), followed by a quantitative phase utilising questionnaires and measurement of electrodermal activity (n=65 individuals with neovascular AMD). The findings from initially exploring the patient experiences associated with the intravitreal treatment using thematic analysis, were apprehension, a dull-aching and sharp pain during injection, and prolonged soreness and irritation of up to 36 hours post-injection affecting their sleep and recovery. Building on the qualitative outcomes, questionnaires were then used to assess pain (Short-Form McGill Pain Questionnaire, SF-MPQ; Visual Analogue Scale, VAS), anxiety (State-Trait Anxiety Inventory) and wellbeing (Warwick-Edinburgh Mental Wellbeing Scale) at baseline, and at 1-2 hours and 24 hours post-treatment. A physiological measure, EDA (electrodermal activity) was used as one of the primary outcomes to objectively examine patients' level of arousal during the intravitreal injection procedure.

This study employed multiple linear regression models to explain the predictor variables associated with pain at 1-2 hours and 24 hours post-treatment for VAS and MPQ (main component of SF-MPQ). The optimum multiple regression model identified significant predictor variables, the injection SCR (Skin Conductance Response) amplitude, baseline state anxiety, type of anti-VEGF (aflibercept) and bilateral injections, explained 38% of the variance in VAS scores. The injection SCR amplitude was the most significant predictor of pain at both 1-2 hours and 24 hours post-treatment. Also, questionnaire data reported that at 24 hours post-treatment, 4.7% of participants continued to experience severe sharp, aching or tender pain, and 15.6% reported feeling a moderate tiring-exhausting pain.

A qualitative study exploring the impact of COVID-19 on patient experience was undertaken involving semi-structured telephone interviews (n=17 individuals with neovascular AMD). Nearly half of the participants reported perceived vision deterioration, with some losing their ability to drive. Most participants felt anxious of losing their eyesight due to lack of timely care and absence of communication with the practice. Isolation and fear of losing eyesight impacted participants' wellbeing with some reporting feeling lonely and depressed. Integrating these findings with individual perspectives captured a comprehensive understanding of the emotional and physical qualities of pain. Adherence to treatment was a key priority for patients over pain and COVID-19 health risks.

An understanding of pain during and following intravitreal injections may inform clinical practice on implementing pain assessment tools, providing consistent verbal instructions to patients on avoiding contact with the injected eye and advising them on specific pain relief techniques, including topical ice application to self-manage their pain at home. High injection SCR amplitudes and baseline state anxiety may also inform clinical practice on assessing patients' anxiety at regulated intervals and advising on nurturing self-talk and relaxation techniques to manage their apprehension. Engaging communications to reassure and strengthen patient confidence in their treatment course are meaningful and valuable qualities to patients receiving intravitreal injections.

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Abbreviations

ANOVA	Analysis of Variance
AMD	Age-related macular degeneration
ANS	Autonomic Nervous System
Anti-VEGF	Anti-vascular endothelial growth factor
AREDS	Age-related Eye Disease Study
BCVA	Best-Corrected Visual Acuity
BPS	Biopsychosocial
CNS	Central Nervous System
CNV	Choroidal neovascularisation
COVID-19	Coronavirus
DW	Durbin-Watson test
EDA	Electrodermal activity
EM	Eye marking
ER-SCRs	Event-Related Skin Conductance Responses
ES	Eyelid Speculum
IASP	International Association for the Study of Pain
IQR	Inter-Quartile Range
IN	Injection
IVI	Intravitreal injection
MPQ	Main component of SF-MPQ
MPQ0	Main component of SF-MPQ baseline

MPQ1	Main component of SF-MPQ 1-2 hrs post-treatment
MPQ24	Main component of SF-MPQ 24 hrs post-treatment
NRS	Numeric rating scale
OCT	Optical Coherence Tomography
PPI	Present Pain Intensity
PPI0	Present Pain Intensity baseline
PPI1	Present Pain Intensity 1-2 hrs post-treatment
PPI24	Present Pain Intensity 24 hrs post-treatment
RPE	Retinal pigment epithelium
SCL	Skin Conductance Level
SD	Standard Deviation
SEM	Standard Error of the Mean
SC	Skin Conductance
SCR	Skin Conductance Response
SF-MPQ	Short-Form McGill Pain Questionnaire
STAI	State-Trait Anxiety Inventory
STAI0	State-Trait Anxiety Inventory baseline
STAI1	State-Trait Anxiety Inventory 1-2 hrs post-treatment
STAI24	State-Trait Anxiety Inventory 24 hrs post-treatment
STATE0	State Anxiety baseline

STATE1	State anxiety 1-2 hrs post-treatment
STATE24	State anxiety 24 hrs post-treatment
TRAIT0	Trait Anxiety baseline
TRAIT1	Trait anxiety 1-2 hrs post-treatment
TRAIT24	Trait anxiety 24 hrs post-treatment
VA	Visual Acuity
VAS	Visual Analogue Scale
VAS0	Visual Analogue Scale at baseline
VAS1	Visual Analogue Scale 1-2 hrs post-treatment
VAS24	Visual Analogue Scale 24 hrs post-treatment
VEGF	Vascular Endothelial Growth Factor
VIF	Variance Inflation Factor
WEMWBS	Warwick-Edinburgh Mental Wellbeing Scale
WEMWBS0	Warwick-Edinburgh Mental Wellbeing Scale baseline
WEMWBS1	Warwick-Edinburgh Mental Wellbeing Scale 1-2 hrs post-treatment
WEMWBS24	Warwick-Edinburgh Mental Wellbeing Scale 24 hrs post-treatment

Chapter 1
Background on age-related macular degeneration and intravitreal injections

This chapter provides an overview of age-related macular degeneration (AMD) and intravitreal injections. The chapter summarises the prevalence of AMD and its multifactorial nature. Additionally, the chapter explores the pathogenesis of AMD, which is influenced by a complex interplay of genetic, environmental, and lifestyle factors.

To provide a more comprehensive understanding of AMD, the chapter covers the classification of the disease and its different subtypes. In particular, it focuses on neovascular AMD. The chapter also discusses the various diagnostic tools and techniques used to identify and monitor AMD, including visual acuity testing, fundus photography, and optical coherence tomography.

With a particular emphasis on intravitreal injections, which have transformed the management of neovascular AMD in recent years, the chapter outlines the different agents used in these injections and their respective molecular structures.

1.1. Introduction

Globally, AMD is the 4th most common cause of sight impairment in the elderly after cataract, uncorrected refractive error, and glaucoma (Flaxman et al. 2017), and the leading cause in developed countries, including the UK (Bourne et al. 2014; Bunce et al. 2015; Colijn et al. 2017; Flaxman et al. 2017). In 2010, about 600 000 people in the UK were diagnosed with AMD, with this number expected to rise to 1.3 million by 2050; nearly 400 additional cases every day (Minassian et al. 2011; Bishop et al. 2016). Among those aged ≥65 years and ≥80 years, the estimated prevalence for neovascular AMD was 2.5% (95% CI 1.8% to 3.4%) and 6.3% (95% CI 4.5% to 8.6%), with 60% (n=122,000) of the incidences reported in the female population (Owen et al. 2012). Developing neovascular AMD in one eye, there is approximately 40-50% risk to develop into bilateral within 5 years (Birch and Liang 2007). There are several risk factors including lifestyle (e.g. smoking, alcohol consumption), genetic (e.g. CFH; complement factor H, age-related maculopathy susceptibility 2/high-temperature requirement A serine peptidase; ARMS2-HTRA1, CFI; complement factor I) and environmental (e.g. solar radiation) components implicated in AMD (Chakravarthy et al. 2010; Lu et al. 2021; Yates et al. 2007). Nevertheless, epidemiological data have established that age and smoking were the most significant factors associated with the burden of retinal disease (Mitchell et al. 2002; Kawasaki et al. 2008). There is still substantial ambiguity to whether factors such as body mass index, alcohol consumption, sunlight exposure, or gender increase the risk of its development (Chakravarthy et al. 2010). This is mainly because of the multifactorial nature of AMD, in

addition to the heterogeneity between studies basing their research on different criteria for diagnosis, non-standardised definitions of disease or different examination methods.

Studies have investigated the impact of mineral supplementation and antioxidants on AMD with the aim of developing effective strategies to slow or prevent its progression (Evans & Lawrenson, 2017; Lawrenson & Downie, 2019). The Age-Related Eye Disease Study (AREDS) (Davis et al. 2005) aimed to establish a severity scale for AMD and investigate the effects of nutritional supplements on the progression of the disease. Results showed that high doses of vitamins C and E, beta-carotene, and zinc significantly reduced the progression to advanced AMD and associated vision loss. Patients taking the AREDS formulation with high doses of vitamins C and E, beta-carotene, and zinc had a 25% reduction in the progression to advanced AMD, compared to those taking a placebo. A subsequent study, the Age-Related Eye Disease Study 2 (AREDS2) (Chew et al. 2012) examined modifications to the original AREDS formula; it added lutein and zeaxanthin, omega-3 fatty acids, or reduced the dose of zinc and beta-carotene. Based on the study results, it was determined that omega-3 fatty acids did not have a significant impact on the formulation. The study findings also suggest that the combined use of lutein and zeaxanthin is a safe and effective substitute for beta-carotene in related formulations.

1.2. Pathogenesis

An increase in oxidative stress due to a reduction in protective mechanisms or an increase in number and concentration of active photo-oxidative reaction species are believed to contribute to the pathogenesis of AMD (Strauss 2005). Pathological processes, including choroidal neovascularisation and vascular leakage disrupt the Bruch's membrane, the retinal pigment epithelium (RPE) and the photoreceptors leading to neovascular AMD. Figure 1.2.1 provides a visual representation of the transverse section of a normal eye. RPE is a cellular layer located underneath the photoreceptor cells (figure 1.2.2). Packed of pigment granules, called melanosomes (absorb excess light), the RPE protects the retina against light damage (vision blurriness) (Strauss 2005; van Lookeren Campagne et al. 2014). The outer segment of the retina and the RPE receive their blood supply from two sources: the central retinal artery and the choroidal blood vessels. As one of the most highly vascularized tissues of the body, the choroid primarily acts as an oxygen and nutrient supplier to the outer retina (Nickla and Wallman 2010). A highly anastomosed network of capillaries, the choriocapillaris forms part of the choroidal vasculature, located below the outer collagenous layer of the Bruch's membrane, and connects to venules and arterioles in the Sattler's layer (Bhutto and Lutty 2012). The microvessels, and the macrovessels in the Haller's layer function interchangeably to maintain constant blood flow and oxygen tension in the retina (van Lookeren Campagne et al. 2014).

A reduced ability to absorb light energy is a significant factor in the cascade of biological events leading to AMD (Strauss 2005). An increase in oxidative stress mainly because of a decline in cellular protective mechanisms or an increase in the reactive oxygen species (free radicals) are thought to contribute to the pathogenesis of AMD. Studies have reported that the RPE undergoes significant age-related changes, such as a decrease in cell density, accumulation of lipofuscin, and impaired phagocytic activity (Curcio et al. 2010; Zhang et al. 2022). An age-related reduction in α-tocopherol (antioxidant) causes accumulation of toxic substances giving rise to apoptotic processes that eventually lead to cell death. Other important age-related characteristics are changes in pigmentation. These morphological changes include reduction of melanosomes and increase in lipofuscin granules, which again results in the production of oxygen species (Strauss 2005). Drusen appear in the earliest stage of AMD, and as the disease progresses to intermediate or advanced stage, these drusen can grow in size (Bressler et al. 1994; Klein et al. 1997). Drusen are small yellow deposits and are an important sign of AMD. Drusen accumulate in the RPE and BM and consist of metabolic end products such as lipoproteins and other hydrophobic materials (Bhutto and Lutty 2012).

Moreover, earlier studies have also reported that oxidative stress can relate to the induction of advanced glycation end products (AGEs) in BM, which may play a key role in the induction of CNV (Strauss 2005; Dong et al. 2009; Klettner and Roider 2009). Hypoxia is a leading feature of neovascular AMD resulting in elevated levels of the transcription factor, hypoxia-inducible

factor-1 (HIF-1) which upregulates cytokines, including VEGF, platelet-derived growth factor-B (PDGF-B) and other hypoxia-related gene products, for example, angiopoietin-2 (Prentice et al. 2011; Balaiya et al. 2013; Blasiak et al. 2014). Pathological inducers lead to the build-up of drusen, containing the complement components, C3a and C5a that initiate immuno-inflammatory processes (Nozaki et al. 2006). Chronic inflammation induces macrophages in the macular region (figure 1.2.3) to secrete cytokines and disequilibrate the concentrations of proangiogenic and antiangiogenic factors, VEGF and the pigment epithelial-derived factor (PEDF), respectively (Strauss 2005). An imbalanced system is characterised by an increasing ratio of antiangiogenic/proangiogenic factors; higher levels of VEGFs and/or lower levels of PEDFs in the retina. Highly selective for vascular endothelial cells, VEGF-A enhances the process of neovascularisation, wherein newly grown blood vessels branch from the choriocapillaris to form the CNV membrane (CNVM) leading to vision impairment. VEGF belongs to the platelet-derived growth factor (PDGF) family consisting of VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PlGF) (Pasqualetti et al. 2007) and acknowledging its role in angiogenesis is the ideal target for the treatment of ocular disease including neovascular AMD (Senger 2010), as well as in proliferative diabetic retinopathy (Simó et al. 2014) and in tumour growth (Carmeliet 2005).

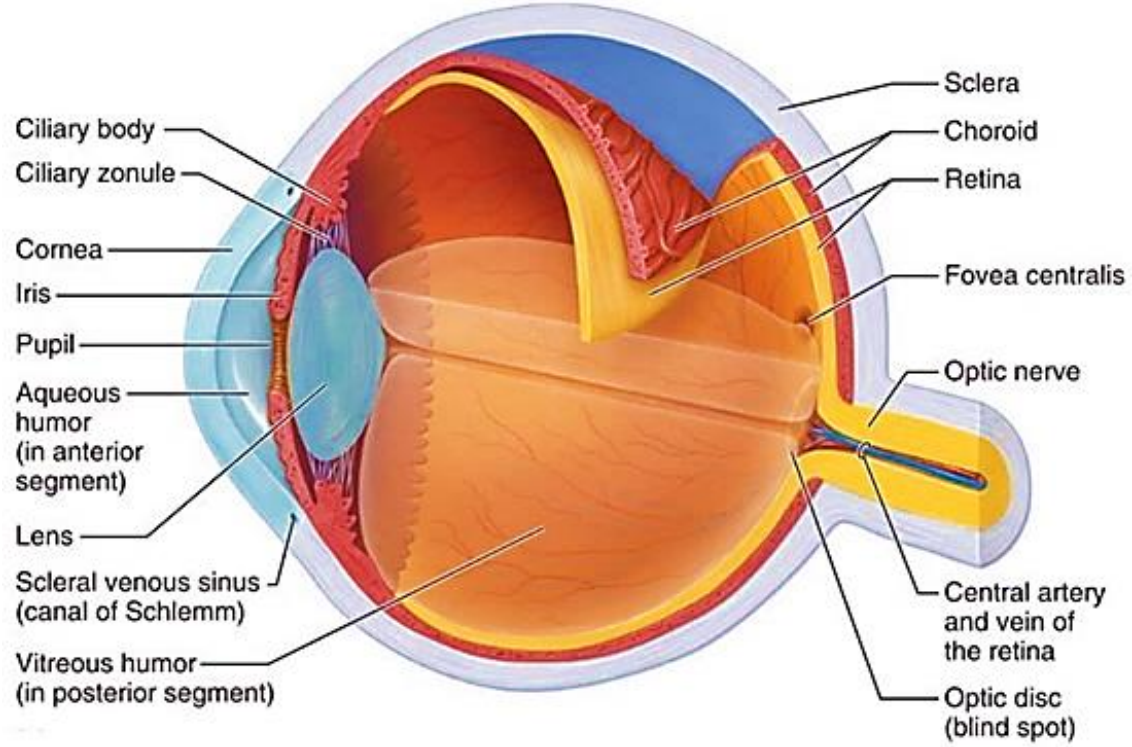

Figure 1.2.1 - Transverse section of a normal human eye. From Marieb (2014a).

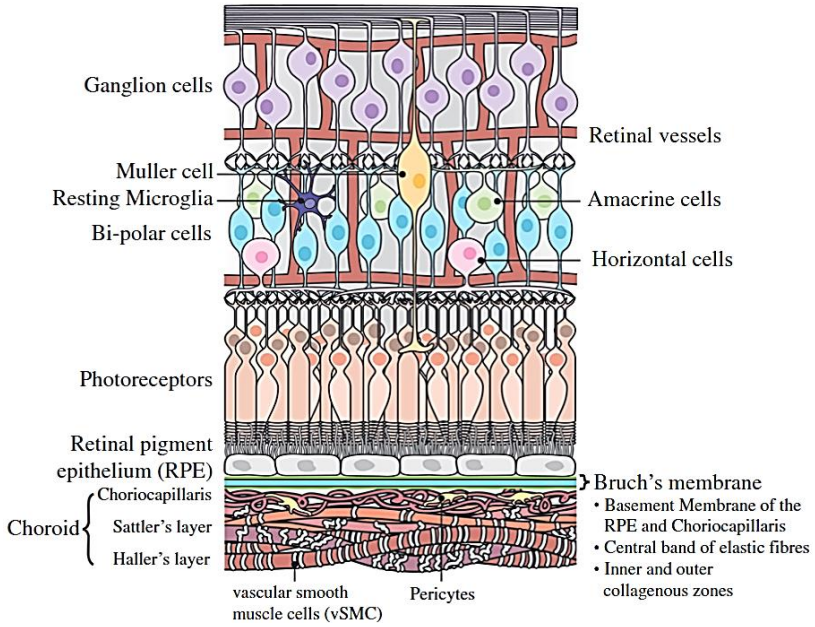

Figure 1.2.2 - Detailed segment of the retina of the normal eye. Structures primarily affected in age-related macular degeneration (AMD) include retinal pigment epithelium (RPE), Bruch's membrane (BM), the choroid divided into 3 layers; the choriocapillaris, Sattler's layer, Haller'slayer. From van Lookeren Campagne et al. (2014).

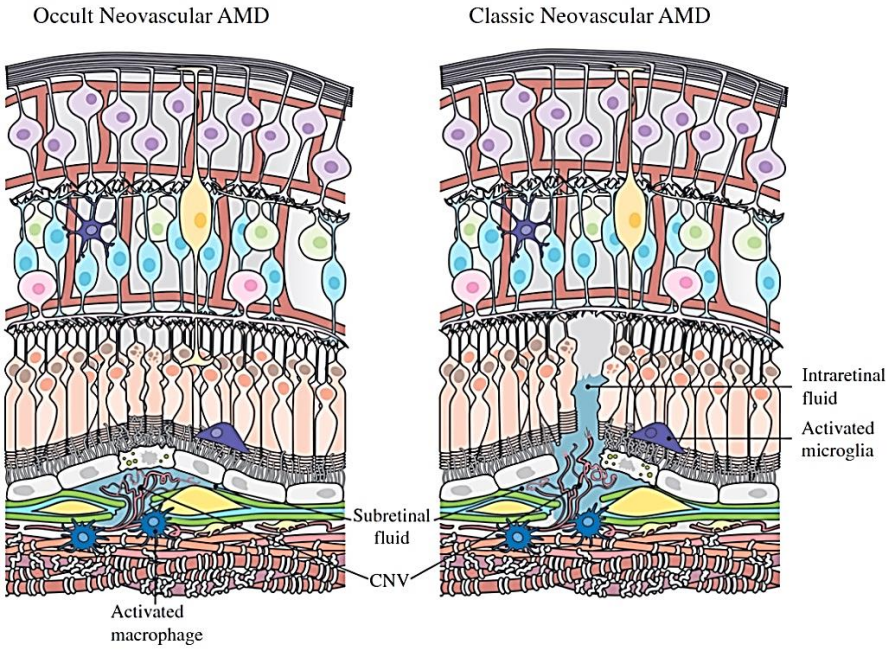

Figure 1.2.3 - Structure of a retinal eye with occult and classic neovascular AMD Pathological features shown include activated microglia, activated macrophages, choroidal neovascularisation, subretinal and intraretinal fluid. From van Lookeren Campagne et al. (2014).

1.3. Classification

Several classification/grading systems have been proposed to provide standards for clinical practice and scientific research over the years (Bird et al. 1995; Smith et al. 2001; van Leeuwen et al. 2003; Seddon et al. 2006; Klein et al. 2007). Most have adopted standardised grading of stereo fundus photographs, with a standard ETDRS grade and templates to grade key features, and the use of clinical data to assess the classification system of AMD, and its prevalence (Mitchell et al. 2002; Klein et al. 2006). Evaluation criteria for the ARM grading system (Klein et al. 1991) has evolved to become stricter and standardised (International ARM Epidemiological Study). Re-defined by the International ARM Epidemiological Study (Bird et al. 1995), this system was characterised by having minimal or moderate non-neovascular age-related changes in the macula, exclusive of visual acuity. Morphologic biomarkers including the presence of advanced RPE atrophy or CNV was an essential criterion to establish the diagnosis of atrophic or neovascular AMD, respectively. The Age-Related Eye Disease Study (AREDS) (Davis et al. 2005) classification system is commonly used because of its high applicability in clinical settings, defining four AMD categories based on the morphological findings of drusen, atrophy, and neovascularisation. The clinical features and classifications are presented in table and figure 1.3.1.

AMD Classification	AREDS Category	Clinical Features
No AMD	1	No or few small drusen (<63 µm in diameter)
Early AMD	2	Multiple small drusen, few intermediate drusen (63-123 µm in diameter), or mild RPE abnormalities.
Intermediate AMD	3	Numerous intermediate drusen, at least one large drusen (125 µm or larger in diameter), geographic atrophy (a sharply demarcated, usually round or oval, area of atrophy of the RPE not involving the centre for the fovea).
Advanced AMD	4	Geographic atrophy of the RPE involving the foveal centre or any evidence of choroidal neovascularisation

Table 1.3.1 – A summary of the four-stage classification of AMD from the AREDS Details from Davis et al. (2005). AMD = Age-related macular degeneration.

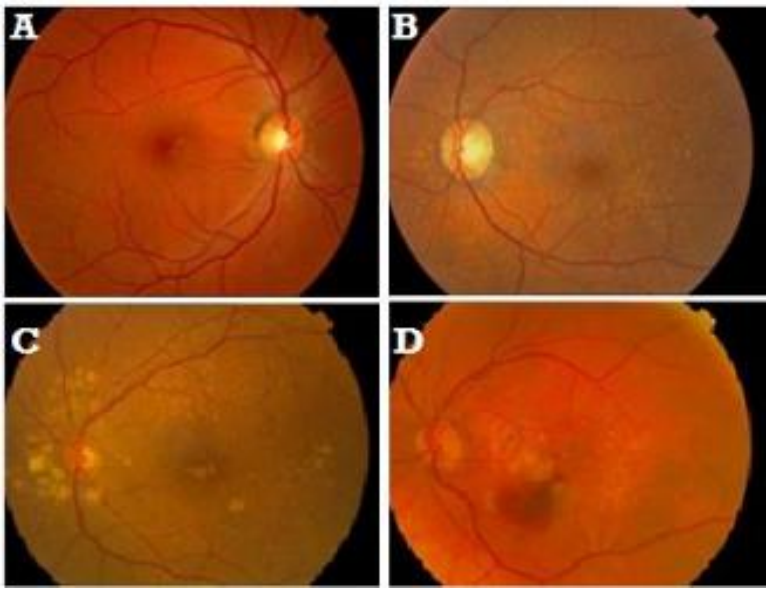

Figure 1.3.1 – Fundus images with increasing AMD severity. A) An AMD category 1 (no AMD). B) An AMD category 2 (Early AMD): showing small, yellow drusen deposits around the macular region and paracentral hyperpigmentation. C) An AMD category 3 (intermediate AMD) – small, intermediate, and large-sized drusen with most being outside the macular centre. D) An AMD category 4 (advanced AMD) -subretinal haemorrhage in the presence of wet AMD. AMD = Age-related Macular Degeneration. From Luis Arias and Jordi Monés (2011).

1.4. Diagnosis and intravitreal injections

Neovascular AMD can affect one or both eyes at the same time or sequentially. Patients with AMD typically report symptoms, such as scotomata (grey or black spots), metamorphosia (object distortions), or a painless progressive blurring of their central visual acuity (Mathenge 2014; NICE 2018). The difficulty in performing critical tasks that require high resolution central vision, for example watching television, driving, writing, and reading has a substantial effect on their quality of life (Solomon et al. 2014a). The measurement of central visual field (using an Amsler grid to reveal any distortion of the centre of vision, in the macula and/or fovea), retinal imaging and visual acuity are routinely applied for the diagnosis, monitoring and management of AMD (Cook et al. 2008). Digital retinal imaging was initially introduced early in the 1990s. Commonly used imaging techniques are colour fundus photography, fluorescein angiography (FA), indocyanine green angiography (ICGA), optical coherence tomography (OCT), and fundus autofluorescence (FAF). The recent development of high-resolution digital cameras applied on OCT and fundus autofluorescence techniques has markedly improved the sensitivity of detection of AMD (Srinivasan et al. 2008; Witkin et al. 2009; Holz et al. 2017). FA is a powerful imaging modality and a diagnostic tool to categorise choroidal neovascular lesion according to its morphological appearance, into classic and occult types (figure 1.3.1) (Luis Arias and Jordi Monés 2011). Fundus photography has been crucial in the diagnosis of sub-retinal exudation, lipid and blood at the onset of visual symptoms. OCT, on the other hand (figure 1.4.1), is a non-invasive imaging technique that uses light

waves to capture cross-sectional images of the retina, and adjacent structures such as the choroid, retinal pigment epithelium, optic nerve head, and the anterior structures of the eye (Mowatt et al. 2014).

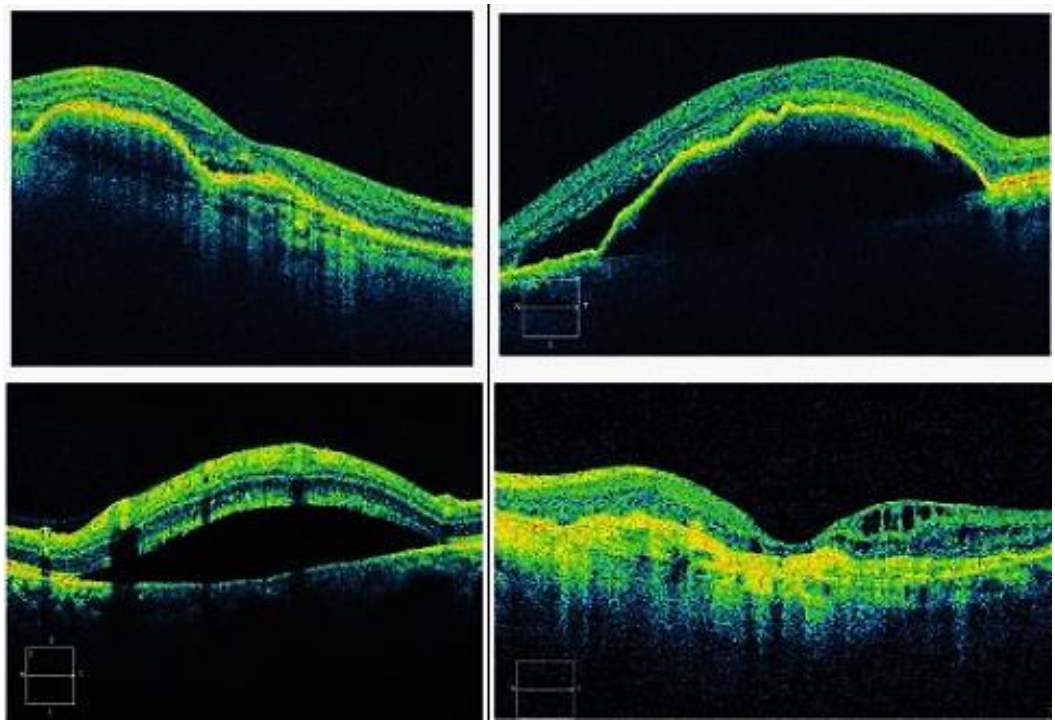

Figure 1.4.1 – Optical coherence tomography (OCT) displaying characteristic histological components in neovascular AMD. Top-left: haemorrhagic detachment; Top Right: serous detachment; Bottom Left: neurosensory retinal detachment, and Bottom Right: intra-retinal fluid. From João Pedro Marques and Rufino Silva MD (2018).

The introduction of anti-VEGF treatment in clinical practices over the past decade has revolutionised the treatment of neovascular AMD in ophthalmic care (Brown et al. 2006b; Rosenfeld et al. 2006a; Heier et al. 2012; NICE 2018; Pearce et al. 2022). With the advent of anti-VEGF injections and verteporfin photodynamic therapy (PDT), previous commonly used treatments, such as thermal laser photocoagulation are no longer recommended. Thermal photocoagulation of CNV was associated with a higher risk of visual loss immediately after treatment, despite its

effectiveness in slowing disease progression (Virgili et al. 2006). These findings were consistent with Morris et al. (2007) indicating that PDT has not shown any significant visual improvement, only prevented clinically significant visual loss. Clinical trials (of minimum 1-year follow-up) established the efficacy and safety of intravitreal anti-VEGF agents, including pegaptanib (Eyetech Pharmaceuticals 2004; Gragoudas et al. 2004), ranibizumab (Genentech 2006; Rosenfeld et al. 2006b), and bevacizumab (Genentech 2007; Tufail et al. 2010) for the treatment of neovascular AMD. In addition to the currently available anti-VEGF agents, a new drug, faricimab, has recently been approved for the treatment of neovascular AMD in the UK.

Faricimab, a novel bispecific antibody targeting both angiopoietin-2 and vascular endothelial growth factor-A, has shown promising results in clinical trials for neovascular AMD. The STAIRWAY trial demonstrated non-inferiority of faricimab compared to monthly ranibizumab in maintaining visual acuity at week 52, with a dosing interval of up to 16 weeks (Khanani et al. 2020). Similarly, the TENAYA and LUCERNE trials found that faricimab was non-inferior to aflibercept in terms of visual acuity gains at week 48, with a dosing interval of up to 16 weeks (Heier et al. 2022). These results suggest that faricimab has the potential to reduce the treatment burden associated with current anti-VEGF therapies while maintaining or improving visual outcomes in patients with neovascular AMD.

The three most common treatment regimens for administering anti-VEGF agents are fixed, as needed (PRN), and treat and extend. In the fixed regimen, injections are given at a set interval, such as every 4 to 8 weeks. The PRN regimen involves administering injections only when there is evidence of disease activity, such as fluid accumulation or worsening visual acuity. The treat and extend regimen involves gradually increasing the time between injections if the disease is stable, while shortening the time if there is evidence of disease activity. Numerous clinical trials have compared these three regimens, and their findings have helped guide clinical practice. The fixed regimen has been shown to be effective in maintaining visual acuity and reducing disease activity, but it requires frequent visits and injections, which can be inconvenient for patients. The PRN regimen is more flexible, but it may result in undertreatment and disease progression. The treat and extend regimen is an attractive compromise that reduces the number of injections while maintaining disease control. Recent studies have also examined the safety and cost-effectiveness of these regimens, particularly in the UK. For example, the IVAN trial (Chakravarthy et al. 2013) compared monthly and PRN treatment with two different anti-VEGF agents and found no significant difference in visual acuity outcomes or adverse events between the regimens. The TREX-AMD trial (Wykoff et al. 2015) compared treat and extend with monthly dosing and found similar visual acuity outcomes between the two regimens, but a reduced injection burden with the treat and extend approach.

Modern pharmacological interventions for the management of choroidal neovascularisation in AMD antagonise the VEGF at the receptor sites, primarily located on the surface of vascular endothelial cells. VEGF is a secreted signalling protein, and its upregulation in pathological ocular neovascularisation results in a more prevalent binding and activation of its receptors leading to neovascular AMD (Weis and Cheresh 2005). By inhibiting the signalling pathways responsible for angiogenesis, anti-VEGF agents can slow the progression of the disease and help to preserve vision (Kamoun et al. 2017; Hu et al. 2021). These pathways, such as the PI3K-Akt and MAPK pathways, are crucial for regulating essential cellular processes such as proliferation, migration, and survival (Sun et al. 2012; Zhang et al. 2020).

Pegaptanib (Eyetech Pharmaceuticals 2004; Gragoudas et al. 2004) was the first FDA approved anti-VEGF agent for the treatment of neovascular AMD, however it was largely replaced by ranibizumab (Genentech 2006; Rosenfeld et al. 2006b), and bevacizumab (Genentech 2007; Tufail et al. 2010) in clinical care. Subsequent clinical trial studies, including ANCHOR 2006 (Brown et al. 2006b) and CATT 2011 (Martin et al. 2011) have assessed the effectiveness of ranibizumab and bevacizumab to reveal better visual outcomes; clinical and statistical significance in maintaining and improving visual acuity. Ranibizumab is a recombinant humanised monoclonal antibody fragment that binds to and inhibits all human VEGF-A isoforms. Ranibizumab has a molecular weight of approximately 48 kilodaltons. It is indicated for the treatment of several eye conditions

including neovascular AMD and diabetic macular oedema. Conversely, bevacizumab is a recombinant humanised monoclonal antibody that also binds to all VEGF-A isoforms but has a larger molecular weight than ranibizumab; 149 kilodaltons.

Studies by Bakri et al. (2013) and Shah et al. (2014) show that bevacizumab and ranibizumab have comparable systemic safety profiles. However, Shah et al. (2014) observed a slightly higher incidence of cardiovascular events with bevacizumab compared to ranibizumab, although the difference was not statistically significant. Similarly, Moja et al. (2014) conducted a meta-analysis of nine randomised controlled trials involving 3665 participants and found no significant differences in the incidence of serious systemic adverse events between bevacizumab and ranibizumab. However, long-term safety outcomes of these drugs remain unclear, necessitating further research with robust designs and larger sample sizes to confirm these results.

Aflibercept (Regeneron 2011) on the other hand is a dimeric glycoprotein with a molecular weight of 97 kilodaltons; soluble decoy receptor that chimeric protein targets vascular endothelial growth factors: VEGF-A, VEGF-B and placental growth factor (Sharma et al. 2014; EyeWiki 2021). Compared to ranibizumab and bevacizumab, aflibercept combines the second binding domain of the VEGFR-1 receptor and the third domain of the VEGFR-2 receptor fused to the Fc domain of immunoglobulin-G.

Faricimab is a 150kDa-sized bispecific antibody that targets both VEGF and angiopoietin-2 (Ang-2) (Nicolò et al. 2021). This dual mechanism of action has the potential to achieve greater suppression of pathological angiogenesis and provide higher efficacy in treating neovascular AMD (Heier et al. 2022). In addition, faricimab has a longer duration of action than ranibizumab, and may reduce the need for frequent injections (Liberski et al. 2022; Regula et al. 2016).

1.5. Conclusion

First, this chapter provided a summary on neovascular AMD and intravitreal anti-VEGF injections. A systematic literature review was then conducted to identify the factors associated with pain and discomfort in patients with neovascular AMD receiving intravitreal injections. Generally, patients receiving an intravitreal injection experience low to mild pain, and this applies to all identified factors, including anaesthetic effectiveness, comparison of needle sizes, injection site and incision, use of the InVitria device, and influence of practitioners (nurses and doctors). While many studies have been identified in examining patients' pain intensity during intravitreal injections, controversial findings reported suggest that additional approaches may be necessary to explore the individual pain experience; experience varies between injections. Considering the chronicity of AMD and recurrence of intravitreal injections, it is therefore important to gain an in-depth understanding of patients' experiences using combined approaches of self-report questionnaires, qualitative interviews, and objective physiological measures, such as electrodermal activity.

Chapter 2
Understanding pain and associated theories

Pain management is an important area in clinical care. Undertreated pain has been associated with increased risk of surgical complications, prolonged rehabilitation, reduced quality of life, and development of chronic pain. Despite an increased focus on pain management and advances in the understanding of the mechanisms underlying pain processing, the individual differences in pain sensitivity as well as the complex physical, psychological, and social phenomena remain a clinical challenge in pain research. Hence, understanding the concept of integrating pain sciences into clinical practice may contribute to the development of improved interventions for pain management.

This chapter provides an overview of the anatomical structures and physiology of pain, and critically examines the definitions and the theoretical models of pain and the associated theoretical models of emotion. The main objective was to identify a suitable theoretical construct to help the understanding of patient experiences associated with intravitreal injections.

2.1. Anatomy and physiology of pain

Pain perception is a dynamic function of the peripheral and central nervous system in notifying the body of actual or potential harmful stimuli. Pain has been defined as a subjective and an unpleasant (noxious) sensory and emotional experience, consisting of sensory-discriminative, behavioural, cognitive, and emotional elements (Merskey et al. 1979). Several studies have used neuroimaging to demonstrate the activation of a distributed cortical neuronal network, the 'pain matrix', in response to nociceptive input elicited in both acute and chronic pain. Also, various structures, for example, the primary and secondary somatosensory system, insular, anterior cingulate cortex and prefrontal cortex, the periaqueductal gray and the thalamus were highlighted as the key elements of the 'pain matrix'. Pain can be described as a multidimensional response that communicates within a large brain network of nociceptors, peripheral neurons, the spinal cord, and higher-order brain structures.

This section reviews the literature related to the anatomical and physiological features of the nervous system in relation to pain. Studying the structure and function of the nervous system is important to recognise the existence of nociceptors with specialised functions in pain sensation, to understand the different types of pain and associated mechanisms, and to gain the knowledge in explaining peripheral pain mechanisms in ocular pain.

2.1.1. The nervous system

The human nervous system can be divided into two major parts: the central nervous system (brain and spinal cord) and the peripheral nervous system (cranial, spinal, and peripheral nerves, sensory and motor nerve endings which lie outside of the central nervous system) (Brodal 2003; Rea 2015a). Both the brain and the spinal cord (SC) are comprised of gray and white matter, but these differ structurally. The SC gray matter contains a H-shaped area of gray matter in the central region and surrounded by white matter. Conversely, the gray matter of the brain is found in the 'outer' area in the cerebral cortex. The white matter encompasses supporting glial cells and myelinated axons, whereas the gray matter is comprised of neurons. Compared to the gray matter containing cell bodies, nerve synapses and dendrites, the mainly glycolipid composition of myelin sheath is responsible for the characteristic white appearance of the white matter. Neurones are specialised cells within the nervous system that are broadly classified into: a) afferent or sensory neurones; transmission of information on light, touch, and sound from peripheral receptors to the CNS, b) efferent or motor neurones; transmission of information away from the SC to the effector organs, and c) interneurons; integration of information within a neuronal network in the CNS (figure 2.1.1) (Brodal 2003). Figures 2.1.2 and 2.1.3 illustrate the structure and function of key components of a neurone, including a soma, dendrites, axons, terminal buttons, and synaptic vesicles. These features facilitate neuronal activity and the rapid communication via action potentials that results in the contraction of cardiac or smooth muscle and the secretion of glands (effector organs).

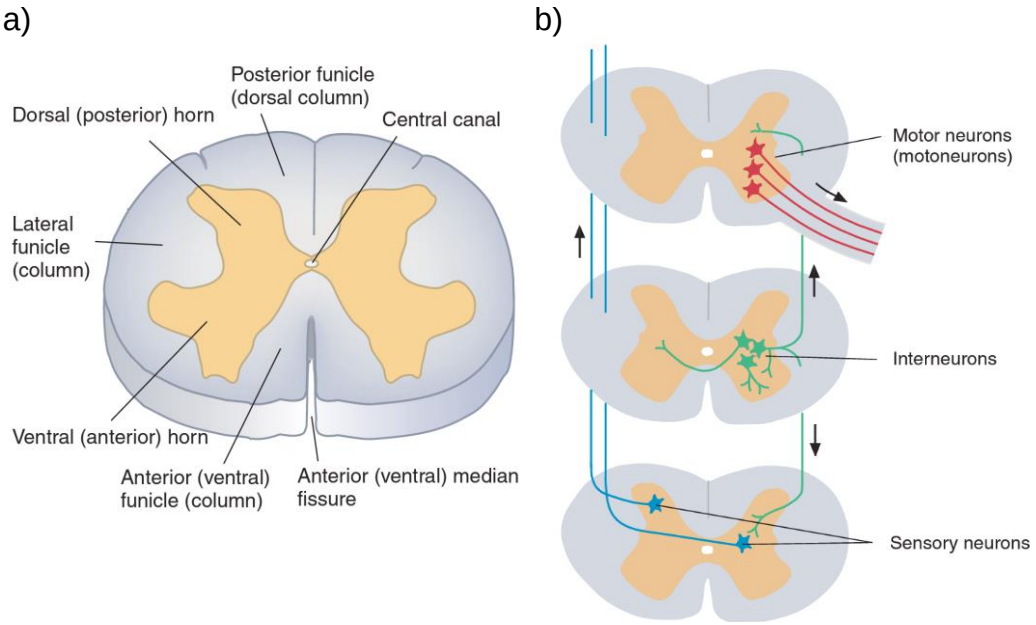

Figure 2.1.1 – Schematic representation of spinal cord and connection to the peripheral nervous system. a) Cross-section of the spinal cord; b) Functional divisions of the nervous system to illustrate the three types of neurones: sensory (afferent), interneurons, and motor (efferent). From Brodal (2003).

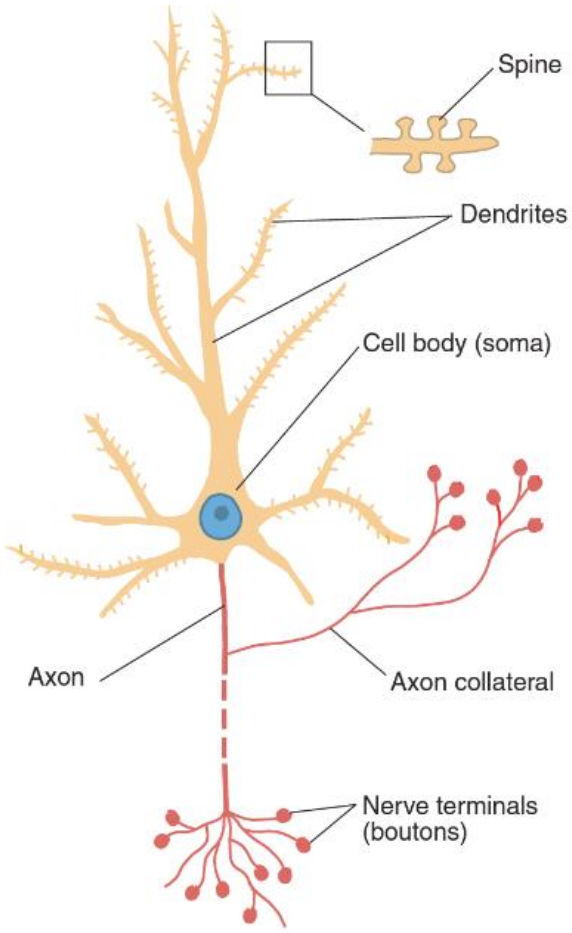

Figure 2.1.2 – Overview of the structure of a neurone. From Brodal (2003).

Anatomical Feature of Neuron	Function
Soma (cell body)	Protein synthesis (abundance of Nissl substance/body) Location of neurofilaments (maintenance of neuron and structural support) "Powerhouse" of neuron Location of nucleus, nucleolus and Nissl body (location of rough endoplasmic reticulum (and ribosomes)
Dendrites	Cellular extensions Majority of input to neuron arrives here via dendrites (via the dendritic spine)
Axon	Transmission of the electrical impulse (action potential) away from the neuronal cell body (soma) To allow for communication with nearby neurons
Axon terminal	Dilated terminal region of the axon Release of neurotransmitter (from the vesicles) into the synaptic cleft to communicate with the dendrite of the next neuron it targets
Axon hillock	The region close to the soma where the axon originates from Location of the voltage gated sodium channels Most excitable part of the neuron May receive information into this point too
Myelin sheath	Propagation of electrical impulses along the axon Increased electrical resistance No voltage gated channels
Nodes of Ranvier	Location of voltage gated ion channels Location of ion exchangers (e.g. Na^+/K^+ and Na^+/Ca^{2+}) Aids rapid propagation of electrical impulses along the axon
Synapse	Structure capable of transmitting chemical or electrical signals Position of pre and postsynaptic area for communication between two neurons (e.g. axon terminal of one neuron and dendrite of adjacent neuron)

Figure 2.1.3 – Function of the structural components of a neurone. From Rea (2015b).

Neuronal communication is elicited via a process called synaptic transmission occurring through two main modalities: electrical or chemical. Electrical synapses are in the form of gap junction pores acting as passive channels that allow the ionic current to flow between presynaptic and postsynaptic cells, whereas chemical synapses relate to the release of neurotransmitters; an action potential triggers the presynaptic neurone to release neurotransmitters into the synaptic cleft which then bind to receptors on the post-synaptic membrane, regenerating an action potential in the postsynaptic neurone. Examples of neurotransmitters include glutamate,

aspartate, and serotonin, and at least 20 neuropeptides involved in transmitting pain impulses have been identified, including substance P, vasoactive intestinal peptide, calcitonin gene-related peptide and somatostatin. Table 2.1.1 outlines the main neurotransmitters of the nervous system.

Neurotransmitters	**Description**
Acetylcholine	Main neurotransmitter at neuromuscular and neuroglandular junctions. Causes excitation of neurones in muscles and endocrine glands.
Glutamate	Causes excitation of neurones in the central nervous system. Involved in the rapid neurotransmission of acute pain associated with Aδ fibres.
γ-aminobutyric acid (GABA)	Causes inhibition of neuronal receptors in the central nervous system.
Substance P	Causes excitation of neurones. Main neurotransmitter within the dorsal horn of the spinal cord. Associated with relatively slow excitatory connections, and hence with the persistent, chronic pain sensations transmitted by C fibres.
Noradrenaline	Concentrated in the brainstem and causes either neuronal inhibition or excitation.
Serotonin	Concentrated in the brainstem and is involved in the regulation of temperature, sensory perception, sleep, and moos and causes neuronal inhibition.
Dopamine	Concentrated in the midbrain and is involved in the regulation of emotional responses and subconscious movements of the skeletal muscles. Causes neuronal inhibition in dendrites.

Table 2.1.1 – Neurotransmitters involved in pain pathways. From Brodal (2003).

2.1.2. Pain receptors and primary afferents

This section presents the pain principles, including nociceptors and pain fibres responsible for transmitting pain signals and examines the main pain pathways and types of pain. A sensation of pain is described as nociceptive meaning that is sensitive to noxious stimuli, such as pinching, pricking or exposure to irritant substances (Brodal 2003; Rea 2015b; Steeds 2016; Martini et al. 2017). Fundamentally, there are four distinct processes that occur in nociception: transduction, transmission, perception, and modulation. The basic illustration on pain transmission is illustrated in figure 2.1.4 below.

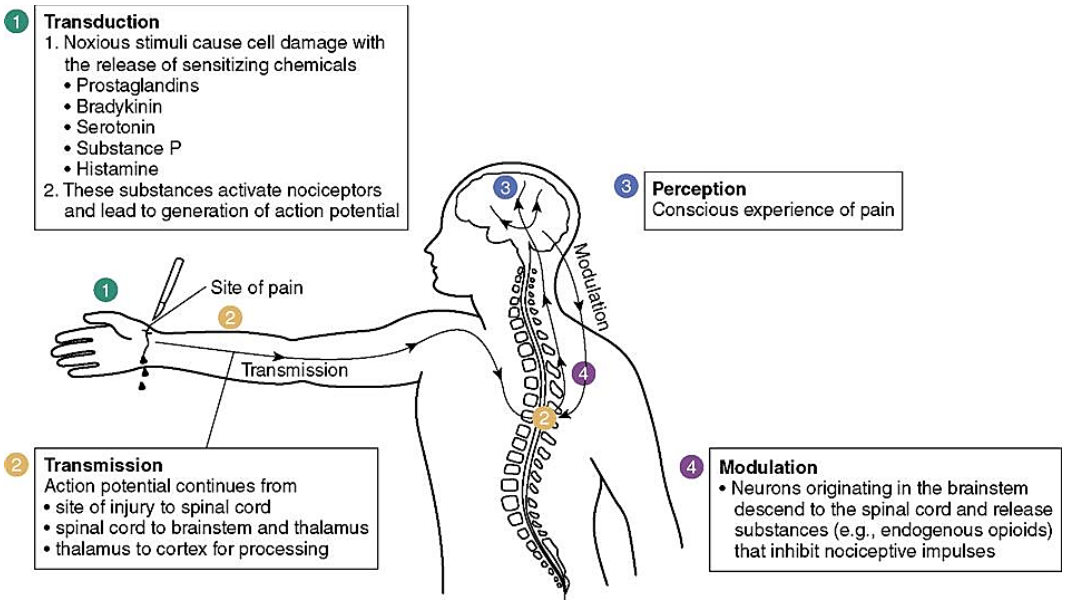

Figure 2.1.4 – Summary of processes in nociception. 1) Transduction occurs in response to the release of chemical mediators e.g. prostaglandins, bradykinin. 2) Transmission involves the conduct of the action potential (peripheral, site of injury) to the spinal cord, then the brainstem, thalamus and cerebral cortex. 3) Perception of pain in the higher brain areas e.g. anterior cingulate cortex, and 4) Modulation involves signals to the spinal cord to modify incoming impulses. From Nurse Key (2016).

Stimulation of the dendrites of a nociceptor causes depolarization (Rea 2015b). Nociceptors are sensory receptors in tissues which are activated by potentially noxious stimuli that are responsible for the transduction of 'noxious' information into electrical signals (receptor potentials) (Brodal 2003; Rea 2015b). These potentials are initiated because of a shift in electric charge distribution within the cell membrane, a process referred to as depolarisation. Stimuli that initiate depolarisation (opening of Na^+ channels) above the threshold potential of -55 mV, produce an action potential in the pain nerve fibres that is transmitted through axons into the dorsal root ganglion, then the SC and into the CNS. The formation of an action potential can be divided into 6 steps presented in figure 2.1.5 below.

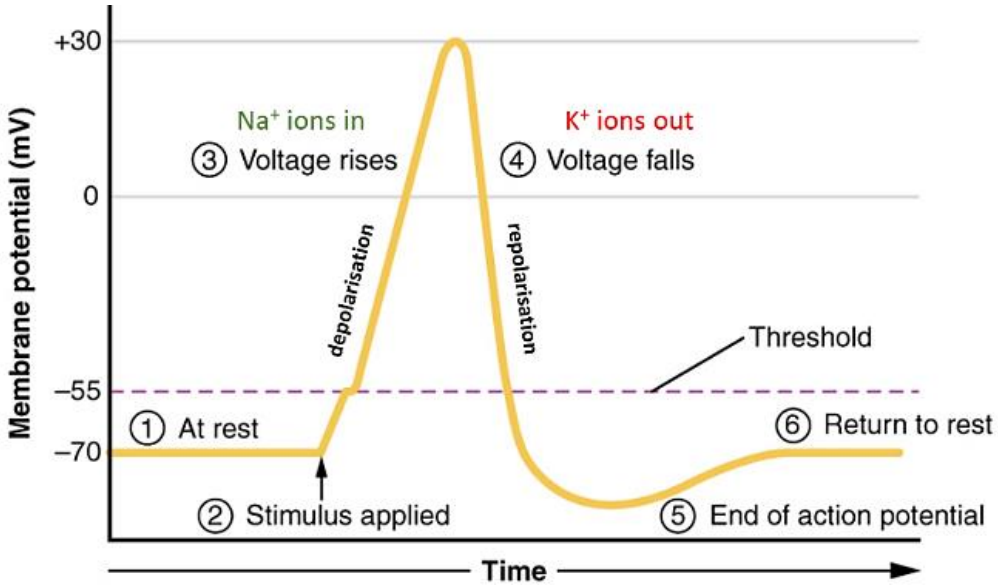

Figure 2.1.5 – Initiation of action potential. Resting membrane potential. 2) Sensory stimulation causing the target cell to depolarise toward the threshold potential. 3) If the threshold of excitation is reached, all Na+ channels open and the membrane depolarises. 4) At the peak action potential, K+ channels open and K+ begins to leave the cell. At the same time, Na+ channels close. 5) The membrane becomes hyperpolarised as K+ ions continue to leave the cell. The hyperpolarised membrane is in a refractory period and cannot fire. 6) The K+ channels close and the Na+/K+ transporter restores the resting potential. From Rea (2015b).

Nociceptors are described as high-threshold receptors and are widely distributed in somatic structures (skin, muscles, joints, bones) and visceral structures (liver, gastrointestinal tract), with a varying stimulus specificity (Brodal 2003; Dubin and Patapoutian 2010). For instance, some nociceptors respond only to intense mechanical stimuli (mechanoreceptors), others to chemical, inflammatory substances (chemoreceptors), while others detect extreme change in heat or coldness (thermoreceptors). Nevertheless, most nociceptors are polymodal thus responding to a range of stimuli, compared to silent nociceptors that require prolonged stimulation to respond to 'normal' pain-provoking stimuli (Martini 2017). Structurally, nociceptors are the free nerve endings of the primary afferent neurons; the Aβ fibres, Aδ fibres and C fibres (table 2.1.2). This section predominantly focuses on the functional distinction between Aδ and C axons as these are primarily involved in the transmission of pain and provides a detailed description of the underlying neuroanatomy of the pain system (Dubin and Patapoutian 2010). Existing research recognises that Aδ axons conduct signals more rapidly than C fibres and play a key role in regulating 'first pain', whereas C fibres are responsible for 'second pain'. Hence, after a noxious stimulus, the initial experience is described as a highly localised, brief, pricking sensation (first pain) followed by a longer lasting, burning, aching and more diffuse sensation (second pain) (Steeds 2016; Koeppen and Stanton 2017). The Aδ fibres and C fibres have cell bodies in either the dorsal root ganglia or trigeminal ganglion and terminate in the dorsal horn of the SC. The dorsal horn is divided into laminae (called Rexed laminae) (figure 2.1.6).

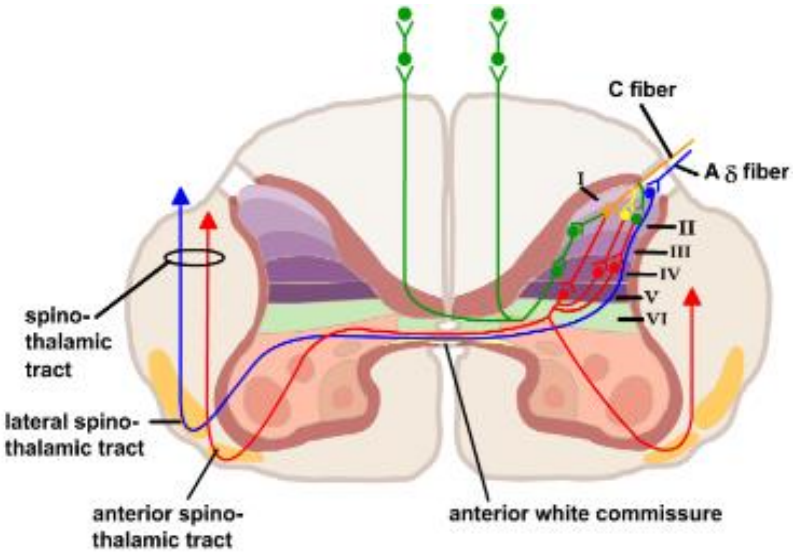

Figure 2.1.6 – Synaptic innervation of the primary afferent nociceptors into the spinal cord. Electrical signals are predominantly transmitted by the Aδ fibres which enter the dorsal horn in the ventro-lateral bundle of the dorsal root and synapse with second-order neurons in the laminae I and V of the dorsal horn, whereas C fibres enter via the ventral root and synapse into the lamina II (substantia gelatinosa). From Steeds (2016).

Fibre characteristics	Aβ (myelinated)	Aδ (thinly myelinated)	C (unmyelinated)
Fibre diameter	6-12 µm	2-5 µm	<2 µm
Conduction velocity	35-75 m/second	5-15 m/second	0.5 – 2 m/second
Distribution		Body surface, muscles, joints	Most tissues
Sensory receptor	Mechanoreceptors	Nociceptors, thermoreceptors, mechanoreceptors	Thermoreceptors, mechanoreceptors, sympathetic postganglionic nociceptors
Sensation	Touch, pressure, vibration, limb movement	Sharp pain, pricking, well localised, rapid (1st pain)	Burning pain, aching, diffuse, slow (2nd pain)
Position of synapse within dorsal horn of spinal cord	Laminae III-V	Laminae I and V	Lamina II (substantia gelatinosa)

Table 2.1.2 – Characteristics of primary afferent fibres. From Steeds (2016).

2.2. Sensory innervation in the ocular surface

2.2.1. Ocular Nociceptors

Compared to the high density of cutaneous mechanoreceptors, the primary afferent fibres are less abundant in the eye surface (Belmonte 2013), although some have been reported in the conjunctiva and eyelids (Oduntan and Ruskell 1992). Also, sensory nerves of the cornea are thin (therefore are relatively easy to block with topical anaesthetic). While the eyeball contains mechanoreceptors responding to noxious mechanical stimuli (physical contact with objects, presence of foreign bodies), most nociceptors are polymodal therefore activated in response to both mechanical and thermal stimulation, and to endogenous inflammatory products (Belmonte et al. 2004). The eye surface is predominantly innervated by high-threshold cold thermoreceptors (transient variations of 0.1°C or less when temperature decreases below 33°C) that extend into the cornea, limbus, and bulbar conjunctiva (Belmonte and Gallar 2011; Belmonte et al. 2015). Table 2.2.1 and figure 2.2.1 illustrate the characteristics and location of ocular nociceptors, respectively.

Nociceptors	Density	Primary afferent fibres	Description
Mechanoreceptors	15%	Aδ	▪ Mechanical forces ▪ Low threshold compared to cutaneous mechanoreceptors ▪ Fast, short-lasting impulse discharge (1st pain, identify presence and velocity of change of the stimulus)
Polymodal	70%	Aδ, C-fibres	▪ Mechanical forces, heat (>39°C) ▪ Noxious cold (<29°C) ▪ Exogenous chemical irritants ▪ Endogenous chemical mediators released by damaged corneal tissue/inflammatory cells, potassium ions, ATP, prostaglandins, amines, cytokines, growth factors ▪ Irregular, continuous discharge, ~ proportional to the stimulus intensity (majority of polymodal nociceptors are of the C-fibre type; 2nd pain)
Cold-sensitive thermoreceptors	10-15%	Aδ, C-fibres	▪ Depolarise when transient corneal surface <33°C (sensitive to reductions of 0.1°C or less) ▪ Sensitive to cooling of the surface (application of cold air or cold solutions)

Table 2.2.1 – Characteristics of ocular nociceptors. Details from Belmonte et al. (2015).

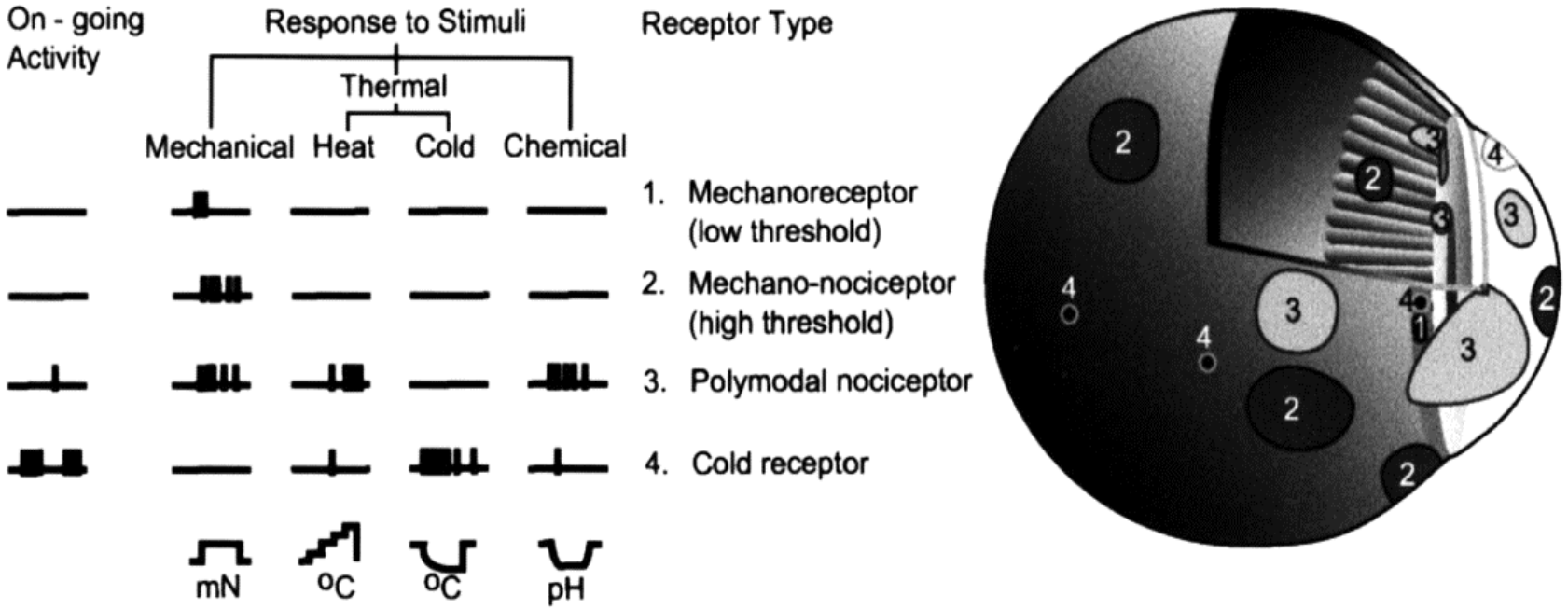

Figure 2.2.1 – Functional types of nociceptors innervating the ocular surface. Left panel illustrates the functional activity of the types of ocular sensory receptor (mechanoreceptors to low and high threshold activities, polymodal and cold receptor) responding to mechanical, thermal (heat or cold), and chemical stimuli showing the discharge of nerve impulses. Right panel shows a schematic illustration of the eyeball to indicate the location and receptor field size of the different types of ocular receptors. From Belmonte et al. (2004).

2.2.2. Types of ocular pain

Diseases leading to impaired vision such as open-angle glaucoma, cataract, retinal degeneration, or AMD normally cause no pain, however manipulation of the ocular surface, for example during surgery or a contact lens fitting may induce an acute local injury (nociceptive pain). Other defensive mechanisms elicited by nociceptive pain comprise of protective reflexes, for instance blinking, tearing and pupil constriction, head withdrawal and rubbing of the eye (Belmonte et al. 2015). Additional modulatory mechanisms include local inflammation, initiating the release of various chemicals, such as protons, prostaglandins, leukotrienes (bradykinin, 5HT, histamine) and cytokines (interleukins, TNF). The direct stimulation of nociceptor nerve terminals further results in the production of local neuropeptides (substance P, neurokinin A) (Dubin and Patapoutian 2010).

On the other hand, an ocular pathology such as uveitis can cause rapid pain (nociceptive inflammatory pain) resulting from the release of inflammatory cells or cellular aggregates in the anterior chamber or the orbit (Friedman et al. 2013; Harthan et al. 2016). Patients with uveitis commonly experience blurry vision due to ciliary muscle spasm, as well as redness and pain, with the latter being described as dull, aching and throbbing (Agrawal et al. 2013). Other common ocular inflammatory diseases include scleritis, conjunctivitis and corneal inflammation (Belmonte et al. 2015). Nociceptive pain describes the normal activation of nociceptors in response to actual or potential tissue damage, in contrast with neuropathic pain produced by a lesion or injury of the somatosensory nervous system (Belmonte et al. 2015;

Galor et al. 2015). Trigeminal neuralgia is an example of neuropathic pain that originates from periocular areas, including the face and the mouth. This type of inflammatory pain may range from dental pain (the most common in this region) to myofascial pain, headache, and neuritis (Bista and Imlach 2019). Neuropathic trigeminal pain commonly results from injury or disease of one or more nerve roots of the trigeminal ganglion, including nerve trauma and compression of the trigeminal nerve root (Tseng et al. 2012; Leal et al. 2014).

Ocular pain is a common phenomenon following an acute local injury (Levin et al. 2011). Stimuli acting on the eye at a higher-than-normal intensity that may potentially cause cell damage, activate nociceptors that send signals to higher-order brain structures, including the thalamus and the cerebral cortex involved in pain perception. Pain in the eye persists until healing occurs, however if inflammatory activity occurs repeatedly, it may grow into a chronic phenomenon (Basbaum et al. 2010). For example, in dry eye disease the reduced tear secretion leads to inflammation and peripheral nerve damage causing sensitisation of the polymodal and mechanoreceptor nerve endings and an increase in the activity of the cold thermoreceptors evoking unpleasant symptoms of ocular dryness and pain (Belmonte et al. 2015). Peripheral sensitisation occurs in response to inflammatory mediators acting on transient receptor potential cation channels, decreasing the threshold of nociceptors for activation. The nociceptors begin to initiate pain signals spontaneously which cause chronic pain (Huang et al. 2006).

2.2.3. The trigeminal pathway

The first-order neurons are in the dorsal root ganglion. Each pain tract (figure 2.2.2) originates in different spinal cord regions and ascends to terminate in different areas in the CNS. In the eye, sensory innervation arises from the trigeminal somatosensory system (figure 2.2.3). The eye and periocular structures are innervated by the peripheral axons of neurons located in the trigeminal ganglion travelling through the trigeminal ophthalmic nerve and branch out to reach all ocular tissues apart from the lens and the retina (Levin et al. 2011; Belmonte 2013). Nociceptors in the cornea transform the stimuli into a discharge of nerve impulses conveyed through ascending ipsilateral (1^{st} order) trigeminal neurones in the peripheral nervous system (ocular structures, trigeminal ganglion, and brainstem). The trigeminal sub-nucleus in the brainstem ultimately drives the impulses to higher-order brain structures (thalamus, amygdala, cerebral cortex) through contralateral (2^{nd} order) trigeminal neurones. When the neural impulses reach the somatosensory cortex, the location (e.g. the eye) and intensity of pain is perceived, until healing takes place.

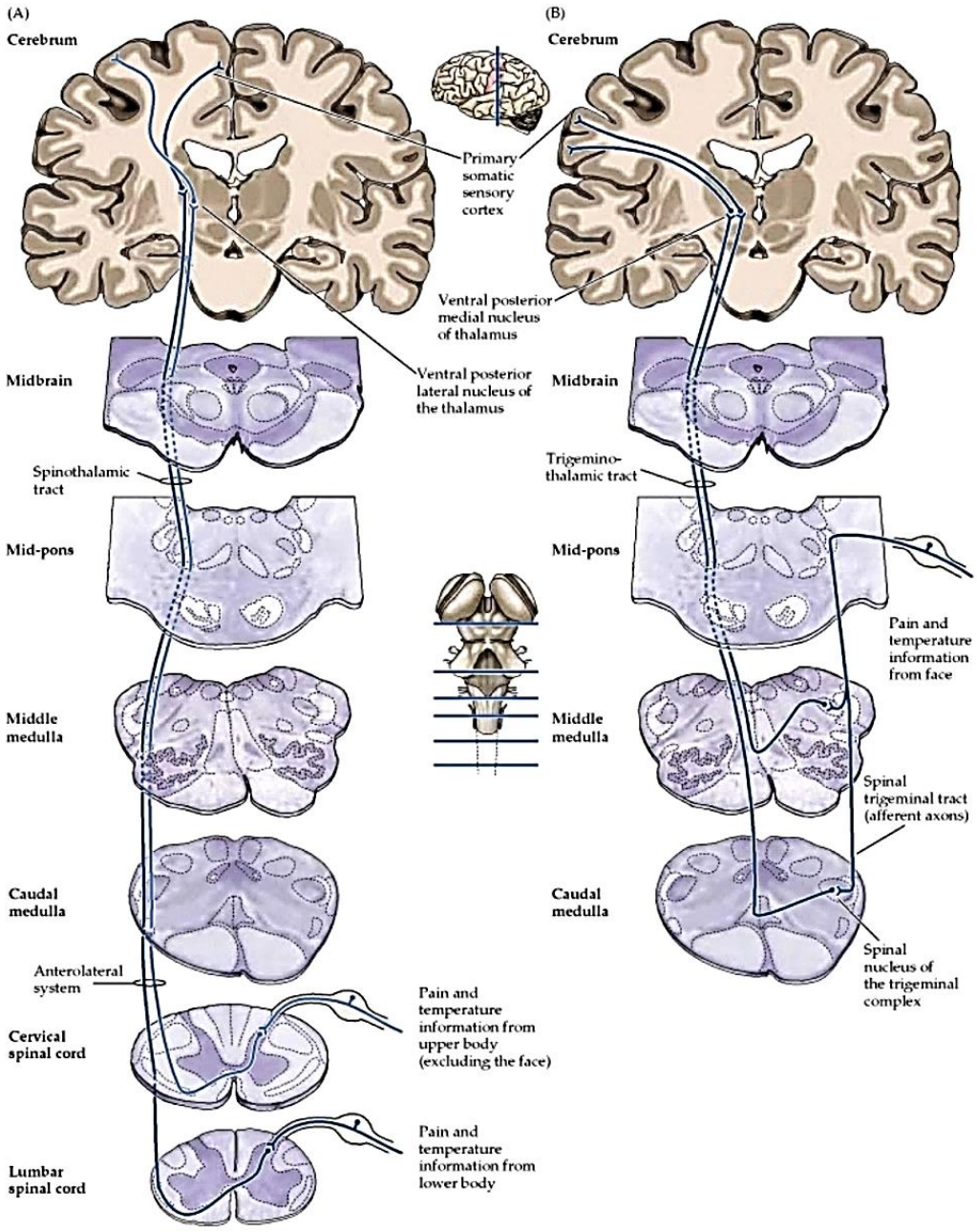

Figure 2.2.2 – Major pathways for the perception of pain. A) The spinothalamic tract, and b) the trigeminal tract. From Derrickson and Tortora (2019).

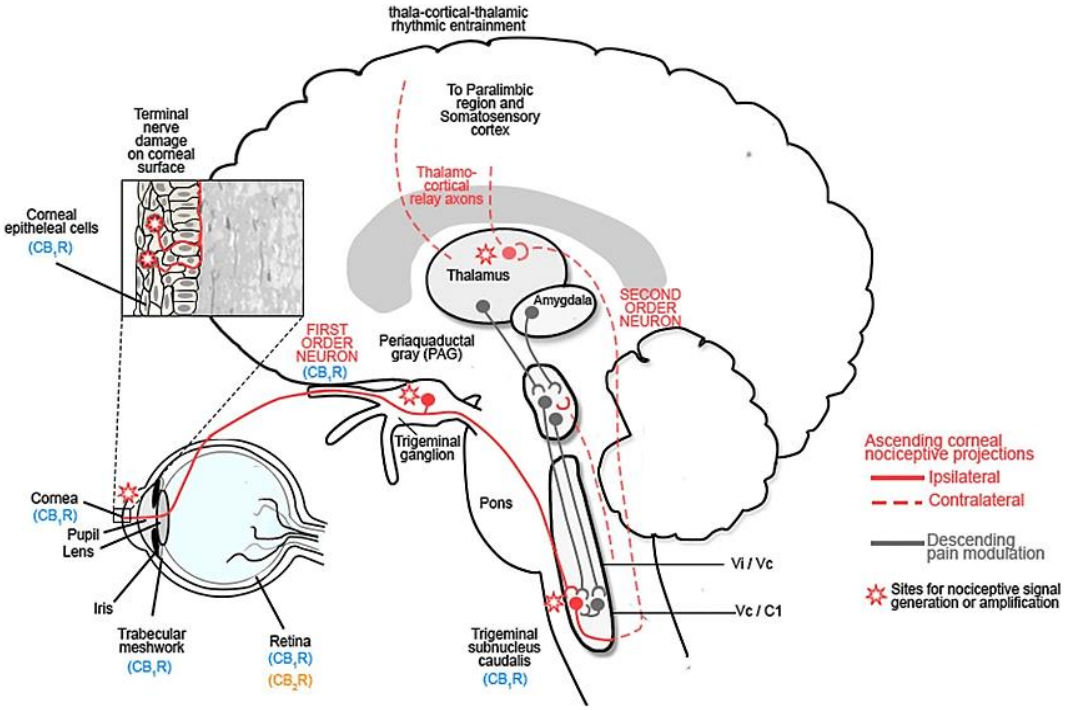

Figure 2.2.3 – The ocular sensory pathway. First order neurons (ascending ipsilateral projections) project to the trigeminal ganglion and synapse with second order neurons (ascending contralateral) in the trigeminal subnucleus caudalis before projecting to the spinothalamic pathways and the thalamus or the periaqueductal gray (PAG). Third order neurons (descending projections) from the thalamus relay information to the somatosensory cortex and paralimbic region, while those from the PAG modulate trigeminal activity. CB_1R, cannabinoid receptor type I; CB_2R, cannabinoid receptor type 2; Vi/Vc, subnucleus interpolaris/caudalis; Vc/Ci, caudalis/upper cervical transition zone. From Galor et al. (2015).

This section has presented the anatomical and physiological features of pain, also providing examples of sensory innervation in the ocular surface and common types of ocular pain. The following section is an overview of the pain definitions recognised in the literature and associated theories.

2.3. A review of pain definitions and theories

The aim of this section was to first gain an understanding of the different pain definitions provided in the literature and then to review the theories of pain and emotion. Developing a theoretical understanding of pain and associating this information with patients' experiences of intravitreal injections may identify additional factors that could impact the intensity of pain reported.

The ability to experience pain keeps humans alert of harmful situations and raises awareness for possible existing conditions or diseases. A widely recognised definition of pain in the literature of scientific and clinical research dates to 1979 (Merskey et al. 1979; Merskey and Bogduk 2002):

> *"…unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of tissue damage, or both."*

This currently used definition of pain has been established by the International Association for the Study of Pain (IASP) adapted by the World Health Organisation (WHO) since the 1990s. Over the years, various definitions have been established to describe and understand pain in medical literature (Merskey et al. 1979; Fields 1999; Pasero and McCaffery 2011; Treede et al. 2019). Therefore, the following is a review of pain definitions to identify an appropriate description in understanding the patient experience in this study.

2.3.1. Defining pain

The IASP definition of pain was established in 1967, when (Sternbach 1968) first represented pain as:

> *"a harmful stimulus which signals current or impending tissue damage", a "pattern of responses which operate to protect the organism from hurt" or a "private, personal sensation of hurt".*

Another proposal focused on the sensory aspect in response to painful stimuli:

> *"that sensory experience evoked by stimuli that injure or threaten to destroy tissue defined introspectively by person as that which hurts"* (Mountcastle 1974)

While Merskey defined pain as:

> *"an unpleasant experience which can be primarily associated with tissue damage or describe in terms of such damage, or both" and said that, "the relationship of pain with the experience of damage to the body, and without making any assumption as to causes, it provides a framework whereby the statements of patients who describe bodily experiences like burning, aching, stabbing, etc. can be assessed, investigated and compared."* (Merskey et al. 1979).

More recently, the IASP definition has been critiqued by authors who support a rationalised definition of the pain experience based on existing phenomenological theories (Cohen et al. 2018). For example, the authors

discussed that the use of a single descriptor, such as ‘unpleasant’ lacks meaning and misinterprets the depth of pain experience. Despite their approaches to redefine pain, it can be argued that the IASP definition of pain is superior from multiple perspectives.

The involvement of psychological factors implies multidimensionality in pain experience. The IASP definition of pain defines pain as a subjective experience (associated with first-person perspective) mediated by physiological changes in the sensory system, and under the influence of emotional aspects:

> *“If they regard their experience as pain, and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain.”* (Merskey and Bogduk 2002).

Also, physical indicators of pain are not necessary for an individual to report pain; “*actual or potential tissue damage*”.

Cohen et al. (2018) on the other hand have provided a new definition of pain:

> *“Pain is a mutually recognisable somatic experience that reflects a person’s apprehension of threat to their bodily or existential integrity”*

Although, in their review of redefining pain (Cohen et al. 2018; Treede 2018), the multidimensional nature of the pain experience has not been explored. This thesis supports the multidimensional nature of pain (Melzack

1975), that qualitative diversity in the assessment of pain is necessary to gain an in depth understanding of the patient experience that may help inform of more effective management strategies. The systematic literature review (Chapter 4) has highlighted that most ophthalmic research focuses on assessing the intensity over pain quality. This could explain the controversial findings reported in the literature (Rodrigues et al. 2007; Tailor et al. 2011) since pain can be complemented by varying qualitative properties (sensory-discriminative, affective-motivational and cognitive-evaluative) (Melzack 1975), outcomes that have been underexplored in patients receiving intravitreal injections.

Secondly, Cohen et al. (2018) also supported that objectivity (third person perspective) was required for pain to exist, however pain has been widely described as a subjective phenomenon (Melzack 1973; McCaffery and Beebe 1989; Melzack and Katz 2006; Kourkouta and Papathanasiou 2014; Treede 2018). While the interpretation of the observer may affect the validity of such behaviour during pain assessment, subjective self-report approaches allow participants to describe their own experiences, expressing their personal opinions and emotions. Subjectiveness therefore has feelings, and no objective assessments currently exist to adequately measure pain (Herr et al. 2006), nevertheless objective instruments, such as electrodermal activity (Christie and Venables 1973) can be used to complement subjective measures in the assessment of pain.

Non-verbal communication is another major barrier in clinical practice. To address this, (Pasero and McCaffery 2011) recommended a hierarchy of pain assessment techniques to be routinely adapted in care settings. These involved the implication of a structured, multilevel systems approach, such as eliciting a self-report from patient, then identifying potential causes of pain and observing the patient behaviour (Herr et al. 2011). While Merskey discussed pain focusing on tissue damage, (McCaffery 1968) defined pain as:

> *"whatever the experiencing person says it is, existing whenever the person says it does."*

McCaffery's clinical definition of pain does not rely on physical damage although it focuses on a nursing, caring approach to emphasise the subjective, personal and social nature of pain (McCaffery and Beebe 1989). Through her work in the field of pain management (McCaffery and Beebe 1989; McCaffery and Ferrell 1995), McCaffery supported that,

> *"pain assessment includes the use of evidence-based*, *reliable assessment tools with a goal of capturing and documenting patient-reported pain outcomes. Patient self-report is the standard of care for evaluating pain*".

McCaffery's contributions in the clinical assessment of pain has informed nurses of effective mechanisms to recognise patients' suffering and advising on interventions to alleviate their symptoms, improve outcomes, and increase the overall quality of life (McCaffery and Ferrell 1995; McCaffery and Ferrell 1997; Herr et al. 2006; Wells et al. 2008). McCaffery

supported the use of patient-reported models of addressing pain, such as the 0-10 scale (McCaffery and Beebe 1989; McCaffery 2002a) and encouraged clinical staff to interact with patients via a 5-minute conversation, to spend quality time listening actively to their concerns and identify strategies that may improve their experiences (McCaffery 2002b).

Patient-reported outcomes, patient-practitioner communication, physiological changes, treatment anxiety, and quality of life and wellbeing are important factors that need to be acknowledged for delivery of high-quality healthcare and clinical research. Studying the IASP definition of pain and McCaffery's definition of pain, both addressed the aforementioned factors, and so these two definitions will be used to underpin this study:

- "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of tissue damage, or both*". (Merskey, 1979)

- "*Whatever the experiencing person says it is, existing whenever the person says it does*."(McCaffery 1968)

Combining pain measures to account for both objective, physiological aspects in Merskey's definition and subjectiveness in McCaffery's definition, complement each other in understanding patients' experiences associated with intravitreal injections. Given the multidimensional nature of pain, the evaluation of aspects such as intensity, duration and location is necessary

for an accurate pain assessment and an effective pain management. Multiple components in the pain experience have been linked to existing theories and imaging studies in neuroscience. There have been major advancements over the years in the emergence of theoretical frameworks particularly influenced by psychological aspects, and these theories will be studied to define and shape the findings of this work.

2.3.2. Theories of pain

Several theoretical frameworks have been proposed to provide a physiological explanation of the pain experience. The Intensity Theory, the Specificity Theory, Pattern Theory and the Gate Control Theory have been the most influential theories of pain perception since the 17th century (Kennis 1988; Perl 2007; Rey 1995; Moayedi and Davis 2013). These pain theories, as well as the Neuromatrix Theory (Melzack 1999) have focused their research on a biological level, to understand sensory modalities and neurotransmission. Conversely, a recently developed theory, the Biopsychosocial Pain Model (Gatchel et al. 2007) explains pain perception as an interaction of biological, psychological, and societal factors that are distinctive at an individual level. As the original primary source publications for the early historical studies conducted in the 19th century were unobtainable in the literature search, the source of information was derived from the works of Moayedi and Davis (2013).

2.3.2.1. Intensity Theory (Erb, 1874)

The Intensity Theory defines pain as an emotion, based on the intensity of the stimulus and central summation of the signals (Moayedi and Davis 2013). This explains the different terminologies used over the years i.e. intensive (or summation) theory of pain in history of the pain research. The sense of touch was the initial concept describing this theory, based on Aristotle's idea of pain. Further experiments performed on patients with syphilis (degenerated dorsal columns) produced pain on repeated tactile stimulation, although below the threshold for tactile perception. Repeated stimulation of different types of stimuli caused unbearable pain to patients. These findings have led to the conclusion that summation of subthreshold stimuli in the dorsal horn cells has occurred that might have caused the unbearable pain experience. A neurophysiological model can be used to describe this summation effect, based on the convergence of neuronal networks (higher sensory input) and summation in the grey matter of the spinal cord (figure 2.3.1). The theory posits that nociceptors are not differentiated into low- and high-threshold stimulus types. Instead, it suggests that pain is defined by the intensity of the stimulus and a central summation effect. Primary afferent neurones transmit intensity-coded impulses to wide-dynamic range (WDR) neurones in the dorsal horn (spinal level). Weakly triggered WDR projections indicate low threshold activity by innocuous events, whereas strong activation indicates high-threshold activity by noxious (painful) stimuli. The theory also supports central summation of sub-threshold stimuli in the spinal cord that can increase the intensity of pain from innocuous to a noxious pain experience.

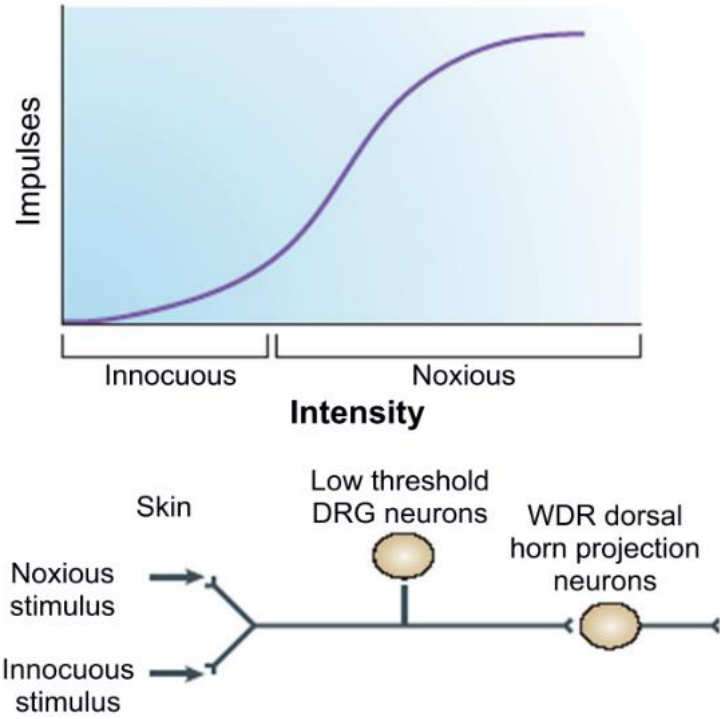

Figure 2.3.1 – Schematic illustration of the association between stimuli and primary afferent activity in Intensity Theory. DRG, dorsal root ganglion; WDR, wide dynamic range neurones. From Moayedi and Davis (2013).

2.3.2.2. Specificity Theory (Von Frey, 1895)

The specificity theory has been formally developed in the 19th century, characterised by existing dedicated pathways specific to each somatosensory modality (Moayedi and Davis 2013). In this model, receptors and first order sensory neurones (primary afferents) are characterised as modality-specific neurones as they are distinctly linked to each of the somatic sensations such as temperature, proprioception, touch, or pain (Dubner et al. 1978). The specificity theory distinguishes a noxious from a non-noxious stimulus and supports the concept that non-noxious mechanical stimuli are encoded by low-threshold mechanoreceptors that carry their impulses to dedicated primary afferents, projected to second-order neurones that process information in the spinal cord or brainstem.

Similarly, a noxious stimulus can still activate a dedicated sensory pathway, however a nociceptor of a higher threshold needs to be stimulated, and project to specifically “higher” pain centres through pain fibres. The somatosensory pathway has been demonstrated in humans in 1664 by Rene Descartes and was characterised as a perception that existed in the brain, distinguishing the sensory nociception from the actual perceptual pain experience (Moayedi and Davis 2013). His original theory suggested that pain intensity was responsible for the extent of tissue damage. Developing his theory on pain, Descartes first described nerves as hollow tubules that conveyed both sensory and motor information. Research however was limited at the time to account for pain perception in the absence of any identifiably tissue pathology or to explain why pain may be perceived in a part of a body that is absent. Pain research has addressed these phenomena with the development of the Gate Control Theory (Melzack 1973).

Moayedi and Davis (2013) explained that in 1811, Charles Bell proposed an alternative description of the anatomy of the nervous system to Descartes. Bell illustrated a model showing the brain as a heterogeneous structure; nerves were characterised as bundles of heterogeneous neurones with distinguished function that consisted of different sensory neurones that were stimulated in response to different types of stimuli. For example, vision and nociception differ from the perceptual experience of sight and pain, respectively. Building on Bell’s discoveries, Francois Magendie, a French physician, conducted neurophysiological experiments to explain distinct

neuronal pathways projected to and from the spinal cord; the ventral and dorsal root, respectively. Their investigations led to the development of the Bell-Magendie Law (figure 2.3.2) which suggested distinct pathways, that posterior roots only contain sensory fibres, whereas ventral spinal roots contain motor fibres, and input into the dorsal root is transmitted unidirectionally to motor neurones in the ventral horn. These aspects played a fundamental role in the organisation of the nervous system.

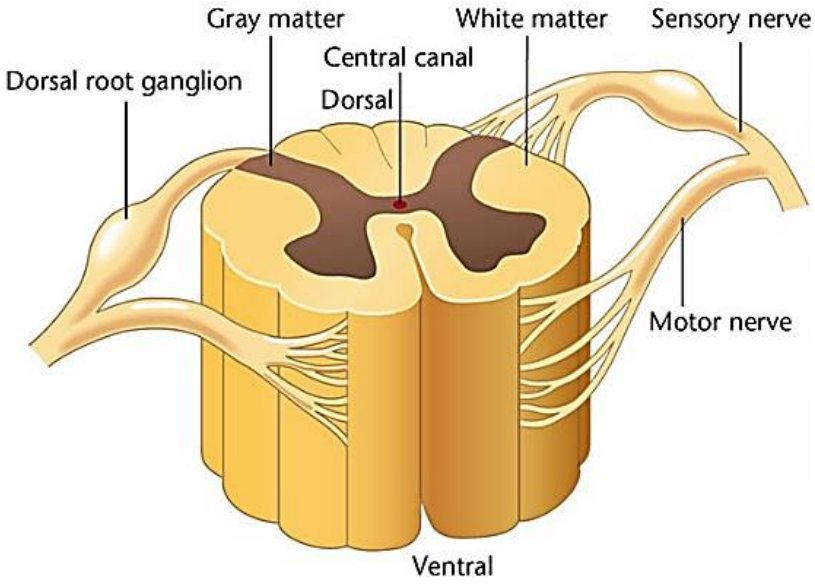

Figure 2.3.2 – Bell-Magendie Law and schematic illustration of the spinal cord. The dorsal root contains only afferent fibres and transmits sensory information to downstream neurones. The ventral root contains only efferent fibres and the cell bodies of motor neurones found in the ventral horn. From Martini et al. (2017).

Around the turn of the 20th century, Max Von Frey and Sir Charles Scott Sherrington, advanced the Specificity Theory (Moayedi and Davis 2013) (figure 2.3.3). Von Frey, an Austrian-German physiologist, applied discrete pressures on different spots on the human skin and specified the presence of cutaneous sensory mechanoreceptors linked to four different

somatosensory modalities, including cold, heat, touch, and pain. Pain was presented as an independent tactile quality, associated to free nerve endings distributed in the skin. Sherrington then used cellular techniques to study the anatomical and physiological structure of the nervous system and developed a theory on its integrative action. The physiologist used the simple reflex arc model to describe the specificity of neurones aligned with the four basic modalities recognised earlier by Von Frey. His experiments supported the selective action of nociceptors to “lower the excitability threshold of the reflex arc for one kind of stimulus and heighten it for all others.” This selective approach is what distinguishes the Specificity Theory from the Intensity Theory. Subsequent research studied the association between myelinated primary afferent fibres and mechanical noxious stimuli (Burgess and Perl 1967) and identified the nociceptive, unmyelinated afferent fibres linked to polymodal nociceptors and high-threshold mechanoreceptors. Explained in the theory, each somatosensory modality (touch or pain) is encoded by specialised sensory neurones (nociceptors), which are located in the DRG, a collection of neuronal cell bodies that includes the cell bodies of nociceptors. These nociceptors synapse onto associated primary afferent nerve fibres that are sensitive to that specific stimulus. Noxious stimuli activate DRG nociceptors; at threshold or near threshold level, to transmit impulses through distinct peripheral afferent neurones that project to the dorsal horn (spinal level) and to higher pain centres (e.g. amygdala and hypothalamus). Innocuous stimuli are encoded by low-threshold nociceptors and the signals are carried through primary afferents that project to the spinal cord and brainstem.

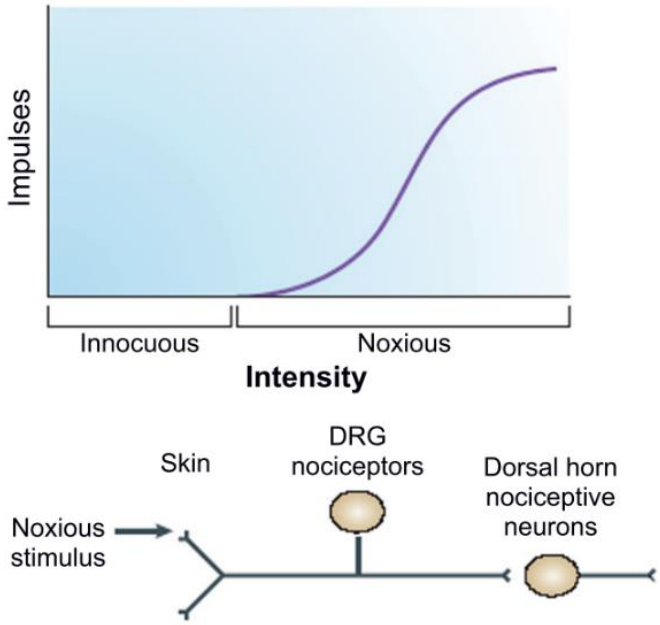

Figure 2.3.3 – Schematic illustration of the association between stimuli and primary afferent activity in Specificity Theory. DRG, dorsal root ganglion. From Moayedi and Davis (2013).

2.3.2.3. The Pattern Theory (Nafe 1934)

This theory states that there are no specialised neurones in the skin, and this is mainly the distinct aspect from the Specificity Theory. It supports the idea that different types of aesthetics stimulate a single nerve which will initiate an impulse formed by a spatiotemporal pattern that involves the firing of peripheral nerves encoding the stimulus type and intensity. The peripheral nerves are composed of rapidly conducting Aδ-fibres and slowly conducting C-fibres. Further, the theory also introduces the concept of central summation which involves the combination of peripheral signals from these fibres at the level of the spinal cord (dorsal horn neurones). These signals then ascend to higher centres of the brain for interpretation. Figure 2.3.4 presents characteristics of the Pattern Theory. Nevertheless, the Pattern Theory does not account for individual perceptual differences

and psychological factors and for this reason it is unable to provide a full explanation of the outcomes examined in this study; the relationships between pain and treatment-related anxiety. According to the theory, no specialised peripheral nociceptors exist in the skin; nociceptors respond to a dynamic range of stimulus intensities. Pain perception depends on the differences in the distribution and patterns (in time) of the impulses transmitted through a single nerve fibre (cell 1, cell 2 and cell 3) that has distinct responses to innocuous and noxious stimuli.

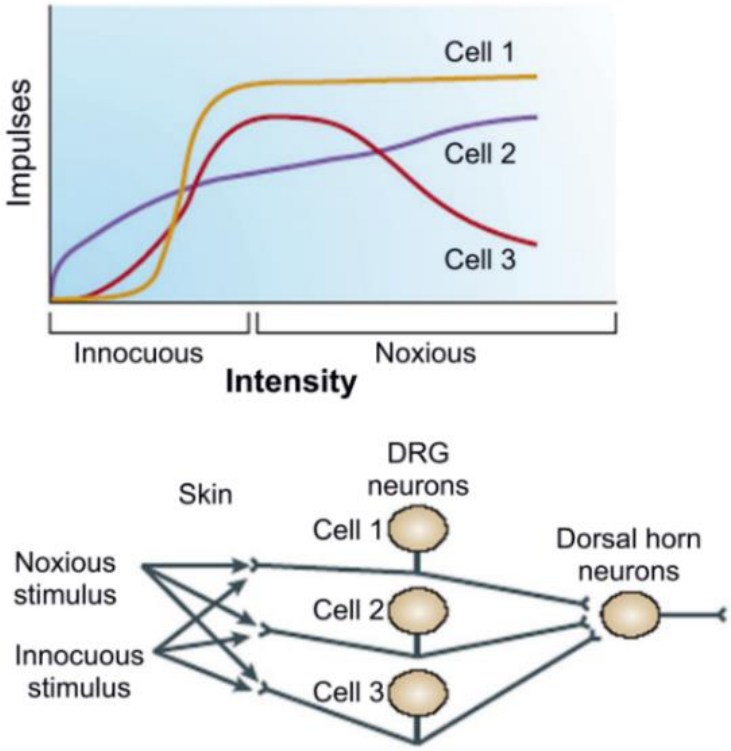

Figure 2.3.4 – Schematic illustration of the association between stimuli and primary afferent activity in Pattern Theory. It proposes that the modality and location of a stimulus are encoded by the pattern of activity across a population of fibres in somatic sense organs, including DRG neurones. The information is then transmitted to the dorsal horn of the spinal cord where central projection neurons decode this information by analysing the pattern and distribution of their discharges. This enables the brain to distinguish between different types and intensities of stimuli. DRG, dorsal root ganglion. From Moayedi and Davis (2013).

2.3.2.4. The Gate Control Theory (Melzack and Wall, 1965)

The Gate Control Theory incorporates neural components to explain the drawbacks between the Pattern and Specificity Theories of pain. In their seminal paper, Melzack and Wall (1965) developed an advanced theoretical model to first illustrate the complex anatomical structures of the nervous system organisation, and secondly, to describe the pain mechanisms elicited during pain perception. The modern conceptualisation of pain is principally based on the Gate Control Theory that accounts for psychological phenomena in the maintenance of pain symptoms (Melzack and Wall 1965; Melzack and Wall 1996). Distinct from the effects of tactile physical stimuli, top-down emotional and cognitive influences such as anxiety, fear or attention can influence the modulating mechanisms described in this theory, and thus play an indirect role in pain perception (e.g. top-down factors can promote survival and prepare the individual to make adaptive decision).

The theory implies that when injury occurs, pain is only experienced when the nociceptive input reaches a threshold that exceeds the inhibition elicited, leading to the opening of the gate that allows activation of central pathways responsible for passing information to higher pain centres of the brain, such as the amygdala and hypothalamus. One of the key aspects of the Gate Control Theory is modulating the activity of the system prior to evoking pain perception (Melzack 1990); used experimental and clinical evidence to develop a model to schematically represent their proposed Gate Control Theory of pain, as well as describe the anatomical structures, along with

their associated mechanisms. Their model illustrated three specific regions within the spinal cord: the substantia gelatinosa, the dorsal column, and first transmission cells. This theory supports the idea that the substantia gelatinosa within the spinal cord acts as a neurological “gate” to control the passage of pain signals to higher brain centres.

Figure 2.3.5 is a representation of the Gate Control Theory model. Cells within the substantia gelatinosa and transmission cells are synaptically innervated by primary afferent neurones that consist of both large myelinated Aβ-fibres and small unmyelinated C-fibres. Descending fibres that originate in supraspinal regions and project to the dorsal horn can also play a modulatory role in this gate mechanism. These fibres form part of the Gate Control pathway or loop system, though at the time, Melzack and Wall lacked clear interpretation of this concept, which involved ascending signals affecting descending modulatory pathways that connected to the gate control system. It is now well established that the hypothesised modulatory system involves descending small-fibre projections from higher cortical regions that contribute to this gating mechanism (Treede 2016). The substantia gelatinosa (SG) and first transmission (T) cells within the dorsal horn are synaptically innervated by primary afferent fibres; large myelinated Aβ-fibres and small unmyelinated C-fibres. SG acts as a neurological “gate’’ to control the passage of noxious stimuli from the spinal cord onto higher pain centres. The model demonstrates the inhibitory (-) effect of the SG on the terminals of the primary afferent neurones. The gating mechanism is dependent on the balance in the activity of Aβ-fibres and C-fibres. Activity

of the Aβ-fibres on the SG cells facilitates (+) the inhibitory effect of SG (closes the gate) at the terminals that synapse onto the T-cells. C-fibre activation leads to a disinhibitory effect (inhibition of the SG inhibitory effect), which facilitates the opening of the SG gate. Depolarisation of the T-cells (second-order wide dynamic range; WDR neurones) initiates pain signals and pain perception (Action System). A specialised system of Aβ-fibres (Central Control) activates certain cognitive processes that influence the modulating properties of the spinal gating mechanism via descending fibres.

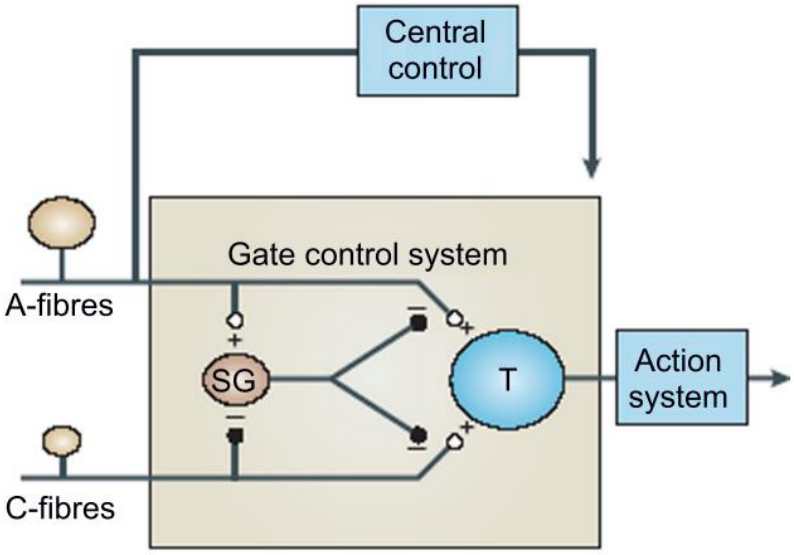

Figure 2.3.5 – Schematic illustration of the association between stimuli and primary afferent activity in Gate Control Theory. The substantia gelatinosa (SG) acts as a gate in the dorsal horn of the spinal cord that can either allow or prevent pain signals from ascending to the brain. The nociceptive pathway includes A-fibres and C-fibres, which have different effects on pain modulation. A-fibres can facilitate the inhibitory function (gate closes), while C-fibres can lead to a disinhibitory effect that facilitates the opening of the gate. T, transmission neurones. From Moayedi and Davis (2013).

The ventromedial prefrontal cortex, the hypothalamus, and the amygdala all synapse onto the periaqueductal grey area (PAG) in the brain; theorised to be part of the descending pathway (closes the gate) due the strong correlation with activation of this area placebo induced hypoalgesia (Wager

and Atlas 2015). Considering the psychological component, the Gate Control Theory has been widely used in the clinical setting and contributed to the development of pain management strategies (Gatchel 2004). For instance, negative states of mind, such as helplessness and anger can increase the intensity of the sensory input (opening the “gate”), whereas strategies focusing on coping and stress reduction stimulate the closure of the “gate”. Therefore, promoting positive and encouraging health behaviours may lessen pain perception and improve patient experience.

As outlined by Melzack and Wall (1996, p.165), the Gate Control Theory of pain accounted for several observations including the following: 1) the variable relationship between injury and pain; (2) non-noxious stimuli can sometimes produce pain; (3) the location of pain and tissue damage is sometimes different; (4) pain can persist long after tissue healing; (5) the nature of the pain and sometimes the location can change over time; (6) pain is a multi-dimensional experience; and (7) there is a lack of adequate pain treatments.

2.3.2.5. The Neuromatrix Theory of Pain (Melzack 2001)

The Neuromatrix Model of Pain is an extension to the Gate Control Theory (Melzack 1990; Melzack 1999). The idea was initially to build on a phenomenon of “phantom limb” pain, where individuals reported experiencing “real” pain in the absence of that limb Hence pain does not rely on a single pain centre, but instead on a neuronal network of multiple brain structures that can modulate pain perception in the absence of

sensory stimulation. This theory model proposes that pain is a multidimensional experience produced by multiple experiences (Gatchel et al. 2007; Moayedi and Davis 2013). A neurosignature is a specific characteristic pattern in the neuromatrix (Melzack 2001). The model (figure 2.3.6) reflects the processing of pain throughout the neuromatrix through inputs of cognitive-evaluative, sensory-discriminative and affective-motivational functions, and outputs that produce pain perception, action programs and stress-regulation programs.

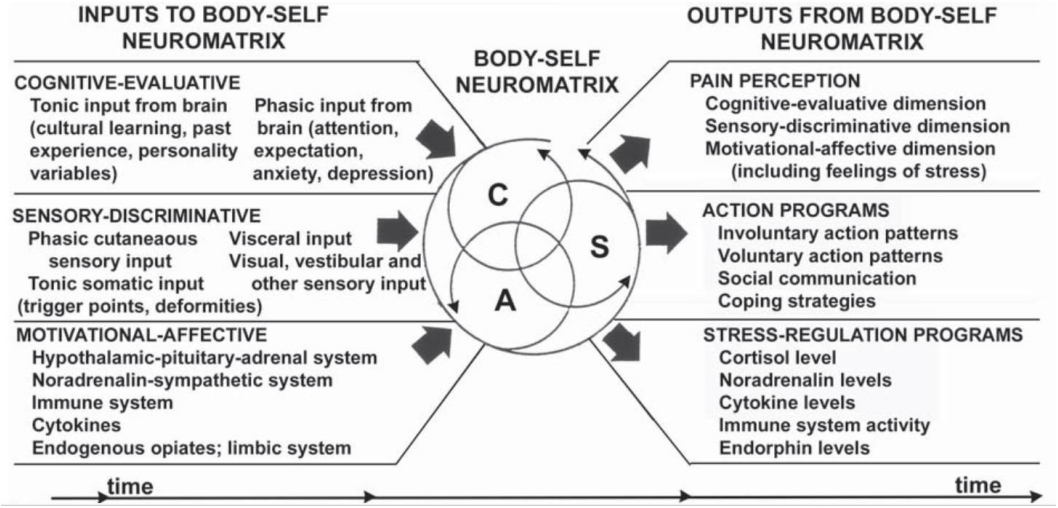

Figure 2.3.6 – The Neuromatrix Theory of Pain. From Melzack (2001).

An important component of the theory is that it recognises that pain perception is an outcome of the interaction of interdependent processes; perceptual, behavioural, and homeostatic systems in response to injury and chronic stress (Melzack, 2001). Recent advances in neuroimaging and pharmacological studies (Peyron et al. 2000; Peyron et al. 2002; Iannetti et al. 2005; Tracey 2008; Legrain et al. 2011; Davis and Moayedi 2013) have demonstrated the activity of multiple interconnections within the brain. Functional magnetic resonance imaging and positron emission tomography

imaging techniques have well illustrated the activation of the pain matrix in response to nociceptive input elicited in acute or chronic pain (Bassett and Bullmore 2009). Nociception exists without necessarily causing the feeling of pain but is still involved in the peripheral and central processing of stimuli to initiate brain responses (Hofbauer et al., 2004; Lee et al., 2009). Studies have also used electroencephalography and magnetoencephalography to illustrate the extensive activation of subcortical and cortical brain structures (Tracey 2008). In the context of pain, these studies have commonly identified structures within the matrix to be the primary and secondary somatosensory system, insular, anterior cingulate cortex, prefrontal cortex, periaqueductal gray, and the thalamus. Others have also investigated how changes in the affective, discriminative, or emotional dimensions, factors such as attention, distraction, anticipation, emotions, and hypnotism can affect these mechanisms associated with pain perception (Levine et al. 1982; Miron et al. 1989; Petrovic et al. 2000; Peyron et al. 2000; Legrain et al. 2002; Villemure and Bushnell 2002; Porro 2003; Ohara et al. 2004; Iannetti et al. 2005; Kupers et al. 2005). For example, a study has demonstrated that anxiety worsens pain through activation in the hippocampus (Ploghaus et al. 2001) and described how the use of accurate preparatory information during medical and dental procedures makes the hippocampal formation adapt to the worst possible outcome using behavioral responses to alleviate pain during anxiety.

2.3.2.6. The Biopsychosocial Model

As the Gate Control and Neuromatrix Theories strained to explore how the mind-body relationship relates to the pain experience, the biopsychosocial perspective shapes pain as a dynamically complex process. The biopsychosocial (BPS) (figure 2.3.7) model was first introduced in medicine by Engel in 1977 and thoroughly addressed in (Lehman et al. 2017). The theory was developed following the inability of the traditional biomedical model to explain the influence of social, psychological, and behavioural factors on an individual's belief and behaviour in relation to health and disease (Gatchel et al. 2007). For instance, chronic pain patients experience elevated levels of stress which can exacerbate the pain experience and affect body's homeostasis (Gatchel 2004). The BPS model presents pain as a psychophysiological behaviour pattern determined by the interaction among biological, psychological, and social factors, "Any model that focuses on only one of these dimensions will be incomplete and inadequate" (Gatchel et al. 2007; Roditi and Robinson 2011; Wippert and Wiebking 2018). The interaction of these factors modulates the interpretation of symptoms and hence has a strong influence on the variability of pain experience. For example, neural pathways associated with pain detection and those that link pain with negative emotion become relatively less active, while those related to pain control are activated (Ashar et al. 2017). The theoretical knowledge discussed in this section can be used to inform clinical practice on the diagnosis and utilising techniques to recognise and manage dimensions of pain, such as psychosocial factors; increased

anxiety and depression in chronic pain (Hulla et al. 2019) to help improve the patient experience.

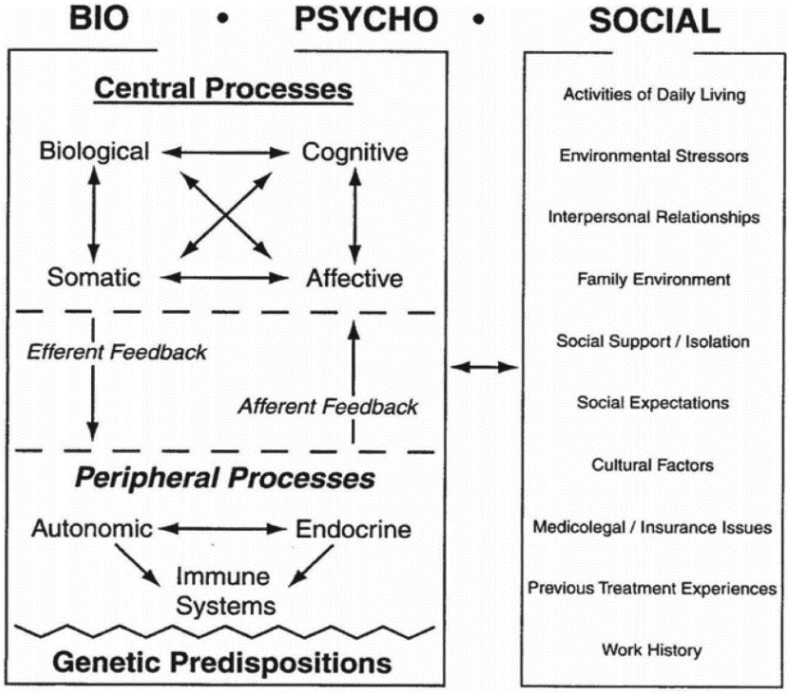

Figure 2.3.7 – A conceptual model of the biopsychosocial interactive processes involved in health and illness. First domain (BIO): biological factors; tissue damage, genetic factors, and endogenous pain inhibition. Second domain (PSYCHO): psychological factors; anxiety, depression, coping strategies, and social learning. Third domain (SOCIAL): social factors; ethnicity, family history, and cultural factors. From Gatchel (2004).

2.3.3. Theories of emotion

Prior to investigating and exploring the factors associated with pain in intravitreal injections, it is essential to understand the theoretical models of emotion to understand and define anxiety and arousal in the context of pain research. Thus, the following section is a summary of several common theories of emotion. The different emotional states can be described as combinations of physiologic arousal, psychological arousal and subjective experiences driven by cultural and societal factors. Different theories of

emotion have been developed to understand the inter-relationship of the various components of emotion, explaining how and why people experience emotion. These theories can be categorised into the peripheral (James-Lange theory), central (Cannon-Bard theory) and cognitive theory (Schachter-Singer two-factor theory; Lazarus' mediational cognitive theory) (figure 2.3.8).

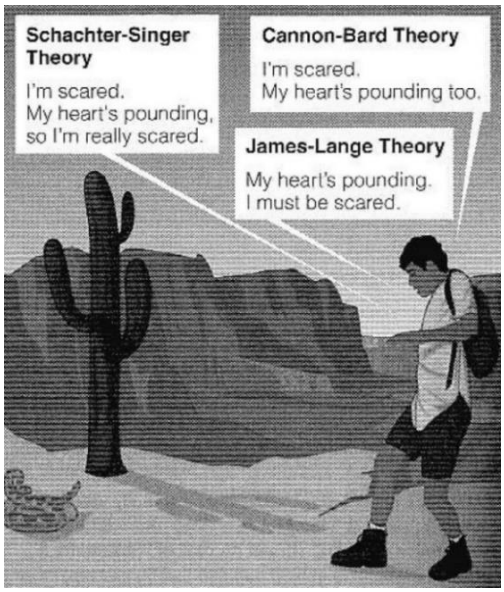

Figure 2.3.8 – Theories of emotion. The James-Lange theory proposes the emotion (fear) is the result of arousal (heart pounding). According to Cannon and Bard, the experience of the emotion alongside the experience of the arousal. Schachter and Singer's two-factor model proposes that arousal and cognition combine to create emotion. From Schachter and Singer (1962).

2.3.3.1. The James-Lange theory

According to the James-Lange Theory, people experience emotion following physiological arousal; physiological changes mediated by the autonomic nervous system (sympathetic activity), such as increased heart rate, respiration rate and sweating (James 1884; Lang 1994) (figure 2.3.9). The two theorists, William James and Carl Lange explained that subjective experiences are directly related to autonomic responses and proposed a

model to illustrate the emotional experiences: "*We feel sorry because we cry, angry because we strike, afraid because we tremble*" (James, 18, p. 190). This theory also posits that different physiological states define the different emotional experiences and that there is reduced emotional experience in people with spinal cord injury (SCI) due to a loss in peripheral bodily feedback. However, several studies established contradictory results that there is no emotional impairment in SCI. The James-Lange theory model has been strongly challenged by many theorists, including Walter Cannon.

Figure 2.3.9 – The James-Lange theory model.

2.3.3.2. The Cannon-Bard theory

Contrary to the James-Lange theory, the physiologist Walter Cannon challenged the James-Lange theory model, arguing that people can undergo physiological changes without experiencing emotion (figure 2.3.10). For example, when people feel cold or hungry, or during physical exercise the heart and breathing rates increase to support the working muscles with sufficient oxygen and nutrients to function efficiently. Neither of these cases indicate experiences of anxiety or fear. Furthermore, people can experience similar physiological changes, although these may not only indicate one emotion but several different emotions. This is because

emotions, such as fear and anger, share similar physiological effects on the ANS, including changes in the cardiovascular, respiratory and electrodermal measures (Kreibig 2010; Boucsein 2012a).

Later in the 1930s, the physiologist, Philip Bard, developed the Cannon-Bard theory which states that physiological arousal and emotional experience can occur simultaneously, yet can function independently (no causal link between them (Strack et al. 2019). The Cannon-Bard theory of emotion says that, "*the experience of an emotion is accompanied by physiological arousal*." This means the limbic system is activated in response to stimuli contributing to the experience of emotion while the ANS is receiving signals to initiate physiological arousal.

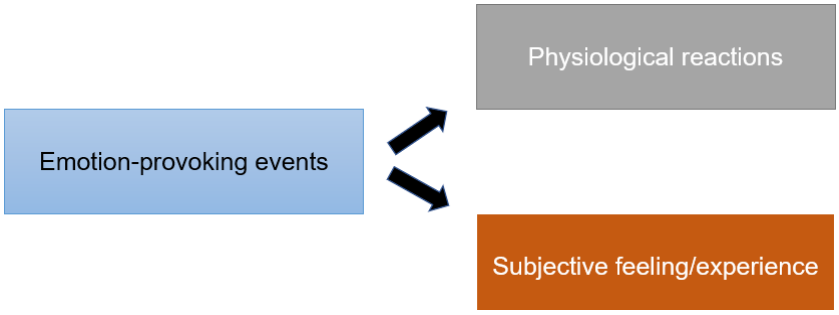

Figure 2.3.10 – The Cannon-Band theory model.

2.3.3.3. The Schachter-Singer two-factor theory

Later in the 1960s, Stanley Schachter and Jerome Singer described emotion as an experience composed of two factors: physiological arousal and the cognitive interpretation of that arousal; emotion = arousal + cognition (Schachter and Singer 1962) (figure 2.3.11). Their proposed model concurs well with both the James-Lange theory and the Cannon-Bard theory in that people infer emotions after they experience physiological

arousal and that the same pattern of physiological arousal can give rise to different emotions. However, they argued that the emotion experience is determined by the cognitive labelling of a physiological arousal response (Schachter and Singer 1962). For example, the ophthalmic patient, who has a fast heartbeat (tachycardia) and sweaty hands, attributes these physiological changes to the fact they are anxious about having an eye injection. Further, arousal feedback can have an intensifying effect on emotional states, and this arousal emotion relationship is partly controlled by causal attributions regarding the source of arousal (Schachter and Singer 1962).

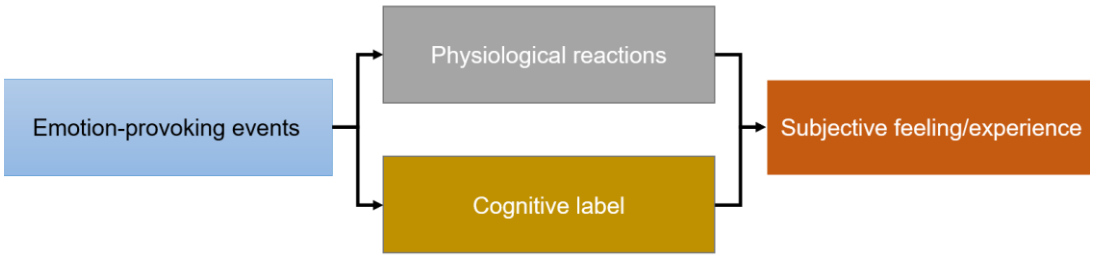

Figure 2.3.11 – The Schachter-Singer two-factor theory model.

2.4. Identifying a theoretical construct for pain in intravitreal injections

Individual variability in psychological appraisal of a given situation and prior subjective experiences could affect the degree to which individuals' respond emotionally to a stimulus since they are informed by individual experiences, backgrounds, and cultures. Studying the theories of pain and emotion presented a general understanding of the role of psychophysiological

factors in the presentation of pain which can inform clinical practice in improving assessment and treatment.

The selection of the biopsychosocial (BPS) model for this study is based on its alignment with the experimental methodology employed in this thesis. The BPS model, which has been widely adopted in the understanding of chronic pain (Gatchel et al. 2007), has also been shown to be relevant in the context of acute pain (Foster et al. 2018; MacDonald et al. 2021), such as that experienced in intravitreal injections. Patients undergoing repeated intravitreal injections for neovascular AMD may experience anxiety, stress, and fear associated with the procedure, in addition to the physical discomfort and pain caused by the injection. Addressing these factors through the BPS model highlights the importance of a holistic approach to pain management in ophthalmology practice. The use of patient-focused interviews in clinical practice has been proposed to assist clinicians identifying a patient-specific scientific BPS model (Smith et al. 2013). This can have important implications for identifying factors that affect patient's subjective experience. Patient-focused interview methods have been suggested to be used in practice, such that clinicians can identify a scientific BPS model specific to each patient with an agreed-upon, evidence-based patient-centred interviewing method can be beneficial as these are reproducible and can elicit relevant patient information.

Also, the ocular sensory system is made up of first and second order neurones, higher pain centres, and shares common pathways and

defensive mechanisms with the Gate Control Theory. These comprise of protective reflexes, such as blinking, tearing and pupil constriction, head withdrawal and rubbing of the eye. The Gate Control Theory of Pain acknowledges for individual perceptual differences and multidimensionality that could be strongly influenced by past experiences, anxiety and a host of cognitive and psychological factors which are commonly challenged in a clinical setting. Similarly, the Schachter-Singer two-factor theory model accounts for differences in psychological appraisal. For example, individuals who had previously experienced an incident causing a painful eye injury are more likely to experience a greater negative emotional response in a similar situation (Koechlin et al. 2018), such an effect may again be anticipated as more painful in similar injuries.

Pain has been described as a subjective, unpleasant experience and this also means that the individual tolerance level of pain varies accordingly. Assessing pain using subjective questionnaires are presumably affected by patients' predetermined levels of pain, which is why incorporating an objective measure of pain may provide a more accurate and precise measure of pain. EDA is an objective physiological measure; an index of sympathetic arousal measuring skin conductance responses (SCRs) to reflect peripheral signals associated with affective and emotional aspects (Boucsein et al. 2012; Boucsein 2012a). Using techniques to identify physiological data specific to pain may provide important objective information to better standardise pain assessment.

Chapter 3

Exploring the physiology, measurement, and clinical applications of electrodermal activity

The objective measurement of physiological arousal is a key aspect of research in various fields, including healthcare. Electrodermal activity (EDA) is one measure that can provide valuable insights into the physiological responses of patients undergoing intravitreal injections. EDA is a sensitive indicator of changes in sympathetic nervous system activity, which can be measured by the conductance of the skin, influenced by sweat gland activity. To fully comprehend EDA, it is essential to have knowledge of the anatomy and physiology of the skin and sweat glands. This chapter will provide an overview of the integumentary system, including the skin and its appendages, and its role in regulating various functions such as thermoregulation and water balance. Moreover, the chapter will discuss the methodological approaches used to measure EDA and its components, including skin conductance level (SCL) and skin conductance response (SCR), as well as their application in clinical research. An understanding of the measurement and analysis of EDA will help in elucidating the physiological arousal of patients undergoing intravitreal injections and in identifying ways to improve their experience.

3.1. Introduction

To the author's knowledge, the association between objective physiological characteristics and patient reported outcomes on pain or anxiety is understudied in ophthalmology research, particularly for intravitreal injections. A search of the literature revealed two studies which investigated the changes in systolic blood pressure during intravitreal injections (Berger et al. 2019; Mekala et al. 2021a). Berger et al. (2019) found a significant increase in systolic blood pressure during preparatory procedures prior to injection and identified age and anxiety levels (associated to discomfort after last injection) as predictors of high systolic blood pressure during injection. Mekala et al. (2021) demonstrated an increase in systolic blood pressure prior to and during injection in patients who have received less than 5 intravitreal injections. This group of patients has also reported experiencing higher levels of mild-to-moderate pain prior to and following injection. In this section, electrodermal activity (EDA) is introduced as an objective measure of activation of the sympathetic nervous system. EDA has been applied in a wide range of laboratory and clinical settings to investigate anxiety, pain (Court et al. 2008; Picard et al. 2016; Bari et al. 2018a; Bari et al. 2018b), as well as attention, memory, and decision making (Molins, Ayuso and Serrano, 2021; Sari et al. 2021).

Commonly known as galvanic skin response, EDA has been one of the most powerful non-invasive measures in psychophysiological research for over 130 years (Naveteur and Freixa Baque 1987; Bradley and Lang 2000; Bonnet and Naveteur 2004; Benedek and Kaernbach 2010; Boucsein

2012a; Picard et al. 2016). EDA can be characterised as an indirect measure for defining sympathetic changes of the autonomic nervous system (ANS) from the electrical properties of the skin (Boucsein 2012a). Several names and acronyms have been used in publications to describe electrodermal activity, such as galvanic skin conductance (GSC), skin conductance (SC), galvanic skin resistance (GSR, inverse of conductance), electrodermal response (EDR), or skin conductance response (SCR), which is an identifiable characteristic on the EDA waveform (Dawson et al. 2009). Identification of the electrical properties of the skin were first established in the 19th century by the German physiologist, DuBois-Reymond (Filkestein 2003) (figure 3.1.1). Electrodermal phenomena were then demonstrated in 1878, by Hermann and Luchsinger, examining the secretory activity provoked by stimulation of the sciatic nerve, with substantial work later identifying the relationship between skin conductance and local processes of the skin (Edelberg 1977). The following section aims to address the concepts of skin conductance with respect to the anatomy of skin and sweat glands, and the physiology of the electrodermal system.

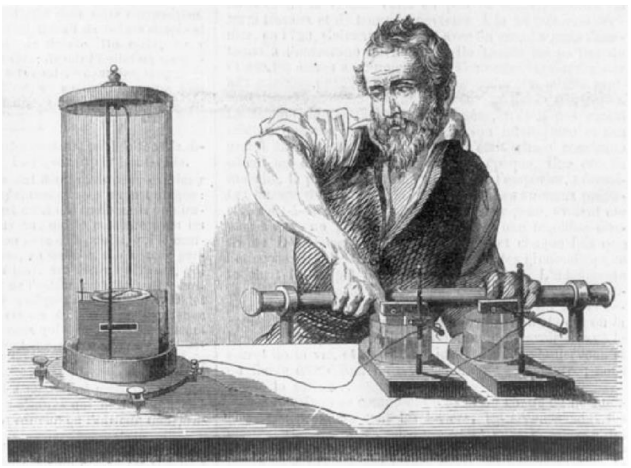

Figure 3.1.1 – Du Bois-Reymond's demonstrating current signalling processes. From Filkestein (2003).

3.2. Anatomy of skin and sweat glands

3.2.1. The Integumentary System

The integumentary system comprises the skin and its appendages, such as exocrine sweat glands, sebaceous glands, apocrine sweat glands, eccrine sweat glands, hair follicles, and nails, primarily distributed in the dermis and forming the cutaneous membrane. Cutaneous receptors, such as mechanoreceptors (pressure), nociceptors (pain), and thermoreceptors (temperature), found in the reticular layer and an extensive network of blood vessels branching through the dermis, are additional features of this system (Bartholomew, 2013). The skin acts as the primary interface between the body and the external environment, providing protection against physical, chemical, and biological damage (table 3.2.1) while regulating thermoregulation and water excess under the control of the autonomic nervous system (ANS) (Marieb, 2014b). Thus, the integumentary system is vital for maintaining homeostasis.

3.2.1.1. Structure of the skin

The skin is the largest organ of the body accounting for 15% of total adult weight (Kolarsick et al. 2011) and is composed of three anatomically different layers; the epidermis, the dermis, and the hypodermis (also known as the subcutaneous layer) (Kanitakis 2002). A schematic illustration of the human skin structure is presented in figure 3.2.1.

Functions	How accomplished
Protects deeper tissues from	
▪ Mechanical damage (pumps)	Physical barrier contains keratin, which toughens cells; fat cells to cushion blows; and both pressure and pain receptors, which alert the nervous system to possible damage.
▪ Chemical damage (acids and bases)	Has relatively impermeable keratinised cells; contains pain receptors, which alert the nervous system to possible damage.
▪ Microbe damage	Has an unbroken surface and “acid mantle” (skin secretions are acidic and thus inhibit microbes, such as bacteria). Phagocytes ingest foreign substances and pathogens preventing them from penetrating into deeper body tissues.
▪ Ultraviolet (UV) radiation (damaging effects of sunlight or tanning beds)	Melanin produced melanocytes offers protection from UV damage.
▪ Thermal (heat or cold) damage	Contains heat/cold/pain receptors.
▪ Desiccation (drying out)	Contains a water-resistant glycolipid and keratin.
Aids in body heat loss or heat retention (controlled by the nervous system)	Heat loss: By activating sweat glands and by allowing blood to flush into skin capillary beds so that heat can radiate from the skin surface. Heat retention: By not allowing blood to flush into skin capillary beds.
Aids in excretion of urea and uric acid	Contained in perspiration produced by sweat glands.
Synthesises vitamin D	Modified cholesterol molecules in skin converted to vitamin D in the presence of sunlight.

Table 3.2.1 – Functions of the Integumentary System. Details adapted from Marieb (2014b).

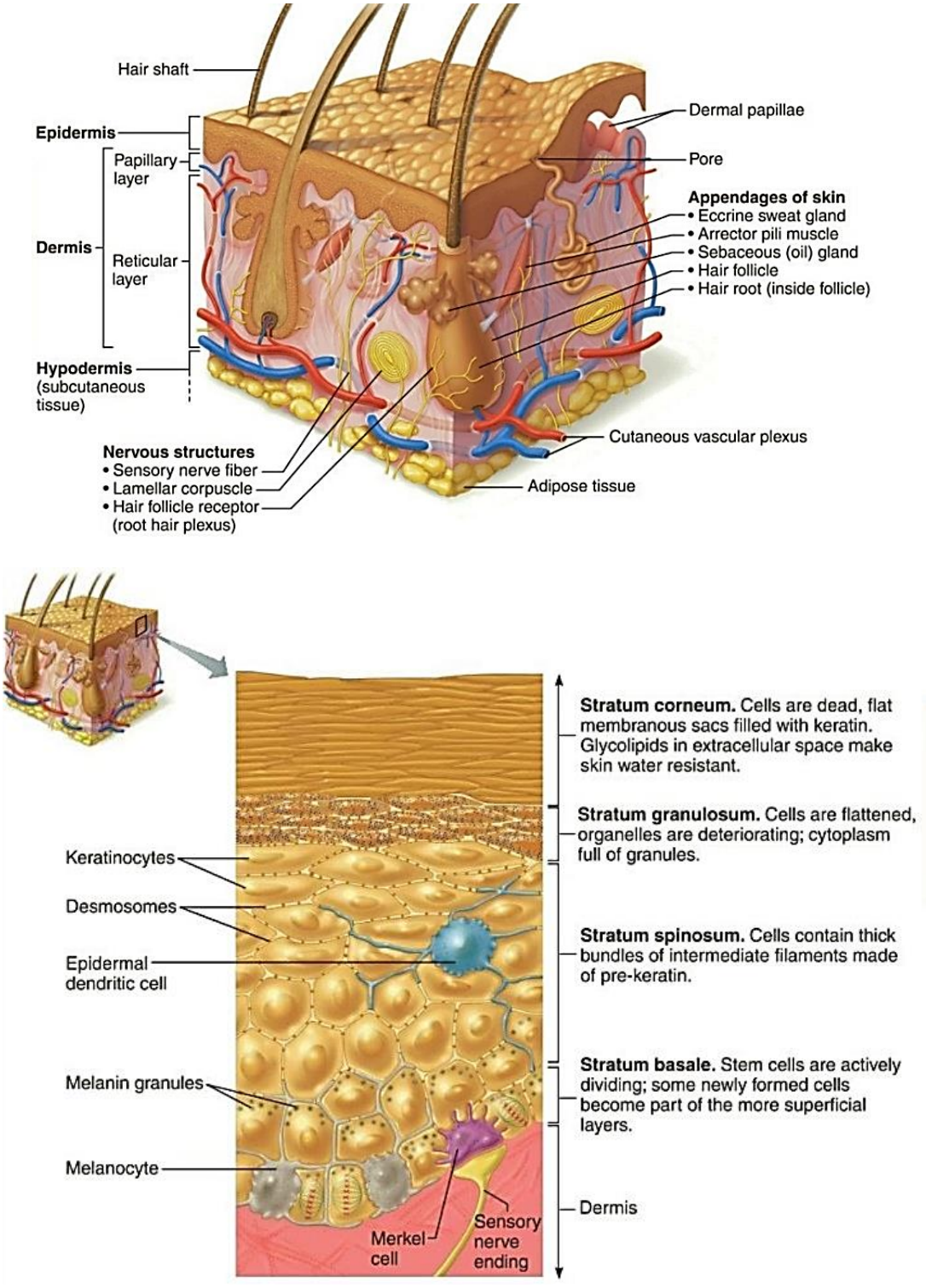

Figure 3.2.1 – Human skin structure schematic illustration. Upper panel: skin layers (epidermis, dermis, hypodermis). Lower panel: layers and cells of the epidermis. From Marieb (2014b).

The outermost layer, the epidermis, has five layers including the basal layer, prickle cell layer, granular layer, horny cell layer, and the translucent layer (figure 3.2.1) (Boucsein 2012a; Marieb 2014b). The basal layer, also known as the stratum germinativum, produces cells such as melanocytes, Langerhans cells, and keratinocytes. Keratinocytes, which make up 80% of the cells in the epidermis, synthesise keratin, a protein that protects against harmful environmental factors (Kolarsick et al. 2011). The keratinocytes eventually migrate to the stratum corneum, which is the layer of fully mature keratinocytes that continuously shed and replace by cells from deeper layers (Kolarsick et al. 2011; Bartholomew 2013; Marieb 2014b). As young adults age, the shedding of cells in the epidermis slows down, and the complete cell turnover is estimated to be 45-50 days in elderly adults. The stratum corneum is thicker at the palms and soles, which is ideal for electrodermal activity recording.

The dermis supports the epidermis and has two layers: the papillary layer and the reticular layer. The papillary layer, which is the upper layer, contains capillary loops that provide nutrients and oxygen to the epidermis. The reticular layer, on the other hand, is thicker and consists of dense connective tissue. The hypodermis, also known as the subcutaneous tissue, is deep in the dermis and composed of areolar and adipose tissues. Although not part of the integumentary system, it plays a crucial role in mobility across the skin surface, nutrient storage, and providing insulation (Martini et al. 2017). Overall, the skin’s various structures and functions work together to protect the body from environmental factors and regulate body temperature.

3.2.1.2. Sweat glands

Three types of sweat glands have been identified in the skin: apoeccrine, apocrine and eccrine sweat glands (Bartholomew 2013). However, histological findings on the existence of apoeccrine glands have been controversial (Bovell et al. 2007), therefore there will be no further reference to apoeccrine glands in this section. The eccrine and apocrine sweat glands (table and figure 3.2.2), the sebaceous glands, and hair follicles are initially formed in the epidermis and during the developmental stage they are grown down into the dermis layer. Apocrine sweat glands are located in the subcutaneous fat of the dermis and consist of secretory tubules connected to an excretory duct, which discharges sweat into the hair follicles. In contrast, eccrine sweat glands are found in the hypodermis and produce sweat that is secreted directly onto the skin surface through sweat pores. The human body has between 1.6 to 4 million eccrine sweat glands, with the highest densities on the palms, forehead, and soles (Freedman et al. 1994; Taylor and Machado-Moreira, 2013). Sweat gland density decreases with aging (Montagna and Parakkal, 1974; Catania et al. 1980). Eccrine sweat glands have a complex structure, consisting of the intraepidermal spiral duct, straight dermal portion, and coiled secretory duct (Kolarsick et al. 2011; Boucsein, 2012a).

Psychological (or emotional) sweating occurs in response to anxiety, fear, and pain-associated stimuli (Naveteur and Freixa Baque 1987; Asahina et al. 2003; Ellaway et al. 2010; Harker 2013). Considering the high sweat gland density in the palms and that measuring sweat gland responses are

more readily obtained from surfaces of high sweat gland density implies that emotional sweating is primarily produced by eccrine gland activity. Electrodermal activity is therefore associated to the changes occurring in sweat gland activity in response to psychological phenomena.

Sweat Gland Type	Structure of glands	Secretory contents	Sweat discharge
Apocrine	Coiled, tubular	Thick, cloudy, and odorous fluid	Hair follicles
Eccrine	Coiled, tubular	Watery fluid: Sensible perspiration (99% water, electrolytes (NaCl), organic nutrients, peptides, waste products, pH=4.0-6.8)	Skin surface

Table 3.2.2 – Characteristics of apocrine and eccrine sweat glands. Details from Boucsein (2012).

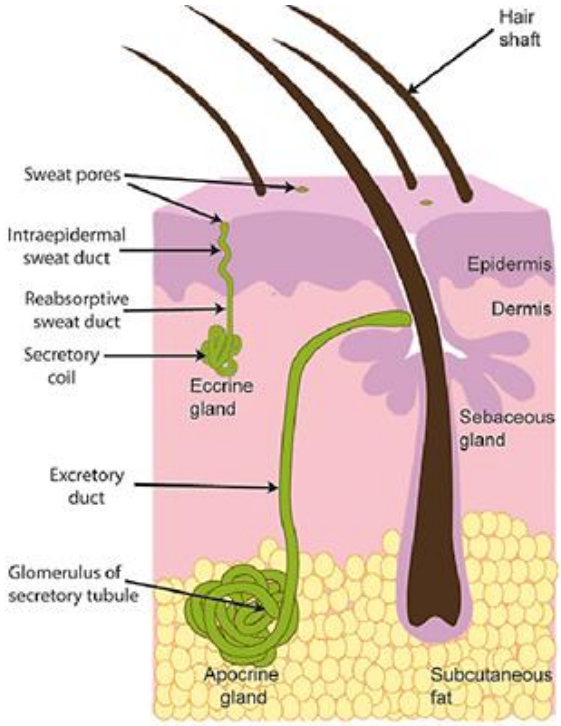

Figure 3.2.2 – Schematic illustration of apocrine and eccrine sweat glands. From Hu et al. (2018).

3.3. Electrodermal activity and skin conductance

The autonomic nervous system (ANS) maintains the physiological systems within our body in a state of equilibrium (balancing the sympathetic and parasympathetic activity), referred to as homeostasis. For example, autoregulatory processes may include an increase in blood pressure, heart rate, pupil dilation, vasoconstriction and sweating in response to events of high psychological arousal; the characteristic ‘fight or flight’ response sympathetic activity (Loggia et al. 2011; Posada-Quintero 2016). EDA has been reported to be regulated by the limbic system, motor system (the premotor cortex, basal ganglia), and reticular formation centres within the brainstem and thalamus (Asahina et al. 2003; Ellaway et al. 2010; Boucsein et al. 2012; Picard et al. 2016; Posada-Quintero and Chon 2020), nevertheless, the amygdala has been characterised as the main brain centre to be involved in psychological and social behaviour and autonomic function (Asahina et al. 2003; Masaoka and Homma 2003; Williams et al. 2006).

The central nervous system (CNS) controls sweat secretion via the autonomic nervous system through the release of neurotransmitters and peptides (Brodal 2003). Sweat glands possess M3-muscarinic receptors and adrenoceptors which are part of the sympathetic nervous system (Riedl et al. 1998; Storm 2008; Gill et al. 2017; Avila-Alvarez et al. 2020). Studies evaluated pharmacological effects of atropine, a muscarinic receptor antagonist in rats to demonstrate blockage of muscarinic cholinergic stimulation and the role of acetylcholine in sweating (Grant et al. 1991). Rats

injected with pilocarpine, a muscarinic receptor agonist have shown sweating function, whereas untreated rats lacked sweating responses. Acetylcholine is the primary neurotransmitter of the parasympathetic nervous system regulating smooth muscle contraction and vasodilation, while noradrenaline is involved in the postganglionic sympathetic transmission (Boucsein 2012a; Posada-Quintero 2016; Posada-Quintero and Chon 2020). In the past it was thought that both the sympathetic and parasympathetic nervous systems controlled the EDA, more recently it has been proven that sudomotor transmission is cholinergic which implies that sweating is regulated by the sympathetic release of acetylcholine (Christie and Venables 1973; Shields et al. 1987). A recent review of the literature on this topic, Posada-Quintero and Chon (2020) underline that most sweat glands control thermoregulation, although eccrine sweat glands found on the palmar and plantar surfaces respond primarily to psychological stimuli than to thermal stimulation. This is because of the regional variance in response thresholds at these regions (Christie and Venables 1973). For example, psychological stimuli elicit sweat secretion at a lower threshold (amplitude of smaller sudomotor bursts) compared to a more intense and sustained thermal stimulation necessary to reach a higher threshold (amplitude of larger sudomotor bursts) to activate sweat gland activity. Nishiyama et al. (2001) used video microscopy and microneurography to associate the spike density of sudomotor burst and sweat gland activity (figure 3.3.1), also demonstrating a high correlation between bursts of sympathetic nerve activity and the amplitude of rapid transient events in the EDA.

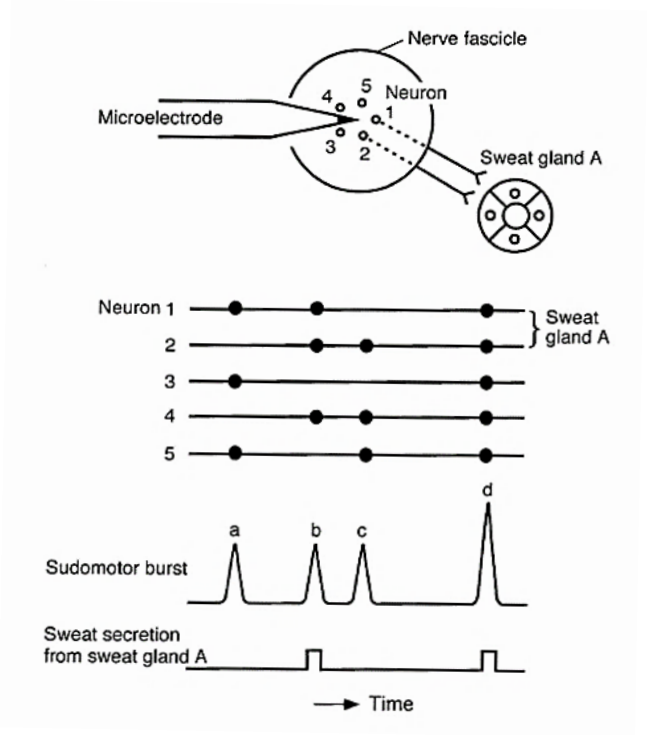

Figure 3.3.1 – Associating the amplitude of sudomotor burst to sweat gland activity. The spike density of sudomotor burst relates to the corresponding sweat secretion from sweat gland A (neuron 1 and neuron 2). From Nishiyama et al. (2001).

Electrodermal activity works by means of bioelectromagnetism; the discipline that examines the electric, electromagnetic, and magnetic phenomena which arise in biological tissues (Malmivuo and Plonsey 1995; Boucsein 2012b). For example, a single sudomotor fibre was estimated to innervate approximately 1.28 cm^2 of skin area and recording an average firing rate of about 0.62 Hz (Macefield and Wallin 1996). A single nerve burst (spike) characterises the firing rate of multiple fibres corresponding to an observable skin conductance response (SCR) (Christie and Venables 1973). The amplitude of the spike (measured in microsiemens, μS) was found to be linearly correlated to the number of recruited sweat glands (Freedman et al. 1994; Nishiyama et al. 2001) and therefore it can be inferred that the SCR amplitude can be interpreted as an index of

sympathetic activity. Established by Fowles (1986), the single effector model of sweat gland activity associates the levels of sympathetic arousal to the release of sweat through several ducts within the sweat glands at different levels. The sweat glands can be described as resistors in the model, hence the higher the sweat gland activity, the more the sweat that arises and larger number of sweat ducts are filled. Consequently, lowering the resistance in set of parallel resistors to identify observable EDA responses. The stratum corneum (outermost of the skin) is penetrated by the sweat glands from underlying cells, and as those ducts fill up, the layer becomes a relatively good conductor (Edelberg 1977; Fowles 1986; Malmivuo and Plonsey 1995). Sweat can be described as a weak electrolyte since it consists of about 0.3% sodium chloride (NaCl) salt solution (Boucsein 2012a). The hydrophilic nature of the corneum and the flow of sweat across the corkscrew duct pathway result in a rise in the skin conductance, also leading to a change in the skin potential (Christie and Venables 1973).

To summarise, exposure to acute stressful events initiates immediate physiological and behavioural responses (Naveteur et al. 2005; Rahma et al. 2022). Thus, psychological sweating results from the enhanced activation of sympathetic nervous system in response to these phenomena (Harker 2013; Lima et al. 2019). Research on electrodermal activity has been multidivergent, although in recent years there has been an increasing interest in pain research (Bonnet and Naveteur 2004; Ledowski et al. 2007; Aslanidis et al. 2018; Bari et al. 2018b; Aqajari et al. 2021).

3.4. Measurement and interpretation of electrodermal activity components

There are three different methods of measuring EDA (Malmivuo and Plonsey 1995): a) without the application of an external current, which is therefore called the endosomatic method, and two exosomatic methods which either, b) apply direct current (DC) via electrodes on the skin or c) apply alternating current (AC) instead. This thesis adapts an exosomatic, with direct current (0.5V) applied through two self-adhesive electrodes attached on the palmar surfaces of the skin of the non-dominant hand, is the standard laboratory technique used to assess the skin conductance (figure 3.4.1) (Fowles 1986; Boucsein et al. 2012). Studies have further supported the placement of electrodes on the distal phalanxes in preference to medial phalanxes, reporting significantly greater skin conductance amplitudes and skin conductance levels (Freedman et al. 1994; Boucsein 2012b). The EDA complex consists of two principal components; background slow tonic (skin conductance level: SCL) and rapid phasic activity SCR. SCRs can be characterised by stimulus-specific responses (ER-SCRs) or non-specific responses (NS-SCRs) (figure 3.4.2 and table 3.4.1). It is important to recognise that the tonic EDA (also known as the SCL) generates a constantly moving baseline. In other words, the background tonic SCL is constantly changing within an individual and can differ markedly between them (Dawson et al. 2009; Tseng et al. 2022). This has led some researchers to misinterpret the tonic EDA, taking the average of the entire waveform, inducing fluctuations from NS-SCRs or ER-SCRs.

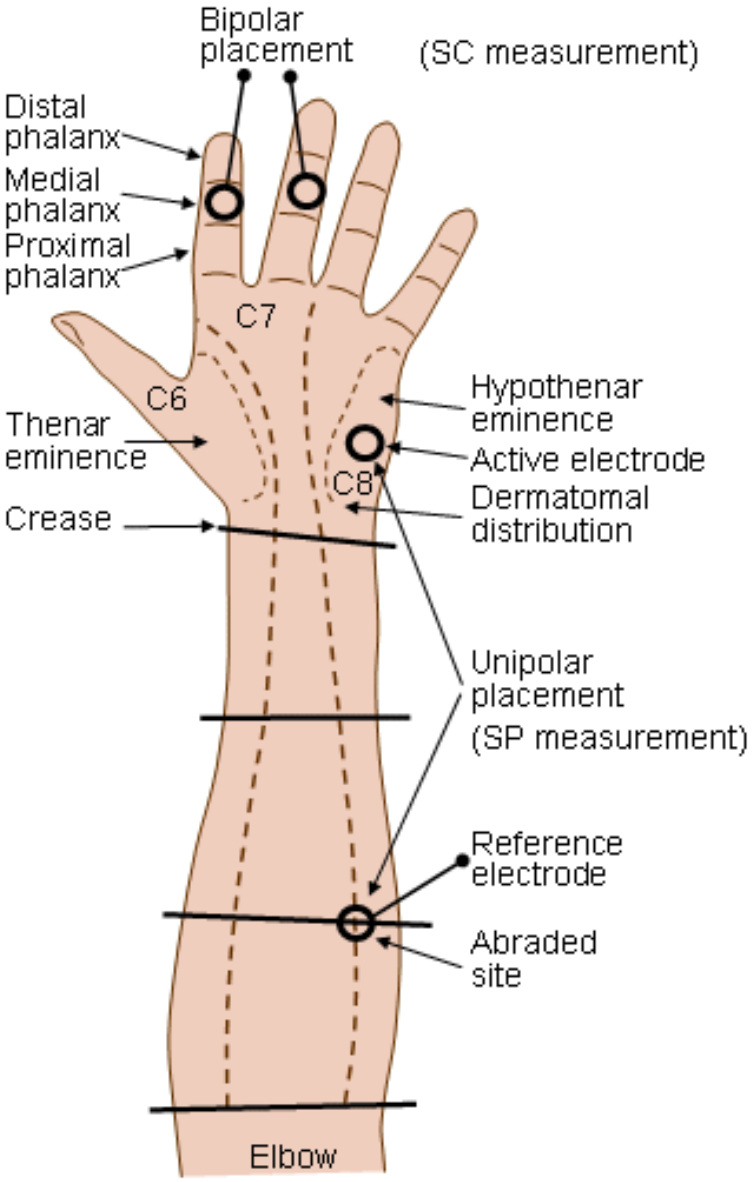

Figure 3.4.1 – Electrode sites on the palm for the measurement of skin conductance. Bipolar placement of electrodes on the index and middle finger of the non-dominant hand, either on the distal or medial phalanxes are the recommended electrode sites to record skin conductance. From Venables and Christie (1980).

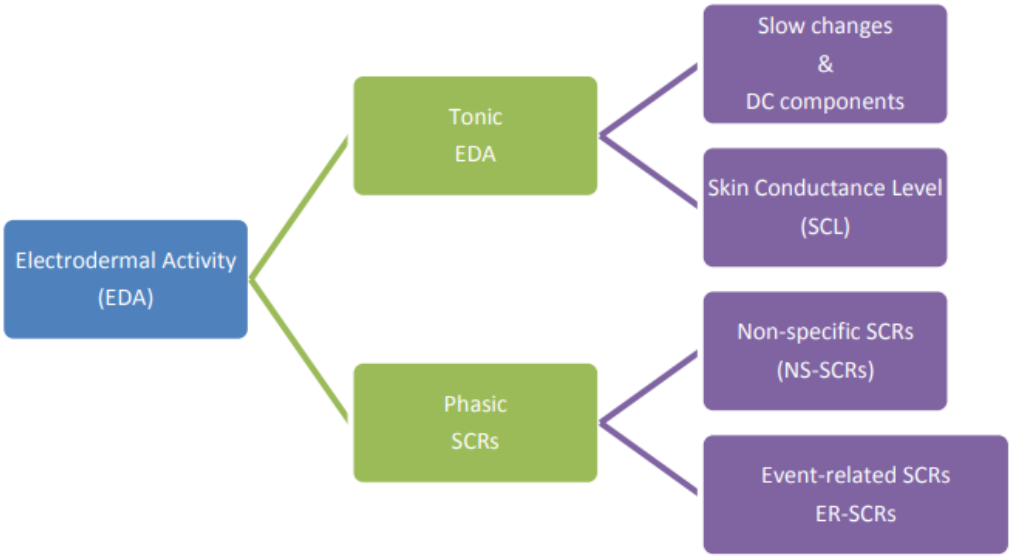

Figure 3.4.2 – Schematic representation to define EDA responses. EDA is reflected by tonic (background slow levels) and phasic (rapid phasic) components, which are subdivided into tonic SCL, and phasic NS-SCRs or ER-SCRs, respectively. The NS-SCRs occur in the absence of eliciting stimuli, whereas ER-SCRs arise in response to specific eliciting stimuli. Abbreviations: EDA, electrodermal activity; SCL, skin conductance level; NS-SCRs, non-specific skin conductance responses; ER-SCRs, event-related skin conductance responses. Details adapted from Boucsein et. al (2012).

Measure	Definition
Skin Conductance Level (SCL)	Tonic level of electrical conductivity of skin
Skin Conductance Response (SCR)	Phasic change in electrical conductivity of skin
Non-Specific SCR (NS-SCRs)	SCRs that occur in the absence of an identifiable eliciting stimuli
Frequency of NS-SCRs	Rate of NS-SCRs that occur in the absence of identifiable stimuli over time
Event-related SCR (ER-SCR)	SCRs that can be attributed to a specific eliciting stimuli

Table 3.4.1 – Definitions of electrodermal responses. Details from Boucsein et al. (2012).

Although great variability exists between individuals in different experimental situations, some very general estimations of ‘average’ strength values can be provided. Amplitudes of phasic SCRs can typically range from threshold to a maximum of 2-3 µS, whereas SCL can range between 1-40 µS, as originally mentioned by Venables and Christie (1980), however average values are usually between 2-16 microsiemens (µS). Frequency of NS-SCRs are quite variant, but estimations suggest an average of 1-3 per/min (baseline), and in high arousal these signals can increase to around 2025 per/min (Boucsein et. al. 2012). A typical representation of ER-SCR is shown in figure 3.4.3.

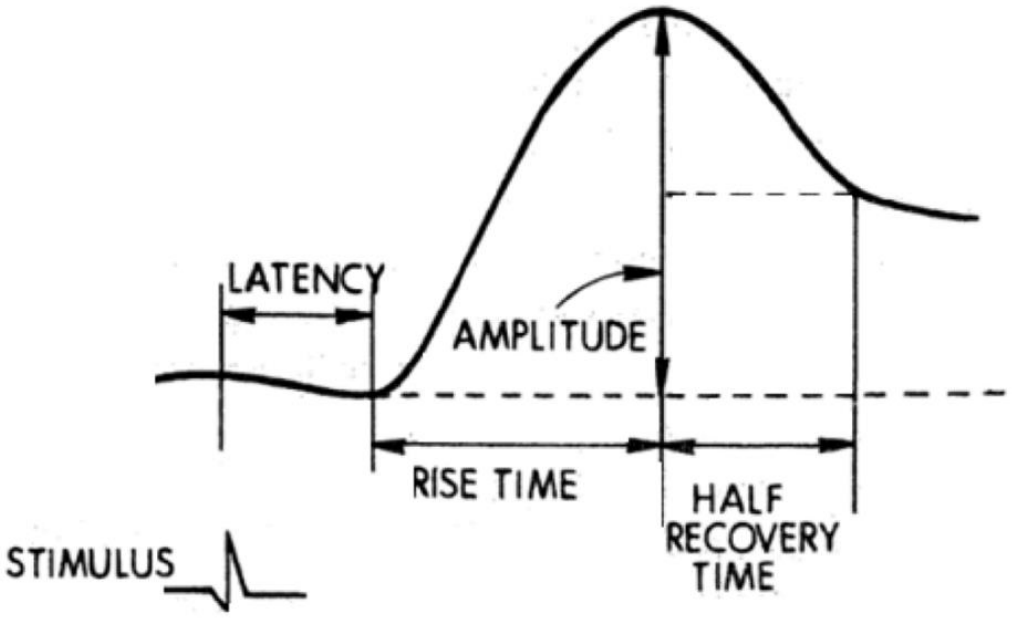

Figure 3.4.3 – A graphical representation of the components of an ER-SCR. Latency (usually 1-3 sec) is the period between stimulus onset and SCR response onset. Deflections in the signal that occur before this period are defined as NS-SCRs. The amplitude is the maximum peak elicited by the event-related response. From Dawson et al. (2001).

3.5. Applications in clinical research

EDA measurements have been previously used in the assessment of pain neonates (from birth to 1 month of age) (Sorm et al. 2013), infants (first year of life) (Dalal 2013; Macko 2013), children (from infancy until adolescence) (Sabourdin 2013), neonates (Sorm et al. 2013) and adults (Sugimine 2020; Aslanidis 2018; Ledowski 2006, 2007, 2009; Storm 2005, 2007), and also anxiety in optometric research (Margrain et al., 2003; Jones et al., 2013). The unpleasant sensation of acute pain in adults is an important contributor to the postoperative stress response (Ledowski et al. 2009). Therefore, to be able to evaluate the severity of pain is an important aspect of peri- and postoperative care to explore ways of relieving pain, managing anxiety, and improving wellbeing and treatment adherence.

In a pilot study of 25 patients, Ledowski et al. (2006) recorded the number of fluctuations within the mean skin conductance per second (NFSC) to study the influence of postoperative pain on skin conductance. NFSC is a parameter previously used by Storm et al. (2000) study to assess pain-related stress in pre-term infants, whereby researchers found significant differences in the NFSC before and after a heel stick procedure. Ledowski et al. (2006) evaluated the relationship between subjective measures of pain such as NRS, and the observed NFSC signals finding a significant correlation between the two techniques ($r=0.625$; $P<0.01$). The authors proposed a cut-off value of NFSC of 0.1 (reported 89% sensitivity and 67.7% specificity). The NFSC parameter has been shown to be superior to other physiological measures, such as heart rate and blood pressure in the

objective evaluation of pain. Ledowski et al. 2006 recorded blood pressure and heart rate during NRS rating and calculated a weak correlation between blood pressure and the values of NRS ($r=0.191$; $P<0.05$), but no correlation was observed between heart rate and NRS. Consistent with these findings, Aslanidis et al. (2018) have also identified EDA parameters to be a more valid measure in the recording of pain compared to other physiological approaches such as cardiovascular (heart rate, systolic arterial pressure, mean arterial pressure, diastolic arterial pressure), respiratory rate or bi-spectral index monitoring. The pilot study examined changes in skin conductance during painful stimulation in sedated adult intensive care unit patients and their findings revealed EDA to be a promising measure in the evaluation of pain in the intensive care unit.

The NFSC parameter was proposed as a potentially more reliable tool for monitoring pain compared to the mean SC parameter. However, subsequent studies have yielded inconsistent results regarding correlation with NRS scores (Ledowski et al. 200 6; Harisson et al. 2006). As the authors reported (Ledowski et al. 2006) this is mainly because SC was greatly affected by factors such as the specific placement of the electrodes, also showing high inter-individual variability in the recorded measures. However, in another study 3 years later, Ledowski et al. (2009) failed to confirm similar findings regarding NFSC and postoperative pain, reporting a moderate to low sensitivity (50%) and specificity (60%). In line with these conclusions, Czaplik et al. (2012) also reported inconsistencies, obtaining a poor sensitivity of 41.2% to detect NRS>2, with an altered threshold criterion

of NFSC to be >0.13, instead of 0.1 used by Ledowski et al. (2006, 2009). In this case, we can query the appropriateness of using NFSC parameter to assess pain alone, since another study supported the use of NFSC in emotional distress (Gunther et al. 2013).

More recent studies have strongly recommended the use of SCRs reporting adequate results in the evaluation of acute pain. Storm et al. (2018) measured SCRs on the first postoperative day. Authors of the study reported a higher sensitivity of SCR (93%) to indicate moderate or severe pain (NRS>3), and a lower specificity (33%), although a cut-off of SCR≥0.20 was used on all data. SCR reliably discriminated between pain and other stressors after the surgery, with Eriksson et al. 2008 also reporting a discrimination between pain and tactile stimuli in infants and neonates. Consistent with these observations, Macko et al. (2013) concluded that 'peaks per second' was the most valid parameter to evaluate SC in infants, since it was not influenced by any physiological artefacts, such as oxygen saturation or heart rate. Sugimine et al. (2020) demonstrated that normalised SCL could differentiate various thermal pain intensities (32°C, 46°C, 47°C, 48°C), whereas NFSC had not significantly reflected the temperature changes. Moreover, normalised SCL measures showed that they could better distinguish the common physical stimuli (heat, mechanical, cold) from other sympathetic stimuli, such as noisy auditory and visual pain-evoking stimuli compared to NFSC. The authors have also examined the correlation between skin conductance and NPS. The intra-individual analysis showed that normalised SCL correlated better with NPS than

NFSC; 70% of participants (16/23) illustrated a significant correlation ($P<0.001$) between normalised SCL and NPS compared to NFSC correlating with NPS in 35% of participants (8/23). Based on the findings of this study it can be concluded that normalised SCL may be used as an objective measure to quantitatively detect physical pain.

Controversies in the findings of EDA studies mainly exist due to the inter-individual variability in the study population. For example, Storm et al. (2005) reported a higher sensitivity (86%) of NFSC to measure pain, however their study population were anaesthetised patients which suggests that their findings were limited to physiological stress, compared to the Ledowski et al. (2009). Factors including the level of noise, medication and anxiety can highly affect the sympathetic tone of individuals, thus the frequency of fluctuations per se. It is important to account these variables, in addition to the EDA tonic baseline to make valid conclusions on the relationship between skin conductance and pain.

3.6. Conclusion

This chapter highlighted the importance of understanding EDA measurement and analysis for comprehending physiological responses. The following systematic literature review aims to identify factors contributing to pain and discomfort during intravitreal injections. The purpose of this review is to provide valuable insights into the various anaesthetic techniques, procedural differences, and pain assessment tools used during intravitreal treatment.

Chapter 4

Factors associated with pain and discomfort during intravitreal injections: a systematic literature review

Intravitreal injections have become a common treatment option for retinal diseases such as age-related macular degeneration and diabetic retinopathy. While these injections have demonstrated high efficacy in preventing vision loss and improving visual outcomes in many cases, they are frequently associated with significant pain and discomfort for patients. Various factors have been identified that may contribute to the pain experienced during the injection, including the type of anaesthetic used, the duration of the procedure, and the injection site. Additionally, elderly patients may be more susceptible to pain and discomfort during the injection process. This chapter aims to explore the pain experienced by patients during intravitreal injections, providing insight into the pain assessment tools used. The effectiveness of different anaesthetic techniques, needle size, and injection techniques in reducing pain during the procedure will be examined. The findings are presented in tables, with a qualitative synthesis of the data to provide a comprehensive analysis of the patient experience during intravitreal injections. The findings of this review were incorporated in the development of the research protocol (Appendix C), to identify most appropriate research methodologies to understand the individual patient experience associated with pain.

4.1. Introduction

Neovascular age-related macular degeneration (AMD) is a prevalent cause of severe vision loss affecting millions of individuals worldwide (Ferris et al. 2013). Currently, the standard of care for neovascular AMD treatment involves the use of intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents, resulting in a significant improvement in visual acuity and a reduction in the incidence of blindness (Solomon et al. 2014). Despite the widespread use of intravitreal injections, they are associated with significant discomfort and anxiety for patients (Boyle et al. 2018b). There is a critical gap in the understanding of the patient experience of intravitreal injections, and an urgent need to investigate the factors that contribute to pain experienced by patients during the procedure (Thetford et al. 2013).

Studies have investigated the efficacy and safety of different anaesthetic techniques used during intravitreal injections, including topical, subconjunctival, and peribulbar anaesthesia (Chen et al. 2019). Variables such as the type of anaesthesia used, the concentration of the anaesthetic, and the time between anaesthetic administration and anti-VEGF injection have all been found to impact patients' overall pain experience (Moisseiev et al. 2012).

Other factors that may influence pain during intravitreal injections include needle size, injection site, and injection complications (Haas et al. 2016). Researchers have compared larger diameter needles (26-27 gauge) to

smaller diameter needles (29-30 gauge), with smaller, sharper needles being preferred by patients due to lower pain scores (Rodrigues et al. 2011). Practitioners' experience and skill level can also impact patients' pain experience and overall satisfaction with the procedure (Boyle et al. 2018a).

Despite the significant discomfort associated with intravitreal injections, it is crucial to investigate the efficacy and safety of frequently applied procedures to enhance patient experience and adherence to treatment. As ongoing intravitreal injections are required, it is imperative to continue investigating the patient experience and factors that contribute to pain during the procedure. This systematic literature review aims to explore the current state of research on intravitreal injections and neovascular AMD, with a specific focus on the patient experience of pain during the procedure.

4.1.1. Aims and objectives

The aim of this literature review was to identify factors that contribute to pain experienced by patients receiving intravitreal injections for the treatment of neovascular AMD.

Primary objective was to investigate the effectiveness of various anaesthetic methods, injection sizes, and techniques in minimising pain experienced by patients during intravitreal injections, while also taking into account the role of nurse practitioners and the use of assisting devices for intravitreal injection delivery. This review also aimed to provide an overview of commonly used pain assessment tools for intravitreal injections.

4.2. Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and PRISMA 2015 protocols (PRISMA-P) guidelines (Moher et al. 2015).

4.2.1. Eligibility criteria

To be considered eligible for inclusion in this systematic review, studies were required to meet the predetermined criteria outlined in the Patient, Intervention, Comparator, and Outcome (PICO) framework, as detailed in table 4.2.1.

PICO Component	Inclusion Criteria	Exclusion Criteria
Population	Studies including patients diagnosed with neovascular AMD	Studies that encompass other retinal diseases and do not include individuals with AMD.
Intervention	Patients received at least one intravitreal injection of an anti-VEGF agent (ranibizumab, bevacizumab, aflibercept, pegaptanib).	Study that only studied corticosteroids, immunomodulatory agents, or platelet-derived growth factor (PDGF) inhibitors.
Comparison	Not applicable	Not applicable
Outcome	Visual analogue scale (VAS) for pain. Other studies that used different numerical scales to assess pain, but were still valid pain assessment tools, were also discussed.	Studies were excluded from selection if they did not include quantitative analysis of pain or did not have VAS pain score as the primary outcome measure.

Table 4.2.1 – Patient, Intervention, Comparator, and Outcome (PICO) framework.

There were no eligibility restrictions based on the type of anti-VEGF or treatment regimen used. The types of studies included were randomised and non-randomised controlled trials, prospective and retrospective cohort studies, pre- and post-intervention studies, case-control studies, and analytical cross-sectional studies. Studies conducted on patients receiving treatment at outpatient clinics, hospital-based services, or through primary care providers, with no restrictions on location or geographical area. Studies were excluded if interventions for neovascular AMD other than intravitreal anti-VEGF injections were evaluated. Moreover, conference abstracts were excluded owing to the inability to critically assess the findings.

4.2.2. Information sources

Studies were identified from systematic searches of electronic sources. The following databases were searched: PubMed/MEDLINE, Embase, PsychINFO, and Web of Science. Additionally, possible data were identified from conferences attended and hand searching. A targeted search of specific journals, including Social Science and Medicine, Journal of Applied Physiology, Qualitative Research, Qualitative Health Research, and Journal of Mixed Methods Research, was also conducted. The reference lists of all included papers and relevant systematic reviews were also screened to identify any additional studies.

4.2.3. Search strategy

Preliminary searches were conducted in Ovid MEDLINE to identify relevant published studies. The extracted keywords and index terms from these articles were then used to develop the final search strategy. To ensure a comprehensive search, this strategy was further adjusted as needed for other databases using Medical Subject Heading (MeSH) trees. The limits used in the search strategy were to include studies published from the year 2000 onwards and in the English language. The search strategy was last executed, and results were updated in December 2018. An example of a search strategy carried out on the PubMed database is presented in table 4.2.2.

4.2.4. Selection process

In the initial screening stage, one reviewer (CY) thoroughly searched the literature and screened titles and abstracts according to selection criteria. In the second phase, the same reviewer assessed full texts to eliminate studies meeting exclusion criteria. While the research team discussed the included papers, it should be noted that no other reviewers independently selected articles. Full-text articles were reviewed to confirm eligibility.

DATABASE	PubMed	Items found
Search	Strategy	
#1	“"neovascular AM”"[Title/Abstract] OR nAMD[Title/Abstract] OR nARMD[Title/Abstract] OR“"wet AM”"[Title/Abstract] OR“"exudative AM”"[Title/Abstract])	2834
#2	(pain[Title/Abstract] OR discomfort[Title/Abstract] OR92nject92t*[Title/Abstract] OR fear[Title/Abstract] OR stress[Title/Abstract] OR distress[Title/Abstract])	1386234
#3	(intravitreal[Title/Abstract] OR“"eye injectio”"[Title/Abstract] OR“"ocular injectio”"[Title/Abstract] OR anti-VEGF*[Title/Abstract] OR anti-angiogenic*[Title/Abstract] OR antiangiogenic*[Title/Abstract] OR ranibizumab[Title/Abstract] OR lucentis[Title/Abstract] OR pegaptanib[Title/Abstract] OR bevacizumab[Title/Abstract] OR aflibercept[Title/Abstract] OR“"anti-vascular endothelial growth factor”"[Title/Abstract])	45822
#4	#1 AND #2 AND #3	25
#5	“"pain scale”"[Title/Abstract] OR“"pain score”"[Title/Abstract] OR questionnaire*[Title/Abstract])	437257
#6	#1 AND #3 and #5	36
#7	(adherence[Title/Abstract] OR well-being[Title/Abstract]] OR satisfaction[Title/Abstract] OR experience[Title/Abstract] OR social[Title/Abstract] OR psychosocial[Title/Abstract] or psychological[Title/Abstract])	1243618
#8	#1 AND #2 AND #7	67
#9	#4 OR #6 OR #8	112
#10	#9 AND “2000/01/01”[pDat]:”2018/12/31”[pDat]	112

Table 4.2.2 – Example of search strategy of the PubMed database.

4.2.5. Data collection process

The researcher (CY) collected data from the selected studies. The following information was recorded: study background (authors, year, country, study design), population characteristics (sample size, mean/median age, gender, diagnosis), interventions (anaesthetic agent and technique applied, type of anti-VEGF used, needle size and techniques), pain assessment tools and grading, timescale of measurement, and outcomes (mean/median pain score reported during application of the anaesthetic and/or intravitreal injection, or at follow-up visits, and the statistical analysis reported of pain scores including mean/median, standard deviation/range, and p-value).

4.2.6. Study risk of bias assessment

The Cochrane Collaboratio''s risk of bias tool (Higgins et al. 2011) and the Risk Of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool (Sterne et al. 2016) were used to evaluate the methodology of the selected randomised controlled trial (RCT) and non-randomised controlled trial (NRCT) studies.

4.2.7. Data synthesis

A descriptive qualitative synthesis was conducted to gain a comprehensive understanding of the anaesthetic methods used in intravitreal treatment, to explore differences in needle size and injection techniques, pain assessment tools, and the patient experience associated with pain during or following intravitreal injection. Some of the studies reported unclear data

in terms of the clinical and demographic characteristics of the samples within the intervention groups. This lack of clarity in the data made it challenging to compare the results of the studies and synthesise them into a meaningful analysis. As a result, conducting a meta-analysis was not feasible due to the heterogeneity in the methodological approaches and outcomes of the studies.

4.3. Results

4.3.1. Study selection

The initial search (phase 1) identified 446 distinct citations across various electronic databases. An additional 30 relevant articles were found through a search conducted on Google Scholar and by scanning literature reviews. Subsequently, 19 studies were selected for phase 2 after a comprehensive evaluation of their abstracts. Of the 19 studies initially selected, two were excluded as anti-VEGF agents were not administered for intravitreal injections, while 3 others were excluded for various reasons, including one conference abstract, one study not evaluating pain during injection, and one study that did not implement any pain assessment tool. Ultimately, 14 studies were retained for the final selection. A flowchart depicting the process of literature search and selection is presented in figure 4.3.1.

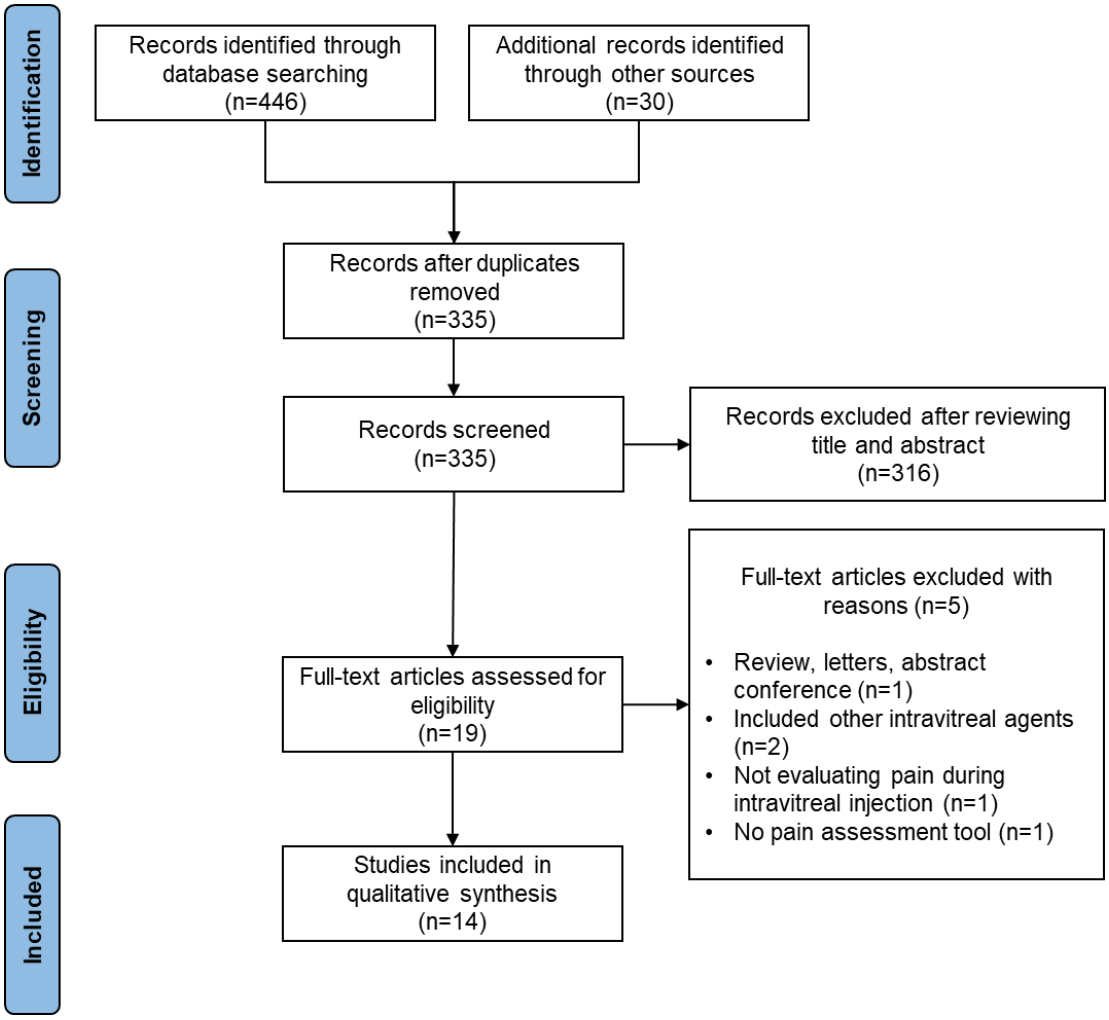

Figure 4.3.1 – PRISMA Flow Chart. Illustration of literature search and selection criteria.

4.3.2. Study characteristics

A summary of the study characteristics is shown in figure 4.3.2. The 14 studies included in the review were conducted in Brazil (Andrade and Carvalho, 2015; Cintra et al. 2009; Rodrigues et al. 2011; Van Asten et al. 2015), Canada (Yau et al. 2011), Israel (Moisseiev et al. 2014), Spain (Sanabria et al. 2013), Austria (Haas et al. 2016), Turkey (Güler et al. 2015), UK (Ratnarajan et al. 2013) and USA (Blaha et al. 2011; Cohen et al. 2014; Davis et al. 2012; Rifkin & Schaal, 2012) from 2009 to 2016. Studies reported the use of ranibizumab, bevacizumab, aflibercept, and triamcinolone with a total sample size of 1672 participants. These studies evaluated the effectiveness of different anaesthetic agents and techniques in intravitreal injections, using various pain assessment scales such as the visual analogue scale (VAS), numerical rating scale (NRS), Wong-Baker faces scale, or other validated pain rating scales.

References	Participants			Intervention		Outcome measures		
	Study design	Sample size, age, gender	Diagnosis	Groups by AE/Needle techniques	Agent injected	Tools & grading	Timescale	Pain Rating of Injection
Andrade & Carvalho 2015 (Brazil)	RCT, prospective	N=92 45 females, 47 men, Mean age=66.4 ± 11.6 yrs, (43-91)	AMD DME BRVO CRVO	G1: proparacaine; G2: proparacaine + SC injection of 2% lidocaine; G3: 2% lidocaine gel	BVZ	VAS (0-10)	Immediately post-IVI 10 min, 1 hr, 6 hrs, and 24 hrs post-IVI	G1: 3.2 ± 1.7 G2: 1.0 ± 1.0 G3: 1.0 ± 1.1 p<0.05
Blaha 2011 (USA)	RCT, prospective	N=24 15 females, 9 males, Mean age=90 yrs, (7-93)	AMD	G1:0.5% topical proparacaine; G2:0.5% topical tetracaine; G3: topical proparacaine + 4% lidocaine pledget; G4:topical proparacaine + SC injection of 2% lidocaine	RNZ, BVZ	Validated pain scale (0-10)	Immediately post-IVI	G1: 2.8 (0-8) G2: 3.1 (0-10) G3: 3.0 (0-9) G4: 2.3 (0-6) p=0.28
Cintra 2009 (Brazil)	RCT, cross-sectional	N=60 26 females, 34 males, Mean age=59.3 yrs (46-70)	AMD DME	G1: Topical 0.5% proxymetacaine chlorhydrate; G2: SC 2% xylocaine; G3: Peribulbar 2% xylocaine	BVZ	100-mm VAS	15 mins post-IVI	G1: 5 (0–22) G2: 3 (0–25) G3: 0 (0–11) p=0.002*
Cohen 2014 (USA)	RCT, prospective	N=57 37 females, 20 men Mean age= 82 ± 11 yrs	AMD DME CRVO	G1: Sham lidocaine injection; G2: Topical Lidocaine Gel; G3: Topical Lidocaine Gel + SC Lidocaine	RNZ, BVZ, ABP	Wong-Baker FACES	Immediately post-IVI 4 hrs post-IVI 24 hrs post-IVI	G1:1.93,G3:0.75; p<0.001

Figure 4.3.2 – Summary of study characteristics. RCT: randomised controlled trial, NRS: non-randomised controlled trial, AMD: age-related macular degeneration, DME: diabetic macular edema, BRVO: branch retinal vein occlusion, DVH: Diabetic vitreous haemorrhage, CRVO: central retinal vein occlusion, CME: cystoid macular edema, PDR: proliferative diabetic retinopathy, CRS: central serous chorioretinopathy, BVZ: bevacizumab, RNZ: ranibizumab, ABP: aflibercept, TAC: Triamcinolone, VAS: visual analogue scale, SC: subconjunctival, IVI: intravitreal injection.

Davis 2012 (USA)	RCT, prospective	N=120 G1: 80.18 ± 8.62 yrs (50–94); 24 females, 16 males G2: 78.85 ± 9.16 yrs (55–92); 25 females, 15 males G3: 75.60 ± 12.08 yrs (36–90); 18 females, 22 males	AMD	G1:0.5% topical proparacaine ;G2: topical proparacaine + 4% lidocaine pledget; G3: 3.5% lidocaine gel	BVZ, RNZ, TAC	NRS (0-10)	10 secs post-IVI	G1:1.78 ± 1.44,G2: 1.75 ± 1.46,G3:1.48 ± 1.58; p=0.38
Güler 2014 (Turkey)	NRS, comparative	N=70 36 females,34 males Age=60.43 ± 12.13 (range 42 to 83)	AMD DME DVH CRVO BRVO CRS	G1: RNZ (0.5 mg/0.05 mL) injected with a 30-gauge needle; G2: BVZ (1.25 mg/0.05 mL) dispensed into 27-G needle	RNZ, BVZ	VAS (0-10)	Immediately post-IVI	G1: 1.06 ± 0.91 (0-3), G2: 1.94 ± 1.55 (0-7); p=0.005
Haas 2016 (Austria)	RCT	N=280 G1: 56 females, 48 males, Mean age= 72.26 ± 11.27 G2:54 females. 50 males, Mean age= 74.69 ± 11.03	AMD	G1: 27-G needle G2: 30-G needle	BVZ	VAS (0-10) Wong-Baker FACES	Immediately post-IVI	G1:2.05 ± 1.35, G2:1.85 ± 1.55; p>0.18; G1:1.97 ± 1.52, G2:1.88 ± 1.59;(p>0.59)

Figure 4.3.2 – Summary of study characteristics (continued). RCT: randomised controlled trial, NRS: non-randomised controlled trial, AMD: age-related macular degeneration, DME: diabetic macular edema, BRVO: branch retinal vein occlusion, DVH: Diabetic vitreous haemorrhage, CRVO: central retinal vein occlusion, CME: cystoid macular edema, PDR: proliferative diabetic retinopathy, CRS: central serous chorioretinopathy, BVZ: bevacizumab, RNZ: ranibizumab, ABP: aflibercept, TAC: Triamcinolone, VAS: visual analogue scale, SC: subconjunctival, IVI: intravitreal injection.

References	**Study design**	**Sample size, age, gender**	**Diagnosis**	**Groups by AE/Needle techniques**	**Agent injected**	**Tools & grading**	**Timescale**	**Pain Rating of Injection**
Moisseiev 2012 (Israel)	NRS, prospective,	N=218 120 females, 98 males Mean age= 75.1 ± 10.1 yrs (42–96)	AMD DME PDR CME	G1: superonasal G2: inferonasal G3: superotemporal G4: inferotemporal	BVZ	100-mm VAS	Immediately post-IVI	Overall mean=17.4 ± 17.1 (0-84) G1:18.52,G2:12.18 G3:19.98 G4:18.90 p=0.073 Nasal vs Temporal: p=0.111; Superior vs Inferior: p=0.065
Ratnarajan 2013 (UK)	NRS	N=200	AMD DME RVO	G1: conventional technique, G2: conjunctival mould	-	VAS (0-10)	Immediately post-IVI	G1: 2.58 (0–10), G2: 1.38 (0–7); p<0.01
Rifkin and Schaal (USA)	RCT, prospective	N=60 34 females, 26 males	AMD DME CRVO	G1: 0.5% TetraVisc (tetracaine HCl 0.5% gel); G2: proparacaine HCL drops; G3: tetracaine HCL drops	BVZ, RNZ, TAC	VAS (0-10)	15 mins post-IVI	G1: 3.39 ± 2.26 G2: 3.17 ± 2.18 G3: 3.05 ± 2.01 p<0.01*
Rodrigues 2011 (Brazil)	RCT, prospective	N=205 121 females, 84 males Mean age=70 ± 12.7 yrs (26 to 92)	AMD DME PDR CME	G1: 26-G needle; G2: 27-G needle; G3: 29-G needle; G4: 30-G needle	BVZ	NRS (0-10)	Immediately post-IVI	Patients injected with 26- or 27-G needles experienced more pain compared to 29- and 30-G needles (p<0.001)

Figure 4.3.2 – Summary of study characteristics (continued). RCT: randomised controlled trial, NRS: non-randomised controlled trial, AMD: age-related macular degeneration, DME: diabetic macular edema, BRVO: branch retinal vein occlusion, DVH: Diabetic vitreous haemorrhage, CRVO: central retinal vein occlusion, CME: cystoid macular edema, PDR: proliferative diabetic retinopathy, CRS: central serous chorioretinopathy, BVZ: bevacizumab, RNZ: ranibizumab, ABP: aflibercept, TAC: Triamcinolone, VAS: visual analogue scale, SC: subconjunctival, IVI: intravitreal injection.

References	**Study design**	**Sample size, age, gender**	**Diagnosis**	**Groups by AE/Needle techniques**	**Agent injected**	**Tools & grading**	**Timescale**	**Pain Rating of Injection**
Sanabria 2013 (Spain)	RCT, prospective	N=156	AMD CNV DME RVO	GA: tetracaine + naphazoline, GB: lidocaine, G1: tobramycin, G2: tobramycin + diclofenac	BVZ, RNZ	NRS (0-10)	Immediately post-IVI 30 mins post-IVI 24 hrs post-IVI	2.77 ± 2.12 whole group 2.85 ± 2.23 GA Vs 2.67 ± 2.00 GB; p=0.73 1.84 ± 2.45 G2 Vs 1.75 ± 1.83 G1; p=0.46
Van Asten 2015 (Brazil)	RCT, crossover	N=36 13 females, 23 males Mean age= G1: 71.3 ± 14.5, G2:6.3 ± 11.3	AMD CNV DME RVO	G1: 30-G needle G2: 33-G needle	BVZ	NRS (0-10)	Immediately post-IVI	G1: 3.1 ± 2.6 G2: 2.8 ± 2.3 p=0.758
Yau 2011 (Canada)	RCT, prospective	N=93 56 females,37 males Mean Age= G1:83.6 ± 6.0 G2:79.5 ± 9.9 G3:82.1 ± 7.7	AMD	G1:0.5% tetracaine HCL drops + 4% lidocaine pledget for 10 G2:0.5% tetracaine HCL G3:4% cocaine + epinephrine 1/100.000 drops	RNZ	100 mm-VAS Wong-Baker FACES	Immediately post-IVI 15 mins post-IVI	G1: 20 ± 18 G2: 23 ± 24 G3: 22 ± 1.8 p=0.549 G1: 18 ± 21 G2: 19 ± 20 G3: 20 ± 15 p>0.05

Figure 4.3.2 – Summary of study characteristics (continued). RCT: randomised controlled trial, NRS: non-randomised controlled trial, AMD: age-related macular degeneration, DME: diabetic macular edema, BRVO: branch retinal vein occlusion, DVH: Diabetic vitreous haemorrhage, CRVO: central retinal vein occlusion, CME: cystoid macular edema, PDR: proliferative diabetic retinopathy, CRS: central serous chorioretinopathy, BVZ: bevacizumab, RNZ: ranibizumab, ABP: aflibercept, TAC: Triamcinolone, VAS: visual analogue scale, SC: subconjunctival, IVI: intravitreal injection.

Anaesthetic methods

This systematic literature review aimed to evaluate different anaesthetic techniques used for IVI pain management. The included studies reported the following anaesthetic techniques: proparacaine eye drops (Blaha et al. 2011; Davis et al. 2012; Rifkin and Schaal, 2012a; Andrade and Carvalho, 2015) (4 studies), tetracaine (Blaha et al. 2011; Yau et al. 2011; Rifkin and Schaal, 2012a; Blaha et al. 2011; Sanabria et al. 2013) (5 studies), proxymetacaine (Cintra et al. 2009) (1 study), 4% lidocaine pledgets or 4% cocaine (plus adrenaline 1/100 000) (Blaha et al. 2011; Davis et al. 2012; Yau et al. 2011) (3 studies), subconjunctival injection of 2% lidocaine (Blaha et al. 2011; Cohen et al. 2014; Andrade and Carvalho, 2015) (3 studies), and 2% lidocaine gel (Davis et al. 2012; Cohen et al. 2014; Andrade and Carvalho, 2015) (3 studies).

Among these techniques, subconjunctival 2% lidocaine injection was found to be the most effective in preventing pain during IVI compared to the other techniques, as reported in several studies (Cintra et al. 2009; Blaha et al. 2011; Rifkin and Schaal, 2012a; Cohen et al. 2014; Andrade and Carvalho, 2015). However, only three studies reached statistical significance (Rifkin and Schaal, 2012a; Cohen et al. 2014; Andrade and Carvalho, 2015).

Andrade and Carvalho (2015) conducted a randomized controlled trial to evaluate the effectiveness of subconjunctival lidocaine or lidocaine gel in reducing pain associated with intravitreal injection of bevacizumab. The study included 92 participants with age-related macular degeneration,

diabetic macular edema, branch retinal vein occlusion, or central retinal vein occlusion. Participants were randomly assigned to one of three groups, including group 1 receiving proparacaine, group 2 receiving proparacaine and subconjunctival injection of 2% lidocaine, and group 3 receiving 2% lidocaine gel. The primary outcome measure was the pain level measured using a visual analogue scale immediately after the injection and at 10 minutes, 1 hour, 6 hours, and 24 hours post-injection. The study found that the addition of subconjunctival lidocaine or lidocaine gel significantly reduced pain compared to proparacaine alone. Moreover, the study demonstrated a clinically significant pain score difference of at least 12 mm on a 100 mm-VAS scale. The authors also reported that subconjunctival lidocaine was more effective in preventing eye movements and pain (37.9% patients reported excellent experiences) compared to proparacaine drops (19.4% poor and 61.3% fair) and 2% lidocaine gel (67.7% good experiences). Lidocaine gel and subconjunctival lidocaine had statistically similar VAS pain scores, however, lidocaine gel was reported to be associated with a higher risk of post-procedure infections, such as keratitis (19.4%).

Needle size and techniques

The included studies in the review compared various needle diameters for injecting ranibizumab or bevacizumab in terms of reported pain score during intravitreal injections. The main focus was on comparing the 27-gauge and 30-gauge needles, with three studies included in the review (Rodrigues et al. 2011; Güler et al. 2014; Haas et al. 2016). Additionally, two studies

compared smaller (31- or 33-gauge) and larger (26- and 29-gauge) needle diameters, which were also included in the review (Rodrigues et al. 2011; Van Asten et al. 2015). Among the four selected studies, only Güler et al. (2014) included both ranibizumab and bevacizumab agents, while the rest of the studies exclusively focused on patients receiving intravitreal injections of bevacizumab.

Rodrigues et al. (2011) examined the correlation between injection techniques for intravitreal injections, pain intensity, and vitreal reflux. The study enrolled 205 participants who underwent bevacizumab injections, with 62.4% of the cohort receiving IVT injections via partially or totally tunnelled incisions. The authors report a notable proportion of eyes (44.4%) demonstrating some degree of vitreal reflux, while the remaining 55.6% exhibited no reflux. No significant association between age and either pain intensity or vitreal reflux was found. The severity of pain did not differ significantly across all four types of incisions ($p>0.05$). However, patients who were injected with 26- or 27-G needles reported significantly higher levels of pain compared to those who received 29- and 30-G needles ($p<0.001$).

Van Asten et al. (2015) examined pain scores associated with bevacizumab injections using 30-G and 33-G needles. The study revealed that the mean pain score for the 30-G needle was 3.1 ± 2.6, while the mean pain score for the 33-G needle was 2.8 ± 2.3. However, the difference was not statistically significant ($p=0.758$), indicating that the use of a 33-G needle may not offer

a clinically significant reduction in pain during intravitreal bevacizumab injection compared to the traditional 30-G needle.

Investigators have explored not only the comparison of pain scores between different needle gauges, but also the examination of the ideal angle and site of needle incision. One study, Moisseiev et al. (2012) evaluated the impact of injection site on pain scores following bevacizumab intravitreal injection. The study showed an overall mean pain score of 17.4 ± 17.1 (range 0-84) on the 100-mm VAS. The differences in pain scores among the four injection sites (superonasal, inferonasal, superotemporal, and inferotemporal) were not statistically significant ($p=0.073$), as well as between nasal versus temporal injection sites ($p=0.111$) and superior versus inferior injection sites ($p=0.065$).

Assisting injection device

Only one study has investigated the comparison of pain levels between the conventional free-hand technique and the use of an assisting device (Ratnarajan et al. 2013). The study involved the evaluation of pain experiences of 200 patients who received intravitreal injections using the 10-cm VAS to assess their pain levels. Additionally, the patients were asked to report their preference for the device used for the injection. The results showed that the conjunctival mould technique using the assisting device resulted in significantly lower pain levels (mean score of 1.38, range 0-7) compared to the free-hand technique (mean score of 2.58, range 0-10) ($p<0.01$). Additionally, 50% of patients who had previously undergone the

free-hand technique found the conjunctival mould technique less painful, while 43% reported no difference in pain. These findings suggest that the use of the conjunctival mould technique with the assisting device may be the preferred method for delivering intravitreal injections, as it results in less pain for patients.

4.3.3. Risk of bias within studies

Figure 4.3.3 provides a visual representation of the risk of bias summary for RCT studies. Out of the RCT studies analysed, only four (35%) were determined to have a low risk of bias based on their random sequence generation and allocation concealment methods. Most studies (55%) were deemed unclear due to insufficient information regarding their randomisation process. One study was listed as having a high risk of bias due to the use of an inappropriate randomisation method. Figure 4.3.4 also includes the risk of bias summary for non-randomised controlled trials. More comprehensive information about the studies, including their assessments and details collected, can be found in the Appendix A and B.

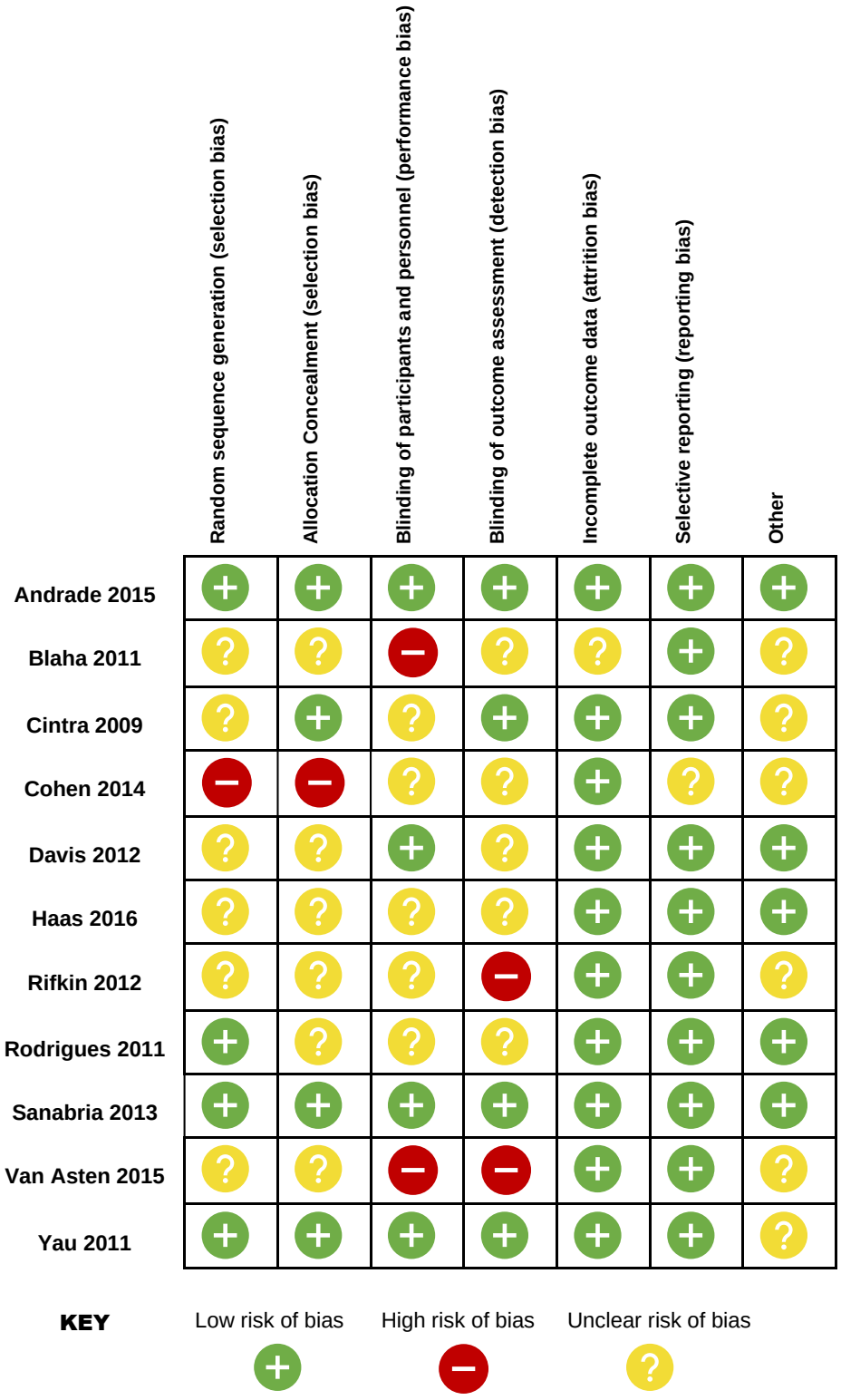

Figure 4.3.3 – Risk of bias summary (randomised controlled trials) using the Cochrane Collaboration's tool.

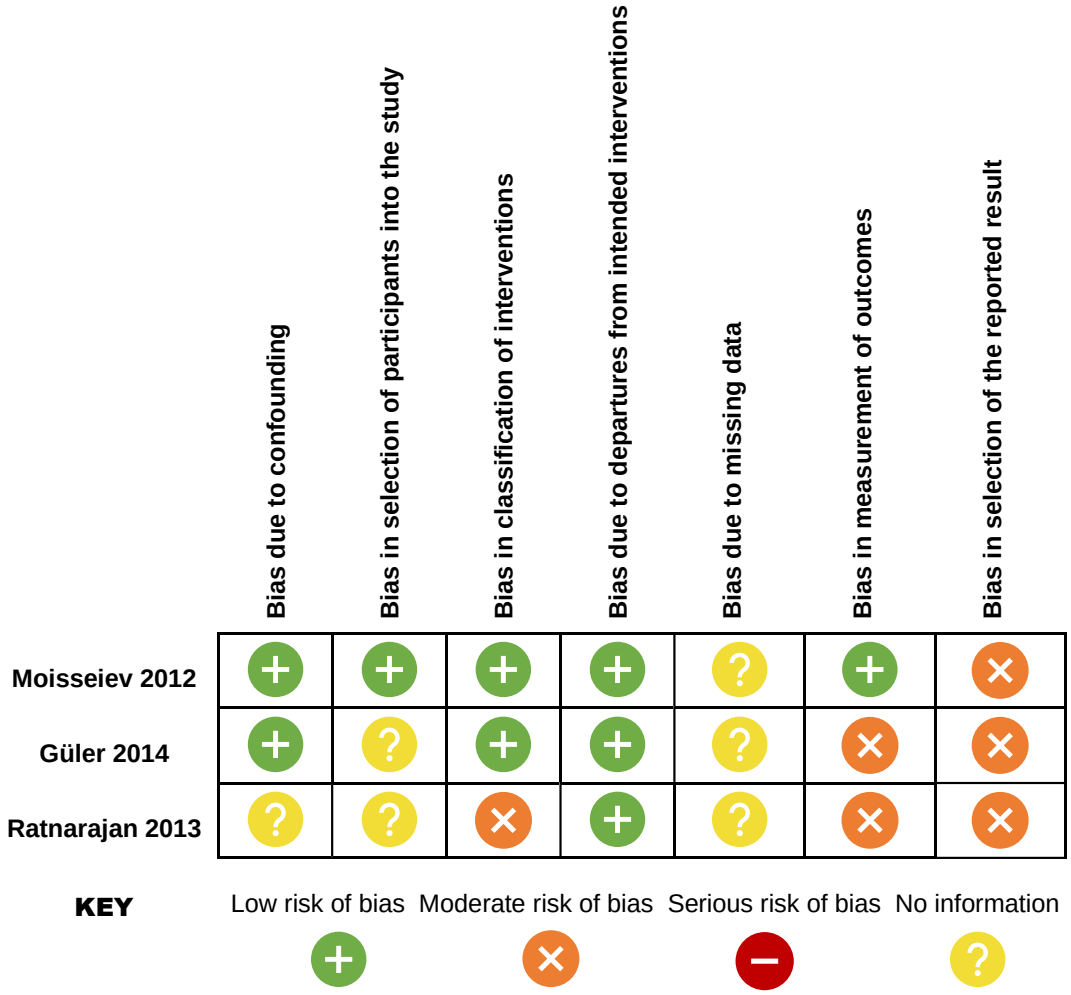

Figure 4.3.4 – Risk of bias summary (non-randomised controlled trials) using the ROBINS-I tool.

4.4. Discussion

This systematic literature review found that mild pain was commonly reported in studies involving intravitreal injections of anti-VEGFs regardless of the anaesthetic technique, needle size, incision, and location employed. While most studies presented non-significant results, the analysis suggests that mild pain is a consistent outcome of IVI procedures. To ensure the validity of the findings, the studies included in the review were evaluated for potential biases. The assessment of bias revealed a moderate level of evidence supporting the conclusions.

No method of anaesthesia prior to intravitreal injection has been shown to eliminate pain completely when measured subjectively. Subconjunctival anaesthesia was the preferred during the intravitreal injection, however, the invasiveness of the technique was associated with significantly higher pain scores. Patients receiving subconjunctival or peribulbar anaesthesia were also at higher risk to develop subconjunctival haemorrhage (Cintra et al. 2009; Blaha et al. 2011; Andrade and Carvalho 2015). Drug delivery by these routes is more invasive, and these arising complications hinder the effectiveness of the treatment. The prolonged anaesthesia that lidocaine gel provides (Cohen et al. 2014; Andrade and Carvalho 2015), in addition to its efficacy on pain relief and reduced risk of haemorrhage or chemosis, makes lidocaine gel a powerful local anaesthetic in the management of pain in intravitreal treatment. The viscosity of the gel is believed to lengthen contact time with the ocular surface and provide sustained topical anaesthesia at low concentrations (Page and Fraunfelder 2009). However, Cohen et al.

(2014) established contradictory findings, reporting patient satisfaction towards subconjunctival anaesthesia. The authors explained the lack of significance of previous studies, because of reduced time for anaesthetic to take effect, since subconjunctival 2% lidocaine has a higher onset time.

There was only one study (Andrade and Carvalho, 2015) that reported a noteworthy clinical improvement in pain scores, with a minimum change of 12 mm on a 100 mm scale. Bird and Dickson (2001) demonstrated that the clinical significance of changes in pain varies depending on the patient's initial VAS score. Patients reporting higher levels of pain in the upper third of the VAS (≥67 mm) require a greater absolute difference in VAS scores to achieve clinically significant pain relief compared to patients with lower baseline pain in the lower third of the VAS (<34 mm). In contrast to previous findings (Todd et al. 1996; Kelly 2001), where a change of 13 mm was considered clinically significant (mean difference between current and preceding scores when the participant reporting "a little worse" or "a little better" pain), Bird and Dickson (2001) observed that this level of improvement was only consistent with the benchmark value in patients with a VAS score below 34 mm. Patients with scores between 34 and 66 mm and those with scores ≥67 mm reported a clinically significant change in pain with mean differences of 17±10 mm and 28±21 mm, respectively. Their data prompted a re-evaluation of the concept of minimally clinically significant and emphasised the importance of considering the baseline intensity of pain when evaluating treatment effectiveness in clinical practice

Whilst the most widely used technique in clinical practices is topical anaesthesia (Mittra et al. 2000) mainly because of its ease of application, the preferences of individuals differed in the Cohen et al. (2014) study. To the author's knowledge, this was the first study to consider individual's choice of anaesthesia (patients selected anaesthetic preference in initial visit and given the opportunity to change their preference in follow-ups) at the conclusion of the study, and at 4- and 24-hour follow-up telephone calls. Patients were given the choice to change their preference of anaesthesia up to three times, following their initial study visit. Most patients in the study (n=50, 88%) preferred subconjunctival anaesthesia over topical anaesthesia. This finding was controversial to previous research and illustrates the need to introduce different methodological research approach, including qualitative research to gain an in-depth understanding of these phenomena.

Setting patients' anaesthetic preference as the primary endpoint has led to different conclusions on the anaesthetic technique that works best in intravitreal treatment. Further investigations are still necessary to replicate these outcomes. Nevertheless, topical anaesthesia offers the advantage of allowing non-medical healthcare professionals to conduct intravitreal injections. This is an important development in healthcare, as it allows for greater access to this procedure and potentially reduces wait times for patients. Additionally, it can help alleviate the burden on medical professionals by delegating certain tasks to non-medical staff. Austeng et al. (2016) were the first to conduct a randomised controlled trial of nurse-

delivered intravitreal injections of anti-VEGF agents to examine safety, cost and patient satisfaction within a 12-month period. A mixed methods approach was used to examine patients' satisfaction; included a modified patient satisfaction questionnaire (5-point grading scale), and an open-ended question given to patients not reporting maximum satisfaction, as to enhance their understanding on patients' discomfort and wellbeing during their visit. Moreover, asking patients in their last visit to guess whether they have been injected by a doctor or a nurse would add insight on patients' perception of the practitioner, relating it with their experience during the treatment. Dacosta et al. (2014) have previously raised anxiety issues reported by patients when receiving an injection from a nurse. Masking the patients to the practitioner administering the injection, as implemented by Austeng et al. (2016), it is a critical step as to eliminate the risk of confounding due to behavioural aspects, such as fear or anxiety.

Patient satisfaction is important in the context of intravitreal injections, encompassing factors such as medical care quality, communication effectiveness, accessibility, convenience, and overall experience (Shayan et al. 2021). Patients' satisfaction can be influenced by pre-injection counselling effectiveness, healthcare provider competence and professionalism, and comfort and support during and after the intravitreal injection. Including patient satisfaction as a secondary objective alongside pain outcomes can improve healthcare provider'' understanding of the patient experience, allowing for identification of areas for improvement and adjustments to care practices to ensure effective pain management and a

positive patient experience. Nurse-led ranibizumab treatment was well accepted by patients and staff members (Varma et al. 2013; Dacosta et al. 2014; Michelotti et al. 2014). In Michelotti et al. (2014), researchers audited 3,355 injections carried out by trained nurses over a period of 17 months, with only 12 minor events reported (0.36% subconjunctival haemorrhage and corneal abrasion), and no cases of serious adverse events. The reported complications were consistent with DaCosta et al. (2014) also finding no serious complications other than 5.7% (N=228) cases of subconjunctival haemorrhage.

Variation in the needle sizes used for anti-VEGF injections compared between larger diameter needles (26- 27-gauge) and smaller diameter needles (29- and 30 gauge), with the 30-gauge to be the recommended size for the delivery of ranibizumab, bevacizumab and aflibercept (The Royal College of Ophthalmologists 2018). In the studies examined, there was no clear consensus for using either the 27- or 30-gauge needle to deliver intravitreal injections. Rodrigues et al. (2011) and Guler et al. (2014) reported that the use of 27-gauge needle was statistically more painful than 30-gauge needle, calculating significance of $p<0.001$, and $p=0.005$, respectively. The fact that 30-gauge needles require less force to penetrate the sclera (Pulido et al. 2007) supports the surgeons' choice of using 30-gauge. However, the authors of Guler et al. (2014) study included patients that were injected with either ranibizumab (30-gauge) or bevacizumab (29-gauge). Not limiting their study in the application of a single anti-VEGF could act as a confounding factor in the interpretation of their findings. According

to Tailor et al. (2011) the insertion of the needle was reported to be the most unpleasant step, followed by the placement and removal of drape, and insertion of speculum. These data were consistent with Thetford et al. (2013) study, exploring further the experiences of the individuals. Moisseiev et al. (2012) have evaluated the correlation between pain associated with intravitreal bevacizumab injection and the location of the injection, finding no significant difference between the quadrants. The authors explained that less pain was associated with the injection site that is more convenient for the ophthalmologist to perform.

The Precivia, previously known as InVitria is a disposable device that simplifies and standardises the intravitreal injection (FCI 2021). The unique design of the device allows the angle (fixed 28°) and entry site (fixed 5.60 mm depth; 3.5 mm distance from the limbus) of needle insertion to be kept standard, making the procedure faster and more predictable. The researchers in the Ratnarajan et al. (2013) study demonstrated a statistically significant reduction in pain using the InVitria device over the conventional technique. However, the authors have not specified the variability or frequency of the reported pain scores. Furthermore, 50% (N=42) of the patients who had previously received the injection with the conventional technique (Total N=84), found the injection with the InVitria device less painful, 43% (N=36) reported no difference, and 7% (N=6) found it more painful. The surgeons recalled 89% (N=89) to be “straightforward”, 10% (N=10) to be ‘moderate’ and only 1% (N=1) was considered ‘difficult’, in terms of ease of needle insertion. The authors explained that the surgeon

described the ease of insertion as difficult, since two patients were squeezing their eyelids excessively during the insertion of the mould, and it was challenging to administer the drug. The findings reported by Michelotti et al. (2014) were consistent with Ratnarajan et al. (2013) study, reporting patients' preference on the use of the assisting device. While significant discomfort is not commonly reported, patients may also report a burning sensation, normally associated with the use of povidone-iodine to disinfect the surface of the eye. The use of povidone-iodine however is essential to reduce the risk of post-injection complications, such as endophthalmitis. Povidone-iodine was proved to be safe for preoperative disinfection (asepsis of periocular skin, eyelashes, and eyelid margins) in ocular surgery, despite its irritant properties (Papanikolaou et al. 2011).

The variability in the demographics of included patients, such as patients' age, gender, previous number of intravitreal injections and retinal disease could explain the inconsistency in the reported findings. More specifically, Haas et al. (2016) reported a significant positive correlation between patients' age and pain; greater pain in females (VAS: p=0.0219; Wong-Baker: p=0.0067), and number of previous injections (VAS: r=0.234, p=0.0007; Wong-Baker: r=0.216, p=0.0017), yet no difference was found between 27- and 30-gauge needle. Studies indicated that women have lower pain thresholds (Kozak et al. 2005; Segal et al. 2016). This may explain an increased sensitivity to induced pain and clinical pain experiences in the female population compared to males. On the contrary, most studies obtained no significant correlation between age and gender,

and pain scores, whilst another study (Rifkin and Schaal 2012b) obtained contradictory results: average pain scores in men where significantly higher than women. Confounding factors such as the emotional state may explain the inconsistency in the findings of the various studies. Application of anxiety questionnaires, for example the State–Trait Anxiety Inventory (STAI) pre- and post-intravitreal injections may provide additional information to identify different personalities in terms of patients' anxiety and arousal levels. In this context, 'arousal' is the physiological correlate of anxiety. This technique was previously assessed to study individuals' anxiety in ophthalmic practice (Margrain et al. 2003).

Several techniques were identified to improve patients' experiences during treatment, for example, handholding (Shaughnessy et al. 2022), listening to music reported a significant reduction in anxiety (Chen et al. 2012), as well as engaging discussions, including type of language between patient and practitioner. Interaction skills training has been developed to inform practitioners of coping mechanisms to manage patient anxiety (Kern et al. 2005). Other procedural techniques include the application of anaesthesia (Cintra et al. 2009; Blaha et al. 2011; Rifkin and Schaal 2012a; Andrade and Carvalho 2015)**,** as well as pre-filled syringes for intravitreal injection (Rasul et al. 2016) and the use of InVitria, a novel injection assisting device (Ratnarajan et al. 2013). Segal et al. (2016) established that pre-procedural anxiety to pain in intravitreal bevacizumab injections. Anxiety itself may not show significant differences (Kayikcioglu et al. 2017), yet higher levels of anxiety prior to the injection were correlated with more perceived pain during

intravitreal bevacizumab injections (Segal et al. 2016). Patients experiencing pain during and after their anti-VEGF injection can have implications on their level of satisfaction with the practitioner injecting, as well as their wellbeing. Upcoming concerns could also affect patients denying receiving further advice from their healthcare centre, and eventually discontinuing their treatment. Prior to receive an intravitreal injection, aspects such as high levels of fear or anxiety, either because of the fear of the “unknown” (Thetford et al. 2013) being highly concerned of the complications of the injection procedure.

There has been a substantial amount of work in the field of pain research associated with the intravitreal injection treatment, however it is important to acknowledge that there is a gap in understanding the patient experience. The intensity of pain may depend on, but not limited to procedure-related factors including anaesthetic effectiveness, procedural steps, needle size, injection site and injection complications (Moisseiev et al. 2012; Thetford et al. 2013). Other aspects are likely to influence pain, such as practitioner skills, patient’s personality, gender, number of injections, threatening of vision loss, anticipation, patient fear or anxiety that add more complexity to the interpretation of the findings related to pain (Boyle et al. 2018a). Since ongoing intravitreal injections are required, investigating the efficacy and safety of frequently applied procedures is essential to enhance patient comfort and their adherence to treatment. The use of topical anaesthesia in intravitreal injections represents a positive step towards more efficient and accessible healthcare. Applied qualitative research adds insight to our

understanding of patients' feelings and attitudes toward undergoing repeated anti-VEGF injections (Boyle et al. 2018b). Future studies should consider interviewing patients about their individual preferences on the anaesthetic techniques and base their conclusions on both their anaesthetic choice and quantitative pain assessment.

The selection of articles for this review may have introduced bias and limited the scope of the findings. Specifically, the exclusion of certain studies could have resulted in valuable information being overlooked. In addition, the absence of an independent assessment of study findings may have led to biased interpretations of the data. Furthermore, the quality of the studies varied and risk of bias was identified, which may have reduced the reliability of the review's conclusions. Heterogeneity across the studies may have introduced confounding factors, further reducing the precision of the findings. Inadequate reporting of clinical and demographic information also limited the reliability of the data. These limitations highlight the need for a more comprehensive and rigorous review process, including wider consideration of studies and independent assessment of findings, to ensure the validity and reliability of the conclusions. Future research should aim to address these limitations by incorporating a broader range of studies, using independent assessment of study findings, and improving the reporting of clinical and demographic information.

Chapter 5
The Methodological Rationale of Mixed Methods Research Design: Worldviews, Data Collection, and Integration

This chapter focuses on the concepts of mixed methods as a research design and provides a detailed explanation of the rationale behind the selection of the methodology and design of the studies undertaken in this thesis. It also provides a summary of the worldviews, data collection types, and justification of the selected methodologies implemented in this research with an overview on design challenges and integration approaches.

5.1. Introduction

According to Tashakkori and Teddlie (2003) (p. 711), mixed methods research has been defined as "*a type of research design in which qualitative and quantitative approaches are used in types of questions, research methods, data collection and analysis procedures, and/or inferences*". Creswell and Guetterman (2018) provided another definition of mixed methods as "*an approach to inquiry involving collecting both quantitative and qualitative data, integrating the two forms of data, and using distinct designs that may involve philosophical assumptions and theoretical frameworks*". All research approaches have underlying philosophical assumptions (worldviews) that guide the researcher and reader. Mixed methods research assumes a worldview or several worldviews (Tashakkori and Teddlie 2003; Creswell and Clark 2007; Creswell and Guetterman 2018). Different names have been used in the literature, such as "*integrating*" (Steckler et al., 1992) or "*combined research*" (Creswell, 1994); "*quantitative and qualitative methods research*" (Fielding and Fielding, 1986), or "*mixed methodology*" (Tashakkori and Teddlie 1998). Researchers undertaking mixed methodology have in recent decades described it as "*mixed methods research*" (Bryman 2006; Creswell 2018) that acknowledges the approach as a distinct methodology and method, and this is the name adopted in this thesis. In mixed methods research, both qualitative (open-ended) and quantitative (close-ended) data are collected, analysed, and interpreted in response to research questions or hypotheses (Tashakkori and Teddlie 2003; Schoonenboom and Johnson 2017; Creswell 2018). Several methods can be used to collect qualitative data

(table 5.1.1) including interviews, observations, journals, photographs, or audio-visual materials. In contrast, quantitative data includes close-ended information, such as surveys, questionnaires, and psychophysiological measures. The basic idea of the definition is that mixed methods research combines (integrates) qualitative (thematic data) and quantitative (numeric data) approaches to provide a better understanding of the research problem than either of each alone (Bryman 2006; Creswell 2009; Fetters et al. 2013; Bazeley 2017). Integration is a unique aspect to mixed methods. The approach to the order of collection of data, may also vary, where quantitative and/or qualitative phases may be concurrent or sequential (Creswell 2018). Qualitative research can be considered more time consuming when compared to quantitative research, and the results may potentially be influenced by the researcher's personal biases; reflexivity of the researcher (Johnson and Onwuegbuzie 2004). In contrast, quantitative research relies on numerical data and applies statistical analysis techniques to analyse and explain results collected. Quantitative data collection is relatively quick, data analysis is less time consuming, and the research results are relatively independent of the researcher, and a useful strategy to study a larger population sample. Quantitative data collection methods however follow structured procedures, and the measurements lack an adequate explanation of "how" or "why" do for example people experience in this way, compared to qualitative research methods (Mays and Pope 1995; Malterud 2001). Either approach alone raises validity issues, hence emerging both qualitative and quantitative phases can increase confidence in the research findings.

Data Collection Types	Options Within Types	Advantages of the Type	Limitations of the Type
Observations	▪ Complete participant: researcher conceals role ▪ Observer as participant: role of researcher is known ▪ Participant as observer: observation role secondary to participant role ▪ Complete observer: researcher observes without participating	▪ Researcher has a first-hand experience with participant ▪ Researcher can record information as it occurs ▪ Unusual aspects can be notices during observation ▪ Useful in exploring topics that may be uncomfortable for participants to discuss	▪ Researcher may be seen as intrusive ▪ Private information may be observed that researcher cannot report ▪ Researcher may not have good attending and observing skills ▪ Certain participants (e.g. children) may present special problems in gaining rapport
Interviews	▪ Face-to-face: one-to-one, in-person interview ▪ Telephone: researcher interviews by phone ▪ Focus group: researcher interviews participants in a group ▪ Virtual interview via video-calling	▪ Useful when participants cannot be directly observed ▪ Participants can provide historical information. ▪ Allows researcher control over the line of questioning	▪ Provides information designated place rather than the natural field setting ▪ Researcher's presence may bias responses ▪ Not all people are equally articulate and perceptive

Table 5.1.1 – Qualitative data collection types. This table includes material from Bogdan & Biklen (1992), Creswell & Poth (2018), and Merriam (1998).

Documents	▪ Public documents: minutes of meetings or newspapers ▪ Private documents: journals, diaries, or letters	▪ Enables a researcher to obtain the language and words of participants ▪ Can be accessed at a time convenient to researcher: an unobtrusive source of information ▪ Represents data to which participants have given attention ▪ As written evidence, it saves a researcher the time and expense of transcribing	▪ Not all people are equally articulate and perceptive ▪ May be protected information unavailable to public or private access ▪ Requires the researcher to search out the information in hard-to-find place ▪ Requires transcribing or optically scanning for computer entry ▪ The documents may not be authentic or accurate
Audio-visual digital materials	▪ Photographs ▪ Videotapes ▪ Art objects ▪ Computer messages ▪ Sounds ▪ Film	▪ May be an unobtrusive method of collecting data ▪ Provides an opportunity for participants to directly share their reality ▪ It is creative in that it captures attention visually	▪ May be difficult to interpret ▪ May not be accessible publicly or privately. ▪ The presence of an observer may be disruptive and affect responses

Table 5.1.1 – Qualitative data collection types. This table includes material from Bogdan & Biklen (1992), Creswell & Poth (2018), and Merriam (1998) (continued).

A worldview can be described as a set of beliefs that guide action (Guba 1990, p.17), also as paradigms (Mertens 2010); epistemologies and ontologies (Crotty 1998). Worldviews are seen as a general philosophical orientation about the world and nature of research (Creswell 2018) that support researchers, based on their past experiences, communities, and beliefs. Constructivism, postpositivism, pragmatism, and realism are widely discussed worldviews in the literature and a brief description is given below.

- Constructivism involves an understanding of individual experiences and multiple participant meanings (e.g. through semi-structured interviews and open-ended questions) allowing the generation of meaning (a hypothesis) to be tested in the quantitative phase. Researcher relies as much as possible on the views of the participant (Creswell 2018).

- Postpositivism supports a deterministic philosophy that reflects the need to identify and assess the causes (if any) that influence outcomes (e.g. identify variables in the quantitative phase that can influence patients' experiences). All variables collected in the qualitative phase can be reduced into small, discrete set to test (reductionism) to comprise with the hypotheses and research questions of the quantitative phase. In developing numeric measures of observations, key assumptions are followed in support of this position (Creswell and Clark 2017; Creswell and Guetterman 2018). Postpositivism may also support the implementation of multiple approaches to address complex human

phenomena, and to help minimise personal biases of the researcher (Miller 2000).

- Biesta and Burbules (2003) suggest that key concepts in a pragmatic approach to social science are experience, actions, and consequences. Pragmatism emphasises using knowledge or experience to define the research actions, and practical consideration of the experimental process or experiment as it relies on scientific inquiry (knowledge and meaning). Pragmatism can be used as an adequate foundation for concurrent or parallel types of designs, while paradigms may shift during a sequential design in which one starts from a constructivist perspective (qualitative) and then shifts to a postpositivist (quantitative worldview) (Creswell 2021).

- Realism suggests the idea of the independence of reality from human thoughts relying on the scientific approach for gathering subject-specific knowledge (Maxwell and Mittapalli 2010). Therefore, the researcher adapts the methodologies depending on the situation. Inquiry starts from a position where theories are already established and affect the data.

5.1.1. Mixed methods design approaches

The use of qualitative and quantitative research methods was predetermined and planned during the study design, and these processes have been accurately implemented during data collection and analysis. Thus, this study has adapted a fixed mixed methods design (Creswell 2018) and a typology-based approach to support the study's purpose and questions. There is a wide range of available classifications of types of mixed methods designs that methodologists have advanced (Tashakkori and Teddlie 2003; Creswell 2021), nevertheless the most implemented in the literature includes basic mixed methods research designs, such as the convergent parallel design, the explanatory sequential design, and the exploratory sequential design, illustrated in figure 5.1.1. The convergent mixed methods design is one in which the researcher conducts quantitative research roughly at the same time (parallel design) with qualitative research. The data collected are then integrated and interpreted to provide a comprehensive analysis of the research problem. Explanatory sequential mixed methods on the other hand involve conducting the quantitative research initially, analysing the quantitative data collected and then conducting qualitative research to build on the quantitative research outcomes. The initial quantitative phase is followed by the qualitative data collection phase (sequential). Exploratory sequential mixed methods first apply qualitative research methods followed by the quantitative data collection and analysis, hence the reverse sequence from the explanatory sequential design. The researcher initially explores the experiences of the participants, analyse the data, and then use this information to build into a

second quantitative phase (instrument tool) or generate a hypothesis. Embedded mixed methods is an example of a concurrent design and consists of a small amount of either qualitative data or quantitative data that are included within a larger qualitative or quantitative framework. This design uses an interactive approach to allow researchers to develop a combined understanding of the research problem.

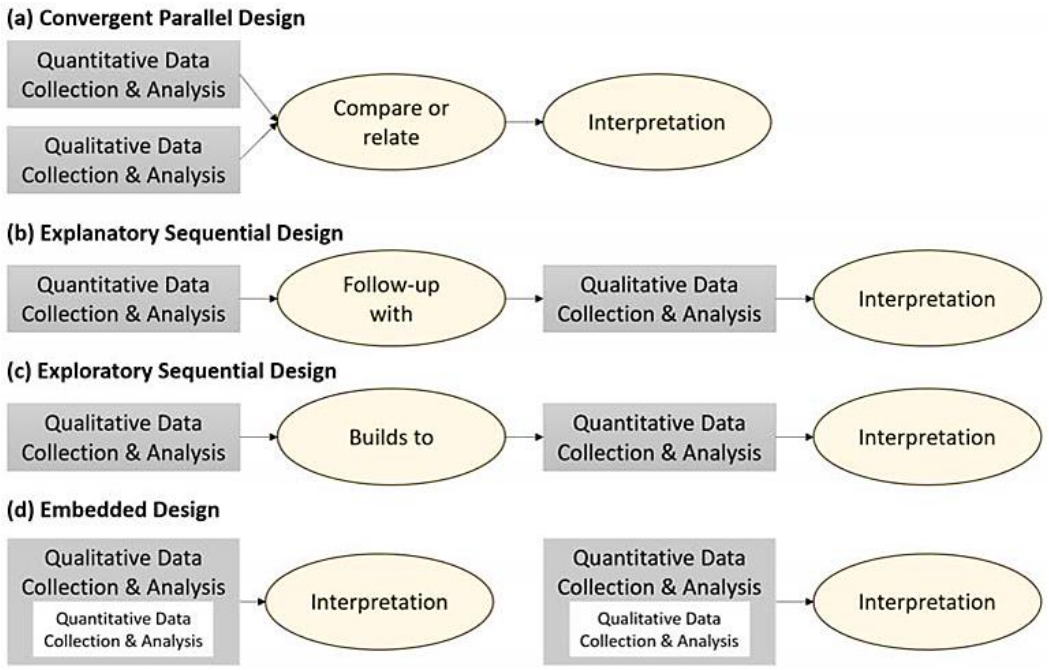

Figure 5.1.1 – Basic Mixed Methods Designs. From Creswell (2018).

5.2. Mixed Methods Research in this Study

5.2.1. Justification for choosing mixed methods research

The decision to construct a mixed methods design was based on the value that mixing both qualitative and quantitative data expands on the context of the research to understand the patient experience in intravitreal injections and strengthens the overall conclusions drawn in this thesis (Fetters et al. 2013; Maxwell et al. 2015; Creswell 2018). For example, the systematic literature review conducted in Chapter 4 demonstrated that most of the research implemented numerical pain scales to examine the patient experience during intravitreal injections, however the outcomes reporting the overall patient experience as average measures may not be representative of the individual experience. Despite the significance of the variables examined, intravitreal injection procedures, type of anaesthesia, needle size or injection site, the findings reported were controversial. This implies that quantitative research is insufficient to fully understand pain in this context and the analysis using an integrative approach of qualitative and quantitative data is essential to elaborate or build on the outcomes of one another. This concept is further supported by the theoretical construct reviewed in this thesis supporting that the combination of biopsychosocial phenomena (BPS model) as well as the pain definitions adapted in this research, "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of tissue damage, or both*" (Merskey, 1979), "*Whatever the experiencing person says it is, existing whenever the person says it does*."(McCaffery 1968).

One of the key strengths of this thesis is the mixed methods approach which expands the depth, scope, and richness of the research (Fetters et al. 2013; Creswell 2018). Mixed methods research is now increasingly employed in optometry (Nollett et al. 2019b; MacFarlane et al. 2022), nursing and health services research (Granel et al. 2020; Brady et al. 2021). In this thesis, a pragmatist perspective was adapted as a research paradigm (Biesta and Burbules, 2003) supporting the concept that reality has the potential to change, and as a problem-oriented philosophy, several strategies have been adapted during the project's time period to successfully meet the research aims and answer the research questions most effectively using both qualitative and quantitative research methods.

5.2.2. Exploratory Sequential Mixed Methods Design

5.2.2.1. Purpose of Statement

An exploratory sequential mixed methods design was adapted in this thesis (Creswell 2018). This mixed-methods study addresses pain and discomfort experienced by patients with neovascular AMD receiving intravitreal injections of anti-VEGF agents, and the impact on their treatment adherence and wellbeing. The purpose of this exploratory sequential mixed methods design was to first qualitatively explore with a small sample, to design features and generate a hypothesis (e.g. variables associated with pain and discomfort). and then examine these features with a larger sample. The first phase of the study involves a qualitative exploration of the experiences of patients and healthcare practitioners using one-on-one semi-structured interviews. From this initial exploration, the qualitative findings will be used

to explore patient experiences and develop quantitative features to be further assessed in the quantitative phase. The second phase of the study incorporated quantitative design approaches including questionnaires (to measure pain, anxiety, and wellbeing) and objective physiological measure of electrodermal activity.

5.2.2.2. Design challenges

During the design stage of the mixed methods study, three primary characteristics were carefully examined including priority, implementation, and integration (Creswell 2018). Priority refers to the relative importance or weighting of the quantitative and qualitative methods for answering the study's questions. Implementation relates to the phase of collecting the data which can be concurrent, sequential, or multiphase combination (Tashakkori and Teddlie 2003; Creswell 2018). Finally, the appropriate point of integration within the mixed methods design was decided; integration can occur during the stage of data interpretation and reporting, during data analysis or data collection and/or at the level of research design (Fetters et al. 2013).

Implementation

The purpose of using an exploratory sequential mixed methods design was to initially gain a comprehensive understanding of patient and practitioner experiences related to intravitreal injections. The systematic review provided valuable insights into the procedures and practices involved in the administration of intravitreal injections, covering critical aspects such as the selection of appropriate anaesthesia and needle techniques, and the

implementation of pain assessment tools to evaluate patient pain. However, the field of intravitreal injections has limitations in terms of qualitative research. Additionally, practitioner perspectives on patient experiences during intravitreal injections were considered an important aspect to study further. The initial phase of the design aimed to identify factors related to pain, discomfort, or anxiety during an intravitreal injection procedure, and to explore any procedural differences and routine examinations.

Conducting practitioner interviews is crucial to gain a comprehensive understanding of both patient experiences and procedural differences in intravitreal injections at the participating site. While patient perspectives provide valuable insights into their needs, preferences, and expectations, practitioner perspectives can identify potential barriers or limitations in care delivery and provide insights into how best to optimise care processes and procedures. Practitioner interviews can help identify differences in injection techniques and the use of adjunctive treatments, which may affect the patient's overall experience and outcomes.

Secondly, the qualitative themes identified (phase 1) were assessed to examine whether they generalise to the sample population, a phenomenon that could in practice be associated with variables and data collected in the quantitative phase (phase 2). The qualitative phase 1 was divided into patients' and practitioners' interviews allowing comparison between the two data sets (patient vs practitioner experiences) with the researcher building on participant responses using revised topic guides and prompts in

subsequent interviews to gain an in-depth understanding of the topic under investigation. To study adherence to treatment, patients were asked an open-ended question of their intention to return for future treatment. Advanced mixed methods designs incorporate more complex components and according to Nastasi et al. (2007) form part of a multi-stage mixed method framework. Despite the several examples proposed in the literature associated with advanced, complex mixed method designs (Tashakkori and Teddlie 2003; Creswell 2018), this study followed an exploratory mixed methods design, and the qualitative components and follow-up measurements in phase 2 were employed to provide a better understanding of the individual patient experience and answer the central questions of this thesis.

Integration and Reporting

Using both qualitative and quantitative methods to address different questions or aspects of the overall study aim, provides thorough detail into the analysis procedures and study outcomes (Creswell 2018). Qualitative research is useful in discovering the meaning of individual experiences (Merriam 1998). In this thesis, integrating the research findings provides an in-depth understanding of the patients' and practitioners' experiences of the intravitreal injection procedures. Levels of integration in mixed-methods research are presented in figure 5.2.1.

The first linking of data occurs at the design-level with the use of a sequential design; the results from the first phase (patients and practitioner

qualitative findings) would be used to build the second phase of the research design (Fetters et al. 2013). The semi-structured interviews will be thematically analysed (Braun and Clarke 2006; Braun and Clarke 2019), and the themes identified will be used to build the quantitative features (event-markers) for the measurement of electrodermal activity.

The second linking of data occurs through methods, implementing a triangulation approach (Fetters et al. 2013; Carter et al. 2014) to compare (agreement, dissonance) between the responses to the interview questions of the patients and practitioners. A narrative passage was used to convey the findings of the analysis (Creswell and Guetterman 2018) including a discussion of the themes (subthemes, specific illustrations, multiple perspectives from individuals, and quotations).

The third linking of data to fully address the research questions, occurs at the interpretation-level integration (Fetters et al. 2013) combining the qualitative data from phase 1 of the study with the quantitative data from phase 2 using the weaving approach on a concept-by-concept basis. This allowed bringing together of quantitative and qualitative data to draw an overall interpretation of the insights beyond the information gained from separately discussing the qualitative or quantitative results: the findings agreed (convergence), offered complementary information on the same issue (complementarity), or appeared to contract each other (discrepancy) (Fetters et al. 2013).

Integration Level	*Approaches*
Design	3 Basic designs
	Exploratory sequential
	Explanatory sequential
	Convergent
	4 Advanced frameworks
	Multistage
	Intervention
	Case study
	Participatory—Community-based participatory research, and transformative
Methods	Connecting
	Building
	Merging
	Embedding
Interpretation and Reporting	Narrative—Weaving, contiguous and staged
	Data transformation
	Joint display

Figure 5.2.1 – Levels of integration in mixed-methods research. From Fetters et al. (2013).

5.2.3. Selection of a qualitative data collection method

While the original research protocol included focus groups as the primary collection approach for the qualitative research, potential biases were carefully examined during the design stage of the research protocol and replaced with one-on-one semi-structured interviews. Reflecting on the purposes of this research and accounting the perspective of the target population, patients with neovascular AMD, one-on-one interviews were considered a superior methodology to focus groups, primarily because of the sensitive nature of the topic investigated. For example, participant responses could be biased during a focus group discussion leading to misleading outcomes. Nevertheless, focus group discussions can encourage participants to share their experiences by hearing others expressing similar issues or experiences of their own. A focus group allows

participants to interact with each other, debate, raise discrepancies and argue. For instance, rich, in-depth data can be collected from interesting focus group discussions and comparisons between group members. However, the responses of the participants in the group may not be mutually exclusive which might result in invalid or inaccurate data collection of the sample population. Emotional aspects such as psychological pressure can often persuade participants to give opinions that they feel will be generally respected by the group, not necessarily true to their thoughts of the topic. Likewise, the presence of one or two 'dominant' participants in the group may repress the opinions of others who may lack confidence to develop arguments and conflicts during the discussion. In that context, one-on-one interviews in this study were selected since participants will only be sharing their experiences with the researcher. Consequently, this adds another aspect to the researcher's role.

Interviews prioritise the individual's experience and this was the primary interest in this study to develop an in-depth understanding of the experiences of patients who receive intravitreal injections to treat neovascular AMD. The researcher acting as the moderator of the focus group can have a significant influence on the outcomes of the study. Lacking control of the group discussion for instance might lead to misleading outcomes that fail to expand on the understanding of the problem or explain the research questions. In a one-on-one interview the researcher focuses on a single participant, being able to identify respondent's body language, to lead an in-depth discussion of the topic, and the lack of experience of

conducting interviews is not a limiting factor in this one-on-one approach. Semi-structured interviews follow a structure of open-ended questions. The interview topic guide was structured to deliver qualitative research questions and using multiple prompts to guide the interview into a more detailed discussion, specific to the research problem. Prompts used throughout the interviews can explore different viewpoints of the problem and can optimise the lack of group dynamics in individual interviews.

5.2.3.1. Definitions of a code and a theme

At the beginning of gathering data, coding was performed concurrently with the interviewing processes, to inform the researcher of additional questions of interest that arise from the participants' sharing experiences. The first source of an interview can have a significant influence in determining the categories we create and the ideas we carry through the analysis. It is useful to maximise the potential for variety in concepts, selecting a second item that contrasts in some important way with the first. Coding is one of several methods of working with and building knowledge about data; used in conjunction with annotating, memos, linking and modelling. A code is an abstract representation of an object or phenomenon (Braun and Clarke 2006; Braun and Clarke 2019). It involves taking text data, segmenting sentences (or paragraphs) or images into categories and labelling those categories. The coding process was therefore used to generate a description of the people as well as categories or themes for analysis (e.g. treatment-related anxiety, minimising burden of therapy, managing pain and

ocular discomfort, motivation to continue treatment, willingness to continue with anti-VEGF treatment).

NVivo 12 software (QSR International) was used to assist in analysing the data. The software can incorporate both text and image data, the features of storing and organising data, the search capacity of locating all text associated with specific codes, interrelated codes or making queries of the relationship among codes. The data were coded by organising and categorising information into emergent themes using an iterative strategy and comparative method until all meaningful data had been coded. The strategies used for qualitative analysis include illustrative quotes in the reports using an inductive approach, which means that the themes and explanations were derived primarily from a close reading of the interview data, not fitting the data to pre-existing concepts or ideas from theoretical concepts (Braun and Clarke 2006, 2019).

Thematic analysis of the coded data will involve processes such as line-by-line coding, aggregation, and the construction of themes, consistent with (Braun and Clarke 2006). Codes sharing specific commonalities will be then grouped into the same theme. Themes initially analysed for each individual case and across different cases can then be shaped into a general description. Case classification (persons) will be created to associate interview data with attribute information (columns of cases, and demographic information). A case is a core structural element in NVivo

representing the details (e.g. interview data, recording, texts, demographics, additional observations) of each participant.

5.2.3.2. Conceptualisation of saturation and thematic analysis

One approach to the sample size issue follows the idea of saturation, which comes from grounded theory (Charmaz 2014; Corbin and Strauss 2015). The theory supports that data collection can stop when the categories (or themes) are saturated – when collecting new data no longer presents new insights or reveals new properties. However, this approach depends on a pre-determined sample size and was unsuitable for the purposes and timeline of this research. Data saturation is one of the most common techniques in health sciences to justify sample size in qualitative research. More recently, Braun and Clarke (2021) pointed out that the quality of coding is not demonstrated by an objective agreement or consensus between researchers, but from thorough engagement with the data (challenge is to select what to explore) and a reflexive interpretation to understand the meaning of participant responses.

Other principles associated with sampling involve conducting a minimum of ten interviews, purposive diversity sampling, and determining a stopping criterion (Francis et al. 2010). Although the principles outlined in the Francis et al. (2010) are based on theory-based interview studies, they share similar recommendations and applications with Braun and Clarke (2021). For example, authors highlight the continuous refinement of the interview development process and updating of interview topic guides. Similarly, the

qualitative research in this thesis adopts this approach to gain a deeper understanding of patient'' experiences with intravitreal injections. Purposive sampling was also used in this thesis to ensure diversity in the sample, specifically by including patients of different ages, genders, and injection histories (i.e., varying numbers of intravitreal injections administered).

During the analysis stage, the researcher interpreted the interview data with consideration for the context and depth of the responses for addressing the research question and continued this iterative process until no new themes emerged. This allowed for a final sample to be determined based on saturation of themes (Braun and Clarke 2021). This study also supports the principle of information power over data saturation, that "*the more relevant information a sample holds, the fewer participants are needed*" (Malterud et al. 2016). Reflecting on these values, the analysis centered on the researcher's engagement with the data and interpretative judgment about when to stop the coding process. Initial themes were then generated and reviewed by the researcher. The methods and analyses of each of the qualitative research studies are further addressed in Chapters 6 and 7.

5.2.4. Self-report measures

Table 5.2.1 provides an overview of the characteristics of self-report questionnaires in the assessment of pain, identified in the systematic literature review (Chapter 4). In this research work, pain was measured using the Short-Form McGill Pain Questionnaire (SF-MPQ), comprised of the Visual Analogue Scale (VAS), Main Component (MPQ) and Present

Pain Intensity (PPI) index. These measurements indicated high validity for the measure of acute pain (Bijur et al. 2001; Gauthier et al. 2014), also increasingly implemented in ophthalmology research to assess pain in intravitreal injections (Yau et al. 2011; Rifkin and Schaal 2012a; Georgakopoulos et al. 2017) and dry eye disease (Kalangara et al. 2017; Farhangi et al. 2019; Yoshikawa et al. 2021). The VAS was also chosen for its simplicity and adaptability to a broad range of populations (e.g. including the elderly), also taking into consideration the feasibility of administering the measure in a clinical setting. The State and Trait Anxiety Inventory (STAI) (Spielberger et al. 1983) is one of the most widely used questionnaires to measure anxiety (Mertens et al. 1234; Bakotic and Radosevic-Vidacek 2013; Davey et al. 2013; Kayikcioglu et al. 2017). Spielberger et al. (1983) differentiates between the concept of 'trait' anxiety (e.g. person's 'proneness' to anxiety) and "state" anxiety as a transient experience of anxiety. Thus, trait anxiety is a personality trait, therefore an individual high in trait anxiety will be more susceptible to experiencing higher anxiety levels. State anxiety reflects subjective feelings of apprehension or anxious anticipation in response to a stressful event. Patients receiving intravitreal injections may experience either state or trait anxiety, depending on their personality (trait), or the actual situation they are experiencing at that point in time (e.g. about to receive an injection into the eye). Recognising the multidimensional nature of pain, implementing STAI scores would help provide an understanding of the patients' experiences associated to anxiety, also examining potential associations with pain.

Assessment	Content	Response Scale	Number of items
Wong-Baker FACES Scale (Donna Wong and Connie Baker 1988)	Faces (emotional) scale	No pain (=0) to worst pain imaginable [=10 (or 100)]	Single-item scale
Visual Analogue Scale (VAS) (Hayes and Patterson, 1921)	Continuous scale (horizontal or vertical line) 10 cm (100 mm) in length Anchored by 2 verbal descriptors	No pain (=0) to worst pain imaginable [=10 (or 100)]	Single-item scale
Numeric Rating Scale (NRS)	Numerical	0 (no pain) to 10 (worst possible pain)	11-point scale
Verbal Categorical Rating-Scale (VRS)	Adjectives (words/phrases)	no pain = 0, mild = 1, moderate = 2 or severe = 3	4-point categorical scale
McGill Pain Questionnaire (MPQ) (Melzack, 1975)	Descriptors: sensory, affective, evaluative, supplementary; NCW; PRI (S); PRII); PPI index	Discrete points, 1-6 5-point pain intensity scale a	78 descriptors; dimension 1-10: sensory, 11-15: affective, 16: evaluative, 17- 20: supplementary single-item scale
Short-Form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987)	15 descriptors (11 sensory; 4 affective) PPI index VAS	0 = none, 1 = mild, 2 = moderate or 3 = severe. 5-point pain intensity scale a no pain (=0) to worst pain imaginable [=10 (or 100)]	15 descriptors: 11 sensory, 4 affective single-item scale single-item scale

Table 5.2.1 – An overview of the characteristics of pain assessment methods. Notes: 0 (no pain), 1 (mild), 2 (discomforting), 3 (distressing), 4 (horrible); 5 (excruciating) Abbreviations: VAS (visual analogue scale); NRS (numeric rating scale); VRS (verbal rating scale); MPQ (McGill Pain Questionnaire); SF-MPQ (short-form McGill Pain Questionnaire); NCW (number of chosen words); PRI (S) (pain rating index sum); I (R) (pain rating index rank); PPI (present pain intensity).

5.2.5. Personal reflections: The researcher's perspective

Reflexive thinking can be incorporated into the study by writing notes on our personal experiences. In this section, the researcher describes the contextual intersecting relationship with the participants interviewed to increase the credibility of the findings and strengthen the understanding of the work (Berger, 2015).

> *I am a White, Greek Cypriot, middle class, young adult female, with no disability, having no prior relationship with the participants in this study. Three words that define me include: patience, gratitude, and ambition. Growing up in Cyprus, then living and studying in the United Kingdom for the past 8 years has helped me gain more openness to diversity, developing a better understanding of other people and cultures. Studying BSc Pharmacology and MSc Neuroimaging provided me with an in-depth knowledge on the various mechanisms of drug action, diagnostics, and therapeutics available for broad healthcare programs such as Medicine, Pharmacy, and Nursing. My educational background is one of the reasons that my research has focused on patient experiences aiming to explore patient feelings, ideas, and concerns regarding intravitreal injections. Whilst my expertise primarily relied on the effectiveness and safety of pharmacologic interventions, the patient's perspective is a key element in the quality of care and considerably an area of interest that inspired me to investigate further.*

During the initial planning stage, I have enhanced my understanding of AMD, the intravitreal injection procedure and patient experiences through literature reviewing and the professional roles involved in the care of patients with AMD. I have spent extended time in the hospital clinic whilst data collecting and observing day to day running and interactions for the purposes of achieving a better understanding of their behaviours and reactions. At the start of the observation, I felt empathy instantly and incorporated these experiences in the interviewing process. For example, motivational interviewing techniques were applied to build trust with patients and expressing empathy in cases who reported experiencing pain. Phrases used included: "I feel sad to hear that you experienced this.", "I can see that you are upset.", or "Thank you for sharing this information with me."

Chapter 6

A qualitative study of patients' and practitioners' experiences of intravitreal injections for age-related macular degeneration: Why do they think it is painful?

This chapter reports a qualitative study, the first phase of the exploratory sequential mixed methods design aiming to explore the experiences of patients receiving intravitreal anti-VEGF injections for neovascular AMD and the practitioners' views. The qualitative data collected were used to generate a hypothesis to be tested with a larger sample in the second quantitative phase. Additionally, the procedural steps identified in the interview data were implemented as event markers in the measurement of electrodermal activity during the intravitreal injection procedure (Chapter 8). Whilst previous research associated with intravitreal injections have focused on assessing pain during treatment, this study also provides considerable insight into post-injection experiences and patients' adherence to treatment.

6.1. Introduction

Approximately 67 million people in the EU are currently affected by AMD (Li et al. 2020), with the latest available data from Macular Society estimating 1.5m cases in the UK (Macular Society 2018; NICE 2018). While there is no definitive cure for AMD, existing treatment modalities for neovascular AMD aim to impede disease progression and preserve eyesight with early intervention. Intravitreal injections of anti-VEGF agents are the most effective treatment currently available. Several randomised controlled clinical trials have extensively demonstrated the safety and efficacy of anti-VEGF treatment (Brown et al. 2006a; Rosenfeld et al. 2006a; Rosenfeld et al. 2006b; Martin et al. 2011a; Chakravarthy et al. 2012), however patients reported experiencing ocular pain during treatment (Boyle et al. 2018). Pain can also have significant implications on treatment adherence, potentially hastening vision loss (Sii et al. 2018). In patients with AMD, mental health problems such as depression (Robin et al. 2010) and anxiety (Ulhaq et al. 2022) persist and can negatively impact adherence and treatment efficacy.

Whilst the ideal treatment regimen remains open to review (Rayess et al. 2015), treatment commonly commences with the administration of three loading doses at monthly intervals, followed by regular monthly reviews on disease progression and additional treatment on a *pro re nata* basis (The Royal College of Ophthalmologists 2018). Implementation of a treat-and-extend regimen in clinical practice has been recommended as most appropriate in the delivery of promising visual and anatomical outcomes, and a lower treatment burden (Ross et al. 2020). Reviewing the IASP and

McCaffery's definition of pain in Chapter 2, pain has been described as a subjective experience (Katz and Melzack 1999) and that, "*patient self-report is the standard of care for evaluating pain*" (McCaffery 1968). As outlined in Chapter 4, several studies have evaluated pain using VAS or numerical pain rating scales to examine for example, the type of anaesthetic (Cintra et al. 2009; Blaha et al. 2011; Yau et al. 2011; Rifkin and Schaal 2012a; Andrade and Carvalho 2015), the InVitria assisting device (Ratnarajan et al. 2013), procedural steps (Tailor et al. 2011), injection site (Moisseiev et al. 2012) or needle size (Rodrigues et al. 2011; Haas et al. 2016). The instillation of anaesthetic eyedrops, needle insertion and placement or removal of the surgical drape were identified the most common factors to causing pain and discomfort in the intravitreal injection procedure (Tailor et al. 2011). However, the wide variation in pain scores reported in Tailor et al. (2011) suggests that the use of standardised numerical measures to determine pain severity misrepresents the individual pain experience. This implies that qualitative perspectives are necessary to gain insight into aspects of the pain experience. For example, Thetford et al. (2013) conducted narrative interviews to compare patients' expectations to their actual experience of the treatment, although pain was not the principal focus of this study.

Previous studies investigating patients' experience of intravitreal injections have examined anxiety (Chua et al. 2009; Segal et al. 2016; Senra et al. 2017), quality of life (Finger et al. 2013; Wang et al. 2015) and adherence to treatment (Polat et al. 2017; Boyle et al. 2018b; Obeid et al. 2018). For example, Polat et al. (2017) reported that perceptual factors, such as fear

of the injection and disbelief of the effectiveness of the treatment influenced patients' decision to attend follow-up appointments. Patient-practitioner communication is therefore a key attribute in the patient journey. Understanding how practitioner behaviour and provision of information contribute to a positive patient experience may help develop strategies for improved adherence to treatment.

Although previous research has examined patient experiences, qualitative perspectives in the assessment of pain and anxiety related to anti-VEGF injections are still insufficiently explored, to the author's knowledge. This study therefore explored patients' experiences of injections and the practitioners' views from a qualitative perspective. The objectives were: a) to identify key variations in treatment procedures that may influence pain, and b) to gain insights into the post-injection experience and treatment adherence.

6.2. Methods

6.2.1. Study Design

A qualitative design was selected to achieve the research objectives. This involved semi-structured, one-to-one interviews with patients and practitioners. Qualitative research is suitable in exploring and understanding the meaning of individual experiences (Merriam 1998; Corbin and Strauss 2015). Interviews consisted of open-ended questions to offer flexibility in data collected allowing participants to express their personal experiences,

opinions and views on the topics discussed (Creswell and Guetterman 2018).

6.2.2. Ethical approval

This study was reviewed and approved by the National Health Service Wales and the South-East Wales Research Ethics Committee (19/WA/0004) on January 16, 2019. The study was based on the principles stated in the Declaration of Helsinki and written informed consent was gained from each participant.

6.2.3. Recruitment and sampling

Participants were recruited from a hospital eye clinic in Wales, UK. Patients and practitioners were purposively selected to meet eligibility criteria and to recruit a diverse range of ages and genders, where possible (Francis et al. (2010); Creswell and Guetterman 2018). Opinions can differ between different age groups, gender, and previous experience of the intravitreal injection procedure, therefore collecting these characteristics may support our understanding of the individual experience reported.

The initial analysis sample for the patient and practitioner groups was determined based on Francis et al. (2010) principles, with a provisional sample size ranging between 10 to 13 participants, and purposive diversity sampling. Additionally, a provisional sample size range of 10 to 13 participants for each group was deemed appropriate as it balances the need for diversity while also enabling detailed exploration of the topic. Performing

site visits at the Eye Clinic during the design stage of this study, it was observed that there were approximately 15 healthcare practitioners performing intravitreal injections. Hence, based on this limited capacity and the fact that some of the questions referred to specific standardised procedures performed, a smaller sample size was chosen for the healthcare practitioners. The final sample size was determined by the researcher's interpretation of achieving data saturation, at the point where the research aims and reaching consensus on the data collected have been addressed (Braun and Clarke 2019). The principle of information power over data saturation was also supported as the quality of interview data was considered an important aspect to achieve the study aim (Malterud et al. 2016).

6.2.4. Inclusion and exclusion criteria

In relation to study participants, inclusion criteria were patients aged 50 years or above based on the standards defined by NICE clinical guidelines for AMD diagnosis (NICE 2018), diagnosed with neovascular AMD by a consultant ophthalmologist and undergoing anti-VEGF treatment at the time of the study. Patients were excluded if they had a history of retinal pathology other than neovascular AMD, suffering from very poor hearing, or had received less than six intravitreal injections. Contrary to expectations, previous anecdotal evidence in the Macular Society publication Sideview (Autumn 2014) showed that patients receiving less than six intravitreal injections were less likely to have experienced pain. Since this study aimed to gain an understanding of pain or discomfort associated with the

intravitreal injection procedure, individuals who had received less than six intravitreal injections were not eligible to participate. Practitioners eligible for participation consisted of those who were registered nurses, ophthalmologists, or optometrists and performed intravitreal injections during the course of the study. Participants who were unable to communicate in English or Welsh were excluded from the study.

6.2.5. Topic guides and data collection

The topic guides (Appendices D and E) were initially developed from themes identified in the literature review presented in Chapter 4. Patients' topic guide included the following sections: 1) background on health condition, 2) treatment satisfaction and quality of care, 3) treatment concerns, 4) experience of intravitreal injections, 5) wellbeing, 6) strategies to improve experience, and 7) demographics. Practitioners' topic guide included: 1) background on managing patients with AMD, 2) intravitreal injection procedure, 3) experiences of patients with AMD receiving intravitreal injections, and 4) demographics. The interview schedules were piloted, and an additional question was added on the patients' topic guide: "*Is there anything that has changed in your daily life because of your pain/discomfort*?". I also obtained feedback on my interviewing.

The researcher adapted to participant responses using probes and member checking (respondent validation) to gain an in-depth understanding of the topic under investigation (Creswell and Guetterman 2018). Topics raised by participants were confirmed and expanded in subsequent interviews. In this

context, interview questions deviated from the planned topic guide. Examples of phrases used as probes and member checking were, "*Could you tell me more about that?*", "*What do you mean by that?*", "*How did you react when you found out about AMD?*", "*So earlier you talked about… is this correct?*". Moreover, the researcher explained purpose and nature of the study and the expected duration of the interviews before taking consent, also reassuring participants of the confidentiality of their data. Patient interviews were undertaken face-to-face at either the participant's own home or in private meeting room at Cardiff University, according to individual preference. Practitioner interviews occurred at their workplace office. Interviews took place between May and September 2019 and were audio-recorded with the Olympus VN-541PC device.

6.3. Data processing and analysis

Each participant was assigned a pseudonym to ensure confidentiality and anonymity. Interview data were transcribed verbatim and thematically analysed with the support of NVivo statistical software version 12 (QSR International). A six-step process of inductive thematic analysis was used to analyse the data as outlined by (Braun and Clarke 2006) (table 6.3.1). This involved familiarising with the data, initial coding and labelling of data, searching for themes, reviewing themes, defining, and naming themes, and producing the report in order to support the analysis and interpretation of the data.

Initial themes were generated and reviewed by the principal researcher (C.Y.). In order to develop "*a richer more nuanced reading of the data*" (Braun and Clarke 2019), a collaborative approach was used in the coding process and producing the report: transcribed interviews (4 patient cases, 3 practitioner cases) were randomly selected and independently coded by another 2 researchers of the team (A.W. and J.A.), followed by discussion of themes identified in relation to the research question. According to "best practice", a journal (series of memos) was kept during and following data collection to document aims, key decisions, observations and comments made throughout the study to facilitate reflexivity (Creswell and Guetterman 2018). Data source triangulation was used to strengthen the findings by collecting data from both patients and practitioners (Carter et al. 2014).

Phase	Examples of procedure for each step
Familiarising oneself with the data	Transcribing data; reading and re-reading; noting down initial codes
Generating initial codes	Coding interesting features of the data in a systematic fashion across the dataset, collating data relevant to each code
Searching for the themes	Collating codes into potential themes, gathering all data relevant to each potential theme
Involved reviewing the themes	Checking if the themes work in relation to the codes extracts and the entire dataset; generate a thematic 'map'
Defining and naming themes	Ongoing analysis to refine the specifics of each theme; generation of clear names for each theme
Producing the report	Final opportunity for analysis selecting appropriate extracts; discussion of the analysis; relate back to research question or literature; produce report

Table 6.3.1 – A six-step process of thematic analysis. From Braun and Clarke (2006).

6.4. Results

6.4.1. Characteristics of study participants

Participant characteristics were collected to evaluate the representativeness of the sample (table 6.4.1). Data saturation was reached with 21 interviews, 14 patients and 7 practitioners. Patients and practitioners had a median age of 82 (range 70-95) and 37 (range 28-59) years; and had a median number of 18 (range 6-50) injections and 3 (range 1-11) years of injection experience, respectively. It should be noted that the dosing

regimen was not examined as part of the participant characteristics in the current study. Therefore, the patients who were interviewed in this study might have been subjected to different treatment regimens at varying times throughout their treatment course. All participants were English-speaking. Patient and practitioner interviews ranged from 14 to 45 minutes (median = 26 minutes) and 10 to 35 minutes (median = 19 minutes), respectively. Participants are identified as PA for patients and OPT, NUR and OPH for healthcare practitioners to include optometrists, nurses and ophthalmologists respectively, followed by an identification number.

Participants	Characteristic	Value
Patients	Age, median (range), years	82.5 (70-95)
	Female sex, No. (%)	9 (64)
	Number of injections, median (range)	20.5 (6-50)
	Place of primary residence, No. (%)	
	Lives alone	6 (43)
	Lives with family	8 (57)
Practitioners	Age, median (range), years	37 (28-59)
	Female sex, No. (%)	6 (86)
	Qualification, median (range), years	9 (6-19)
	Injection experience, median (range), years	3 (1-11)
	Occupation, No. (%)	
	Nurse	4 (57)
	Ophthalmologist	2 (29)
	Optometrist	1 (14)

Table 6.4.1 – Patient and Practitioner Characteristics.

6.4.2. Themes

Thematic analysis revealed 3 main themes that represent the patient journey: 1) fear of losing eyesight and effect of apprehension on patient adherence to treatment; 2) variability in pain experience during treatment; and 3) post-injection experience and impact on patient recovery (table 6.4.2).

Overall, the interview data suggest that apprehension, pain during needle insertion, and the long-lasting side-effects had a substantial impact on the patient experience. Varying levels of pain and discomfort were described. Despite anticipated anxiety, pain or discomfort during or following the injection, participants recognised the importance and benefits of the treatment and considered the injections as their only option to help preserve their eyesight. The fear of losing eyesight was a strong driver to adhering to treatment. Table 6.4.3 provides quotations comparing patients' and practitioners' responses in the themes identified.

Theme	Subtheme(s)
Fear of losing eyesight and apprehension on patient adherence to treatment	Fear of the “unknown” and the feeling of suspicion
	Fear of losing eyesight and recognising treatment benefits
	▪ *Coping mechanisms to manage apprehension* ▪ *In adherence with treatment* ▪ *Feeling worried to stop receiving treatment* ▪ *Feeling lucky and grateful*
Variability of pain perception during treatment	Preparation steps
	▪ *Instillation of anaesthetic eyedrops* ▪ *Application of chlorohexidine/povidone-iodine* ▪ *Placement of eyelid speculum* ▪ *Placement of surgical drape*
	Intravitreal injection: expecting vs experiencing
	▪ *The feeling of pressure* ▪ *Experiencing pain and discomfort* ▪ *Injection technique*
	Impact of quality-of-care delivery on patient experience
	▪ *Observation and reflective practice* ▪ *Patient-practitioner interaction: meeting the needs of every individual*
Post-injection experience and impact on patient recovery	Instructions and provision of patient information leaflets
	Expected side-effects
	Patient-reported side-effects associated with pain
	Pain relief techniques

Table 6.4.2 – Main themes generated from the thematic analysis.

THEME 1:

Fear of losing eyesight and apprehension on patient adherence to treatment

This theme represents an exploration of the initial concerns with respect to fear of intravitreal injections and of losing eyesight. This theme relates to factors contributing to fear of the unknown and the feeling of suspicion, treatment-related anxiety, fear of losing eyesight and recognising treatment benefits. It also describes coping mechanisms adapted by patients and practitioners to manage apprehension and anxiety.

Subtheme 1.1. - Fear of the "unknown" and the feeling of suspicion

When patients were initially informed by their consultant of the need for intravitreal injections necessary to treat neovascular AMD, most expressed concerns at having an injection into the eye. The thought of having a needle entering the eye, and particularly living with the uncertainty of not knowing what the procedure entailed was most frightening:

> *"Oh, I had no idea of what was going on and I'll just say I was always frightened."* (PA08)

> *"I was a bit scared, you know, cause when I say to people who aren't gonna have an eye injection, oh, they say, how can you do that?"* (PA09)

The patient expressed that receiving the injection immediately during their first visit had a significant impact on their experience. They stated that it made a big difference compared to the prospect of going home and worrying about it. According to the patient, the practitioner suggested doing the

injection right away, which gave the patient a sense of certainty to the procedure*:*

> *"And I had one [injection] straightaway, which made a big difference, I think, rather than going home and thinking, oh, you know… it was so quickly, you know. Let's do it now [the practitioner said]. I thought, well that's it. I'm in it now."* (PA06)

Most patients experienced anxiety in anticipation of and during the treatment procedure. Participants PA03, PA05 and PA06 described the need to continuously remind themselves to keep still during the insertion of the needle, nevertheless thoughts of potential threats made them feel vulnerable instead:

> *"But you know what's coming when she says don't move, don't move… And you're afraid that you'll move… The morning, you know you're going, oh that doesn't feel right today, you're not consciously thinking, oh, I don't want to go. But it does affect the way you're feeling. It's strange. And it's because you know what's coming, I think. I mean, I can't say you would get used to it…"* (PA06)

> *"The trick is to remain absolutely still. I find that sometimes a bit difficult because I'm anxious and I know what's going on and I move my eyeballs."* (PA05)

> *"And sometimes when you see them filling the injection, I'm thinking oh don't look, don't look at the needle."* (PA03)

Andy also reported that it is the *"whole procedure*" that builds-up his nervousness and apprehension, from the time he undertakes pre-injection procedures until the time of the injection:

> *"Every time you get anxious. You get the first part done, and then the second part with the photograph. And then they call your name you think, here we go, but you know, it's just the whole procedure. And then you come out and think well, here we are. But it's not something that you look forward to."* (PA07)

Similarly, Judith associated her experiences with the injection procedure being long, but she showed clear understanding of the necessities to meet clinical guidelines. Judith had received a total of fifty intravitreal injections, but she reported feeling nervous and "*short of breath*" every time she was having her treatment:

> *"… they put the other drops, then they start with the iodine… And that seems so long. If you could just go in there and have it done right away with just the drops… But waiting for that and all that you then go... [demonstrates nervousness] and of course I am short of breath actually… getting anxious, you know, lying down there."* (PA10)

Remembering a painful past experience, patients worried about injury to their eye:

> *"And she grabbed the needle and then she couldn't get the needle out. So, it did hurt quite a bit…The problem is, now I know what's coming. Just the thought of having a needle in."* (PA07)

In comparison, the practitioners recognised patients' feelings of apprehension, including fear, anxiety, and suspicion prior to and during the injection procedure:

> "*It's always the unknown which is more scary..."* (OPH2)

"Normally patient says it's the thought of it you know… they just feel lining something in their eye. They are startle." (OPH1)

Familiarising with the environment and clinical procedures helped some patients feel more secure:

"I think I got to the stage, um, where I know exactly what's going to be happening so…that part of it doesn't worry me at all. Apprehensive, but as soon as I sit in that and lay in that chair and go down, she puts this cage thing in on my eyelids… that's when I start getting a little bit wound up. And as soon as it's in, I'm fine." (PA08)

Subtheme 1.2. - Fear of losing eyesight and recognising treatment benefits

- Coping mechanisms to manage apprehension

The practitioners used their observations of responding to the needs and preferences of patients in managing their treatment-related anxiety. Examples included rapport-building, reassurance, and distraction techniques, such as speaking to patients, holding their hand, asking them to relax and concentrate on their breathing or wiggling of their toes:

"I ask them to take a deep breath. Most of them they say it's very nice because they concentrate on breathing, and they don't feel it." (NUR3)

"…*you just got to be very patient with them and just try and reassure them*." (NUR2)

"*I like the opportunity of communicating. It eases the nervous tension*." (PA05)

"The nurse always holds your hand. I feel more relaxed." (PA11)

- In adherence with treatment

Practitioners' interactions with patients to explain how they could benefit from injections was an important factor in adherence. Understanding treatment benefits for preserving eyesight influenced patients' intention to accept the treatment plan:

"…talking to the patients in a nice way, in a gentle way, sometimes you can convince them of the benefits of an injection." (OPH2)

"*I would never discontinue the treatments because that's what enables me to still read and drive.*" (PA14)

"I find it marvellous really. I'm pleased with the way it's gone, and I can see my daughter and watch the news more." (PA01)

"Very apprehensive or like go to into my own mind or force myself to believe that if I didn't have these injections, then I was going to lose sight completely. ... so that's why I put myself through it all the time because I know in the end it's for my own benefit." (PA08)

"Every time I go, I know I got to have it done." (PA04)

- Feeling worried to stop receiving treatment

Some patients expressed concerns about disease progression when their appointment was rescheduled to a later date:

"I always have it every 8 weeks… One time I went for 11 weeks and that really worried me because I thought, oh my goodness what's going to happen to my eye?" (PA03)

"…occasionally it's been a bit longer than six weeks which I'm not very happy about. Because I don't think it should be longer than six weeks." (PA02)

- Feeling lucky and grateful

All patients expressed feeling grateful for the treatment, generally perceiving fear of losing eyesight to be worse over their anticipated apprehension:

"I'm very grateful to the NHS because the injections I know are very expensive." (PA14)

"I'll do anything to keep my sight." (PA13)

"It's a very small thing to pay to keep your sight. I think that is excellent and we are very lucky to have it." (PA10)

"*…and I don't think I would ever turn it down. I wouldn't say I can't have it done, you know."* (PA06)

"*That's what it is you know. If they're gonna do something to see if they can help me. Well, you know. Carry on!*" (PA04)

THEME 2:

Variability in pain experience during treatment

This theme relates to factors associated with the intravitreal injection procedure reported to impact the patient experience. These include, a) the application of anaesthetic drops and chlorhexidine/povidone-iodine, b)

placement of eyelid speculum, c) placement of surgical drape, and d) injection. It also highlights the varying levels of pain reported and the impact of quality-of-care delivery on patient experience.

Subtheme 2.1. - Preparation steps

- Instillation of anaesthetic eyedrops

Patients most commonly reported experiencing a stinging or burning sensation during application of the anaesthetic eyedrops:

> *"When they put the drops on, the second one I think it is, makes it burn a little bit."* (PA04)

> *"It stung a bit..."* (PA05)

- Application of chlorohexidine/povidone-iodine

Chlorhexidine or povidone-iodine are used as antiseptic agents applied on the surface around the area of the eye. Molly has described her experiences with povidone-iodine covering her face and reported a stinging sensation, though short-lasting and not of concern:

> *"You know, it [iodine] either goes running down in here. Not that it matters, or you know you think oh god that was a bit... It stings for a second but then when they start putting the other injections…you don't know it's there."* (PA03)

- Placement of eyelid speculum

The placement of an eyelid speculum is essential for intravitreal procedures to isolate the patient's lids and lashes from the needle and injection site, and also to provide a sterile field. Judith reported never having any concerns

with the eyelid speculum, as the nurses apply plenty of eyedrops to anaesthetise the eye:

> *"Actually, they put so many drops in and it seems too numb…and of course she's just waiting because there's so much going on before the injection, cause they put a hell lots of drops in…"* (PA10)

- Placement of surgical drape

Surgical drape is used to prevent or reduce the incidence of infections. Participants expressed different opinions on the application of the drape. Neither patient 10 nor patient 4 found the draping unpleasant, instead, the drape acted like a "barrier" to prevent them looking directly at the nurse holding the needle:

> *"Well, I'm glad when that's done [drape placement]. Cause you can't see otherwise, the hand goes back and forth…"* (PA10)

> *"And they clean my eyes and then the put over my face like a mask thing so that you don't see the injection coming towards you…"* (PA04)

Others felt uncomfortable at the beginning, but their experience has improved once they were familiarised with the procedure:

> *"The thing that goes over your face [the drape] that's not very nice… I was scared when I first went first couple of times, but now I got used to it."* (Margaret)

However, there was one particular case, who felt as though he was not getting enough air when the drape was placed with it covering his face:

"…then they put this face [drape] over, which I find a little bit, um, awkward… I'll do say do you mind if I don't use it because I hate breathing warm air…I feel uncomfortable with that on." (PA08)

Subtheme 2.2. - Intravitreal injection: expecting vs experiencing

The eye clinic commonly administered anti-VEGF agents, ranibizumab or aflibercept as part of the intravitreal injection procedure. Most patients experienced a stinging sensation or reported a "*bump*" felt on the eye upon needle entry, or "*breaking through the surface*".

- <u>The feeling of pressure</u>

"But it's all of a sudden having a pressure on the eye as the needle tries to break through the surface." (PA08)

Andy, reported holding his breath and tensing up at the time of the needle entry, resulting in the needle being difficult to be removed causing him pain:

"… that was the worst experience because I uh, instead of relaxing, I can't stop. And apparently there's muscles in your eye. And because it hurts, I tend to hold my breath and tense up." (PA07)

- <u>Experiencing pain and discomfort</u>

The pain experience varied across individuals some described it as dull aching, mild, like a "*pinprick*", or "*when you're having your tooth out*", whilst others experienced a sharp pain because of perceived lack of anaesthesia:

"I didn't have enough anaesthetic. It was quite sharp." (PA12)

"It is just like a pinprick only a bit harder." (PA10)

"But sometimes I just feel like the injection you get when you're having your tooth out. Very mild pain." (PA05)

"You then wait for the torture, I call it… The injection. Bloody awful…it's a bad experience. When they push the needle into your eye, it's like a dull aching pain..." (PA07)

Whereas practitioners reported that it is unusual to encounter patients who experience pain. The dissonance between patients' and practitioners' perceptions of the patient experience was expressed by one as:

"*It's very rare it happens I must say… Not even one patient in a week*." (NUR3)

"…you can reassure them that this is not going to be painful." (OPH2)

"They say, it's a common practice, you don't experience any pain. But you do. It's not pleasant." (PA07)

- Injection technique

The practitioner further explained that a skilled injection technique required "knowledge of anatomy" and "experience" to lessen a painful injection, consistent with patients' perception of the technical ability of the individual performing the injection:

"I hold the bevel parallel to what I know the anatomical alignment of the sclera fibres. Then when you go in, you don't really cut any of these fibres. That's when the pain is felt less." (OPH2)

"The injections vary. It's like anything that involves a technique. Some nurses and doctors have a better technique than others." (PA14)

"So only one out of all the 35 injections I've ever had this hurt. And I thought, oh my god, I hope I will never have her again… She was a doctor." (PA03)

Most patients perceived the injection as painful, but "*instant*" and *"over quickly*":

"It's bearable. I'm sure there are much worse things than having this done…It's painful, but over very quickly." (PA06)

"Well, it's only instant. It's soon as they pull the needle out, it's, the pain is gone. I expected it to be bad, but there was just a short pain for one second…that was easy." (PA07)

*"…it is painful, but over very quickly…" (*PA10)

Subtheme 2.3. - Impact of quality-of-care delivery on patient experience

Practitioners explained that their level of expertise relied on their ability to make clinical judgments, and upon continual learning and evaluation of performance. Adapting their practice to patients needs aimed to developing and maintaining patient rapport and trust.

- Observation and reflective practice

When patients reported pain, a nurse practitioner reflected on her practice:

"One patient would come and say, oh I felt that…Of course you would reflect…What could have I done better? It's constantly improving your practice based on what the patient has told you." (NUR4)

Strategies were adapted, such as applying more anaesthetic or waiting longer than normal for the anaesthetic to take effect:

> *"What I do is when they had a drop of iodine in after the anaesthetic, I ask if it stings. If it stings, then maybe they need more anaesthetic."* (NUR2)

> *"If you give a bit of more time for the anaesthetic to settle is a much better experience for the patient…That patient might be somebody whom you need to wait for a little bit more."* (NUR4)

- Patient-practitioner interaction: meeting the needs of every individual

The injection procedure was demanding, nevertheless the practitioners maintained professionalism including positive attitude, and acknowledged the importance of adapting their own practice to meet patient needs:

> *"We adjust to the patient. Let's say we have a little old lady who cannot stretch herself at the chair, we offer to give her the pillow."* (NUR4)

> *"…the InVitria [assisting injection device] might not be a good idea, so I put a drape for anxious patients. Because you need patients' cooperation when you want to put the InVitria."* (OPH2)

> *"If they've got breathing problems…I would probably get my colleague to sort of hold up the corner [of the drape] …so their face is not so covered."* (NUR1)

> *"…she will lift the corner up [of the drape] and just so I can get fresh air, which is fine."* (PA08)

"Talk to the patient… You want to make them feel as they can trust you and that's a really important part to get that sort of therapeutic relationship going… Patients will know you. They will know how you work, and they will know exactly what to expect…" (NUR1)

"We try to be very professional. We will not show that we feel like that [fatigue]…" (NUR3)

THEME 3:

Post-injection experience and impact on patient recovery

This theme represents an exploration of the side effects following an intravitreal injection.

Subtheme 3.1. - Instructions and provision of patient information leaflets

Consistent with clinical protocol, clear instructions and provision of information leaflets encouraged patient participation in their health care and advised them on their antibiotic prescription, common side-effects, and potential complications of intravitreal injections:

"*Sometimes the pressure can go up after the injection and that can give pain… In future, tell them to take Diamox [acetazolamide], a pressure loading tablet before you inject.*" (OPH2)

"*Next day, you get floaty things and think, I hope that's all right. But then you look at the leaflets and yes, that can happen*." (PA06)

"*We will give the antibiotic to take home and the instruction on how they will have it, and a proper leaflet, in case there is any problem when they go home…*" (NUR4)

Patients were instructed to use chloramphenicol antibiotic eyedrops four times a day for four days:

> "*Came home and complied with their instructions…They gave me the antibiotic and used it four times a day for four days.*" (PA13)

Subtheme 3.2. - Expected side-effects

Following their injection, patients reported feeling sensitive and experiencing discomfort when exposed to sunlight. This is a result of the use of mydriatic drops for pupil dilation, a standard procedure applied in eye examinations. All patients however were advised to wear a hat and sunglasses and asked to be accompanied by another person following their treatment. Blurred vision, watery eyes, grittiness, "*floating discs", or "it feels you got sand in your eye"* were also experienced:

> "*Floaters, sometimes spots in the eye that sort of flick around a little bit. But normally after a day or two it wears off… It's like having a fly in your eye…*" (PA08)

> "*And sometimes you have a lot of floaters. It can leave you with a little sort of floating disks, but they are temporary, they go.*" (PA14)

> "*…there's a big black blob… it's like a black mess."* (PA06)

> *"… quite gritty feeling sometimes. And sometimes worse, sometimes okay. So that has varied over the injections. I've had occasions when it waters a lot and occasions when it feels you got sand in your eye."* (PA03)

Subtheme 3.3. - Patient-reported side-effects associated with pain

Soreness, eye pain and irritation were described by many patients following their intravitreal injection which were reported to last between 24 and 36 hours. Some patients also associated their experiences with headaches and the anaesthetic wearing off, also leading to trouble resting or sleeping:

> "*When the numbness wears off, it then starts to feel a bit sore so often*..." (PA11)

> *"But then I'll come home and as the anaesthetic wears off, which is about four hours later… And then very often I'm getting very gritty and sore… I can't sleep, honestly because of the irritation is there all the time... It's itchy. Very itchy."* (PA08)

> "*The aftereffects of the injection I think are worse than the injection itself… Little pain, a little discomfort, a little dryness…It's only for maybe 24-36 hours and then it's fine.*" (PA14)

> *"I have had a headache sometimes. I don't suffer with headaches, never have. But um, I sort of have an ache just by there [demonstrates on side of eye]"* (PA09)

Practitioners explained that povidone-iodine may cause eye dryness and that innocent rubbing or blinking of the injected eye frequently causes corneal abrasion which can contribute to a painful experience:

> "*The iodine dries the eye out, so they get discomfort that night and the next day.*" (OPT1)

"*Very often when they come out of the injection, they start blinking or they rub their eyes and this will create a scratch, corneal abrasion. This is very painful once the anaesthetic goes away…*" (OPH2)

Subtheme 3.4. – Pain relief techniques

Pain resulting in sleep disturbances can have negative implications on patients' postoperative recovery. To manage post-injection pain, patients reported applying a hot compress or taking paracetamol and resting:

"*If you have an injection first thing in the morning, if there is any discomfort, the worst is over by the time you go to bed… If it's a late injection and my eye is very sore, then I might have a very restless night... I get a like a compress with hot water on my eye.*" (PA14)

"*After the injection sometimes, I take a couple of paracetamol.*" (PA05)

Practitioners generally advised patients to take their usual pain relief medication including paracetamol or ibuprofen to manage any pain at home:

"*If they feel that they would have any discomfort, I will always advise them to take some paracetamol if they wanted to.*" (NUR2)

Main Theme	Subtheme(s)	Illustrative Quotations		Comment
		(Patients)	(Practitioners)	
Fear of losing eyesight and apprehension on patient adherence to treatment	Fear of the "unknown" and the feeling of suspicion	"I mean the fact that I would just have to have a needle in my eyeball is not very good." (PA02)	"Normally patient says it's the thought of it you know… they just feel lining something in their eye. They are startle." (OPH1)	Agreement
	In adherence with treatment	"So relieved to find you could have some treatment that you didn't really mind. It was better than nothing." (PA12) "Well one of my consultants. And he was very reassuring. And I put my confidence and trust in him." (PA05)	"…talking to the patients in a nice way, in a gentle way, sometimes you can convince them of the benefits of an injection." (OPH2)	Agreement
	Coping mechanisms to manage apprehension	"I'm now going to give you the injection [they say] …they prepare you for it." (PA14) "They always do it. When you're in a chair, you don't know where to put your hands really. And she would always hold your hand." (PA09)	"I explain step by step, so they're involved. Most patients, I realise, they like that." (NUR3) "If there is someone who is particularly anxious the healthcare assistant would always make sure they hold their hand, so they got some sort of comfort there." (OPT1)	Agreement

Table 6.4.3 – Comparison of patients' and practitioners' perspectives on the treatment experience. Abbreviations: PA, patient; OPT, optometrist; NUR, nurse; OPH, ophthalmologist.

Main Theme	Subtheme(s)	Illustrative Quotations		Comment
		(Patients)	(Practitioners)	
Variability of pain perception during injection	Intravitreal injection: expecting vs experiencing	"…there's a sting and a pressure. And that's the same…that's the only way they can get it in you know." (PA06) "…they say, it's a common practice, you don't experience any pain, but you do. It's not pleasant." (PA07)	"There is a lot of anaesthetic used…you should not feel anything from that side of things… What they should really feel is a pressure…" (OPT1) "…you can reassure them that this is not going to be painful." (OPH2)	Dissonance
	Impact of quality of care delivery on patient experience	"She said, I like to wait." (PA06)	"The time is not a bad thing because you need time for the anaesthetic to work better and for your iodine to clean the eye better. Sometimes working too quickly is not a good idea." (OPH2)	Agreement
		"And she always gets hold of your hand just to reassure you, so she can feel the tension that's going in there." (PA08) "…she will lift the corner up [of the drape] and just so I can get fresh air, which is fine." (PA08)	"If there is someone who is particularly anxious the HCA [healthcare assistant] holds their hand, so there that they have got some sort of comfort there." (OPT1) "If they've got breathing problems…I would probably get my colleague to sort of hold up the corner [of the drape] …so their face is not so covered." (NUR1)	Agreement

Table 6.4.3 – Comparison of patients' and practitioners' perspectives on the treatment experience. Abbreviations: PA, patient; OPT, optometrist; NUR, nurse; OPH, ophthalmologist (continued).

Main Theme	Subtheme(s)	Illustrative Quotations		Comment
		Patients	**Practitioners**	
Post-injection experience and impact on patient recovery	Instructions and provision of patient information leaflets	"And before I left the hospital I went to my consultant and told him and he said, don't worry. Blurriness will clear very quickly. And it did." (PA05) "And I mustn't rub it, you know." (PA14) "It's antibiotics. And you have to take them 4 times a day, 16 altogether. And they say you can carry on. Sometimes I do it for 5 days." (PA03)	"It gives a bit of a blur initially…you have to explain these things to them. If they're not being informed about it, they ring because they're worried about it." (OPH2) "Give them careful instructions not to rub the eye." (OPH2) "And if your eye is dry or gritty, you can use more of that [chloramphenicol], it won't harm. It just eases the eye, like you know, the grittiness and the dryness of the eye." (NUR3)	Agreement
	Home remedies for ocular pain	"They just say to take paracetamol if you do [feel pain]." (PA06) "I get a like a compress with hot water to hold of my eye." (PA14)	"If they felt that they would have any discomfort, I would always advise them to take some paracetamol if they wanted to." (NUR2) "I think most of them will kind of go to bed with a cold compress on their eye afterwards. That is what they generally report." (OPT1)	Agreement

Table 6.4.3 – Comparison of patients' and practitioners' perspectives on the treatment experience. Abbreviations: PA, patient; OPT, optometrist; NUR, nurse; OPH, ophthalmologist (continued).

6.4.3. Additional analysis

This section presents two illustrations of the interview data to gain an understanding of the procedures performed before, during and after an intravitreal injection. The results of this analysis along with the observations noted at the study site will be used to design the quantitative features (event markers) for the measurement of electrodermal activity during intravitreal injections (Chapter 8).

> "*Before we see the patient, we need to have the patient's notes… we have a system where we have a lot about how the treatment is going, So, we have the Medisoft, and we also have the patient's notes in front of us, so we check everything is there. You've got the doctor's prescription. Obviously, there's an appointment. And then the patient before they actually see us for the injection, they should have had their visions done. Eye drops and the scan. So once all of them have been done, we call the patient. You will do an identification checklist first. It's all documented. When we've done that identification checklist, we need to make sure that the patient is happy to have another treatment. So, we consent. Verbal consent at least. Because the written consent has already been done during their first appointment. These are all under the protocol. And then we check for allergies. So, if the patient is happy that we're going to carry on, the health care support workers who are assisting us because normally there are two nurses in the treatment room… We've got the health support worker to assist us, and then the nurse practitioner who does the actual injection. Once everything is okay to go ahead the assistant will do all the anaesthetic drops and then all the required drops, and also the iodine*." (NUR4)

"*…first thing I would do is check the patient's details, so I make sure I've got the right patient… also check the screen to make sure the right drug is given and which eye and clarify this then with the patient. Then I will get my assistant to put anaesthetic drops in. We use oxybuprocaine. In that time period then when they're doing that obviously we will recheck details as well we'll also instil some iodine. Obviously if the patient is allergic to iodine, we wouldn't use iodine we'd use chlorhexidine… I will obviously be scrubbing at this time. So, I clean my hands with iodine solution or chlorhexidine solution. Once that's done then I will set up my trolley, so I have a sterile trolley, I've got sterile gloves on... my mouth is covered with a mask, I've got a gown on, because obviously we don't want any droplets going on to the eye when I'm injecting cause there's infection. What I'd do then is set up, then clean the eye, and my patient is ready. Obviously, you want to make sure that the needle is covered just before you use it and what I'll do then I'd put more anaesthetic and more antiseptic in. I will then put the drape on, put the speculum in, add another drop of anaesthetic in just before I give the injection. Mark the eye, inject in the needle and out, and obviously take everything away then. Before I take the speculum out, I check that the patient can see my hand and able to catch my fingers and check that they're feeling okay afterwards. We will then describe to them or tell them about the antibiotics they need to take. So, we give antibiotics for four days after the injection. We'll go through that with them, give them some leaflets if they need to have, emergency contact numbers and then if everything is okay then there's no problems, patient will go home."* (NUR1)

6.5. Discussion

Building on previous work (Tailor et al. 2011; Moisseiev et al. 2012) that focused on quantitatively assessing pain during anti-VEGF treatment, this study aimed to explore patients' and practitioners' perspectives using an in-depth qualitative approach to gain insight into patient experience and treatment adherence. The results of this study revealed that post-injection ocular pain is more common than previously recognised with soreness and irritation experienced up to 36 hours following most anti-VEGF injections. Furthermore, the analysis showed the value of patient-practitioner interactions to facilitate understanding of treatment expectations and individual needs. It has also emphasised the need of monitoring and assessing pain before and immediately after injection.

Ocular surface irritation, vitreous inflammation, or an increase in intraocular pressure (IOP) (Lerebours et al. 2016; The Royal College of Ophthalmologists 2018) have been described as common causes of pain. Most patients in this study reported side-effects including eyes watering, grittiness, soreness, and irritation 4-6 hours after treatment. Experiencing pain and discomfort can be associated with the return of full corneal sensitivity around 40 minutes after application of anaesthesia, or because of the irritant properties of iodine (Papanikolaou et al. 2011). Another important finding was the long-lasting ocular pain between 24- and 36-hours affecting patients' sleep and recovery, an outcome that has not previously been described in studies of patient experience (Thetford et al. 2013; Polat et al. 2017; Boyle et al. 2018b). Headache reported in the current study may

reflect previous observations (Pang et al. 2015; Lerebours et al. 2016) on the association between headaches, ocular pain and an elevated IOP following intravitreal injection. Practitioners discussed in reviewing patients' medical records to determine history of allergies, ocular infections and IOP to treat patients accordingly.

Consistent with the literature (Finset 2013; Michelotti et al. 2014; Elvira 2017), this research found that providing clear instructions and acknowledging patient fears, concerns or expectations builds rapport and can contribute to a positive patient experience. Provision of information leaflets after treatment helped patients recognise common side-effects, thus a helpful and reassuring source of information. Moreover, providing simple and specific instructions on their prescription antibiotics and to avoid touching, rubbing, or scratching the injected eye can help lessen itching and pain. These findings corroborate the ideas of Boyle et al. (2018) who highlighted the importance of patient engagement with treatment. However, the chronicity of AMD and the routine nature of the anti-VEGF injections could lead patients to perceive pain as less salient, influenced by previous experiences reported in this study. Practitioners should consider routinely warning patients of possible pain and advice on pain relief techniques for ocular pain, such as local ice compress (Li and Wang 2016) and analgesic use (Sanabria et al. 2013). Ice for instance, had shown effectiveness as a local anaesthetic during injection (Lindsell et al. 2015) and significantly reduced patients' pain, burning and discomfort at 10 minutes post-injection (Yahalomi et al. 2020).

It has been suggested that morphological changes to the sclera have been associated with repeated intravitreal injections believed to contribute to greater difficulty with needle insertion (Zinkernagel et al. 2015). Patients who participated in this study have received less than median 18 intravitreal injections have not responded any differently regarding their pain experience during the needle entry compared to those who received 18 or more injections. Nevertheless, particularly anxious patients reported experiencing pre-treatment anxiety even after repeated injections. Segal et al. (2016) found a significant correlation between increased pre-treatment anxiety and perceived pain in intravitreal injection. Based on the results of this study, this could be explained by the typical reported reactions of anxious patients, including muscle tension, eye blinking, or “jumping”. According to Oztas et al. (2016), these responses could potentially result in ocular surface abrasion by increasing the likelihood of altering the needle position during injection. This finding was also reported by one of the practitioners during our interview sessions.

Previous studies have quantitatively assessed pain and discomfort but with insufficient explanation of the reasons as to why patients reported these sensations (Tailor et al. 2011; Yau et al. 2011; Moisseiev et al. 2014; Andrade and Carvalho 2015). Conversely, Segal et al. (2016) compared pain VAS scores to VAS for anxiety scores and found a correlation between preprocedural anxiety and pain in intravitreal injections. Consequently, a qualitative approach was employed in this study to provide in depth insight of patients’ feelings (Green and Thorogood 2014) and to explore aspects of

the patient experience associated with pain, discomfort or anxiety that were not emphasised in these previous studies. One of the most important factors identified by patients was the build-up of anxiety and apprehension about intravitreal injections, particularly for their first treatment. Patients however recognised the importance of repeated intravitreal injections to prevent disease progression and to preserve eyesight. The fear of losing their eyesight was more important consideration than fear of the procedure. Their initial feelings were considerably reduced following an injection as many of their anxiety or fears were linked to not knowing what to expect, 'the thought of a needle going into the eye', and possible risks of the treatment, such as stroke or heart attack as reported in the clinical guidelines (The Royal College of Ophthalmologists 2018). These findings substantiate previous findings in the literature (Tailor et al. 2011; Thetford et al. 2013) with patients reporting the actual experience of the injection to be less unpleasant than was expected. While generally patients feel relief following their first injection, the findings of the current study found a small number of patients being apprehensive every time they underwent treatment.

Anti-VEGF intravitreal injections are the most performed ophthalmic procedure worldwide (Brown et al. 2006a; Rosenfeld et al. 2006a; Avery et al. 2014). Our findings revealed varying degrees of patient discomfort and reporting dissonance between patients' expectations and their actual experiences during injection (table 6.4.3). Some patients reported a pressure, but others experienced a dull aching, sharp or just a mild pain, different to practitioners' views on a feeling of pressure. Practitioners

typically use the term ‘pressure’ to reassure patients, however, mutual trust and providing realistic expectations are important aspects of treatment (Dacosta et al. 2014). Practitioners reported the importance of technical competency and continuing professional development. This is consistent with professional guidelines (The Royal College of Ophthalmologists 2018), indicating that practitioners should periodically review and evaluate their performance (Flaxel et al. 2020). Not all practitioners acknowledged the proportion of patients experiencing pain and this highlights the importance of implementing patient feedback.

In the current study, procedure-related pain was commonly reported, with patients identifying the needle entry as associated with the greatest pain and discomfort. Pain was described as dull aching, instant, and mild. According to Tailor et al. (2011), the insertion of the needle was the most unpleasant step, followed by the placement and removal of drape, and insertion of speculum. One patient found the placement of the drape causing uncomfortable breathing, an issue not previously reported in the literature (Tailor et al. 2011; Thetford et al. 2013; Boyle et al. 2018b; Berger et al. 2019). Additionally, patients seeing surgical instruments such as the use of scissors to cut the drape close to their eyes (Tailor et al. 2011), or seeing the surrounding practitioners (Mekala et al. 2021b) caused anxiety. However, contemporary drapes used at this hospital have a pre-cut hole. The use of different drapes in clinical practice might therefore explain discrepancies in the studies exploring patient experience.

Currently, no method of anaesthesia prior to intravitreal injection has been shown to eliminate pain completely, but topical anaesthesia was commonly used because of its ease of application (Blaha et al. 2011; Yau et al. 2011). A 0.4% solution of oxybuprocaine used in the clinic under study, delivers a maximum anaesthetic effect after 5 minutes when administered at 90-second intervals and lasts for 15-20 minutes however, it is known to cause greater initial stinging than proxymetacaine (Brayfield 2017; NICE 2019). Participants reported a stinging or burning sensation following application of anaesthetic eyedrops, consistent with previous findings (Tailor et al. 2011; Thetford et al. 2013). Further, participants noticed variability in the volume of eyedrops they received between treatments that could relate to differences in the drug efficacy. Also, a brief, stinging sensation was reported for the application of iodine. The use of chlorhexidine or iodine however is essential to reduce the risk of post-injection complications (The Royal College of Ophthalmologists 2018), such as endophthalmitis, although none were reported in this study. The irritation that patients experienced following their treatment is likely to be associated with the known irritant properties of iodine used for the asepsis of periocular skin, eyelashes, and eyelid margins (Papanikolaou et al. 2011). The findings of this study support allowing enough time to reach adequate anaesthesia, however alternative methods may be investigated to meet patient needs, such as subconjunctival injection and anaesthetic gel (Yau et al. 2011; Andrade and Carvalho 2015).

Non-adherence to treatment has previously been linked to fear of the injection and disbelief regarding its benefits (Polat et al. 2017). Our study supports that establishing and maintaining a therapeutic relationship contributes to patients' confidence and engagement with their treatment course (Dacosta et al. 2014; Dang et al. 2017). Patients' motives for continuing treatment were related to their understanding of the severity of the consequences of untreated AMD and the treatment benefits, giving them the ability to carry out daily living activities.

6.5.1. Strengths and limitations

Purposive sampling can be susceptible to researcher bias, however, to minimise this, judgements were based on the eligibility criteria of the sample. Individual interviews were conducted in a private setting assuring participants of the confidentiality and anonymity of their data to reduce social desirability response biases. In this single-centre study, the findings presented may not be transferable to other regions of the UK or countries, particularly where protocols differ. However, a thorough description of the research context and sufficient data collected through in-depth interviews was presented, to allow readers to assess whether the findings are transferable to their context.

6.6. Conclusion

Ocular pain was a widely reported side-effect in many but not all anti-VEGF injections, with soreness and irritation commonly reported to last for up to 36 hours affecting patient recovery. Practitioners should adapt pain assessment tools to evaluate the patient experience during and following each injection and deliver ongoing information to support patients in managing pain at home. All patients recognised the importance of adhering to treatment to reduce the risk of further vision loss, despite their anticipated anxiety and experiencing pain or discomfort during or following their treatment.

6.7. Development of quantitative features

From the analysis of the interview data of healthcare practitioners, the following quantitative features will be used as event markers in the measurement of electrodermal activity in Chapter 8:

1. Anaesthetic eyedrops (oxybuprocaine hydrochloride/proparacaine hydrochloride)
2. Povidone-iodine/chlorhexidine
3. Placement of surgical drape
4. Placement of eyelid speculum
5. Anaesthetic eyedrops (oxybuprocaine hydrochloride/proparacaine hydrochloride)
6. Eye marking
7. Intravitreal injection (Ranibizumab, Aflibercept)
8. Antibiotic eyedrops (chloramphenicol)
9. Removal of eyelid speculum
10. Removal of surgical drape
11. Povidone-iodine/chlorhexidine washout

6.7.1. Hypothesis generation

The interview data analysis identified the three most significant factors to be influencing patient experience during treatment. These include: 1) application of anaesthetic and povidone-iodine/chlorhexidine drops, 2) placement of surgical drape, and 3) intravitreal injection. Hence, it could be hypothesised that these factors will be associated with a higher level of arousal during intravitreal treatment and therefore recording of higher electrodermal activity responses. Additionally, it may be the case therefore that these variations could be significant predictors of pain.

Chapter 7
The impact of the COVID-19 pandemic on patients with neovascular AMD receiving intravitreal injections: a qualitative study

This Chapter is a qualitative study of the patient experiences during the COVID-19 pandemic. This has been an additional study to the original research protocol of the thesis, nevertheless, the findings of this study provide an in-depth understanding of the psychosocial impact of COVID-19 on the patient experience, with some participants reporting vision deterioration and expressing feelings of anxiety and loneliness.

7.1. Introduction

On March 11, 2020, the World Health Organization (WHO) formally declared the global coronavirus (COVID-19) pandemic (World Health Organisation 2020). There have been 621 million confirmed cases and 6 million deaths worldwide, with nearly 24 million cases in the UK (as of 20 September 2022) (ourworldindata.org/coronavirus-data 2021; Worldometer 2022). The COVID-19 pandemic had a profound impact on health care systems and interfered with routine practice in all fields of medicine including ophthalmology (Borrelli et al. 2020; Korobelnik et al. 2020; Petrovski et al. 2020; The Royal College of Ophthalmologists 2020; Wickham et al. 2020). Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents are the first line treatment in neovascular age-related macular degeneration (AMD), polypoidal choroidal vasculopathy, and diabetic macular oedema (Nikkhah et al. 2018). Existing research recognises the importance of regular intravitreal injections to slow disease progression (Mitchell et al. 2010). Recent work has established that delayed anti-VEGF treatment due to COVID-19 has led to loss of visual acuity (Song et al. 2021; Yeter et al. 2021; Kim et al. 2022; Sekeroglu et al. 2022; Szegedi et al. 2022).

Routine ophthalmic clinical examination in close proximity to patients has raised concerns in ophthalmology practice regarding coronavirus transmission, thus increasing the risk of infection exposure (Petrovski et al. 2020; Seah et al. 2020). Consequently, risk stratification and triage systems were recommended early in the pandemic to prioritise and manage patients

who were at high risk of rapid and significant disease progression (The Royal College of Ophthalmologists 2020). Additional guidelines also included information on how to inform patients about their appointments, reassuring them of their safety against COVID-19 infection risks. Nevertheless, the volume of patient visits and intravitreal injections declined dramatically during the COVID-19 pandemic with a 75% and 53% reduction, respectively reported in an Italian medical retina clinic (Borrelli et al. 2020). Concerns were raised about patients experiencing fear of contagion and uncertainty accessing public transport and visiting hospitals for their routine intravitreal injections, anecdotally feeling, "*too scared to see a doctor or optician*" (Macular Society 2020). Also, it has previously been observed that patients perceived personal safety as an important concern when travelling by public transport to and from their appointments (Boyle et al. 2018b).

It is well established that delayed follow-up and treatment have been associated with permanently vision loss in patients diagnosed with AMD, glaucoma, and diabetic retinopathy (Foot and MacEwen 2017). For example, Arias et al. (2009) reported that delayed initiation of the treatment course led to significant loss in visual acuity. Recently, investigators have demonstrated that people with neovascular AMD experienced the greatest vision loss during the COVID-19 pandemic compared to those with retinal vein occlusions or diabetic macular oedema (Stone et al. 2021). Additionally, the impact of COVID-19 on AMD care has resulted in decreased diagnoses and delays in treating new AMD cases and led to inferior baseline clinical characteristics and short-term visual outcomes

(Borrelli et al. 2021). High rates of depression have been reported in patients with a vision impairment (Evans et al. 2007; Nollett et al. 2019a) and fear of sight loss during the pandemic may worsen patients' depressive and anxiety symptoms affecting their mental health (Senra et al. 2016; Heesterbeek et al. 2017).

Although extensive research has been carried out on hospital reorganisation and restructuring, and short-term visual and structural outcomes, to the author's knowledge, there have been few empirical investigations into the perspectives of patients with AMD on treatment adherence and challenges faced at the time of COVID-19. Living with neovascular AMD and shielding during the COVID-19 pandemic may exacerbate patients' sense of uncertainty and fear of vision loss that could negatively impact their mental health. This qualitative study aimed to explore the experiences of patients with neovascular AMD regarding the COVID-19 pandemic and their intravitreal treatment. The objectives of this research were to gain insight into the patients' perspectives on the limitations to eye care, how they perceived delayed treatment, and how any anxiety and fear associated with COVID-19 risks have influenced patients' perceptions regarding treatment adherence.

7.2. Methods

7.2.1. Study design

Using a qualitative design, one-on-one semi-structured interviews were conducted remotely to better understand the individual experience of patients (Merriam 1998) during the COVID-19 pandemic. This study was reviewed and approved by the National Health Service Wales and the South East Wales Research Ethics Committee (19/WA/0004) on 19 August 2020. The study adhered to the principles stated in the Declaration of Helsinki and patients verbally consented to participate in the interview.

7.2.2. Method of recruitment and sampling

Potential participants who were identified prior to the onset of the COVID-19 pandemic for the study, "*Measuring electrodermal activity during intravitreal injections and evaluating the factors associated with post-treatment pain*" (Chapter 8) were invited to take part in this research via email or letter requests. Participants were recruited from a hospital eye clinic in Wales, UK using purposive sampling to meet eligibility criteria and diversity in experiences in terms of age and gender (Creswell and Guetterman 2018).

The study's initial sample analysis was conducted by applying the principles set forth by Francis et al. (2010). The researcher determined a provisional sample size of 10 to 13 participants and ensured a varied participant pool using purposive sampling. The decision on the final sample size was shaped by the richness of the data and the researcher's interpretation for

addressing the research question (Braun and Clarke 2021). The principle of information power (Malterud et al. 2016) was also supported to achieve the study aim.

7.2.3. Inclusion and exclusion criteria

Eligibility criteria required individuals to be aged 50 and above, to have a diagnosis of neovascular AMD, to be enrolled in a clinic for receipt of anti-VEGF therapy on or after March 23rd, 2020 (start of lockdown in Wales, UK), and to be able to provide informed consent. Exclusion criteria for patients included retinal pathology other than neovascular AMD, suffering from very poor hearing or unable to communicate in English.

7.2.4. Topic guides and data collection

The design of the topic guide (Appendix F) was based on themes identified from reviewing the literature on patients with vision impairment (Foot and MacEwen 2017; Nollett et al. 2019a; Macular Society 2020) and the effect of COVID-19 on ophthalmology services (Lim et al. 2020; Petrovski et al. 2020; Seah et al. 2020). Participants were also asked the two Whooley questions: "*During the last month, have you been bothered by feeling down, depressed, or hopeless?*" and "*During the last month, have you been bothered by having little interest or pleasure in doing things?*" (Whooley 2016) to gather information on their general health, in line with the NICE guidelines on depression (NICE 2022).

Interviews were conducted via telephone between November 2020 and February 2021. The researcher verbally explained the aims and nature of

the study before taking consent, and reassured participants of the confidentiality of their data. Verbal consent and interviews were recorded on an audio recorder (Olympus VN-541PC device).

Interviews consisted of open-ended questions allowing participants to express personal experiences and give their opinions on the topics discussed. The following is a list of questions included in the interview topic guide (Appendix F) for this study:

- *What is your knowledge on COVID-19? Do you understand the risks of COVID-19 to your general health?*
- *Have you had COVID-19, or experienced COVID-19 symptoms that required you to go to the hospital?*
    - *What did your healthcare provider tell you about COVID-19?*
    - *What have you heard about COVID-19?*
- *Did you have any concerns when you visited the hospital? Can you give an example?*
- *How does the Eye Clinic monitor your condition and provide guidance?*
- *How helpful were they for you? Were you satisfied with the outcomes?*
- *Do you understand the reasons your treatment has been triaged or delayed? Could you tell me more about it?*
- *Has COVID-19 risks influenced your decisions to attend appointments or continue treatment? Could you elaborate on that? What does that mean to you?*

- *Have you noticed any changes in your vision? How did you deal with that?*
- *What kind of support would be helpful for you at this time?*
- *Have you missed any of your appointments during the period of the pandemic? Why?*
- *Tell me about the place where you live. Who lives there with you?*
    - *How do you get to appointments? Has this changed?*
    - *What do isolation and social distancing mean to you?*
    - *What do you think is the hardest thing about isolation and social distancing? How do you deal with that?*
- *How have you felt about COVID-19 over the past few months? What words would you use to describe your experiences?*
- *Has this affected your daily routine activities that you usually enjoy?*
- *Have you used or currently using any strategies to cope with that? What support would you need to address that?*

A flexible approach permitted the researcher to use prompts and follow-up questions to gain further knowledge on the topic discussed (Creswell 2013). Member checks were also applied during the interview process to determine accuracy of the information collected (Creswell and Guetterman 2018). To ensure the trustworthiness of the interview data, member checks were used for confirmability by using prompts and follow-up questions to encourage participants to clarify their responses and provide additional insights. In this context, interview questions evolved from the planned topic guide. Participants were offered the opportunity to ask questions, add any other

information they considered important. Interview data were collected and analysed by the author (C.Y.).

7.2.5. Data processing and analysis

Interview data were anonymised, transcribed verbatim by a professional transcription service, and thematically analysed using an inductive (reflexive) approach (Braun and Clarke 2019), with the support of NVivo (version 12, QSR International) data analysis software. Data were analysed using the six-phase procedure suggested by Braun and Clarke (2006) which included familiarising with the data, initial coding and labelling of data, searching for themes, reviewing themes, defining, and naming themes, and producing the report in order to support the analysis and interpretation of the data. Reflecting on the values discussed in (Braun and Clarke 2021) the analysis centered on the researcher's engagement with the data and interpretative judgment about when to stop the coding process. Initial themes were then generated and reviewed by the first author (C.Y.). Producing the report involved a collaborative approach; themes were discussed with members of the research team to develop "*a richer more nuanced reading of the data*." (Braun and Clarke 2019).

7.3. Results

7.3.1. Characteristics of study participants

Participant characteristics are presented in table 7.3.1. Saturation was reached with 17 interviews. Patients had a median age of 79 (range 59-90) and 11 (65%) were female. There were 10 (59%) and 7 (41%) patients who reported living with their family or alone, respectively. A total of 16 (94%) participants responded negatively to both Whooley questions, and only 1 (6%) participant responded positively to one. This individual reported undergoing treatment for depression. At the time the interviews were conducted, 5 (29%) participants received their first dose of COVID-19 vaccine. All participants were English-speaking. Interviews ranged between 14 and 32 minutes (median = 17 minutes). Notably, dosing regimen was not captured in this study, and patients may have undergone varying treatment regimens at different stages of their treatment course.

Characteristic	Value
Age, median (range), years	79 (59-90)
Female sex, No. (%)	11 (65)
Ethnicity, No. (%)	
White Welsh	15 (88)
White British	1 (6)
Mixed British/Indian	1 (6)
Place of primary residence, No. (%)	
Lives alone	7 (41)
Lives with family	10 (59)
Responses to Whooley questions	
Negative, No. (%)	16 (94)
Positive, No. (%)	1 (6)
Vaccination status, No. (%)	
Vaccinated (one dose)	5 (29)
Unvaccinated	12 (71)

Table 7.3.1 – Participant characteristics.

7.3.2. Qualitative results

Thematic analysis revealed three main themes: 1) COVID-19 exposure risk and association with treatment adherence, 2) Patients' concerns and expectations related to care, and 3) Effects of isolation and social distancing on wellbeing (table 7.3.2). The results in this study provide important insights into the negative impact of lockdown and isolation on patients' health and wellbeing. Adapting to changes in daily routine helped most participants to manage loneliness, however those with co-existing AMD, cataract, and other underlying chronic conditions, felt more restricted to an active lifestyle; feelings of anxiety and depression were more common.

Theme	Subtheme(s)
COVID-19 exposure risk and association with treatment adherence	Feeling safe in the healthcare setting
	Priority of vision preservation over COVID-19 risk
	Factors contributing to missed appointments and delayed treatment
	Vision deterioration and loss of independence
	Interrupting loading phase in newly diagnosed patients with AMD
	Fear of permanent vision loss
Patients' concerns and expectations related to care	Patients' needs and communicating treatment progress
	Frustration at failure to follow-up patient contact
	Insecurity and fear of falling following intravitreal injection
Effects of isolation and social distancing on wellbeing	Impact of lockdown on lifestyle and socialising
	Challenges faced by those with AMD in addition to other comorbidities
	Feelings of anxiety, depression, and loneliness

Table 7.3.2 – Main themes and subtheme(s) generated from the thematic analysis.

THEME 1:

COVID-19 exposure risk and association with treatment adherence

At the recruitment site, COVID-19 restrictions had affected ophthalmology practice, reducing capacity within the hospital eye services. Scheduled appointments for routine intravitreal injections were cancelled, and a backlog of follow-ups and delays in referral appointments was identified at the time of the study.

Subtheme 1.1. – Feeling safe in the healthcare setting

To keep staff and patients safe, the hospital implemented safety measures, including masks or face coverings, protective equipment, disinfection, patient screening and waiting area modifications. Patients reported the hospital was well-organised and felt safe during their visit:

> "… *there was a nurse there waiting, taking your temperature and I'd already got a mask on, and I'd used my own sanitiser, but it was all day waiting for you… They had masks on… And it was all nice and clean.*" (P03)

Subtheme 1.2. – Priority of vision preservation over COVID-19 risk

A common view amongst participants was recognising that adherence to routine intravitreal injections, in any case, was essential to preserve eyesight. They expressed willingness to attend their appointments despite concerns and media exposure of COVID-19 related risks:

> "*But I never missed an appointment…I have never had to rearrange one or anything, I have gone whenever they have said*." (P08)

"*I was concerned, but the concern of my eyes was more overpowering… We're pretty active, we do all the gardening, I cook... Everything I do, I do it with my eyes and without your eyes those things are just impossible to do*." (P10)

"*I was happy to go and have my injection, I wasn't scared*." (P17)

Subtheme 1.3. – Factors contributing to missed appointments and delayed treatment

Transportation issues and health related problems were the main factors that influenced patients' decision to cancel their appointment:

"*I cancelled an appointment, but that was not because I was afraid to go, it was 9 o'clock in the morning and I knew I wouldn't be able to get there. So, I did cancel it, but I haven't had any further referral*." (P01)

"*The last one I was supposed to go to I had so much pain from the prostate cancer that my back was aching so much I couldn't go*." (P12)

Additionally, the Eye Clinic faced an unprecedented demand on the appointment scheduling with some individuals reporting administrative errors:

"*They made a mistake once and sent the wrong date, on one appointment they said I hadn't turned up… then they found out that my paperwork had gone somewhere else and had been lost*." (P08)

One of the patients was told that she, "*must have slipped through the net"* (P11).

Subtheme 1.4. – Vision deterioration and loss of independence

All patients recognised treatment benefits and importance of adherence to routine intravitreal injections to stabilise disease progression, reporting satisfaction with their visual outcomes. However, delayed care was believed to result in patients experiencing vision deterioration:

"*The distortion started to go, but now it's all come back because of COVID and not being able to get my regular injections… it's more or less as if all the work we've done is undone really."* (P05)

"*I've had very much longer periods between my eye injections and my sight is not quite as good as it was, I think because of it…it's been a long time since my last appointment, which is worrying."* (P07)

"*I have lost low vision now because I haven't been having them regular*." (P08)

Two participants also reported loss of their driving ability:

> "*It is getting worse… While I was having the injections, things seemed to be stable, but since the last one, doesn't seem to be so good and I've had to stop driving*." (P01)

> *"They said to me that, my vision is now on the peripherals of not being able to drive any longer."* (P09)

Subtheme 1.5. – Interrupting loading phase in newly diagnosed patients with AMD

In a treat-and-extend regimen, treatment is initiated with a loading phase consisting of three consecutive monthly injections of anti-VEGFs, followed by monthly injections until disease activity is resolved, at which point the interval for the subsequent injection can be extended by up to 12 or 16 weeks. Newly diagnosed patients with AMD reported disruption of their loading phase schedule, with one person developing complications such as haemorrhage:

> "*So, I had two courses then in, one in January, one in February of Avastin, however, by the time I was ready to have the third the epidemic started… I couldn't have the third*." (P10)

> "…*I had actually gone for an emergency to Specsavers and that's when they told me that you have probably a haemorrhage at the back of your eyes. He was very nice, very helpful and he told me exactly*

what was happening, but he said you need an injection straightaway." (P17)

Cancellation of routine eye care has resulted in a significant increase in the intravitreal injection treatment backlog during the COVID-19 pandemic (Borrelli et al. 2020). The Eye Clinic made consistent efforts in informing all outpatients about appointment cancellations on intravitreal treatment, nevertheless their disease progression was not actively monitored.

Subtheme 1.6. – Fear of permanent vision loss

Concerns were expressed about the risk for permanent vision loss and revealed signs of vulnerability. Talking about this matter a participant said:

"*I could see it was slipping back again, the edges were curvy or wavy …and I tried to get help… I couldn't get help, there was no optician open, there was no consultants to see. I was afraid I was going to lose my eyesight before I got treatment."* (P10)

A small number of those interviewed alluded to the notion of delayed treatment in urgent care:

"*Rang the Consultant and said, I'm getting really worried that I'm going to lose sight and he rang up the hospital…they said she's not a priority, he said have a look at the form, it says urgent. And then finally I got an appointment*." (P10)

> "…*they were doing clinic at the [private hospital name] for people that their vision was deteriorating, had my vision deteriorated? And I said yes, it definitely had. And they said okay, well we are sending out appointments to people whose vision has deteriorated, I never heard any more*." (P13)

In addition to the disruption of intravitreal injections, patients with AMD also faced significant delays for cataract surgery. They described a large backlog of 10 months (46 weeks), with some experiencing worsening of the condition:

> *"…Boots the chemist said I have got cataracts in both eyes and that they need to be removed… there is a 46-week waiting list. So obviously I would like to get my cataracts sorted out as soon as possible. But you know I have just got to wait now, so that's a bit of a downside."* (P09)

In summary, COVID-19 restrictions significantly affected routine intravitreal treatment for patients with AMD, with the administrative team facing ongoing pressures in managing patients' appointment scheduling. Nearly 50% of the participants in this study described worsening of their eyesight and their inability to access timely treatment, living with the uncertainty of disease progression and fear of sight loss. Risks associated with COVID-19 infection have not influenced patient decisions in continuing treatment, however restrictions implemented had delayed intravitreal treatment for both urgent and non-urgent cases.

THEME 2:

Patients' concerns and expectations related to care

Three discrete reasons for concern and frustration were identified. First, lack of consistent communication to address patient needs. Second, failure to follow-up patient contact. Third, uncertainty on treatment outcomes and vision changes.

Subtheme 2.1. - Patients' needs and communicating treatment progress

The participants overall demonstrated that they would like to be more involved in their treatment discussions and be able to ask the Consultant specific questions and share concerns associated with their journey. Participants commented:

> "*I think that's the only thing I got about the eye clinic, you never get any update on your eyes, face-to-face with your consultant. I haven't spoken to [the consultant] must be…two years now… it would be nice now and again to have reassurance*…" (P03)

> "*I couldn't read the board like I did before… So, I wondered then had my sight got worse? I couldn't ask anyone; they all do different jobs… But if now and again we saw a doctor and he could explain if you are getting better, or if it's working."* (P08)

Patients facing treatment delays and uncertainty on follow-up appointments during the pandemic led to increased anxiety and fear:

"…*when I asked them, when would be my next appointment, they said we'll be getting in touch. Well now that leaves me, am I going to be a four week or am I going to be a six week and up to now I haven't heard from anybody… that's the kind of thing that is worrying*." (P10)

"*This is my eyesight, I want to see my grandchildren, I want to see my great grandchild, I want to be able to see their faces, but I just feel left out and missed, overlooked*." (P13)

Some felt that they needed more support and reassurance during the pandemic about their treatment course and follow-up appointments:

"*Well, I haven't had any guidance, or they haven't monitored anything because as I say the last appointment was the 11th of June 2020 … and I haven't seen anybody since then*." (P01)

"*Maybe a phone call once a month, how are you doing, how are you coping. I think they ought to have something like a community support nurse… I know they are stretched, and I do sympathise with them because they were inundated with COVID."* (P13)

Subtheme 2.2. - Frustration at failure to follow-up patient contact

There were some negative comments about the Eye Clinic's answering services and poor communication. Frustration was evident in a number of people's experiences. For example, participants commented:

"They have an answer machine on the end of their line … and that makes me very angry because you leave a message, and no-one gets back to you. So that doesn't make you feel or give you any confidence or make you feel good…" (P05)

"*The eye clinic had gone on for the whole year and I'd been missed out and that upset me more than anything… I feel angry, I feel angry about it. They really need to get their act together, they need to change their system because it's not working*." (P13)

Subtheme 2.3. - Insecurity and fear of falling following intravitreal injection

It is common for patients to experience blurriness of vision following their injection which is why patients are advised to travel home with assistance. However, hospitals have implemented a restricted visitor access between March 2020 and December 2020 to limit the spread of COVID-19. One patient reported fear of falling down the stairs:

"*…because of Covid they're not allowing anybody with you to come in for the injection… that makes me feel a bit insecure because after you get the injection, if I can't see properly I might fall down the stairs or after the injection if the eye is hurting and it's a bit difficult, if I don't have anybody there with me… it just makes it a little bit stressful*." (P17)

Ineffective communication with the hospital has led to patient dissatisfaction. Patients complained about the hospital's appointment service and lack of communication, expressing feelings of frustration. Patients experiencing uncertainty on their routine intravitreal injections and follow-up appointments also reported feeling anxious and worried about unmet expectations and fear of losing sight. Poor communication can have a negative impact on perceived care quality and patient experience (Elvira 2017).

THEME 3:

Effects of isolation and social distancing on wellbeing

The high volume of media coverage during the pandemic aimed to maximise public adherence to self-isolation and social distancing measures. This theme came up for example in discussions of the challenges and impact of COVID-19 control measures on wellbeing.

Subtheme 3.1. - Impact of lockdown on lifestyle and socialising

Questioning patients about the impact of lockdown on their daily routine activities and feelings of loneliness has evoked mixed responses. Some felt that their social life has been constricted:

> *"… it did affect my aqua aerobics, because they stopped it altogether… and that is not good for me because I do need to keep going because that's part of my social life as well."* (P01)

"*It means I can't hug my grandchildren and that's very sad and I feel that I've missed out on a year of their lives really."* (P11)

Participants reported ways to cope with feeling lonely and to interacting safely with their family, friends, or neighbours. They explained that engaging in healthy behaviours such as activities that they normally enjoyed, for example regular walking and staying motivated helped them adapting to change during the pandemic:

"I try to read The Times every day… I do a Sudoku every day, I try to play the piano most days and obviously I watch the television, I go for a walk every day, so I'm okay." (P14)

"*Well to me it hasn't been a bad experience because I've written a book… I'm in contact with lots of people who are involved in this book because it's a true story and I have found life quite interesting*." (P07)

Subtheme 3.2. - Challenges faced by those with AMD in addition to other comorbidities

Prolonged restrictions and social distancing measures increased daily living challenges for people experiencing sight loss alongside other chronic conditions, such as cancer or asthma. Prolonged restrictions have also impacted the hospice population who relied on sustaining social interaction. For example, inpatient hospice facilities had limited or prohibited visits from families. A patient with underlying chronic conditions receiving hospice care commented that:

"*…I've had prostate cancer… … Covid came along, and we were discharged. If I wanted anything to happen it would be for the day centre to open in [name of Hospice Care Centre]. It gave me a purpose you know."* (P12)

"*This backlog of people waiting to have their cataracts removed. So that's had an influence on it, which obviously reflects on my eyesight*." (P09)

"My guide dog does not see things like raised pavements as an obstacle and I have tripped so many times and fallen over raised pavements. I've broken my arm, everything. What worries me is people automatically rush to help you, and then the two-metre rule goes out of the window." (P13)

"I've developed asthma… And now with my breathing difficulty, I have to even be careful because I have to carry my inhaler with me, so I mean it was just one thing, now it's two things, so it's leaving me even more depressed..." (P17)

Subtheme 3.3. - Feelings of anxiety, depression, and loneliness

Social distancing and lockdown restrictions can impact mental health, triggering symptoms such as anxiety, stress, and depression. A participant reported that:

> "*So, it's left me severely depressed and full of anxiety, and lonely.*" (P17)

A lack of social opportunity or a change in circumstance can lead to feelings of loneliness and isolation:

> *"I live with my husband, but he is at work the whole day. I'm on my own and I've only the supermarket to go to. So, do shopping and that's because I can't meet people."* (P17)

> "*Bored, depressed, anxious... When I go into a shop – because of my visual impairment I take a long time to recognise something in a shop… I've got to pick it up and spend ages reading it, and then I realise there's a queue of people behind me waiting. I then get very anxious because I am holding up the queue and I am forever saying to people oh please go past, go past, I am so sorry. So, it makes me very, very anxious*." (P13)

7.4. Discussion

During the first wave of the COVID-19 pandemic between March and September 2020, patients with neovascular AMD in this study sample perceived lack of hospital communication and high uncertainty on their routine intravitreal treatment, living with the fear of potential vision loss. It was found that COVID-19 risks have not influenced patient decisions in discontinuing their routine injections, however inability to access eye care led some patients to experience vision deterioration resulting in loss of independence and mobility. Our results also provide important insight into the challenges posed by COVID-19 to patients with multiple comorbidities. Social distancing and isolation had negatively affected the wellbeing of most patients, especially in those with co-existing AMD, cataract, asthma, and cancer, reporting feelings of depression, anxiety, and loneliness. This study highlights the need for community engagement and information provision for social and emotional support to improve access to eye care and to support patients' wellbeing.

Adherence to intravitreal treatment is crucial for decreasing avoidable vision loss in neovascular AMD. Interestingly, all 17 participants in this study were unanimous in the view that adhering to their routine intravitreal treatment to preserve eyesight overpowered their fear of infection from COVID-19. This finding is contrary to previous studies which have reported that non-adherence to intravitreal treatment was associated with fear of contracting COVID-19 infection (Macular Society 2020; Ashrafzadeh et al. 2021; O'Connor et al. 2021; Rozon et al. 2021). For example, Rozon et al. (2021)

found that in a sample of 160 enrolled participants, the 13% responded that they "*would rather become blind than getting the COVID-19"* and the 12% "*considered not going to an appointment to limit the risks of being infected by COVID-19"*. This discrepancy could be attributed to the differences in study design, sample size and demographic characteristics. For instance, a qualitative research design with purposive sampling was adapted in this study to gain insight into patients' feelings and concerns compared to questionnaire research that targets larger sample sizes to develop prediction models of higher accuracy and precision.

The disruptions to treatment because of the COVID-19 pandemic could expose people living with eye diseases to an increased risk of permanent visual loss (Foot and MacEwen 2017). The second major finding was that half of the patients interviewed in this study experienced deterioration of their vision indicating the need for examination or urgent care. This finding broadly supports the work of other studies in this area linking delayed treatment with poor functional outcomes (Takahashi et al. 2015; Borrelli et al. 2020; Stone et al. 2021; Zhao et al. 2021; Szegedi et al. 2022). For example, Stone et al. (2021) found that delayed treatment (defined as more than 8 weeks from last review) had a significant impact on patients' visual acuity, reporting that 38.1% (74 eyes) had lost more than 5 letters compared to their baseline visual acuity. Despite re-established intravitreal treatment after lockdown, loss of visual acuity persisted during follow-up appointments, because of the prolonged interval in clinical visits (6.0 vs 19.6 weeks) and intravitreal injections (11.6 vs 29.4 weeks) in the first wave of

COVID-19 pandemic (Sekeroglu et al. 2022; Szegedi et al. 2022). The evidence from this study questions the efficiency of risk stratification and a triage system implemented in the site under investigation, during the study period.

Good communication and provision of clear information and guidance have been found to facilitate a positive patient experience improving the quality of care (Jenkinson et al. 2002; Rapport et al. 2019). Issues associated with lack of responsiveness to patient phone calls and appointment scheduling complications during the pandemic were particularly prominent in the interview data. These findings were also reported by O'Connor et al. (2021) and could suggest operational deficiency in hospital's administration system. Additionally, some patients felt that they had been neglected, while others experienced feelings of anger, anxiety, and concern. These views surfaced mainly in relation to patients' unmet expectations for follow-up and fear of further sight loss, in accord with recent studies (Rozon et al. 2021; Ting et al. 2021). Despite efforts made to maintain a sustainable ophthalmology practice (The Royal College of Ophthalmologists 2020), the rapidly evolving epidemiology of COVID-19 provoked substantial interruption of both urgent and non-urgent care in the AMD clinic. This combination of findings suggests the need for digital transformation in ophthalmology, to develop a structured phone system to assist with patient follow-up queries (O'Brien et al. 2017) and provision of remote consultations or monitoring to maintain eye care services during the pandemic (Gale et al. 2019; Wickham et al. 2020).

Psychosocial problems associated with isolation are more prominent among the vulnerable population including the elderly and those with pre-existing mental conditions (Perrin et al. 2009). Some patients in this study particularly emphasised experiencing anxiety and loneliness, consistent with previous reports of other epidemic and pandemic diseases (Taylor et al. 2008; Perrin et al. 2009; Tucci et al. 2017). For example, driving is one of the key aspects to personal independence (Fenwick et al. 2017; Paulus et al. 2017). For a small number of participants in the study, inability to access timely treatment for AMD or cataracts was the reason for losing their driving ability. Mylona et al. (2022) found that patients with neovascular AMD experienced reduced wellbeing with moderate clinical significance, particularly patients who reported a higher impact of COVID-19 on their treatment course. The loss of mobility can be discouraging, and fear of vision worsening can have a negative impact on mental health. Effective support and referral to other services as needed is important to assist patients with neovascular AMD experiencing anxiety, fear, or loneliness. Information provision of support groups involved in helping visually impaired people is necessary to help improve patient satisfaction.

7.4.1. Strengths and limitations

A limitation of this study is that the researcher relied on vocal cues over the participant's facial or behavioural responses, and this could compromise rapport and influence interpretation of findings. Samples were also collected from a single hospital setting performing intravitreal injections. Hence the findings may not apply to sites with different intervention protocols or management strategies against COVID-19. In this regards, further studies need to include wider range of population groups and to compare different hospital systems on risk stratification and triage. Further research should be undertaken to fully understand how this approach works and its implications on patient experience. Despite the probes used to gain additional information on the topic of discussion, participants' responses varied with some providing more detailed information on their experiences whilst others used shorter answers. In spite of its limitations, the findings of this research provide insights on the experience of patients with neovascular AMD and elucidates the extend to which their everyday living is impacted due to COVID-19 effects on ophthalmic care.

7.4.2. Conclusion

This study provides an insight into the experiences of patients with neovascular AMD during the COVID-19 pandemic. From the study, the 3 key findings are:

1. Patients experienced vision deterioration and felt more vulnerable to loss of independence and mobility than before COVID-19.
2. Isolation and social distancing have resulted in patients with co-existing AMD and other chronic conditions feeling lonely and depressed.
3. COVID-19 risks have not influenced patient decisions in continuing their routine intravitreal injections, instead they expressed concerns and felt anxious and terrified of losing sight due to lack of timely care.

Implications for future research and recommendations to practice are discussed using a narrative approach in Chapter 9 of this thesis.

Chapter 8
Measuring electrodermal activity during intravitreal injections and evaluating the factors associated with post-treatment pain

This chapter reports the quantitative study of this thesis, the second phase of the exploratory sequential mixed methods design. The systematic literature review in Chapter 4 presented factors associated with the experience of patients during the intravitreal injection procedure. It was recognised that self-report measures were not representative of the individual pain experience, and the combination of an objective physiological measure, such as electrodermal activity (EDA) may be used to supplement and validate these outcomes. Furthermore, the qualitative data presented in Chapter 6, participants described pain during injection as dull aching, instant and mild. They also reported long-lasting pain following injection and experienced soreness and irritation up to 36 hours affecting their sleep and recovery. The application of anaesthetic eyedrops (oxybuprocaine) and disinfection conditions (povidone-iodine, chlorhexidine), placement of the surgical drape, and the intravitreal injection (using 30-guage needle) were identified as potential predictors of pain.

8.1. Introduction

Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) is widely used for the treatment of retinal neovascular diseases, including neovascular age-related macular degeneration (AMD) (The Royal College of Ophthalmologists 2018). Commonly used anti-VEGFs include ranibizumab (Rosenfeld et al. 2006b; Martin et al. 2011b; Solomon et al. 2014b), aflibercept (Sarwar et al. 2016; Singh et al. 2017) and brolucizumab (Dugel et al. 2020; Pearce et al. 2022), and their frequency of administration depends on the regimen implemented in the clinical practice, whether *pro re nata* (as required) or treat and extend (up to 16 weeks) (Arendt et al. 2019). While the clinical efficacy of intravitreal anti-VEGF injections is well established (Hughes and Sang 2006; Melamud et al. 2008; Ogura et al. 2015), the invasive nature of the treatment has been shown to impact patient experience (Tailor et al. 2011; Sanabria et al. 2013; Thetford et al. 2013; Boyle et al. 2018b; Shin et al. 2018). Following anti-VEGF injections patients can experience pain, blurred vision, floaters, redness (Chong et al. 2010; Baumal et al. 2020), and more serious complications including sterile intraocular inflammation and infectious endophthalmitis (Cox et al. 2021). However, pain during injection is the most common complication broadly investigated in the literature (Yau et al. 2011; Moisseiev et al. 2012; Doguizi et al. 2017; Inaltekin et al. 2021). Since AMD is a chronic, progressive disease and multiple injections are often required, the pain and discomfort experienced by patients cannot be neglected (McClard et al. 2021).

Studies using self-report measures have been conducted on the perception of pain and factors associated with pain during intravitreal anti-VEGF injection. Procedure-related factors such as needle insertion, placement of the surgical drape and eyelid speculum were identified as significant indicators of pain (Tailor et al. 2011). Additionally, there are contradictory results in the pain scores reported for anaesthetic effectiveness (Kozak et al. 2005; Kaderli and Avci 2006; Blaha et al. 2011; Rifkin and Schaal 2012a; Cohen et al. 2014; Andrade and Carvalho 2015) and needle characteristics such as needle gauge, injection site and needle insertion (Rodrigues et al. 2007; Moisseiev et al. 2012; Güler et al. 2015; Haas et al. 2016; Loureiro et al. 2017). Anaesthesia before intravitreal injection varies widely in clinical practices, and includes topical eyedrops (e.g. proparacaine, lidocaine), topical lidocaine gel, topical pledgets, and subconjunctival or peribulbar lidocaine injections (Cintra et al. 2009). Other factors with a potential effect on pain include age, gender, injection history (Rifkin and Schaal 2012a; Haas et al. 2016; Shin et al. 2018), and type of anti-VEGF used (O Oshodi 2007; Rodrigues et al. 2011; Bilgin and Bilak 2019; Ertan et al. 2020). Anxiety has been previously recognised in ophthalmic care, such as intravitreal injections (Segal et al. 2016; Kayikcioglu et al. 2017; Shin et al. 2018; Herranz-Heras et al. 2020; Inaltekin et al. 2021), routine eye examinations (Margrain et al. 2003; Court et al. 2008), and cataract surgery (Zhu et al. 2020; Akoglu et al. 2021). However, little is known about the individual experience of pain and anxiety, and patient wellbeing associated with intravitreal injections.

Unlike self-reports, objective measures, such as electrodermal activity (EDA) (Boucsein 2012a) are less susceptible to social desirability bias and can capture aspects of emotional response that are beyond respondents' conscious control (Ciuk et al. 2015). EDA can be described as a psychophysiological indicator of emotional arousal and it is important to highlight that it is a multifaceted phenomenon, thus EDA has been used in several widely divergent areas of research to examine pain (Dubé et al. 2009; Loggia et al. 2011; Aslanidis et al. 2018a; Bari et al. 2018b), anxiety (Court et al. 2008), cognitive stress (Rahma et al. 2022) and depression (Bonnet and Naveteur 2004). Changes in EDA are related to the stimulation of eccrine sweat lands in the skin to reflect the sympathetic nervous system activity in response to emotional stimuli (Malmivuo and Plonsey 1995; Dawson et al. 2009; Boucsein 2012a). Court et al. (2008) evaluated patients' anxiety levels during a contact lens fitting consultation reporting high levels of arousal during the communicative interaction between the patient and optometrist. In this context, 'arousal' is the physiological correlate of anxiety. To the author's knowledge, the relation between objective physiological characteristics and patient reported outcomes on pain is understudied in ophthalmology research, particularly for intravitreal injections.

Whilst studies have investigated the impact of baseline patient characteristics on perceived pain with intravitreal injection, to the authors knowledge, no studies have assessed EDA during the intravitreal injection procedure. Such an assessment of physiological responses could provide

understanding of emotional, sensory, and cognitive modulation of pain experiences (Merskey et al. 1979).

8.1.1. Study objectives

Objective 1: To objectively assess pain at selected procedural steps of the intravitreal treatment and to explore the relationship between pain experienced and the different procedures used, patient demographics and wellbeing.

Objective 2: To explore characteristics such as patient demographics and clinical factors that might affect the degree of pain following intravitreal injections.

Objective 3: To evaluate the independent association of the characteristics identified with pain following intravitreal injections.

8.2. Methods

8.2.1. Study design

A cross-sectional observational design was used to examine the electrodermal activity in relation to pain, anxiety, and wellbeing measurements in patients with neovascular AMD receiving an intravitreal injection. Patients were recruited from a hospital eye clinic in Wales, UK from January 2020 to May 2021. The protocol of this study was reviewed and approved by the National Health Service Wales and the South-East Wales Research Ethics Committee (19/WA/0004) in January 2019. The study was based on the principles stated in the Declaration of Helsinki and written informed consent was obtained from all participants.

8.2.2. Participants

Eligible participants included patients with neovascular AMD, aged 50 and above, who were due to receive an intravitreal anti-VEGF injection in at least one eye. Patients with retinal pathology other than neovascular AMD (e.g. glaucoma or diabetes), with a cardiac pacemaker, who suffered from very poor hearing or unable to communicate in English or Welsh were excluded from this study. The recruitment process involved weekly screening of patient medical records by their care team to identify eligible patients, and ensuring that the practitioners, researchers, and staff members on-site were fully informed about the study. A consecutive sampling technique was employed to approach eligible participants via mail, email or telephone until the required sample size was achieved. To implement consecutive sampling, the scheduling appointment lists were thoroughly reviewed to

identify potential participants who were scheduled to receive an injection. These individuals were then approached in a sequential order.

8.2.3. Procedure

Figure 8.2.1 presents an overview of the experimental design. Prior to commencing the study, all participants received an explanation of the research. On obtaining written informed consent, all participants were then remotely interviewed to collect demographic data, including age, gender, and ethnicity, and additional characteristics such as alcohol and caffeine consumption, and current smoking status (Appendix I). On arrival at the eye clinic, electrodes were attached to the participant for measuring the electrodermal activity during the intravitreal injection procedure. Questionnaires on pain (SF-MPQ: MPQ, PPI) (Melzack 1987), anxiety (STAI) (Spielberger et al. 1983) and wellbeing (WEMWBS) (Tennant et al. 2007) were remotely administered at 3 timepoints; baseline, 1-2 hours and 24 hours post-treatment to quantitatively assess ocular pain, anxiety and wellbeing. Prior to their scheduled appointment for intravitreal injection (participation day), the VAS was sent directly to participants via mail to complete the baseline measure. After the procedure, two extra copies of the VAS along with a pre-paid envelope, were provided to participants in person to complete at 1-2 hours and 24 hours post-treatment and returned to the researcher via mail. The order of questionnaire administration was randomised; used a number generator to assign random ordering of each questionnaire at each timepoint (baseline, 1-2 hours and 24 hours post-treatment).

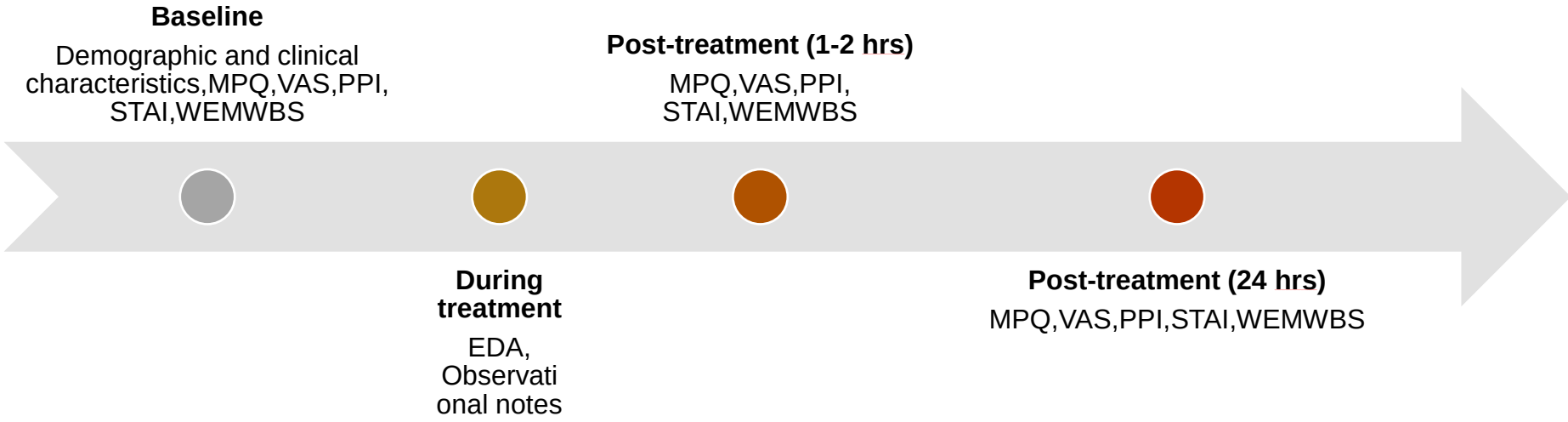

Figure 8.2.1 – Overview of experimental design. Study comprised 4 timepoints, with key study activities undertaken at each. Baseline: collected demographic and clinical details of participants. The questionnaires (VAS, MPQ, PPI, STAI, WEMWBS) were administered at 3 timepoints: baseline, and at 1-2 hours and 24 hours post-treatment. During treatment, the participant's electrodermal activity was recorded and observed the procedures performed. MPQ = Short-Form McGill Pain Questionnaire Main Component; VAS = Visual Analogue Scale; PPI = Present Pain Intensity; STAI = State-Trait Anxiety Inventory; WEMWBS = Warwick-Edinburgh Mental Wellbeing Scale; EDA = Electrodermal activity.

8.2.3.1. Objective measure

- ***Electrodermal Activity***

Electrodermal activity is an objective measure of physiological arousal recorded during the intravitreal injection procedure. Tonic and phasic EDA components have been examined to collect data on the sample variability. The primary variable was the analysis of event-related skin conductance responses (ER-SCRs) as a measure of amplitude to compare different procedural steps and to identify higher levels of arousal during the intravitreal injection procedure.

8.2.3.2. Subjective measures

- ***Pain assessment***

Pain was assessed at baseline, 1-2 hours and 24 hours post-treatment using the Short-Form McGill Pain Questionnaire (SF-MPQ) tool (Melzack 1987) to support a more rapid acquisition of data compared to the standard MPQ. The SF-MPQ has yielded evidence of good validity and reliability (Raja and Melzack 2005; Gauthier et al. 2014) commonly used to assess pain in both clinical and research settings. The questionnaire can be found in Appendix L.

- ***Main Component***

Sensory (11 items) and affective (4 items) categories of the standard form. The most common sensory words were throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, and splitting. In the affective category, the most frequently used words were tiring-

exhausting, sickening, fearful, and cruel-punishing. These items (descriptive words) were rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate and 3 = severe. If a specific word did not describe the patient's pain, it was rated as "0." Adding the rank values of the above 15 questions, provides the score of the main component of the SF-MPQ (MPQ), which was scored out of a total of 45. A higher score of the MPQ reflected more serious pain (Melzack 1987).

- ***Visual Analogue Scale (VAS)***

The VAS pain score provides an intensity score of the pain experienced. The VAS allowed participants to self-rate their eye pain on a 100mm horizontal grading scale of subjective pain assessment with the left side signifying "no pain at all" and the right-side signifying "the worst possible pain".

- ***Present Pain Intensity Index (PPI)***

The Present Pain Intensity (PPI) index is a measure of the magnitude of pain experienced by an individual and is a six-point verbal rating scale that indicates overall pain intensity and includes six levels: 0, none; 1, mild; 2, discomforting; 3, distressing; 4, horrible; and 5, excruciating. Higher numbers indicate more severe pain (Melzack 1987).

The researcher explained to participants the questionnaire and marking of the VAS 100mm horizontal line and clarified that their responses should reflect the pain intensity of their injected eye at that point in time.

- ***Anxiety assessment***

Levels of state and trait anxiety were measured using the State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1983). The STAI has 40 items, 20 items allocated to each of the state anxiety and trait anxiety subscales. Respondents had the ability to answer each question on a 4-point Likert-type scale. In each of the 4-point gradients, scores are scored from 1 to 4. Responses for the state anxiety scale assess intensity of current feelings “at this moment”: (1) not at all, (2) somewhat, (3) moderately so, and (4) very much so. Responses for the trait anxiety scale assess frequency of feelings “in general”: (1) almost never, (2) sometimes, (3) often, and (4) almost always. The scores attributed to the questions are summed leading to a final score of state and trait anxiety. Higher scores indicated higher levels of anxiety. The questionnaires can be found in Appendices J and K.

- ***Mental wellbeing assessment***

The WEMWBS (Tennant et al. 2007) (Appendix M) was used to measure positive aspects of wellbeing, examining both hedonic and eudaemonic aspects of mental health, such as positive affect, positive functioning, and satisfying interpersonal relationships. For instance, hedonic aspects of mental health may include feeling happy and enjoying life, while eudaemonic aspects may involve feeling that one's life has meaning and purpose. The WEMWBS includes items that assess both of these domains, such as "I've been feeling optimistic about the future" (hedonic) and "I've been feeling that what I do in my life is valuable and worthwhile" (eudaemonic). Other items measure satisfying interpersonal relationships,

such as "I've been feeling loved" and "I've been feeling close to other people". Participants are required to choose the statement that best describes their experience over the past two weeks using a 5-point Likert-type scale. All items are scored positively, from 1 (none of the time) to 5 (all of the time) and a total scale score is calculated by summing the 14 individual item scores (14–70). However, in medical research, Rasch analysis is incorporated as a robust strategy of evaluating the psychometric properties of a questionnaire, also to converting ordinal Likert scale values into a linear logit scale suitable for parametric testing (Aryadoust et al. 2019). In this study, the WEMWBS scores were converted into logit scores using a validated scoring table (Appendix O) established in Cassels (2017), who evaluated the psychometric properties on patients with AMD. Lower logit scores indicated a low level of wellbeing. The overall score for each questionnaire was calculated as the sum of logit scores for all items divided by the number of questions answered.

8.2.3.3. Covariates

In addition to the demographic details, medical records were extensively examined to obtain data on participants' complete eye history including diagnosis, routine examinations and procedure records, such as the number of intravitreal injections received to date, anti-VEGF administered, site of injection; eye(s) treated and best-corrected visual acuity (BCVA). Finally, duration of treatment, number of anaesthetic drops administered and rest time following anaesthetic application were also collected for each participant.

8.2.3.4. Outcome measures

The primary outcome measure was the VAS pain score 1-2 hours and 24 hours post-treatment. Secondary outcome measures were the scores of the MPQ, the PPI scores, STAI and WEMWBS at 1-2 hours and 24 hours post-treatment.

8.2.4. Sample size calculation

Studies suggested that a change of 13 mm on the VAS is clinically significant, however Bird and Dickson (2001) found that the clinical significance of changes in pain depends on the patient's initial VAS score. Patients with higher levels of pain require a larger difference in VAS scores to achieve clinically significant pain relief. These findings highlight the importance of considering baseline pain intensity when evaluating treatment effectiveness.

In the original research protocol, the sample population was powered (e.g. n=120) to allow comparison between 3 key factors: (1) the use of InVitria assisting device to administer intravitreal injection, (2) the healthcare practitioner administering the intravitreal injection (nurse vs. doctor), and (3) analysis of 3D-OCT images to evaluate injection site characteristics, such as location, incision angle and diameter, presence of vitreous influx, or integrity of adjacent conjunctive/sclera. Due to COVID-19 restrictions aimed at minimising patient contact in hospitals, data collection on injection site characteristics had to be discontinued. Additionally, the InVitria device was no longer available, resulting in the use of only two comparator groups for

the power calculation: (1) type of anti-VEGF administered (ranibizumab vs bevacizumab), and (2) the healthcare practitioner administering the intravitreal injection (nurse vs. doctor). Thus, the sample size was calculated to detect a 13 mm difference, with the level of significance set at a p=0.05 (type I error rate, α) and a power of 80% (1 - β). An additional 15% was added to account for a possible non-parametric analysis and a further 20% allowance for attrition/missing data based on previous studies. Hence, the sample size of 40 participants per group (n=80) was determined to be adequate to test the study's hypothesis. However, the emphasis of the sample calculation has shifted to the multiple linear regression analysis as the primary statistical analysis.

The multiple regression models are limited to one factor (predicting variable) per 10 participants (Altman 1991). For the multiple linear regression analysis, power calculations indicated that a sample size of 52 participants including an additional 20% allowance for attrition/missing data was sufficient to detect a large effect size (f^2=0.35) with a statistical power of 0.80 based upon 5 predictor variables. These calculations were completed with the software G*Power 3.1 (Erdfelder et al. 2009).

8.2.5. Equipment and data acquisition parameters

EDA signals were acquired using the BIOPAC MP36 data acquisition unit and Student Lab 4.1 software (BIOPAC Systems UK 2021a) (figure 8.2.2) with the latter used to set up the acquisition parameters, for event marking, data filtering and analysis. Raw, unfiltered EDA data were measured as skin

conductance in units of microsiemens (μS) using a direct current (DC), constant voltage (12V DC 1 amp) as an external excitation source across the silver-silver chloride (Ag/AgCl) electrodes (Dawson et al., 2007; Handler et al., 2010). Skin conductance (μS) was measured on Channel 3 at a 2 kHz sampling rate.

8.2.6. Electrodes

EDA electrode setup consisted of disposable, isotonic gel (0.5% NaCl) electrodes (EL507, BIOPAC Systems, Inc.) (figure 8.2.4) and an EDA electrode lead set (SS57L, BIOPAC Systems, Inc.) (figure 8.2.3). The two electrodes were attached on the distal phalanx of the index and middle finger of the participant's hand (ipsilateral to the study eye) (figure 8.2.5) at least 10 minutes prior to recording for the electrode gel to penetrate in the deeper layers of the skin to ensure a stable electrical connection. According to standard recommendations, the distal phalanges of the fingers showed a greater responsivity compared to the medial and proximal phalanges (Freedman et al. 1994; Boucsein et al. 2012; Boucsein 2012a). An isotonic, 0.05 molar NaCl, electrode paste (GEL101A) (BIOPAC Systems UK) was also applied on the electrodes to obtain good conductivity. The primary reason for attaching the electrodes to the hand ipsilateral to the study eye was to reduce the risk of detached electrodes in the case of handholding during the procedure. Also, to reduce the risk of potential artifacts or noise signals in the EDA recording. It was observed from the hospital visits during the design stage of this project that assistant nurses hold the patients' hand ipsilateral to the injected eye.

8.2.7. Experimental design

The procedural steps performed during an intravitreal injection procedure were defined as the EDA event markers in this study. Event markers reflecting the procedural steps of the intravitreal treatment were determined in the previous study (Chapter 6) also from observations in the injection room at the hospital site and were set-up on BIOPAC Student Lab 4.1.5 software (BIOPAC Systems UK) using hotkeys (table 8.2.1). The injection accounted for both the insertion of the needle and delivery of the anti-VEGF solution (aflibercept, ranibizumab). Equipment set-up at the hospital site (injection room), including the BIOPAC MP36 data acquisition unit and laptop are presented in figures 8.2.6 and 8.2.7.

Hotkey	Event	EDA Response type
F1	Baseline (pre-treatment)	SCL
F2	Baseline (post-treatment)	SCL
F3	Application of anaesthetic drops	ER-SCR
F4	Application of povidone-iodine/chlorhexidine	ER-SCR
F5	Placement of surgical drape	ER-SCR
F6	Placement of eyelid speculum	ER-SCR
F7	Marking	ER-SCR
F8	Injection	ER-SCR
Esc	Application of antibiotic drops	ER-SCR
F9	Removal of eyelid speculum	ER-SCR
F11	Removal of surgical drape	ER-SCR
F12	Povidone/iodine/chlorhexidine washing	ER-SCR

Table 8.2.1 – Set-up of event markers on BIOPAC Student Lab 4.1.5 software (BIOPAC Systems UK). Skin Conductance Level (SCL), Event-Related Skin Conductance Response (ER-SCR).

Figure 8.2.2 – BIOPAC MP36 data acquisition unit features. Four channels (CH1-4), "*electrode check*" for electrode impedance, direct current (DC) input (12 VDC at 1 Amp), USB 2.0).

Figure 8.2.3 – SS57LA EDA lead. connects to a single input channel (e.g., CH3) to record EDA.

Figure 8.2.4 – Disposable EL507 electrodes and GEL101A isotonic electrode gel. Latex-free electrodes, Ag/AgCl contact, wet gel (0.5% chloride salt), electrode contact diameter: 11 mm, electrode contact area: 95 mm2, size: 27 mm x 36 mm, backing: 1.5 mm thick foam.

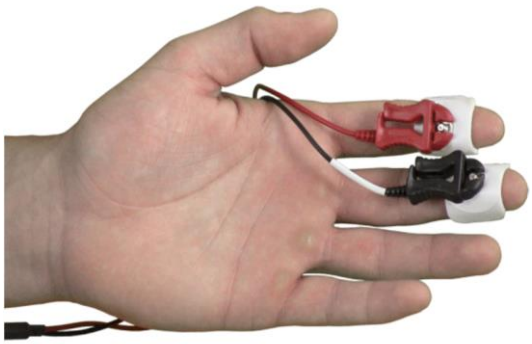

Figure 8.2.5 – EDA electrode setup. Leads snap to two disposable EL507 electrodes that are attached to the distal phalanx of the index and middle finger of the participant's hand. From BIOPAC Systems Inc. (2022).

Figure 8.2.6 – Experiment set-up at the hospital site (injection room). The injection is performed while the patient is sitting on a reclining chair. BIOPAC MP36 data acquisition unit connected to notebook laptop (*Acer TravelMate B117-M*) for data recording.

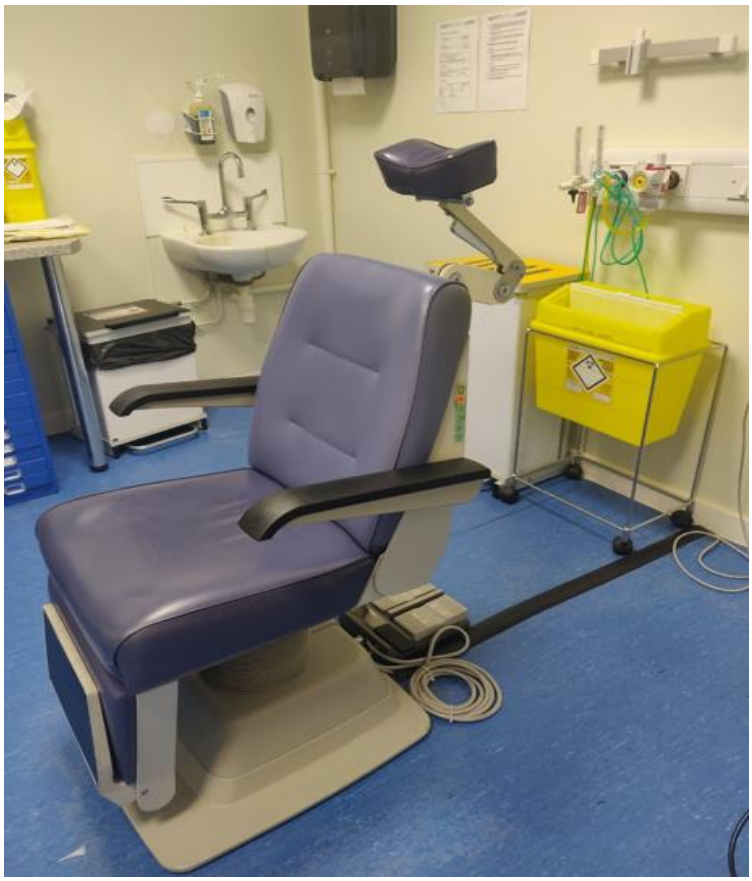

Figure 8.2.7 – Injection room at the hospital site.

8.2.8. Procedure of Intravitreal Injection

For the purpose of baseline measurement, before and after treatment, participants were asked to sit upright and relax, with their forearms placed on the armrest in a comfortable position. The SS57LA EDA lead was then attached to the two electrodes and participants were asked to take a deep sharp breath to ensure reactivity and functionality of the EDA recording. The baseline measures of skin conductance were recorded for 3 to 5 minutes; participants were instructed to refrain from moving their hand which was connected to the electrodes. During treatment, event markers were placed during the EDA recording to reflect ER-SCRs. The researcher observed how anxious participants were reassured during the intravitreal injection procedure. The observations made during the intravitreal procedure were important in ensuring the accuracy of the qualitative data collected in this thesis, as well as providing valuable insights into the communication dynamics between healthcare practitioners and patients. Following treatment, participants were disconnected from all electrodes and were reminded that they would receive a follow-up call after they went home (1-2 hours post-treatment) and at 24 hours to administer the questionnaires (VAS, MPQ, PPI, STAI, WEMWBS). To accommodate participants who demonstrated a strong preference for completing the questionnaires on their own, verbal explanations of each questionnaire section were provided during two follow-up phone calls conducted at 1-2 hours and 24 hours post-treatment. The purpose of these calls was to ensure that all participants were provided with the necessary information to accurately and effectively complete the questionnaires.

8.3. Electrodermal activity analysis

All EDA analysis was carried out using Student Lab 4.1 software (BIOPAC Systems UK 2021a).To analyse EDA responses as results of stimuli, and to investigate variation within subjects and between stimuli, several EDA parameters were calculated. In order to compute these parameters, the SCRs onsets and peaks were first specified. Locating the onsets and peaks was performed analogous to the procedure presented. A complete list of all the extracted variables from EDA responses and included in the data analysis is given in table 8.3.1.

8.3.1. Pre-processing

8.3.1.1. Data filtering

Raw EDA waveforms were examined to identify any significant artifacts that would lead to invalid measurements. Artifacts or noise signals can result from improperly attached electrodes (Dawson et al. 2009; Boucsein et al. 2012). Firstly, the continuously recorded EDA signal (raw EDA) was duplicated, then filtered using a 1 Hz FIR low pass filter (sample rate = 2000; number of coefficients = 8000) to eliminate high-frequency noise content and to improve the detection of ER-SCRs. Secondly, a 0.05 Hz IIR high pass filter (default, Q = 0.707) was applied to extract the phasic EDA component, which was then subtracted from the filtered EDA to obtain the tonic EDA component. Figure 8.3.1 provides an overview of the data filtering steps.

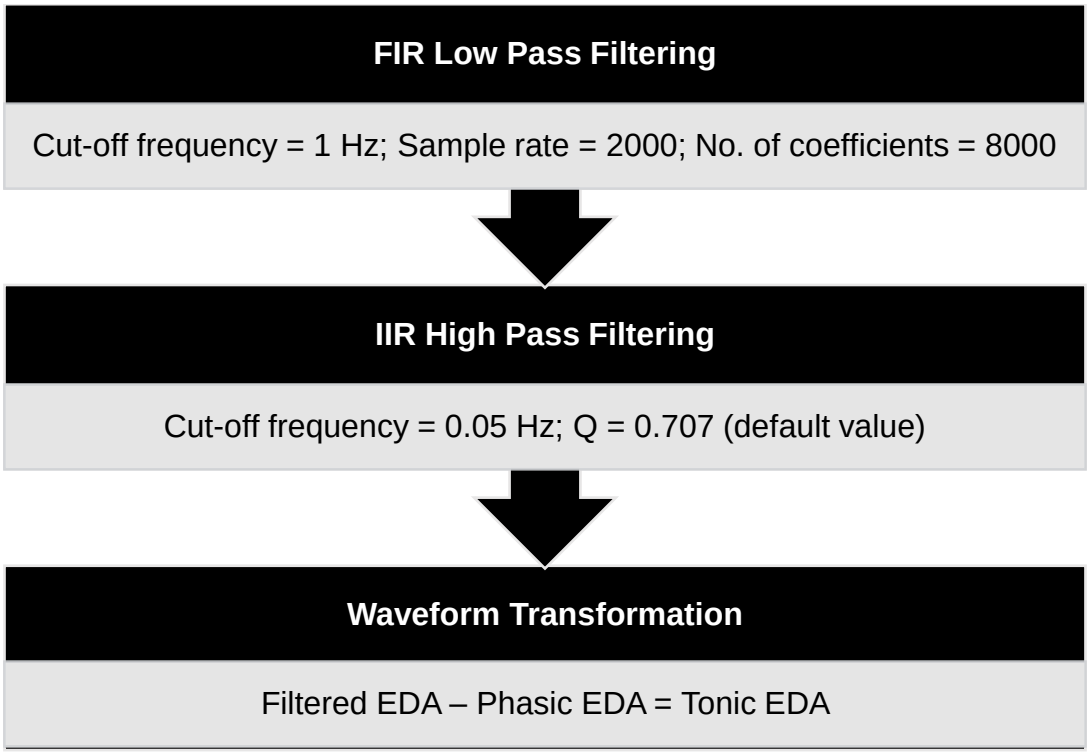

Figure 8.3.1 – Applied data filtering steps on BIOPAC Student Lab 4.1 software. Finite Impulse Response (FIR) low pass filtering and infinite impulse response (IIR) high pass filtering. Cut-off frequency, sample rate and coefficient input as per guidelines on EDA data filtering procedures (Boucsein et al. 2012; BIOPAC Systems UK 2022c).

Components	Measurements	Parameters
Phasic	ER-SCRs	SCR_amp, SCR_Tris, SCR_lat
Tonic	Slow changes & background noise signal	SCL

Table 8.3.1 – Electrodermal activity (EDA) components and parameters extracted for analysis. Event-related skin conductance responses (ER_SCRs) are characteristic of the phasic EDA component. Parameters of interest include the skin conductance response amplitude (SCR_amp) using trough-to-peak methodology, maximum amplitude (Maximum_amp), rise time (SCR_Tris), and SCR_lat (latency). Tonic EDA component represents slow changes and background characteristics of EDA signal. Parameter of interest was the skin conductance level (SCL). SCR_amp, maximum_amp and SCL were measured in microsiemens (μS), and SCR_Tris and SCR_lat in seconds (s).

8.3.2. Parameter extraction

Figure 8.3.2 shows an example of the different components of EDA recorded from a participant, including the raw EDA, phasic EDA, and tonic EDA, as visualised in BIOPAC Student Lab 4.1.5 software.

8.3.2.1. Phasic EDA component

EDA can be characterised by standard features, typically defined for a specific SCR (μS). The researcher applied the 'Find Cycle' routine under the analysis option linked to pre-set measurement box options (time, peak-to-peak, delta T, maximum). Initially, the researcher performed manual analysis via the I-Beam procedure to identify and mark the waveform onset and ER-SCR peak on the phasic EDA waveform. Waveform onset was detected (latency time 1 to 5 s) after presenting the documented events (or stimuli) that occurred during the intravitreal injection procedure. ‘Find Cycle’ analysis (figure 8.3.3) was then performed to calculate the ER-SCR amplitude (μS) using the trough-to-peak methodology, the latency time (s) between stimulus application and ER-SCR onset, and rise time (s), all measured with respect to the occurrence of the stimulus.

The ER-SCRs were plotted as waveforms (time series graphs) to highlight the differences between participant responses during the placement of eyelid speculum, eye marking and injection. Firstly, the phasic EDA data were downsampled (from 2000 Hz to 3.6 Hz) to enable plotting of the datapoints. Then, a time window of 10 seconds using the I-beam was used to acquire the data of each ER-SCR and waveform data were extracted.

8.3.2.2. Tonic EDA component

SCL (μS) qualifies as an appropriate measure of sympathetic activation. However, tonic EDA generates varying baseline among individuals as well as within an individual. Therefore, simple averaging performed over the whole signal is inadequate to extract a precise measure of tonic EDA. To overcome this challenge, the tonic EDA was divided into discrete windows outside stimuli timeframe to reflect changing baseline levels. Onset and offset markers were inserted on the tonic EDA waveform to obtain the SCL during the rest period (baseline pre-treatment), 7 post-stimulus periods and recovery period (baseline post-treatment). Table 8.3.2 illustrates code names assigned to SCL parameters. A 2 to 5s window was used for detecting the onset of SCL measurement of the tonic EDA waveform following response peak, consistent with the recovery time of ER-SCRs which varied across the stimuli. For determining the offset of SCL measurement, a 2s window was calculated prior to the onset of subsequent ER-SCRs. 'Find Cycle' analysis (figure 8.3.4) was implemented to calculate the mean amplitude of the SCL responses within the specified periods. The SCL was computed as the average skin conductance value across varying time windows (stimuli were not time-fixed). The first 10 seconds of EDA data were discarded based on the observation that data acquisition required 10 seconds for stabilisation.

Event code	Event Name
Rest	
BS0	Baseline (pre-treatment)
Post-stimulus	
PS1	Application of anaesthetic & povidone-iodine/chlorhexidine drops
PS2	Application of povidone-iodine/chlorhexidine with cotton wool
PS3	Placement of surgical drape
PS4	Placement of eyelid speculum
PS5	Eye marking
PS6	Injection & Antibiotic drops
PS7	Removal of surgical drape, removal of eyelid speculum, povidone-iodine/chlorhexidine washing
Recovery	
BS1	Baseline (post-treatment)

Table 8.3.2 – Events representing the tonic electrodermal activity (EDA) component extracted in distinct time-windows for the analysis of the skin conductance level (SCL).

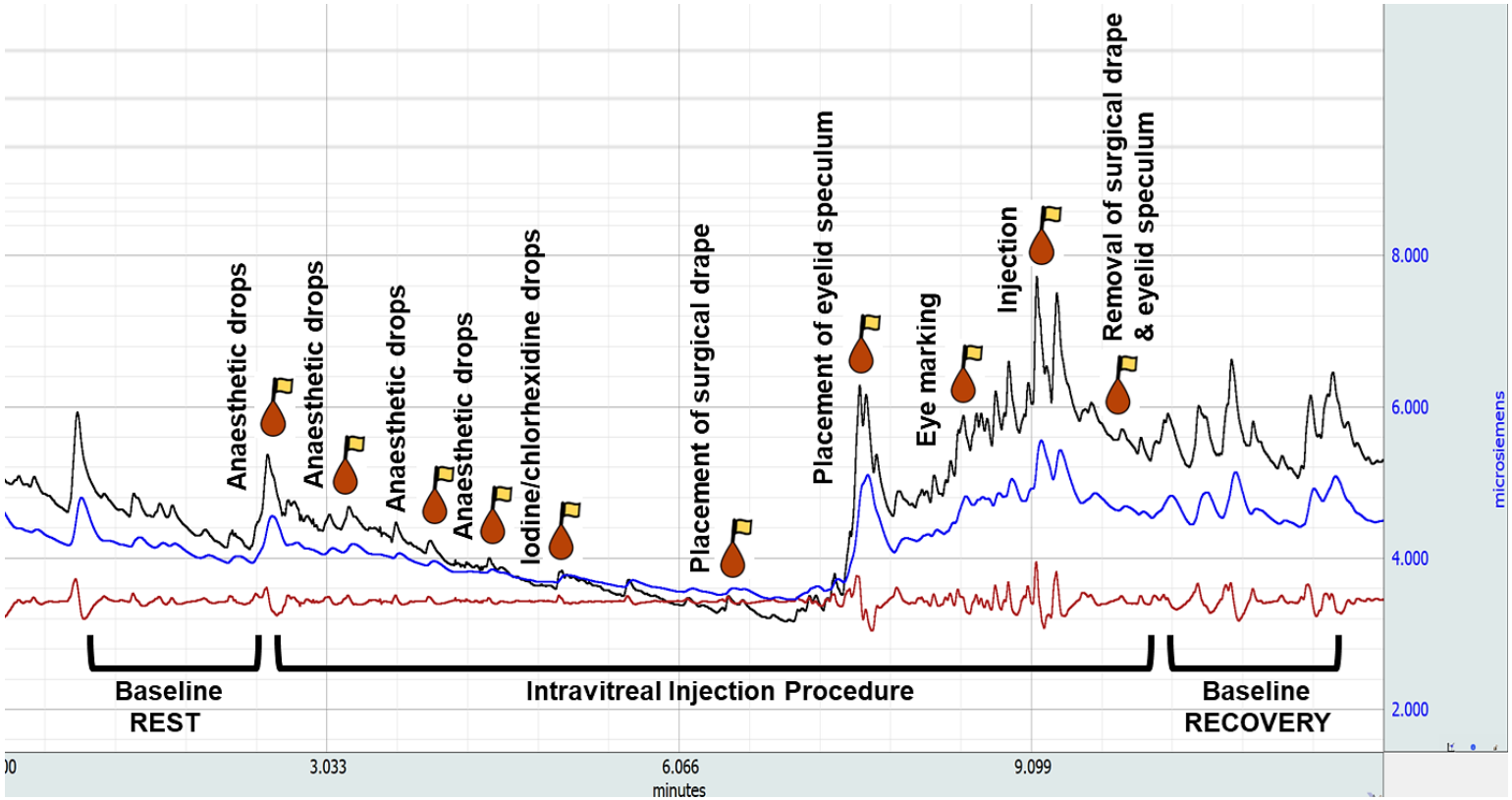

Figure 8.3.2 – Graph illustrates the different components of Electrodermal Activity (EDA) from a participant. Recording of EDA (µS) in BIOPAC Student Lab 4.1.5 software. Raw EDA (black), Phasic EDA (red), Tonic EDA (blue). Event markers (representing stimulus application) were placed during the intravitreal injection procedure (real-time). Stimulus, waveform onset using a bracket, and the corresponding ER-SCRs.

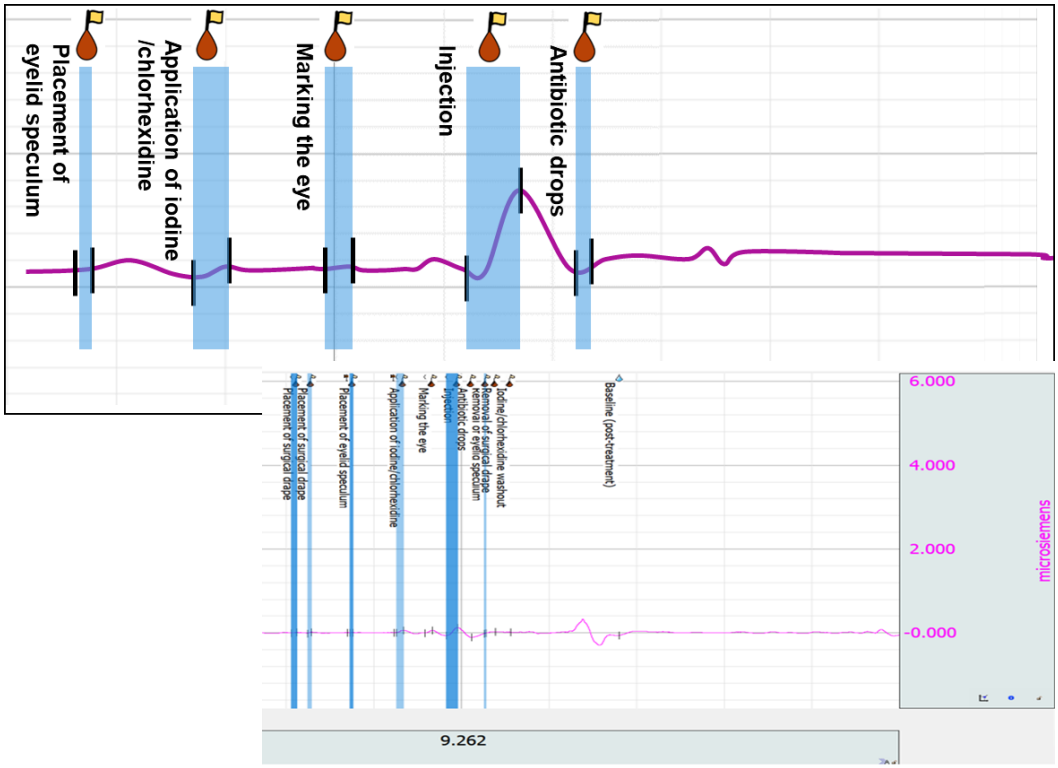

Figure 8.3.3 – Graph illustrates the Phasic Electrodermal Activity (EDA) response from a participant. Graph shows the '*Find Cycle*' analysis that was performed on BIOPAC Student Lab 4.1.5 software to calculate the following parameters of the phasic EDA component: the Event-Related Skin Conductance Response (ER-SCR) amplitude (μS), latency time (s) between stimulus application and ER-SCR onset, and rise time (s). The width of the highlighted blue bands represents the different rise time values of each ER-SCR. The '*Find Cycle*' analysis was performed following manual analysis via the I-Beam procedure to identify and mark waveform onset and peak value for each ER-SCR (amplitude threshold > 0.01 μS). Event markers (representing stimulus application) were placed during the intravitreal injection procedure (real-time). Stimulus , waveform onset using a bracket, and the corresponding ER-SCRs .

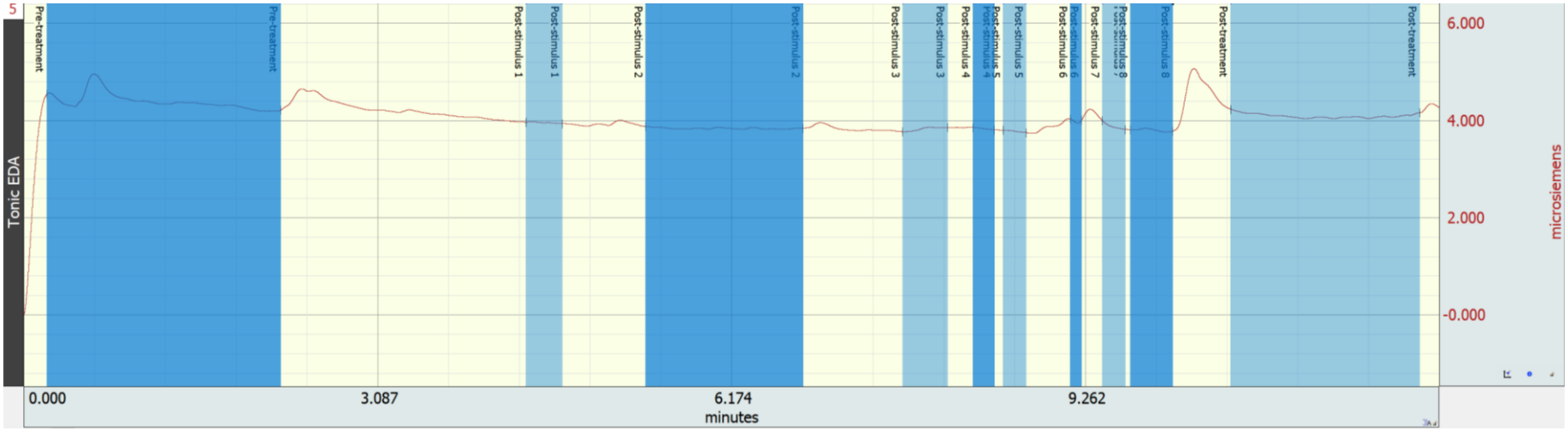

Figure 8.3.4 – Graph illustrates the 'Find Cycle' analysis that was performed on BIOPAC Student Lab 4.1.5 software to calculate parameters of the Tonic EDA component as a measure of Skin Conductance Level (SCL). Parameters: Post-Stimulus 1 (PS1, application of anaesthetic & povidone-iodine/chlorhexidine drops), Post-Stimulus 2 (PS2, application of povidone-iodine/chlorhexidine with cotton wool), Post-Stimulus 3 (PS3, placement of surgical drape), Post-Stimulus 4 (PS4, placement of eyelid speculum), Post-Stimulus 5 (PS5, eye marking), Post-Stimulus 6 (PS6, injection & antibiotic drops), Post-Stimulus 7 (PS7, removal of surgical drape, removal of eyelid speculum, povidone-iodine/chlorhexidine washing). These parameters represent the changes in mean SCL between procedures and data were analysed in distinct time-windows due to procedural irregularities. An optimal time-window was used to analyse the Baseline pre-treatment (BS0) and Baseline post-treatment (BS1) parameters. Time-windows are represented by the highlighted blue bands.

8.4. Statistical analysis

All exploratory and statistical analysis were performed using the RStudio software (version 2022.02.0+443), with $p<0.05$ considered statistically significant for all analyses, unless otherwise stated. Descriptive and inferential statistics were used to analyse the data. Categorical variables were reported as percentages and frequencies, while continuous variables were reported as mean ± standard deviation if normally distributed, also the median and interquartile range (IQR) if non-normally distributed. Shapiro normality tests and normal Q-Q plots were used to determine the normality of distribution. To examine differences between baseline, at 1-2 hours and 24 hours post-treatment, continuous variables were compared with repeated measures (within subjects) ANOVA, or the Friedman's χ^2 test for ordinal or non-normally distributed data. Paired t-test and Wilcoxon signed-rank tests were used to analyse within-subject data, and independent t-test and Wilcoxon rank sum test for subgroup analysis. Because of the multiple testing performed in this study, post-hoc analysis with Bonferroni correction was used to control the type I error rate in the variables. A bivariate analysis using Spearman's rank and Pearson correlation coefficients was conducted to assess the correlation between the variables.

A simple linear regression model using Ordinary Least Squares (OLS) coefficient estimates was carried out to examine potential predictor variables related to post-treatment pain (response variable). Scatterplot and correlation matrices were also used to further explore the distributions of the pair variables. Then, multiple linear regression analysis was used as an

explanatory model to study the effect of different variables in pain at 1-2 hours and 24 hours post-treatment. Any predicting variables that were significantly correlated with each other were not included into the same multiple regression model. Additionally, the Adjusted R^2 (modified version of Multiple R^2) was reported (Pandey 2020; Statology 2020) as the percent of the variance explained by the model. The Adjusted R-squared adjusts for the number of predictors in a regression model,

$$Adjusted\ R^2 = 1 - (1 - R^2) * \frac{(n-1)}{n-k-1}$$

Where: R^2, the R^2 of the model; n, the number of observations, and k, the number of predictor variables. This statistical measure is essential for an explanatory model in multiple regression since $Adjusted\ R^2$ can be used to compare the fit of regression models with different number of predictors to acquire the most significant model. Hence, the $Adjusted\ R^2$ was used as a measure of explanatory power (Minitab Blog 2013; Valchanov 2018).

Regression assumptions were assessed in accordance with methods described by (Altman 1991). The assumptions of linear regression are that: 1) The outcome variable should have a normal distribution for each value of the predictor variable, 2) The variability of the outcome variable should be the same for each value of the predictor variable, and 3) The relation between the two variables should be linear (Altman 1991). The assumptions of each linear regression model were examined using statistical tests and diagnostic plots as summarised in figure 8.4.1.

Additionally, outliers were assessed using Leverage plots and Cook's distance (D) for each observation, and influential outliers (observations of large effect on the outcome and model accuracy) were thoroughly examined prior to excluding them from the regression model. Any point with a Cook's Distance over 4/n (where n is the total number of observations) was considered to be an outlier (Cook D, 1977).

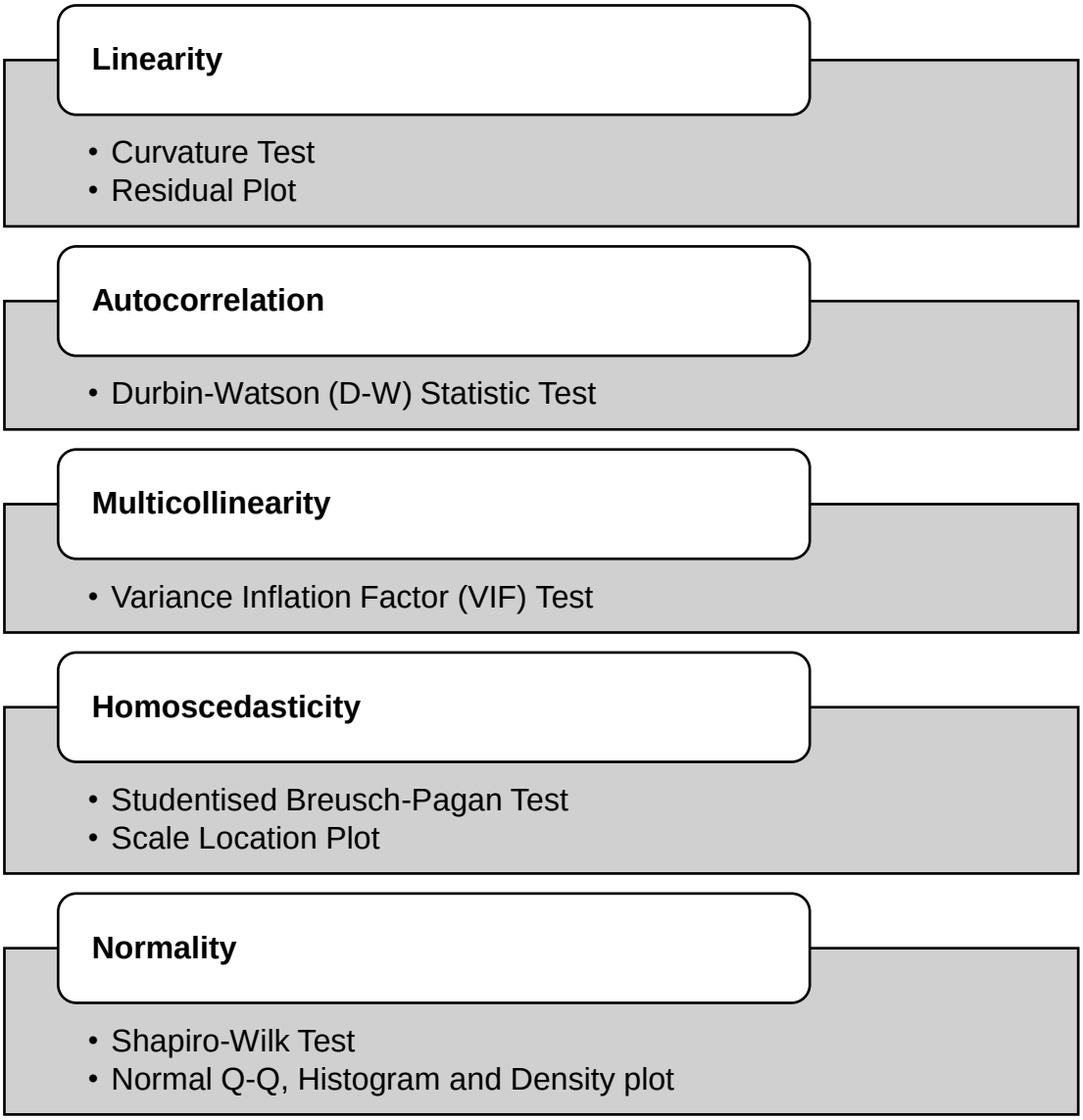

Figure 8.4.1 – A summary of the statistical tests and diagnostic plots to assess the assumptions of linear regression models.

8.5. Results

Initially, each variable and the distribution of the data are examined prior to performing any comparisons between the 3 study time points (Section 8.5.1). Then, the demographic and clinical characteristics of the sample and summary statistics of EDA and questionnaire data are presented, as well as data visualisations to identify potential predictor variables for the multiple linear regression analysis on pain at 1-2 hours and 24 hours post-treatment (Section 8.5.2). At this point, additional statistical tests and diagnostic plots are performed to evaluate the validity of the regression models.

The first section of analyses examines the sample data using descriptive statistics including central tendency, measures of dispersion and graphical representations. This is important for representing all data collected in the study to provide an accurate representation on the sample characteristics, questionnaire self-reported outcomes and EDA parameters. The second section of analyses uses applied inferential statistics using comparison and correlation tests for identifying potential independent variables (predictors) to explain the changes in pain experienced post-treatment (response variable). In the final section, a correlation matrix was produced to explore the degree of correlation between all possible pairs of variables, highlighting the strongest predictors. Multiple linear regression was then used to test whether the selected predictors significantly explained pain at 1-2 hours and 24 hours post-treatment.

In the present study, missing observations (NA's) are reported in the dataset. Missing observations occurred for four main reasons: a) noise artifacts significantly disrupting the EDA signal and analysis of the SCR was inconclusive, 2) signals were acquired normally however no identifiable SCR was elicited within latency to the event, 3) EDA data susceptible to unreliable measurements of baseline SCL post-treatment (BS1) in participants under same-day binocular treatment, and 4) due to participant dropouts because of hospital appointment cancellation or loss to follow-up after their treatment.

8.5.1. Assessment of normality

The normality of the distribution of data was assessed using the Shapiro-Wilk test and verified using normal Q-Q plots. Only the WEMWBS (logit transformed) was normally distributed, $p>0.05$. The outcomes, SCL, speculum, marking and injection SCR amplitude, VAS, MPQ, PPI, and STAI were found not to be normally distributed $p<0.05$, even after log, square root and cubic transformation. The Shapiro-Wilk test results are shown in Appendix N.

8.5.2. Descriptive statistics, comparisons, and correlations

8.5.2.1. Demographic and clinical characteristics

A total of 270 potential participants were contacted via mail, email, or telephone, with the response rate comprising 24% of the total number contacted. The study used a convenience sample of 65 patients with neovascular AMD who were undergoing intravitreal injection treatment.

Among the patients, 37 (57%) were female and 28 (43%) were male. The participants' ages ranged from 60 to 90 years (median = 76). Most patients were identified as White Welsh 57 (88%) with 6 (9%) White British, 1 (1.5%) White Scottish and 1 (1.5%) Mixed British/Indian. The ethnic diversity of the sample was limited but overall representative of the area where the data were collected, consistent with latest published data that 93% of the Welsh population are White (StatsWales 2020).

Regarding the clinical characteristics, the total number of intravitreal injections ranged from 2 to 67 (median = 15), with patients receiving unilateral injections ranging from 2 to 48 (median = 12) on the eye assessed in this study. In terms of the type of anti-VEGF injected, 24 (36%) patients received aflibercept while 41 (64%) patients had ranibizumab in at least one eye. Furthermore, 2 (3%) and 8 (12%) of patients had unilateral and bilateral pseudophakia, while 1 (2%) and 4 (6%) were diagnosed with unilateral and bilateral cataracts, respectively. Daily caffeine consumption (coffee/tea) ranged from 0 to 10 cups (median = 4), and 0 to 4 cups (median = 1) were consumed prior to study participation on the day of the treatment. Regarding the smoking status, 12% of the study participants were current smokers. When participants were asked about their alcohol consumption, 5 (8%) reported that they never consumed alcohol, 11 (17%) at least 4 times per week, 12 (18%) 2 to 4 times per month, 13 (20%) monthly or less, with the majority 24 (37%) reporting alcohol consumption of 2 to 3 times per week. Table 8.5.1 illustrates the demographic and clinical characteristics of the sample.

Characteristic		Value
Age, median (range), years		76 (60 - 90)
Gender, n. (%)		
Female		37 (57)
Male		28 (43)
Ethnicity, n. (%)		
White Welsh		57 (88)
White British		6 (9)
White Scottish		1 (1.5)
Mixed British/Indian		1 (1.5)
Intravitreal injections, median (range)		
Total in record		15 (2 - 67)
Eye injected		12 (2 - 48)
Anti-VEGF, n. (%)		
Aflibercept	OD	14 (21)
	OS	4 (6)
	OU	6 (9)
Ranibizumab	OD	16 (25)
	OS	20 (31)
	OU	5 (8)
BCVA (logMAR), median (range)		
OD		0.4 (0.1 - 1.3)
OS		0.4 (-0.1 - 1.3)
Pseudophakia (IOL), n. (%)		
No		56 (86)
Unilateral		1 (2)
Binocular		8 (12)
Cataract, n. (%)		
No		59 (91)
Unilateral		2 (3)
Binocular		4 (6)
Smoking, n. (%)		
Yes		12 (18)
No		53 (82)
Caffeine consumption, median (range), cups		
Daily		3 (0 - 10)
Study day		1 (0 - 4)
Alcohol consumption, n. (%)		
Never		5 (8)
Monthly or less		13 (20)
2-4 times per month		12 (18)
2-3 times per week		24 (37)
4+ times per week		11 (17)

Table 8.5.1 – Demographic and clinical characteristics of patients. (N = 65). *Oculus Dexter* (OD – right eye), *Oculus Sinister* (OS – left eye), *Oculus Uterque* (OU – both eyes), Intraocular Lens (IOL).

8.5.2.2. Electrodermal activity (EDA)

Figures 8.5.1 – 8.5.3 illustrate time-series waveforms of the measured SCR amplitudes (peak responses) corresponding to the procedural steps including placement of the eyelid speculum, eye marking and intravitreal injection. The data have been downsampled from 2000 Hz to 3.6 Hz using BIOPAC Student Lab 4.1.5 software and graphically plotted over a 10-second time-window using RStudio software. The figures below present varying rise times, peaks, and slopes between participants. On closer inspection of the responses, it can be observed that there is a decline in amplitude (below 0.0 µS) between 7.5 s and 10 s that may account for participants' inhalation and as a function of the filter response corresponding to the decreasing tonic SCL (BIOPAC Systems UK 2022b).

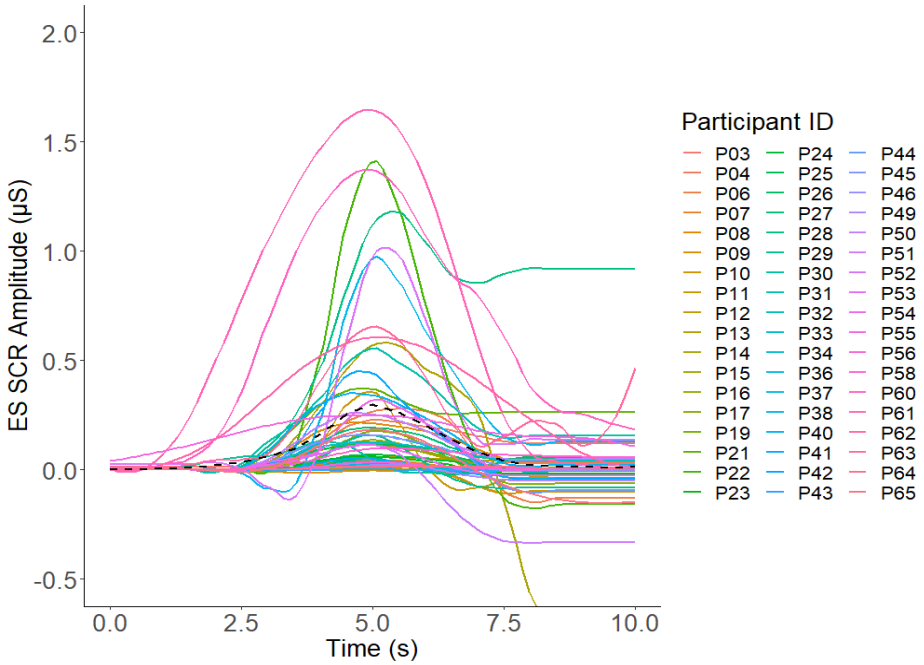

Figure 8.5.1 – Waveform of participants' skin conductance response (SCR) amplitude (µS) during placement of speculum (ES) over a 10-second time-window. Mean is plotted as dashed line. Data downsampled from 2000 Hz to 3.6 Hz using BIOPAC Student Lab 4.1.5 software. Graph plotting using RStudio software. N = 54, missing observations (NA's) = 11.

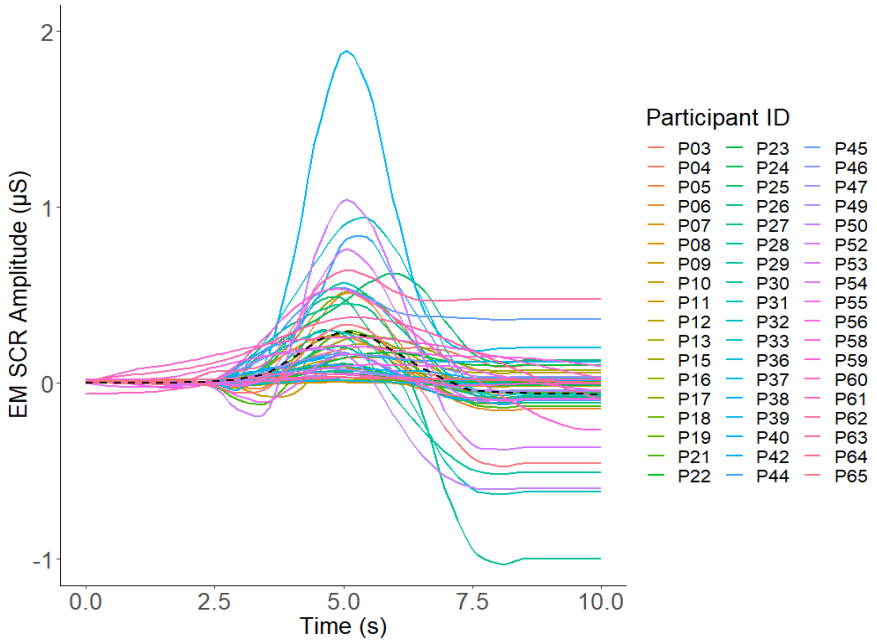

Figure 8.5.2 – Waveforms of participants' skin conductance response (SCR) amplitude (µS) during marking (EM) over a 10-second time-window. Mean is plotted as dashed line. Data downsampled from 2000 Hz to 3.6 Hz using BIOPAC Student Lab 4.1.5 software. Graph plotting using RStudio software. N = 54, missing observations (NA's) = 11.

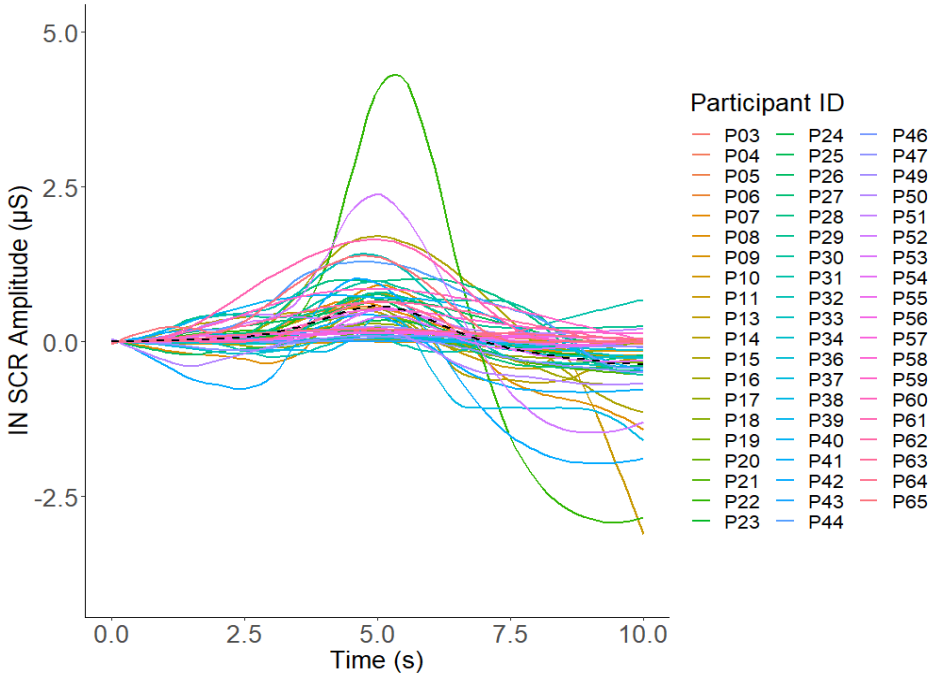

Figure 8.5.3 – Waveforms of participants' skin conductance response (SCR) amplitude (µS) during injection (IN) over a 10-second time-window. Mean is plotted as dashed line. Data downsampled from 2000 Hz to 3.6 Hz using BIOPAC Student Lab 4.1.5 software. Graph plotting using RStudio software. N = 59, missing observations (NA's) = 6.

Table 8.5.2 provides the descriptive statistics for the latency, rise time and amplitude measures of the ER-SCRs including anaesthesia, disinfection, placement of speculum, marking, and injection. Latency is the period between the application of the procedural step and the onset of its associated SCR and this is taken into consideration to accurately identify the ER-SCR. Latency values varied between 1 and 3 seconds, consistent with guidelines on electrodermal activity (Dawson et al. 2009; Boucsein et al. 2012). The mean SCR amplitude ± SD for the placement of speculum was 0.25 μS (± 0.34) and the median score ± (IQR) was 0.14 μS (± 0.24). Also, marking had a mean SCR amplitude of 0.29 μS (± 0.35) and a median of 0.19 μS (±0.36). As anticipated, the mean SCR amplitude during injection was observed to be higher than the other two variables (figure 8.5.5), the placement of speculum and marking, calculating a mean of 0.56 μS (± 0.68) and median of 0.35 μS ± (0.52). In addition to the amplitude measures, rise time may also be used to examine participant variability in the responses. As with the amplitude measures, it can also be observed that the injection had the highest mean ± SD rise time (figure 8.5.4), 2.28 s (± 1.39), followed by marking, 1.98 s (± 0.95) and speculum, 1.88 s (± 0.80). Table 8.5.3 presents the descriptive statistics for the tonic SCL data. For example, baseline at pre-treatment (BS0) and post-treatment (BS1) had a median of 6.11 μS (IQR=4.54, 7.93) and 6.16 μS (IQR=4.48, 8.77), respectively. In figures 8.5.6 and 8.5.7 a high variability of SCL between participants can be observed, considering the number of outliers presented, in addition to the range of scores (e.g. PS5: range = 1.41 – 22.60 μS).

Square root transformation has been applied to the tonic electrodermal activity, SCL (μS) to normalise the distribution and allow for parametric testing, consistent with guidelines on electrodermal activity (Boucsein et al. 2012). Normality assessed by Shapiro-Wilk's test ($p>0.05$). Paired t-test with Bonferroni correction was performed to compare the baseline SCL at pre-treatment (BS0) and post-treatment (BS1), reporting no statistically significant differences between the groups, $p>0.05$ ($p=0.54$).

Figure 8.5.5 shows comparison of the transformed phasic electrodermal activity, √SCR amplitudes (μS) to during placement of the speculum (ES), marking (EM), and injection (IN). Square root transformation was applied to normalise the amplitude and removal of an outlier (id:22) to allow for parametric testing. Normality assessed by Shapiro-Wilk's test ($p>0.05$). A repeated measures ANOVA was performed to compare the effect of the ES, EM and IN on the SCR amplitude. There was a statistically significant difference in SCR amplitude between at least two groups, $F(2,98) = 17.1$, $p=4.3e^{-7}$). Pairwise paired t-tests with a Bonferroni correction revealed that the pairwise differences, between speculum and injection SCR amplitude ($p=2.3e^{-6}$), marking and injection SCR amplitude ($p=5.6e^{-4}$), respectively were statistically significant, $p<0.0001$ and $p<0.001$. Not statistically significant differences between speculum and marking SCR amplitude, $p>0.05$ ($p=0.22$).

Phasic Skin Conductance Response (SCR)								
Latency (s)								
Parameter	Median	Range	IQR	Mean	SD	95% CI	SEM	NA's
Drops	1.84	1.04 – 2.84	1.44, 2.37	1.90	0.56	[1.72, 2.08]	0.09	27
Disinfection	1.76	1.33 – 2.26	1.61, 1.87	1.74	0.28	[1.57, 1.91]	0.08	52
Speculum	1.93	1.00 – 3.00	1.71, 2.46	2.03	0.54	[1.88, 2.18]	0.07	11
Marking	1.95	1.01 – 3.00	1.57, 2.39	1.95	0.54	[1.80, 2.10]	0.07	11
Injection	2.09	1.03 – 2.97	1.59, 2.62	2.09	0.61	[1.93, 2.25]	0.08	6
Rise Time (s)								
Parameter	Median	Range	IQR	Mean	SD	95% CI	SEM	NA's
Drops	1.62	0.35 – 4.26	1.29, 1.97	1.82	0.89	[1.52, 2.11]	0.15	27
Disinfection	1.58	0.86 – 3.20	1.30, 1.87	1.73	0.74	[1.28, 2.17]	0.21	52
Speculum	1.72	0.47 – 4.14	1.34, 2.48	1.88	0.80	[1.68, 2.10]	0.11	11
Marking	1.78	0.55 – 5.67	1.38, 2.42	1.98	0.95	[1.73, 2.24]	0.13	11
Injection	2.03	0.45 – 9.46	1.54, 2.63	2.28	1.39	[1.92, 2.64]	0.18	6
Amplitude (µS)								
Parameter	Median	Range	IQR	Mean	SD	95% CI	SEM	NA's
Drops	0.08	0.01 – 0.67	0.03, 0.25	0.16	0.18	[0.10, 0.22]	0.03	27
Disinfection	0.04	0.02 – 1.72	0.02, 0.21	0.29	0.48	[-0.04, 0.54]	0.13	52
Speculum	0.14	0.01 – 1.44	0.05, 0.29	0.25	0.34	[0.16, 0.34]	0.05	11
Marking	0.19	0.01 – 1.96	0.06, 0.42	0.29	0.35	[0.20, 0.39]	0.05	11
Injection	0.35	0.01 – 4.30	0.16, 0.68	0.56	0.68	[0.38, 0.74]	0.09	6

Table 8.5.2 – Descriptive statistics for the phasic skin conductance response (SCR) latency (s), rise time (s) and amplitude (µS) measures. Parameters: anaesthesia (AD), disinfection conditions (disinfection), speculum (ES), marking (EM), and injection (IN). IQR = Inter-Quartile Range (Q1, Q3), standard deviation (SD), 95% confidence interval (CI), standard error of the mean (SEM) and missing observations (NA's).

Tonic Skin Conductance Level (SCL) (µS)								
Parameter	Median	Range	IQR	Mean	SD	95% CI	SEM	NA's
BS0	6.11	1.90 – 17.91	4.54, 7.93	6.75	3.28	[5.92, 7.58]	0.42	4
PS1	5.31	1.61 – 18.92	3.86, 7.77	6.32	3.62	[5.39, 7.25]	0.46	4
PS2	5.27	1.45 – 17.81	3.65, 7.55	6.03	3.40	[5.16, 6.90]	0.44	4
PS3	5.23	1.43 – 19.71	3.69, 7.50	6.22	3.70	[5.26, 7.17]	0.48	5
PS4	5.47	1.42 – 19.60	3.77, 7.82	6.41	3.78	[5.44, 7.38]	0.48	4
PS5	5.57	1.41 – 22.60	4.18, 8.47	6.82	4.06	[5.77, 7.86]	0.53	5
PS6	5.99	1.42 – 18.57	4.30, 6.64	6.64	3.55	[5.71, 7.57]	0.47	7
PS7	5.93	1.39 – 19.16	4.05, 8.03	6.54	3.61	[5.61, 7.47]	0.47	5
BS1	6.16	1.55 – 19.22	4.48, 8.77	6.98	3.80	[5.88, 8.08]	0.55	17

Table 8.5.3 – Descriptive statistics for the tonic skin conductance level (SCL) measures. Parameters: baseline (pre-treatment) (BS0), post- anaesthetic drops (PS1), post-disinfection conditions (PS2), post- surgical drape (PS3), post- speculum (PS4), post-marking (PS4), post-injection (PS5), post-washing (PS6), baseline (post-treatment) (BS1). IQR = Inter-Quartile Range (Q1, Q3), standard deviation (SD), 95% confidence interval (CI), standard error of the mean (SEM) and missing observations (NA's).

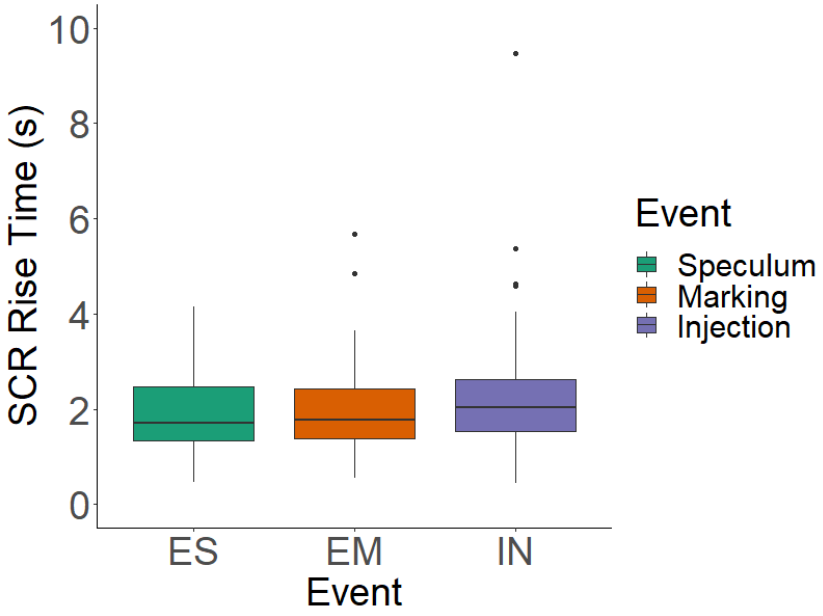

Figure 8.5.4 – Box and whisker plots showing SCR rise time (s). Eye marking (EM), Eyelid Speculum (ES), Injection (IN). Medians (± Inter-Quartile Range) were 1.72 ± (1.15), 1.78 ± (1.04) and 2.03 ± (1.04) respectively for Speculum (ES), Marking (EM), and Injection (IN). The black circles (●) represent outliers. ES (N = 54), EM (N = 54), IN (N = 59). Missing observations (NA's): ES (NA's = 11), EM (NA's = 11), IN (NA's = 6).

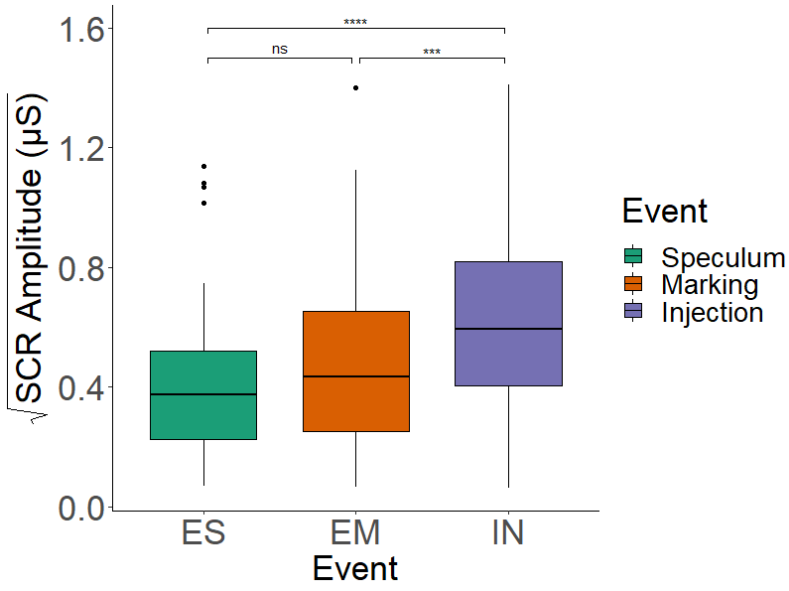

Figure 8.5.5 – Paired samples comparison between square root transformed SCR Amplitude (µS) of event-related skin conductance responses during the intravitreal injection procedure. Pairwise paired t-tests with Bonferroni correction were used to test the variables. The injection (IN) SCR amplitude was significantly higher than the speculum (ES) and marking (EM) SCR amplitudes, **** = $p<0.0001$ and *** = $p<0.001$. SCR = Skin Conductance Response.

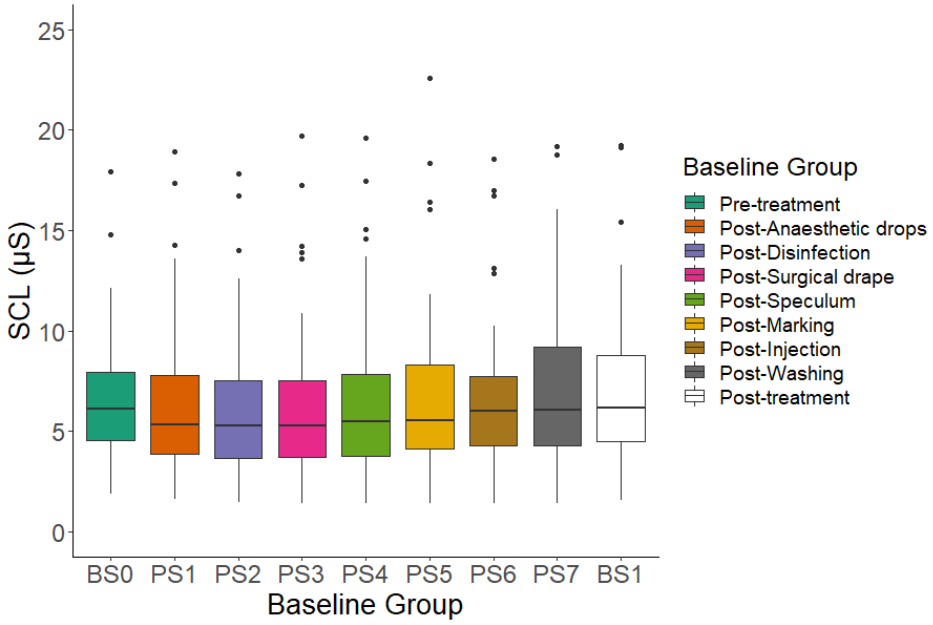

Figure 8.5.6 – Tonic EDA activity amplitude categorised by baseline group. Tonic EDA calculated as mean amplitude of SCL activity in time-windows between events.

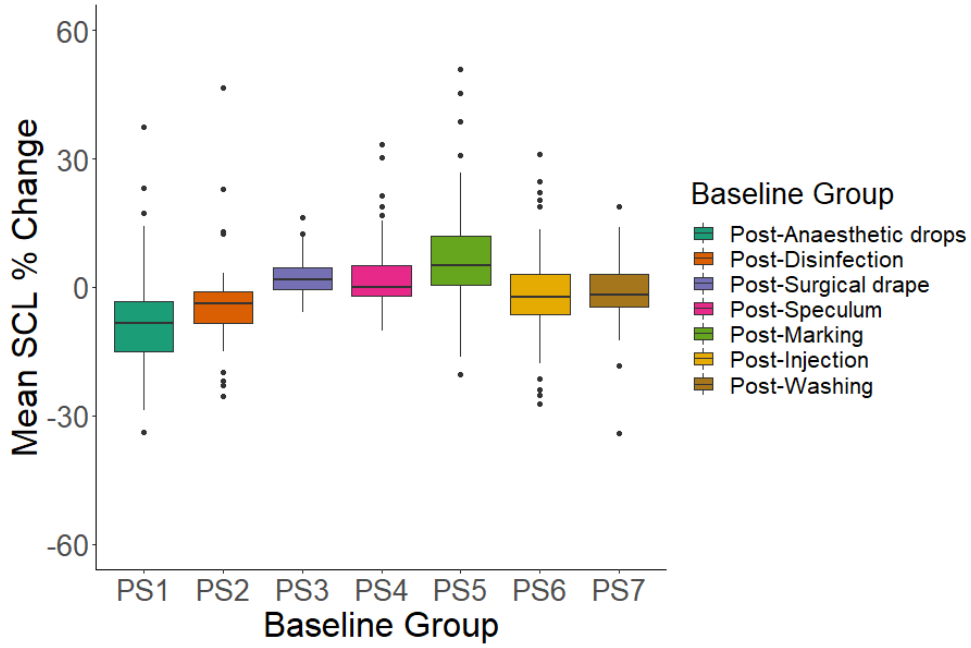

Figure 8.5.7 – Mean SCL % change categorised by baseline group. Baseline groups were calculated as the % change in baseline SCL (x2 − x1) / x1) × 100, in which x1 represents the initial baseline value (pre-stimulus) and x2 represents the current baseline value (post-stimulus). For example, to calculate the baseline % change after the application of anaesthetic drops (PS1), the mean SCL (µS) during baseline pre-treatment (BS0, x1) was subtracted from the mean SCL (µS) calculated after the application of anaesthetic drops (x2), then divided by the initial mean SCL (µS) during baseline pre-treatment (BS0, x1), and multiplied by a 100. This approach was used in the subsequent procedural steps.

8.5.2.3. Questionnaire data

- **Visual Analogue Scale (VAS)**

Figure 8.5.8 presents the VAS scores at baseline (VAS0), 1-2 hours (VAS1) and 24 hours post-treatment (VAS24). The median scores ± (IQR) at baseline, 1-2 hours and 24 hours post-treatment were 0.00 (± 0.00), 14.50 (± 31.25), and 3.50 (± 22.25). For example, N=9 participants reported experiencing pain at baseline measurement (VAS scores = 2, 2, 3, 11, 15, 19, 20, 20, 29). The quartile scores and data boxplots indicate that the VAS scores at 1-2 hours and 24 hours post-treatment were positively skewed. Also, VAS scores at 1-2 hours had a higher dispersion compared to 24 hours post-treatment.

A Friedman test of differences among repeated measures, VAS0, VAS1, and VAS24 was conducted and rendered a χ^2 of 77.5 which was significant ($2.2e^{-16}$). Further analysis using pairwise Wilcoxon signed rank test with a Bonferroni correction specified that differences were statistically significant, $p<0.0001$ between all groups; baseline and 1-2 hours post-treatment ($p=3.8e^{-10}$), baseline and 24 hours post-treatment ($p=3.2e^{-7}$), 1-2 hours post-treatment and 24 hours post-treatment ($p=1.8e^{-5}$).

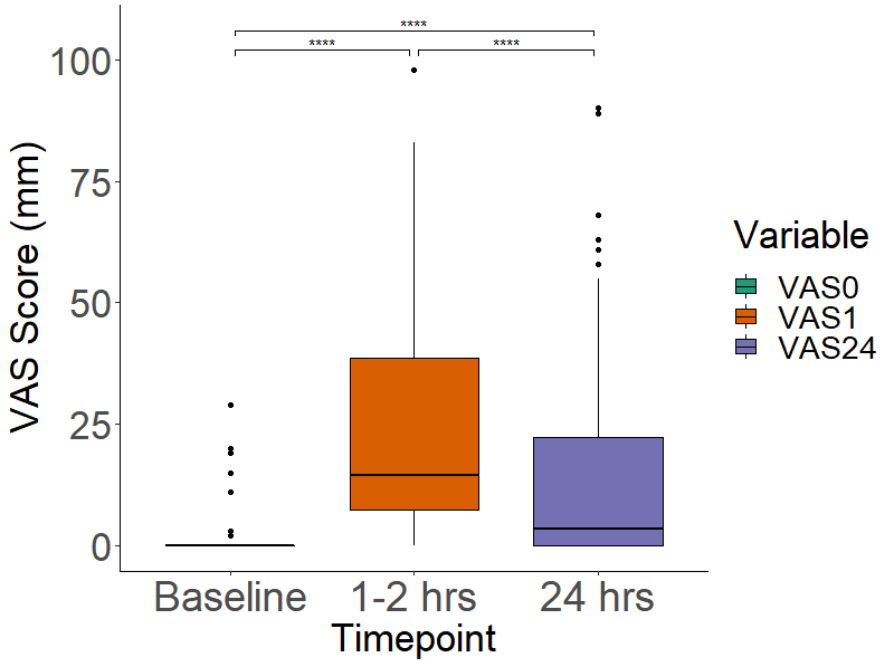

Figure 8.5.8 – Paired samples comparison between Visual Analogue Scale (VAS) scores at baseline (VAS0), 1-2 hours (VAS1) and 24 hours post-treatment (VAS24). Wilcoxon signed-rank test with Bonferroni correction was used to test the variables. VAS scores were significantly different at all 3 timepoints. **** = $p<0.0001$, N = 64 per paired sample, missing observations (NA's) = 1.

- **Short-form McGill Pain Questionnaire Main Component (MPQ)**

Figure 8.5.9 presents the MPQ scores at baseline (MPQ0), 1-2 hours (MPQ1) and 24 hours post-treatment (MPQ24) and a summary of the scores is provided in table 8.5.4. The median scores ± (IQR) at baseline, 1-2 hours and 24 hours post-treatment were 0.00 (± 0.00), 39.00 (± 4.00), and 29 (± 4.25). A high number of outliers has been identified in the data. For example, N=7 participants reported experiencing pain at baseline measurement (MPQ scores = 1, 2, 2, 3, 5, 8, 10). The quartile scores and data boxplots indicated that the MPQ scores at 1-2 hours and 24 hours post-treatment were positively skewed (mean>median).

It is also interesting to note the variety in the qualitative descriptors used to describe the pain experience in the sensory and affective subscale (tables 8.5.5 and 8.5.6). For example, at 1-2 hours post-treatment, 39% of participants experienced mild aching pain, 37.5% tender pain, and 6.3% and 4.7% of the total sample respectively reporting severe aching and tender pain. Also, 6.3% participants described their experience as severe stabbing, sharp pain, and tiring-exhausting. At 24 hours post-treatment, 4.7% (n=3) of participants continued to experience severe sharp, aching, or tender pain, and 15.6% feeling a moderate tiring-exhausting pain. This study has also identified one particular case (ID:19) with prolonged severe sharp, aching and tender pain at both 1-2 hours and 24 hours post-treatment.

A Friedman test of differences among repeated measures, MPQ0, MPQ1 and MPQ24 was conducted and rendered a χ^2 of 70.6 which was significant ($p=4.7e^{-16}$). Further analysis using pairwise Wilcoxon signed-rank test with Bonferroni correction, showed that differences were statistically significant, $p<0.0001$ and $p<0.001$ between all groups; baseline and 1-2 hours post-treatment ($p=5.8e^{-9}$), baseline and 24 hours post-treatment ($p=3.8e^{-7}$), 1-2 hours post-treatment and 24 hours post-treatment ($p=7.5e^{-4}$).

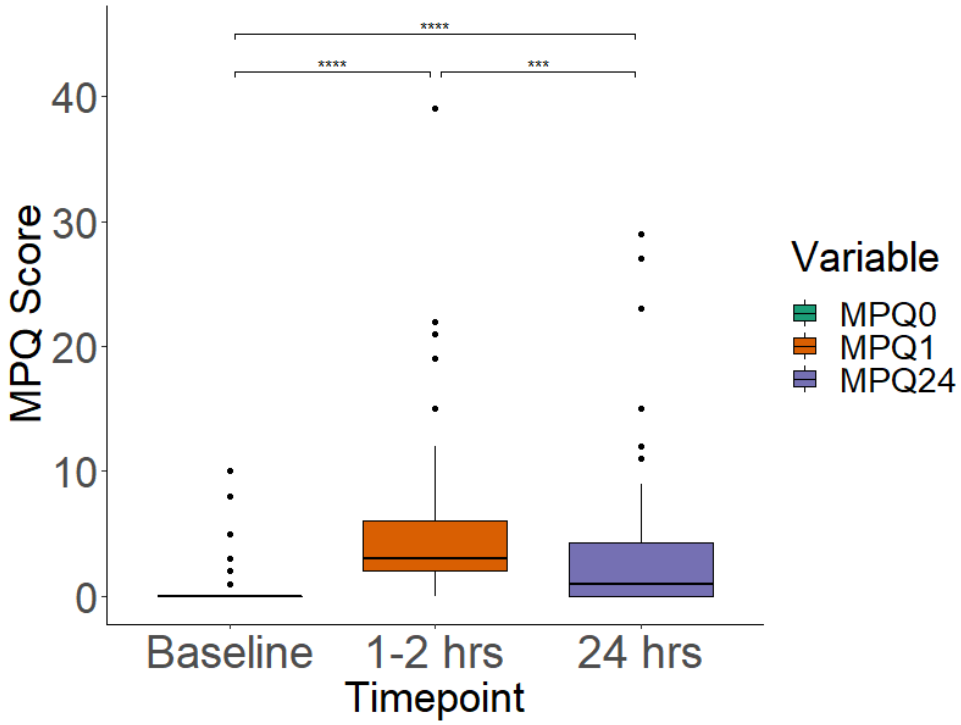

Figure 8.5.9 – Paired samples comparison between Short-Form McGill Pain Questionnaire (SF-MPQ) Main Component (MPQ) at baseline (MPQ0), 1-2 hours (MPQ1) and 24 hours post-treatment (MPQ24). Wilcoxon signed-rank test with Bonferroni correction was used to test the variables. MPQ scores were significantly different at all 3 timepoints. **** = $p<0.0001$, *** = $p<0.001$, N = 64 per paired sample, missing observations (NA's) = 1.

Timepoint	Measure	Median	Range	IQR	Mean	SD	95% CI	SEM
Baseline	S	0	0 – 7	0.0, 0.0	0.34	1.24	[0.03, 0.65]	0.15
	A	0	0 – 4	0.0, 0.0	0.14	0.64	[-0.02, 0.30]	0.08
	Total	0	0 – 10	0.0, 0.0	0.48	1.75	[0.04, 0.92]	0.22
1-2 hrs post-treatment	S	3	0 – 28	1.75, 5.25	4.41	4.67	[3.24, 5.58]	0.58
	A	11	0 – 11	0.0, 1.0	0.95	2.16	[0.41, 1.49]	0.27
	Total	39	0 – 39	2.0, 6.0	5.36	6.41	[3.76, 6.96]	0.80
24 hrs post-treatment	S	19	0 – 19	0.0, 3.0	2.91	4.39	[1.81, 4.01]	0.55
	A	11	0 – 11	0.0, 1.0	0.83	1.89	[0.36, 1.30]	0.24
	Total	29	0 – 29	0.0, 4.25	3.73	6.06	[2.22, 5.24]	0.76

Table 8.5.4 – Short-Form McGill Pain Questionnaire (SF-MPQ) Main Component (MPQ) scores. Summary of the sensory and affective subscales of pain sensation at baseline, 1-2 hours and 24 hours post-treatment. N = 64, missing observations (NA's) = 1. IQR = Inter-Quartile Range (Q1, Q3), SD = Standard Deviation, 95% CI = 95% Confidence Interval, SEM = Standard Error of the Mean.

Descriptors of pain	No pain	Mild	Moderate	Severe
Sensory subscale				
Throbbing	42 (65.6)	15 (23.4)	7 (10.9)	0 (0.0)
Shooting	57 (89.1)	3 (4.7)	3 (4.7)	1 (1.6)
Stabbing	49 (76.6)	7 (10.9)	4 (6.3)	4 (6.3)
Sharp	47 (73.4)	4 (6.3)	9 (14.1)	4 (6.3)
Cramping	61 (95.3)	0 (0.0)	2 (3.1)	1 (1.6)
Gnawing	59 (92.2)	2 (3.1)	3 (4.7)	0 (0.0)
Hot-burning	48 (75.0)	8 (12.5)	5 (7.8)	3 (4.7)
Aching	24 (37.5)	25 (39.1)	11 (17.2)	4 (6.3)
Heavy	51 (79.7)	10 (15.6)	3 (4.7)	0 (0.0)
Tender	24 (37.5)	24 (37.5)	13 (20.3)	3 (4.7)
Splitting	62 (96.9)	1 (1.6)	1 (1.6)	0 (0.0)
Affective subscale				
Tiring-exhausting	45 (70.3)	9 (14.1)	6 (9.4)	4 (6.3)
Sickening	58 (90.6)	3 (4.7)	2 (3.1)	1 (1.6)
Fearful	56 (87.5)	3 (4.7)	3 (4.7)	2 (3.1)
Punishing-cruel	62 (96.9)	0 (0.0)	0 (0.0)	2 (3.1)

Table 8.5.5 – Descriptors of the patient's pain experience on the sensory and affective subscales of pain sensation 1-2 hours post-treatment. Data are presented as number (%). N = 64, missing observations (NAs) = 1. Descriptors are rated on an intensity scale of: 0 = no pain, 1 = mild, 2 = moderate, and 3 = severe.

Descriptors of pain	No pain	Mild	Moderate	Severe
Sensory subscale				
Throbbing	53 (82.8)	6 (9.4)	5 (7.8)	0 (0.0)
Shooting	59 (92.2)	1 (1.6)	4 (6.3)	0 (0.0)
Stabbing	56 (87.5)	2 (3.1)	5 (7.8)	1 (1.6)
Sharp	53 (82.8)	4 (6.3)	4 (6.3)	3 (4.7)
Cramping	60 (93.8)	2 (3.1)	2 (3.1)	0 (0.0)
Gnawing	60 (93.8)	3 (4.7)	1 (1.6)	0 (0.0)
Hot-burning	58 (90.6)	5 (7.8)	1 (1.6)	0 (0.0)
Aching	36 (56.3)	16 (25.0)	9 (14.1)	3 (4.7)
Heavy	54 (84.4)	7 (10.9)	3 (4.7)	0 (0.0)
Tender	35 (54.7)	19 (29.7)	7 (10.9)	3 (4.7)
Splitting	61 (95.3)	2 (3.1)	1 (1.6)	0 (0.0)
Affective subscale				
Tiring-exhausting	46 (71.9)	6 (9.4)	10 (15.6)	2 (3.1)
Sickening	58 (90.6)	4 (6.3)	1 (1.6)	1 (1.6)
Fearful	59 (92.8)	2 (3.1)	2 (3.1)	1 (1.6)
Punishing-cruel	60 (93.8)	1 (1.6)	2 (3.1)	1 (1.6)

Table 8.5.6 – Descriptors of the patient's pain experience on the sensory and affective subscales of pain sensation 24 hours post-treatment. Data are presented as number (%). N = 64, missing observations (NA's) = 1. Descriptors are rated on an intensity scale of: 0 = no pain, 1 = mild, 2 = moderate, and 3 = severe.

- **Present Pain Intensity (PPI) index**

Figure 8.5.10 presents the PPI scores at baseline (PPI0), 1-2 hours (PPI1) and 24 hours post-treatment (PPI24). The median scores ± (IQR) at baseline, 1-2 hours and 24 hours post-treatment were 0.00 (± 0.00), 1.00 (± 2.00), and 1.00 (± 1.15). The quartile scores and data boxplots indicated that the MPQ scores at 1-2 hours were positively skewed (mean>median) also having a higher dispersion compared to 24 hours post-treatment. A Friedman test of differences among repeated measures, PPI0, PPI1, and PPI24 was conducted and rendered a χ^2 of 66.3 which was significant ($p=1.8e^{-14}$). Further analysis using pairwise Wilcoxon signed rank test with a Bonferroni correction specified that differences were statistically significant, $p<0.0001$ and $p<0.01$ between all groups; baseline and 1-2 hours post-treatment ($p=8.5e^{-9}$), baseline and 24 hours post-treatment ($p=1.5e^{-6}$), 1-2 hours post-treatment and 24 hours post-treatment ($p=0.002$).

Figure 8.5.11 presents the descriptors of the PPI scores at baseline, 1-2 hours and 24 hours post-treatment and a summary of the scores provided in table 8.5.9. At both 1-2 hours and 24 hours post-treatment variable responses can be observed with the majority of participants reporting mild pain at 1-2 hours (30%), and no pain at 24 hours post-treatment (48%). Also, 27%, 6% and 9% of the participants reported a discomforting, distressing and horrible pain, respectively at 1-2 hours post-treatment, with one participant reporting excruciating pain. At 24 hours post-treatment, 13%, 11% and 2% of participants reported discomforting, distressing and horrible pain.

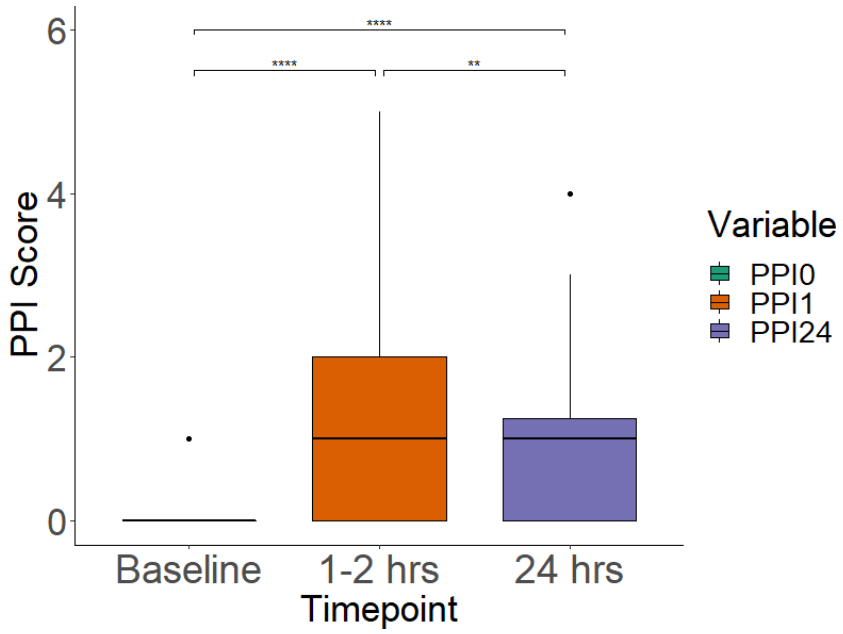

Figure 8.5.10 – Paired samples comparison between Present Pain Intensity (PPI) scores at baseline (PPI0), 1-2 hours (PPI1) and 24 hours post-treatment (PPI24). Wilcoxon signed-rank test with Bonferroni correction was used to test the variables. **** = p<0.0001 and ** = p<0.01, N = 64 per paired sample, missing observations (NA's) = 1.

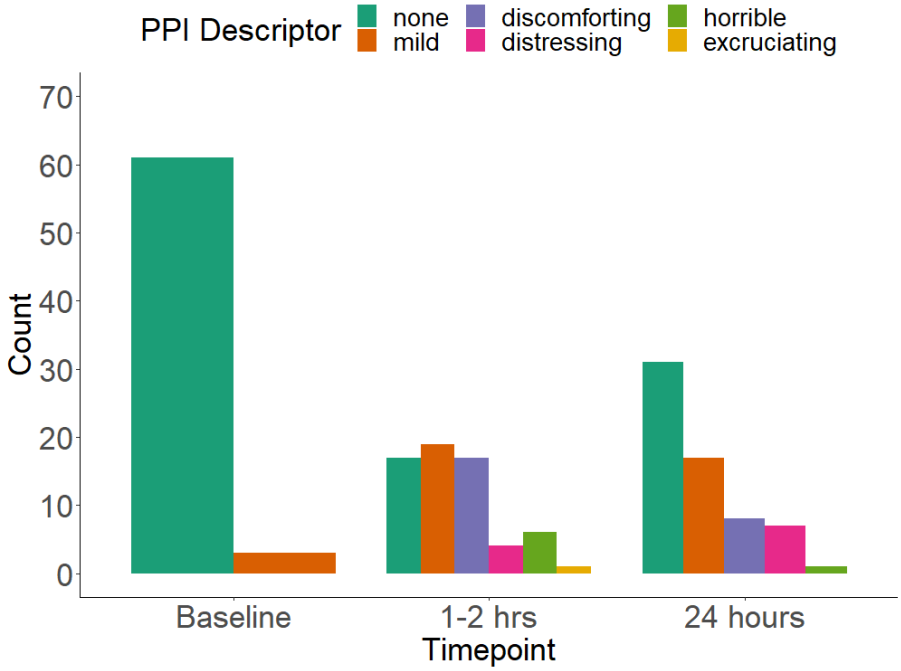

Figure 8.5.11 – Bar chart of Short-Form McGill Pain Questionnaire (SF-MPQ) Present Pain Intensity (PPI) scores at baseline, 1-2 hours and 24 hours post-treatment. Number of participants (%) - Baseline: None = 61 (95.3), Mild = 3 (4.7); 1-2 hrs post-treatment: None = 17 (26.6), Mild = 19 (29.7), Discomforting = 17 (26.6), Distressing = 4 (6.2), Horrible = 6 (9.4), Excruciating = 1 (1.6); 24 hrs post-treatment: None = 31 (48.4), Mild = 17 (26.6), Discomforting = 8 (12.5), Distressing = 7 (10.9), Horrible = 1 (1.6), Excruciating = 0 (0.0). N = 64, missing observations (NA's) = 1.

- **State and Trait Anxiety Inventory (STAI)**

Figure 8.5.12 presents the total STAI scores at baseline (STAI0), 1-2 hours (STAI1) and 24 hours post-treatment (STAI24). The median scores ± (IQR) at baseline, 1-2 hours and 24 hours post-treatment were 58 (± 17.5), 58 (± 24.0), and 56 (± 23.5). It can be observed that the difference between the scores reported at the three timepoints was small, although many outliers were identified at baseline. Also, data were positively skewed (mean>median).

Figure 8.5.13 presents the state anxiety scores at baseline (State0), 1-2 hours (State1) and 24 hours post-treatment (State24). The median scores ± (IQR) at baseline, 1-2 hours and 24 hours post-treatment were 28 (± 11.25), 26 (± 14.50), and 26 (± 14.75). It can be observed that the difference between the scores reported at the three timepoints was small. Also, data were positively skewed (mean>median) at all 3 timepoints with outliers identified.

Figure 8.5.14 presents the trait anxiety scores at baseline (Trait0), 1-2 hours (Trait1) and 24 hours post-treatment (Trait24). The median scores ± (IQR) at baseline, 1-2 hours and 24 hours post-treatment were 31 (± 11.25), 30 (± 12.50), and 29 (± 11.00). It can be observed that the difference between the scores reported at the three timepoints was small. Also, data were positively skewed (mean>median) at all 3 timepoints with outliers identified.

A Friedman test of differences among repeated measures of state anxiety, State0, State1, and State24 was conducted and rendered a χ^2 of 3.1 which was not significant, $p>0.05$ ($p=0.59$). Similarly, no statistically significant differences were obtained for trait anxiety, Trait0, Trait1, and Trait24, reporting a χ^2 of 2.5, $p=0.28$. Summary of the STAI data is provided in table 8.5.7.

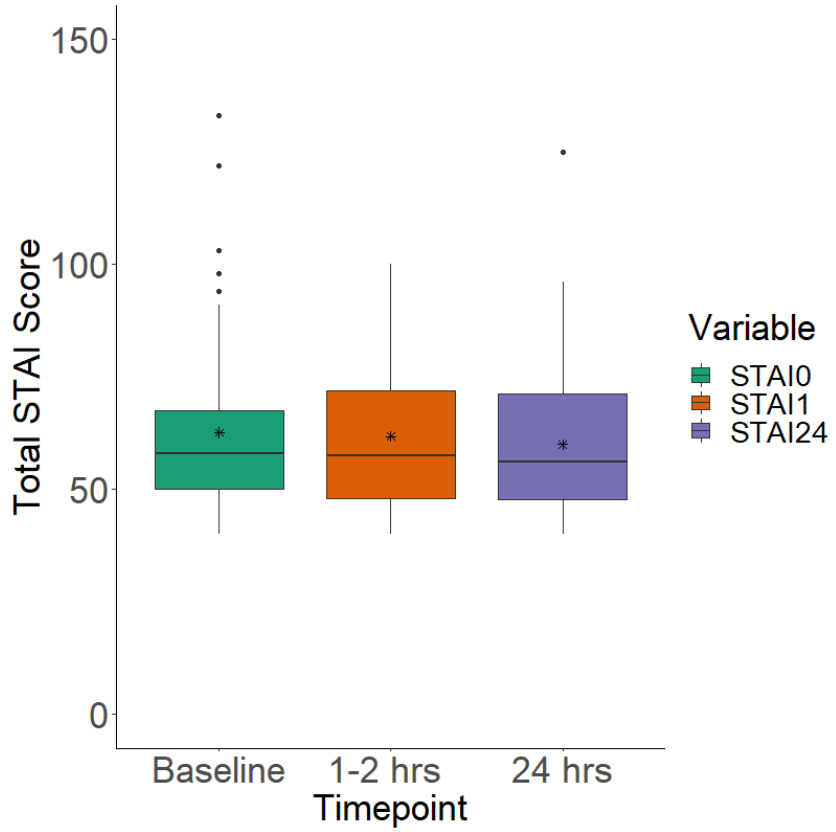

Figure 8.5.12 – Box and whisker plots showing Total State and Trait Anxiety (STAI) scores at baseline, 1-2 hours and 24 hours post-treatment. The asterisk (*) indicates the mean location of each paired sample. Mean scores ± SD for STAI at baseline, 1-2 hours and 24 hours post-treatment were 62.62 ± 19.40, 61.71 ± 16.18 and 59.98 ± 18.04, respectively. Medians (± Inter-Quartile Range) were 58 ± (17.50), 58 (± 24.0), and 56 (± 23.5) respectively for Baseline (STAI0), 1-2 hours post-treatment STAI1), and 24 hours post-treatment (STAI24). The black circles (●) represent outliers. N = 64, missing observations (NA's) = 1.

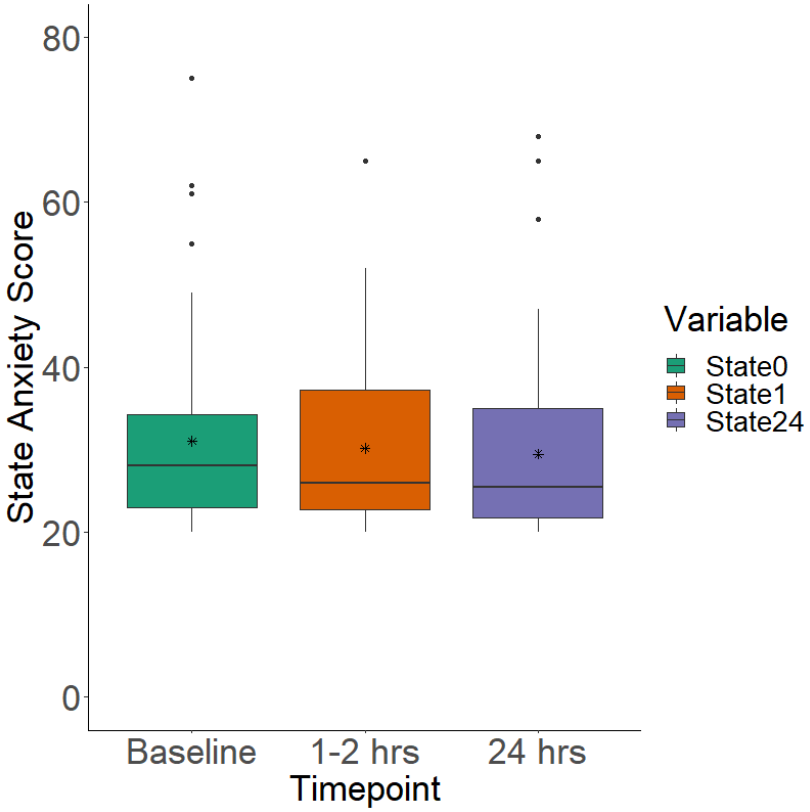

Figure 8.5.13 – Box and whisker plots showing State Anxiety scores at baseline, 1-2 hours and 24 hours post-treatment. The asterisk (*) indicates the mean location of each paired sample. Mean scores ± SD for State Anxiety at baseline, 1-2 hours and 24 hours post-treatment were 31.02 ± 11.43, 30.19 ± 9.76 and 29.47 ± 10.84, respectively. Medians (± Inter-Quartile Range) were 28 (± 11.25), 26 (± 14.50), and 26 (± 14.75) respectively for Baseline (State0), 1-2 hours post-treatment (State1), and 24 hours post-treatment (State24). The black circles (●) represent outliers. N = 64, missing observations (NA's) = 1.

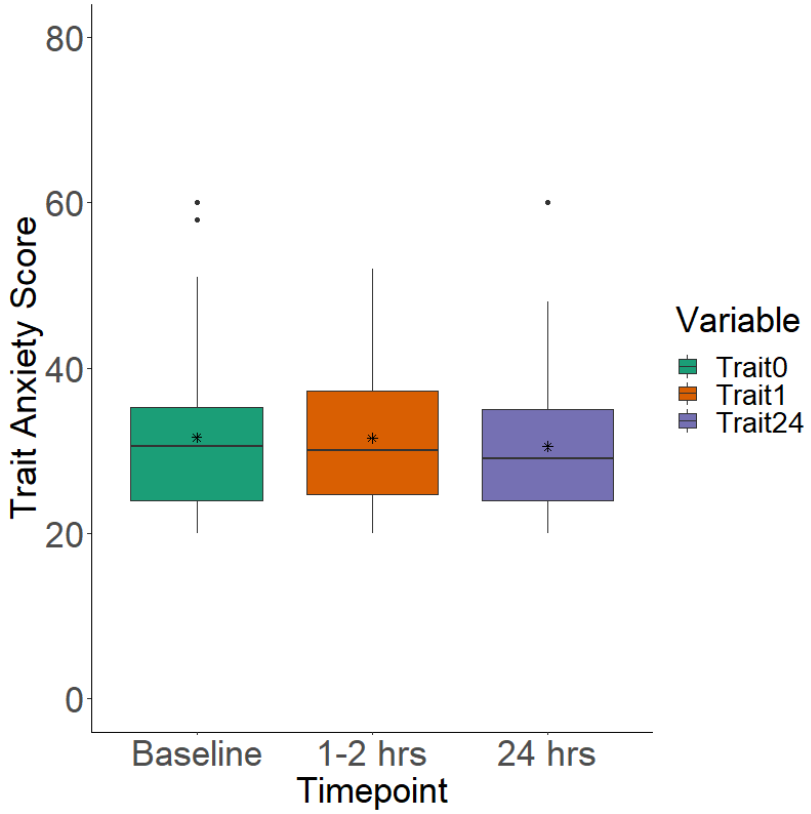

Figure 8.5.14 – Box and whisker plots showing Trait Anxiety scores at baseline, 1-2 hours and 24 hours post-treatment. The asterisk (*) indicates the mean location of each paired sample. Mean scores ± SD for Trait Anxiety at baseline, 1-2 hours and 24 hours post-treatment were 31.61 ± 9.26, 31.55 ± 8.39 and 30.52 ± 8.70, respectively. Medians (± Inter-Quartile Range) were 31 (± 11.25), 30 (± 12.50), and 29 (± 11.00), respectively for Baseline (Trait0), 1-2 hours post-treatment (Trait1), and 24 hours post-treatment (Trait24). The black circles (●) represent outliers. N = 64, missing observations (NA's) = 1.

- **Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)**

Figure 8.5.15 presents the logit transformed WEMWBS scores at baseline (WEMWBS0), 1-2 hours (WEMWBS1) and 24 hours post-treatment (WEMWBS24). The median scores ± (IQR) at baseline, 1-2 hours and 24 hours post-treatment were 2.43 (± 1.64), 2.57 (± 1.77), and 2.44 (± 1.54). The mean scores ± SD at baseline, 1-2 hours and 24 hours post-treatment were 2.40 ± 1.19, 2.50 ± 1.19, and 2.41 ± 1.30. It can be observed that the difference between the scores reported at the three timepoints was small and the data were normally distributed (mean ~ median). A summary of the WEMWBS data is provided in table 8.5.8. A repeated measures ANOVA was performed to compare the differences in WEMWBS scores at baseline, 1-2 hours and 24 hours post-treatment, showing no statistically significant differences, $F(2, 128) = 0.63$, $p=0.53$ ($p>0.05$); no significant difference. Table 8.5.9 presents a summary of the results obtained from the questionnaire data.

8.5.2.4. Other analyses

- **Comparison of gender differences in electrodermal activity**

The Wilcoxon rank-sum test showed no statistically significant differences between the baseline pre-treatment SCL (µS), BS0 ($p=0.20$, $r=0.17$), nor the baseline post-treatment SCL (µS), BS1 ($p=0.26$, $r=0.17$) between the female and male groups. Although, statistically significant differences of small effect size were found in the marking SCR amplitude between the female and male groups ($p=0.04$, $r=0.27$), and the injection SCR amplitude ($p=0.04$, $r=0.27$), $p<0.05$.

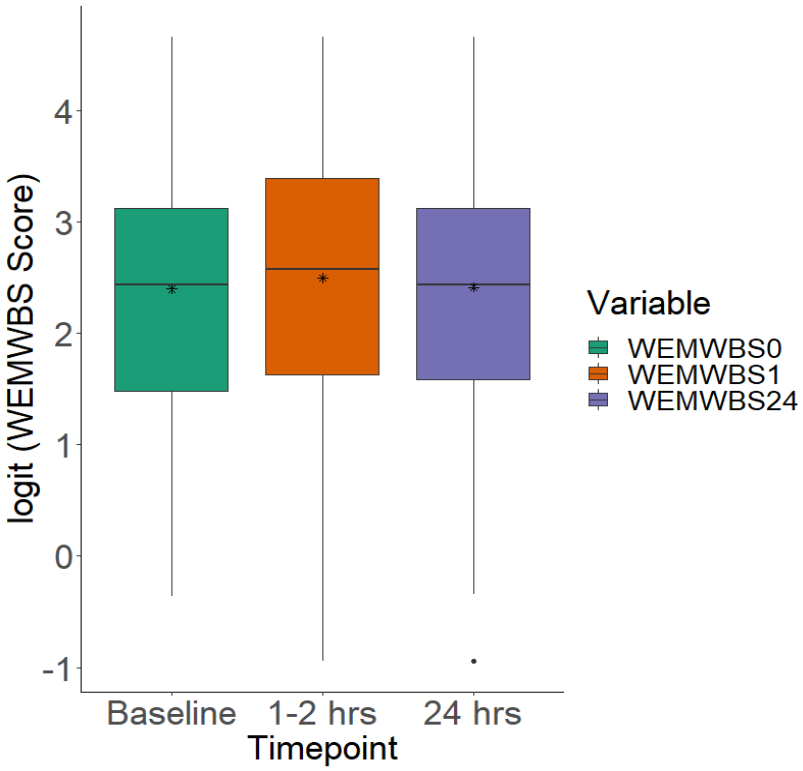

Figure 8.5.15 – Box and whisker plots showing the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) in logit transformation at baseline, 1-2 hrs and 24 hrs post-treatment. The asterisk (*) indicates the mean location of each paired sample. Mean scores ± SD for WEMWBS at baseline, 1-2 hours and 24 hours post-treatment were 2.40 ± 1.19, 2.50 ± 1.19, and 2.41 ± 1.30, respectively. Medians (± Inter-Quartile Range) were 2.43 (± 1.64), 2.57 (± 1.77), and 2.44 (± 1.54), respectively for baseline (WEMWBS0), 1-2 hours post-treatment (WEMWBS1), and 24 hours post-treatment WEMWBS24). The black circles (●) represent outliers. N = 64, missing observations (NA's) = 1.

Timepoint	Measure	Median	Range	IQR	Mean	SD	95% CI	SEM
Baseline	Trait	31	20 – 60	24.00, 35.25	31.61	9.26	[29.30, 33.92]	1.16
	State	28	20 – 75	23.00, 34.25	31.02	11.43	[28.16, 33.88]	1.43
	Total	58	40 – 133	50.00, 67.50	62.62	19.40	[57.78, 67.47]	2.43
1-2 hrs post-treatment	Trait	30	20 – 52	24.75, 37.25	31.55	8.39	[29.45, 33.65]	1.05
	State	26	20 – 65	22.75, 37.25	30.19	9.76	[27.75, 32.63]	1.22
	Total	58	40 – 100	48.00, 72.00	61.71	16.18	[57.67, 65.75]	2.02
24 hrs post-treatment	Trait	29	20 – 60	24.00, 35.00	30.52	8.70	[28.35, 32.69]	1.09
	State	26	20 – 68	21.75, 35.00	29.47	10.84	[26.76, 32.18]	1.35
	Total	56	40 – 125	47.75, 71.25	59.98	18.04	[55.47, 64.49]	2.25

Table 8.5.7 – State and Trait Anxiety Inventory (STAI) scores at baseline, 1-2 hours and 24 hours post-treatment. N = 64, missing observations (NA's) = 1. IQR = Inter-Quartile Range (Q1, Q3), SD = Standard Deviation, 95% CI = 95% Confidence Interval, SEM = Standard Error of the Mean.

Timepoint	Median	Range	IQR	Mean	SD	95% CI	SEM
Baseline	2.44	-0.36 – 4.66	1.49, 3.12	2.40	1.19	[2.10, 2.69]	0.15
1-2 hrs post-treatment	2.57	-0.94 – 4.66	1.63, 3.40	2.50	1.19	[2.21, 2.79]	0.15
24 hrs post-treatment	2.44	-0.94 – 4.66	1.58, 3.12	2.41	1.30	[2.09, 2.73]	0.16

Table 8.5.8 – Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) logit transformed scores at baseline, 1-2 hours and 24 hours post-treatment. N = 64, missing observations (NA's) = 1. IQR = Inter-Quartile Range (Q1, Q3), SD = Standard Deviation, 95% CI = 95% Confidence Interval, SEM = Standard Error of the Mean

	Baseline			1-2 hrs post-treatment			24 hrs post-treatment		
Variable	Median	Range	IQR	Median	Range	IQR	Median	Range	IQR
MPQ	0	0 – 10	0.0, 0.0	3.0	0 – 39	2.00, 6.0	1.0	0 – 29	0.00, 4.30
VAS	0	0 – 29	0.0, 0.0	14.5	0 – 98	7.25, 38.5	3.5	0 – 90	0.00, 22.25
PPI	0	0 – 1	0.0, 0.0	1.0	0 – 5	0.00, 2.00	1.0	0 – 4	0.00, 1.25
STAI	58	40 – 133	50.0, 67.5	57.5	40 – 100	48.00, 72.0	56	40 – 125	47.75, 71.25
logit WEMWBS	2.44	-0.38 – 4.66	1.49, 3.12	2.57	-0.94 – 4.67	1.63, 3.40	2.44	-0.94, 4.66	1.58, 3.12

Table 8.5.9 – Questionnaire data results summary. Median, range, and Inter-Quartile Range (IQR) scores for baseline, 1-2 hours and 24 hours post-treatment. Short-Form McGill Pain Questionnaire (SF-MPQ) Main Component (MC), Visual Analogue Scale (VAS), Present Pain Intensity (PPI) index, State-Trait Anxiety Inventory (STAI) and logit-transformed Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS). Number of observations = 64, missing observations (NA's) = 1.

8.5.2.5. Exploring the variables affecting post-treatment pain

In this section, the relationship between several independent (predictor) variables and the outcome of interest, pain at 1-2 hours and 24 hours post-treatment was evaluated. The purpose of the analyses (Tables 8.5.10 – 8.5.14) and presentation of data using scatterplot matrices (Figures 8.5.16 – 8.5.19) was to investigate trends, detecting patterns of interest that will enable us to identify potentially significant predictor variables to explain pain following the intravitreal injection procedure. Additionally, the systematic literature review on pain and discomfort during intravitreal injections (Chapter 4), theoretical models of pain perception and emotions described in Chapter 2, as well as the qualitative research findings of this thesis (Chapter 6) improved the understanding into how patient experience can be influenced by a combination of factors including physiological and emotional states. In so doing, for the purposes of the analysis, other than the statistical outcomes obtained in this section, variables understood to be related to pain were also assessed in the regression models. Examples of the multiple linear regression models are further described in Section 8.5.2.6.

The visual analogue scale is one of the most common measures for pain intensity in clinical and research applications, including ophthalmology (Chapter 4). VAS score was therefore selected as the primary outcome measure in multiple linear regression analysis to facilitate the discussion of the findings with respect to previous research on pain in intravitreal injections. In addition to the primary regression models, it has been drawn to the attention the diverse responses in the sensory and affective subscale

of the MPQ. In the interest of regression model evaluation of the predictive variables, a secondary regression analysis was performed on the sum of the intensity rank values of total descriptors.

As shown in table 8.5.10, none of these differences were statistically significant, except for the type of anti-VEGF ($p<0.05$). From these data, the aflibercept group reported significantly higher pain scores at 1-2 hours post-treatment compared to the group of participants who received an intravitreal injection of ranibizumab. Overall, post-treatment pain did not differ between males and females, although, a smaller p-value was calculated at 24 hours post-treatment which implies a larger difference in the median scores of the two distributions at this timepoint. Data from this table can be compared with the data in table 8.5.11 which shows the results of the correlational analysis. As presented in the table, there is a significant positive correlation ($p<0.05$) between the predictor variables, state anxiety (baseline), $r(62) = 0.29$, injection amplitude, $r(58)= 0.27$, VAS (baseline), $r(62)= 0.30$, and the outcome variable, VAS score at 1-2 hours post-treatment. Some of these data relationships, such as state and trait anxiety (baseline), and the injection SCR amplitude can also be identified in the scatterplot matrix (figure 8.5.16) by showing a weak, positive, linear association with the VAS score. A positive monotonic relationship can also be observed in the scatterplot matrix (figure 8.5.17) between state and trait anxiety (baseline), Spearman's rho with Bonferroni correction, $r(62) = 0.65$, $p<0.001$. Additional correlation analyses demonstrated that the injection was significantly correlated to both the speculum, $r(55) = 0.48$, $p<0.001$ and marking

amplitude, r(56) = 0.33, p<0.05), and the state anxiety measures had a strong negatively correlation to WEMWBS at baseline, r(62) = -0.59; 1-2 hours post-treatment, r(62) = -0.57; and 24 hours post-treatment, r(62) = -0.69, p<0.001). Incorporating correlated variables in the regression model as predictors is likely to introduce multicollinearity. Problematic effects arise including coefficient estimates can become highly sensitive to minor changes in the model, increases the variances of the sampling distributions and a correct model is more challenging to be justified appropriately (Binova 2021). Moreover, the VAS score at baseline, r(62)=0.35, p=0.00 and injection SCR amplitude, r(58)=0.27, p=0.04 were positively correlated to the VAS score at 24 hours post-treatment, p<0.05 (table 8.5.13). In terms of the secondary outcome measure, MPQ, no statistically significant correlations, p>0.05 were shown between the examined predictors and MPQ at 1-2 hours post-treatment (table 8.5.12) and although the VAS score was correlated to the MPQ score at 24 hours post-treatment, p<0.05 (table 8.5.14) further observations using scatterplots showed that VAS data at baseline were zero-inflated thus the analyses obtained were not accurate.

Furthermore, while the variables, wellbeing, speculum and marking amplitudes have been examined in the regression model analysis as potential predictors, only the baseline state anxiety and the injection amplitude are presented in tables 8.5.11, 8.5.12, 8.5.13 and 8.5.14 as they have showed a higher association with the outcome measures.

	Post-treatment VAS Scores (mm)			
Variable	*1-2 hrs*	*p*	*24 hrs*	*p*
Age (yr)	Median (IQR)		Median (IQR)	
60-69 (n = 14)	3.58 (3.40, 5.81)	0.49	1.41 (0.00, 2.87)	0.24
70-79 (n = 32)	3.53 (1.93, 5.02)		1.73 (0.00, 3.66)	
80-90 (n = 19)	4.30 (3.15, 7.21)		4.06 (0.43, 3.64)	
Gender				
Female (n = 37)	18 (10.00, 38.00)	0.32	6 (1.00, 23.00)	0.10
Male (n = 28)	11 (4.50, 32.50)		1 (0.00, 12.00)	
Laterality				
RE (n = 30)	16 (10.00, 25,00)	0.25	3 (0.00, 20.00)	0.39
LE (n = 24)	10 (4.75, 21.25)		4 (0.00, 15.75)	
BI (n = 11)	40 (5.50, 75.00)		11 (1.50, 32.00)	
Anti-VEGF				
Aflibercept (n = 24)	25 (13.50, 33.74)	0.02*	6 (0.50, 24.50)	0.31
Ranibizumab (n = 41)	11 (4.00, 22.00)		3 (0.00, 19.00)	
No. of previous injections				
0 – 5 (n = 12)	17 (9.50, 71.00)	0.20	8.0 (2.0, 29.75)	0.22
6 – 15 (n = 24)	11 (3.50, 19.50)		2.0 (0.0, 15.00)	
16 – 30 (n = 17)	11 (9.00, 25.00)		3.0 (0.0, 18.00)	
> 30 (n = 12)	45 (10.50, 63.50)		8.5 (1.75, 44.25)	
IOL				
Yes (n = 9)	20.5 (8.75, 46.25)	0.73	1.5 (0.00, 34.25)	0.93
No (n = 56)	14.0 (5.75, 35.00)		4.0 (0.00, 19.75)	
Cataract				
Yes (n = 6)	51.5 (14.00, 77.00)	0.21	19 (12.75, 21.50)	0.17
No (n = 59)	14.0 (5.75, 34.00)		3 (0.00, 22.00)	
Smoking				
Yes (n = 12)	22 (13.25, 54.75)	0.11	12.5 (4.50, 24.50)	0.18
No (n = 52)	13 (4.00, 31.25)		3.0 (0.00, 19.75)	
Alcohol				
Never (n= 11)	14.0 (9.00, 19.00)	0.95	6.0 (0.00, 15.00)	0.47
Monthly (n = 12)	16.5 (8.75, 40.75)		9.5 (0.00, 29.00)	
Weekly (n = 30)	12.0 (7.00, 31.75)		2.5 (0.00, 13.50)	
Daily (n = 11)	19.0 (6.50, 48.50)		6.0 (1.50, 36.50)	

Table 8.5.10 – Demographic and clinical factors affecting Visual Analogue Scale (VAS) scores following intravitreal injection at 1-2 hours and 24 hours. VAS = visual analogue scale; Anti-VEGF = anti-vascular endothelial growth factor; IOL = intraocular lenses. Calculated using Wilcoxon Rank Sum Test or Kruskal-Wallis Test, $p<0.05$ with Bonferroni correction.

Predictor variable	Outcome variable: VAS1		
	rho	*95% CI*	*p*
State Anxiety (baseline)	0.29	[0.08, 0.52]	0.01*
VAS (Baseline)	0.30	[0.02, 0.48]	0.02*
Age	-0.05	[-0.30, 0.19]	0.60
Best-Corrected Visual Acuity	-0.08	[0.40, 0.56]	0.52
Total No. of previous injections	0.07	[-0.21, 0.28]	0.74
IVI procedure duration	0.16	[-0.17, 0.34]	0.23
Injection Amplitude	0.27	[-0.06, 0.44]	0.04*

Table 8.5.11 – Correlations between predictor variables and outcome variable, Visual Analogue Scale at 1-2 hours post-treatment (VAS1). State anxiety (baseline), r(62) = 0.29, p=0.01; Visual Analogue Scale (VAS0, baseline), r(62)= 0.30, p=0.02, Injection Amplitude, r(58) = 0.27, p=0.04. were found to be moderately correlated with VAS score at 1-2 hours post-treatment. Spearman's rho, $p<0.05$ with Bonferroni correction. IVI = Intravitreal Injection.

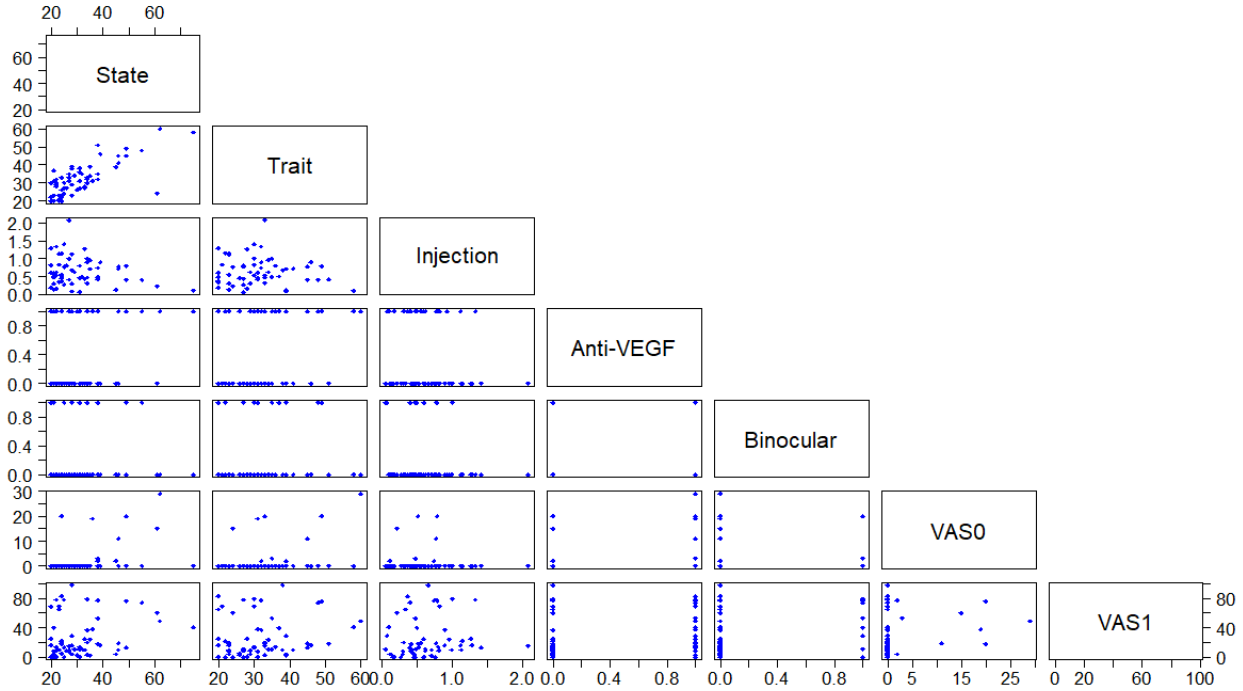

Figure 8.5.16 – Scatterplot matrix to explore pairwise relationship between different predictor variables and outcome variable, Visual Analogue Scale score at 1-2 hours post-treatment (VAS1) for the multiple linear regression analysis. As can be seen from the figure above, there is an increasing trend between the state anxiety (baseline), trait anxiety (baseline), injection amplitude and the outcome variable, VAS1 score. Hence, these variables, in addition to the type of anti-VEGF (ranibizumab, aflibercept) and same-day binocular injection will be further examined in the multiple linear regression model to identify significant predictors of pain at 1-2 hours post-treatment. Observations for visual analogue scale at baseline (VAS0) fit poorly due to excess of zero scores. A strong positive relationship can be observed between state and trait anxiety, thus, to meet the assumption of no multicollinearity in linear regression only one of these two variables will be included in the model (the variable that explains more of the variance in the regression model).

Predictor variable	Outcome variable: MPQ1		
	rho	*95% CI*	*p*
State Anxiety (baseline)	0.23	[0.04, 0.49]	0.07
VAS (Baseline)	0.20	[-0.04, 0.43]	0.12
Age	-0.20	[-0.43, 0.05]	0.11
Best-Corrected Visual Acuity	-0.13	[-0.40, 0.10]	0.31
No. of previous injections	-0.03	[-0.20, 0.29]	0.84
IVI duration	0.13	[-0.13, 0.37]	0.33
Injection Amplitude	0.18	[-0.14, 0.36]	0.17

Table 8.5.12 – Correlations between predictor variables and outcome variable, Short-Form McGill Pain Questionnaire Main Component total score at 1-2 hours post-treatment (MPQ1). Spearman's rho with Bonferroni correction, reporting no statistically significant correlation, $p>0.05$. IVI = Intravitreal Injection.

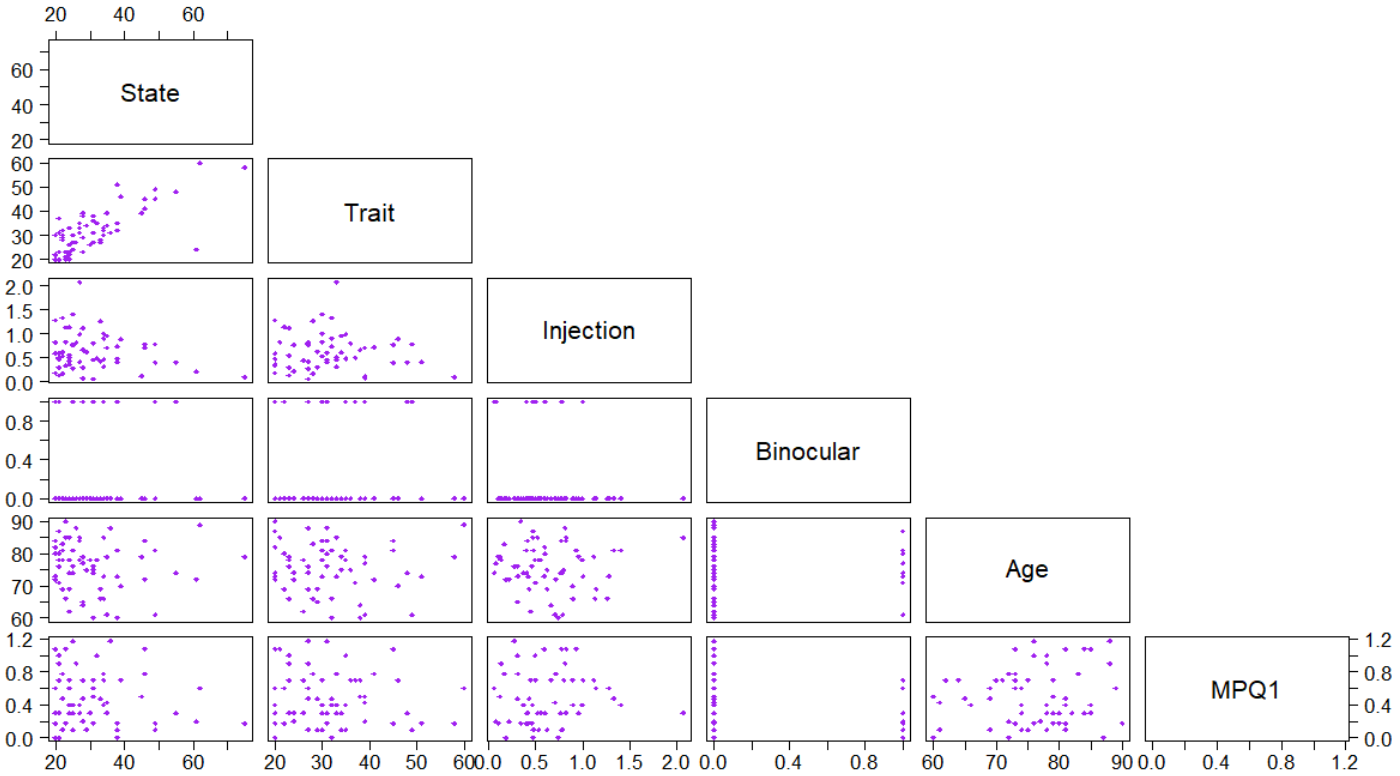

Figure 8.5.17 – Scatterplot matrix to explore pairwise relationship between different predictor variables and outcome variable, Short-Form McGill Pain Questionnaire Main Component at 1-2 hours post-treatment (MPQ1) for the multiple linear regression analysis. As can be noticed from the figure above, there is a general positive relationship between the state anxiety, trait anxiety, injection, and the outcome variable, MPQ1, with many observations closer to zero may indicate a weak relationship. These variables will be further examined in the multiple linear regression model to identify significant predictors of pain at 24 hours post-treatment.

Predictor variable	Outcome variable: VAS24		
	rho	*95% CI*	*p*
State Anxiety (baseline)	0.19	[-0.03, 0.44]	0.14
VAS (Baseline)	0.35	[0.10, 0.54]	0.00*
Age	0.12	[-0.11, 0.37]	0.34
Total No. of previous injections	0.03	[-0.16, 0.33]	0.80
IVI procedure duration	0.11	[-0.21, 0.29]	0.39
Injection Amplitude	0.27	[-0.10, 0.40]	0.04*

Table 8.5.13 – Correlations between predictor variables and outcome variable, Visual Analogue Scale at 24 hours post-treatment (VAS24). Visual Analogue Scale (VAS, baseline), r(62)= 0.35, p=0.00; and Injection Amplitude, r(58) = 0.27, p=0.04 were found to be moderately correlated with VAS24 score. Spearman's rho, p<0.05 with Bonferroni correction. IVI = Intravitreal Injection.

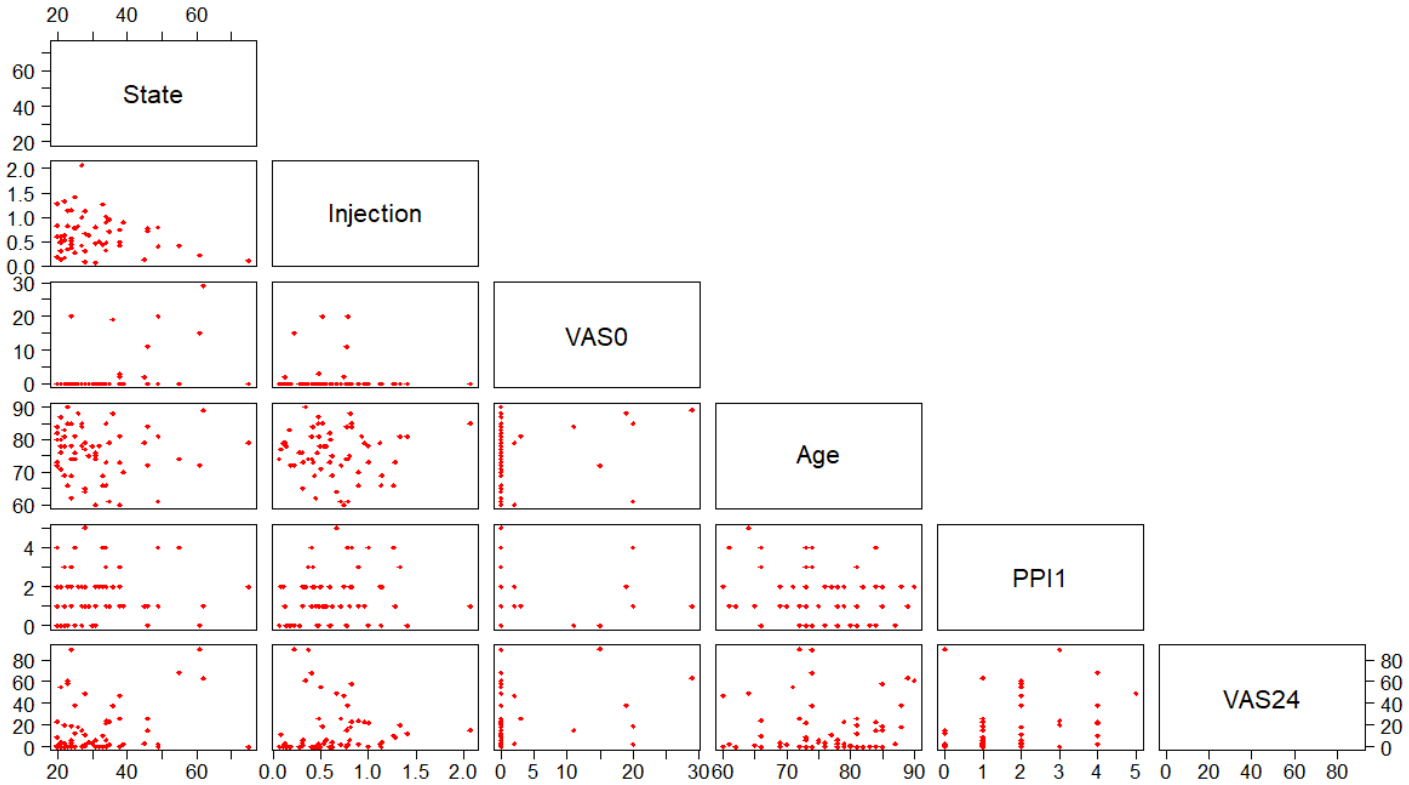

Figure 8.5.18 – Scatterplot matrix to explore pairwise relationship between different predictor variables and outcome variable, Visual Analogue Scale score at 24 hours post-treatment (VAS24) for the multiple linear regression analysis. As can be seen from the figure above, there is an increasing trend between state anxiety, trait anxiety and the VAS24, however there are many widespread observations, also due to excess of zero scores may indicate a weak relationship. These variables will be further examined in the multiple linear regression model to identify significant predictors of pain at 24 hours post-treatment.

Predictor variable	Outcome variable: MPQ24		
	rho	*95% CI*	*p*
State Anxiety (baseline)	0.19	[0.10, 0.54]	0.13
Visual Analogue Scale (Baseline)	0.33	[0.14, 0.57]	0.00*
No. of previous injections	0.09	[-0.04, 0.43]	0.49
Age	0.08	[-0.17, 0.32]	0.52
Injection Amplitude	0.12	[-0.19, 0.32]	0.36

Table 8.5.14 – Correlations between predictor variables and outcome variable, Short-Form McGill Pain Questionnaire Main Component (MPQ) total score at 24 hours post-treatment (MPQ24). Visual Analogue Scale (VAS, baseline) at baseline, r(62) =0.37, was found to be moderately correlated with MPQ24 score. Spearman's rho, $p<0.05$ with Bonferroni correction. IVI = Intravitreal Injection.

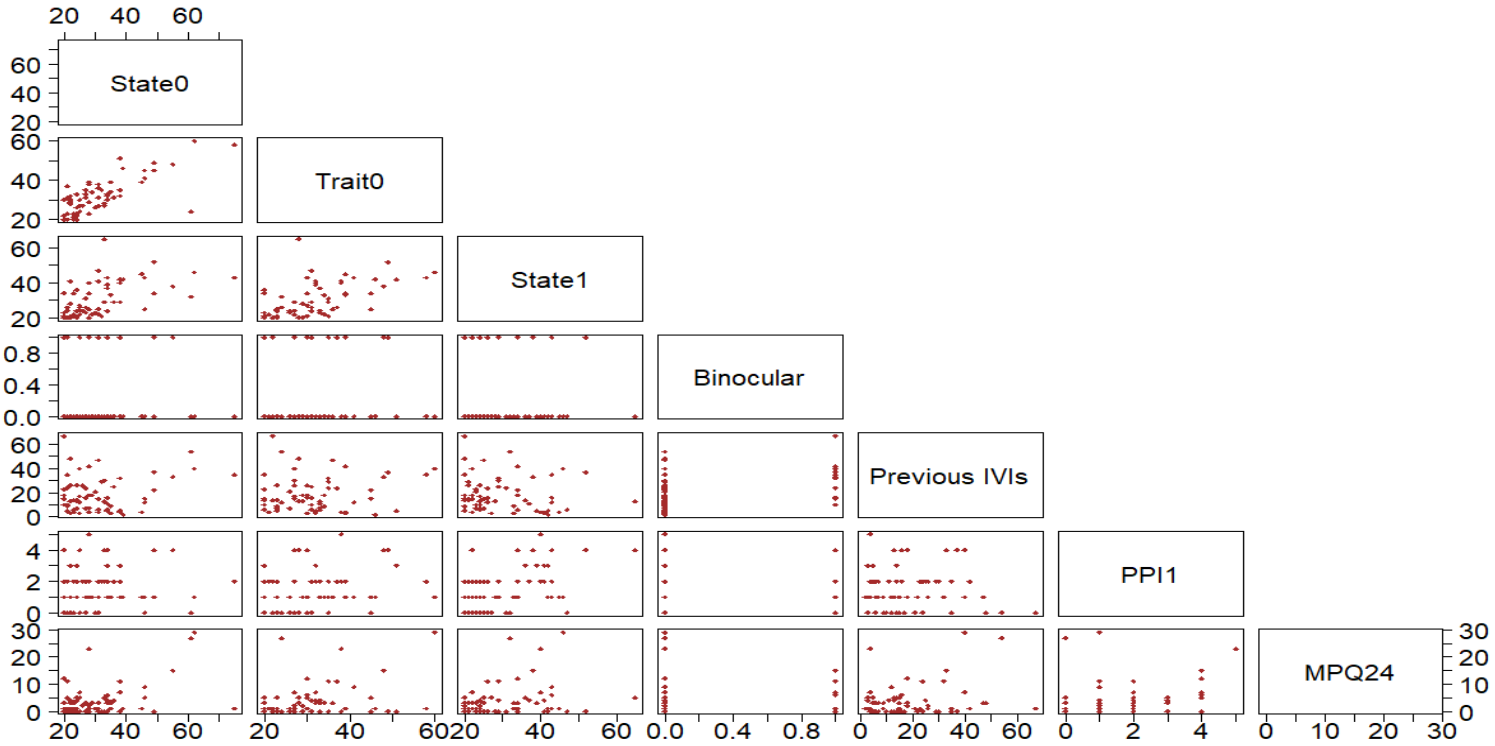

Figure 8.5.19 – Scatterplot matrix to explore pairwise relationship between different predictor variables and outcome variable, Short-Form McGill Pain Questionnaire Main Component at 24 hours post-treatment (MPQ24) for the multiple linear regression analysis. As can be noticed from the figure above, there is a positive relationship between the state anxiety (baseline and at 1-2 hours post-treatment), trait anxiety (baseline), number of previous injections, and the outcome variable, MPQ24. Although, many observations closer to zero may indicate a weak relationship. These variables will be further examined in the multiple linear regression model to identify significant predictors of pain at 24 hours post-treatment.

8.5.2.6. Multiple Linear Regression Models

In Section 8.5.2.5 potential predictor variables were explored for pain following intravitreal injections using correlation analyses and scatterplot matrices. On the basis of the statistical analyses and theoretical understanding of pain in intravitreal injections, the following variables have been examined in the regression models to predict post-treatment pain at 1-2 hours and 24 hours post-treatment: injection SCR amplitude, previous number of intravitreal injections, baseline state anxiety, type of anti-VEGF, same-day binocular injection, and cross-examined with demographics including gender, age, alcohol consumption and current smoking status, as well as clinical characteristics such as BCVA, IOL and cataract. From this point onwards, the injection SCR measures are presented as square root transformed amplitudes. Applying square root and cubic root transformations on the outcome variables, and identification and removal of influential outliers in the data, regression models met the assumptions of linearity, homoscedasticity, and normality (figures 8.5.21 8.5.23, 8.5.25). Consistent with the guidelines previously discussed in this thesis (Section 8.4) on multiple regression models (Altman 1991), this study considered a maximum of 6 predictor variables to represent the sample of 65 participants, also evaluating the number of missing observations in the sample analysed. In this study, 3 multiple linear regression models (tables 8.5.15, 8.5.16, 8.5.17) are reported to explain pain following intravitreal injections at 1-2 hours and 24 hours post-treatment.

- **Model 1:**

Table 8.5.15 provides a summary of the multiple linear regression model 1, square root transformed, $\sqrt{VAS1} = -1.36 + 2.82(Injection) + 1.49(Anti\text{-}VEGF, aflibercept) + 0.09(State\ Anxiety) + 2.05(binocular)$. The results indicated that the model was a significant predictor of pain at 1-2 hours post-treatment, Adjusted $R^2 = 0.38$, $F(4,51)$, $p = 1.47e^{-5}$. Figure 8.5.20 presents the fitted multiple linear regression model to the predicted data on VAS score at 1-2 hrs post-treatment.

- **Model 2:**

Table 8.5.16 provides a summary of the multiple linear regression model 2, square root transformed, $\sqrt{MPQ} = 0.69(Injection) + 1.12(Binocular) + 0.02(State\ Anxiety)$. The results indicated that the model was a significant predictor of pain at 1-2 hours post-treatment, Adjusted $R^2 = 0.25$, $F(4,52)$, $p=0.00$. Figure 8.5.22 presents the fitted multiple linear regression model to the predicted data on MPQ score at 1-2 hrs post-treatment.

- **Model 3:**

Table 8.5.17 provides a summary of the multiple linear regression model 3, cubic root transformed, $\sqrt[3]{VAS24} = -0.20 + 1.26(Injection) + 0.91(Binocular) + 0.03(State\ Anxiety)$. The results indicated that the model was a significant predictor of pain at 24 hours post-treatment, Adjusted $R^2 = 0.13$, $F(3,54)$, $p=0.02$. Figure 8.5.24 presents the fitted multiple linear regression model to the predicted data on VAS score at 24 hrs post-treatment.

Model 1	**Outcome Variable: VAS Score 1-2 hrs post-treatment**			
Predictor Variable	*β*	*Standard error*	*t-value*	*p*
Injection	2.82	0.76	3.73	0.000 ***
Anti-VEGF	1.49	0.62	2.40	0.020 **
State Anxiety	0.09	0.03	3.38	0.001 **
Binocular	2.05	0.75	2.72	0.009 *

Table 8.5.15 – Multiple linear regression model on 1-2 hours post-treatment pain measuring Visual Analogue Scale (VAS) score. Model 1: Square root transformed, √VAS1 = -1.36 + 2.82(Injection)*** + 1.49(Anti-VEGF, aflibercept)** + 0.09(State Anxiety)** + 2.05(binocular)*. Residual standard error: 2.102 on 51 degrees of freedom (outliers removed = 19, 36, 56), (6 observations deleted due to missingness); Multiple R-squared: 0.41, Adjusted R-squared: 0.38, F-statistic: 8.99 on 4 and 51 DF, $p=1.47e^{-5}$. β, slope/estimated coefficient; significance: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1;

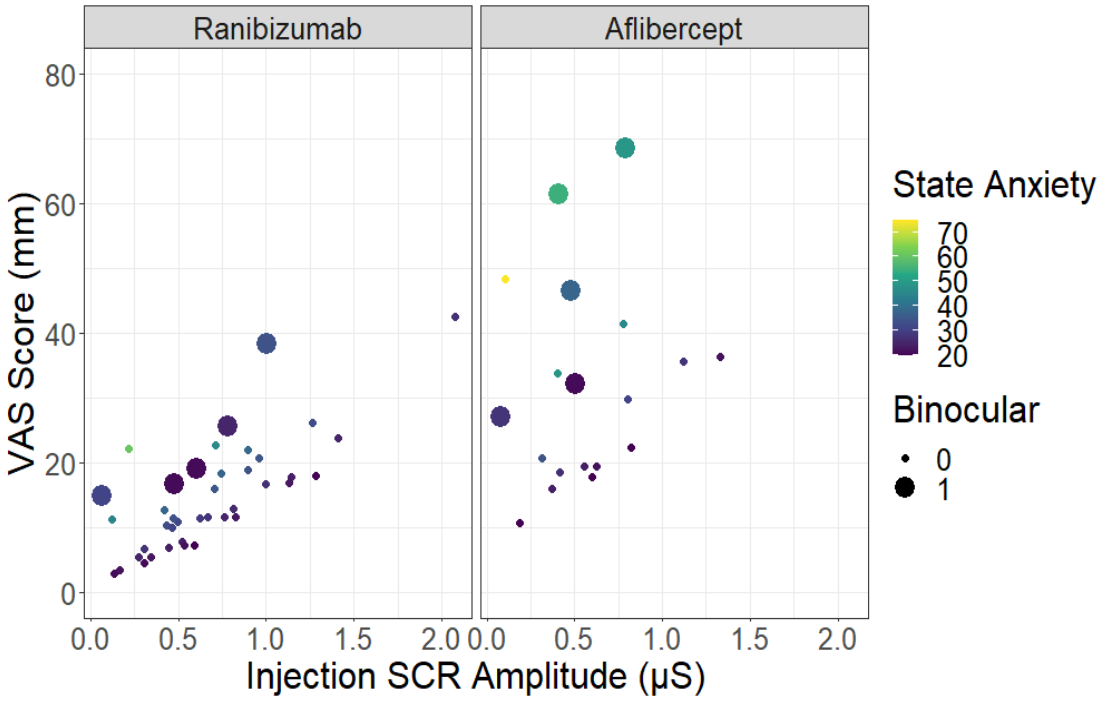

Figure 8.5.20 – Fitting the multiple linear regression model 1 to the predicted data on VAS score at 1-2 hrs post-treatment. Increased injection SCR amplitude, increased state anxiety at baseline, injected with aflibercept, or receiving same-day binocular injections predict a higher VAS score. VAS = Visual Analogue Scale, SCR = Skin Conductance Response. Model 1 was the most optimum regression model explaining 38% of the variance in VAS score.

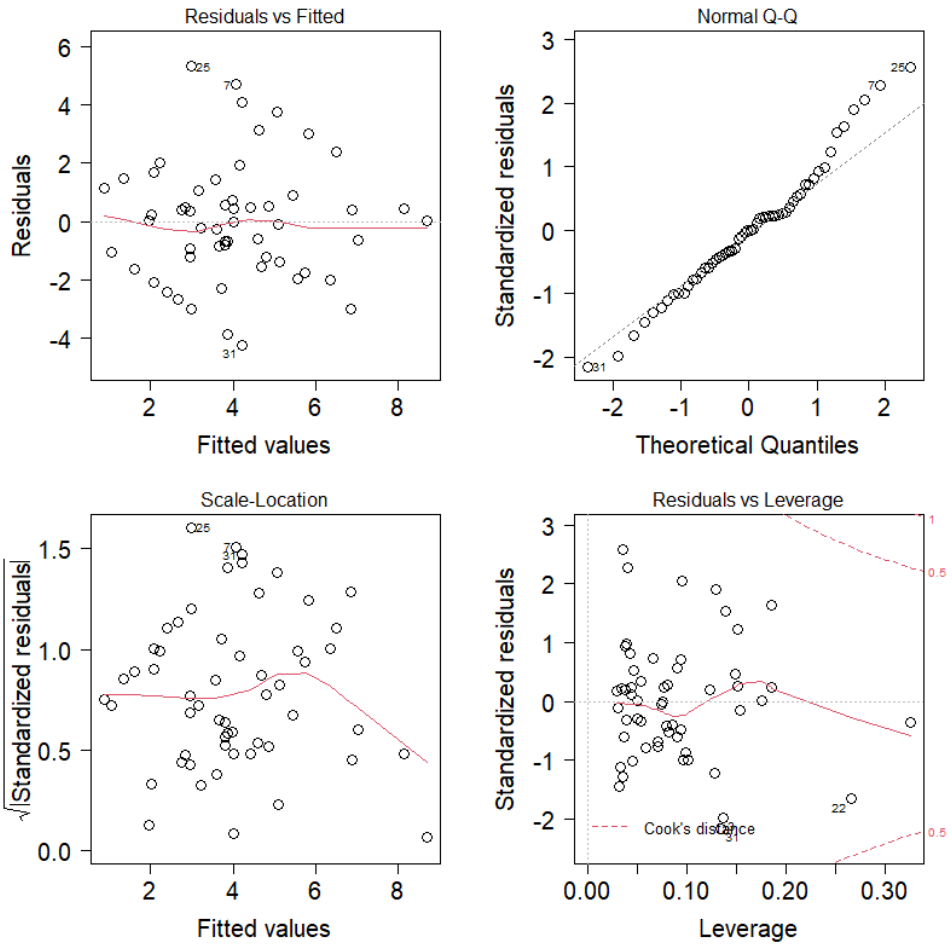

Figure 8.5.21 – Diagnostic plots for Visual Analogue Scale 1-2 hours post-treatment (VAS1) Model 1: Homoscedasticity assumption was checked using a studentised Breusch-Pagan Test; BP = 5.5914, df = 5, p = 0.348. The Durbin-Watson statistic was used to detect the presence of autocorrelation reporting a value of -0.07, D-W statistic = 2.06, p = 0.904. Since p > 0.05 it can be concluded there is no significant autocorrelation between errors. Additionally, variance inflation factor was calculated for all predictor variables to validate the assumption of multicollinearity reporting values <5; Injection = 1.08, Anti-VEGF = 1.19, State Anxiety = 1.08, Binocular = 1.06, hence no multicollinearity between predictor variables. Shapiro-Wilk test indicated that the model fitted normal distribution, W = 0.98, p=0.31. Normality holds since p>0.05. Residual, histogram, and density plots are presented for regression model validation; the errors are independent and normally distributed. Influential outliers (observations: 19, 36, 56) identified using Cook's D (0.06, 0.10, 0.10 respectively) and diagnostic plots were removed.

Model 2	**Outcome Variable: MPQ Score 1-2 hrs post-treatment**			
Variable	*β*	*Standard error*	*t-value*	*p*
Injection	0.69	0.34	2.02	0.05 *
Binocular	1.12	0.36	3.12	0.00 **
State Anxiety	0.02	0.01	1.97	0.05 .

Table 8.5.16 – Multiple linear regression model on 1-2 hours post-treatment pain measuring Short-Form McGill Pain Questionnaire Main Component total score (MPQ1). Model 2: Square root transformed, √MPQ = 0.69(Injection)* + 1.12(Binocular)** + 0.02(State Anxiety)**.** Residual standard error: 0.97 on 52 degrees of freedom (outliers removed = 19, 31, 56), (6 observations deleted due to missingness); Multiple R-squared: 0.30, Adjusted R-squared: 0.25, F-statistic: 5.62 on 4 and 52 DF, p=0.00. β, slope/estimated coefficient; significance: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1;

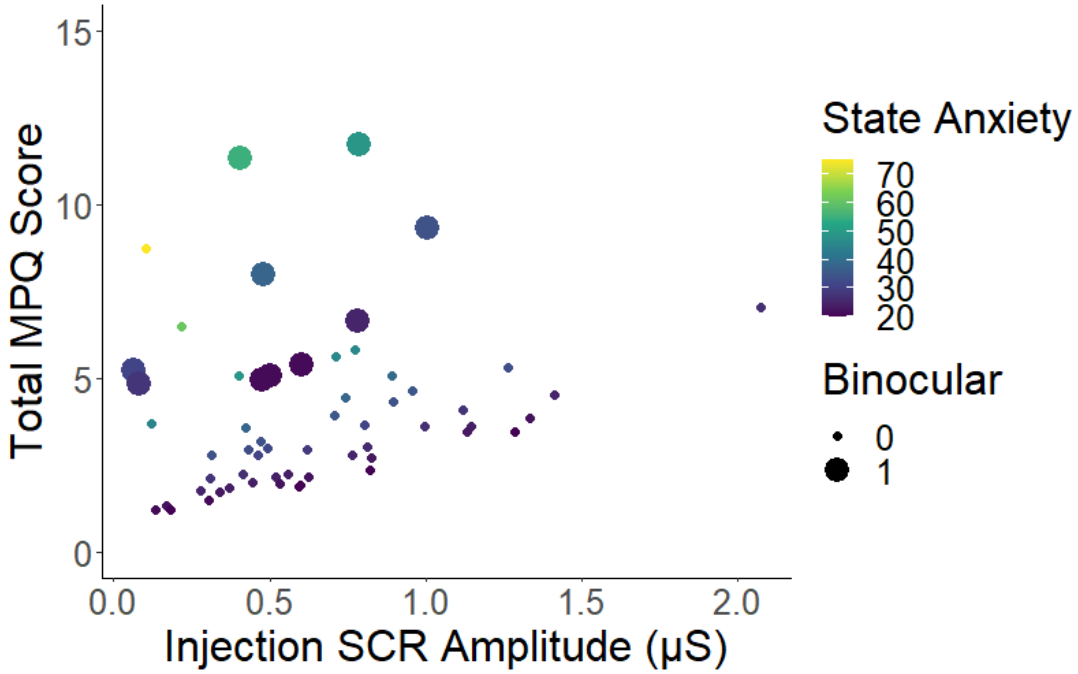

Figure 8.5.22 – Fitting the multiple linear regression model 2 to the predicted data on MPQ score at 1-2 hrs post-treatment. Increased injection SCR amplitude, increased state anxiety at baseline, or receiving same-day binocular injections predict a higher MPQ score. The regression model also reported to explain 25% of the variance in the MPQ score. MPQ = Short-Form McGill Pain Questionnaire Main Component, SCR = Skin Conductance Response.

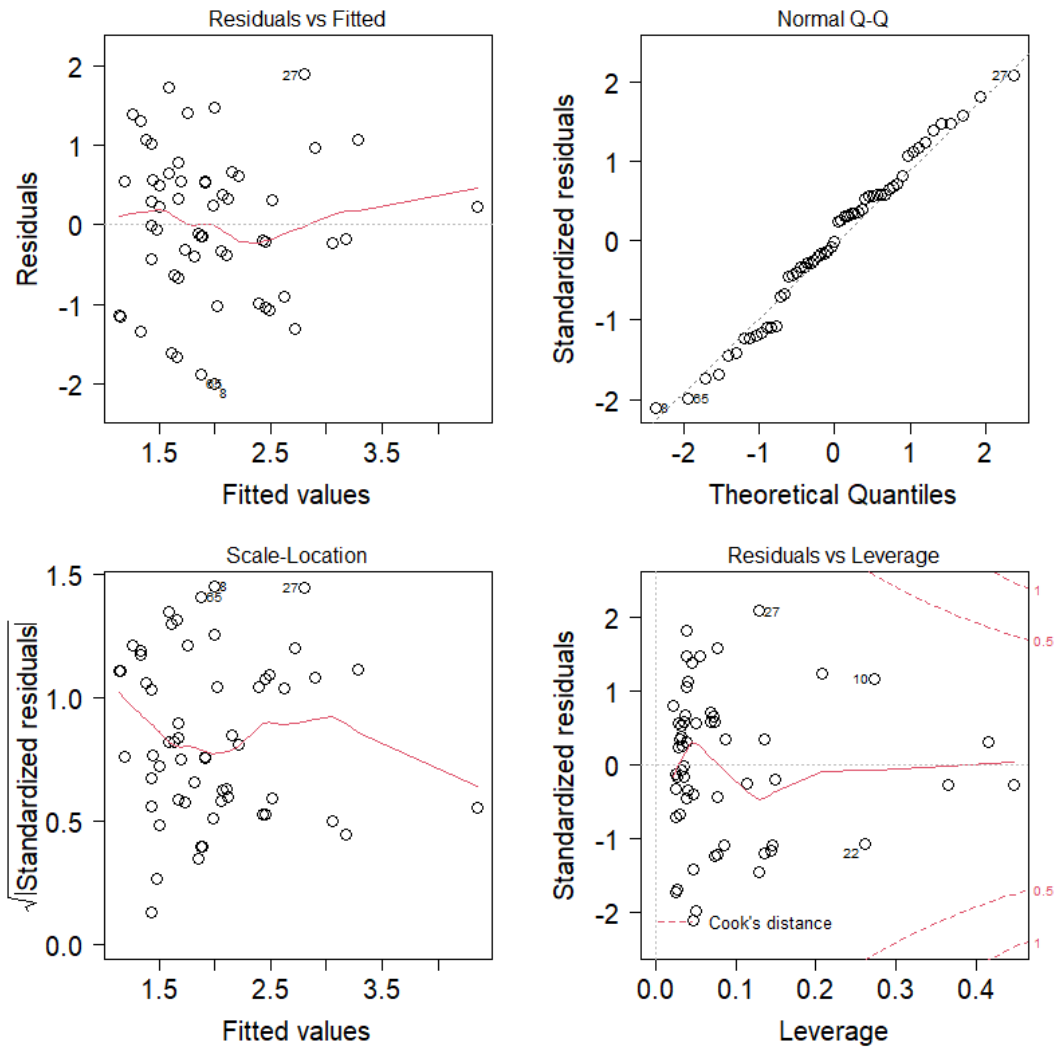

Figure 8.5.23 – Diagnostic plots for the Short-Form McGill Pain Questionnaire Main Component (MPQ) score 1-2 hours post-treatment Model 2: Homoscedasticity assumption was checked using a studentised Breusch-Pagan Test; BP = 1.08, df = 4, p = 0.90. The Durbin-Watson statistic was used to detect the presence of autocorrelation reporting a value of -0.09, D-W statistic = 2.09, p=0.77. Since p>0.05 it can be concluded there is no significant autocorrelation between errors. Additionally, variance inflation factor was calculated for all predictor variables to validate the assumption of multicollinearity reporting values <5; Injection = 1.06, Binocular = 1.04, State Anxiety = 1.17, hence no multicollinearity between predictor variables. Shapiro-Wilk test indicated that the model fitted normal distribution, W = 0.98, p = 0.60. Normality holds since p>0.05. Residual, histogram, and density plots are presented for regression model validation; the errors are independent and normally distributed. Influential outliers (observations: 19, 31, 56) identified using Cook's D (0.07, 0.12, 0.17 respectively) and diagnostic plots were removed.

Model 3	**Outcome Variable: VAS Score 24 hrs post-treatment**			
Predictor Variable	*β*	*Standard error*	*t-value*	*p*
Injection	1.26	0.46	2.71	0.01 **
Binocular	0.91	0.46	1.98	0.05 .
State Anxiety	0.03	0.02	1.61	0.11

Table 8.5.17 – Multiple linear regression model on 24 hours post-treatment pain measuring Visual Analogue Scale (VAS) score. Model 3: Cubic root trransformed, $\sqrt[3]{}$VAS24 = -0.20 + 1.26(Injection)** + 0.91(Binocular) **.** + 0.03(State Anxiety). Residual standard error: 1.31on 54 degrees of freedom (outliers removed = 56), (6 observations deleted due to missingness); Multiple R-squared: 0.17, Adjusted R-squared: 0.13, F-statistic: 3.80 on 3 and 54 DF, p = 0.02. β, slope/estimated coefficient; significance: 0 '***' 0.001 '**' 0.01 '*' 0.05 '**.**' 0.1 ' ' 1;

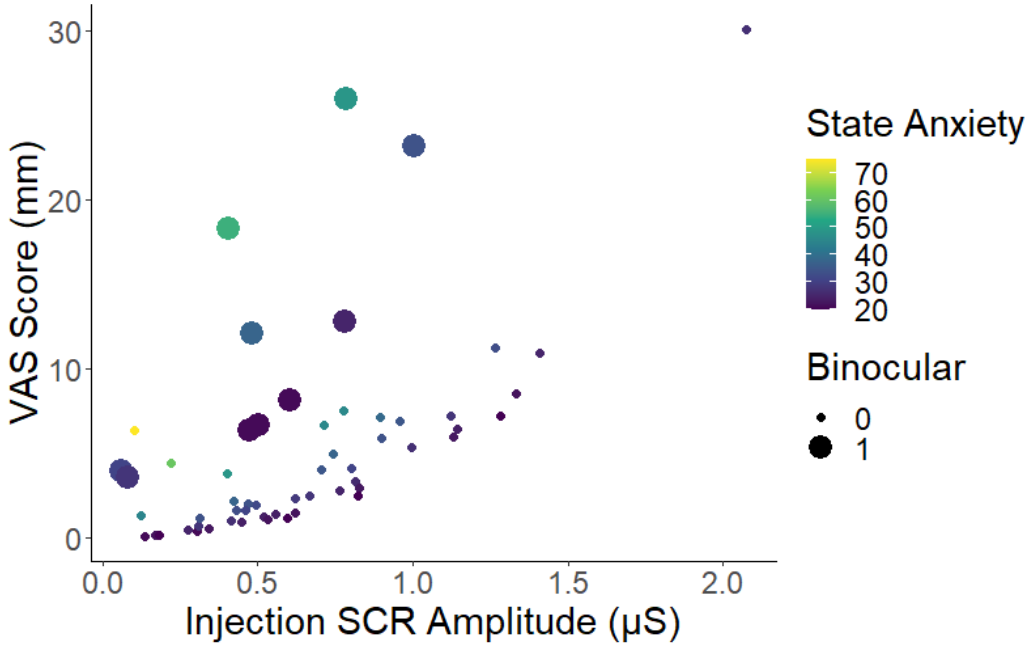

Figure 8.5.24 – Fitting the multiple linear regression model 3 to the predicted data on VAS score at 24 hrs post-treatment. Increased injection SCR amplitude, increased state anxiety at baseline, or receiving same-day binocular injections predict a higher VAS score. While the data presented shows the association between the predictor variables and VAS score, it can be observed that the fitted regression model does not accurately predict the high VAS scores obtained in the data (highest VAS score predicted = 30 mm). This is due to the high zero-inflation in the VAS scores, and the less frequently reported high VAS scores at 24 hours post-treatment. Also, the regression model only explained 13% of the variance in the VAS score. VAS = Visual Analogue Scale, SCR = Skin Conductance Response.

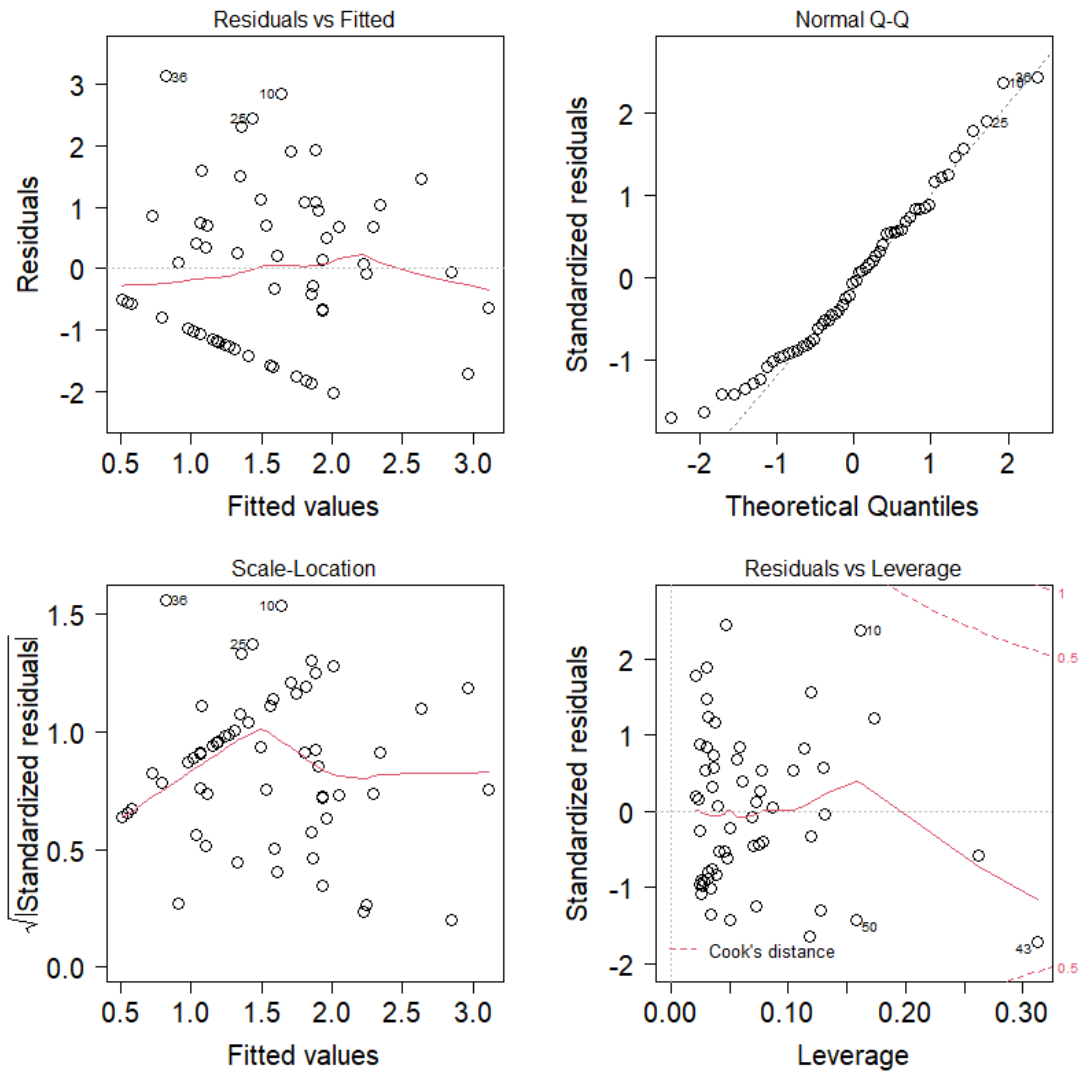

Figure 8.5.25 – Diagnostic plots for Visual Analogue Scale 24 hours post-treatment (VAS24) Model 3: Homoscedasticity assumption was checked using a studentised Breusch-Pagan Test; BP = 3.43, df = 3, p = 0.33. The Durbin-Watson statistic was used to detect the presence of autocorrelation reporting a value of 0.04, D-W statistic = 1.88, p = 0.67. Since p>0.05 it can be concluded there is no statistically significant autocorrelation between errors. Additionally, variance inflation factor was calculated for all predictor variables to validate the assumption of multicollinearity reporting values < 5; Injection = 1.07, Binocular = 1.02, State Anxiety (baseline) = 1.05. Hence no multicollinearity between predictor variables. Shapiro-Wilk test indicated that the model fitted a normal distribution, W = 0.96, p = 0.09. Normality holds since p>0.05. Diagnostic plots are presented for regression model validation; the errors are independent and normally distributed. Influential outlier (observation: 56) was identified calculating Cook's D = 0.07 and studentized residual = 2.68 and using diagnostic plots. Residuals and standardised residuals plots indicate unequal error variances, observed from the data showing patterned distribution; likely to be affected from the zero-inflated scores in the data.

8.6. Discussion

In the present chapter, it has been demonstrated that EDA can make a substantial contribution in associating patients' physiological arousal with varying levels of pain and discomfort during an intravitreal injection procedure. Post-treatment pain was assessed using the VAS (Visual Analogue Scale), MPQ (sensory and affective subscale of qualitative pain descriptors), and the PPI (Present Pain Intensity) index. Participants reported significantly higher pain scores in all measures at both 1-2 hours and 24 hours post-treatment. Visual analogue scale was the primary outcome of this study. One of the key findings in this chapter, on multiple linear regression analysis, intravitreal injection SCR amplitude (coefficient β = 2.82; p = 0.00), baseline state anxiety (coefficient β = 0.09, p = 0.001), binocular injection (coefficient β = 2.05, p = 0.009) and the anti-VEGF, aflibercept (coefficient β =1.49, p=0.001) were significantly associated with degree of pain at 1-2 hours post-treatment and accounting for 38% of the variance explained in the regression model (table 8.5.15). Finding that the injection SCR amplitude was the most significant predictor variable for pain at 1-2 hours and 24 hours post-treatment has implications for promoting more research to consider integrating objective assessments in exploring the pain experience.

Age and gender may play a confounding role in EDA measurement, hence accounting for these variables in the analyses was essential to make valid interpretations of the research outcomes. Previous studies using the VAS have examined the relationships between pain intensity and age, reporting

contradictory results, that older patients experienced higher pain (Haas et al. 2016), lower pain (Rifkin and Schaal 2012a), or no difference between age groups in pain intensity during intravitreal injections (Shin et al. 2018). In this study, age was evaluated against all pain outcomes including the VAS, PPI and MPQ, showing no correlation and no difference between stratified age groups (60-69, 70-79, 80-90), perhaps narrower age range than the other studies (e.g. only elderly groups here). These results are consistent with those of Sanabria et al. (2013) who also evaluated pain experience of similar age groups at different timepoints following intravitreal injections. Moreover, the analysis has shown that older participants had a significantly lower tonic SCL at baseline ($r = -0.27$, $p<0.05$), however no significant age effects have been identified on the phasic ER-SCRs. The lower tonic SCL is likely to be related to structural differences in the peripheral and central nervous system, such as reduced sweat gland density (Catania et al. 1980) and gray matter volume in the limbic system (Sequeira and Roy 1993). In terms of gender differences, significantly higher responses of physiological arousal were identified in women during marking and injection, although the effect size was small ($r=0.27$). Also, gender was not identified as a predictor variable for post-treatment pain. According to previous studies (Kozak et al. 2005; Mogil and Bailey 2010), women are more likely to perceive pain compared to men due to higher level of activity in the endogenous opioid system that controls pain sensitivity, differences of spatial patterns in brain imaging, and a stronger analgesic response.

In Chapter 6 of this thesis, factors were identified using thematic analysis that influenced the patient experience associated with the intravitreal injection procedure. As part of phase 1 of the exploratory sequential mixed methods design, it was hypothesised that application of oxybuprocaine 0.4%, povidone-iodine 5% solution/chlorhexidine, 0.1%, placement of surgical drape and the injection would be significant indicators of the patient experience, more likely to be associated with higher levels of pain and discomfort. Consequently, higher ER-SCRs would be elicited. With respect to the first study objective, the findings highlight higher responses during injection, compared to placement of the speculum and marking. Some authors have reported on the effectiveness of EDA in examining emotional arousal during the anticipation of unpleasant or painful stimuli (Schestatsky et al. 2007; Bradley et al. 2008; Dubé et al. 2009; Loggia et al. 2011; Bari et al. 2018b; Lima et al. 2019). In a study conducted by Bari et al., (2018) on healthy participants, a linear association was demonstrated between the intensity of electrical painful stimuli and the amplitude of SCRs. It may be the case therefore that these variations in the amplitude of procedural steps are characterised by differences in pain intensity and there is a potential for bias from personal (subjective pain threshold, skin temperature, moisture levels) and environmental factors (room temperature). Since the study was not designed to evaluate pain specificity, it was not possible to distinguish pain-specific stimulations from unpleasant, or high intensity potentially autonomic responses (e.g. marking vs injection). Furthermore, to comment on the SCR amplitude during marking of the eye, it is believed that the

phasic electrodermal activity reflected the participants' anticipation to the practitioner leaning forward to mark the eye using a calliper.

Furthermore, EDA has also become a critical research tool for analgesia monitoring in intensive care (Aslanidis et al. 2018a), as well as in peri- and post-operative procedures (Ledowski et al. 2006; Martinez Castellanos et al. 2013; MacNeill and Mayich 2020; Aqajari et al. 2021). In this study, analysis of the tonic SCL illustrated the changing level of participants' general arousal throughout the intravitreal injection procedure. With respect to the application of topical anaesthesia (0.4% oxybuprocaine hydrochloride) at the start of the procedure, an overall reduction from baseline SCL was observed. This is due to the blockade action of the anaesthetic on the nociceptive and other sensory nerve terminals innervating the cornea (Palte 2012). For this reason, it was impractical to perform accurate analyses of the SCR amplitudes associated with anaesthesia and disinfection conditions. Moreover, because of the nature of the experimental design in line with the standard clinical procedures (The Royal College of Ophthalmologists 2018), time intervals between events varied significantly in participants and was regarded inadequate to acquire accurate SCL responses, also because of the slow drifting signal of tonic activity. A time interval of at least 10 seconds has been recommended in the literature (Dawson et al. 2009; Boucsein 2012b; Boucsein et al. 2012). Thus, SCL data were used for observational purposes only, excluded from statistical analysis.

In previous studies investigating the pain intensity associated with the intravitreal injections (Moisseiev et al. 2012; Shin et al. 2018; Inaltekin et al. 2021) there has been little discussion about factors influencing post-treatment pain. Pain has been previously reported to last on average between 3 and 7 days (Rifkin and Schaal 2012b). In the study, pain was assessed at 1-2 hours and 24 hours post-treatment. The results of the current study showed a wide range of pain scores among participants, as evidenced by the high standard deviation of ± 31.25 mm and ± 22.25 mm for the median VAS score at 1-2 hours and 24 hours post-treatment, respectively.An interesting finding is that the injection amplitude, baseline state anxiety and same-day binocular injection explained most of the variance in all 3 of the regression models on pain at 1-2 hours and 24 hours post-treatment. This observation might also indicate reliability of the outcome measures, since pain intensity was examined using both the VAS as well as the sum of the intensity rank values of total descriptors in SF-MPQ. In this study, the adaptation of the SF-MPQ is particularly useful in studying both the qualitative and quantitative aspects of pain, offering an effective way to understand the components and outcomes of the patient experience. Compared to the VAS which has been widely adopted in intravitreal injections (Yau et al. 2011; Moisseiev et al. 2012; Rifkin and Schaal 2012a; Haas et al. 2016), the sensory and affective subscale of descriptors provided a more descriptive information on the changes in symptoms over a 24 hour period to reflect the patient experience. The SF-MPQ has been previously used in ophthalmology research to evaluate the analgesic effect of cyclooxygenase inhibitors and non-steroidal anti-

inflammatory agents (Georgakopoulos et al. 2017; Makri et al. 2017; Makri et al. 2018) on post-treatment pain following intravitreal injections.

To the author's knowledge, no research has been found to account for electrodermal activity as a potential predictor variable of pain perception following intravitreal injections. In this study, 3 multiple linear regression models were demonstrated to identify the most significant factors affecting post-treatment pain in the sample population. The most optimum regression model showed that injection SCR amplitude, state anxiety (baseline), type of anti-VEGF (aflibercept) and same-day binocular injections explained 38% of the variance in pain experienced at 1-2 hours post-treatment ($F(4, 51) = 8.99$, $p = 1.47e^{-5}$, $R^2 = 0.41$, R^2 Adjusted = 0.38). Despite the fact that this model explains 38% of the variance in post-treatment pain, in terms of the sample size and using 4 predictor variables, it highlights the significance of both emotional and physiological factors influencing the patient experience.

Previous studies studies (O Oshodi 2007; Rodrigues et al. 2011; Bilgin and Bilak 2019; Ertan et al. 2020) have compared the effect of different types of anti-VEGF including ranibizumab and aflibercept on the pain experience during injection, with only one study demonstrating a significant difference and that was higher pain during injection with aflibercept (Bilgin and Bilak 2019). In this study, a 30-gauge needle size was used in the administration of both ranibizumab and aflibercept. The findings support that participants receiving aflibercept reported significantly higher pain experience at 1-2 hours post-treatment ($p=0.02$) while no difference was found at 24 hours

following the injection. The systematic literature review in Chapter 4 identified several factors associated with the intravitreal injection such as differences in needle size, injection site and incision of needle insertion reported to influence pain experienced during and following treatment. For instance, 27-gauge compared to 30-gauge needles led to a more painful experience during (Güler et al. 2015) and following treatment (Rodrigues et al. 2011), however this finding was controversial as other studies demonstrate no significant difference (Rifkin and Schaal 2012a; Haas et al. 2016; Loureiro et al. 2017). A possible explanation for obtaining higher pain scores in the aflibercept group may be the method used to administer the injection. For instance, compared to ranibizumab, aflibercept was not pre-loaded and required aseptic preparation and proper priming of the needle ensuring no air bubbles are present in the solution (The Royal College of Ophthalmologists 2018). Also, aflibercept has been associated with higher intraocular pressure immediately after intravitreal injection (Muto and Machida 2020), and severe vitreous or anterior chamber inflammation (Greenberg et al. 2019).

Many recent studies (Kayikcioglu et al. 2017; Senra et al. 2017; Boyle et al. 2018b) have demonstrated that patients receiving intravitreal injections experience high anxiety levels. Segal et al. (2016) found a positive correlation between higher anxiety levels and increased pain experienced during intravitreal injection in their study. STAI is the “gold standard” for measuring preoperative anxiety (Spielberger et al. 1983; Dalal et al. 2015). In this study, no association was found between baseline anxiety (state and

trait) and the participants' amplitude response as a measure of emotional arousal during injection, however state anxiety was a significant predictor of pain at 1-2 hours post-treatment ($p<0.001$). In their review of the impact of preoperative anxiety on the intensity of postoperative pain, Stamenkovic et al. (2018) identified the importance of assessing preoperative anxiety and providing a focused anaesthesia plan in the management of anxious patients. Although previous research has reported higher anxiety levels in younger patients (Herranz-Heras et al. 2020), the analysis conducted in this thesis did not produce significant results to support a correlation between age and anxiety levels. Higher levels of anxiety have been commonly reported in the literature associated with intravitreal injections (Segal et al. 2016; Kayikcioglu et al. 2017; Shin et al. 2018; Herranz-Heras et al. 2020; Inaltekin et al. 2021). In this study, no significant differences were found in the level of anxiety (state and trait) prior to and following the intravitreal injection procedure. One unanticipated finding, although of moderate effect ($r = -0.31$, $p<0.05$) was the negative correlation between state anxiety and the baseline SCL. Also, SCL showed no significant correlation with trait anxiety scores. This discrepancy could be attributed to the fact that the questionnaires at baseline were administered at different timepoints prior to the intravitreal injection procedure and hence may not represent the true level of anxiety. For example, participants who had scheduled an early morning injection, questionnaires were administered the night before, whereas participants receiving an afternoon injection, the questionnaires were administered in the morning of the day of the treatment.

8.6.1. Strengths and limitations

One of the limitations of this study was the fact that there were many missing observations from the procedural steps (anaesthetic application, disinfecting conditions, placement of surgical drape) in the electrodermal activity measures, in addition to the short time interval during the intravitreal treatment that limited the accuracy of these EDA data to be included in the main analyses. Event-related SCRs were the main focus in this study to examine peak responses specific to the procedure applied during the treatment, although future work may consider different parameters, such as spontaneous fluctuations, non-specific responses. Secondly, only the procedural steps performed in the first intravitreal injection were evaluated as potential predictors in the regression analysis in participants who received two intravitreal injections on the day. As described in this study, the primary outcome measure, VAS at 1-2 hours and 24 hours post-treatment was transformed using a square and cubic root transformations to meet assumptions of linear regression analysis. Although data were normalised, the zero scores and influential high scores may have influenced the precision of the models, particularly measuring pain at 24 hours post-treatment as data were more zero-inflated; as observed from the fit regression graph, model predicted lower pain scores than the actual data obtained in this study (figure 8.5.24). This study investigated factors associated with pain and discomfort during and after an intravitreal injection procedure.

8.6.2. Conclusion

Overall, this study further supports the idea that implication of psychological factors such as emotional arousal and anxiety as well as procedural factors including type of anti-VEGF and same-day binocular injections provided a deeper insight into the experiences of patients following treatment. One of the more significant findings to emerge from this study is that the measure of electrodermal activity during injection was the strongest predictor in all 3 of the multiple linear regression models. This approach may be useful in expanding the understanding of how heightened physiological activity and emotional arousal in a clinical setting can substantially affect patients' experience and recovery following treatment. General discussion, overall thesis limitations and future work are thoroughly discussed in Chapter 9.

Chapter 9
General Discussion

In this chapter I highlight the key findings of my mixed-methods research in an integrative manner through narrative to meet the overall aim of the thesis. The chapter discusses the implementation and impact of my research in a wider context. Finally, the strengths and limitations of the thesis, future research, and conclusion are also discussed.

9.1. Summary of findings

Valuing the emotional attributes that encompass pain perception in ophthalmic care can contribute to a better understanding of the individual patient experience. In this thesis, I address the impact of emotional state and anxiety on the pain perception and discomfort of patients with neovascular AMD following their intravitreal anti-VEGF treatment. For the purposes of advancing the understanding of patient experience in intravitreal injections, this thesis adapted an exploratory sequential mixed methods design. First, a systematic review was undertaken to investigate factors associated with pain and discomfort during intravitreal injections, with a particular emphasis on anaesthetic and injection techniques, procedural steps and pain assessment tools. This helped in developing the topic guides for the interviews by exploring relevant areas of inquiry. Then, a qualitative study was undertaken to explore the patients' experiences of injections and the practitioners' views (Chapter 6). Following that, an additional qualitative study provided further insights into how patients perceived delayed treatment during the COVID-19 pandemic and the impact on their health and care (Chapter 7). Finally, a quantitative study combined objective measures of electrodermal activity to examine patients' level of arousal at selected procedural steps, subjective-self report questionnaires on pain, anxiety, and wellbeing, to investigate the patient experience before, during and after the intravitreal injection procedure (Chapter 8). Table 9.1.1 summarises the key findings of Chapters 6-8.

Chapter 6: A qualitative study of patients' and practitioners' experiences of intravitreal injections for age-related macular degeneration: Why do they think it is painful?
▪ A minor group of patients experience prolonged soreness and irritation of up to 36 hours following most anti-VEGF injections, now recognised as more common than previously thought. Further research is needed to establish their wider applicability.
▪ Build-up of anxiety and apprehension were commonly reported phenomena at the early stages of the treatment course, however some patients felt apprehensive every time they underwent treatment.
▪ Effective patient-practitioner communication helps patients to recognise the severity of untreated neovascular AMD and supports their adherence to treatment.
▪ Undermanaged pain greatly impacts patients' experiences as long-term administration of injections are commonly needed. Practitioners should assess and control pain during and immediately after injection and convey consistent guidance to patients to self-manage their pain.
Chapter 7: The impact of COVID-19 pandemic on patients with neovascular AMD receiving intravitreal injections: a qualitative study
▪ Patients experienced vision deterioration and felt more vulnerable to loss of independence and mobility.
▪ Isolation and social distancing have resulted in patients with co-existing AMD and other chronic conditions feeling lonely and depressed.
▪ COVID-19 risks have not influenced patients adhering to their intravitreal treatment, instead they expressed concerns and felt anxious and terrified of losing sight due to lack of timely treatment.
Chapter 8: Measuring electrodermal activity during intravitreal injections and evaluating the factors associated with post-treatment pain
▪ Phasic electrodermal activity was significantly higher during injection (insertion of needle and delivery of the anti-VEGF solution).
▪ At 24 hours post-treatment, 4.7% of participants continued to experience severe sharp, aching or tender pain, and 15.6% reported feeling a mild tiring-exhausting pain.
▪ Multiple linear regression identified the injection SCR amplitude, type of anti-VEGF (aflibercept), state anxiety at baseline and bilateral injections as the most significant predictor variables of pain at 1-2 hours post-treatment, $F(4,51) = 8.99$, $p = 1.47e^{-05}$, explaining 38% of the variance in the model.
▪ The injection SCR amplitude was the most significant predictor variable of pain at both 1-2 hours and 24 hours post-treatment.

Table 9.1.1 – Summary of key findings: Chapter 6, Chapter 7, and Chapter 8. SCR = Skin Conductance Response.

9.2. Understanding the patient experience before and during intravitreal treatment

In Chapter 6, I present qualitative data on how patients with neovascular AMD perceive the intravitreal injection procedure and the practitioners' views on the matter. Thematic analysis provided rich and deep insights into the experience of participants before, during and after their injection and their perspectives on adherence to treatment. Three main themes were identified from the analysis: 1) fear of losing eyesight and apprehension on patient adherence to treatment, 2) variability of pain perception during treatment, and 3) post-injection experience and impact on patient recovery. The multidimensional and descriptive nature of the qualitative findings has shown to be valuable in recognising the subjective nature of participants' perception of pain and discomfort, as well as the integral role of psychological aspects including fear and anticipatory anxiety in shaping the patient experience. For example, participants associated their apprehensive behaviour with a previous painful experience: "*And she grabbed the needle and then she couldn't get the needle out…*" (PA07), and generally described that the nature of the treatment consisting of several procedural steps prior to the injection makes them feel anxious: "…*and of course I am short of breath actually… getting anxious, you know, lying down there*." (PA10) Despite their prior experience of injections and familiarity with the clinical environment, some participants felt apprehensive every time they underwent treatment. This also accords with the quantitative analysis in Chapter 8, which showed that there was no statistically significant association between level of anxiety and the number of previous injections.

These results are consistent with those of previous studies (Chen et al. 2012; Kayikcioglu et al. 2017; Chan et al. 2020; Gualino et al. 2020; Herranz-Heras et al. 2020).

Contrary to expectations, in this study, state anxiety at baseline was negatively correlated to tonic SCL and not associated to injection SCR amplitude (Chapter 8, Section 8.5.2). As previously addressed as a limitation (Chapter 8, Section 8.6), administering the questionnaires for some participants the night prior to their intravitreal treatment may have undervalued the true level of state anxiety reported as a baseline measure to represent the "*subjective feelings of tension, apprehension, nervousness, and worry…"* (Spielberger et al. 1983) at the time prior to receiving the injection. For example, at baseline, this study reports mean state anxiety scores of 31.02 ± 11.43 compared to higher scores of 45.08 ± 5.57 in Kayikcioglu et al. (2017), a study evaluating anxiety in a similar population receiving intravitreal injections. However, their study population also included treatment-naïve patients (receiving an intravitreal injection for the first time) that could explain the higher state anxiety scores due to their inexperience with the procedure and clinical environment.

Consistent with past research in this area (Tailor et al. 2011; Yau et al. 2011; Thetford et al. 2013; Moisseiev et al. 2014; Boyle et al. 2018b; Crabb et al. 2019; Inaltekin et al. 2021), this study also supports variations in procedure-related pain during injections (insertion of needle and delivery of the anti-VEGF solution). In Chapter 6, the qualitative findings demonstrated varied

responses across participants in relation to their experiences during injection. Some reported feeling a pressure on their eye, an instant, dull aching, mild or sharp pain, while others described it as a "*like a pinprick, only a bit harder*". These results are consistent with those observed in Thetford et al. (2013) who also stated patients experiencing an instant, prick or sharp feeling. These descriptions may supplement the inter-individual variability in phasic electrodermal activity during injection, despite the potential for bias from personal and environmental factors earlier discussed in this thesis (Chapter 8, Section 8.6). The electrodermal activity findings during the intravitreal injection procedure showed that the injection elicited the highest SCR amplitude, illustrating significantly higher levels of arousal compared to the placement of eyelid speculum and marking of the eye (Chapter 8, Section 8.5.2). The combination of self-report and objective measures complemented each other and provide detailed description on both the quality and intensity of the pain experienced in line with the definitions of pain underlying this study: "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of tissue damage, or both.*" (Merskey et al. 1979), and "*Whatever the experiencing person says it is, existing whenever the person says it does.*" (McCaffery 1968) outlined in this thesis (Chapter 2).

This thesis (Chapter 6) also highlights coping mechanisms used by practitioners to manage patients' treatment-related anxiety, including rapport-building, reassurance, and communication techniques helping patients to relax and focus on their breathing: "*I ask them to take a deep*

breath. Most of them they say it's very nice because they concentrate on breathing, and they don't feel it." (NUR3), "*Talk to the patient… You want to make them feel as they can trust you.*" (NUR1), "*I like the opportunity of communicating. It eases the nervous tension*." (PA05). Moreover, practitioners in this study acknowledged the importance of adjusting their own practice to meet patient needs: "*Let's say we have a little old lady who cannot stretch herself at the chair, we offer to give her the pillow*." (NUR4), "*If they've got breathing problems…I would probably get my colleague to sort of hold up the corner [of the drape] …*" (NUR1). Handholding (Shaughnessy et al. 2022) and having a neck pillow and verbal warning prior to injection (Gomez et al. 2016) have previously been reported to improve the patient experience. Whilst this study has not investigated the impact of implementing these techniques on the patients' anxiety level, overall, these results concur with the author's observations in the treatment room while recording the electrodermal activity during the intravitreal injection procedure (Chapter 8). The qualitative data presented in this thesis were also in line with Thetford et al. (2013) findings which found positive patient responses to nurses' reassurance and explanations of the procedures. Contemporary studies acknowledged that patients made efforts in managing their anxiety through meditation and reassuring self-talk (Boyle et al. 2018b), however no such coping mechanisms were reported in this thesis.

9.3. Understanding the patient experience following intravitreal treatment

In Chapter 6, notably, ocular pain was a widely reported side-effect during most anti-VEGF injections, with soreness and irritation commonly reported to last for up to 36 hours affecting patient recovery: "*And then very often I'm getting very gritty and sore… I can't sleep, honestly*…" (PA08), "*The aftereffects of the injection I think are worse than the injection itself*…" (PA14). Practitioners interviewed in this study explained that the return of full corneal sensitivity following anaesthetic application, or the irritant properties of iodine could lead to experiencing pain and discomfort, consistent with the literature and clinical guidelines (Papanikolaou et al. 2011; The Royal College of Ophthalmologists 2018). Building on these findings, the quantitative analysis performed in Chapter 8 validated these observations. Self-report measures of pain demonstrated statistically significant differences at both 1-2 hours and 24 hours post-treatment compared to baseline. Furthermore, as previously addressed (Chapter 8, Section 8.6), the main component of the SF-MPQ provided a more comprehensive understanding of the patient experience following intravitreal injections. Despite most participants showing a reduction in symptoms at 24 hours post-treatment, it has been recognised that 4.7% of participants continued to experience severe sharp, aching or tender pain, and 15.6% reported feeling a mild tiring-exhausting pain. For instance, at 1-2 hours post-treatment the median score was 3 (0 – 39) compared to 1 (0 – 29) at 24 hours post-treatment out of a total score of 45. The findings at 1-2 hours post-treatment are consistent with previous research (Makri et al.

2018), however this thesis reports a greater range of pain scores which indicates greater variability of pain perception in the studied population. In general, mild pain has been commonly reported following intravitreal injections (Rifkin and Schaal 2012b; Sanabria et al. 2013).

To the author's knowledge, this is the first study to explore qualitative descriptors of pain that establish a connection between patients' experiences and more severe symptoms. Consequently, to examine the variability in the pain scores reported at 1-2 hours and 24 hours following intravitreal injections, multiple linear regression analysis was used to identify the most significant predictor variables affecting post-treatment pain. The most optimum regression model showed that the injection SCR amplitude, state anxiety (baseline), type of anti-VEGF (aflibercept) and bilateral same-day injections explained 38% of the variance of pain at 1-2 hours post-treatment. Notably, the injection SCR amplitude was the most significant predictor variable in all 3 of the multiple linear regression models (Chapter 8, Section 8.5.2.6). As earlier addressed in this thesis (Chapter 8, Section 8.6), this finding may describe a combined effect of emotional, physiological, and biological factors influencing the patient experience, consistent with the multidimensional nature of pain (Merskey et al. 1979).

9.4. Patient adherence to treatment: “I’ll do anything to keep my sight”

In this thesis, all participants were well informed of the types of macular disease, associated risks, and expressed a strong understanding of the diagnostic examinations and treatment protocol of their intravitreal injections. In Chapter 6, the qualitative data supports that clear instructions and provision of information leaflets helped patients to acknowledge the severity of the consequences of untreated AMD, also advising them on their antibiotic prescription and common side-effects, including blurred vision and grittiness following their intravitreal injections. These findings are consistent with the literature (Dacosta et al. 2014; Dang et al. 2017) expanding on the key value of patient-practitioner communication and continuous efforts in providing trust to motivate patients engage with their treatment course. Participants interviewed in this study unanimously perceived fear of losing their eyesight of higher concern than their anticipated apprehension and painful experiences during and following intravitreal injections: “…*so that's why I put myself through it all the time because I know in the end it's for my own benefit*.” (PA08), “*It’s a very small thing to pay to keep your sight. I think that is excellent and we are very lucky to have it.*” (PA10)

Timely treatment is incredibly meaningful to patients with neovascular AMD, and this has been particularly prominent during the first wave of the COVID-19 pandemic (Mylona et al. 2022). In Chapter 7, I present qualitative data on the impact of COVID-19 on the experiences of patients with neovascular AMD and their adherence to treatment. Three main themes were identified

from the thematic analysis: 1) COVID-19 exposure risk and association with treatment adherence, 2) patients' concerns and expectations related to care, and 3) effects of isolation and social distancing on wellbeing. Anticipating the increased risk of severe illness from COVID-19, participants in this study yet described their eyesight as the most significant aspect in their health and daily living. Understanding the significance of timely treatment, participants reported feeling worried and anxious of losing their eyesight during COVID-19 due to delayed treatment: "*I could see it was slipping back again, the edges were curvy or wavy …and I tried to get help… I couldn't get help. I was afraid I was going to lose my eyesight before I got treatment.*" (P10), "*… my sight is not quite as good as it was, it's been a long time since my last appointment, which is worrying*." (P07) One of the main findings of this study is recognising that nearly half of the participants interviewed reported experiencing deterioration of their vision, in line with the research (Takahashi et al. 2015; Borrelli et al. 2020; Stone et al. 2021; Zhao et al. 2021; Szegedi et al. 2022) associating delayed treatment with poorer functional outcomes, as well as expanding the risk of permanent vision loss (Foot and MacEwen 2017).

Consistent with the literature on past epidemic and pandemic diseases (Taylor et al. 2008; Perrin et al. 2009; Tucci et al. 2017), this thesis also emphasises the psychosocial impact of COVID-19 on patients living with neovascular AMD (Chapter 7, Section 7.3). For example, isolation and social distancing had substantially affected the wellbeing of participants with multiple comorbidities; co-existing AMD, cataract, asthma, and cancer: "*I*

then get very anxious because I am holding up the queue [at the shop] and I am forever saying to people oh please go past, I am so sorry." (P13), "*I've developed asthma… And now with my breathing difficulty. I have to even be careful because I have to carry my inhaler with me… So, it's left me severely depressed and full of anxiety, and lonely*." (P17) Being diagnosed with neovascular AMD, intravitreal injections have given purpose to several patients into gaining back their reading abilities, personal independence and mobility, considerably important drivers to their wellbeing (NICE 2015; Fenwick et al. 2017; Paulus et al. 2017). However, the prolonged restrictions on accessing ophthalmic care due to COVID-19 (Petrovski et al. 2020; Seah et al. 2020; The Royal College of Ophthalmologists 2020) led to exacerbated effects on the patient experience leading to rapid disengagement from daily activities and social life, encompassing initial fears of isolation and loss of independence: "… *it did affect my aqua aerobics… and that is not good for me because I do need to keep going because that's part of my social life as well*." (P01), "*They said to me that, my vision is now on the peripherals of not being able to drive any longer*." (P09). Additionally, having a life purpose drives older adults to become motivated in their activities, sustaining independence and social life, all contributing factors to a positive wellbeing (Irving et al. 2017). For instance, the qualitative data in Chapter 7 identified examples of coping mechanisms participants adapted during the COVID-19 pandemic to keep them engaged and motivated: "*I try to read The Times every day… I do a Sudoku every day, I try to play the piano most days and obviously I watch the television, I go for a walk every day, so I'm okay*." (P14) Mental wellbeing has been

associated with the positive aspects of the individual's everyday functioning (Ryan and Deci 2001), greatly affected during the era of COVID-19.

During the COVID-19 pandemic, lack of consistent communication on treatment progress, failure to follow-up patient contact and uncertainty on treatment outcomes and vision changes were highlighted in this thesis as the key reasons for participants voicing concern and frustration. These findings were in line with contemporary studies (Rozon et al. 2021; Ting et al. 2021) understanding that patients' unmet expectations for follow-up had a significant influence on their experiences. Despite the prominent operational issues that the eye clinic has faced during the pandemic, some participants generally expressed the need of engaging in their treatment progress: "*I couldn't read the board like I did before… So, I wondered then had my sight got worse? I couldn't ask anyone. it would be nice now and again to have reassurance…*" (P03)

9.5. Research implications and recommendations

It has become increasingly accepted that pain is not simply a sensation generated by nociceptors, but a perceptual phenomenon with emotional qualities. The opinions, concerns, and personal experiences of participants in the qualitative research studies presented in this thesis indicate a remaining gap on how pain is managed in intravitreal injections. Not all practitioners in this thesis acknowledged the proportion of patients experiencing pain and this highlights the importance of implementing strategies to evaluate the patient experience. This combination of findings

also provides some support for the conceptual premise that previously perceived pain during injection could relate to patients' negative psychological state in subsequent treatments. It has been recognised, that in general intravitreal injections can be stressful events for the majority of participants, despite their history of prior injections and familiarity with the clinical environment. Taking into consideration the chronicity of AMD and routine nature of intravitreal injections, it is vital for practitioners to be able to identify and document painful experiences, in addition to continuing their efforts to manage patients' apprehension, keeping them engaged and motivated (Boyle et al. 2018b).

It is the human factor within healthcare that elevates the individual experience, consequently the focus should be on establishing a centralised team, or enhancing the services provided by the Eye Clinic Liaison Officer (ECLO) (Cardiff and Vale UHB 2023; RNIB 2023) within the patient services department responsible for undertaking telephone follow-ups on patients undergoing intravitreal injections. Follow-up activities may consist of numerical rating scales to assess the severity of pain, short telephone interviews to identify and document symptoms and patient concerns and communicating pain management techniques where appropriate. While a patient advice and liaison service within the NHS Wales is accessible for patient feedback (NHS Wales 2022), its implementation into managing patient experience is still limited.

Identifying patients with severe pain following intravitreal treatment may also be used to inform future injections to account for alternative clinical procedures. For example, in addition to the anaesthetic application consistent with standard procedures (NICE 2018; The Royal College of Ophthalmologists 2018), administering a single drop of a non-steroidal anti-inflammatory drug, nepafenac 0.1% prior to the intravitreal injection was found to significantly reduce pain immediately and up to 6 hours post-treatment in a small randomised crossover trial (Makri et al. 2018). As previously discussed, (Chapter 4) the literature on anaesthetic effectiveness presented contradictory results (Yau et al. 2011; Cohen et al. 2014; Andrade and Carvalho 2015; Alex et al. 2021) which indicates that the focus should be on implementing supplementary steps in the intravitreal injection procedure, instead of changes in anaesthesia. In this thesis, the multiple linear regression model also predicted higher pain at 1-2 hours post-treatment in participants treated with aflibercept and who have received bilateral same-day intravitreal injections (Chapter 8, Section 8.5.2.6). Therefore, application of topical nepafenac 0.1% could be suggested as a plausible approach to patients treated with aflibercept or receiving bilateral same-day injections. While a definitive pain management technique following intravitreal injection is yet to be established, a corticosteroid, loteprednol has been recently approved to undergo clinical trials to determine its efficacy in pain reduction compared to nepafenac 0.3% and lubricant eyedrops (Vishak 2022). Engaging discussions with patients and providing specific and consistent instructions following their injections may also be adapted to explain possible experiences of irritation and soreness

and communicate pain relief techniques to self-manage their pain. For instance, prompting patients to avoid touching, rubbing, or scratching the injected eye, and advising on simple techniques such as topical ice applications (Li and Wang 2016; Yahalomi et al. 2020) and oral paracetamol (Sanabria et al. 2013) if safe for the patient.

Although the prevalence of depression in AMD is well known (Evans et al. 2007; Nollett et al. 2016; Nollett et al. 2019a), a less investigated area is wellbeing. In Chapter 8, wellbeing was found to be negatively correlated to state anxiety. Integrating this finding with the qualitative data obtained in Chapter 7, provides strong insights into how loss of independence, isolation, and an inactive social life and physical activity could worsen individual wellbeing and subsequently affect state anxiety. The literature demonstrated that positive attitudes to ageing (Bryant et al. 2012) and physical activity (Kazeminia et al. 2020) significantly reduced anxiety in the elderly. In addition to the provision of patient information leaflets, promoting local support groups and discussing available resources with patients to help them cope with lifestyle changes, encouraging them to join online communities (NICE 2015; Macular Society 2022; NHS England 2022) can be considered as part of the patient experience and engagement strategy within the patient advice and liaison service. Additionally, this thesis also highlights that generally participants reported feeling apprehensive prior to their intravitreal treatment (Chapter 6, Section 6.4) and that state anxiety at baseline was identified as a significant predictor variable of pain at 1-2 hours post-treatment (Chapter 8, Section 8.5.2.6). Thus, more efficient coping

mechanisms are needed to manage patients' anxiety prior to undergoing an intravitreal injection procedure, possibly focusing on the individual level. While an intravitreal injection procedure follows a standard protocol (NICE 2018; The Royal College of Ophthalmologists 2018), a useful strategy could be for clinical practices to implement anxiety assessment tools at regulated intervals throughout the patients' treatment course. For instance, the visual analogue scale for anxiety (VAS-A) has been commonly used in clinical practice for its rapidity and accessibility to evaluate anxiety levels of patients undergoing intravitreal injections (Herranz-Heras et al. 2020; Wasser et al. 2022). Identifying a patient cohort that reports moderate to severe levels of anxiety can inform practitioners to advise those patients on approaches to manage their apprehension prior to the injection, including meditation and nurturing self-talk. Alternative sources, such as musical intervention (Chen et al. 2012; Chan et al. 2020) and relaxation techniques using pre-recorded respiratory relaxation sessions have also shown to be effective in improving anxiety (Ouadfel et al. 2021).

By combining the findings obtained in Chapters 6 and 7, it can be understood that participants were generally pleased with the way practitioners communicated their support and reassurance during the intravitreal injection procedure to meet their needs. However, a gap was identified within the delivery of patient services whereby participants expressed their concerns of not been given the opportunity to discuss their treatment progress during a face-to-face consultation. The ongoing pressure on ophthalmology services in the era of COVID-19 also highlighted

the barriers to deliver timely care and support to patients with AMD (Lim et al. 2020; Petrovski et al. 2020; Safadi et al. 2020). It is therefore necessary to revise current management systems and services using innovative approaches whereby patients can access continuous support through virtual consultations via a network of community optometrists, nurse practitioners, and ophthalmologists. Although still a growing field, teleophthalmology has great potential as an integral clinical tool in providing remote diagnosis and treatment monitoring in individuals with vision impairment, including AMD and glaucoma (Kotecha et al. 2015; Rathi et al. 2017; Gan et al. 2020; Kern et al. 2020; Chandra et al. 2022). Face-to-face consultations on the other hand provide a more personalised experience for patients and social connectedness. It has been well recognised in this thesis that communication and human interaction are key aspects for participants' health and care, consequently it is important to find the proper balance between face-to-face and remote consultations.

9.6. Strengths and Limitations

One of the key strengths of this thesis is the mixed methods approach which expands the depth, scope, and richness of the research (Creswell 2018). Despite the importance of patient experience in ophthalmology, there remains a paucity of evidence on the qualitative perspectives of patients receiving intravitreal injections for the treatment of neovascular AMD. The initial qualitative study (Chapter 6) allowed me to explore patients' beliefs and attitudes, as well as the practitioners' views to identify factors influencing the patient experience and ultimately build an understanding of

these phenomena in the quantitative study (Chapter 8). Implementing a triangulation strategy (Carter et al. 2014) allowed comparison of patients' and practitioners' perspectives to identify discrepancies, strengthening the findings of my qualitative research. In this thesis, using an exploratory sequential mixed methods design provided a more comprehensive, insightful view of patients' emotional state, anxiety, and pain perception associated with intravitreal injections.

To the author's knowledge, this is the first study to examine electrodermal activity in intravitreal injections and builds strong foundations for future research in this field. The integration of subjective and objective measures, in addition to the assessment of multiple factors eliminated the risk of self-report bias at a certain level and enhanced the validity of the analysis and conclusions drawn from our representative population. Evaluating pain, anxiety, mental wellbeing, and accounting for demographic and clinical characteristics provided a dynamic interplay between biological and psychological factors that helped define the experiences of patients with neovascular AMD receiving intravitreal injections.

The main limitation of this work is the fact that it was a cross-sectional single-centre study. Consequently, definitive conclusions cannot be drawn about the influence of these factors on the level of pain reported at 1-2 hours and 24 hours post-treatment. It is also important to point out that substantial work of the quantitative study was undertaken in the era of COVID-19. Restrictions and additional safety measures implemented within the clinical

practice, in addition to the potential effects of COVID-19 on the participants' treatment course and psychological state might have influenced the outcome measures reported in this thesis. However, this was beyond the control of this thesis and discussing the findings using an integrative approach provided a comprehensive understanding of the patient experience. Although the findings may be limited to external validity, they could be applicable in clinical practices adapting equivalent standard protocols for intravitreal injections.

Despite the challenges faced during the COVID-19 pandemic, a total of 103 participants (n=96 patients with neovascular AMD, n=7 healthcare practitioners) have been recruited in this thesis. A limitation of this study is that the sample of participants mostly represented Caucasians and it is well known that AMD extends beyond this population. This limits the generalisability of the findings to different population groups since pain threshold has been reported to vary between ethnic/racial groups (Campbell and Edwards 2012) and this could affect the pain scores reported. Nevertheless, the sample of participants was representative of the Welsh population (93% identified as White) and its homogeneity of the older adult population accurately represents people with AMD globally.

The most optimum multiple linear regression model in this thesis explained 38% of the variance of pain at 1-2 hours post-treatment. Nevertheless, the zero inflated distributions and highly influential pain scores have reduced the accuracy of the multiple linear regression models to predict higher levels

of pain at both 1-2 hours and 24 hours post-treatment. Other dependent variables not examined in this thesis could have possibly explained more of the variance of pain at 24 hours post-treatment. Notwithstanding its limitations, this work offers valuable insights into the factors affecting pain at 1-2 hours and 24 hours post-treatment, but still, further studies are needed in order to validate these findings.

This thesis has not reported participants who underwent any additional surgical procedures (e.g. ocular, pelvic, or cardiac surgery) prior to their participation in this study that could potentially introduce bias in the reported outcomes. Nevertheless, besides the small group of participants reporting ocular pain at baseline, the rest have confirmed they did not experience any form of pain prior to participating in the study. Also, none of the participants reported undertaking pain-relief medication prior to their intravitreal treatment.

Another limitation that was beyond the control of this thesis was that the study site monitoring for patients receiving intravitreal injections was predominantly managed by nurse practitioners. Nevertheless, this thesis (Chapter 8) consisted of a total of 13 different injectors (10 nurse practitioners, 3 ophthalmologists) and a varied range of the outcome measures was reported. Conversely, ophthalmologists were responsible for performing intravitreal injections on treatment-naive patients. Recruiting treatment-naive patients in this study posed some challenges. Firstly, there was inadequate time to engage with potential participants as the diagnostic

examinations for neovascular AMD were only reviewed on Thursdays, with intravitreal injections performed same day, if needed. Secondly, the injection room in the ward was of smaller capacity, raising safety implications.

9.7. Future research

A natural progression of this work is to further investigate these outcomes in a multicentre study with a larger population sample of patients with neovascular AMD. Evaluating procedural differences in the intravitreal injection protocol implemented in clinical practices across Wales could provide additional insights on the patient experience. It is also worth noting that larger population samples may support a greater degree of accuracy on the regression models that will allow the prediction of higher levels of pain following intravitreal injections. Comparing changes in electrodermal activity between different types of anaesthesia (e.g. subconjunctival, topical, pledgets), needle sizes (e.g. 27-gauge, 30-gauge, 33-gauge needle), anti-VEGFs (e.g. aflibercept, ranibizumab, brolucizumab) or use of intravitreal injection assisting devices (InVitria) may be valuable to further assess the validity of electrodermal activity in this field. An initial interest of this thesis was to investigate whether the InVitria device improved the patient experience, however it was discontinued by clinical practice prior to commencing research in this area. Nevertheless, it still remains of interest to be examined in future work.

Further study is needed to determine whether additional factors not evaluated in this thesis, for example, age of AMD diagnosis, previous painful experience, IOP and injection site characteristics using anterior segment OCT (AS-OCT) could explain the degree of pain following intravitreal injections. The latter was part of the original research objectives in this thesis and although it was withdrawn due to COVID-19 restrictions on hygiene and limiting patient contact in the study site, it remains an area of research interest. AS-OCT imaging can be a valuable tool for evaluating injection site characteristics and minimising patient discomfort during ocular injections. Future research could focus on identifying additional injection site characteristics that may impact healing time, the risk of complications, and patient discomfort. Anterior-OCT could also be used for monitoring injection site characteristics during the recovery period, assessing the efficacy of different injection techniques, and identifying patients who may be at higher risk for complications. This could help medical professionals tailor treatment protocols to the specific needs of individual patients and further reduce the risk of discomfort and complications.

Moreover, anti-VEGF intravitreal injections are also used to treat other eye conditions, including diabetic macular oedema, non-proliferative diabetic retinopathy, proliferative diabetic retinopathy and retinal vein occlusion, thus this work can expand beyond the AMD population. Although methodologically challenging, it would also be valuable to include treatment-naïve patients and conduct some long-term studies to evaluate any changes in electrodermal activity and the outcomes reported in this thesis,

particularly wellbeing. Considerably more methodological work is required to relate the phasic electrodermal activity, SCR amplitude measures to pain intensity during intravitreal injections. Assessing inter-individual variability in terms of pain threshold and tolerance could help to establish a greater degree of accuracy on this matter. Further experiments might consider using a dolorimeter as a pain threshold test prior to the intravitreal injection procedure. Also, self-report measures such as NRS can be used to evaluate pain at the selected procedural steps to examine their correlation to electrodermal activity.

Finally, this thesis lays the groundwork for future work to evaluate the effectiveness of implementing the research recommendations into clinical practice. Very little is currently known about the patient experience and feedback management services in ophthalmic care, consequently further exploration is required to provide definitive facts; to review established patient experience frameworks and organisational implications. Despite the methodological challenges, engaging with optometrists, nurse practitioners and ophthalmologists may provide substantial support in promoting evidence-based management in AMD services.

9.8. Final remarks

Overall, this thesis provides an evidence base for the use of an objective physiological measure, electrodermal activity as a promising research method of evaluating real-time changes in arousal in response to varying levels of pain and discomfort during intravitreal injection procedures. The findings support the most significant measures of pain at 1-2 hours post-treatment in identifying those with a higher injection SCR amplitude, a higher level of state anxiety at baseline, those receiving an anti-VEGF injection of aflibercept or same-day bilateral injections. At 24 hours post-treatment, 4.7% of participants continued to experience severe sharp, aching or tender pain, and 15.6% reported feeling a mild tiring-exhausting pain. This exploratory sequential mixed-methods study

In conclusion, integrating models of external support in the NHS may reduce the workload on the health services and initiate a more robust communication and share of experiences between patients and practitioners. Timely follow-up and adapting a patient-focused culture within the AMD services could support patients' confidence in their treatment progress and strengthen the quality of care. While further work is required to establish the viability of adapting pain and anxiety assessment tools in AMD services, the findings of this thesis emphasise that consistent and specific verbal instructions as well as reassurance and engaging communication with practitioners are especially meaningful to patients and should serve as principal strategies in managing the patient experience.

9.9. Dissemination and publication of research findings

A summary of the findings will be provided to the study participants involved in this research. The findings of this thesis will also be disseminated to the clinical staff at the Cardiff Eye Unit at the University Hospital of Wales to increase their awareness of the research implications and to critically evaluate the outcomes to determine their potential translation to their practice. Other stakeholders including Optometry Wales, Macular Society, and our funder, the Abbeyfield Research Foundation, as well as public involvement groups via the Health and Care Research Wales.

With the return of in-person events and meetings following the COVID-19 pandemic, the findings of this thesis will be disseminated through presentations at national and international conferences, as well as journal articles.

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11. Appendices

Appendix A: The Cochrane Collaboration's tool – assessing risk of bias in included studies

	The Cochrane Collaboration's tool for assessing risk of bias in randomised trials						
		Domain					
	Study	**Random sequence generation (selection bias)**	**Allocation Concealment (selection bias)**	**Blinding of participants and personnel (performance bias)**	**Blinding of outcome assessment (detection bias)**	**Incomplete outcome data (attrition bias)**	**Selective reporting (reporting bias)**	**Other bias**
ANAESTHETIC METHODS	Blaha 2011	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. Randomised block design with a unique sequence of 4 anaesthetic agents, but concealment not described in sufficient detail to allow a definite judgement.	Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.	The study did not address this outcome.	The study did not address this outcome.	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.	Sampling: 80% power reported, but not evaluated.
		Unclear	**Unclear**	**High**	**Unclear**	**Unclear**	**Low**	**Unclear**

	Cintra 2009	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.	Sequentially numbered, opaque, sealed envelopes.	Insufficient information to permit judgment of 'Low risk' or 'High risk'.	Retinal specialist evaluating the pain score outcomes was blinded.	No missing outcome data.	All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.	Insufficient information to assess whether an important risk of bias exists.
		Unclear	**Low**	**Unclear**	**Low**	**Low**	**Low**	**Unclear**
	Cohen 2014	Sequence generated by some rule based on hospital or clinic record number. Patients with an even medical record number received subconjunctival anaesthesia in the right eye; patients with an odd medical record number received subconjunctival anaesthesia in the left eye.	Medical record number.	Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.	The study did not address this outcome.	No missing outcome data.	Insufficient information to permit judgement of 'Low risk' or 'High risk'.	Study limitations not discussed (3 patients treated with different medications in each eye). Insufficient information to assess whether an important risk of bias exists.
		High	**High**	**High**	**Unclear**	**Low**	**Unclear**	**Unclear**

	Davis 2012	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. Allocation concealment not described.	Insufficient information to permit judgment of 'Low risk' or 'High risk'.	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding.	No missing outcome data.	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.	Sampling: power calculation (80% to detect difference of 0.681 between the group probability scores). Study limitations described and approaches to minimise detection bias. Used standardised script to explain to patients the interpretation of the pain scale.
		Unclear	**Unclear**	**Unclear**	**High**	**Low**	**Low**	**Low**
	Andrade & Carvalho 2015	Used a computer random number generator.	Sequentially numbered, opaque, sealed envelopes.	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.	No missing outcome data.	The study protocol is not available but it is clear that the published reports include all expected outcomes.	Provision of demographic and clinical characteristics of participants.
		Low	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**

	Kaderli & Avci 2006	The investigators describe a non-random component in the sequence generation process. **High**	Randomisation procedure is restricted to ensure an equal number of patients are allocated to each treatment group within each site. **High**	Insufficient information about the randomisation process to permit judgement of 'Low risk' or 'High risk'. **Unclear**	The study did not address this outcome. **Unclear**	The study did not address this outcome. **Unclear**	Not all of the study's pre-specified primary outcomes have been reported. **High**	Insufficient rationale or evidence that an identified problem will introduce bias. Limited data on participant characteristics. **Unclear**
	Rifkin 2012	Insufficient information about the randomisation process to permit judgement of 'Low risk' or 'High risk'. **Unclear**	Insufficient information to permit judgement of 'Low risk' or 'High risk'. Allocation concealment not described. **Unclear**	The study did not address this outcome. **Unclear**	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. **High**	No missing outcome data. **Low**	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified. **Low**	Potential bias in multiple testing and reporting significance. Insufficient information to assess whether an important risk of bias exists. **Unclear**

	Sanabria 2013	Generation of a sequence of random number.	Sequentially numbered, opaque, sealed envelopes.	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.	No missing outcome data.	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.	The study appears to be free of other sources of bias.
		Low	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
	Yau 2011	Generation of a sequence of random number.	Sequentially numbered, opaque, sealed envelopes.	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken (double blinded).	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.	No missing outcome data.	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.	Insufficient rationale or evidence that an identified problem will introduce bias. No discussion of study limitations and potential gender bias.
		Low	**Low**	**Low**	**Low**	**Low**	**Low**	**Unclear**

Needle size and techniques	Haas 2016	Insufficient information about the randomisation process to permit judgement of 'Low risk' or 'High risk'.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. Allocation concealment not described.	Insufficient information to permit judgment of 'Low risk' or 'High risk'.	The study did not address this outcome.	No missing outcome data.	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified.	Analysis of co-factors including patients' demographics (age and gender) and clinical characteristics (right eye, left eye, number of previous intravitreal injections).
		Unclear	**Unclear**	**Unclear**	**Unclear**	**Low**	**Low**	**Low**
	Van Asten 2015	Insufficient information about the randomisation process to permit judgement of 'Low risk' or 'High risk'.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. Allocation concealment not described.	Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.	Surgeon's beliefs on needle safety/effectiveness may affect technique/outcome reporting during injections.	No missing outcome data.	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.	The study included patients with AMD, diabetic macular edema, retinal vein occlusion, and other. Participant characteristics were overrepresented in the study population.
		Unclear	**Unclear**	**High**	**High**	**Low**	**Low**	**Unclear**

	Rodrigues 2011	Throwing dice **Low**	Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’. Method of concealment is not described in sufficient detail to allow a definite judgement. **Unclear**	Insufficient information to permit judgment of ‘Low risk’ or ‘High risk’. **Unclear**	The study did not address this outcome. **Unclear**	No missing outcome data. **Low**	All of the study’s pre-specified primary outcomes have been reported. **Low**	The study appears to be free of other sources of bias. Participant characteristics analysed with regard to age, gender, and the eye of injection. Number of previous surgeries including intravitreal injections was assessed. **Low**

Appendix B: ROBINS-1 tool – assessing risk of bias in included studies

ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions								
		Domain						
	Study	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to departures from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**
Needle size and techniques	Güler 2014	All intravitreal injections were performed into the inferotemporal quadrant (standardisation). Conducted subgroup analysis according to two age groups: <65 and ≥65. **Low**	No information is reported about selection of participants into the study or whether start of follow up and start of intervention coincide. **No information**	Intervention status is well defined and intervention definition is based solely on information collected at the time of intervention. **Low**	Any deviations from intended intervention reflected usual practice. Adhering to the guideline, standardised procedures for intravitreal injection were followed. **Low**	No information is reported about missing data or the potential for data to be missing. **No information**	The methods of outcome assessment were comparable across intervention groups. The outcome measure is only minimally influenced by knowledge of the intervention received by study participants (injection vs topical gel application is objective), and the outcome assessor. Outcomes of pain for 27- and 30-gauge needles may vary by assigned anti-VEGF agent, ranibizumab and bevacizumab, due to mechanism and tolerability. **Moderate**	The outcome measurements and analyses are consistent with a priori plan, there is no indication of selection of the reported analysis from among multiple analyses, and there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results. **Moderate**

	Ratnarajan 2013	No information on whether confounding might be present. Lack of demographic or clinical data (age, gender, diagnosis, previous injection experience may lead to misclassification of the study population, exposure or outcome status, resulting in biased estimates of the intervention effects. **No information**	No information is reported about selection of participants into the study or whether start of follow up and start of intervention coincide. **No information**	Anti-VEGF agent, setting, dose, needle size and incision were clear and explicit. Intervention status is well defined, but some aspects of the assignments of intervention status were pre-determined. **Moderate**	Any deviations from intended intervention reflected usual practice (intravitreal procedures). **Low**	No information is reported about missing data or the potential for data to be missing. **No information**	The outcome measure is only minimally influenced by knowledge of the intervention received by study participants (conventional technique group vs conjunctival mould group), and the outcome assessor. High standard deviation in two groups can increase bias risk by introducing data variability, making it difficult to detect significant differences, even if they exist. **Moderate**	There is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results. **Moderate**

	Moisseiev 2012	Conducted subgroup analysis according to age, gender, number of injections, diabetes mellitus or lens status. **Low**	All participants who would have been eligible were included in the study. **Low**	Intervention status is well defined and based solely on information collected at the time of intervention. **Low**	Any deviations from intended intervention reflected usual practice (intravitreal procedures). **Low**	No information is reported About missing data or the potential for data to be missing. **No information**	Although the injecting physician was not blinded to the study, the locations of the injections were assigned in a randomized manner based on the last two digits of the patients' ID numbers. **Low**	There is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results. **Moderate**

Appendix C: Research Protocol

Investigation of pain and discomfort associated with anti-VEGF injections (Version 3.0)

Short title: Patient experience of injections in age-related macular degeneration

IRAS Number: 245666
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1. Background and Rationale

Age-related macular degeneration (AMD) is **the leading cause of blindness** in the UK[1], with 50% of the population experiencing some visual symptoms of AMD by the age of 75 years[2]. Whilst early AMD is not associated with significant visual loss, advanced disease affects central vision used for detail (e.g. reading). Advanced AMD presents either as a **gradual onset** Atrophic (Dry) or **rapid** onset Neovascular (Wet) form, occurring in in one or both eyes, whilst atrophic eyes can transform into the neovascular form. The disease commonly leads to **difficulties performing activities of everyday living** and sufferers can **experience risk of falls, loss of independence and depression**[3].

Since the approval of the anti-vascular endothelial growth factor (VEGF) agent, ranibizumab (Lucentis) (NICE 2008), administered by (intravitreal) injection into the eye, the prognosis for patients with Neovascular AMD has improved dramatically. However, ongoing injections are required to maintain

visual function, consequently compliance with treatment is paramount to prevent progression to disability. Whilst the visual outcomes and safety implications of treatment are well established, **pain and anxiety are less well understood** and most significantly the role with respect to intention to return (compliance) has not yet been investigated.

Pain after injections was cited as a clear issue that is important to patients, in the Macular Society publication Sideview (Autumn 2014). Albeit anecdotal, the following selected quotes from a Macular Society moderated blog (hosted on healthunlocked.com) illustrate patient concerns and suggests possible factors that influence pain experienced:

JKS44 commented *"my eye was extremely painful after my very first Lucentis injection & was dreading the next ones […] I now insist on extra anaesthetic & waiting before cleaning & each jab has just been a little uncomfortable, but not painful".*

Carolreta commented *"I am delighted to report that my sixth injection caused no pain - they finally used no iodine and instead cleaned the eye with chlorhexidine which seemed to do the job. […]I had suffered so much pain after the first five…"*

A pilot survey we conducted at a Macular Society meeting in Bristol reflects these concerns. Eight attendees with a history of anti-VEGF treatment were asked how many of their injections were painful and to rate the pain experienced. They had undergone 3-20 injections each and reported that 20% **of all injections received were considered to be "painful"**. Although not a representative sample this result is consistent with a study of diabetic macular oedema patients, treated with intravitreal injections of ranibizumab, where eye pain was experienced by 14.6% of participants [4], furthermore a qualitative study of 22 patients' experiences found pain and discomfort to be common with many participants feeling ill-informed regarding some side-effects[5].

Whilst some studies have assessed pain associated with intravitreal injections, only subjective or qualitative measures were used [5,6,15,16,7–14], most commonly numerical [12–14] or visual analogue scales (VAS) [6–10,15,16] and in one case qualitative interviews[5]. None of these studies included **objective physiological measures of pain**, such as Electrodermal activity (EDA). Furthermore, the use of statistical averaging of scores in these studies is misleading and can overlook individually painful treatments. For example, Tailor et al.[8] who quantified the "distress" experienced at each step of a routine injection using a VAS showed that participants used the entire scoring range for many steps assessed, this suggests a **wide variety of pain experienced** that is not reflected in the averages reported in this type of quantitative study.

Studies have also shown significant variations in the delivery of an intravitreal injection [17–19], whilst adhering to best practice guidelines[20]. Some of these variables have been compared in the literature, with respect to the type of anaesthetic[12–16] the InVitria® injection assistance device[11] and administration by nurse practitioners[21]. However, these studies have not directly and specifically addressed the individual experience of pain and anxiety, patient wellbeing or intention to return (compliance).

Electrodermal activity (EDA) can be used as a physiological indicator of anxiety, a measure closely associated with pain[22–25], and is a technique that has previously used in ophthalmic research[26]. The technique works by monitoring changes in electrical resistance of the skin, which is altered by the activity of the eccrine sweat glands related to the innervation of the sympathetic system, reflecting the state of arousal. EDA is minimally invasive technique that only requires the attachment of 2 sensors to the patient's fingertips. This technique provides an **objective measure** of anxiety (pain) that **uniquely can be measured during an injection**, allowing a direct and objective step by step comparison of pain with injection procedures to be undertake and allows comparison with conventional subjective measures.

Anterior segment Optical Coherence Tomography (OCT) can provide hi-resolution images allowing visualisation of the injection site. Rodrigues et al. [27] used OCT to measure vitreal reflux following intravitreal injections, although failed to show an association with pain, but to our knowledge, **no other studies have compared injection site appearance to pain or the wider patient experience**. Of note, an earlier study by Kozak et al. [28], compared conventional images of the injection site for 2 different needles, and reported that the incision and needle impact could influence patient comfort.

We believe pain associated with intravitreal injections, used to treat Neovascular AMD, has not been satisfactorily investigated with regard to the individual or the impact on progression to disability. We therefore propose an **observational cross-sectional study** following a **mixed methods (qualitative & quantitative)** approach incorporating imaging of the injection site with EDA, combined with conventional pain VAS, wellbeing and 'intention to return' questionnaires that focus on the individual treatment episode.

2. Aims and hypotheses

Objective: To evaluate pain and anxiety experienced by patients with neovascular AMD receiving intravitreal injections of anti-VEGF agents, and the impact on their compliance with treatment and well-being.

Aim 1: To objectively assess pain/discomfort or anxiety at each procedural step of the treatment.

We hypothesise that significant changes to the pain/discomfort or anxiety outcomes will occur at some procedural steps.

Aim 2: To identify key variations in treatment procedures that may be predictive of patient experience.

We hypothesise that semi-structured interviews will determine the three most significant factors.

Aim 3: To evaluate the relationship between pain/anxiety experienced and the key variations in treatment procedures (identified in aim 2).

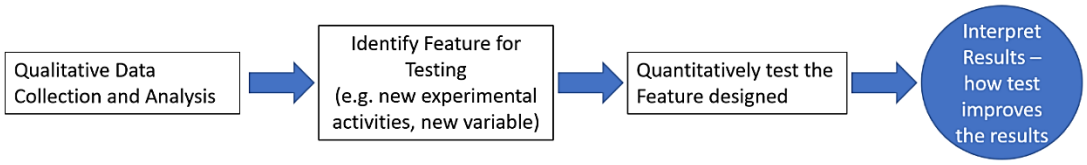
We hypothesise that moderate to strong relationships between objectively measured pain (EDA) and factors identified in aim 2 will be present.

Aim 4: To explore the individual patient experience of intravitreal injections based on pain/anxiety and compliance with respect to previous injection experience, patient demographics and wellbeing.

We hypothesise that the findings will support anecdotal evidence from individual patient experiences and practitioner observations.

1. Study Design and Methods

This is an observational, cross-sectional study, following a mixed methods approach – Exploratory Sequential Design (Three-Phase Design) [29]



Our study is divided into 3 parts:

Part 1 Patient experiences: Data collection and analysis of patient experiences.

Part 2 Practitioner experiences: Data collection and analysis of healthcare practitioners' perspectives on pain/discomfort and anxiety, and the identification of procedural differences.

Part 3 Experience of individual treatments: Evaluation of patient pain/discomfort or anxiety before, during and after anti-VEGF injection.

To address aim 2:

At the outset of the project, semi-structured interviews will be undertaken, to gain qualitative insight into the treatment procedures that patients consider to be linked to pain or discomfort *(part 1).* The semi-structured interviews will be conducted with 10-20 patients undergoing intravitreal injections, consistent with the ideal group size.[29] The themes identified by the patient semi-structured interviews will be used to inform questions in the

semi-structured interviews with healthcare practitioners. The researcher will conduct semi-structured interviews with 8-12 ophthalmologists and nurse practitioners who perform intravitreal injections to identify routine treatment procedures and procedural differences *(part 2).*

Part 1 Patient experiences: Potential participants will be identified, who can provide in-depth descriptions about their experiences receiving intravitreal injections (e.g. had at least 6 injections, in line with the probability of experiencing pain). NHS patients with neovascular AMD will be recruited from an Ophthalmology Clinic at University Hospital of Wales, with the aid of the collaborator, Mr Sanjiv Banerjee, a Consultant Ophthalmologist and direct healthcare team, who will identify suitable potential participants (based on the inclusion/exclusion criteria). These will be initially informed by their ophthalmologist/nurse during their routine eye examination, also provided with an information sheet to keep. Potential participants interested in the study may:

a) Be introduced directly to the researchers who will provide study details
b) Choose to provide contact details to allow researcher to contact them with study details
c) Be provided with study details and the researchers contact details to enable potential participant obtain further information/ask questions.

Semi-structured face-to-face interviews will be conducted at the Cardiff University School of Optometry and Vision Sciences, or at the participant's own home, depending on their preference. The interview will last about 1 hour. Participants will be reimbursed by £10 to cover the cost of travel, if required.

Inclusion Criteria is the following:

a. Diagnosed with Neovascular AMD
b. Received at least 6 intravitreal anti-VEGF injections
c. Aged 50 and above

Exclusion Criteria is the following:

a. With known retinal pathology other than neovascular AMD (e.g. glaucoma or diabetes)
b. Suffer from very poor hearing
c. Unable to communicate in English or Welsh, or provide informed consent

Part 2 Practitioner experiences: Ophthalmologists and nurses will be recruited from an Ophthalmology Clinic at University Hospital of Wales, with the aid of the collaborator, Mr Sanjiv Banerjee, a Consultant Ophthalmologist. Potential participants will be provided with an information sheet to keep and directly contact the primary researcher if interested to take part. Semi-structured face-to-face interviews will take place at an agreed private room at the University Hospital of Wales and will last about 30 minutes.

Inclusion Criteria is the following:

a. Practitioners who currently perform intravitreal injections
b. Able to communicate in English or Welsh

Analysis: The verbatim interview transcripts will be reviewed, thematically coded (summarisation, categorisation, counting frequency of responses, with concepts and coding agreed on by research team and collaborator), and where possible, mapped to clinical guidelines (Royal College of Ophthalmologists, 2009), for subsequent reporting of summary statistics.

<u>To address aim 1:</u>

80 NHS patients* (without ocular pathology, other than neovascular AMD), due to receive an intravitreal anti-VEGF injection, in at least 1 eye, will be recruited whilst attending for their monthly consultation at the University Hospital of Wales, Cardiff *(part 3).* To allow comparison, participants will be stratified by the key factors identified in aim 2.

Part 3 Experience of individual treatments: NHS patients will be recruited from an Ophthalmology Clinic at University Hospital of Wales, with the aid

of the collaborator, Mr Sanjiv Banerjee, a Consultant Ophthalmologist and direct healthcare team, who will identify suitable potential participants (based on the exclusion/inclusion criteria). Potential participants will be initially approached by their ophthalmologist/nurse during their routine eye examination, also provided with an information sheet to keep.

Potential participants interested in the study may:

a) Be introduced directly to the researchers who will provide study details
b) Choose to provide contact details to allow researcher to contact them with study details
c) Be provided with study details and the researchers contact details to enable potential participant obtain further information/ask questions.

The study will not take place on the same day as the initial approach where the potential participant will be provided with the PIS and researcher contact details. Consent will be obtained at a future hospital appointment.

Inclusion Criteria is the following:

- Neovascular AMD patients
- Aged 50 and above
- Male or Female
- Participants who are due to receive an intravitreal anti-VEGF injection, in at least one eye
- Participants who, following a full explanation of the study, are willing and able to take part

Exclusion Criteria is the following:

- With known retinal pathology other than neovascular AMD
- Unable to use a telephone (e.g. caused by very poor hearing)
- Unable to communicate in English or Welsh or provide informed consent

- Motor skill issues that can effect marking VAS and recording of the EDA

**Power calculation based on a conservative pairwise comparison to detect a 13 mm clinical difference on a VAS with an assumed SD of 17.1, alpha 0.05 and 80% power for 2 comparative factors. An additional 15% is added to account for a possible non-parametric analysis, and a further 20% allowance for attrition/missing data based on previous studied. Therefore 40 per group (2 group total: 80).*

Baseline: Full medical and ocular history, AMD treatment history, including previous injections, and demographics.

Subjective: The validated short-form McGill pain (SF-MPQ)[30] and State-Trait Anxiety Inventory Form Y (STAI-Y)[31] questionnaires will be used to characterise the features of pain and anxiety whilst state of wellbeing will be measured using the validated Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)[32] pre-injection and at 0 and 24 hours post-injection. Participants will also be asked to mark a pain visual analogue scale (VAS) that will be returned by post to the researchers. An open question addressing 'intention to return' for future treatments will be included as a measure of compliance. As participants are likely to have reduced vision, large print copies of all questionnaires and VAS scales will be provided in advance and administered by telephone interview for consistency. Based on experience, each telephone interview will last 10-15 minutes.

Injection procedure: The researcher will observe, time and document the injection procedures such as anaesthetic type used (informed by aim 2 outcomes).

Objective pain: Electrodermal activity (EDA) will be recorded with the Biopac MP36 physiologic amplifier (Linton Instruments Ltd, UK) for the duration of the injection procedure. Sensors will be attached to the fingertips

of the middle and index fingers of the hand on the contralateral side to the injected eye, and EDA monitored throughout the treatment.

Analysis: Pain VAS will be measured to provide a quantifiable measure of pain. Rasch analysis will be applied to the SF-MPQ, STAI-Y and WEMWBS questionnaire scores. The results and the intention to return question will be collected for each administration time point. Patient pain will be compared between the identified factors (from aim 2), and against wellbeing, intention to return and injection site parameters, using analysis of variance (ANOVA), or non-parametric equivalent (e.g. Friedman test), with repeated measures as appropriate. Sub-analysis with secondary factors identified in aim 1 & 2 will also be undertaken.

<u>To address aims 3 & 4</u>

Data obtained from aims 1 & 2 will be used to perform an event-based comparison of procedures (steps) and objective pain (EDA) measured during each treatment episode. In addition, exploratory data techniques, principle component analysis and feature selection by machine learning, will be applied to data obtained for aim 1 to ascertain the stronger predictor variables for pain during and/or following treatment.

2. Summary of Procedures to be carried out in chronological order:

a. Study Part 1 *(1 hour)*

To be carried out at the Cardiff School of Optometry and Vision Sciences/participant's own home

- Informed Consent
- Semi-Structured Interviews with patients

b. Study Part 2 *(30 minutes)*

To be carried out at the University Hospital of Wales

- Informed Consent

- Semi-structured interviews with ophthalmologists and nurses

c. Study Part 3 *(1.5 hours)*

To be carried out at the University Hospital Wales (UHW), Ophthalmology Clinic

Pre-treatment (remote)

- Verbal Consent
- Medical and Ocular History

Questionnaires to be conducted by telephone/audio conferencing

- **The short-form McGill Pain Questionnaire (SF-MPQ)[30]**. To measure subjective pain (consists of 15 descriptors: 11 sensory e.g. “hot-burning”; 4 affective e.g. “fearful”).

- **State-Trait Anxiety Inventory Form Y (STAI-Y)[31].** To measure subjective anxiety state, consists of 20 item responses e.g. “I feel calm” or “I am tense”.

- **Visual Analogue Scale (VAS)**[13] A psychometric scale used in questionnaires to measure pain intensity. Anchored by “no pain” (score of 0) and “worst imaginable pain” (score of 100 [on 100-mm scale]).

- **The Warwick Edinburgh Mental Well-Being Scale; WEMWBS (Well-Being Questionnaire)**[32] (NHS Health Scotland, University of Warwick and University of Edinburgh, 2006). To measure subjective mental well-being and psychological functioning. Composed of 14 item responses (e.g. “I’ve been feeling relaxed”).

Treatment

- **Informed Consent**

Electrodermal Activity (EDA) [33]. Two gel electrodes attached to index and middle finger of one hand. Leads connect electrodes to Biopac recording hardware.

- EDA Baseline (2-4 minutes).

- Participants will undergo the intravitreal injection procedure, and simultaneous EDA recording.

- EDA post measurement (2-4 minutes). Following measurement EDA electrodes removed from fingers.

Post treatment (at 0-1 hour) (remote)

- Repeat administration of the SF-MPQ, WEMWBS and STAI-Y questionnaires, and Visual Analogue Scale (VAS).

- Researcher will ask the open-ended question on 'intention to return' for future treatments, and record down the answers.

- Patient provided with paper copies of follow up questionnaires (SF-MPQ, VAS, WEMWBS and STAI-Y questionnaires) and a stamp addressed envelope. Patient informed they will be contacted by telephone in 24 hours for follow up questions.

Post treatment (at 24 hour ± 2 hours) (remote)

Telephone Call: Researcher will administer and complete the questionnaires (SF-MPQ, WEMWBS, STAI-Y) over the phone. Researcher will also ask participants the open-ended question on 'intention to return for future treatments' and record down their answers. Participants will be asked

to mark on the pain VAS (to be returned by post to the researchers for analysis).

d) Study Part 4 (*30 minutes*) (approved amendment on page 12)

To be conducted remotely by telephone/audio conferencing

- Verbal Consent
- Semi-Structured Interviews with patients

5. Ethical Considerations

All procedures to be used are non-invasive, there is minimal risk to participants and there are not complex organisational or legal issues.

- All research participants will be informed of the risks and benefits of taking part in the study.

- Informed consent will be obtained before involving the patients in the study (including screening procedures and access to medical record).

- Informed consent will be obtained for involving the healthcare practitioners in the study.

- All racial/ethnic groups will be eligible to participate in our study. Participants will not be discriminated against because of any protected characteristics.

- Participants involved in Part 1 or Part 4 of the study can also take part in part 3.

<u>Patient Medical Records</u>

a. The primary researcher (*Christina Yiallouridou*) will require access to medical and ocular records (e.g. total number of intravitreal injections, previous complications, and medication).

- To determine further participant eligibility and to allow for the interpretation of data.

- Only the primary researcher will have access to patient medical records. All information will be pseudo-anonymised before passed to the rest of the research team members.

Questionnaires and Interviews

a. Patients will be asked to complete questionnaires, be involved semi-structured interviews and follow-up telephone interviews. These will be administered remotely by telephone/audio conferencing, consistent with social distancing measures.
b. Healthcare Practitioners will be involved in semi-structured interviews.

Patients and Healthcare Practitioners have the right to decline to participate, and the right to withdraw from the research at any time, without giving a reason.

c. Semi-structured interviews will be audio recorded and transcribed for purposes of content analysis, in addition to the recording of field notes.

We will obtain consent for participants agreeing to be audio recorded during their interview. We will explain to participants that all the information collected will remain confidential. If participant does not provide consent to be audio recorded, detailed notes will be taken instead. Field notes will be taken as a precaution against issues with audio resolution.

d. Involvement in interviews can have emotional consequences.

Due to the sensitive nature of the interview, any potential 'risks' of participating would come as a result of the discussion. For example, if a discussion point reminded participating of a particular painful or distressing experience. It is the researcher's responsibility to keep the discussion on topic and to elicit needed responses. The researcher will provide real

opportunities during the session for participant to withdraw at any time or refuse to answer.

e. Participants may have a partial hearing loss.

A microphone will be used to aid participants with a partial hearing loss. A hearing device will also be provided. Those who have total inability to hear will be excluded.

Electrodermal activity (EDA)

EDA is measured as skin conductance using a low frequency constant voltage (12 vdc) as excitation source across the skin electrodes. The BIOPAC MP36 hardware has been used as a physiology teaching tool for educational research. The researcher will be trained to use the equipment safely; in application of electrodes and setting up the recording. EDA recording has been used safely for many years in psychophysiological studies, and we are aware of no cases of adverse events.

a. Patients have the right to decline to participate, and the right to withdraw from the research at any time, without giving a reason.

b. To record EDA, we require a power supply (to connect the MP36R hardware and the monitor).

- The MP36R satisfies the Medical Safety Test Standards affiliated with IEC60601-1 and is designated as Class I Type BF medical equipment - provides protection against electric shock, particularly regarding allowable leakage currents and reliability of the protective earth connection (if present), and has isolated or floating (F - type) applied part or parts. To note, device is CE marked.

- Linkage cables are designed to release if pulled.

- Portable appliance testing (PAT) will be undertaken on all portable electrical equipment.

- For safety purposes, no equipment will be stored at the hospital. All equipment will be transported back to the university after each session finishes.

c. It is not advisable to pause the procedure if patient requires a break, since this may bias the skin conductance responses measured.

- This is unlikely to occur since patient will be prepared to receive intravitreal injection and informed by the practitioner to remain in situ until the treatment procedure ends.

d. Hygiene:

- In cases of extremely oily skin, the skin surface will be softly cleaned with water or alcohol (e.g. using Alcohol Disposable Wipe Prep Pads, Biopac Systems UK).

- Disposable 'dry' electrodes will be used – new pair of electrodes will be used for each patient to minimise risk of infection. Electrodes are sealed in individual airtight foil packets.

- GEL101 will be applied on the electrodes in case they dry out. GEL101 is a non-irritating, isotonic gel primarily used as a conducting gel paste.[33]

- Hard surfaces of laptop and EDA hardware will cleaned with hard surface disinfectant wipes between participants.

- Consistent with standard aseptic techniques the researcher’s hands will be washed before and after any contact with the patient. The

researcher will wear a face mask and disposable gloves, and any hair will be tied back. Researcher will adopt general clinic dress.

- If researcher observes any signs of irritation/swelling on the surface area that the electrodes will be attached to, the participant will be excluded from the study.

Part 4 Patient Experiences during COVID-19

1. Background and Rationale

The global coronavirus (COVID-19) outbreak had been declared a public health emergency of international concern. As of 8th June 2020, there are 4.8 million confirmed cases and 303,000 deaths worldwide, with nearly 240,000 cases in the UK (gisanddata.maps.arcgis.com). The pandemic increases the system challenges in the National Health Service to protect patients and healthcare practitioners from disease transmission, particularly in ophthalmology practices which consist of routine use of reusable equipment in close contact with patients and the potential contamination of instruments[34,35]. Routine intravitreal injections are necessary for patients with neovascular age-related macular degeneration (AMD) in order to halter disease progression and preserve eyesight[36].Hospitals and eye clinics have implemented procedures to prioritise and manage patients who are at "*high risk of rapid, significant harm if their appointment is delayed*."[37] Nevertheless, lockdown measures and the media coverage of the novel COVID-19 risks spreading national fear may act as barriers to treatment adherence, as patients reported feeling, *"too scared"* to attend their routine eye appointments[38]. Poor adherence to treatment increases the risk of irreversible sight loss which may also result in patients experiencing depressive and anxiety symptoms affecting their mental health[39].

Guidelines implemented in AMD services[37] included information on how to inform patients about their appointments and to reassure them of their safety against COVID-19 infection risks, as well as support those who are not permitted hospital attendance through remote consultations. Our recent

qualitative study on patient experiences associated with intravitreal injections identified, “Fear of losing eyesight and apprehension on patient adherence to treatment” as one of the main themes. We found that effective communication improved patients’ adherence to treatment, recognising the benefits of the injections over apprehension to preserve their eyesight: *“But you know, if you want to save your sight, it's very small thing to pay to keep your sight. I think that is excellent and we are very lucky to have it.”* [patient 10, 89 yrs] They also reported feeling worried when their injection appointment was postponed or cancelled: *“I was a little worried about that…I wouldn’t like to be discharged and then have to rely on my own judgment.”* [patient 14, 71 yrs]

Our findings support that fear of losing eyesight was more important than the anticipated apprehension of the injections[5]. Increased anxiety and fear related to COVID-19 potentially raises implications for treatment adherence. A recent report from the Macular Society (2020) has raised concerns of patients experiencing fear of contagion and uncertainty accessing public transport and visiting hospitals for their routine intravitreal injections. They reported: “*I was dreading my appointment at the beginning of coronavirus, I was thinking I really didn't want to go.*” Personal safety when travelling on public transport was previously associated to patients’ visual impairment and reported as an important concern when they travelled alone to and from the hospital[40]. A retinal specialist at a hospital also observed a significant decrease in the number of patients attending for their treatment and reported, *“We had a waiting room area of 50 chairs with four people at the most. For more or less four or five weeks we didn't have a single person come in.”*

Delayed follow-up and delayed treatment were previously associated with permanently reduced vision in patients diagnosed with glaucoma, AMD, and diabetic retinopathy[41]. Arias et al. (2009) also reported that delayed initiation of treatment in patients with newly diagnosed AMD led to progressive vision loss[42]. COVID-19 risks may exacerbate peoples’ fears about public transportation and could negatively impact their mental health and

adherence to treatment, hence, we plan to undertake this study to explore the impact of COVID-19 on patients undergoing anti-VEGF therapy.

2. Research Aim/Question(s)

Overall Aim:

To explore the perceptions of patients with neovascular AMD on COVID-19 risks in relation to their adherence to treatment.

Research Questions:

- What are patients' perspectives on the limitations to eye care and how do they perceive triaged or delayed treatment?
- How have anxiety and fear associated to COVID-19 risks influenced patients' perceptions for treatment?
- What role do virtual clinics and telephone meetings play in supporting and maintaining essential health services for AMD patients?
- What is the impact of social distancing on treatment adherence and how does it differ across groups, particularly vulnerable groups (aged ≥70 years) who live alone?

3. Study design and methods of data collection

3.1. Research design

This is an additional study, following on the themes identified in "Part 1 Patient Experiences", to address new research questions about the impact of COVID-19.

This study will use a qualitative design in which semi-structured interviews will be conducted via telephone or audio conferencing (consistent with social distancing measures). Interviews will last about 30 minutes. All interviews will be audio-recorded. Compared to questionnaire research, interviews allow a more meaningful engagement with patients. In-depth interviews will seek to explore meaning and perceptions of vulnerable

patients with sight loss to gain a better understanding of how COVID-19 influences patients' experiences and their adherence to treatment.

4. Sample and Recruitment

4.1. Recruitment

Participants were identified and recruited from the Ophthalmology Clinic, University Hospital of Wales. Participants who fall in the following 2 categories will be eligible to take part in the study:

a) Recruited participants for "Part 1 Patient Experiences" who have provided an informed consent to be contacted for future research.
b) Recruited participants for "Part 3 Experience of Individual Treatments" (no informed consent obtained/no data collected due to COVID-19 disruption) will be approached remotely following Ethical Approval.

Participants will not be recruited through Patient Identification Centres (PICs) or publicity.

4.2. Sampling

Patients were recruited using purposive sampling to meet eligibility criteria and to collect data from a range of ages and genders. The targeted sample size is 10-20 patients, informed by models of qualitative research[43] and following the principle that the more focused nature is the study and more useable data are collected from each individual, the fewer participants are needed[44].

4.3. Eligibility criteria

Inclusion Criteria:

- Males or Females
- Aged 50 and above (based on prevalence and incidence of neovascular AMD)
- All racial/ethnic backgrounds
- Able to communicate in English or Welsh
- Able to provide informed consent (have capacity)

- Diagnosed with neovascular AMD and enrolled in a clinic for receipt of anti-VEGF therapy on or after March 23rd 2020 (start of lockdown in Wales, UK).

Exclusion Criteria:

- Unable to provide informed consent (lack of capacity)
- Suffer from very poor hearing
- With known retinal pathology other than neovascular AMD (e.g. glaucoma or diabetes)

5. Ethical Considerations

a. Participants will be recruited from an outside Cardiff University site, namely the Ophthalmology Clinic at the University Hospital of Wales.
Cardiff University will be acting as sponsor and all interviews will be conducted remotely. Patients have the right to decline to participate, and the right to withdraw from the research at any time, without giving a reason.

b. Telephone interviews/video conferencing will be audio recorded and transcribed for purposes of thematic analysis.
We will obtain verbal consent for participants agreeing to take part in the study and to be audio recorded during their interview. We will explain to participants that all the information collected will remain confidential. If participant does not provide consent to be audio recorded, detailed notes will be taken instead.

c. Involvement in an in-depth interview can have emotional consequences.
The researcher will be responsible to keep the interview on topic and to elicit needed responses. The researcher will provide opportunities during the session for participants to have a break, withdraw at any time, refuse to answer, or set another interview date.

d. **Participants might show depressive symptoms during the interview.** The interviewing will stop, and the researcher will be responsible to refer these participants back in their clinical team/GP. We will obtain consent for participants agreeing to this referral process prior to conducting the interviews.

6. Data Analysis

Audio-recorded interviews will be transcribed verbatim, reviewed and thematically coded (Braun and Clarke 2006) (coding scheme agreed on by research team and collaborator) with the support of NVivo 12, a qualitative analysis software (QSR International).

Appendix D: Interview Topic Guide for Patients

Investigation of pain and discomfort associated with anti-VEGF injections

Part 1 Patient Experiences

Patient Semi-Structured Interview Guide

This topic guide should be used as reference during qualitative interviews with patients. The precise questions used will vary according to what is discussed. The interviews will be semi- structured and will explore the perspectives of patients having anti-VEGF injections and their experiences and understanding of these procedures.

A: Introductory Script

Thank you for volunteering to participate in this study. Before you consent to taking part in the interview, we will go over the information sheet with you and answer any questions you may have.

Do you remember the last time you had an eye injection? We are interviewing you because we want to better understand the aspects that can affect the experiences of patients who receive injections into the eye to treat wet age-related macular degeneration. So, there are no right or wrong answers to any of our questions, we are interested in your own experiences.

Participation in the study is purely voluntary and your decision to participate, or not participate, will not affect the care you currently receive from eye injections. This interview could take between 30-60 minutes depending on how much information you would like to share. With your permission, I would like to audio record the interview because I do not want to miss any of your comments. All responses will be kept confidential. This means that the interview responses you give will only be shared with research team members using codes to protect your identity and privacy, and any information we include in our report does not identify you as the respondent in any way. Please ask for further explanation if you do not understand a

question during the interview and give yourself time to pause and reflect, if you need it. Are there any questions about what I have just explained?

I will now ask you to read carefully and sign the consent form if you wish to take part. Please let me know if you have any further questions.

Before we start, I would like to remind you that you may decline to answer any question or stop the interview at any time without giving us a reason. Feel free to interrupt me or stop the interview at any time if you need to take a break.

May I turn on the digital recorder?

B: Background

1. Please tell me the story of the health condition that brought you into the clinic. Take your time.

Prompts: loss of vision, blur, support, difficulties in daily life, problems seeing to do certain activities, feelings

   a) How did you deal with that? Whom did you talk to when you had that kind of a problem? Who helped you with any difficulties (Practitioner, family member, friend)?
   b) What were your particular concerns about your health (e.g. driving, reading, sadness/depression)?

2. What usually happens during your eye appointments at the hospital? Prompts: initial discussion, eye tests, eye injection

   a) Do you understand the reason why you are getting the eye injections?
   b) How often do you have to come to the clinic to be assessed (may require injection or not)?
   c) How long have you been receiving the injections at the University Hospital of Wales?

d) How many injections have you received up until now?

C: Experience of Injections

3. How did you feel when you were first told that you would need a series of eye injections to treat your condition?

   Prompts: reactions, thoughts, feelings, concerns, practicalities

   a) What stands out for you about that experience?
   b) Did you have any concerns prior to receiving treatment?
   c) Did you discuss these concerns with your care team?

4. Tell me about your experiences of the injections.

   a) Was there anything you particularly liked about the injection procedure?
      Prompts: care team, quality of care, duration, treatment outcome, confidence in care, safety

      - Could you tell me more about it?
      - What does that mean to you?
      - Are you satisfied with the outcome of the treatments?

   b) Was there anything you did not like about the injection procedure? Prompts: care team, quality of care, procedural steps, injection, pain/discomfort, anxiety, anticipation, safety

      - Could you elaborate on that?
      - How did you feel? Which words would you choose to describe your experience/pain/discomfort?
      - What does that mean to you?
      - How long does your discomfort/pain usually last?

   c) How does pain/discomfort affect your daily life? Prompts: sleep, appetite, mood, medication for pain

- Is there anything that has changed in your daily life because of your pain/discomfort
- Have you used or currently using any strategies to control or decrease your pain/discomfort?

5. Can you think of anything else about the appointment you would like to have changed?

   Prompts: access, organisation, staffing, waiting time, frequency of appointments

6. Is there anything else you would like to tell me?

D: Demographic Information

This information will not be linked to any participant's name. A number will be assigned as a code reference for analysis purposes.

1. Patient Code (to match data from before/after surveys)
2. Gender, Age
3. Place of primary residence (lives alone, lives with family, nursing home, other)

Thank you very much for your time today.

Appendix E: Interview Topic Guide for Practitioners

Investigation of pain and discomfort associated with anti-VEGF injections

Part 2 Practitioner Experiences

Practitioner Semi-Structured Interview Guide

This topic guide should be used as reference during qualitative interviews with practitioners. The precise questions used will vary according to what is discussed. The interviews will be semi-structured and will explore the perspectives of practitioners on the experiences of patients receiving anti-VEGF injections, as well as identify routine treatment procedures and procedural differences.

A: Introductory Script

Thank you for volunteering to participate in this study. Before you consent to taking part in the interview, we will go over the information sheet with you and answer any questions you may have.

We are interviewing you because we want to gain information about your insights into the experiences of patients receiving intravitreal injections to treat wet AMD, and to identify routine treatment procedures and procedural differences.

Participation in the study is purely voluntary. This interview could take between 20-30 minutes depending on how much information you would like to share. With your permission, I would like to audio record the interview because I do not want to miss any of your comments. All responses will be kept confidential. This means that the interview responses you give will only be shared with research team members using codes to protect your identity and privacy, and any information we include in our report does not identify you as the respondent in any way. Please ask for further explanation if you do not understand a question during the interview and give yourself time to pause and reflect, if you need it. Are there any questions about what I have

just explained? I will now ask you to read carefully and sign the consent form if you wish to take part. Please let me know if you have any further questions.

Before we start, I would like to remind you that you may decline to answer any question or stop the interview at any time without giving us a reason. Feel free to interrupt me or stop the interview at any time if you need to take a break.

May I turn on the digital recorder?

A: Background

1. Can you tell me about your experiences of managing patients who have wet age-related macular degeneration (AMD)?

   Prompts: training, consultation, routine examinations, intravitreal injections, imaging, counselling

   - What routine examinations do you or your practice usually carry out?
   - What was the length of the training you received to perform these injections?
   - How long have you been performing intravitreal injections?

B: Intravitreal Injection Procedure

2. Tell me about the intravitreal injection procedure.

Prompts: guidelines, types of anaesthetics, concentrations, needle size, site of injection, anti-VEGF, duration, risks, complications

- Do you follow any particular guidelines for performing the injections?
- Could you tell me in order the procedural steps that you perform? How long does the local anaesthetic effect usually last?
- What follow-up schedule do you use for patients who have been injected?

- Would you make any changes to the procedure based on the comorbidities or specific ocular history of the individual? (e.g. site of injection, anaesthetic type)
- Which anti-VEGF drugs are currently being used in the clinic? Do you have any preference? What is your opinion on Avastin Vs Lucentis/Eylea? Do you recommend analgesics to patients having injections?

C: Experiences

3. Did you have any patients who reported experiencing pain/discomfort during or after the injection?

Prompts: strategies, procedural steps, manage anxiety/nervousness, advice, variations in procedure, explanation of procedure, safety, patient rapport

- How do you deal with those patients? Are you using any strategies to manage pain/discomfort?
- Which procedural steps do you consider less favourable for patients, from your own perspective? What advice would you give to patients with anxiety/nervousness?
- Would you make any changes to the procedure based on the reported experience?

4. Is there anything else you would like to tell me?

D: Demographic Information

This information will not be linked to any participant's name. A number will be assigned as a code reference for analysis purposes.

1) Participant Code
2) Gender/Age
3) Number of years since clinical qualification as an ophthalmic nurse/optometrist/ophthalmologist

Appendix F:
Interview Topic Guide for Patients during COVID-19

Patient experience of injections in age related macular degeneration

Part 4 Patient Experiences during COVID-19

Patient Semi-Structured Interview Guide

This topic guide should be used as reference during qualitative interviews with patients. The precise questions used will vary according to what is discussed. The interviews will be semi-structured and will explore the perspectives of patients having anti-VEGF injections during COVID-19 and their experiences and understanding of continuing treatment.

A: Introductory Script

Thank you for volunteering to participate in this study. Have you received a copy of this information sheet? Before you consent to taking part in the interview, we will go over the information sheet with you and answer any questions you may have.

How are you feeling? We are interviewing you because we want to better understand the aspects that can affect the experiences of patients who receive injections into the eye to treat wet age-related macular degeneration during COVID-19. So, there are no right or wrong answers to any of our questions, we are interested in your own experiences.

Participation in the study is purely voluntary and your decision to participate, or not participate, will not affect the care you currently receive from eye injections. This interview could take between 15-30 minutes depending on how much information you would like to share. With your permission, I would like to audio record the interview because I do not want to miss any of your comments. All responses will be kept confidential. This means that the interview responses you give will only be shared with research team members using codes to protect your identity and privacy, and any

information we include in our report does not identify you as the respondent in any way. Please ask for further explanation if you do not understand a question during the interview and give yourself time to pause and reflect, if you need it. Are there any questions about what I have just explained? May I turn on the digital recorder?

I need to confirm you are willing to take part; I will read a series of statements, can you confirm whether you agree or disagree with each one for the record. Please let me know if you have any further questions.

Before we start, I would like to remind you that you may decline to answer any question or stop the interview at any time without giving us a reason. Feel free to interrupt me or stop the interview at any time if you need to take a break.

B: Demographic Information

This information will not be linked to any participant's name. A number will be assigned as a code reference for analysis purposes.

1. Patient Code (to match data from before/after surveys)
2. Gender, Age, Ethnicity
3. Place of primary residence (lives alone, lives with family, nursing home, other)

C: Background

1. Please tell me the story of the health condition that brought you into the clinic. Take your time.

Prompts: loss of vision, blur, support, difficulties in daily life, problems seeing to do certain activities, feelings

- What were your particular concerns about your health (e.g. driving, reading, sadness/depression)?
- How did you feel when you were first told that you would need a series of eye injections to treat your condition?

Prompts: reactions, thoughts, feelings, concerns, practicalities

2. Do you understand the reason why you are getting the eye injections?

Prompts: initial discussion, provision of leaflets

- How long have you been receiving the injections at the hospital?
- How many injections have you received up until now?

D: Patient Experiences during COVID-19

The Welsh government has placed safety measures on March 23rd due to the COVID-19 outbreak. These measures are followed by NHS sites, including the University Hospital of Wales.

3. What is your knowledge on COVID-19? Do you understand the risks of COVID-19 to your general health?

4. Have you had COVID-19, or experienced COVID-19 symptoms that required you to go to the hospital? (e.g. emergency room, intensive care unit)
    - What did your healthcare provider tell you about COVID-19?
    - What have you heard about COVID-19?
      Prompts: online, from friends, family, news

5. Have you visited the eye clinic during the pandemic? Have your appointments been cancelled or changed?

    a. Did you have any concerns when you visited the hospital? Can you give an example?

Prompts: visits, safety, care team, eye tests, OCT scans, treatment delays, follow-up visits

6. How does the Eye Clinic monitor your condition and provide guidance?
   Prompts: home visits, virtual clinics, telephone meetings, remote consultations

a. How helpful were they for you? Were you satisfied with the outcomes?
b. Do you understand the reasons your treatment has been triaged or delayed?
    - Could you tell me more about it?
    - What would be helpful for you to better understand or remember the instructions about your treatment?
c. Have you noticed any changes in your vision? How did you deal with that? What kind of support would be helpful for you at this time?

7. Has COVID-19 risks influenced your decisions to attend appointments or continue treatment?
    - Could you elaborate on that? What does that mean to you?
    - Have you missed any of your appointments during the period of the pandemic? Why?

8. Tell me about the place where you live. Who lives there with you?

    Prompts: house, apartment, care home

    a. How do you get to appointments? Has this changed?
    b. What do isolation and social distancing mean to you?
        - What do you think is the hardest thing about isolation and social distancing? How do you deal with that?

Prompts: public transport, family member, carer, independence, assistance

9. How have you felt about COVID-19 over the past few months? What words would you use to describe your experiences?
    - Has this affected your daily routine activities that you usually enjoy?

Prompts: exercise, hobbies.

    - Have you used or currently using any strategies to cope with that? What support would you need to address that?

10. Is there anything else you would like to tell me?

PART 1

Appendix G: Part 3 Participant Information Sheet

School of Optometry and Vision Sciences
Ysgol Optometreg a Gwyddorau'r Golwg

Head of School *Pennaeth Yr Ysgol* Professor *Yr Athro* John Wild

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Prifysgol Caerdydd
Heol Maindy
Caerdydd
CF24 4HQ
Cymru, Y Deyrnas Gyfunol

Version: 5.0 (16th November 2020)

PARTICIPANT INFORMATION SHEET

Patient experience of injections in age related macular degeneration

Part 3 – Experience of individual treatments

Dear Sir/Madam,

Cardiff University would like to invite you to participate in our study investigating the experiences of patients receiving eye injections for the treatment of wet age-related macular degeneration.

Before you decide, we would like you to understand why the research is being done and what it would involve for you. Please take time to read this information sheet carefully and do not hesitate to talk to others about the study if you wish. Before any testing takes place, we will go through the information sheet with you and answer any questions you may have. Please ask us if there is anything that is not clear. We are happy to provide you with more information.

PART 1

The following information sheet has two parts:

Part 1 explains purpose of this study and what will happen if you take part

Part 2 gives a more detailed information about the conduct of the study

- **What is this study about?**

Age-related macular degeneration (AMD) is a disease that damages the retina at the back of the eye, which is responsible for good vision. This makes activities such as reading and driving more difficult. AMD is the leading cause of vision loss in the UK, and it mainly affects the elderly. Not all forms of AMD can be treated, but those with wet (neovascular) AMD can be treated with injections into the eye. To slow the progression of the disease and maintain good vision, repeated injections are usually needed. The injections are shown to be safe and favourable, but some patients may have pain and discomfort during or after the treatment. And, we want to learn how this affects their treatment and future visits to the eye clinic. It is thought that improving the patient experience will benefit them and help them in the future.

We are aware that pain and discomfort are clear problems to patients who get eye injections. These can be related to anxiety and can have an influence on their wellbeing and quality of life as well.

In this study, we want to learn about the aspects of the treatment that make patients experience pain/discomfort or anxiety, and how they can affect compliance with treatment and wellbeing.

You have been asked to volunteer in this research because we are looking for individuals with wet AMD, 50 years of age and older, who are receiving injections during their regular consultation at the University Hospital of Wales. You may have previously taken part in an interview with the research team as part of this study.

Our aim is to study the experiences of patients who get injections to treat wet AMD. We will do that by using different methods, for example electrodermal activity (EDA)* and questionnaires (asking about pain/discomfort, anxiety and wellbeing) and an 'intention to return' question. We also want to look at the injection site. We plan to do this by taking an image of the eye using an optical coherence tomography (OCT)*; this will be very similar to any OCT image you may have had taken of the back of your eye by your optician or eye doctor.

**What is Electrodermal Activity (EDA)*

EDA is a measure of the electrical features of the skin, which is known to change when people are anxious or feel pain/discomfort. EDA is measured by two 'sticky' sensors that are placed on to the middle and index finger.

- **What will happen to me if I take part?**

If you decide to volunteer for this study, on the day you are expected to receive next injection, a Cardiff University researcher will go over this information sheet with you in a quiet room. We will explain exactly what will happen in the session and give you an opportunity to ask questions. We will ask you to sign a consent form if you are happy to continue, before any testing takes place. All information given during the process will be kept confidential.

The researcher will be present from the beginning till the end of the session to answer any questions you may have.

At the end of the EDA session, we will use hand-sanitizing wipes to clean the area of the skin surface that we have attached the sensors to.

Before the Treatment (duration of ~20 minutes)

We will contact you by telephone at an agreed time before your treatment. We will collect some information about your medical and eye history, any medications you are currently taking, and about whether you have had any caffeine and alcohol recently. Afterwards, we will ask you to complete three short questionnaires over the phone and make a mark on a pain scale. We will ask you to put this in an envelope and to bring it along at your appointment.

During the Treatment (duration of ~15 minutes)

The researcher will meet you inside the Eye Clinic Unit at the time of your appointment. The nurse/doctor will explain the treatment procedure to you and will set you up for the injection as normal. We will then attach two sensors to the tip of your index and middle finger on one hand, which are similar to a sticky plaster. The researcher will be measuring your response a few minutes before, and throughout the injection procedure. At the same time, the researcher will be taking notes of the procedure. Once the injection procedure is completed, we will wait a few minutes before removing the finger sensors.

After the treatment (duration of ~20 minutes)

When you are ready to leave, we will give you two copies of the questionnaires and a pre-paid envelope to take home. When you arrive home, we will ask you to complete some questionnaires over the phone, and also ask you to make a mark on a pain scale. We would also like to know how you feel the next day.

Follow-Up the following day *(duration of ~15 minutes)*

We will contact you by telephone at an agreed time the next day. We will ask you to repeat the procedure and complete the rest of the questionnaires over the phone, and ask you to make a mark on a pain scale. We will ask you to put all completed questionnaires in the pre-paid envelope and return to us in your own time.

Are there any possible risks or disadvantages from taking part?

There is no additional risk associated with taking part in this study and it will not affect the way you receive your normal treatment. EDA recording has been used safely for many years in pain and anxiety research, and we are aware of no cases of adverse events.

Any potential risks that may be associated with the treatment or ongoing care will be discussed separately with you by your care team.

- **What are the possible benefits of taking part?**

The impact of the findings will primarily benefit patients with AMD, but may not directly benefit you. We hope that the information we get from this study will help us to better understand patient experiences associated with eye injections, and to investigate the potential of using electrodermal activity in ophthalmic research. Finding factors that cause pain/discomfort or anxiety may allow changes to the injection procedures to improve patient experience of treatment for wet AMD. The findings could be applied to all treatments involving eye injection, not just for AMD, and potentially lead to the adoption of more patient-friendly procedures.

- **Do I have to take part?**

No – it is up to you whether you decide to take part or not. Participation in this study is purely voluntary. If you do decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form on the day of your visit for treatment. You may withdraw from the study at any point without giving us a reason. This will not affect you in any way.

- **What if I have any questions**

Please ask a member of the research team if you have any questions (contact details below). We are very happy to discuss any aspect of the study. Please do not send personal information regarding your medical status by e-mail, as this may not be a secure means of communication.

Name	Email Address	Telephone Number
Christina Yiallouridou	YiallouridouC@cardiff.ac.uk	029 20876471
Ashley Wood	WoodA2@cardiff.ac.uk	029 20875063
Jennifer Acton	ActonJ@cardiff.ac.uk	029 20870203

- **What if there is a problem?**

If you do have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If you would prefer to speak with someone who is independent to the study or wish to raise a complaint, you can contact:

Name	Email Address	Telephone Number
Tom Margrain	MargrainTH@cardiff.ac.uk	029208 76118

- **Will my results remain confidential?**

All information that is collected about you during the course of this research will be kept strictly confidential in accordance with the General Data Protection Regulation (GDPR) EU/2016/679 and the Data Protection Act 2018. All information collected during the study will be processed and stored securely by the Cardiff University researchers using password-protected systems. We may share the data we collect with other researchers but will have your personal information coded so you cannot be recognised from it. We will process your personal data on the basis that doing so is necessary for our public task for scientific research purposes.

Cardiff University is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Cardiff University will keep identifiable information about you for 15 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

After 1 year your personal data will be anonymised, meaning we will remove any identifiers that can identify you from the data you have provided. This anonymous information may be kept indefinitely and/or published in support of the research. Other personal data we may have collected, such as your consent to participate in the study will be kept for 15 years following the end of the project.

Cardiff University is the Data Controller and is committed to respecting and protecting your personal data in accordance with Data Protection legislation. You can find out more about how we use your information here: https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection

If you still have queries, concerns or wish to raise a complaint details, the University has a Data Protection Officer who can be contacted at: inforequest@cardiff.ac.uk

Cardiff and Vale University Health Board (UHB) will collect information from you and your medical records for this research study in accordance with our instructions.

Cardiff and Vale UHB will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Cardiff University and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Cardiff and Vale UHB will pass these details to Cardiff University along with the information collected from you and your medical records. The only people in Cardiff University who will have access to information that identifies you will be people who need to contact you about the study or to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Cardiff and Vale UHB will keep identifiable information about you from this study for 15 years after the study has finished.

- **Expenses and payments**

None, although an envelope with pre-paid postage will be provided to participants for returning completed questionnaires.

- **What will happen to the results of this study?**

The results of this study will be used to inform us on the most significant aspects that cause pain/discomfort or anxiety in patients receiving injections for wet AMD. The results will also be analysed and written up for the purposes of a PhD being

conducted by Christina Yiallouridou at Cardiff University. The results may also help us to design future research projects to incorporate EDA in ophthalmic research. The findings of this research may be disseminated to the public by a press release following publication in the academic literature and via charitable websites. The findings will also be presented at national and international scientific conferences and published in journals. You will not be identified in any report or publication. If you wish to be provided with a summary of the research findings at the end of the study, please tick the appropriate box on the consent form.

- **Who is funding and reviewing the research?**

The research is funded by Abbeyfield Research Foundation, a not for profit organisation. This study was reviewed and approved by Cardiff University and the South East Wales Research Ethics Committee.

Appendix H: Consent Form Part 3

CONSENT FORM

Patient experience of injections in age related macular degeneration

Part 3 - Experience of individual treatments

Version: 5.0 (16th November 2020)

Name of Researchers: **Miss Christina Yiallouridou**
Dr Ashley Wood
Dr Jennifer Acton
Prof Heather Waterman

		Please initial box
1	I confirm that I have read and understand the Participant Information Sheet (Version: 5.0) for the above study and have had the opportunity to ask questions.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.	☐
3	I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Cardiff University, from regulatory authorities or from the NHS, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4	I am fully aware that any personal data collected about me will be stored securely, safely and in accordance with Data Protection Act (2018).	☐
5	I agree for my anonymised data to be used in future research and/or educational activities.	☐
6	If you would like to receive a summary of the results of this study, please tick the box.	☐
7	I agree to take part in the above study.	☐

Name of Participant	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Appendix I: Demographic characteristics

Participant Demographic Details:

1. Details			
Name			
Age		**Gender at birth** (please circle)	Male / **Female**
Do you live in a residential or nursing home? (please tick)	Yes No Residential Nursing		
2. Your Ethnic Background (please tick the appropriate box)			
White British White Irish White British mixed White Welsh Mixed/Multiple ethnic groups (e.g. White and Black Caribbean, White and Asian) Black/African/Caribbean/Black British (e.g. Black African, Black Caribbean, Black British) Other ethnic group (e.g. Arab, Chinese, Other) Asian/Asian British (e.g. Indian, Pakistani, Bangladeshi) Black - any other black background Indian Pakistani Any other Asian background			
3. Do you smoke? Please tick the appropriate boxes next to the options			
I have never smoked I used to smoke Quit Date: I am a current smoker How many/day?			
4. How much coffee/tea do you drink?			
Number of cups of coffee/tea you drink daily: Number of cups of coffee/tea you had today:			
5. How often do you have a drink that contains alcohol?			
Never ☐ Monthly or less ☐ 2 – 4 times per month ☐ 2 – 3 times per week ☐ 4 + times per week ☐ Did you have any alcoholic beverages today? Yes / No			

Appendix J: State Anxiety Questionnaire

State-Trait Anxiety Inventory
STAI Form Y-1

Name……Date……..…Age..... Sex: Male

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then write the number in the blank at the end of the statement that indicates how you feel right now, that is, at this moment. There is no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best

S. No.		Not at all	Some What	Moderately so	Very much so
1.	I feel calm	1	2	3	4
2.	I feel secure	1	2	3	4
3.	I am tense	1	2	3	4
4.	I feel Strained	1	2	3	4
5.	I feel at ease	1	2	3	4
6.	I feel upset	1	2	3	4
7.	I am presently worrying over possible misfortunes	1	2	3	4
8.	I feel satisfied	1	2	3	4
9.	I feel frightened	1	2	3	4
10.	I feel comfortable	1	2	3	4
11	I feel self confident	1	2	3	4
12.	I feel nervous	1	2	3	4
13.	I am Jittery	1	2	3	4
14.	I feel indecisive	1	2	3	4
15.	I am relaxed	1	2	3	4
16.	I feel content	1	2	3	4
17.	I am worried	1	2	3	4
18.	I feel confused	1	2	3	4
19.	I feel steady	1	2	3	4
20.	I feel pleasant	1	2	3	4

Appendix K: Trait Anxiety Questionnaire

Self-Evaluation Questionnaire
STAI form Y-2

Name……

DIRECTONS: A number of statements which people have used to describe themselves are given below. Read each statement and then write the number in the blank at the end of the statement that indicates **how you generally feel**. There is no right or wrong answer. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

S. No.		Almost Never	Some - time	Often	Almost Always
21.	I feel pleasant	1	2	3	4
22.	I feel nervous and restless	1	2	3	4
23.	I feel satisfied with myself	1	2	3	4
24.	I wish I could be as happy as others seem to be	1	2	3	4
25.	I feel like a failure	1	2	3	4
26.	I feel rested	1	2	3	4
27.	I am calm, cool, and collected	1	2	3	4
28.	I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29.	I worry too much over something that really doesn't matter	1	2	3	4
30.	I am happy	1	2	3	4
31.	I have disturbing thoughts	1	2	3	4
32.	I lack self confidence	1	2	3	4
33.	I feel secure	1	2	3	4
34.	I make decision easily	1	2	3	4
35.	I feel inadequate	1	2	3	4
36.	I am content	1	2	3	4
37.	Some unimportant thoughts runs through my mind and bothers me	1	2	3	4
38.	I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39.	I am a steady person	1	2	3	4
40.	I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

Appendix L: Short-Form McGill Pain Questionnaire (SF-MPQ)

SHORT-FORM McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

PATIENT'S NAME: _____ DATE: _____

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT-BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____
SPLITTING	0) _____	1) _____	2) _____	3) _____
TIRING-EXHAUSTING	0) _____	1) _____	2) _____	3) _____
SICKENING	0) _____	1) _____	2) _____	3) _____
FEARFUL	0) _____	1) _____	2) _____	3) _____
PUNISHING-CRUEL	0) _____	1) _____	2) _____	3) _____

NO PAIN ——— WORST POSSIBLE PAIN

P P I

0 NO PAIN _____
1 MILD _____
2 DISCOMFORTING _____
3 DISTRESSING _____
4 HORRIBLE _____
5 EXCRUCIATING _____

Fig. 1. The short-form McGill Pain Questionnaire (SF-MPQ). Descriptors 1–11 represent the sensory dimension of pain experience and 12–15 represent the affective dimension. Each descriptor is ranked on an intensity scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe. The Present Pain Intensity (PPI) of the standard long-form McGill Pain Questionnaire (LF-MPQ) and the visual analogue (VAS) are also included to provide overall intensity scores.

Appendix M: Warwick Edinburgh Mental Wellbeing Scale

The Warwick–Edinburgh Mental Well-being Scale (WEMWBS)

Below are some statements about feelings and thoughts.

Please tick the box that best describes your experience of each over the last 2 weeks

STATEMENTS	None of the time	Rarely	Some of the time	Often	All of the time
I've been feeling optimistic about the future	1	2	3	4	5
I've been feeling useful	1	2	3	4	5
I've been feeling relaxed	1	2	3	4	5
I've been feeling interested in other people	1	2	3	4	5
I've had energy to spare	1	2	3	4	5
I've been dealing with problems well	1	2	3	4	5
I've been thinking clearly	1	2	3	4	5
I've been feeling good about myself	1	2	3	4	5
I've been feeling close to other people	1	2	3	4	5
I've been feeling confident	1	2	3	4	5
I've been able to make up my own mind about things	1	2	3	4	5
I've been feeling loved	1	2	3	4	5
I've been interested in new things	1	2	3	4	5
I've been feeling cheerful	1	2	3	4	5

Appendix N: Shapiro-Test Normality Table

Variable	W statistic	p
SCL		
Baseline pre-treatment	0.93	0.00
Baseline post-treatment	0.86	$5.31e^{-5}$
SCR Amplitude		
Speculum	0.66	$5.96e^{-10}$
Marking	0.74	$1.05e^{-8}$
Injection	0.69	$6.76e^{-10}$
Visual Analogue Scale		
Baseline	0.37	$4.35e^{-15}$
1-2 hrs post-treatment	0.82	$1.70e^{-07}$
24 hrs post-treatment	0.71	$7.25e^{-10}$
Main component		
Baseline	0.31	$9.88e^{-16}$
1-2 hrs post-treatment	0.70	$3.31e^{-10}$
24 hrs post-treatment	0.63	$2.06e^{-11}$
Present Pain Intensity		
Baseline	0.22	$2.20e^{-16}$
1-2 hrs post-treatment	0.88	$1.16e^{-5}$
24 hrs post-treatment	0.79	$2.97e^{-8}$
State-Trait Anxiety Inventory		
Baseline	0.87	$1.01e^{-5}$
1-2 hrs post-treatment	0.93	0.00
24 hrs post-treatment	0.89	$2.77e^{-5}$
State		
Baseline	0.82	$3.00e^{-7}$
1-2 hrs post-treatment	0.87	$1.20e^{-5}$
24 hrs post-treatment	0.81	$9.94e^{-8}$
Trait		
Baseline	0.92	0.00
1-2 hrs post-treatment	0.95	0.01
24 hrs post-treatment	0.93	0.00
Warwick-Edinburgh Mental Wellbeing Scale		
Baseline	0.98	0.59
1-2 hrs post-treatment	0.98	0.35
24 hrs post-treatment	0.97	0.18

Appendix O: Rasch analysis – logit scores, WEMWBS

		Response category			
Item		**1**	**2**	**3**	**4**
1	Optimistic	-2.01	0.03	1.89	3.87
2	Useful	-1.43	0.61	2.47	4.45
3	Relaxed	-1.21	0.83	2.69	4.67
4	Interested in other people	-1.52	0.52	2.38	4.36
5	Energy to spare	0.53	2.57	4.43	6.41
6	Dealing with problems well	0.47	2.51	4.37	6.35
7	Thinking clearly	-0.46	1.58	3.44	5.42
8	Good about myself	0.12	2.16	4.02	6.00
9	Close to other people	-0.59	1.45	3.31	5.29
10	Confident	-0.56	1.48	3.34	5.32
11	Make up my own mind	-1.49	0.55	2.41	4.39
12	Loved	-3.11	-1.07	0.79	2.77
13	Interested in new things	-2.85	-0.81	1.05	3.03
14	Cheerful	-2.96	-0.92	0.94	2.92