Functional outcome of retinal oedema and its standard treatment

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I, Filis Mehmedova Ayan, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Some information has been obtained with the help of others; I confirm that any such aid is as indicated below:

- Prof. Sue Lightman helped with the Health Research Authority Application and site initiation process and with the recruitment of participants in the uveitis clinic.

- In my absence, some of the study participants were seen by Sophie Seguin-Greenstein, who measured their reading speeds and performed microperimetry tests.

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Abstract

Macular oedema is a pathological condition of fluid accumulation in the retinal tissues. It is a nonspecific sign of several retinal diseases that in the long term can lead to permanent vision loss. The clinical aspect of macular oedema treatment and vision recovery is reduction of the amount of fluid accumulated in the retina. Due to its complex pathophysiological mechanism, macular oedema has proven challenging to manage. Many unanswered questions remain in the ophthalmology world on this subject.

The development of recent diagnostic tools such as optical coherence tomography allows better understanding of the morphological changes in the retina. Now we are able to detect retinal oedema and characterise it by location, depth, and amount of fluid. Further, clinicians are now able to assess therapeutic response by examining the anatomical structures of the retina. Yet, with techniques offering objective accuracy, emerging reports have shown discrepancies between clinically examined visual acuity, anatomical changes of the retina, and patients' self-reported visual ability. The presence of such discrepancies is also supported by the fact that results achieved by randomised clinical trials rarely align with results attained in real-world settings.

Today, functional vision testing can be performed with several different methods including questionnaires, colour vision tests, reading speed tests, contrast sensitivity tests etc. Nevertheless, none of these methods are widely used in clinical settings, and their predictive capabilities have yet to be explored. Establishing precise methodology for functional vision testing is likely to provide better understanding of patients' treatment response.

This thesis aims to investigate the potential predictive capabilities of functional vision tests and to compare these capabilities with those of well-established, routine ophthalmic examinations such as visual acuity and retinal thickness tests. In the current research, I focused on the following functional examinations: the visual function questionnaire (VFQ-25), reading speed testing, and testing of the contrast sensitivity of the macula area (examined by microperimetry). These techniques allowed very specific and sensitive testing of the functionality of the retina. In addition, I explored functional vision tests and their

association to the routine ophthalmic tests and their ability to detect sub-clinical changes in vision. I believe further research in this area will offer better understanding of the functional vision changes in patients with macular oedema and potentially will help in improving vision-related quality of life.

Publications arising during the period of the thesis

Tomkins-Netzer O, Ismetova F, Bar A, Seguin-Greenstein S, Kramer M, Lightman S. Functional outcomes of macular oedema in different retinal disorders. Progress in Retina and Eye Research 2015;48:119-36.

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Abbreviation list

BCVA	Best corrected visual acuity
BRB	Blood–retinal barrier
BRVO	Branch retinal vein occlusion
CMT	Central macular thickness
CRVO	Central retinal vein occlusion
CSME	Clinically significant macular oedema
CSRT	Central subfield retinal thickness
CZ-MS	Central zone mean sensitivity
DMO	Diabetic macular oedema
DRP	Diabetic retinopathy
ETDRS	Early treatment diabetic retinopathy study
FFA	Fundus fluorescein angiography
HRA	Health Research Authority
ICG	Indocyanine green angiography
IRF	Intraretinal fluid
IVTA	Intra-vitreal triamcinolone acetate
LogMAR	Logarithmic minimum angle of resolution
MNREAD	Minnesota near reading test
MO	Macular oedema
NEI	National Eye Institute

NICE	National Institute of Clinical Excellence
NVA	New vessels of the angle
NVE	New vessels elsewhere
NVI	New vessels of the iris
OCT	Optical coherence tomography
PRP	Panretinal photocoagulation
RPE	Retinal pigment epithelium
RVO	Retinal vein occlusion
SD-OCT	Spectral domain optical coherence tomography
SRF	Subretinal fluid
SUN	Standardization of Uveitis Nomenclature working group
TD-OCT	Time domain optical coherence tomography
UMO	Uveitic macular oedema
VEGF	Vascular endothelial growth factor
wAMD	Wet age-related macular degeneration
WHO	The World Health Organization

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Introduction and overview

Macular oedema (MO) is a visually devastating retinal disease characterised by retinal thickening and visual loss. MO has long been one of the most urgent yet difficult-to-manage conditions in retinal disease. The damage that occurs in the macula can immediately affect the central visual acuity and hence the patient's vision-related quality of life.

During the last few decades, advances in imaging technologies have greatly improved the diagnosis and clinical management of MO. These advances have also led to changes in the clinical assessment of the therapeutic response. In turn, the outcomes of MO treatment have improved as well amongst the most common retinal diseases, namely diabetic retinopathy (DRP), retinal vein occlusions (RVO), and uveitic macular oedema (UMO).

Standard treatment of MO, which has been proven to improve the anatomical changes in the retina, is effective and able to preserve patients' vision. However, the assessment techniques for measuring functional vision improvement have yet to adopt effective, routine clinical measures. Further, differences in the pathophysiological mechanisms in MO development amongst patients with DRP, RVO, or UMO have led to disparity in the treatment response. Hence, it is not known how functional vision is recovered in patients with MO during standard treatment in clinical settings.

The aims of this thesis were threefold:

1. Document visual functional outcomes in patients with retinal oedema treated as part of routine clinical algorithms and settings.
2. Evaluate the prospective role of the functional vision assessments in routine clinical tests in patients with MO.
3. Predict the value of the functional vision assessments in the patient's therapeutic response.

This research project used three measurements – visual acuity (VA), central subfield retinal thickness (CSRT), and central retinal thickness (CRT) – to represent the results

of a routine ophthalmology examination. Functional vision was assessed and described using three functional examinations: the National Eye Institute's Visual Function Questionnaire -25 (VFQ-25); a microperimetry examination (using the MP-1 and Optos SLO MP devices), which measured contrast sensitivity; and the Minnesota Near Reading Test (MNREAD), which measured reading speed.

Chapter 1 provides the background to the clinical problem and outlines the current standard treatment of MO due to DRP, RVO, or uveitis. Chapter 2 describes the design of the study and the methods used to assess clinically measured therapeutic response and functional vision outcomes amongst patients treated according to standard practice. All regular clinical assessment techniques and additional functional examination methods are described in detail in Chapter 2.

Chapters 3, 4, and 5 describe the study results for the observed three patient groups, namely DRP, RVO, and UMO respectively. The results are discussed within the context of prior articles and research projects. The final chapter, Chapter 6, summarises the study's findings and then identifies the study's strengths and weakness, thereby providing guidance for further research.

Chapter 1. Background

1.1 Background

The human visual system is a complex structure that provides us with detailed information of our surroundings. The inner layers of the retina comprise a neural network that transduces light into electrical impulses. The retina as a whole consists the neurosensory retina (NR) and the retinal pigment epithelium (RPE). The RPE, also referred to as the nonsensory retina, is formed by a single layer of cells characterised by a large presence of melanin pigment in the cytoplasm. The neurosensory retina includes all layers of the retina from the photoreceptors to the ganglion cells. These layers, from the outer (RPE side) layers to the inner layers, are as follows:

- Photoreceptor layer – Formed by rods and cones.
- Outer nuclear layer – Formed by the cell nuclei of rods and cones.
- Outer plexiform layer – Formed by the synapses of bipolar cells between photoreceptors.
- Inner nuclear layer – Contains the nuclei of bipolar cells. Bipolar cells are the first neuron cells to receive and process the electrical stimulus from the photoreceptors. Bipolar cells transmit the stimulus to the ganglion cells.
- Inner plexiform layer – Formed of synapses connecting the bipolar, ganglion, and amacrine cells.
- Ganglion cell layer – Contains ganglion cells. Ganglion cells are the second neuron cells to receive and process impulses from the photoreceptors. Ganglion cells transmit the impulses to the thalamus.
- Nerve fibre layer – Formed by the ganglion cell axons. (Kanski and Milewski 2002)

At the centre of the retina is an anatomical structure called the macula. The macula's specific morphologic structure allows for maximal visual resolution (Kanski and Milewski 2002). Within the macula is a 1.5-mm-wide depressed area termed the fovea; the central pit of the fovea is termed the foveala. In the fovea, the photoreceptor layer is entirely cones. The fovea is accountable for maximal VA; hence, the macula is responsible for VA as well. The fovea

approximates to the foveal avascular zone. This zone is an area in the macula with absence of any blood vessels, which allows light to be perceived without dispersion or loss. Visual acuity (VA) thus declines rapidly as we move away from the centre of the macula and towards the periphery. For example, a shift of only 5º eccentricity leads to a 50% decrease in VA as compared with VA at the centre of the macula. As a result, any retinal disease which involves the macular area will result in severe vision deterioration and significantly impact vision-related quality of life.

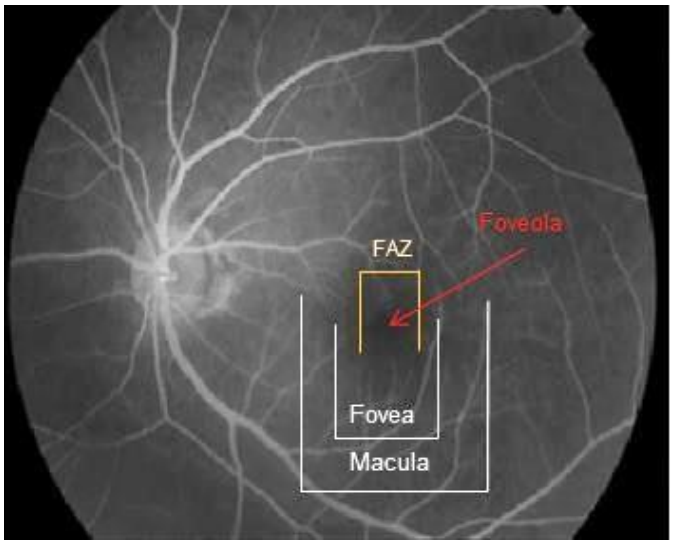


Figure 1- Anatomy of the macula

Fundus fluorescein image of a left eye showing anatomical location of macula, fovea, foveola, and foveal avascular zone (FAZ).

Source: Image acquired by author during research project.

For the purpose of this research project, a comprehensive online literature search of the MEDLINE database was conducted via PubMed. The search was based on the predefined inclusion and exclusion criteria presented in Table 1.

Inclusion criteria	
Population	Patients with macular oedema due to DRP, RVO, or uveitis
Interventions	Intravitreal injections, systemic immunomodulatory treatment, visual acuity, microperimetry, OCT, reading speed, VFQ-25
Outcomes	Clinical efficacy: • Retinal thickness • Visual acuity • Mean contrast sensitivity • Reading speed • VFQ-25 questionnaire
Study design	• Randomised controlled trials • Phase 1, 2, 3, and 4 studies • Prospective and retrospective studies • Reviews • Editorials • Notes • Opinions • Case reports
Search dates	From 15th January 2013 to 1st May 2019
Exclusion criteria	
Population	Patients with macular oedema due to causes other than DRP, RVO, and uveitis (e.g. trauma, intraocular surgery, vascular retinopathies, vitreoretinal traction syndrome, and hereditary retinal dystrophies)
Interventions	• Retinal laser photocoagulation • Investigational drugs and procedures
Outcomes	None
Search dates	From 15th January 2013 to 8th November 2018

Table 1- Selection criteria for published and unpublished studies

The methodology of the literature search is outlined in the flowchart shown in Figure 2.

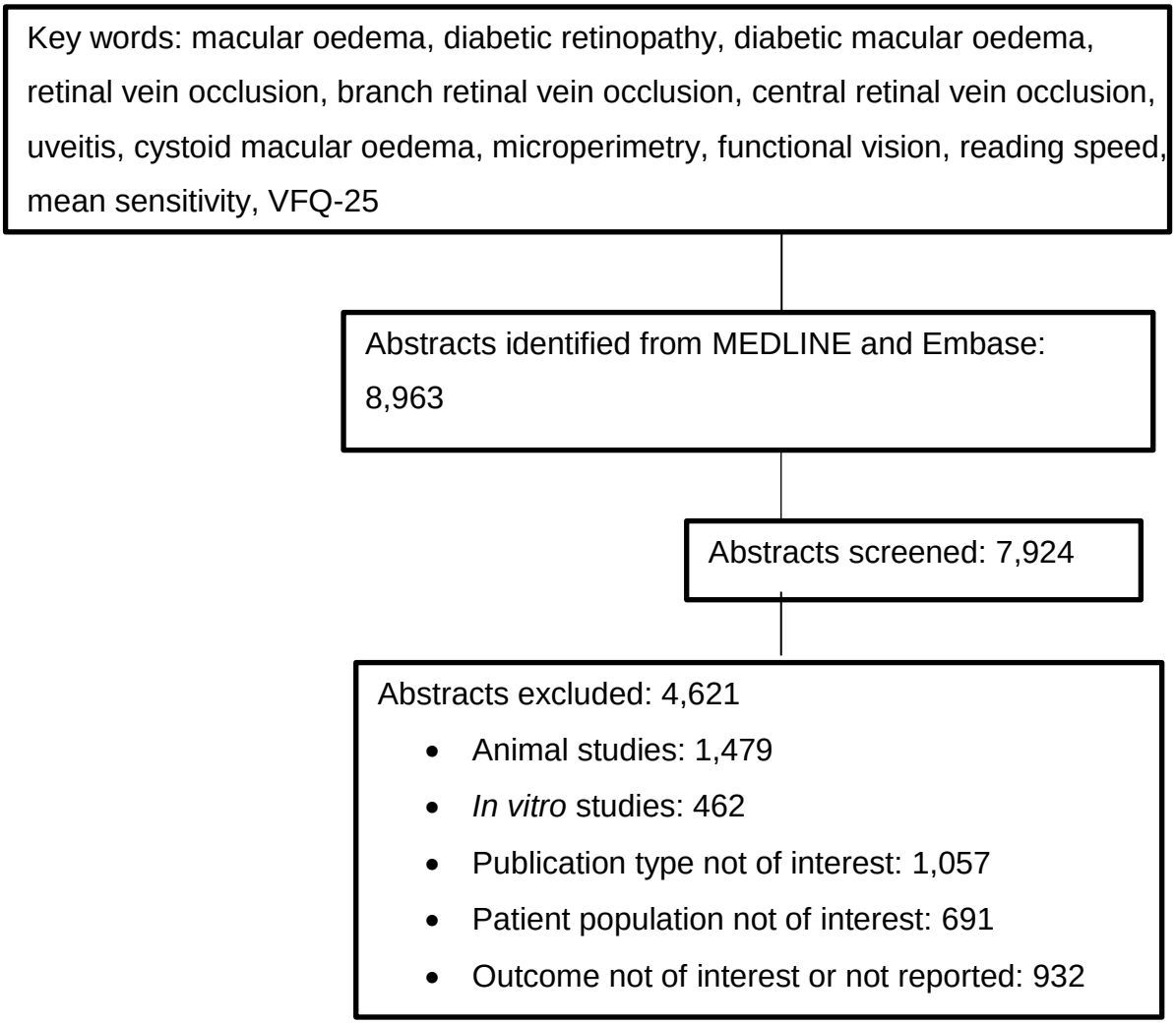


Figure 2- Summary of the reviewed published studies

1.2 Macular oedema: Definition and classification

The condition of fluid accumulation in the macula area is referred to as macular oedema (Coscas 2010). Clinically evaluated, it is a non-specific sign of many retinal pathologies including retinal vein occlusions, diabetic retinopathy, uveitis, trauma, intraocular surgery, vascular retinopathies, vitreoretinal traction syndrome, and hereditary retinal dystrophies (Coscas 2010). Despite advancement in therapeutic approach to retinal disease treatment in macular oedema remains one of the most common causes for vision loss amongst patients with retinal disorders (Ronald Klein et al. 2009; Browning, Stewart, and Lee 2018). There are several classifications of macular oedema based on histological, clinical, ophthalmoscopic, and angiographic findings.

The histological classification of macular oedema is based on the process of fluid accumulation in either the outer plexiform layer or the inner nuclear layer of the retina. This fluid accumulation is associated with the swelling of Muller cells. Muller cells are a type of glial cells; their main function is to maintain the structural and functional stability of retinal cells by regulating, for example, the extracellular environment, K+ levels, glycogen storage, and mechanical support of the neural retina. Macular oedema is thus histologically classified as either intracellular or extracellular oedema (Joussen, Smyth, and Niessen 2007). Intracellular oedema in the retina results in excessive accumulation of sodium ions (Na+) inside the cells and occurs when the blood–retinal barrier (BRB) is still intact. Extracellular oedema is associated with breakdown of the inner or outer BRB. The increased retinal extracellular space causes the macular volume to increase. Progression of extracellular macular oedema depends on the osmotic ($\Delta\pi$) and hydrostatic (ΔP) pressure gradients.

Clinical classification of macular oedema takes several factors into consideration: retinal thickness and duration; extent and distribution of fluid accumulation through the macula; involvement of central or paracentral retina; formation of intraretinal cysts; presence or absence of ischaemia; and active or passive vitreous tractions (Scholl, Kirchhof, and Augustin 2010). Retinal thickness varies throughout the retina, ranging from 251.9 µm to 327.7 µm (von Hanno et al. 2017).

The ophthalmoscopic classification is based on fundoscopic findings and divides macular oedema into two types: focal and diffuse.

- Focal macular oedema is characterised by the presence of localised areas of retinal thickening, derived from focal leakage of individual microaneurysms or clusters of microaneurysms.
- Diffuse macular oedema is derived from extensively damaged capillaries, microaneurysms, and arterioles. It is characterised by more widespread thickening of the macula (Bhagat et al. 2009).

Angiographic classification, based on fundus fluorescein angiography (FFA) findings, also classifies macular oedema into two types: cystoid and non-cystoid.

- Cystoid macular oedema is a process of capillary dilation and leakage which leads to fluorescein pooling in a petaloid pattern in the outer plexiform layer (Henle's layer) during the late angiography phases.
- Non-cystoid macular oedema is the presence of diffuse abnormal permeability of the retinal capillary bed with diffuse leakage. The intraretinal fluid does not accumulate in a cystoid pattern (Richard, Soubrane, and Yanuzzi 1998).

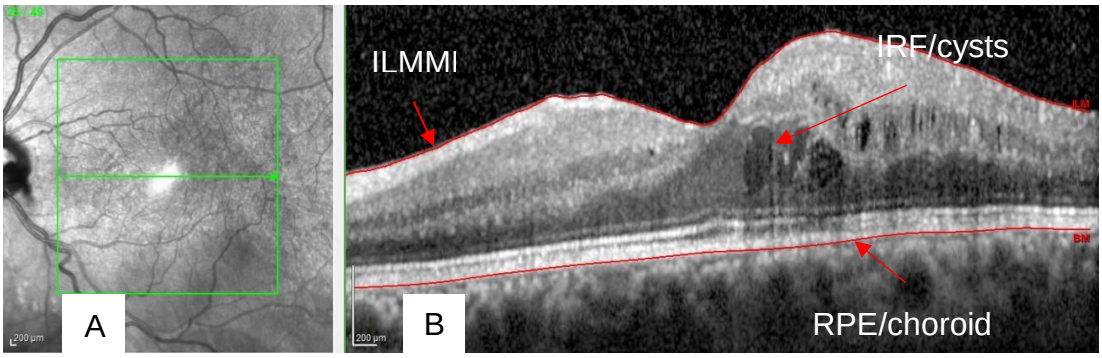


Figure 3- High-resolution spectral-domain optical coherence tomography image of a section through the fovea of the left eye of a study patient

Image A is an infrared image of the left eye with the location of the optical coherence tomography (OCT) scan outlined in green. The green arrow indicates the location of the OCT scan shown in Image B.

Image B is the OCT B-scan of the left eye in the location shown in Image A. The lower red line is the internal limiting membrane. The upper red line is the retinal pigment epithelium/choroid boundary. The image shows intraretinal fluid with cystoid formations.

Abbreviations: **ILMMI** = internal limiting membrane interface; **IRF** = intraretinal fluid; **RPE** = retinal pigment epithelium

Source: Images acquired by the author during the research project.

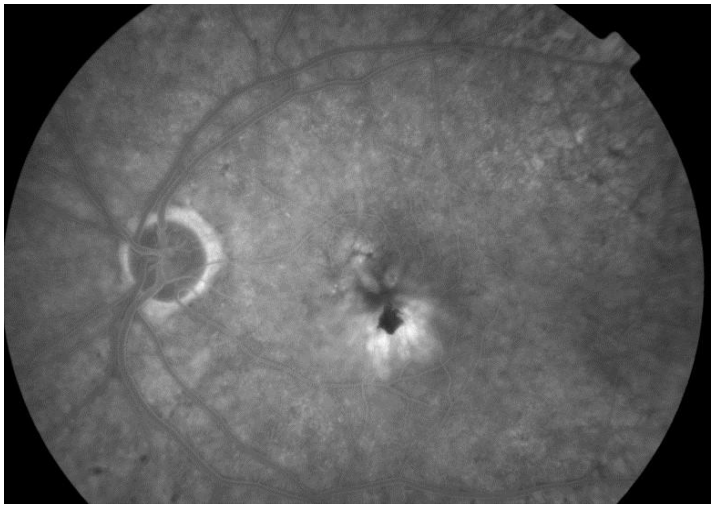


Figure 4- Fundus fluorescein angiography cystoid macular oedema

The image shows late-phase fundus fluorescein angiography with fluorescein staining and cystoid formation of the macula appearing in typical petaloid shape.

Source: Image acquired by author during research project.

1.3 Pathophysiology of macular oedema

The pathophysiology of MO is described as a fluid accumulation in the inner nuclear and outer plexiform layer in the macula area (Cunha-Vaz et al. 2014). This fluid accumulation may lead to rapid visual reduction by altering intraretinal cellular connections. Retinal oedema has a complex nature with many factors contributing to its development.

1.3.1 Pathophysiology of macular oedema: Vascular component

The vascular factor is composed of two barriers: the inner and the outer blood–retinal barriers (BRBs). The first barrier is a functional limit created by tight junctions (zonula occludens) between the endothelial cells lining the retinal vessels. The following barrier results from tight junctions between the retinal pigment epithelium (RPE), or the zonula adherence, and desmosomes (Scholl, Kirchhof, and Augustin 2010). These two BRBs impede free fluid diffusion into the extracellular space in the retina and maintain a stable

environment for normal ocular cell functioning. Disruption of either of the two BRBs causes oedema formation. As a result, osmotic pressure increases and water diffusion becomes continuous. In other words, disruptions in the balance between the capillary filtration rate and the fluid elimination in the extracellular retinal space cause imbalances in osmotic and hydrostatic forces (Cunha-Vaz 2017).

1.3.2 Pathophysiology of macular oedema: Inflammatory component

Many inflammatory mediators and inflammatory cells play a crucial role in the development of inflammatory MO. The identified factors are Angiotensin II, vascular endothelial growth factors (VEGF), prostaglandins, cytokines and chemokines, matrix metalloproteinases, interleukins, P-selectin, E-selectin, vascular adhesion molecule 1, and intercellular adhesion molecule 1. Inflammatory mediators lead to a failure of BRB functioning that results in leukocytes infiltration, increased vascular permeability, extracellular remodelling of the extracellular space, and dysfunction of the endothelial cells (Fardeau et al. 2016).

1.3.3 Ischemia in the pathophysiology of macular oedema

Low levels of oxygen/ischaemia play an essential role in the development of MO. Adenosine triphosphatase synthesis in retinal neuronal cells is very high. In addition, the uptake of metabolic substrates like glucose leads to increased intracellular water levels. This excess water is cleared into the blood, cerebrospinal fluid, or vitreous via Aquaporin 4 water channels. These channels are osmotically connected to Na^+/K^+ gradients across the membranes of retinal neurons, namely glial cells. However, in the hypoxic conditions present with ischaemia, these connections are disrupted. As a result, intracellular sodium and potassium concentrations increase, and the osmotic gradient, in turn, draws water into the cells (Wu et al. 2018; Kusuhara et al. 2018; Widemann et al. 2004). Further types of molecules or ions might be contributing to MO formation, but the detailed pathogenesis is not understood yet.

1.4 Diabetic macular oedema

The definition of clinically significant macular oedema (CSME) was first given in 1985 by the Early Treatment Diabetic Retinopathy Study (ETDRS). CSME includes any of the following features:

- Thickening of the retina at or within 500 µm of the centre of the macula.
- Hard exudates at or within 500 µm of the centre of the macula, if associated with thickening of the adjacent retina.
- A zone or zones of retinal thickening 1-disc diameter from the centre of the macula. (Ghanchi 2012)

CSME is further defined by the ETDRS as describing the disease severity and thereby giving an advantage to retinal laser photocoagulation treatment (“Photocoagulation for Diabetic Macular Edema. Early Treatment Diabetic Retinopathy Study Report Number 1. Early Treatment Diabetic Retinopathy Study Research Group” 1985).

1.4.1 Epidemiology and risk factors for diabetic macular oedema

Diabetes is among the leading causes of death, disability, and economic loss worldwide (Tunstall-Pedoe 2006, 2006; “The Global Burden” n.d.). About 150 million people worldwide suffer from diabetes, and this number is expected to double by 2025 if extensive changes in nutrition status and disease prevalence do not occur (Tunstall-Pedoe 2006). For developing countries, a 40% increase in the number of patients, especially in the working age group (40–59), has been predicted (“The Global Burden” 2013).. Diabetic retinopathy (DRP) is the 5th most common cause for blindness worldwide (WHO 2006), and amongst the diabetic population, MO is the most common cause of visual acuity loss (Klein et al. 2000).

Large studies such as the Wisconsin Epidemiologic Study of Diabetic Retinopathy (n.d.) and the United Kingdom Prospective Diabetes Study (Stratton et al. 2001) have reported the following as risk factors for the occurrence and progression of diabetic macular oedema (DMO): duration of the diabetes, degree of metabolic control, elevated glycosylate

haemoglobin A1c, severity of diabetic retinopathy, hypertension, low socioeconomic status, older age, dyslipidaemia, microalbuminuria, and proteinuria. In addition, the rate of DMO development within 10 years was reported to be 20.1% for type I diabetes patients, 13.9% for non-insulin-using type II patients, and 25.4% for insulin-using type II patients (Klein et al. 2009). The United Kingdom Prospective Diabetic Study further reported that though 63% of the diabetic participants showed no signs of DRP, 37% of participants nonetheless had retinopathy, and 29% of participants showed disease progression (Stratton et al. 2001). Furthermore, in this same study, 22% of the patients without retinopathy had developed it within 6 years (Stratton et al. 2001). DMO has been reported to occur in about 14% of both type I and type II diabetic patients, with significant correlation between the number of retinal microaneurysms and the duration of the disease (Girach and Lund-Andersen 2007). Another study (The Los Angeles Latino Eye Study Group) described the difference in the prevalence of MO amongst various ethnic groups. The study reported that among diabetic Chinese, 25.7% had DRP and 8.9% had MO; among diabetic Caucasians, 24.8% had DRP and 2.7% had MO; among diabetic African Americans, 36.7% had DRP and 11.1% had MO; and among diabetic Hispanics, 37.4% had DRP and 10.7% had MO (Varma et al. 2004).

1.4.2 Pathophysiological mechanism of diabetic macular oedema

Many studies have described the disruption of the inner BRB as the key point at which DMO develops. The vasodegenerative aspect of DRP presents in loss of pericytes, basement membrane thickening, dropout of the microvascular smooth muscles, formation of microaneurysms, accumulation of lipoprotein exudates, and capillary closure (Adamis and Berman 2008). These pathological changes in the retinal vessels lead to continuous vascular leakage and MO formation. Additionally, ischaemic retinas produce numerous factors such as vascular endothelial growth factor (VEGF), nitric oxide, eicosanoid, lipids, cytokines, chemokines, angiotensin II, and disruptions in the renin–angiotensin system; these factors encourage formation of new vessels as the retinas work to overcome hypoxia (Adamis and Berman 2008; El-Asrar et al. 2013). However, the newly formed vessels are unable to cope with the flow of nutrients and only increase the risk of significant visual loss due to intravitreal haemorrhages, retinal fibrosis, or tractional retinal detachment (Adamis and Berman 2008). Some studies have shed light on the varied neuroretinal dysfunctions

that can occur in patients with DRP (David et al. 1988; Simó, Stitt, and Gardner 2018). For example, colour vision loss, contrast sensitivity deterioration, and electroretinogram abnormalities have been documented in patients in the early stages of DRP even before vascular retinopathy becomes clinically evident (Roy, Gunkel, and Podgor 1986; Sokol et al. 1985; Yonemura et al.1962; Romero-Aroca et al. 2016; Kusuhara et al. 2018; Kwon and Jee 2018). In short, many factors contribute to the development of DMO, and its complex nature is not fully understood.

1.4.3 Diagnosis of diabetic macular oedema

In the initial stages of diabetic retinopathy (DRP), patients are generally asymptomatic. As the disease progresses, patients may experience symptoms such as floaters, blurred vision, distortion, and progressive visual acuity loss. Routine ophthalmic examinations can reveal microaneurysms, dot-and-blot haemorrhages, flame-shaped haemorrhages, and oedema and hard exudates. Over time, more prominent signs emerge such as cotton wool spots, venous loops and venous beading, intraretinal microvascular abnormalities, and retinal oedema. These clinical signs indicate the progressive retinal damage that occurs in patients with DRP before new vessel formation. The neovascularisation of the retina is the landmark of proliferative diabetic retinopathy (PDR). Clinically, PDR presents with preretinal and intravitreal haemorrhages, fibrovascular tissue proliferation, and tractional retinal detachments. Untreated DRP causes severe irreversible changes in the retina and may lead to complete blindness. Thus, good screening coverage for patients with diabetes is essential for early diagnosis and prevention of visual loss.

The precise clinical evaluation of DMO can be achieved by using modern imaging techniques like fundus fluorescein angiography (FFA) and optical coherence tomography (OCT). Nowadays, OCT is widely use in daily clinical settings; it is a quick and non-invasive procedure that can visualise intraretinal fluid-filled spaces and quantify the involved area in the macula (Antcliff et al. 2000). However, the gold standard for the diagnosis of MO remains FFA (Böker et al. 2018; Rencová 2010; Levin et al. 2017; Franco-Cardenas et al.

2017; Richard, Soubrane, and Yanuzzi 1998). In this technique, intravenously injected sodium fluorescein and a specialised blue light (490 nm) fundus camera identify any alterations in the blood circulation of the retina and choroid. Incomplete vessels start leaking and cause intraretinal fluid accumulation; the fluorescein can penetrate these oedematous retinal areas and show the macular oedema in the FFA image. However, the FFA technique currently constitutes a qualitative assessment of the retinal vascular system. Fluorescein penetration into the surrounding retina does not necessarily indicate retinal thickening, hence does not necessarily mean presence of MO. Of all the patients who present macular thickening and homogenous intraretinal optical reflectivity in the OCT image, only 60% show detectable leakage in the FFA image (Antcliff et al. 2000). In addition, about 90% of patients with diffuse cystoid leakage present foveal thickening in the OCT image (Kang, Park, and Ham 2004). Therefore, the most effective detection and description of MO requires both methods – the quantitative (OCT) and the qualitative (FFA) methods.

A

B

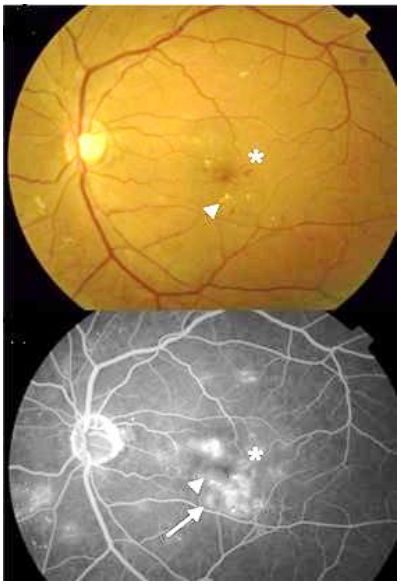


Figure 5- Diabetic macular oedema

Image A is a colour fundus image of a left eye with non-proliferative diabetic retinopathy. The asterisk indicates perifoveal retinal haemorrhages. The triangle indicates hard exudates.

Image B is a fluorescein angiography of a left eye. The asterisk indicates blocked fluorescence due to haemorrhages. The triangle indicates mild perifoveal leakage. The arrow points to micro-aneurysms.

Source: Image acquired by author during research project.

1.4.4 Treatment of diabetic macular oedema

The clinical treatment of MO is based on current understanding of how to inhibit the pathophysiological mechanisms. The two main non-surgical categories for DMO treatment are retinal laser photocoagulation and pharmacological approaches such as systemic steroids, long-acting intravitreal steroids, and anti-VEGF intravitreal medicines.

Retinal photocoagulation was developed in the 1940s. Since its introduction, the technique has evolved immensely as a treatment for MO. The current diabetic retinopathy guidelines (dated December 2012) of the Royal College of Ophthalmologists present clear evidence supporting the benefits of retinal photocoagulation versus no treatment. Photocoagulation

reduces the risk of VA loss and works over long timescale; recovery of VA, in comparison with proactive prevention of VA loss, is more difficult to achieve (Ghanchi 2012). The standard guidelines for focal laser photocoagulation for DMO have been further supported by the findings of the”ETDRS (“Photocoagulation for Diabetic Macular Edema. Early Treatment Diabetic Retinopathy Study Report Number 1. Early Treatment Diabetic Retinopathy Study Research Group” 1985). Focal laser photocoagulation has been recommended as a direct treatment to leaking microaneurysms. Grid laser photocoagulation has been suggested for cases of diffuse macular oedema or non-perfused thickened retina. Scatter laser photocoagulation and focal laser photocoagulation have been suggested for DMO in cases of severe NPDR and for eyes with PDR.

One theory regarding the effectiveness of laser photocoagulation in resolving DMO highlights the laser-induced destruction of oxygen-consuming photoreceptors. Another theory suggests that laser photocoagulation may enable the restoration of a damaged retinal pigment epithelium barrier (Park, Kim, and Roh 2014; Relhan and Flynn 2017; Romero-Aroca 2010; Park, Kim, and Roh 2014). At the same time, this type of DMO treatment is associated with complications such as choroidal neovascularisation, full-thickness retinal breaks, subretinal fibrosis, and visual field defects. In addition, even after photocoagulation, symptomatic paracentral scotomas still remain and may affect patients’ vision-related quality of life. For these reasons, the therapeutic approach to addressing DMO has changed, and clinicians have been prompted to seek more effective therapeutic options like intravitreal triamcinolone acetonide (IVTA) (X. Zhang et al. 2008; Barham et al. 2017; Park, Kim, and Roh 2014). The Diabetic Retinopathy Clinical research group reported a 2-year trial comparing preservative-free intravitreal Triamcinolone and focal/grid laser photocoagulation for DME (Sivaprasad et al. 2010). This report has led clinicians to focus on using less harmful methods such as intravitreal injections.

Current treatments using anti-VEGF with prompt or delayed laser treatment are considered to be the most effective treatments for preserving and restoring vision in patients with DMO (Barham et al. 2017; Moisseiev and Loewenstein 2017; Radda et al. 2019). This statement is supported by the evidence that VEGF levels are elevated in the vitreous and retinas of patients with diabetic retinopathy (Zubair and Ahmad 2019). Pegaptanib (Macugen) was the

first anti-VEGF treatment (specific to the 165 isoform of VEGF-A) to show a favourable effect on DMO (Takamura 2014; Tomić et al. 2017).

Ranibizumab (Lucentis) was the second approved anti-VEGF medicine. The few studies demonstrating the efficacy of combined ranibizumab and laser treatment are as follows:

- The READ-2 study (Ranibizumab for Edema of the mAcula in Diabetes) compared the effect of 0.5 mg intravitreal ranibizumab versus laser photocoagulation versus combined ranibizumab and laser photocoagulation in treatment-naive eyes (Nguyen et al. 2010, 2009; Do et al. 2013).

- The RESOLVE ("Safety and efficacy of ranibizumab in diabetic macular edema") study was a randomised controlled double-masked study evaluating the safety and efficacy of ranibizumab in the treatment of DMO at 12 months (Massin et al. 2010)

- The RESTORE study was a phase III, randomised, double-masked, multicentre trial study evaluating the efficacy and safety of ranibizumab in patients with visual impairment due to DMO (Mitchell et al. 2011).

- The RISE and RIDE studies in the USA evaluated the efficacy of ranibizumab in diabetic macular oedema (Nguyen et al. 2012).

- The DRCR.net study was published comparing 0.5 mg intravitreal ranibizumab with prompt focal/grid laser photocoagulation, 0.5 mg ranibizumab with deferred laser photocoagulation (at least 24 weeks later), 4 mg intravitreal triamcinolone with prompt laser, and sham injections with prompt laser (Cai and Bressler 2017; Bressler n.d.).

Ranibizumab is licensed in the EU for the treatment of centre-involving DMO. NICE recommends ranibizumab as an option for treating eyes with DMO in patients with central retinal thickness greater than 400 µm in OCT ("Diabetic Retinopathy Guidelines" 2013).

Bevacizumab is not licensed for intraocular use in the UK, but it has been extensively used for the treatment of retinal vascular pathology. Several clinical trials have been conducted

with various treatment doses/regimes and comparison groups with short follow-ups (Yilmaz et al. 2011; Goyal, Lavalley, and Subramanian 2011).

- The BOLT study is a prospective randomised trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular oedema comparing bevacizumab to laser treatment (Michaelides et al. 2010).

- The Pan-American Collaborative Retina Study Group (PACORES) reported a retrospective case series of the 2-year outcomes for bevacizumab for diffuse DMO (Poku et al. 2014).

Presently, no reported data directly compares the efficacy of ranibizumab with that of bevacizumab in diabetic macular oedema.

Another anti-VEGF medicine is Aflibercept (VEGFTrap-Eye). It is a soluble VEGF receptor fusion protein that binds to all isoforms of VEGF-A and placental growth factor. Two studies, the VIVID DME and the VISTA DME, were conducted to measure the efficacy of aflibercept in treating diabetic retinopathy. Both studies reported statistically significant reduction in the mean central retinal thickness from baseline to week 52 in patients treated with aflibercept than with the laser control. Specifically, the VIVID DME and VISTA DME studies found -192.4 and -183.1 microns for the 2Q8 arm aflibercept groups and -66.2 and -73.3 microns for the control groups respectively. At week 100, the decrease in mean central retinal thickness was maintained with -195.8 and -191.1 microns for the 2Q8 arm aflibercept groups and -85.7 and -83.9 microns for the control groups in the VIVID DME and VISTA DME studies respectively (“Eylea 40mg/Ml Solution for Injection in a Vial - Summary of Product Characteristics (SmPC) - (EMC)” n.d.).

Several trials have shown the benefits of IVTA (Aksoy et al. 2015; Castro-Navarro et al. 2019; Ichio, Sugimoto, and Kondo 2016; Liu et al. 2015; Sonoda et al. 2014; Watanabe et al. 2016; Zając-Pytrus et al. 2017). Corticosteroids have been shown to increase the resorption of fluid through the RPE, lessen the production of VEGF, inhibit leucocyte–endothelial interaction in the retina, and downregulate adhesion molecules of the retinal vascular endothelium (Cohen and Gardner 2016; Ung, Borkar, and Young 2017). Despite these findings, in long-term use, intravitreal corticosteroids can cause several side effects such us

cataract formation, high IOP, endophthalmitis, and pseudo endophthalmitis (Castro-Navarro et al. 2019; Wang et al. 2015; Zhang et al. 2008; Leal et al. 2007).

Novel clinical trials have demonstrated that both anti-VEGF and steroid agents appear to be superior to conventional laser photocoagulation. As laser burns tend to induce paracentral visual field defects, anti-VEGFs are becoming more extensively used (Striph, Hart, and Olk 1988; Çeliker, Erdağı Bulut, and Şahin 2017; Vujosevic et al. 2010). Anti-VEGF agents and intravitreal steroids have made an enormous difference to patients' visual outcomes after treatment for DMO. Nevertheless, there is no better treatment than laser photocoagulation in cases with retinal neovascularisation (Alasil and Waheed 2014; Sebag and Nguyen-Cuu 2017; Ambresin, Strueven, and Pournaras 2015). The best treatment regimen and patients' response to treatment in the end remain unclear. It is likely that multimodality therapy will play an increasingly important role in the future (Au and Singh 2016).

1.5 Macular oedema in patients with retinal vein occlusion

The pathological condition in the retinal vasculature characterised by obstruction of the retinal venous system by thrombus formation, external compression, or a disease of the vein wall like vasculitis is defined as retinal vein occlusion (RVO) (Denniston and Murray 2013). RVO may involve the central retinal vein (in the case of CRVO) or a branch of the retinal veins (in the case of BRVO) (Green et al. 1981; Spencer and American Academy of Ophthalmology 1985; Frangieh et al. 1982).

1.5.1 Epidemiology and risk factors for retinal vein occlusions

After diabetic retinopathy, RVO has been identified as the second most common cause of reduced vision due to retinal vascular disease (Jaulim et al. 2013; Ip and Hendrick 2018). It has been established that BRVOs occur 2–3 times more often than CRVOs (Green et al. 1981; Spencer and American Academy of Ophthalmology 1985). The current estimates for the prevalence of RVO are derived from large population-based studies such as the Blue

Mountains Eye Study and the Beaver Dam Eye Study and from the combined analysis of the Atherosclerosis Risk in Communities and Cardiovascular Health Studies, which put the prevalence rate of RVO worldwide at 14–19 million (Klein et al. 2000; Mitchell, Smith, and Chang 1996; Wong et al. 2005). A later study reported a prevalence rate per 1,000 persons of 4.42 for BRVO and 0.80 for CRVO (Rogers et al. 2010). The most prevalent risk factor for RVO is hypertension, with up to 64% of RVO patients over the age of 50 exhibiting hypertension ("Risk Factors for Branch Retinal Vein Occlusion" 1993). Another risk factor is hyperlipidaemia, with up to 50% of RVO patients over the age of 50 exhibiting it (Dodson et al. 1982). Furthermore, haematological conditions (e.g. antiphospholipid antibody syndrome, hyperhomocysteinaemia, and myeloproliferative disorders) have also correlated with RVO (Dodson et al. 1982; Bucciarelli et al. 2017; Jaulim et al. 2013; Ponto et al. 2015).

1.5.2 Classification of retinal vein occlusions

According to its anatomical location, RVO is separated into one of two classifications. (1) If the presumed site of the increased venous outflow resistance is located in or behind the lamina cribrosa, and if the entire venous retinal system is involved, RVO is classified as CRVO. (2) If the venous engorgement involves only branches of the retinal venous network, RVO is classified as BRVO. Occlusion of the hemicentral retinal vein is recognised as a variant of CRVO; in this case, the presumed site of the occlusion is one trunk of the intraneural central retinal veins (Brown et al. 2010; Green et al. 1981; "Risk Factors for Central Retinal Vein Occlusion" 1996). In turn, based on the oxygen levels in the retina, CRVOs are subdivided into two types: non-ischaemic and ischaemic. Non-ischaemic CRVOs are the milder form and have good visual outcomes; they may resolve fully or may progress to ischaemic CRVOs. Ischaemic CRVOs present with severe ischaemia, neovascularisation, and irreversible visual loss ("A Randomized Clinical Trial of Early Panretinal Photocoagulation for Ischemic Central Vein Occlusion" 1995). The types of retinal vein occlusions are summarised in Figure 6.

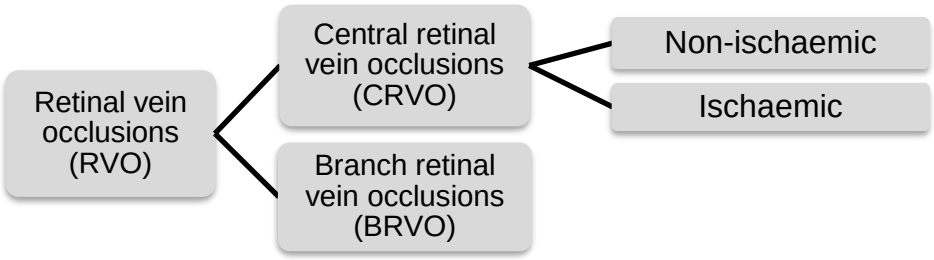


Figure 6- Types of retinal vein occlusions

1.5.3 Specific pathophysiological mechanisms in the development of macular oedema in retinal vein occlusions

Several factors are thought to play a key role in the pathogenesis of thrombotic occlusion in CRVO. Constricted positioning of the central retinal artery and vein in the narrow entry of the lamina cribrosa is thought to be one of the predisposing factors for CRVO. Changes in the blood, slowing of the blood stream, and changes in the blood vessel wall can also contribute to the development of CRVO. In addition, arteriosclerotic changes in the central retinal artery can cause endothelial cell damage, haemodynamic changes, and thrombus formation. CRVO development has also been attributed to the development of a variety of pathological insults at this location, such as glaucoma, inflammation, vasculitis, haemodynamic changes, and increased blood clotting factors (Rothman et al. 2018; Hayreh et al. 2001; Ota et al. 2008; Kolar 2014).

It was postulated that the development of MO due to BRVO can be explained by way of Starling's Law, which concerns the balance between the two types of force that move water in the body (i.e. hydrostatic and osmotic pressure gradients). Per Starling's Law, all fluid change between blood vessels and tissue and the formation and disappearance of oedema can be described as follows:

$FP=(HP\ c - HPif\ ) - (\pi c - \pi\ if),$

$FP=(HPc - HPif) - (\pi c - \pi\ if),$

where FP is the net filtration pressure, HP c is the hydrostatic pressure in the capillary, and HPif is the hydrostatic pressure of the interstitial fluid. The law explains that reduced intravascular pressure in the capillaries and venules will reduce the net filtration pressure and the fluid change into the tissue and hence reduce oedema (Arnarsson and Stefánsson 2000a).

In the pathogenesis of MO in BRVO, Starling's law is based on the breakdown of the blood–retinal barrier (BRB) as a result of damage to the tight junctions of capillary endothelial cells, vitreoretinal adhesion, and secretion into the vitreous of vasopermeable factors produced in the retina (Silva, Faria de Abreu, and Cunha-Vaz 1995; Saika et al. 2001; Aiello et al. 1994; Noma et al. 2006). At the points of arterio-venous crossings, the artery can compress the underlying vein. Thus, in addition to the pre-existing endothelial cell damage, haemodynamic changes such as turbulent blood flow increase the chance of thrombus formation. Once the venous flow is interrupted, fluid moves from the vessels into the retinal tissue (Pe'er et al. 1995). This process depends on the BRB breakdown, the presence and intensity of vitreoretinal adhesion, and the introduction of vasopermeable factors produced by the retina into the vitreous (Arnarsson and Stefánsson 2000b; Stefánsson 2001; Cunha-Vaz 2017; Saika et al. 2001; Aiello et al. 1994; Noma et al. 2006). Notably, Rehak et al. (2009) reported that there is down-regulation of potassium and water channels in Müller cells. Such down-regulation would contribute further to intraretinal fluid accumulation and development of macular oedema.

1.5.4 Clinical presentation of retinal vein occlusions

The early phases of RVO have several characteristic signs. These signs include flame-shaped intraretinal haemorrhages and, in the involved area, cotton wool spots and retinal oedemas. In CRVO, these signs appear in all four quadrants of the retina. In BRVO, retinal changes typically do not cross the horizontal demarcation line. Most RVO patients complain of visual acuity deterioration and visual field loss.

1.5.5 Complications of retinal vein occlusions

Common complaints of patients with RVOs are decreased eyesight and visual field defects. The VA at the time of the disease presentation has been shown to be a strong indicator for prognosis. About 50% of non-treated eyes with BRVO maintain 6/12 vision or better, and 25% of non-treated eyes will have a terminal vision of 6/60 or worse ("Retinal Vein Occlusion (RVO) Guidelines" 2015). In about 20% of RVO cases, neovascularisation can occur the first 6-12 months, depending on the affected area (Coscas et al. 2011). In patients with CRVO, the VA remains lower than 6/60 in 80% of the cases, and more than 44% of patients will develop neovascularisation ("A Randomized Clinical Trial of Early Panretinal Photocoagulation for Ischemic Central Vein Occlusion" 1995). The worst VA outcome tends to appear in cases with ischemic CRVO (Coscas et al. 2011). It has also been reported that one third of perfuse (non-ischaemic) CRVOs if left untreated are likely to convert to non-perfused (ischaemic) CRVOs (McIntosh et al. 2010a; Fukutomi et al. 2018; Dodson, Kritzinger, and Clough 1992). Pathological new vessel formation can appear in 20% of non-perfused CRVOs, and 60% of those cases are likely thereafter to develop neovascular glaucoma and haemorrhages (McIntosh et al. 2010). In comparison with the aforementioned complications, which tend to emerge only in the long term, the typical complications of RVO with involvement of the macula include MO, macular non-perfusion, and vitreous haemorrhages. About 5 to 15% of eyes with RVO can develop MO, but 18 to 40% of those MO cases may show some resolution (Daruich et al. 2018; McIntosh et al. 2010a). Alongside those changes it is quite common to observe visual field loss in patients with RVO. Visual field results can provide clues regarding the location of the anomaly in the retina. RVO is typically accompanied by correlating functional defects in the visual field (Phu et al. 2017). The depth of the defect may depend on a range of factors, such as the extent of the underlying structural loss and the duration since onset.

In summary, the range of RVO complications includes vision loss, visual field changes, MO, vitreous haemorrhage, rubeosis iridis, and neovascular glaucoma (McIntosh et al. 2010a).

1.5.6 Diagnosis of macular oedema in retinal vein occlusions

The most frequently used, non-invasive technique for MO detection is OCT (Fercher et al. 2003). It provides visualisation of the retinal morphology and allows qualitative evaluation of any changes in retinal thickness. The outcome of MO can be either persistent fluid accumulation and intraretinal cyst formation or resolution by causing retinal neurosensory atrophy with irregularities of the pigment epithelium (McIntosh et al. 2010). In order to predict long-term visual outcomes in RVOs, it is of high importance to identify any ischaemia. Although the diagnosis of RVO can be made by retinal ophthalmoscopy, in some cases the differentiation between ischemic and non-ischemic RVO requires performing a fundus fluorescein angiogram (Battaglia Parodi and Bandello 2009). Besides the typical signs of vein occlusion, such as the delay in venous filling, a fundus fluorescein angiogram provides information about the ischaemic area and neovascular formation ("Argon Laser Photocoagulation for Macular Edema in Branch Vein Occlusion" 1984; Janssen et al. 2005).

1.5.7 Treatment of macular oedema in retinal vein occlusions

In 2015, the Royal College of Ophthalmologists updated the clinical guidelines for RVO treatment. A summary of the treatment algorithm for CRVO and BRVO is presented in Figures 7 and 8 respectively ("Retinal-Vein-Occlusion-RVO-Guidelines-July-2015.Pdf" n.d.).

CRVO treatment

Treatment of risk factors
Ophthalmic management

Ischaemic

- If NVI/NVA occurs and the anterior chamber angle is open, urgent PRP is recommended. PRP plus off-license intravitreal bevacizumab can be repeated if NVI/NVA persists.

- If NVI/NVA occurs and the anterior chamber angle is closed and intraocular pressure is raised, urgent PRP with cyclodiode laser therapy / tube shunt surgery is recommended.

Non-ischaemic

If no NVI/NVA occurs and OCT shows evidenc of MO, the following is recommended:

- If VA is ≥6/96, start on either intravitreal anti-VEGF or Ozurdex implant therapy
- If VA < 6/96, offer treatment and monitor patient for NVI/NVA.
- If VA ≥6/12, observe as spontaneous resolution is likely.

Figure 7- Current treatment algorithm for CRVO

Abbreviations: **NVI** = neovascularisation of the iris, **NVA** = neovascularisation of the angle, **MO** = macular oedema, **VA** = visual acuity, **PRP** = panretinal photocoagulation

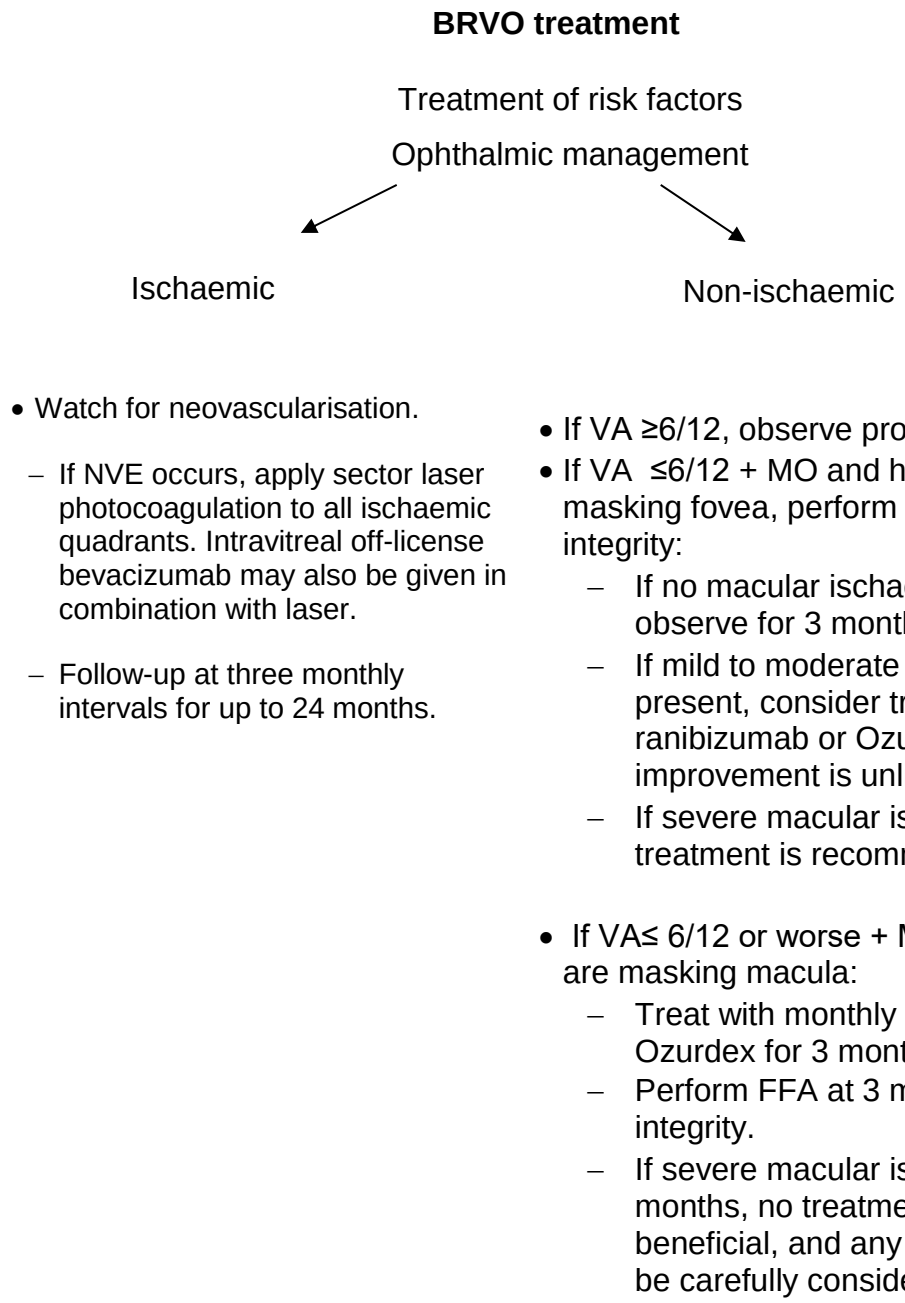


Figure 8- Current treatment algorithm for BRVO

Abbreviations: **NVI** = neovascularisation of the iris, **NVA** = neovascularisation of the angle, **NVE** = new vessels elsewhere, **MO** = macular oedema, **VA** = visual acuity, **PRP** = panretinal photocoagulation, **FFA** = fundus fluorescein angiography

In recent years, the therapeutic strategy has focused on the inflammatory and ischaemic components of macular oedema development by targeting vascular permeability and leaking

vessels (Scholl, Kirchhof, and Augustin 2010; Coscas, Cunha-Vaz, and Soubrane 2017; Beck et al. 2018). Corticosteroids are one of the main pharmaceutical medications currently in use to treat macular oedema in RVO (Ho et al. 2016). They are thought to act by induction of lipocortins, or phospholipase A inhibitor proteins. It is believed that these proteins control the biosynthesis of prostaglandins and leukotrienes, which are potent inflammatory mediators, by inhibiting the common precursor of arachidonic acid. Corticosteroids have also been shown to reduce levels of vascular endothelial growth factor. Amongst corticosteroids, triamcinolone acetonide, dexamethasone, and fluocinolone have shown potential to reduce oedema in RVO (Ip et al. 2009; Zhang et al. 2008; Haller, Bandello, Belfort Jr., et al. 2010; Qian, Zhao, and Xu 2017; Feltgen and Pielen 2015). Nevertheless, their disadvantages are well known and include side effects such as raised intraocular pressure and cataract progression. The triamcinolone acetonide is commercially available as Kenalog (Kenalog, 40 mg/ml; Bristol-Meyers Squibb, Princeton, NJ), which has been used for a long time as an off-label option. Ozurdex, a more potent and water-soluble version, was developed as a slow-release dexamethasone intraocular implant (Allergan Inc., Irvine, California). This option was the first dexamethasone implant for intraocular use approved by the Food and Drug Administration (FDA). Ozurdex shows anti-inflammatory and anti-oedematous effects for a period up to 6 months. It is currently licensed not only for treatment of macular oedema related to RVO, but also for diabetic macular oedema and uveitis-related macular oedema. The latest developed corticosteroid implant is fluocinolone acetonide – Iluvein (Alimera Science). The novelty of this implant is that it releases 0.2 micrograms per day of the total 190 micrograms of fluocinolone acetonide, hence the therapeutic effect lasts for approximately 36 months (Cunha-Vaz et al. 2014). Selected clinical trials presenting treatment efficacy are summarised in Table 2 (Bradshaw et al. 2016).

Study	Method	Mean BCVA change (ETDRS/LogMAR)	Mean CMT change (*μ*m)
Campochiaro et al. (2015) – ORVO	Dexamethasone 0.7 mg (all patients treated with anti-VEGF) (N=17)	4 weeks: +5.8 (ETDRS) 16 weeks: +5.8	4 weeks: −153 16 weeks: −60
Haller et al. (2010) – GENEVA	Dexamethasone 0.35 mg/0.7 mg (N=208) Dexamethasone 0.7 mg/0.7 mg (N=227) Sham/0.7 mg (0–6 months/6–12 months) (N=210)	60 days: +10.2 (ETDRS) 180 days: +6.1 60 days: +10.1 180 days: +6.2 360 days: +6.3 60 days: +4.7 180 days: +3.8 360 days: +6.1	180 days: −103 360 days: −163 180 days: −97 360 days: −166 180 days: −102 360 days: −170
Bezatis et al. (2013) – SOLO	Dexamethasone 0.7 mg (N=54)	8 weeks: +0.3 (LogMAR) 24 weeks: +0.15	8 weeks: −214 24 weeks: −107
“SCORE Study Results | National Eye Institute” (n.d.)	Triamcinolone 1 mg Triamcinolone 4 mg Standard care (N=137)	+5.7 (ETDRS) +4 4.2	+5.7 (ETDRS) +4 4.2
Asano et al. (2007)*	T: Sub-tenon triamcinolone injection C: No sub-tenon triamcinolone injection	Mean baseline BCVA: 2 weeks before injection: 0.501 (0.229) vs. 0.510 (0.141) Mean BCVA at: 1 month: 0.463 (0.359) vs. 0.510 (0.169) 2 months: 0.488 (0.262) vs. 0.501 (0.330) 3 months: 0.499 (0.296) vs. 0.501 (0.212) 4 months: 0.510 (0.203) vs. 0.511 (0.289)	Mean baseline CRT: NA Mean baseline CRT (SD) in μm and NV (treatment vs. comparator) At 2 weeks before injection: 439 (148) vs. 436 (133) 1 month: 315 (142) vs. 443 (150) 2 months: 442 (143) vs. 467 (152) 3 months: 457 (123) vs. 466 (139) 4 months: 449 (150) vs. 459 (128)

Ramezani et al. (2006)*	T: Sub-tenon triamcinolone injection C: No sub-tenon triamcinolone injection	Mean change in BCVA from baseline to 1 month: −0.40 (0.17) vs. −0.00 (0.12)	Mean change in CRT from baseline to 2 months: −273 (108) vs. −115 (71)
Jonas et al. (2005)*	T: Triamcinolone acetonide intravitreal injection (about 20 mg) C: No treatment (results were not given by ischemic status)	Mean baseline BCVA of ischemic patients in treatment arm 1.79 (0.51) Mean change in BCVA of ischemic patients in treatment arm from baseline to best post-operative VA: 1.57 (0.64) [p = 0.10]	NA

Table 2- Summary of studies on steroid treatments for RVO

Outcomes are not directly comparable because study designs and populations varied. For any studies that did not accurately report the number of patients in their analysis, the number has been estimated using the study's figures.

* = BCVA (SD) converted to LogMAR units (Treatment vs. comparator)

Abbreviations: **ORVO** = The Ozurdex for Retinal Vein Occlusion study, **SOLO** = "Functional and anatomical results after a single intravitreal Ozurdex injection in retinal vein occlusion", **GENEVA**: "Sham-controlled randomized trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion", **SCORE** = The Standard care versus COrticosteroid for REtinal vein occlusion trial

Besides corticosteroids, progress in anti-angiogenic drug development has provided clinicians with several new therapeutic agents which are based on the model of modified antibodies versus vascular endothelial growth factors (VEGF) and related molecules. The most commonly used anti-VEGF drugs at this time are ranibizumab (Lucentis), bevacizumab (Avastin), aflibercept (Eylea). Only two anti-VEGF medications are licensed for treatment of RVO-related macular oedema: ranibizumab and aflibercept.

Ranibizumab (Lucentis, Novartis Pharma AG, Basel, Switzerland) was the first anti-VEGF medication licensed. It is also indicated for wet AMD, DMO, and choroidal neovascularisation secondary to pathological myopia treatment. Bevacizumab is a recombinant humanised and chimeric IgG1-type monoclonal antibody. It works against all the isoforms of the VEGF peptide. Several studies have reported that visual acuity and macular edema improved significantly after intravitreal bevacizumab (Noma, Mimura, et al. 2016; Noma, Mimura, and Shimada 2014). One recent study showed that after IVB treatment, there is an increase of retinal venous outflow that may possibly influence the resolution of macular oedema (Noma, Yasuda, et al. 2016). Compared with intravitreal triamcinolone acetonide, intravitreal bevacizumab can achieve better long-term VA outcomes with a much lower rate of adverse events (e.g., cataract and glaucoma), despite the fact that triamcinolone acetonide may achieve equal visual acuity and morphology improvement for the first few months after treatment (Sun and Qu 2015; Hikichi et al. 2014).

The latest anti-VEGF medication approved for the treatment of macular oedema related to RVO is aflibercept (Eylea 40 mg/ml, Bayer Bristol-Meyers Squibb, Princeton, NJ). Aflibercept acts as a soluble decoy receptor which binds VEGF-A and placenta growth factor (PIGF) with higher affinity than their natural receptors, hence can inhibit the binding and activation of these VEGF receptors. Excessive activation of the VEGF1 and VEGF-2 receptors by these factors can result in pathological neovascularisation and increased vascular permeability. The PIGF is also known to promote leucocyte infiltration and vascular inflammation. Aflibercept is also licensed for wet AMD, diabetic macular oedema, and myopic choroidal neovascularisation. Table 3 summarises selected studies in RVO with anti-VEGF treatment.

Study	Method	Mean BCVA change	Mean CMT change (μm)	Mean number of injections
BERVOLT (Kornhauser and Barak 2016)	Bevacizumab 0.05 ml	+0.25 (LogMAR)	−193.9	7.6
BRIGHTER (Tadayoni et al. 2017)	Ranibizumab 0.5 mg	+14.8 (ETDRS)	223.3	4.8
	Ranibizumab 0.5 mg + laser	14.8	−240.1	4.5
	Laser alone (3 + PRN)	+6.0 (6 months)	−89 (6 months)	N/A
VIBRANT (Clark et al. 2016)	Aflibercept 2.0 mg	+17.1 (ETDRS)	−283.9	9
	(6 + 1 per 2 months)	12.2	−249.3	N/A
	Grid laser			
MARVEL (Narayanan et al. 2016)	Ranibizumab 0.5 mg	+18.1 (ETDRS)	−177.1	3.2
	Bevacizumab 1.25 mg (PRN)	15.6	−201.7	3
RABAMES (Pielen et al. 2015)	Ranibizumab 0.5 mg	+17 (ETDRS)	+142.4	3
	Ranibizumab 0.5 mg + laser	6	171.7	3
	Laser only (monthly)	2	−37.6	N/A
COMRADE-B (Hattenbach et al. 2018)	Ranibizumab 0.5 mg (3 + PRN)	+14.15 (ETDRS)	−275	4.7
	Dexamethasone 0.7 mg	9.66	−130	1
BRAVO (Brown et al. 2010)	Ranibizumab 0.3 mg	+16.4 (ETDRS)	−313.6	8.3
	Ranibizumab 0.5 mg	18.3	−347.4	8.4
	Sham/ranibizumab 0.5 mg (6 + PRN)	12.1	−273.7	5.7
HORIZON (12-month open-label extension of BRAVO trial) (Heier et al. 2012)	Ranibizumab 0.3/0.5 mg	+0.9 (ETDRS)	+3.7	2.4
	Ranibizumab 0.5/0.5 mg	−2.3	6.3	2.1

	Sham/ranibizumab 0.5 mg (PRN)	−0.7	35.3	2
RETAIN (Prospective follow-up of a subset of patients from HORIZON study) (Prünte et al. 2016)	Ranibizumab 0.5 mg (PRN)	2 years:	2 years: −7.2	2 years: 2.6
		−0.4 (ETDRS)		
		3 years: +2.6	3 years: −42.5	3 years: 2.1
		4 years: +0.5	4 years: −26.2	4 years: 2.0
SHORE (Campochiaro et al. 2014)	Ranibizumab 0.5 mg PRN	+21 (ETDRS)	−247.8	3.8
	Ranibizumab 0.5 mg (7 + PRN)	18.7	−289.9	7.6

Table 3- Summary of studies on anti-VEGF treatments for RVO

Outcomes are not directly comparable because study design and populations varied. The COMO trial is still ongoing; therefore, no results are available at this time.

Abbreviations: **BERVOLT** = “Bevacizumab for RVO long-term follow-up”, **BRIGHTER** = “Individualized stabilisation criteria-driven ranibizumab versus laser in branch retinal vein occlusion”, **VIBRANT** = "Intravitreal aflibercept for macular oedema following branch retinal vein occlusion”, **RELATE** = “Scatter photocoagulation does not reduce macular oedema or treatment burden in patients with retinal vein occlusion”, **MARVEL** = “A randomized, double-masked, controlled study of the efficacy and safety of intravitreal bevacizumab versus ranibizumab in the treatment of macular oedema due to branch retinal vein occlusion”, **RABAMES** = “Ranibizumab for branch retinal vein occlusion associated macular oedema study”, **BRAVO** = “Ranibizumab for the treatment of macular oedema following branch retinal vein occlusion”, **HORIZON** = “Ranibizumab for macular oedema due to retinal vein occlusions”, **RETAIN** = “Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab”, **SHORE** = “Study evaluating dosing regimens for treatment with intravitreal ranibizumab injections in subjects with macular oedema following retinal vein occlusion”, **COMRADE B** = **“**Efficacy and safety of 0.5 mg ranibizumab compared with 0.7 mg dexamethasone intravitreal implant in patients with branch retinal vein occlusion over 6 months”

Different anti-VEGF medicines can have variable treatment regimens and dosages. The recommended dosage is 0.5 mg, 2.0 mg, and 1.25 mg for ranibizumab, aflibercept, and bevacizumab respectively (Yilmaz and Cordero-Coma 2012; Regnier et al. 2015). Some specialists prefer a monthly injection, while others employ a treat-and-extend or an as-needed (pro rata) regimen (Narayanan et al. 2016; Rezar et al. 2015; Unsal et al. 2015; Ito et al. 2015; Sakanishi et al. 2016; Rush et al. 2014).

1.6 Macular oedema in uveitis

Uveitis is defined as an inflammatory condition of the uveal tract. It is a relatively uncommon disease with prevalence from 58 to 114.5 per 100,000 persons (Smith et al. 2009). Uveitis can affect individuals of any age and occurs in all parts of the world. It can occur as a consequence of various stimuli and may lead to irreversible vision loss (Tsirouki et al. 2018; Lardenoye, van Kooij, and Rothova 2006). Uveitis often leads to significant changes in vision of variable duration and intensity (Suttorp-Schulten and Rothova 1996; Hui et al. 2017; J. Zhang et al. 2016a). For example, many patients have good vision between the inflammatory attacks. The major cause of functional vision loss amongst uveitis patients is MO (Tsirouki et al. 2018; Lardenoye, van Kooij, and Rothova 2006). It is a frequent but not specific complication of uveitis and can be found in all persistent types of uveitis (Fardeau et al. 2016; Markomichelakis et al. 2007; Thurau 2005).

1.6.1 Epidemiology of uveitic macular oedema

Several epidemiological studies and retrospective series have clearly identified MO as one of the most serious long-term complications of chronic posterior uveitis. The prevalence of MO was identified to be between 20 and 70% (Accorinti et al. 2019). MO is also among the leading causes of reduced vision in uveitis patients. Persistent retinal oedema gives rise to chronic changes and can cause permanent damage of central vision (Albaroudi et al. 2017; Markomichelakis et al. 2007; Thurau 2005). The foveal thickening that occurs with significant visual change is more often observed in intermediate uveitis (25–70%) but is also present in

anterior (20–26%), posterior (20%), and panuveitis (35%) uveitis (Pivetti-Pezzi 1987). With uveitis, in contrast to other causes of MO, MO tends to occur in the younger population (Accorinti et al. 2019; Smith et al. 2009).

1.6.2 Classification of uveitic macular oedema

The widely accepted classification of uveitis is based on the involved anatomical site(s). This classification was first proposed by the International Uveitis Study Group (Nussenblatt and Palestine 1989). It has since been recommended by the Standardization of Uveitis Nomenclature (SUN) working group ("Standardization of Uveitis Nomenclature for Reporting Clinical Data. Results of the First International Workshop" 2005). The SUN working group has also defined several terms to describe the clinical course of uveitis. Table 4 presents the SUN working group's classification of uveitis.

Anatomical description based on the primary site of inflammation
Anterior (anterior chamber)
Intermediate (vitreous)
Posterior (retina and choroid)
Panuveitis (anterior chamber + vitreous + retina and choroid)
Disease duration (≤ 3 months = Limited, ≥ 3 months = Persistent)
Disease course
Acute (sudden with limited duration)
Recurrent (repeated disease episodes separated by a >3-month period of disease quiescence)
Chronic (persistent disease with relapses within 3 months of no therapy)

Table 4- The SUN's international scientific uveitis nomenclatures

1.6.3 Specific pathophysiological mechanism of uveitic macular oedema

In uveitis patients, the exact trigger factor varies and is based on their background, associated diseases, and geographic and environmental factors (Foster and Vitale 2013). In

other words, uveitis may be caused by infectious, non-infectious, or neoplastic factors. When the immune system aims to control intraocular inflammation and promote tissue healing, tissue damage can occur in the eye. This damage is caused by abnormal immune system regulation that results in excessive inflammatory responses and further retinal damage. This damage, in turn, can cause several pathophysiological changes in the retinal vasculature leading to the development of MO. The most important point in the pathophysiology of uveitic MO is the disruption of the immune privilege of the eye (Foster and Vitale 2013; de Smet 2017). The interruption of the blood–retinal barrier (BRB) allows blood constitutes and cells to cross into the intraocular space. This issue motivates T-cell activation and differentiation, activation of macrophages, NK-cell lysis of the target cells, and active antigen presentation by MHC class I and class II molecules. The disrupted BRB also causes retinal vascular hyperpermeability, increased extracellular fluid accumulation, and retinal thickening. Structural changes in the retina have been shown to develop within 12–15 days after cell migration and cause significant visual loss (Dace, Chen, and Niederkorn 2008; Jiang, Lumsden, and Forrester 1999; Niederkorn 1997).

1.6.4 Clinical presentation of uveitic macular oedema

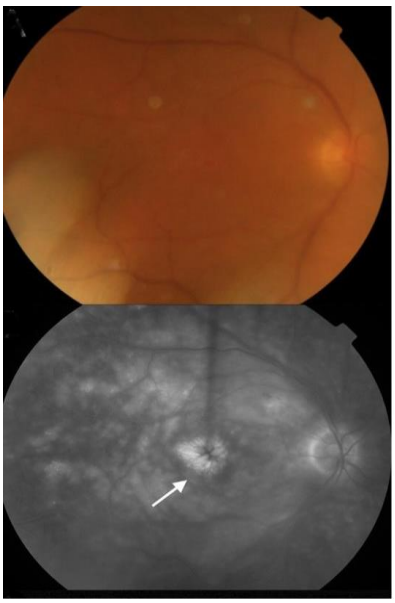
The most common complaints of patients with uveitis are blurred and/or decreased vision, eye redness, eye pain, light sensitivity, and floaters. During the routine slit-lamp examination of the eye, the following findings may be observed:

- Injection of the bulbar conjunctiva if the iris or ciliary body is involved in the inflammation
- Keratic precipitates on the endothelial surface of the cornea
- Keratitis
- Inflammatory cells and proteins in the anterior chamber due to breakdown of the blood–ocular barrier
- In the anterior chamber, deposition of fibrin or white cells (hypopyon)
- Iris synechia, iris atrophy, iris nodules, abnormal vessels, or heterochromia

- Changes in the lens such as cataract formation
- Inflammatory or debris deposits on the surface of the lens
- Increased or decreased intraocular pressure
- Accumulation of inflammatory cells in the vitreous (vitritis)
- Changes in the retina such as retinitis, vasculitis, or neovascularisation of the retina in cases of ischaemic uveitis
- Exudates and fibroglial band formation (snowballs, snowbanking) in the pars plana
- In some cases, inflammatory changes in the optic nerve head
- In some cases, presence of hyphaemia
- Changes in the choroid (choroiditis), though these may not be associated with retinitis

Amongst one of the most severe and long-lasting complications of uveitis is accumulation of fluid in the outer plexiform and inner nuclear layers. This complication results in cystoid macular oedema, which has a typical petaloid pattern in a fundus fluorescein angiogram.

A



B

Figure 9- Cystoid macular oedema

Image A is a colour fundus image of a right eye with intermediate uveitis. The hazy fundus view is secondary to a dense vitritis.

Image B is a fluorescein angiogram of the right eye. The arrow indicates foveal leakage in a petaloid pattern, which corresponds to cystoid macular oedema.

Source: Images acquired by the author during the research project.

1.6.5 Diagnosis of uveitic macular oedema

The diagnosis of uveitis and associated complications such as MO is based on the availability of diagnostic tools and the relationship between the uveitis and the systemic disease. The diagnostic approach to the uveitis patient depends on detailed clinical examination, laboratory evaluation, and special diagnostic techniques like FFA, indocyanine green angiography (ICG), OCT, and electroretinography (Agarwal et al. 2018). Although severe uveitis-associated MO is visible by fundoscopy, small cystic spaces are often difficult to see. Thus, in cases of severe uveitis-associated MO, OCT and FFA are the preferred techniques for quantitative and

qualitative assessment and follow up respectively (J. Li et al. 2019; Astroz et al. 2018). However, in some cases of retinal thickening with RPE dysfunction, inflammation can be localised more in the choroid than in the retinal blood circulation. In such cases, ICG is the better diagnostic technique as it visualises the choroid vessels (Hayashi et al. 2017; Pichi et al. 2017; Yu et al. 2016). Namely, the ICG technique involves intravenous injection of 5% indocyanine green dye solution, which fluoresces in the infrared light spectrum. These wavelengths have the ability to penetrate retinal layers and allow visualisation of the deeper layers' blood circulation with a special infrared-sensitive camera (Herbort 2000; Herbort, Mantovani, and Papadia 2012; Richard, Soubrane, and Yanuzzi 1998). The information provided by choroid angiography is mainly qualitative, and it is commonly used to complement FFA results.

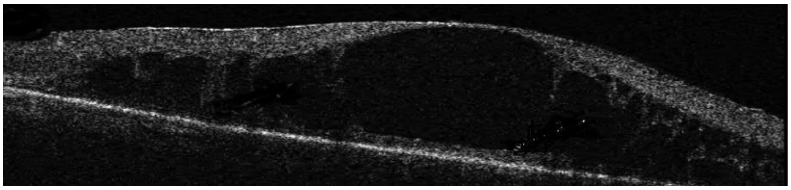


Figure 10- Spectral domain optical coherence tomography (SD-OCT) image of the macula demonstrating large intraretinal cyst formation

Source: Image acquired by author during research project.

1.6.6 Treatment of uveitic macular oedema

The systemic or local treatment of uveitis is based on the direct suppression of any clinically evident inflammation (Pleyer, Pohlmann, and Stübiger 2016; Díaz-Llopis et al. 2009). Corticosteroids are essential drugs that activate phospholipase-A2 inhibitory proteins (Barnes 2011). These proteins control the synthesis of pro-inflammatory mediators like prostaglandins and leukotrienes (Barnes 2011). Steroids inhibit vasodilatation, reduce vascular permeability,

decrease leukocyte migration, and reduce vascular endothelial growth factor (VEGF) levels (Hassan et al. 2019; Lee and Foster 2010). All of these therapeutic effects lead to reduction of the retinal thickness and favourable visual outcomes in patients with uveitis-related MO (Grotting and Papaliodis 2017; Kruh and Foster 2012). High-dose oral corticosteroids appear to be effective in controlling acute disease activity due to their rapid onset of action. The downside is that a high dose (more than 40 mg prednisolone per day) is required to keep the disease under control, and long-term use of intravitreal steroids is associated with significant ocular side effects that may require limited use in certain patients (Ratra et al. 2018; Chirikov et al. 2019). The eye complications that locally administered steroids may cause are summarised in Table 5 (Foster and Vitale 2013).

Ocular	Systemic
Cataract	**Cushingoid changes**
Ocular hypertension	**Frequent infections**
Central serous chorioretinopathy	**Hypertension**
Ptosis	**Fluid retention**
Diplopia	**Diabetes mellitus type II**
Extraocular muscle paresis	**Hyperlipidaemia**
Papilledema	**Atherosclerosis**
Scleral thinning	**Anxiety**
Corneal thinning	**Poor wound healing**
Iris/ciliary body microcysts	**Cardio-vascular events**

Table 5- Ocular side effects of systemic corticosteroid treatment

In children in particular, systemic application of steroids can lead to failure of growth and delayed puberty (Chirikov et al. 2019; Suhler et al. 2017). Unquestionably, the high risk of

associated side effects has led to increased use of locally administered medications (Jaffe et al. 2016; Multicenter Uveitis Steroid Treatment (MUST) Trial Follow-up Study Research Group 2015; Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group et al. 2011, 2015). Locally administered medications can achieve high concentration in the eye, close to the target tissue. There are several options for local administration of corticosteroids – through orbital floor or sub-Tenon injection, around the eye, or into the vitreous (via intravitreal steroids or slow-releasing steroid implants). Table 6 summarises the available corticosteroid drugs and their applications.

Name	Dose	Administration	Indications
Triamcinolone acetonide (TA) Kenalog-40n	4 mg/mL	Intravitreal	Off-label use
Triamcinolone acetonide (TA) TrivarisTM	4 mg/mL	Intravitreal	Approved for ocular inflammatory disease
Triamcinolone acetonide (TA) Triesence	4 mg/mL	Intravitreal	Approved for ocular inflammatory disease
Dexamethasone implant (Ozurdex)	700 µg	Intravitreal	Approved for ocular inflammatory disease
Fluocinolone acetonide (FAc) (Retisert)	0.59 mg	Intravitreal	Approved for ocular inflammatory disease
Fluocinolone acetonide (FAc) (Iluvein)	190 µg	Intravitreal	FDA/EMEA approved for DMO

Table 6- Steroid medication for treatment of ocular inflammation

In order to overcome all side effects of long-lasting treatment with corticosteroids, clinicians today are focusing on using immunosuppressive therapy. By definition, this type of treatment suppresses the development of at least one type of immune reaction in the pathogenesis of uveitis. Since the International Uveitis Study Group provided guidance on immunosuppressive treatment in patients with uveitis, such treatment has typically been the first line treatment in uveitis (Jabs et al. 2000). To achieve good therapeutic control, patients have to be adequately immunosuppressed, but also spared of probable drug toxicity. A summary of available immunosuppressive medication is presented in Table 7 (Foster and Vitale 2013; You et al. 2017; Ratay et al. 2017; Zhao and Zhang 2017; Jabs 2018).

Drug class	Drug name	Therapeutic route and dose	Adverse reactions
Alkylating agents	Cyclophosphamide	1–3 mg/kg/day, PO	Myelosuppression, reversible alopecia, transient blurring of vision, secondary malignancies, sterile haemorrhagic cystitis.
	Chlorambucil	0.15 mg/kg/day, PO	Secondary malignancies, myelosuppression, gonadal dysfunction
Antimetabolites	Azathioprine	1–3 mg/kg/day, PO	Leukopenia, secondary infections, nausea
	Methotrexate	0.15 mg/kg once weekly up to 50mg/week, PO,SC	Bone marrow suppression, diarrhoea, hepatoxicity, ulcerative stomatitis
	Mycophenolate mofetil	2–3 g daily, PO	Gastrointestinal distress, diarrhoea

Table 7- Immunosuppressive drugs by class, name, therapeutic route and dose, and potential adverse reactions

Abbreviations: **PO** = per oral, **SC** = subcutaneous

1.7 Examination of visual function and functional vision

In clinical settings, the visual impact of retinal disease is mainly examined based on subjective eye examinations such as testing of visual acuity, reading speed, colour vision, and contrast sensitivity. Although these tests rely on personal judgment, their combination provides extensive information about patients' symptoms. These tests allow a subjective

judgment based on interactions with anatomical changes in the retina, thus allow clinicians to connect symptoms with disease development and progression.

1.7.1 Visual function

Visual acuity refers to clarity of vision and depends on the optical and anatomical factors of the eye. Anatomical factors are located along the pathway from the retina to the brain. Visual acuity is defined as the visual system's degree of special resolution (Denniston and Murray 2013). The acuity of normal vision is referred to as 20/20 vision, or as its metric equivalent 6/6. This means that at 20 feet (6 metres) the human eye with normal vision can separate contours that are approximately 1.75 mm apart (equivalent to 62 arc) (Carlson and Daniel 2004; Colenbrander 2008). Thus, visual acuity is a function of the eye's capability to separate different stimuli based on the spatial resolution of the densely packed cones (about 180,000 cones/mm^2). Any pathological changes in the normal anatomical density and distribution of the cones in the macula may result in decreased visual acuity. Visual acuity is commonly measured for central retinal fixation by using optotype charts. These charts can feature letters, numbers, Landolt rings, Lea symbols, or other patterns. These charts are used for clinical practice patient screening, refraction, decisions on treatment, and follow-up of disease progression as well as for research purposes. Some optotype charts have disadvantages like non-uniform letter crowding, poor optotype legibility, or non-continuous data; these disadvantages make such charts inappropriate for clinical trials and research purposes (Hazel and Elliott 2002). To record visual acuity, the Early Treatment Diabetic Retinopathy Study (ETDRS) includes charts such as the LogMAR chart, which can be used for statistical analysis (Kuo et al. 2011; Ferris et al. 1982). An observer who can see details as small as 1 minute of visual angle scores LogMAR 0, since the base-10 logarithm of 1 is 0. An observer who can resolve details as small as 2 minutes of visual angle scores LogMAR 0.3, since the base-10 logarithm of 2 is approximately 0.3. Each letter in this chart has a score value of 0.02 log units. As each line consists of 5 letters, the total score for a line on the LogMAR chart represents a change of 0.1 log units (Carlson and Daniel 2004). The formula used in calculating the score is as follows:

LogMAR VA = 0.1 + LogMAR value of the best line read – 0.02 X (number of optotypes read)

Given that each line has 5 optotypes, the equivalent formula is as follows:

LogMAR VA = LogMAR value of the best line read + 0.02 X (number of optotypes missed)

In conclusion, any pathological changes in the retina will cause a reduced number of correctly read letters on the LogMAR chart (von Wedemeyer and Wiegand 2016). However, as other causes exist for reduced vision, further examination is required in order to demonstrate ocular functional abnormalities.

1.7.2 Functional vision

The only way to ensure that all essential visual skills are working properly is to assess the functionality of the vision. Functional vision concerns the subjective eye-related disabilities of patients who maintain eye-related complaints despite having achieved good and stable results on optotype visual acuity charts (El-Gasim et al. 2013). Clinically used methods for recording vision, such as Snellen visual acuity charts, may fail to assess many aspects of visual disability that are identified by persons as being important for their daily function and wellbeing (Bhorade et al. 2013). Hence, further investigation of all aspects of vision, including reading speed, visual field, contrast sensitivity, and colour vision, alongside investigation of changes in the normal retinal anatomy is of high value for the clinical practice.

The recent advantages in medical devices for contrast sensitivity examination allows detailed exploration of even small and mild changes in the visual field. In addition, improved OCT devices offer further detailed information about the associated anatomical changes in the retina. In order to investigate patients' vision-related quality of life, a number of reliable and short questionnaires have also been developed (Mangione et al. 1998; Terheyden and Finger 2019). The National Eye Institute (NEI) sponsored the development of the visual function questionnaire (the VFQ-25) (Mangione et al. 2001; Mangione et al. 1998). The NEI's aim was to create a survey that would measure patients' self-reported vision-targeted health status and thereby identify what health aspects are most important to people who have chronic eye diseases such as macular oedema. The questionnaire measures the effect of visual disability and visual symptoms on patients' health aspects such as emotional well-

being, social functioning, and vision-orientated activities in their daily life. The VFQ-25 is validated for use in several areas such as age-related macular degeneration, glaucoma, cataracts, retinal detachment, vitreomacular traction, diabetic retinopathy, and photocoagulation (Yang et al. 2018; Du et al. 2019; Khoo et al. 2019; Martínez de Carneros-Llorente et al. 2019; Lescrauwaet, Blot, and Jackson 2019).

Despite all the available clinical tests, it is still unclear how to predict everyday visual functional performance. According to a report from the Johns Hopkins Wilmer Eye Institute's Low Vision Service (Unpublished data), the most common complaint of patients is reading and driving difficulties (Rubin 2013). Therefore, it is very important to estimate how well patients with central vision loss will perform everyday visual tasks such as reading or driving. Regarding reading, it has been stated that the primary reason for referral in low vision clinics is reading difficulties. Reading speed is a strong predictor of visual ability and vision-related quality of life (Trauzettel-Klosinski, Dietz, and IReST Study Group 2012); accordingly, improving reading ability is a high priority for patients with visual loss. Furthermore, reading performance has been used as the primary outcome measure for several clinical trials, including trials studying sub-macular surgery (Hawkins et al. 2004; Submacular Surgery Trials Research Group 2005), anti-VEGF (Tufail et al. 2010; Munk et al. 2013; Coco-Martín et al. 2017), treatments for age-related macular degeneration (AMD), and comparison of intraocular lenses following cataract extraction (Akutsu et al. 1992; X. Liu, Xie, and Huang 2018; Kaymak et al. 2017; Kim et al. 2018). Notably, visual acuity is a poor predictor of the maximum reading speed achieved by low-vision patients (Legge et al. 1992, 1992b; Xiong et al. 2018; Ahn and Legge 1995). Therefore, we would expect reading performance, in association with visual acuity and contrast sensitivity, to be highly important clinical outcome measures for judging the effectiveness of therapeutic intervention and vision rehabilitation.

Functional vision concerns the impact of eyesight on quality of life, with consideration to the importance of quality of vision in all human vocations. Visual acuity alone does not measure the functional vision quality desired for everyday tasks. Therefore, the combination of the described tests may provide a better understanding of patients' visual ability and the outcome after standard management of macular oedema.

1.8 Aim and hypotheses

The aim of this thesis was to investigate functional vision recovery in patients who have developed macular oedema (MO) due to one of the three most common retinal diseases: diabetic retinopathy (DRP), retinal vein occlusions (RVO), and uveitic macular oedema (UMO). Specifically, I focus on patients who are treated according to the current standard practices for DRP, RVO, and UMO as described in sections 1.4.4, 1.5.7, and 1.6.6 respectively. There is, in short, a lack of satisfactory evidence regarding functional vision improvement for these patients. Scientific gaps and unanswered clinical questions remain. It is not clear what the first line of treatment for MO should be, when to switch medicines when treating MO, when to re-treat patients, or how to assess poor therapeutic responses. In this thesis, in addition to these research gaps, I looked at the variation in the therapeutic response and visual acuity amongst these three study groups (DRP, RVO, and UMO). In short, this research examines the insufficient evidence of functional vision recovery amongst patients with macular oedema.

The aims of this thesis were threefold:

1. To assess the difference in the response to standard treatment of MO by using routine clinical measures and patients' self-reported functional vision.
2. To investigate the potential role of functional tests such as visual acuity, perimetry mean sensitivity, reading speed, vision-related quality of life to detect subclinical changes in patients' visual outcome.
3. To investigate whether the functional vision change in patients with MO can be perceived differently amongst patients with DRP, RVO, and UMO.

My overall hypothesis is that visual acuity results acquired by routine clinical techniques do not provide sufficient information about patients' functional vision. Hence, by introducing further measures of functional vision assessment, clinicians should be better able to predict the therapeutic response in patients with MO.

This study adopted the following objectives to serve its aims:

1. To investigate routine vision-related clinical outcomes in patients with MO due to DRP, RVO, or uveitis.
2. To investigate functional vision outcomes in patients with MO due to DRP, RVO, or uveitis.
3. To identify which functional vision assessment techniques can be adopted as routine clinical techniques in assessing therapeutic response in patients with MO.
4. To present differences in functional vision recovery in patients with MO due to DRP, RVO, or uveitis.
5. To identify which combination of routine clinical and functional vision assessment techniques can better predict patients' visual acuity after standard treatment of MO due to DRP, RVO, or uveitis.

Chapter 2. Methodology

2.1. Background of the study methods

The aim of this chapter is to introduce the research design and settings. Given the nature of the study, the research was carried out in the routine ophthalmology clinic in two NHS hospitals: Royal County Surrey Hospital and Moorfields Eye Hospital. Routine clinical appointments were conducted. Additionally, a separate research room was used to facilitate all functional vision assessments, which were not part of the routine clinical practice.

2.1.1 Clinical test of vision

A clinical test of vision has two main aims:

- To detect whether the visual system of a given single person can function normally.
- If dysfunction is detected, to obtain the degree and the location of this dysfunction.

Visual acuity testing is one of the most commonly performed assessment techniques in eye clinics. Quantitative measurements of visual acuity go back to the 1600s, when Robert Hooke observed a pair of stars using a telescope and noticed that each star could be easily differentiated from its pair only if the eye was aided (Colenbrander 2008; Frisen 1990; Artes n.d.). In the 1800s, Herman Snellen further developed clinical interest in visual acuity by creating an acuity chart. The literature on visual acuity has since developed to include visual acuity tests that are considered reliable, accurate, valid, sensitive, and specific methods by which to test vision. Visual acuity is always tested in good light and with high contrast, which reflects the function of the retinal cones rather than the rods. Hence, visual acuity testing assesses mainly the function of the closely positioned cones of the fovea and their connection to the brain.

Multiple methodologies are now available for testing visual acuity (Ferris et al. 1982; Colenbrander 2008; Kniestedt and Stamper 2003). Variety can also be observed in the type of optotypes (test objectives), the scaling of optotypes' size, and the ways in which results are described (Frisen 1990).

Currently, letter charts are widely used in traditional clinical practice in the United Kingdom. Charts are designed to eliminate the crowding phenomenon by using equal letter spacing on each line. This space is usually equal to the width of the letters. The optimum number of letters per line is five to ten letters; this number of letters keeps analysis points practical and easy to manage. The size of each letter is distinct from its stroke width in minutes of arc. It is far more common to see the more practical option of converting results into fractions or decimal values. In the UK, for example, fractions are presented in metric values, e.g. 6/24, while in the USA, feet are used, e.g. 20/100. In these fractions, the numerator indicates the distance between the patient and the letter chart (whether in metres or feet), and the denominator presents the distance from which a normal subject can read the optotypes. The fraction value can be easily converted into decimals by considering the slash as a partition sign, e.g. 20/20 is equal to 1.0.

Two commonly used charts are the Snellen visual acuity chart and the Early Treatment Diabetic Retinopathy Study (ETDRS) or LogMAR chart. Figure 11A shows a Snellen visual acuity chart. In the Snellen chart, a distance is ascribed to each line such that the optotypes subtend 5 min of arc; each component of the letter subtends at 1 min of arc. The usual distance from the individual to the chart is 6 metres (200 feet for USA); that distance is used as the denominator. Therefore, if the top line of the chart can only be read at 2-metre distance, the Snellen visual acuity is presented as 2/60, where 60 indicates the distance at which a normal individual could read the top line. Another widely used chart is the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, also known as a LogMAR chart, as shown in Figure 11B (Told et al. 2013). This chart has become widely used in visual acuity testing in research ("First Research Starts in 1974 · About NVRI · National Vision Research Institute" n.d.; I. L. Bailey and Lovie 1976; Grosvenor 2007). Positive LogMAR values indicate vision loss, and negative values represent better visual acuity. This scale is frequently used in research for statistical calculations as LogMAR provides a scientific equivalent to the

clinical statements “vision loss” and “ vision gain”. This scientific equivalent is valid when steps are equal between lines.

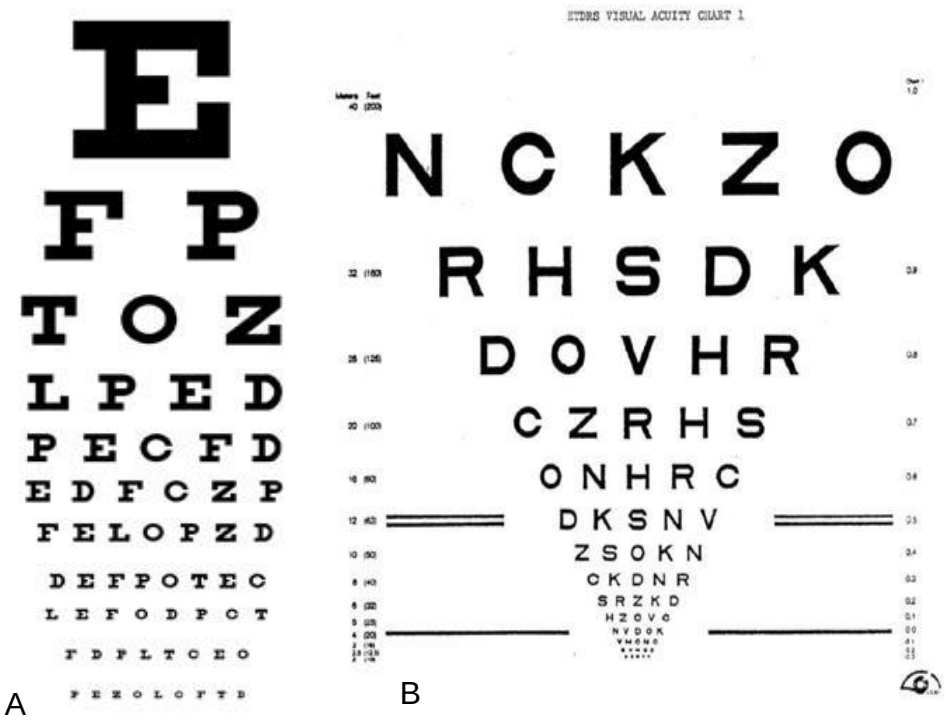


Figure 11- Visual acuity charts

Image A is a Snellen visual acuity chart.

Image B is an Early Treatment Diabetic Retinopathy Study (ETDRS) chart, also known as a LogMAR chart.

Source: Images acquired by the author during the research project.

LogMAR	Snellen
1.0	6/60
0.9	6/48
0.8	6/38
0.7	6/30
0.6	6/24
0.5	6/19
0.4	6/15
0.3	6/12
0.2	6/9.5
0.1	6/7.5
0.0	6/6
-0.1	6/5

Table 8- Snellen visual acuity and LogMAR chart conversions

Source: Table based on the recommendations given by the Royal College of Ophthalmologists (2019).

In UK practice, the ETDRS chart has been so widely adopted that it is starting to replace the Snellen chart. The reason for this is that the ETDRS chart is designed to eliminate inaccuracies observed in the Snellen chart. For example, the number of letters per row on the Snellen chart varies (Chen et al. 2014). Hence, if study results show three letters of visual acuity gain, this result could indicate either one full line, as in the 6/18 line, or only a part of the line, as in the 6/6 row. Another weakness in the Snellen visual acuity chart is the inconsistency in the type of the letters and the spacing used (Lovie-Kitchin 2015; Lim et al. 2010). In order to overcome these inaccuracies, the ETDRS chart has the same number of letters per row (five letters per row); identical spacing between rows on a long scale set up as 0.1 log units; equal space between letters on a long scale; and and letter difficulty on an individual rows balance .

2.1.2 Instruments used in posterior segment examination

Most commonly performed posterior segment examination is done using the slit-lamp (biomicroscopy) method with the help of additional lenses (Gellrich 2016). The biomicroscopy

and the handheld lens can magnify the view up to 40 times and provide a stereoscopic image of the retina (Gellrich 2015). The slit-lamp biomicroscope contains a binocular microscope and illumination system. The ability to move the slit-lamp vertically and horizontally allows each eye to be envisioned without adjusting the patient's position. The total magnification power of binocular slit-lamp microscopes ranges from 10 to 40 times (Denniston and Murray 2013). The height, width, and orientation of the beam can be adjusted to provide a better view of the observed anatomical structure of the eye (Denniston and Murray 2013). The eye examination starts with adjusting the patient's chair, chin rest, and the slit lamp, followed by using the lowest magnification and illumination (Leitman 1988). The examination should follow the medical manner of working from "outside–in", hence the anterior segment assessment should be followed by the posterior segment assessment (Juang and Rosen 1997). The slit-lamp assessment of the posterior segment of the eye is also known as indirect ophthalmoscopy. It is performed with the help of handheld lenses, often with 90D dioptres or similar magnifying power (Shaw et al. 2017; Kanemaki et al. 2017). There are some variances in the optical potentials of different types of lenses. For example, 66D lenses provide greater magnification in comparison with 90D lenses, which offer a wider field of view (Denniston and Murray 2013). After adjusting the patient's position and dilated pupils for better view, the lens is held at 1 cm in front of the eye. The obtained retinal view is inverted and laterally reversed. To view all quadrants of the retina, the clinician asks the patient to look towards the area targeted for examination. The following structures are observed for any abnormalities: the optic disc, optic disc margin, optic disc vessels, retinal vessels, peripheral fundus, and macula.

2.1.3 Optical coherence tomography

Optical coherence tomography (OCT) is a non-invasive, cross-sectional imaging method for the eye that works by measuring optical reflections of different retinal structures (Fujimoto and Huang 2016). In the current OCT devices, the coherence property of the light that reflects off the retinal structure provides information about the delayed time-of-flight from reflective boundaries. That information is then used to calculate the distance of the reflection

sites. OCT imaging is an amended and redeveloped version of the low-coherence reflectometer system (Fujimoto and Swanson 2016; Fercher et al. 2003). A low-coherence light is directed towards retinal tissues. The laser beam is split into two. One part is focused onto the examined tissue. The second part is focused onto a reference mirror. The phenomenon of interference occurs when the backscattered light from both beams is united. The combined signal is detected and measured by an internal photodetector. The estimated location of the backscattered light from the observed retinal structure is defined by using the information gained from the controlled internal reference mirror (Arevalo, Fernandez, and Mendoza 2009; Katkar et al. 2018; Shu, Beckmann, and Zhang 2017). Each assessed point creates information on the longitudinal axis. This process is also called an A-scan and consists of 1024 data points. A two-dimensional (2D) image can be obtained by repeating the procedure at incremental steps along the examined retinal area (Arevalo, Krivoy, and Fernandez 2009; Arevalo et al. 2009).

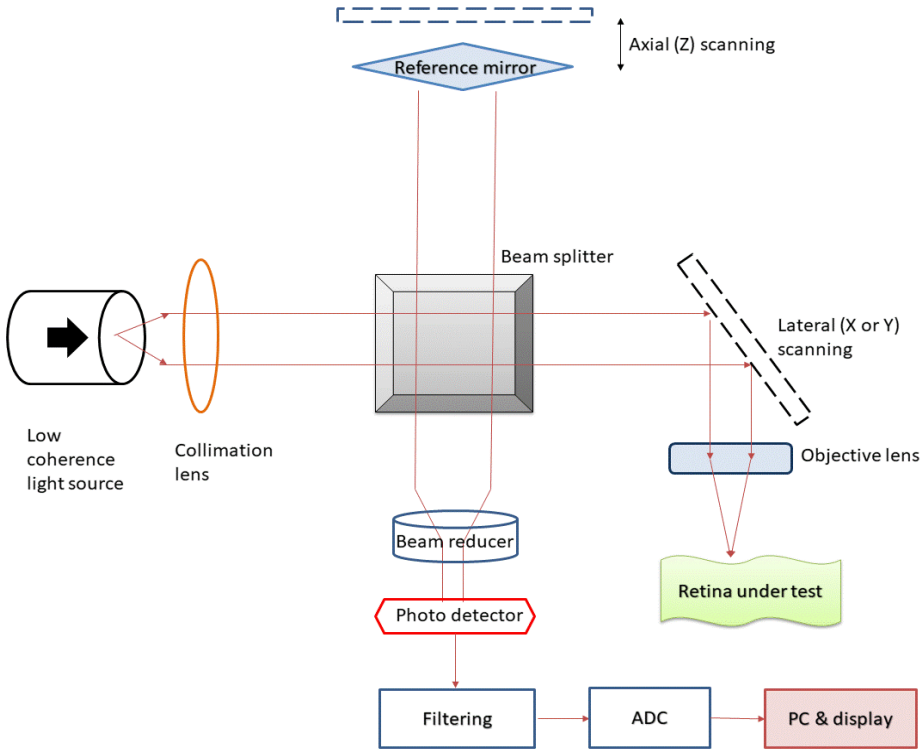


Figure 12- Principles of optical coherence tomography

Source: Image created by author during research project.

The OCT system allows multiple, high-speed longitudinal scans to be obtained in order to provide a 2D map of reflection sites. Therefore, the OCT imaging technique combines from 131,072 to 786,432 data points (depending on the system used) to construct a cross-sectional image (Spaide et al. 2018; Wojtkowski, Kaluzny, and Zawadzki 2012). This image is carried as a tomogram, and it can be displayed with either a colour or grey scale. Brighter colours (red to white) represent high reflectivity, and dim colours (blue to back) correspond to low reflectivity (Wojtkowski, Kaluzny, and Zawadzki 2012; Lumbroso 2013). OCT images can be rendered at a quality of 0.5 µm axial resolution. Time domain OCT (TD-OCT), an earlier version of OCT, is considered to be relatively slow (Li et al. 2016; Chan et al. 2015). The mechanical process of using moving mirrors to detect the time needed for the light to be detected limits the quality of the image and the data captured. With TD-OCT, data can be acquired with an average of 400 A-scans per second. Spectral domain OCT (SD-OCT), a newer adaptation of OCT, can measure the spectrum of wavelengths of the reflected light at the same time. SD-OCT increases axial resolution 2 to 3 fold and speed up to 110 fold in comparison with TD-OCT (Schuman 2008; P. Rao et al. 2017; Gao and Wu 2017).

OCT has been proven to be an effective and reliable imaging technique in ophthalmology. It allows clinicians to assess structural change in the retina during disease progression and therapeutic response (Ruia et al. 2016). In this study, I used two widely available SD-OCT devices: the Spectralis HRA+OCT (Heidelberg Engineering GmbH, Germany) and the Topcon 3D OCT-1000TM (Topcon Corporation, Tokyo, Japan). The Spectralis® has 7 micrometre axial resolution and scans at 40,000 A-scans per second. Currently available high-speed SD-OCT uses an 870-nm wavelength light source that provides excellent imaging of the vitreoretinal interface and retina, but often lacks full-thickness visibility of the choroid due to depth and density of choroidal tissue and light attenuation by the retinal pigment epithelium (Verner-Cole et al. 2014). Recently, the enhanced depth imaging technique was described by Spaide et al. as a technique that could be used with the SD-OCT machine to provide deeper imaging beneath the RPE and into the choroid (Spaide et al. 2018). Hence, use of a longer wavelength light source (1050 nm) with enhanced depth imaging provides greater choroidal

detail compared with 870-nm SD-OCT, but has reduced detail of the vitreoretinal interface (Verner-Cole et al. 2014). For the purpose of this research, SD-OCT with a wavelength of 870 nm was used. The scanning process was set up to volume perform imaging scans at a 30-degree angle. The internal fixation light was central, and the OCT scan width x height was 20x20 degrees (“Spectralis HRA+OCT Spectralis HRA Spectralis OCT Hardware Operating Instructions” 2007; “SPECTRALIS® OCT User Manual Software Version 6.3” 2015). The density of the OCT imaging scan (the spacing between each scan) was 120 µm. The test results show macular thickness on an EDTRS grid (“Spectralis HRA+OCT Spectralis HRA Spectralis OCT Hardware Operating Instructions” 2007; “SPECTRALIS® OCT User Manual Software Version 6.3” 2015).

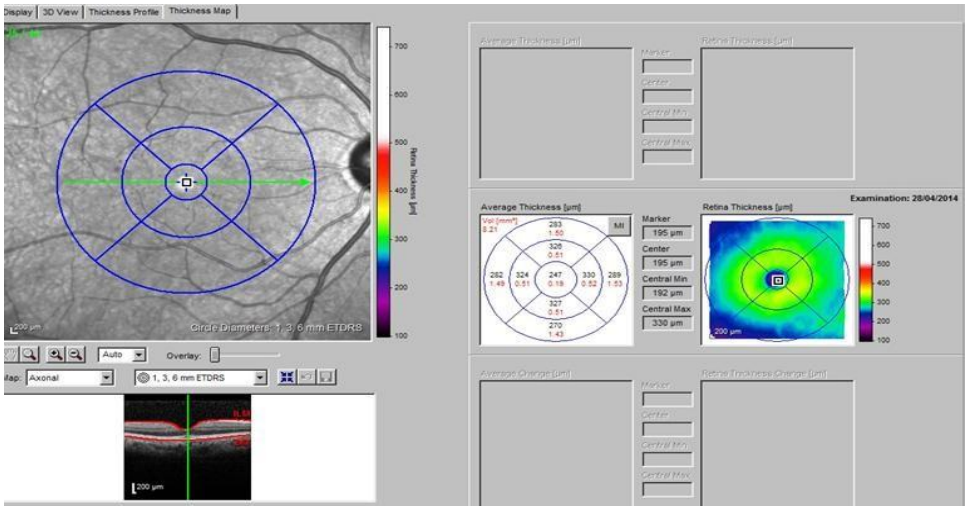


Figure 13- OCT image and ETDRS grid in the Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany)

Source: Images acquired by the author during the research project.

The second system used was Topcon 3D OCT-2000TM (Topcon Corporation, Tokyo, Japan). It is a spectral domain system which has 5–6 µm axial and 20 µm of horizontal resolution. It can obtain 27,000 A-scans per second by using a 840-nm wavelength light source (“3D OCT-2000 Spectral Domain OCT > LITERATURE | Topcon Medical Systems, Inc.” n.d.; “Optical Coherence Tomography 3D OCT-2000 Series,” n.d.). For the purpose of

this study, scans were obtained covering a 6.0 x 6.0 mm square area using a 256 x 128 raster-pattern A-scan. An example is shown in Figure 14.

Figure 14- Colour fundus photo of a left eye with ETDRS grid. Image taken using Topcon 3D OCT-2000TM (Topcon Corporation, Tokyo, Japan)

Source: Image acquired by author during research project.

Table 9 compares the technical characteristics of the two OCT devices used in this research.

OCT device	Topcon 3D OCT-2000TM	Spectralis HRA+OCT
Company name	Topcon Corporation, Tokyo, Japan	Heidelberg Engineering, Germany
Pupil diameter	≥ 2.5 mm	≥ 2.5 mm
Scan type	Colour, fundus autofluorescence, red free	Scanning Laser Fundus Imaging: BluePeak, MultiColor, Infrared Reflectance
Wavelength	840nm	870 nm
Scan mode	Macula: 3D scan; Macula: Radial scan; Macula 7-line raster; Disc 3D scan; Disc Circle scan	MultiColor; BluePeak, Retina, Glaucoma, Anterior Segment, Infrared Reflectance, Widefield Fundus and OCT, Angiography
Scan depth	2.3 mm	1.9 mm
Axial resolution	6 µm	3.9 µm (digital)
Transverse resolution	<20 µm	14 µm
A-scan	27,000 per second	40,000 per second

Table 9- Summary of the technical characteristics of the two OCT devices used in the research

Source: 3D OCT-2000 Spectral Domain OCT > LITERATURE | Topcon Medical Systems, Inc." n.d.; "Spectralis HRA+OCT Spectralis HRA Spectralis OCT Hardware Operating Instructions" (2007); "SPECTRALIS® OCT User Manual Software Version 6.3" (2015)

Today's OCT devices have incorporated several hardware and software advances. These advances have led to variability in retinal measurements and confusion in results interpretation (Giani et al. 2010). Giani et al. (2010) conducted a study aiming to assess variability in the retinal thickness using the most widely used TD-OCTs and SD-OCTs. The authors present how the positions of retinal boundaries in different OCT devices can vary and how, as a result, measurements can be very different. All the OCT instruments in Giani et al.'s study identified the inner retinal boundary as the first interferometric signal after the vitreous hyporeflective space, which corresponds to the internal limiting membrane.

However, the authors show that there are important differences between positioning of the outer retinal boundaries. Giani et al. identify the outer boundary of the Topcon 3D OCT as the inner limit of the retinal pigment epithelium (RPE) layer, while the outer boundary of the Heidelberg Spectralis is Bruch's membrane.

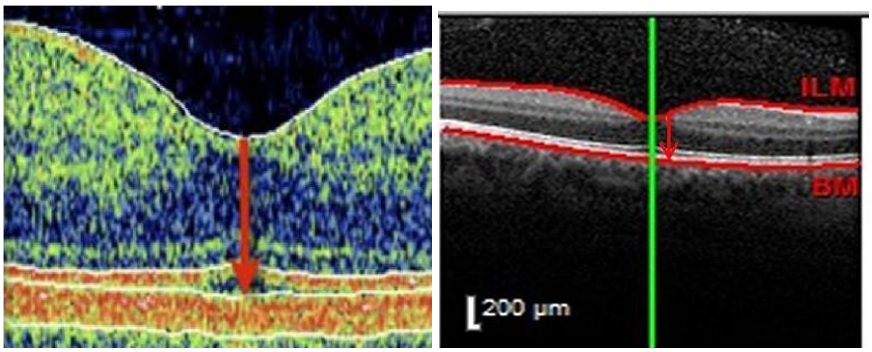


Figure 15- Position of retinal boundaries in OCT devices

Image A shows the Topcon 3D OCT outer limit is at the level of the retinal pigment epithelium (RPE).

Image B shows the Heidelberg Spectralis outer limit is at the level of Bruch's membrane.

Source: Images acquired by the author during the research project.

Giani et al. (2010) used Bland Altman and regression analysis to develop a table that allows conversion and standardisation of results gained by various OCT devices. As Giani et al.'s project was the only research project explicitly studying this precise subject, the following conversion formula was used in the present study to standardise the retinal thickness results from the two SD-OCTs:

Heidelberg Spectralis = Topcon 3D OCT x 0.9 - 10.9

Retinal thickness values calculated with this formula were used for the analysis of this research project. Another alternative for accurate comparison between two different OCT

devices is manual correction of the outer border (Heussen et al. 2012). In a study conducted by Hussine et al. (2012), the authors suggest that standardised correction of the external retinal border may be a useful method for comparing retinal thickness measurements in clinical trials and clinical research studies. The authors further suggest that a standard correction factor between OCT devices may be designed and used to correct all machine extents to a common reference point (Heussen et al. 2012).

2.1.4 Microperimetry devices

Visual acuity, which is considered the gold standard in ophthalmology practice, does not fully reveal functional vision (Owsley and Sloane 1987). One classic test to measure visual function within visual field is to measure the different light thresholds; this test may be considered as a type of luminance contrast sensitivity test. A contrast sensitivity test measures patients' ability to distinguish between small increments of light versus dark (contrast). This type of test is different from the widely used visual acuity testing that takes place during a routine eye exam, as a visual acuity test measures the ability of an eye to recognise smaller optotypes on a standard eye chart. Contrast sensitivity is defined as the ability to detect the lowest lumination difference between an object and the background. Standard visual acuity measurement is done with high-contrast conditions. Thus visual acuity measurement does not provide any information about visual performance in various daily activities such as driving at night or reading in low light (Karatepe, Köse, and Eğrilmez 2017). Patients' vision therefore cannot be fully assessed by evaluating visual acuity alone. Contrast sensitivity, which defines the threshold between the visible and invisible, is also important for basic and clinical vision (Pelli and Bex 2013). The visual field sensitivity is expressed in decibels (dB). The decibel is a unit for expressing the ratio between two physical quantities. One decibel (0.1 asbel) equals 10 times the common logarithm of the power ratio. Though most commonly used to measure sound level, it is also widely used in electronics, signals, and communication research.

There are several different devices for testing the visual field. Among these devices, newer devices called microperimeters have higher resolutions, which allows the detection of smaller

changes in the visual field (Acton and Greenstein 2013; Markowitz 2013). Microperimeters, though still mainly used as a research tool, are starting to be implemented in daily ophthalmology practice for examination of clinical visual function and functional vision (Markowitz and Reyes 2013a). Microperimeters, also known as fundus perimeters, have the technological capability of assessing the visual function and functional vision; previously, assessment of these two aspects could only be accomplished with great difficulty. Microperimeters have been designed to provide a direct association between visual function and retinal changes (Rao et al. 2015; Midena 2007b; Ratra et al. 2012). There are some fundamental differences between microperimetry and standard automated perimetry (Springer et al. 2005; V. Ratra et al. 2012; Acton and Greenstein 2013):

- With microperimetry, spatial resolution can be achieved at an accuracy of half a degree in diameter or even less.
- In microperimetry, test stimuli are projected directly onto the surface of the retina. In standard automated perimetry, test stimuli are projected onto an illuminated screen.
- In microperimetry, the fixation is maintained by eye-tracking technology, which test-retests the same retinal points during the examination. In standard automated perimetry, the fixation is maintained by optical gaze tracking, which tests an area comparative to the size of the natural blind spot.

Today, a few companies produce devices for microperimetry. Not all of these companies' products are comparable. For example, the decibel scales of the Nidek MP-1 (Nidek Technologies, Padova, Italy); Optos OCT SLO (Optos, Dunfermline, Scotland, UK); MAIA (CenterVue, Padova, Italy); and Humphrey (Carl Zeiss, Dublin, CA) instruments are not directly comparable in any way (Markowitz and Reyes 2013b). The microperimetry field in MP-1 is 45 degrees vs. 29.7 degrees in Optos MP. The background luminance is 1.27 cd/m^2 in MP-1 and 10 cd/m^2 in Optos MP. The highest stimuli intensity is set at 128cd/m^2 for MP-1 vs. 125cd/m^2 for Optos MP ("MP1 - Microperimeter Manual," n.d.; "Optos OCT SLO Retina Glaucoma Cornea Analysis User Manual - International Version," n.d.). Thus, MP-1 has a darker background and lighter stimuli presented in comparison with those presented in the

Optos MP. Those different methodological characteristics makes results acquired from different microperimeters not directly comparable. Table 10 provides an overview of the technical aspects of microperimeters.

	MP-1	Optos	MAIA
Refractive error correction diopters	−15 to +15	−12 to +12	−15 to +10
Fundus image	Color digital and Infrared	SLO black and white	SLO black and white
Fundus image size	45 degrees	29.7°	36 degrees
B&W image resolution	768 × 576 pixels	512 × 512 pixels	1024 × 1024 pixels
Fixation monitoring	Eye trackers	SLO	Eye trackers
Fixation registration	25/s	4/sec or 8/sec	25/s
Image registration	Automatic	Simultaneous SLO and OCT	Automatic
Fixation stability estimates	Displayed	displayed	Displayed
Microperimetry field	45 degrees	29.7°	36 degrees
Light source	Halogen	IR diode 830 nm	IR diode 830 nm
Background luminance	1.27 cd/m²	10 cd/m²	1.27 cd/m²
Highest stimulus intensity	128 cd/m²	125 cd/m²	318 cd/m²
Stimulus attenuation	0-20 dB	0-20 dB	0-36 dB
Stimuli	Variety	Variety	Variety
Strategies	Static and dynamic	Static	Static
Retest	Automatic	Automatic	Automatic
Scotopic microperimetry	Included	Absent	Absent
Biofeedback training	included	absent	Included
OCT	Possibility to import images	Included	Absent
Macular integrity index	Differential maps for retinal sensitivity	Absent	Included

IR, infrared iodide dye; SLO, scanning laser ophthalmoscopy.

Table 10- Summary of clinically available microperimeters and their characteristics

Source: Information drawn from Markowitz and Reyes (2013)

The MP-1 (Nidek Technologies, Padova, Italy) microperimeter implements fundus perimetry by facilitating an electronic eye-tracking system for automatic corrections of the eye movement. It contains hardware, software projection, and an acquisition system. Infrared light is projected onto the retina of the test eye. The retinal image is obtained by a black and white, infrared camera with 768x576 pixels at 25 Hz resolution, which practically means one image every 40 msec (Midena 2007a; “MP1 - Microperimeter Manual,” n.d.; Midena and Pilotto 2017). In addition, a colour fundus camera produces a colour fundus image. The correct working distance is set at 47.1 mm, and that distance is maintained by the Purkinje bright spot formed by the reflected infrared rays. The MP-1 system also has a system to correct spherical refractive errors within range from -12.5 to +16 dioptres. Though the first available version of MP-1 microperimetry had only a mesopic test option, newer devices allow for a scotopic test option. For the purpose of the mesopic test, each test eye should undergo 5 to 10 minutes of dark adaptation before testing. The room light should be off during the examination. Patients should have a pupil size at minimum of 3 mm in diameter and should fixate on the object inside the instrument. Each test stimulus is presented at a selected luminance, so the patient reports perception of the test stimulus by pushing a hand-

held button. Thus, this signal is counted as “seen”. If the stimulus is not perceived, the signal is counted as “not seen”. Based on the patient’s response, a light stimulus can range between 0 db (brightest stimulus 40 asb, 127 cd/m^2) and 20 dB (dullest stimulus 4 asb, 1.27 cd/m^2) during the examination. The stimulus size varies between 6.5 and 103 min/arc, which reflects the Goldman stimulus size I-V. Each of these five different stimulus sizes covers a 4-fold greater area, ranging from 0.25 mm^2 for a size I stimulus to 64 mm^2 for a size V stimulus. The Goldmann size III stimulus corresponding to a 4-mm^2 test area is most commonly used, Larger stimulus sizes are used for individuals with poor visual acuity (“Standard Automated Perimetry - EyeWiki” n.d.). The duration of the stimulus can be set up at 100 ms or 200 ms. There is also a variety of shapes and colours among the fixation targets. The most widely used single cross fixation target has luminance at 100 asb, and size can vary between 0.5 and 20 degrees (Nizawa et al. 2017; Midena 2007b). An additional feature of the MP-1 is the automatic tracking system of eye movement, which continuously compares X and Y shifts of the eye to a baseline reference frame (H. Liu et al. 2015). Eye positions are documented 25 times per second. This rate of position documenting permits stimulus location to be correct and presented to the right retinal location, according to the current eye position. The microperimeter calculates and displays the fixation stability of the test eye. The fixation stability is classified by the manufacturer as follows (“MP1 - Microperimeter Manual,” n.d.):

- Fixation is stable if more than 75% of the fixation points are inside a 2-degree diameter circle.
- Fixation is relatively unstable if more than 75% of the fixation points are inside a 4-degree diameter circle and less than 75% are inside the 2-degree diameter circle.
- Fixation is unstable if less than 75% of the fixation points are inside the 4-degree diameter circle.

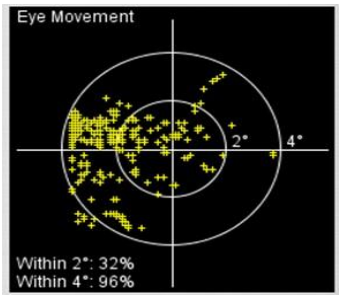


Figure 16- Eye movement map from Optos OCT SLO/MO Microperimetry device

Source: Image acquired by author during research project.

In visual field testing, there are also several standard psychophysical threshold strategies (Seiple et al. 2012). The most widely used is full-threshold strategy 4-2-1 dB. In this strategy, a suprathreshold stimulus is presented, and its intensity is decreased at fixed increments until it cannot be seen, and then increased until it can be seen. The threshold is taken to be equivalent to the intensity of the latest stimulus seen at that test location. Other modified test strategies include 4-2 and fast 2, which are less time consuming, but can lead to underestimation of the results in some cases due to the large dB increments.

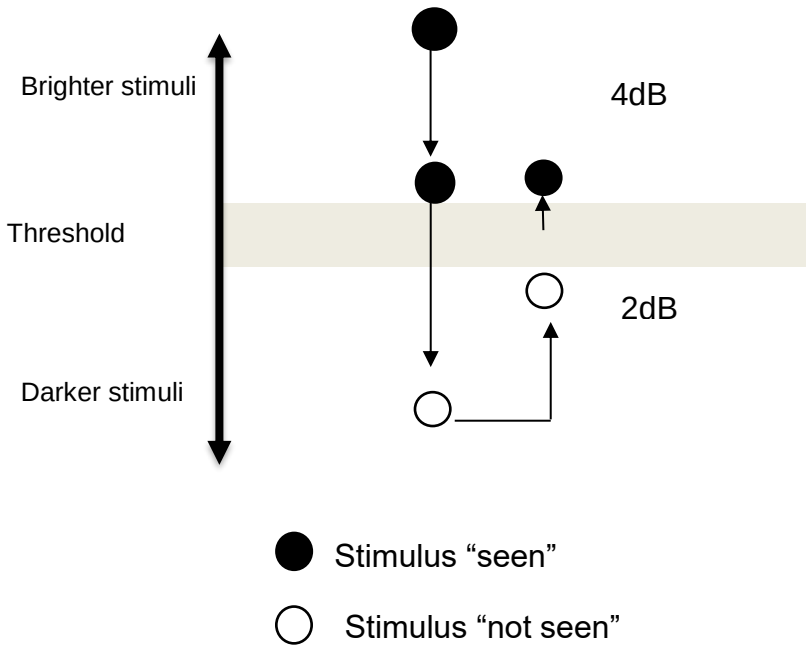


Figure 17- Graphical presentation of full threshold

The full threshold technique requires two responses, reversing from “seen” to “not seen” in 4dB steps and then back to “seen” again with 2dB steps.

At the end of the microperimetry examination, a flash colour fundus photograph with a resolution of 1388 x1038 pixels is taken that covers up to 45 degrees. In order to present the test results, the retinal image is aligned with the infrared reference frame. This alignment allows functional outcomes of the fixation area and sensitivity map to be aligned with the colour fundus image by tracking retinal vessel diameters outside the optic disc. The follow-up function allows re-testing at the same retinal points and under the same settings defined in the previous fundus perimetry examination.

The MP-1S model, which allows scotopic testing, enables examination of the rod functioning in the cone-free area of the retina from 0.6 to 10 degrees eccentrically. The test stimuli are in

the range of blue light up to 500 nm in wavelength and presented at the highest intensity of 0.3232 cd/m^2 (Markowitz and Reyes 2013).

The second microperimetry instrument available on the market was Optos OCT SLO (Optos, Dunfermline, Scotland, UK). This instrument successfully incorporates spectral domain optical coherence tomography (SD-OCT) and a confocal scanning laser ophthalmoscope (Anastasakis et al. 2011; “Optos OCT SLO Retina Glaucoma Cornea Analysis User Manual - International Version,” n.d.). The exceptional characteristic of the Optos SLO device is its ability to relay very accurately function to structure, which allows accurate topographic identification of disease. The light source is an infrared broadband super-luminescent diode with a wavelength of 830 nm. The background luminance of the instrument is 10 cd/m^2, and the stimulus ranges from 0 to 20 dB. The real time image is black and white. The retinal image is captured by a camera with high resolution at 512 x 512 pixels, which covers 29.7° field of view. Automatic focusing also corrects spherical refractive errors in a range from -12 to +12 dioptres. An automatic tracking system allows fundus localisation during the test time according to a retinal vascular-pattern alignment algorithm. The estimates of fixation stability are calculated and presented automatically at the end of the examination. The fixation stability analysis provided by the Optos SLO classifies fixation stability in a similar manner to the MP-1 Nideck, namely by positioning fixation points inside a 2-degree or a 4-degree diameter circular area (H. Liu et al. 2015; Nizawa et al. 2017). The follow-up function is also available in the Optos SLO, allowing retesting and comparing of results from two examinations (Markowitz and Reyes 2013a; Molina-Martín, Piñero, and Pérez-Cambrodí 2017).

The newest instrument to reach the market is the MAIA (CenterVue, Padova, Italy). This microperimeter integrates a high-frequency eye tracker and a line confocal scanning laser ophthalmoscope. The light source is an infrared broadband super luminescent diode with a wavelength of 850 nm. The field covered is up to 36 degrees x 36 degrees with a resolution of 1024 x 1024 pixels. The real-time image is also black and white. The background luminance of the instrument is 1.27 cd/m^2 (“MAIA Handbook Manual,” n.d.). The innovation in MAIA is the wider range of stimuli intensity (0 to 36 dB), which allows the highest stimulus intensity to be presented at 318.47 cd/m^2. An autofocusing system allows correction of

refractive errors in a range from -15 up to +10 diopters. The automatic eye tracking system is locked at complete retinal image and continuously captures fixation changes (Molina-Martín, Piñero, and Pérez-Cambrodí 2017). This device also has non-mydriatic test features, such that the minimum pupil size required is 2.5 mm. Exceptional to the MAIA instrument is the macular integrity assessment module (Jones et al. 2016). The software with its normative databases and statistical analysis module can identify normal age-related decrease in retinal sensitivity from pathological changes. The software calculates the estimated macular integrity index. This parameter is calculated on basis of normative data concerning the probability that threshold values will differ significantly from normal values. The device classifies macular integrity as follows (“MAIA Handbook Manual,” n.d.):

- Normal – loss no larger than 40%
- Suspect – loss between 40% and 60%
- Abnormal – loss greater than 60%

The index is a statistical value that is calculated by use of a neural network multivariate model (the EYEdBTM) (“MAIA Handbook Manual,” n.d.; A.I.Wiki n.d.). The model includes age, average threshold value, a measurement of points with a threshold < 25 dB, and all measured threshold values. It is derived by comparison with the manufacturer's normative data. It also describes the likelihood that threshold values will differ significantly from normal values. The macular integrity index is a numerical value that describes the likelihood that a patient's responses are normal, suspect, or abnormal when compared with age-adjusted normative data. No algorithm for the macular integrity index calculation has been published yet(Dolar-Szczasny, Święch-Zubilewicz, and Mackiewicz 2018). A follow-up function is also available in the MAIA microperimeter instrument. This instrument allows automatic retest of the same locations and retesting with settings identical to those of any previous microperimetry test (“MAIA Handbook Manual,” n.d.). Higher numbers suggest a greater likelihood of pathological findings, while lower values suggest a greater likelihood of normal findings.

Today, microperimeters are commonly used in clinical practice for clinical examination of retinal disorders in order to assess more accurately the impact of the disease and the result of its treatment (Raman et al. 2015; Laishram et al. 2017; Reibaldi et al. 2012; Soliman et al. 2012). Yet, due to the differences in the technical aspects described above, such as background luminance, test stimuli intensity, and the principle of the 4-2-1 strategy, the results from the two microperimeters used in this research are not directly comparable (Seiple et al. 2012; Balasubramanian et al. 2018; H. Liu et al. 2014). Therefore, the outcomes for each microperimeter are presented separately.

2.1.5 Reading speed

Regardless of the technical improvement in diagnosis and follow up of retinal disorders, it is still unclear how to predict everyday visual functional performance. There is a continuous need to assess how well patients with central vision loss will perform everyday visual tasks such as reading and driving. It is also known that clinically measured factors are good enough to predict visual function, but not functional vision. Legge et al. (1992a) showed that clinical factors such as visual acuity were poor predictors of the maximum reading speed achieved by patients with low vision. It is also agreed that clinical reading tests are useful as they provide additional information that is difficult to capture by self-report only. Today, there are several clinically available tests to measure reading ability; however, it remains unclear what is the best way to assess reading performance (Radner 2016a, 2016b, 2017; Radner et al. 1998).

Reading difficulty is amongst the most common complaints of patients who are referred to low vision services (Crossland, Culham, and Rubin 2005). This observation was obtained by data from 1,000 patients evaluated at Johns Hopkins Wilmer Eye Institute’s Low Vision Service, where each patient was asked to state the main reason for requesting referral to the low vision clinic (Rubin 2013). The results showed that for over 60% of the patients, the reason for referral was struggling to read. The second most common reason for up to 5% of the patients was difficulty while driving (Rubin 2013).

A few researchers have stated diverse opinions with regards to the usefulness of measuring functional vision. Some believe that functional vision complaints are not necessarily due to

patient's increased awareness of their eyes' health. Others have indicated that a reading performance-based test provides better information about patients' ability level than any functional vision tests. In addition, reading speed tests are considered as early predictors of functional vision deterioration and incapacity as reading speed tests are less affected by individuals' psychosocial, socio-demographic, and intellectual characteristics (Linn, Hunter, and Linn 1980; West et al. 1997; Guralnik et al. 1989). Discrepancy between self-report and performance-based tests can be suggestive of a transition from visual ability to disability. Thus such a sign is of high importance for patients when visual function has begun to deteriorate, but the person is still able to read correctly all letters on the ETDRS chart (under good contrast conditions). In such cases, the patient can maintain good performance, perhaps by adaptation and modification of the task (Legge et al. 1992). This condition is termed as "preclinical" disability in the geriatric literature (Fried et al. 1991). It is also considered as a vital prognostic factor of future visual functioning.

Reading tests have a long history and are widely described in the literature. Reading tests have served as the primary and secondary outcome measures for several clinical trials examining ophthalmic conditions such as

- the effectiveness of low vision rehabilitation (Binns et al. 2012);
- photocoagulation ("Laser Photocoagulation of Subfoveal Neovascular Lesions in Age-Related Macular Degeneration" 1991);
- sub-macular surgery (Hawkins et al. 2004);
- anti-VEGF treatments for neovascular age-related macular degeneration (Tufail et al. 2010); and
- comparison of intraocular lenses following cataract extraction (Akutsu et al. 1992).

Eduard von Jaeger developed the first known reading tests (Runge 2000a). These original tests are based on steps of sentence fragments of decreasing size presented on a chart. In this chart, the letter size is specified by using J-notations, for example, J1, J2 etc. Although these tests are still in use in some countries, the Jaeger reading cards have been criticised

for their failure to present meaningful size progression (Jose and Atcherson 1977; Runge 2000b).

Another type of clinically available reading test is the Sloan Continuous Text Read Cards (Sloan and Brown 1963). This reading test presents short text sections, with the text size specified in M-units. The amount of the text present on each card varies according to the letter size presented and can vary from few words at 20 metres to a full passage at 1 metre.

An alternative option for reading speed assessment is the Bailey-Lovie near reading chart developed in 1980 (Bailey and Lovie 1976, 1980; Bailey and Lovie-Kitchin 2013; Holladay and Prager 1989). Each card presents from two to six words per line. The size of the letters is presented in LogMAR. Another feature of the Bailey-Lovie near reading charts is the fact that the size of the text decreases each line by a constant percentage.

In 1989, Legge and colleagues introduced the Minnesota near Reading test (MNREAD Test) (Legge et al. 1989, 1992, 1997). It was initially designed as a computer-based test and lately was converted to a printed cards test. The clinically available MNREAD Acuity Chart is designed to measure maximum reading speed and reading acuity (Mansfi et al. 1993; Mansfield, Legge, and Bane 1996; Legge 2006). The chart, as shown in Figure 18, contains a series of standardised sentences in a range of letter size displayed on three lines. Each sentence has 60 characters. The sentences' letter size reduces by 0.1 log unit, ranging from 1.3 logMAR (corresponding to 6/12 when viewed at 40 cm) to 0.5 logMAR (equal to 6/2). The letter size thus decreases in logarithmic fashion, with the smaller letters on the reverse of the chart.

A second parameter which can be measured by the MNREAD test is the maximum reading rate, which is defined as the number of words read correctly per minute with the shortest reading time for that sentence. This reading test allows clinicians to measure a parameter referred to as critical print size. This parameter is the minimum magnification required for greatest reading performance, and it is measured by the smallest letter size that can be read at the maximum speed by the individual (Legge et al. 1989, 1997).

In short, Legge and colleagues defined three parameters in a scoring algorithm for the MNREAD test:

- reading acuity – the smallest print that can be read, but slowly.
- maximum reading rate – the fastest reading rate regardless of print size. The results can be presented as ext/min; word/min; syllables/min; characters/min.
- critical print size – the smallest letter size that allows reading at the maximum rate.

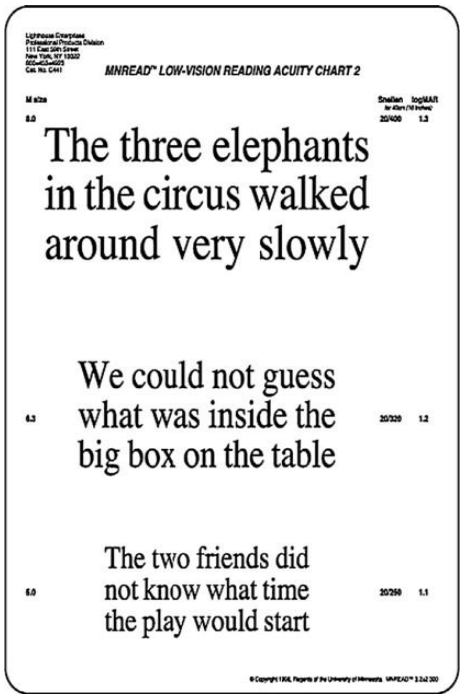


Figure 18- The MNREAD reading chart

The chart contains 3 sentences, each subsequent sentence reduced by a size of 0.1 log units.

Source: Image acquired by author during research project.

The most commonly used reading speed tests are available in many languages, but the International Reading Speed Texts (IReST) test was specifically designed for usage across seventeen languages (Trauzettel-Klosinski, Dietz, and IReST Study Group 2012; Wang et al.

2018). In each language, the test consists of 10 paragraphs of text which are equal in difficulty and length. The test's intention is to examine reading speed under daily situations such as reading newspaper print. Thus, the texts are provided in a size similar to newspaper print. The IReST test's consistent and analogous texts in many languages makes this test suitable for international studies.


In a small town a greengrocer had opened a shop that was located above a deep cellar. Every night, mice came in droves out of this cellar into the shop. They ate apples and pears, grapes and nuts and did not spare the vegetables and potatoes either. No goods that were in the shop were safe from the small intrusive rodents between midnight and sunrise. As long as there was noise in the streets at night and cars were driving by, the mice still stayed quietly in the cellar. But as soon as the old clock on the town hall had struck midnight and it became quiet in the street, they came out in droves, enjoyed the sweet fruits and celebrated real feasts, whose remains filled the owner with despair every morning when he entered the shop. So he tried to protect himself against the mice. At first he set up traps all over the shop.

number of text: 1
name of text: Mice
performance category: AB
number of words: 156
number of syllables: 205
number of characters: 662
reading time in seconds (mean ± SD): 40.4 ± 6.2
reading speed (mean ± SD) words/minute: 236 ± 29

Figure 19- Sample from the International Reading Speed Texts (IReST)

Source: Image acquired by author during research project.

In summary, there are many different clinically available reading speed tests, and the ideal test depends on what we want to know. If the researcher aims to evaluate a patient's reading performance with ordinary text or needs to compare international results, then the IReST test is the most appropriate. If the researcher is interested in the level of restored vision after treatment, then the MNREAD visual acuity test is the most suitable reading speed test.

An additional aspect to be considered is reading aloud versus silently. The literature describes discrepancy between self-reported reading ability and objectively measured reading speed (Ramulu, Swenor, Jefferys, and Rubin 2013; Ramulu, Swenor, Jefferys, Friedman, et al. 2013;

Friedman et al. 1999; Martins and Capellini 2019). One possible reason behind the observed discrepancy is that tests of out-loud reading may not capture reading difficulty adequately. For the purpose of this research, only out-loud reading speed was evaluated. This allowed an objective assessment of the reading performance of all patients involved.

2.1.6 Visual functioning questionnaire- 25

Clinically used methods for recording vision, such as Snellen visual acuity charts, may fail to assess many aspects of visual disability that are identified by persons as affecting daily functioning and wellbeing. There are several reliable and valid short questionnaires which assess vision-related difficulties. However, most of these questionnaires can only capture one dimension of vision-targeted health-related quality of life (Mangione et al. 2001, 1998). The National Eye Institute (NEI) supported the development of the visual function questionnaire- 25 (VFQ-25). This questionnaire aims to measure the sizes of self-reported vision-related health status in patients with chronic eye disease.

Firstly, the fifty-one-item NEI VFQ version was developed. Despite its success, a shorter version was created, namely the VFQ-25.The VFQ-25 contains a set of twenty-five vision-related questions representing 11 vision-related concepts and one further item – the general health-rating question. The VFQ-25 also includes an appendix of additional items, so that researchers can expand the scales up to thirty-nine total items. The VFQ- 25 generates the following vision-targeted subscales (“Vers 2000 VFQ-25 Manual_CM - Manual_cm2000.Pdf” n.d.):

1. global vision rating
2. difficulty with near vision activities
3. difficulty with distance vision activities
4. limitations in social functioning due to vision
5. role limitations due to vision
6. dependency on others due to vision
7. mental health symptoms due to vision

8. driving difficulties due to limitations with peripheral vision
9. colour vision
10. ocular pain

The VFQ-25 has two formats: the interviewer format and its self-administered version. It takes approximately 10 to 15 minutes to complete the interviewer format. The scoring system is a two-step process. Firstly, numeric values of the answers are re-coded according to the scoring rules defined by the NEI VFQ-25's scoring algorithm from August 2000 as presented in Appendix 3. Then each item is converted to a scale ranging from 0 to 100. Secondly, all items within each subscale are converted to create 12 subscale scores. The final scores symbolise the average for all items in that subscale. In order to present a final overall VFQ-25 score, calculations aim to present the average from the vision-related subscale score only. Excluding the general health-rating question gives equal weight to each vision-related subscale. The NEI VFQ-25 has been proven to be a valid and reliable measure of vision-related quality of life in patients with retinal disease, and it has been widely used to study age-related macular degeneration, cataracts, dry eyes, retinal detachment, uveitis, glaucoma, diabetic retinopathy, retinal vein occlusions, strabismus etc. (Choudhury et al. 2016; Chang et al. 2015; Deramo et al. 2003; Fox, O'Keefe, and Lanigan 2018; Hirooka et al. 2017; Khadka, McAlinden, and Pesudovs 2012; Klein et al. 2001; Suñer et al. 2017; Scott et al. 2017; Sheppard et al. 2017; Schippert et al. 2018; Varma et al. 2012; Zhang et al. 2016).

2.2 Review and approval of the research project

For the purpose of gaining the London - Fulham Research Ethics Committee's approval per the National Research Ethics Service guidelines, I designed the following study-specific documents:

- Project proposal
- Study participant consent form
- Patient information leaflet
- General practitioner information letter
- Cover letter to the Health Research Authority
- Research proposal, reviewed and commented on by two independent researchers

In addition to the above-listed documents, a copy of the Visual Functioning Questionnaire- 25 (VFQ-25) and a complete list of the documents attached were sent to the Health Research Authority (HRA). The research project was reviewed and approved by the Ethics Committee on 23rd July 2013. The study was registered under the Research Ethics Committee reference number 13/LO/1005 and under International Research Application System project ID 128193. At this stage, only one site for this study was included: Royal Surrey County Hospital. Thus a study protocol amendment was later proposed that specified reducing the sample size from 200 to 100 and including Moorfields Eye Hospital as a participating site. This amendment was reviewed and approved by the above sub-committee on 12th November 2013. The first patient visit occurred on 28th November 2013.

A monthly update on the recruitment progress was submitted via the UKCTG web port (https://www.ukctg.nihr.ac.uk/home/). The final patient's visit occurred on 28th May 2014. All documents related to the HRA application and review process are itemised in Appendix 3.

2.3 Study design

This project was designed as a multi-site, observational, prospective, non-interventional study evaluating the functional and anatomical outcomes for the treatment of retinal oedema. Study participants were screened during their routine appointments in eye clinics at Moorfields Eye Hospital and Royal Surrey County Hospital. Extensive information about the study aims and objects was given to each participant before obtaining the study participant consent form. For some of the participants, the screening and the baseline visit occurred on the same day. The data collected as part of the routine clinical examination are available in the clinical notes. Additionally, functional visual examinations such as reading speed testing, microperimetry testing, and the interviewer-based VFQ-25 questionnaire were completed and recorded in the separate research room. Patients were reassessed on the third, sixth, and twelfth month after enrolment in the study. Additional clinical appointments were not requested for the purpose of the study. Some patients were lost to follow up as they either failed to attend several hospital appointments or were referred to local hospitals. Barring these exceptions, each study

participant was observed and examined continuously for a period of 1 year or until the patient requested study withdrawal.

2.3.1 Study participants

Study participants were screened during their routine clinical appointments in the ophthalmology clinic in Moorfields Eye Hospital and Royal Surrey County Hospital. The study was designed to allow assessment of the “real-world” management of patients with macular oedema (MO) according to the current NICE clinical guidelines. All patients involved in the study had MO at baseline where the decision to initiate treatment for MO was based on the treating physician’s discretion.

No formal sample size calculation was done for this research. Patient screening in the two NHS hospitals was done routinely during the recruitment period (28th November 2013 to 28th May 2014). A sample size of 30 patients in each group was considered to be the minimum sample size required to achieve a statistically meaningful result.

Participation in the study was entirely voluntary. At the screening visit, the rationale of the study was discussed before the participant consent form was obtained from all participants. All patients had sufficient time to read the patient information sheet and discuss the study with the investigators and others (e.g. family members, friends, and their general practitioner if necessary) before providing written informed consent. The patient information leaflet, participant consent form, and general practitioner information letter, as well as the other study-related documents, are presented in Appendix 3. The inclusion/exclusion criteria were also checked at the screening visit to assess patients’ eligibility for inclusion in the study.

In total, 92 patients provided the signed participant consent form. Of those patients, three were excluded due to poor quality data. Thus 89 patients satisfied the inclusion and exclusion criteria and consented to take part in the study. Hence data were collected from 89 participants.

The study was designed to allow participants to be assessed in regular clinical settings for a period of 1 year. There were four main review time points:

- First visit: Baseline

- Second visit: Third month after baseline visit
- Third visit: Sixth months after baseline visit
- Fourth visit: Twelve months after baseline visit

The 89 participants were divided into three groups based on the primary cause of their MO: the 38 participants who presented with diabetic retinopathy (DRP) were in the DRP Group, the 26 participants who presented with retinal vein occlusion (RVO) were in the RVO Group, and the 25 participants who presented with uveitic macular oedema (UMO) were in the UMO Group. Table 11 shows the number of participants per group and their mean age.

Group	Patients (N)	Mean age (±SD)
DRP	38	62.62(±1.21)
RVO	26	64.92(± 2.99)
UMO	25	54.139(±3.03)
Total	89	60.90(±1.26)

Table 11- Enrolled participants' cause of macular oedema and mean age per group

Abbreviations: **N** = Number of patients; **SD** = Standard deviation of the mean

While some patients had MO presented in one eye, others had MO presented in both eyes. Thus, in this study a total of 118 eyes were examined. Table 12 presents the proportion of right and left eyes across the three study groups.

Group	Eye N (%) (RE = right eye, LE = left eye)
DRP	RE 28 (45.9%) LE 33 (54.1%) Total 61 (100%)
RVO	RE 10 (38.5%) LE 16 (61.5%) Total 26 (100%)
UMO	RE 20 (64.5%) LE 11 (35.5%) Total 31 (100%)

Table 12- Total number of eyes (left and right) per study group

During the observation period, I observed significant variation in the number of patients attending their routine clinical visits. Per the Ethical Committee's approval, we were not allowed to contact these patients or request additional clinical appointments for the purpose of the study. Consequently, this led to fluctuation in the number of patients seen in the clinics, and a significant number of study participants were lost during follow up. In other words, the rate of drop out over the study period was high. Table 13 summarises the number (percentage) of eyes per group that were examined at the third, sixth, and twelfth month study visits.

	Baseline	3 months	6 months	12 months
	N (%)	N (%)	N (%)	N (%)
DRP	61 (51.69%)	31 (26.27%)	35 (8.47%)	9 (1.69%)
RVO	26 (22.03%)	16 (13.56%)	9 (7.63%)	3 (2.54%)
UMO	31 (26.27%)	24 (20.34%)	16 (13.56%)	4 (3.39%)
Total	118 (100%)	71 (60.17%)	35 (29.66%)	9 (7.63%)

Table 13- Number of eyes followed up over the study period

2.3.2 Inclusion criteria

The inclusion criteria were designed to ensure that only patients with MO due to DRP, RVO, or uveitis were included in this study. At the baseline visit, all patients were further checked to ensure they also met the following criteria:

- Age ≥ 18 years old
- Diagnosis of MO at the initial visit identified by SD-OCT with CSRT ≥270 µm at the baseline visit
- Able and willing to attend follow-up appointments in the clinics
- Able and willing to provide informed consent
- Able and willing to perform functional vision testing
- Fluent in English

2.3.3 Exclusion criteria

Patients were not eligible for inclusion in this study if they met any of the following criteria:

- History of a medical condition that, in the opinion of the investigator, would preclude scheduled study visits, completion of the study, or safe administration of study medication
- Insufficient patient cooperation or medial clarity to allow adequate fundus imaging
- No evidence of MO at the baseline visit
- Presence of an ocular condition and/or disease that, in the opinion of the investigator, is responsible for visual loss and/or could affect study assessment
- History of intraocular surgery within 3 months prior to the baseline visit
- Participation in an investigational drug or device study within 1 year prior to the baseline visit in the studied eye
- Laser photocoagulation for MO in the studied eye within 3 months prior to the initial visit
- Use of intraocular, intravitreal, or periocular steroids in the studied eye within 3 months prior to the baseline visit
- Not able and or unwilling to give consent

Patients could withdraw from the study for any reason at any time. They were considered withdrawn if they stated an intention to withdraw or if they became lost during follow-up for any other reason. Patients who were withdrawn from the study were not replaced.

2.3.4 Development of case report form

For the purpose of data collection, a case report form (CRF) specific to the study was developed. The CRF first states the date of the visit; the participant's study number (i.e. the patient's unique identification code for the study); and whether one (left or right) or both of the participant's eyes are included in the study. The CRF then presents participant's past ocular history. The participant's past medical history follows, with the current diagnosis of the test eye(s) pre-defined by the treating clinician as one of the following:

- Mild non-proliferative DRP
- Moderate non-proliferative DRP
- Severe non-proliferative DRP
- Proliferative DRP
- Branch RVO
- Central RVO (ischemic)
- Central RVO (non-ischemic)
- Anterior UMO
- Intermediate UMO
- Posterior UMO
- Other

The CRF covers past ocular treatment next. The form presents the following options for past ocular treatment:

- Panretinal photocoagulation (PRP)
- Macula grid photocoagulation
- Intravitreal triamcinolone acetate injection
- Ozurdex
- Avastin (bevacizumab) intravitreal injection
- Lucentis (ranibizumab) intravitreal injection
- Eylea (aflibercept) intravitreal injection
- Other

The CRF concludes with the following data:

- Visual acuity, recorded as ETDRS letters where possible or alternatively as the Snellen or LogMAR equivalent.

- Any abnormal anatomical condition of the anterior or posterior segment of the eye detected during the ocular status examination conducted as part of the routine clinical examination.
- Reading speed performance as recorded on the MNREAD acuity chart.

Microperimetry test results were printed out and attached to the CRF. A copy of the CRF Version 2.1 can be found in Appendix 3.

2.4 Assessment schedule

Each study visit was designed to follow a routine clinical examination plan. At the screening visit, diagnosis of MO was confirmed, the inclusion/exclusion criteria were reviewed, and the patient information leaflet was presented. At the baseline visit, the participant consent form was obtained, and the general practitioner letter was sent. In some cases, the screening and baseline visits occurred on the same day. For each of the follow-up visits, visual acuity testing, reading speed testing, SD-OCT, microperimetry, and an ophthalmic examination were performed. The same examiner performed all tests for all study participants. Therefore test-retest validation was not required for the purpose of this research. The assessment schedule is summarised in Table 14.

Period	Screening	Baseline	3 months	6 months	12 months
Inclusion/exclusion criteria review	X	-	-	-	-
Diagnosis	X	-	-	-	-
Informed consent form	X	-	-	-	
Patient information sheet	X	-	-	-	-
GP letter	X	-	-	-	-
BCVA	X	X	X	X	X
Reading speed	X	X	X	X	X
OCT	X	X	X	X	X
Microperimetry	X	X	X	X	X
Ophthalmic examination	X	X	X	X	X

Table 14- Study assessment schedule and data collection time points

“X” indicates that the examination was performed

2.4.1 Description of functional vision examination

In this section, we describe the settings and performance of the functional vision tests which were not part of the routine clinical examination. After the visual acuity examination in the clinic, patients were asked to take part in the reading speed test. This assessment was conducted in a separate lighted room, which allowed participants to focus on the task. All patients were tested in the same conditions during the research. The following instructions were given before each reading speed assessment.

- Lift the chart so that no shadows or glare will affect your reading and keep the chart at a distance of 40 cm.
- The assessment administrator stated, “When I say ‘start’, please read the sentence aloud as quickly as you can without making errors. But if you do make an error, or realise that you missed a word, continue to read to the end of the sentence and then go back and correct yourself”.
- Start with the largest sentence and move to the subsequent sentence in decreasing size order.
- Keep going until you cannot read any of the words in a sentence.

Any reading errors were noted, and the time taken to read the sentence was recorded to the nearest 0.1 seconds. Reading time was defined as the time between when the patient was told to ‘start’ and when the patient finished reading the last word in the sentence. During the assessment, the examiner used a blank card to cover the sentence to be read next. The examiner uncovered the sentence and instructed the patient to start reading at the same time. The test results were recorded in the MNREAD Acuity Chart Card 3 provided by the manufacturer and according to the guidance provided in the chart user manual (Appendix 3).

After the reading speed test, participants’ pupils were dilated with Tropicamide 0.5% eye drops to enable examination of the posterior segment of the eye. Retinal thickness was measured as part of the routine clinical examination by using SD-OCT. The settings used for the Spectralis SD-OCT were “macula volume”, which is defined as 7-μm axial resolution and

scans at 40,000 A-scans per second at an angle of 30 degrees. The fixation light was central with size of 20 x 20 degrees, and spacing between each scan was 120 μm. For Topcon 3D OCT, the settings were 6-μm axial resolution and scans at 18,000 A-scans per second. These scans were obtained using a 256 x 128 raster pattern of A-scan covering a 6 x 6 mm area.

As a third step, microperimetry testing was performed. There were two available microperimeters, with one in each of the research units of the two study sites. The Optos OCT SLO was available in Royal Surrey County Hospital, and the MP-1, Nidek Ltd was available in Moorfields Eye Hospital. Both instruments were situated in a separate dark room. The pupil in the tested eye was dilated in order to have a better view of the retina. Each participant was left in the dark room for at least 5 mins for dark adaptation. The non-tested eye was patched. Each participant received detailed instruction about the task, and the demo version was performed for 15 seconds prior to the test. The front lights of the Optos SLO microperimetry were covered to reduce the glare and provide unbiased results for participants tested on this device.

Figure 20- Optos OCT SLO/ Microperimetry exact location of test stimuli in the EDTRS-Polar 3 Microperimetry testing grid pattern

Source: Images acquired by author during research project.

The testing pattern was named “Polar -3” and had the following parameters: 28 stimuli, 12-degree diameters for the pattern, strategy 4-2-1 in both instruments, stimuli interval duration of 1.5 ms, computer-assisted choosing for the eye tracking point, automatic eye-tracking system switched “ON”. This testing pattern allowed the central 12° of the visual field to be tested. This retinal area corresponded to the macula. The estimated duration of the test was automatically calculated to be around 4 mins per eye.

For the purpose of this study, a specific test grid was designed. On the grid, each test point location was identified and recorded on a coordinate system to ensure that the locations were identical. The exact locations of the test points in both microperimeters were identified by using the grid incorporated in the software; thus the locations of all 28 test points were exactly the same in both microperimetry instruments. The grid with test points locations marked in green is presented in Figure 21.

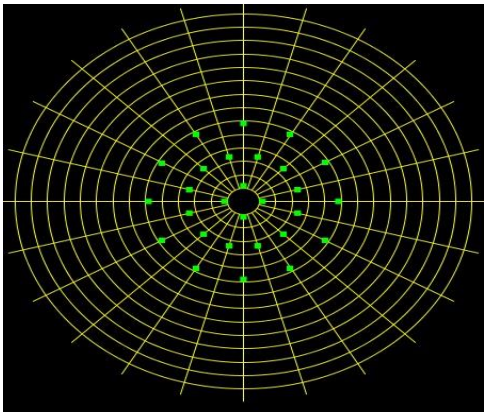


Figure 21- Polar 3 grid

The custom pattern used in the research.

Source: Image acquired by author during research project.

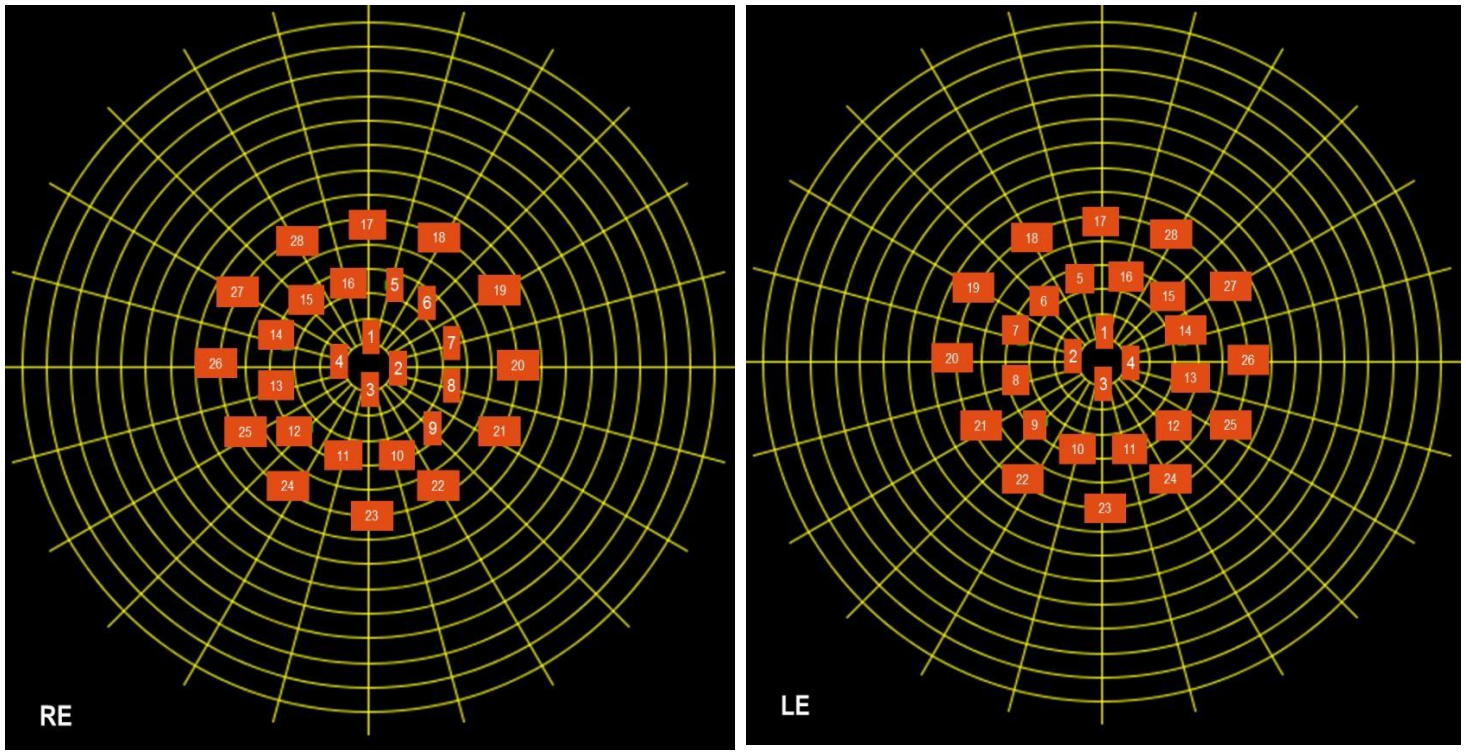


Figure 22- Location and numbering of all test points

RE- Right eye LE - Left eye

Source: Images acquired by author during research project

Point no.	Parallel	Meridian	Point no.	Parallel	Meridian
1	+0.0º	+1.1º	15	-2.3º	+2.5º
2	+1.2º	+0.0º	16	-0.8º	+3.3º
3	+0.0º	-1.2º	17	+0.0º	+5.8º
4	-1.2º	-0.1º	18	+2.9º	+5.0º
5	-0.9º	+3.3º	19	+5.0º	+2.9º
6	+0.9º	+3.3º	20	+5.8º	+0.0º
7	+2.5º	+2.3º	21	+5.0º	-2.9º
8	+3.3º	+0.8º	22	+2.9º	-5.0º
9	+3.3º	-0.8º	23	+0.0º	-5.8º
10	+2.4º	-2.4º	24	-2.9º	-2.9º
11	-0.8º	-3.4º	25	-5.0º	-2.9º
12	-2.5º	-2.5º	26	-5.9º	+0.0º
13	-3.3º	-0.8º	27	-5.0º	+2.9º
14	-3.3º	+0.8º	28	-2.9º	+5.0º

Table 15- Location of the 28 test points in Polar-3 macula grid test pattern

By placing the test points in the described patterns, I made the following assumptions:

- The distance from the disc to the fovea is about 15 degrees, or 4.6 mm, which gives 3.25 degrees per 1 mm approximately.
- The 1-m EDTRS circles lie at 1.625 degrees from the centre of the fovea

As shown in Figure 23, the 3-mm EDTRS circle is situated 4.875 degrees from the centre of the fovea. The inner circle of the EDTRS grid consists of 4 points, and its radius is 0.6 degrees. The second circle consists of 8 points, and its radius is 1.2 degrees. The third circle consists of 12 points, and its radius is 2.5 degrees. These assumptions are necessary to ensure that both microperimeters and the OCT are testing the same area in the retina.

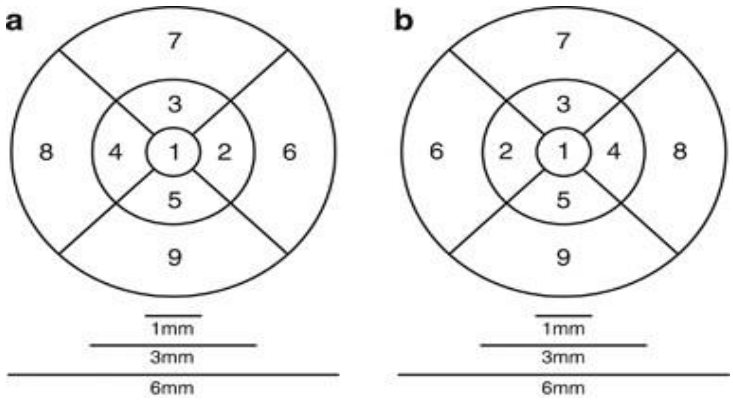


Figure 23- ETDRS grid size

Image A is the ETDRS grid and subfield for right eye.

Image B is the ETDRS grid and subfield for left eye.

Source: Images acquired by author during research project.

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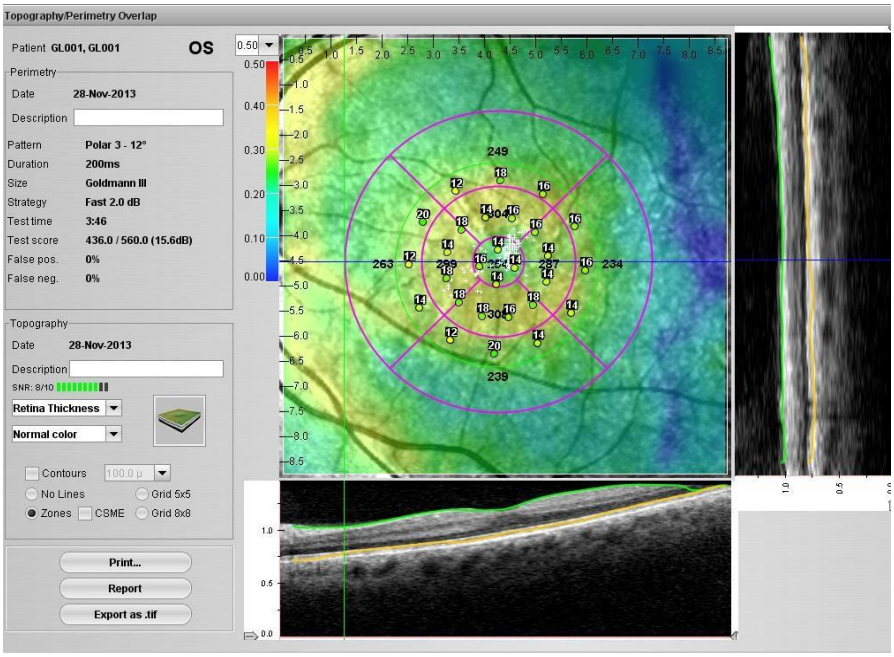

Figure 24- Microperimetry test result from Optos SLO microperimetry instrument

Source: Image acquired by author during research project.

Final microperimetry results were printed and attached to the CRF, where two terminologies were used: the mean sensitivity (MS) and the central zone mean sensitivity (CZ-MS). The MS refers to the mean sensitivity measured in 28 points in the macula area (6 mm in diameter). The CZ-MS refers to the mean sensitivity measured across the 4 points within the fovea area (1 mm in diameter).

Chapter 3. Functional outcomes in patients with macular oedema

3.1 Introduction

Macular oedema (MO) is the most common complication in patients with diabetic retinopathy (DRP), retinal vein occlusion (RVO), and uveitic macular oedema (UMO) (Browning et al. 2018). It also is the most common cause of visual acuity deterioration amongst these retinal conditions. In Chapter 3, I look at the participants in the present study, all of who have MO, as a single group. Section 3.2 summarises the available treatments for patients with MO. Section 3.3 presents the descriptive statistics for the routine clinical measures of the participants' visual acuity (VA) and retinal thickness (CSRT, CMT). Section 3.4 presents a descriptive analysis of the microperimetry, reading speed, and VFQ-25 outcomes in the study participants. Section 3.5 presents the anatomical changes in the participants over the course of treatments. Section 3.6 examines the correlation between routine clinical and functional tests in the participants, and Section 3.7 examines in turn the predicting values of all the clinically examined measures. Finally, Section 3.8 summarises the main findings of the study for the participants overall.

3.2 Therapy in macular oedema

MO is a major complication of several vascular and inflammatory retinal diseases. It is characterised by an abnormal presence of fluid inside the retinal layers of the macula (Durich et al. 2018). In a normal retina, there is constant balance between fluids. In several retinal diseases, this balance is compromised, resulting in abnormal fluid accumulation and ultimately MO formation. It was reported that MO affects about 7 million patients with diabetic macular oedema (Yau et al. 2012) and 3 million patients with RVO (Rogers et al. 2010). It also causes around 40% of visual acuity decline in patients with uveitis (Rothove et al. 1996). Multiple mechanisms are implicated in the development of MO that lead to visual impairment. Visual impairment due to MO could be reversible (if caught in the acute stages) or not reversible (long-standing MO). In the early stage of MO development, the passage of light through the neuroretinal layers is altered

by the hydration state of the retinal cells. Thus, acute central vision loss, a relative central scotoma, metamorphopsia, impaired stereopsis, and disturbed colour vision are common visual function issues (Achiron et al. 2015; Munk et al. 2013). At this early stage, treatment of MO or spontaneous resolution can reverse the visual damage. Long-lasting MO, however, could cause irreversible changes of the retinal structure and lead to permanent loss in vision. The main anatomical damages observed are alterations of the outer limiting membrane, alterations of the photoreceptor segments (outer nuclear layer thinning and outer segment atrophy), and disorganisation of inner retinal layers (Otani et al. 2010; Wakabayashi et al. 2009; Sun et al. 2015). For this reason, an effective and timely approach to the treatment of MO is of vital importance in order to prevent irreversible damage of visual function.

Diabetic macular oedema (DMO) is the most common cause of visual loss in patients with diabetes (Das et al. 2015). For many years, laser (focal and grid) photocoagulation was considered to be the standard of care for DMO. Today, the treatment of DMO has been transformed with the clinical introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections and corticosteroid implants. MO is also the main cause of visual deterioration in patients with RVO (Hayreh et al. 2014); anti-VEGF agents are also the first-line therapy in MO treatment due to RVO (Holtz et al. 2013; Boyer et al. 2012). The anti-VEGF molecules clinically approved for use are ranibizumab (Lucentis, Novartis Europharm Ltd, Horsham, UK), Brolucizumab (Beovue, Novartis Europharm Ltd, Horsham, UK), and aflibercept (Eylea ®, Bayer Pharma, Berlin, Germany). These approved anti-VEGF molecules demonstrated a benefit ratio and superior efficacy compared with laser photocoagulation in large phase 3 clinical trials on DRP (Mitchell et al. 2011; Nguyen et al. 2012; Brown et al. 2013; Wells et al. 2013; Heier et al. 2016). Besides ranibizumab and aflibercept, bevacizumab (a monoclonal antibody used to treat a number of types of cancer) demonstrated efficacy in the treatment of DMO, although its intraocular use is considered off-label. Recently, the Diabetic Retinopathy Clinical Research Network (DRCR.net) evaluated the outcomes of patients with DMO treated with bevacizumab, ranibizumab, or aflibercept (Cai et al. 2017). The Protocol T reported the best outcomes in DMO patients treated with aflibercept (Cai et al. 2017).

Further to the anti-VEGFs, intravitreal corticosteroids are considered to be an effective therapeutic option in RVO treatment. Their effectiveness is due in large part to their anti-inflammatory, anti-angiogenic, and anti-oedemic properties (Haller et al. 2010). They are also widely used in the management of UMO.

Intravitreal corticosteroids are considered as a second-line treatment for patients without significant response to anti-VEGF injections. In 2014, an Ozurdex intravitreal implant (Ozurdex ®, Allergan, Inc., Irvine, CA, USA) was approved for the treatment of DMO and RVO. The medicine contains 700 μg of sustained-release biodegradable dexamethasone. The MEAD study showed that Ozurdex was effective in the treatment of MO due to DRP, with a satisfactory safety profile and a low number of implants (four or five injections over a 3-year follow-up). Notwithstanding the strong efficacy of anti-VEGF and corticosteroid therapies, a substantial proportion of patients do not experience clinically meaningful improvements in vision in their daily lives (Smiddy et al. 2011; Lang et al. 2013; Virgili et al. 2014). Furthermore, frequent intravitreal administration is required to achieve and to maintain the early benefits of MO treatment over a long period of time. This requirement imposes a significant burden on patients and their caregivers by significantly affecting their vision-related quality of life.

MO secondary to uveitis is another important complication. In this complication, a crucial role is played by corticosteroids (topical, periocular, intravitreal, and systemic) and immunomodulatory drugs (biologic and non-biologic). The treatment of uveitic macular oedema (UMO) can be challenging because of its relapsing nature and its affinity to persist in many cases despite good control of intraocular inflammation (Preble et al. 2015). Currently, corticosteroids are widely used as the first-line treatment of UMO because of their fast-acting, anti-inflammatory properties. However, long-term use is not advised because of their local and systemic side effects (Dick et al. 2018). Thus, non-biologic immunomodulatory drugs are used as a second-line treatment for UMO as corticosteroid-sparing agents. This includes anti-metabolites (azathioprine, methotrexate, and mycophenolate mofetil), inhibitors of T-cell signalling (cyclosporine A, tacrolimus, and sirolimus), and alkylating agents (cyclophosphamide). A second option of corticosteroid-sparing agents are biological immunomodulatory agents such as tumour necrosis factor alpha blockers (anti-TNF-α) (Sharma et al. 2009). Currently, there are several medicines available to treat non-infectious uveitis: Adalimumab

(Humira; AbbVie Inc., North Chicago, IL, USA), Infliximab (Remicade ®, Janssen Biotech, Inc., Horsham, PA, USA), Golimumab (Simponi ®, Janssen Biotech Inc.), Etanercept (Enbrel ®, Immunex Corporation, Seattle, WA, USA), Tocilizumab (Actemra ®, Genentech Inc., San Francisco, CA, USA), and Rituximab (Rituxan ®, Genentech Inc.). Although many studies have shown improvement in macular thickness after biological immunomodulatory agents, their safety profile is risky, and they must be used with precautions (Deuter et al. 2017; Sharma et al. 2009; Mesquida et al. 2018; Diaz-Llopis et al. 2012; Constantin et al. 2018; Schaap-Fogler et al. 2014; Tugal-Tutkun et al. 2018).

In summary, MO is a major complication of several vascular and inflammatory retinal diseases, and multiple mechanisms are implicated in its development. The treatment of MO changes depending on the causative retinal disease. For patients with DMO and RVO, different intravitreal drugs are clinically available. These drugs include anti-VEGF injections (ranibizumab and aflibercept) and intravitreal corticosteroids (Ozurdex). However, despite the strong efficacy achieved with these medications, a significant number of patients with MO do not achieve anatomical or functional improvements. Similarly, in patients with uveitis, persistent or reoccurring UMO requires either long-term corticosteroids management or immunomodulatory (biologic or non-biologic) treatment approach. Regrettably, these medicines do not have a good safety profile and require frequent clinical visits.For the reasons listed above, new therapeutic approaches are needed in the treatment of persistent or resistant forms of MO. The expectation is that the new therapeutic modalities will improve not only the anatomical structure of the retina but also functional vision and consecutively the patient’s quality of life.

3.3 Descriptive statistics

As described in Chapter 2 of this thesis, the data collection happened during participants’ routine examinations in the ophthalmology clinics. The data collected included VA, presented as LogMAR, and retinal thickness measures such as central subfield retinal thickness (CSRT) and central macular thickness (CMT). At baseline, of the total 118 eyes observed in the study, 61 eyes were diagnosed with DMO; 26 eyes were diagnosed with MO due to RVO; and 31 eyes had UMO.

Group	Eye N (%)
DRP	RE 28 (45.9%) LE 33 (54.1%) Total 61 (100%)
RVO	RE 10 (38.5%) LE 16 (61.5%) Total 26 (100%)
Uveitis	RE 20 (64.5%) LE 11 (35.5%) Total 31 (100%)

Table 16- Total number of eyes (left and right) per study group

For 1 year, patients attended routine follow-up clinical visits at a frequency based on their eye status and the decisions made by their treating physician. A summary of the number of patients and the number of eyes observed at the study time points is presented in Figure 25.

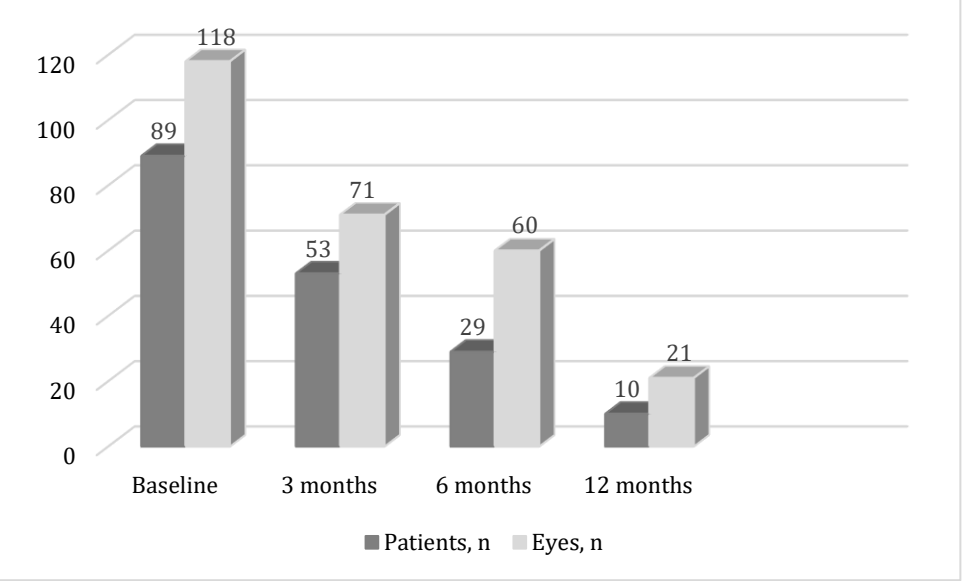

Figure 25- Total number of patients and eyes observed over 1 year of follow-up visits

As shown in Figure 26, the mean visual acuity amongst the observed MO patients was 0.45 ± 0.30 LogMAR at baseline, 0.38 ± 0.35 LogMAR at the 3-month visit, 0.55 ± 0.35 LogMAR at the 6-month visit, and 0.50 ± 0.52 LogMAR at the 12-month visit.

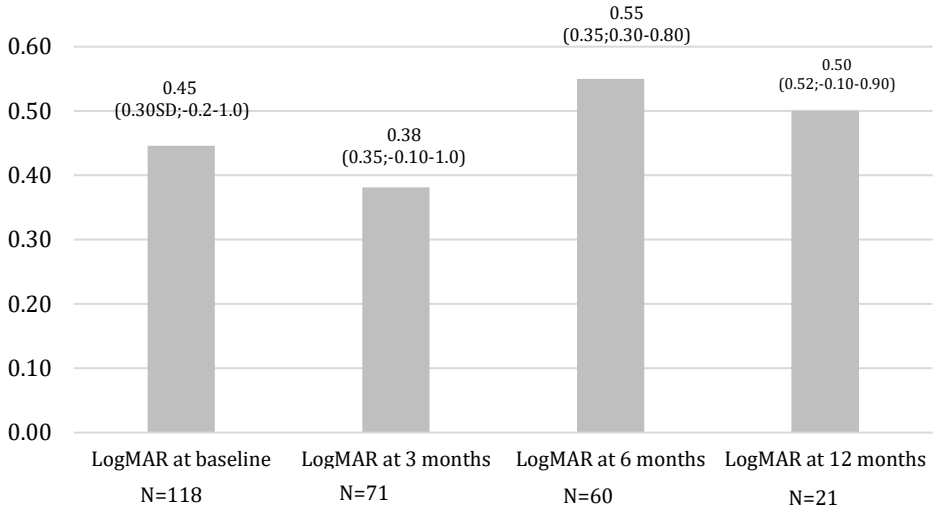

Figure 26- Mean BCVA in all patients observed over 1 year of follow-up visits

The two measures used to examine retinal thickness were CMT and CSRT (see Figure 27). The mean CMT was 393.31 ± 149.29 µm at baseline, 350.51 ± 166.73 µm at the 3-month visit, 323.70 ± 91.25 µm at the 6-month visit, and 363.11 ± 114.31 µm at the 12-month visit. The mean CSRT amongst the observed MO patients was 382.11±162.71 at baseline, 358.92 ± 147.72 µm at the 3-month visit, 362.10 ± 89.64 µm at the 6-month visit, and 367.31 ± 114.71 µm at the 12-month visit.

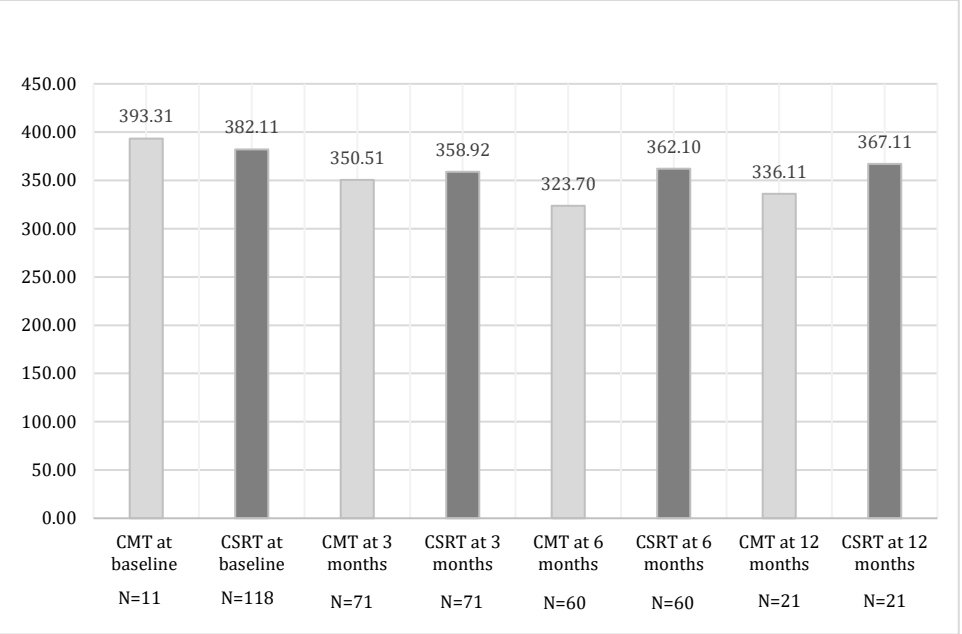

Figure 27- Mean CMT and CSRT in all patients observed over 1 year of follow-up visits.

The Kolmogorov-Smirnov test showed a non-normal distribution of the data (Appendix III), hence the Wilcoxon Signed Ranks Test was used to calculate the observed change from baseline to 3, 6, and 12 months for LogMAR, CMT, and CSRT. A summary of the results is presented in Table 17.

All patients	N	Mean	SD	Minimum	Maximum	*P*-value
LogMAR at baseline	118	0.45	0.30	-0.20	1.00	**0.011**
LogMAR at 3 months	71	0.38	0.35	-0.10	1.00	
LogMAR at baseline	118	0.45	0.30	-0.20	1.00	**0.032**
LogMAR at 6 months	60	0.55	0.35	-0.10	0.80	
LogMAR at baseline	118	0.45	0.30	-0.20	1.00	0.233
LogMAR at 12 months	21	0.50	0.52	-0.10	0.90	
CMT at baseline (μm)	118	393.31	149.29	146	382	**0.035**
CMT at 3 months (μm)	71	350.51	166.73	122	856	
CMT at baseline (μm)	118	393.31	149.29	146	382	**0.041**
CMT at 6 months (μm)	60	323.70	91.25	243	499	
CMT at baseline (μm)	118	393.31	149.29	146	382	0.326
CMT at 12 months (μm)	21	336.11	95.86	230	547	
CSRT at baseline (μm)	118	382.11	162.71	179	766	**0.032**
CSRT at 3 months (μm)	71	358.92	147.92	117	773	
CSRT at baseline (μm)	118	382.11	162.71	179	766	**0.039**
CSRT at 6 months (μm)	60	323.70	91.25	182	441	
CSRT at baseline (μm)	118	382.11	162.71	179	766	0.421
CSRT at 12 months (μm)	21	367.11	114.31	240	607	

Table 17- Change from baseline to 3, 6, and 12 months for LogMAR, CMT, and CSRT in all patients

Number (n), Mean, Standard Deviation (SD), , Range (Min, Max), p-value set at <0.05 level of significance.

3.4 Descriptive statistics for functional vision tests

In this section, I present the descriptive statistics for the functional vision tests – the microperimetry test, the reading speed test, and the VFQ-25 questionnaire – for the study participants overall. Due to the differences in the microperimeters used in this study, the microperimetry results are presented separately for the MP-1 and the Optos SLO.

3.4.1 Microperimetry results

The microperimetry testing was performed by using the MP-1 and the Optos SLO. The summary of the microperimetric results include number of eyes tested with the relevant device (N), mean, standard deviation (SD), standard error of the mean (SE), 95% CI, and Range (Min, Max). The results for the MP-1 and Optos SLO are presented in Figures 28 and 29 respectively.

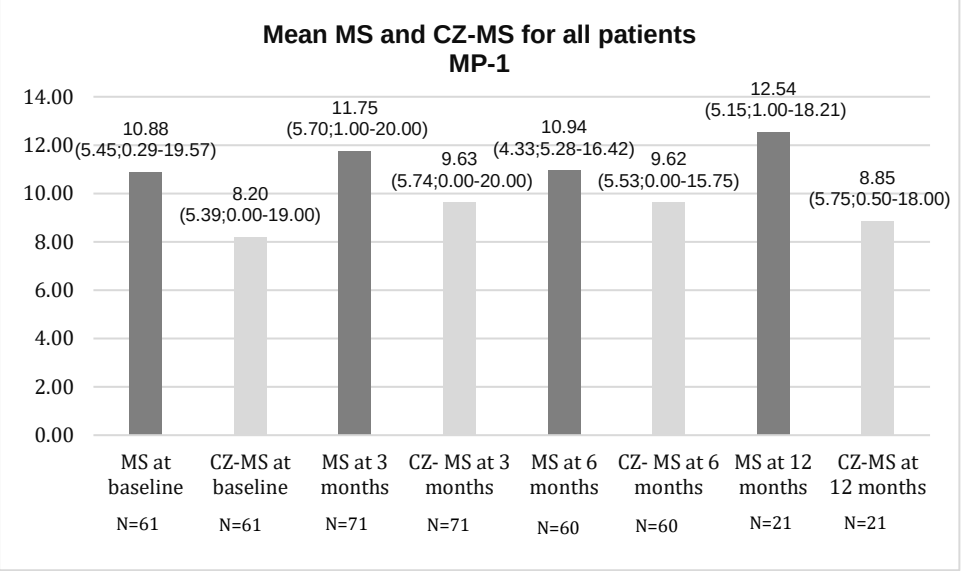

Figure 28- MP-1 descriptive statistics of microperimetry outcomes at baseline, 3-, 6-, and 12-month visits for all patients

Abbreviations: **MS** = mean sensitivity, **CZ-MS** = central zone mean sensitivity, **N** = number of patients

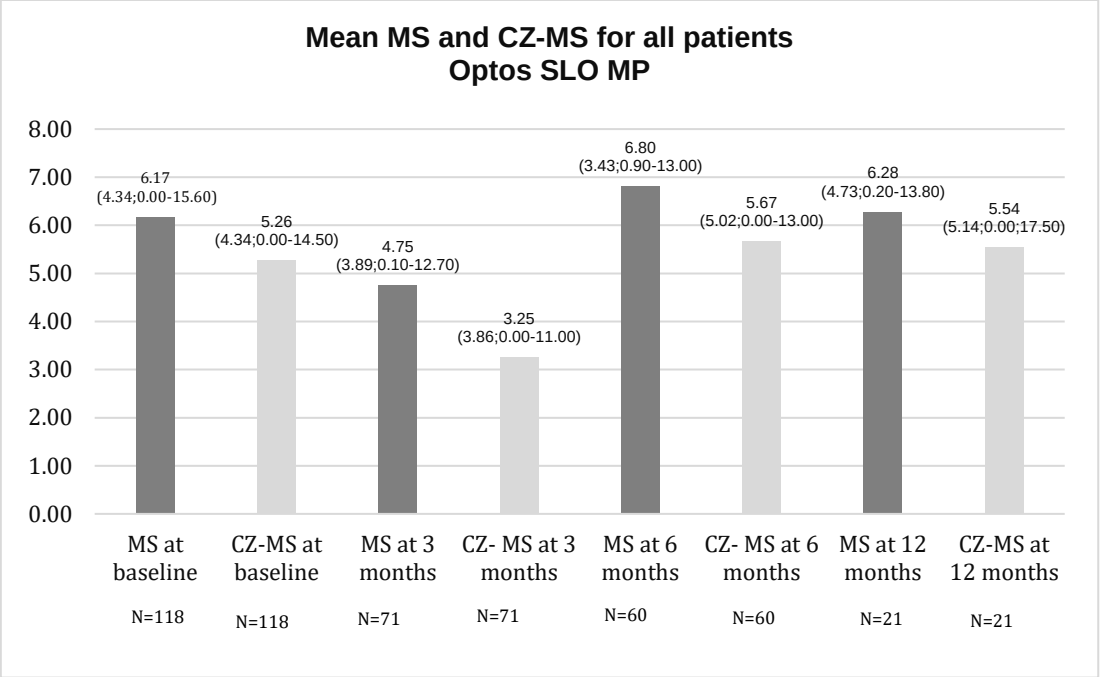

Figure 29- Optos SLO descriptive statistics of microperimetry outcomes at baseline, 3-, 6-, and 12-month visits for all patients

Abbreviations: **MS** = mean sensitivity, **CZ-MS** = central zone mean sensitivity, **N** = number of patients

A noticeable difference is present in the MS and CZ-MS values between the two MP devices. Patients' tested with the MP-1 device have different results (retinal sensitivity ranges from 7 to 12.65 dB) than patients tested with the Optos SLO MP device (retinal sensitivity ranges from 3.75 to 8.73 dB). This difference could be explained by the fact that the MP-1 and the Optos SLO use different background luminance, hence the retinal adaptation is different.

3.4.2 Reading speed results

The functional vision assessment for all study participants included a reading speed test using the MNREAD reading speed card. The following parameters were measured in order to describe the outcomes of the reading speed test:

- LogMAR at last sentence read
- Total reading errors

- Reading acuity in LogMAR
- Estimated max reading speed WPM from plot
- Critical print size in LogMAR

Figures 30 and 31 summarise the results for reading speed measures at baseline, 3-month, 6-month, and 12-month visits. The descriptive statistics included are number (N), Mean, Standard Deviation (SD), Standard Error of the mean (SE), 95% CI, and Range (Min, Max).

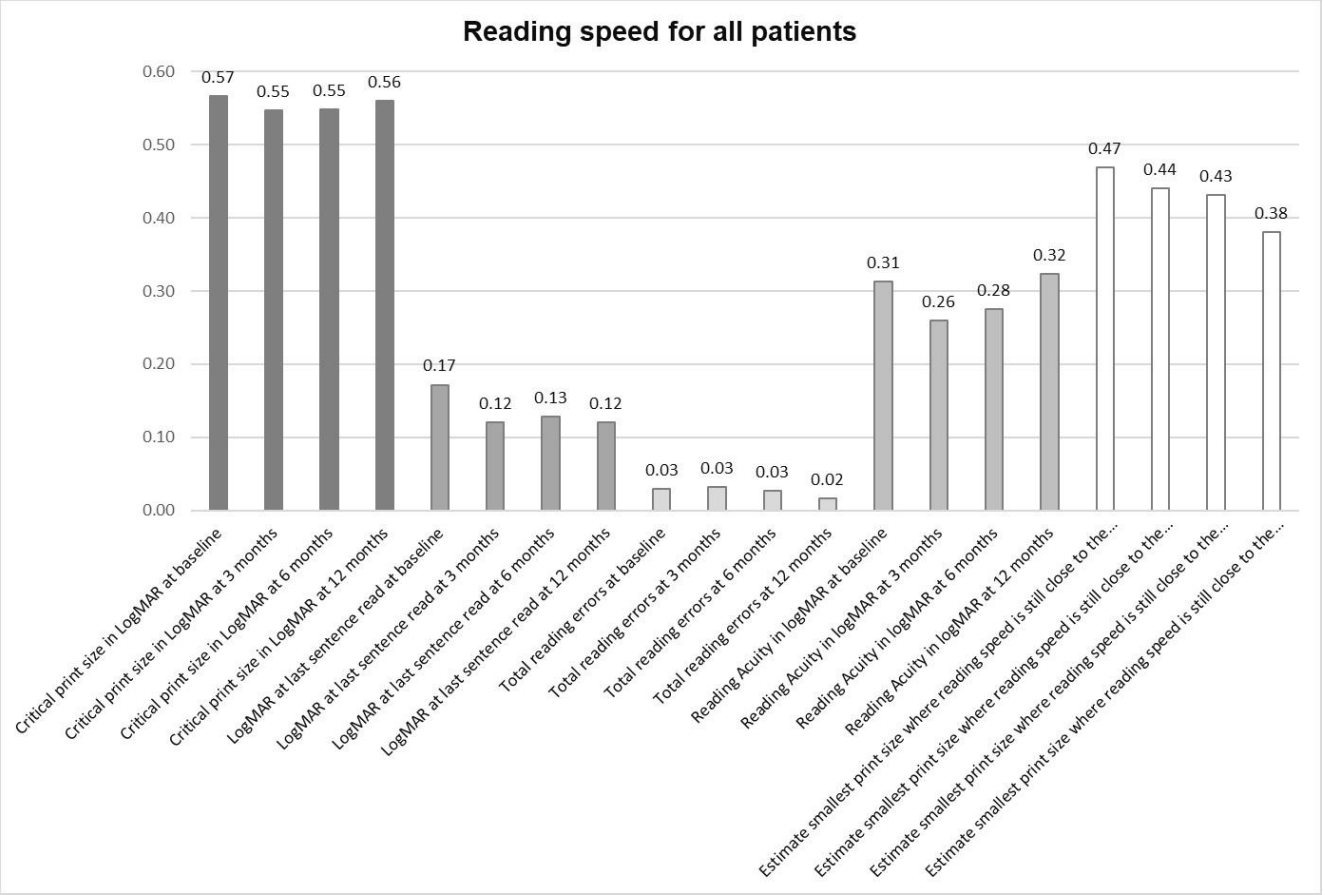

Figure 30- Reading speed measures at baseline, 3-, 6-, and 12-month visits for all patients

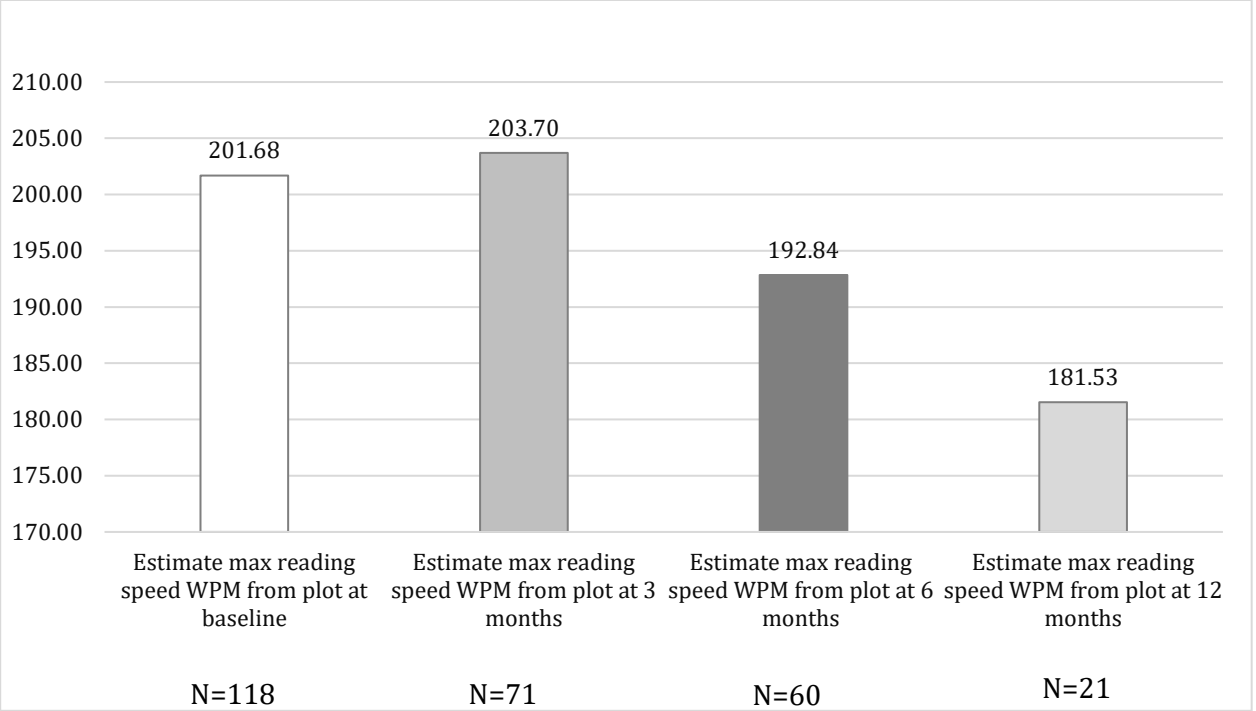

Figure 31- Estimated max reading speed WPM from the plot at baseline, 3-, 6-, and 12-month visits in all patients

I looked at the change from baseline to 3, 6, and 12 months in all reading speed parameters and found that there is statistically significant change from baseline in the following parameters:

- LogMAR at last sentence read at baseline (0.17 ± 0.21 SD) vs. LogMAR at last sentence read at 3 months (0.12 ± 0.25SD) *p-value= 0.021*
- LogMAR at last sentence read at baseline (0.17 ± 0.21 SD) vs. LogMAR at last sentence read at 6 months (0.13 ± 0.19 SD) *p-value = 0.025*
- Total reading errors at baseline (0.03 ± 0.04 SD) vs. Total reading errors at 3 months (0.03 ± 0.04 SD) *p-value = 0.032*
- Reading Acuity in LogMAR at baseline (0.31 ± 0.26 SD) vs. Reading Acuity in LogMAR at 3 months (0.26 ± 0.28 SD) *p-value = 0.015*
- Reading Acuity in LogMAR at baseline (0.31 ± 0.26 SD) vs. Reading Acuity in LogMAR at 6 months (0.28±0.26SD) *p-value = 0.038*
- Estimated smallest print size where reading speed is still close to the maximum at baseline (0.47 ± 0.31 SD) vs. Estimated smallest print size where reading speed is still close to the maximum at 3 months (0.44 ± 0.37 SD) *p-value = 0.045*

- Estimated max reading speed WPM from plot at baseline (202.68 ± 54.83 SD) vs. Estimated max reading speed WPM from plot at 3 months (203.70 ± 54.83 SD) *p-value* = 0.015
- Estimated max reading speed WPM from plot at baseline (202.68 ± 54.83 SD) vs. Estimated max reading speed WPM from plot at 6 months (192.84 ± 49.50 SD) *p-value = 0.041*

Full analysis information on the remaining parameters is available in Appendix-III

3.4.3 VFQ-25

I used the VFQ-25 questionnaire to examine patients' vision-related quality of life. The questionnaire was provided to all participants at the baseline visit. This questionnaire allowed identification of vision-related difficulties in patients' daily life. Based on the data collected from the VFQ-25, the following scores were calculated.

- General Health Score
- General Vision Score
- Ocular Pain Score
- Near Vision Score
- Distance Vision Score
- Social Score
- Mental Health Score
- Role Difficulties Score
- Dependence Score
- Driving Score
- Colour Vision Score
- Peripheral Vision Score

The calculation process, including the VFQ-25 scoring algorithm, is fully described in Appendix 3. Figure 32 presents the summary of the outcomes in percentages.

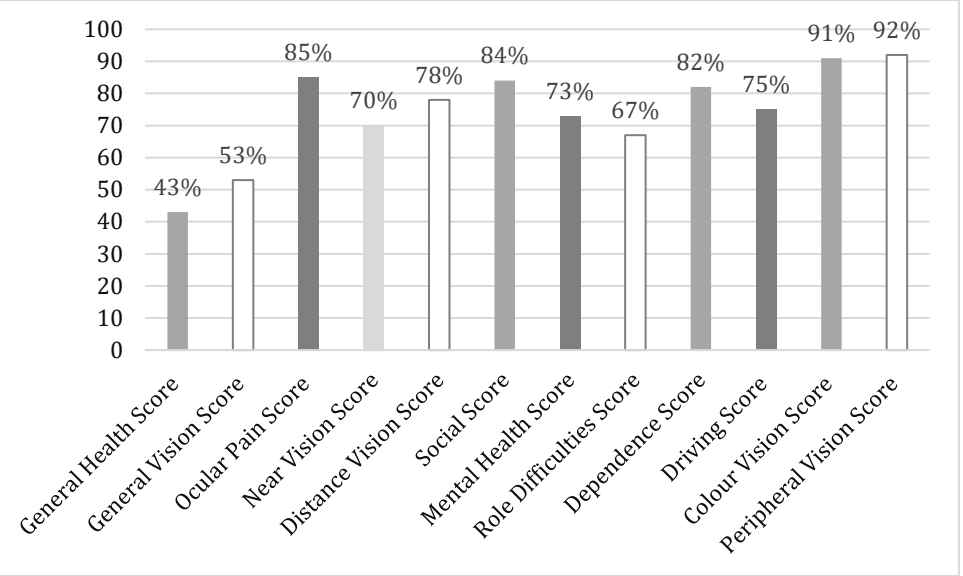

Figure 32- Mean VFQ-25 scores for all patients presented in percentages

Descriptive statistics include number (n), Mean, Standard Deviation (SD), Standard Error of the mean (SE), 95% CI, and Range (Min, Max).

From the results above, it can be seen that a few scores decreased considerably. These were the General Health Score 43% ± 0.26 SD, General Vision Score 53% ± 0.19 SD, Role Difficulties Score 67% ± 0.21 SD, Mental Health Score 73% ± 0.18 SD, Driving Score 75% ± 0.25 SD, Near Vison Score 70% ± 0.24 SD, Dependence Score 82% ± 0.16 SD, Social Score 84% ± 0.20 SD, and Ocular Pain Score 85% ± 0.21 SD.

3.5. Anatomical response to the therapy

In this section, I look at the changes in retinal anatomy during the study period to assess the structural changes in response to the MO treatment. This research examined the change in the percentage of patients with focal and diffuse MO, intraretinal fluid (IRF), subretinal fluid (SRF), haemorrhages, and exudates amongst all study participants.

3.5.1 Focal and diffuse macular oedema

The type of MO in all eyes observed across the study period is shown in Figure 33. At baseline, all study participants had MO: 73 eyes (60.16%) had diffuse MO, and 45 eyes

(38.18%) had focal MO. At 3 months, 10 eyes (10.08%) did not have MO; 22 eyes (30.98%) had focal MO, and 39 eyes (54.92%) had diffuse MO. At 6 months, the number of eyes with no MO was reduced to 9 (15%), 32 eyes (53.33%) had focal MO, and only 19 eyes (31.66%) had diffuse MO. At 12 months, 3 eyes (14.28%) did not have MO, 12 eyes (57.14%) had focal MO, and 6 eyes (28.57%) had diffuse MO. A significant number of patients did not return to the clinic for their 12-month visit. One possible explanation for their absence is that their visual acuity was stable, so they were referred for follow-up in local eye clinics.

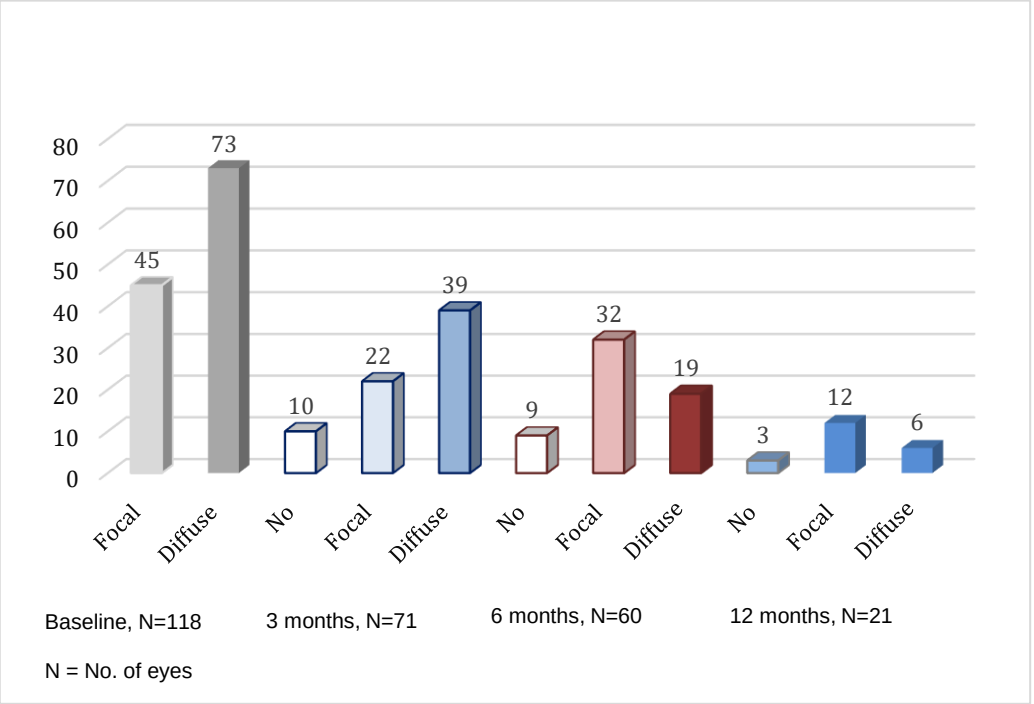

Figure 33- Type of MO in all eyes observed during study period

3.5.2 Intraretinal fluid in all patients

I looked at the location of intraretinal fluid (extrafoveal or subfoveal) during the study visits. I found that 78 eyes (66.10%) had extrafoveal and 38 eyes (32.20%) had subfoveal IRF. At baseline, there were also 2 eyes (1.69%) with no presence of IRF. At the 3- and 6-month visits, the percentage of the eyes with no IRF increased to 12.67% and 6.66% respectively. The majority of the patients remained with extrafoveal IRF at their 3- and 6-

month visits – 59.15% and 55% correspondingly. Some patients presented with subfoveal IRF at their 3-month (28.16%) and 6-month (38.33%) visits too. At the 12-month visits, of the 21 eyes seen, 3 eyes did not have IRF. The remaining eyes had extrafoveal (71.42%) or subfoveal (14.28%) IRF. A summary of the findings is presented in Figure 34.

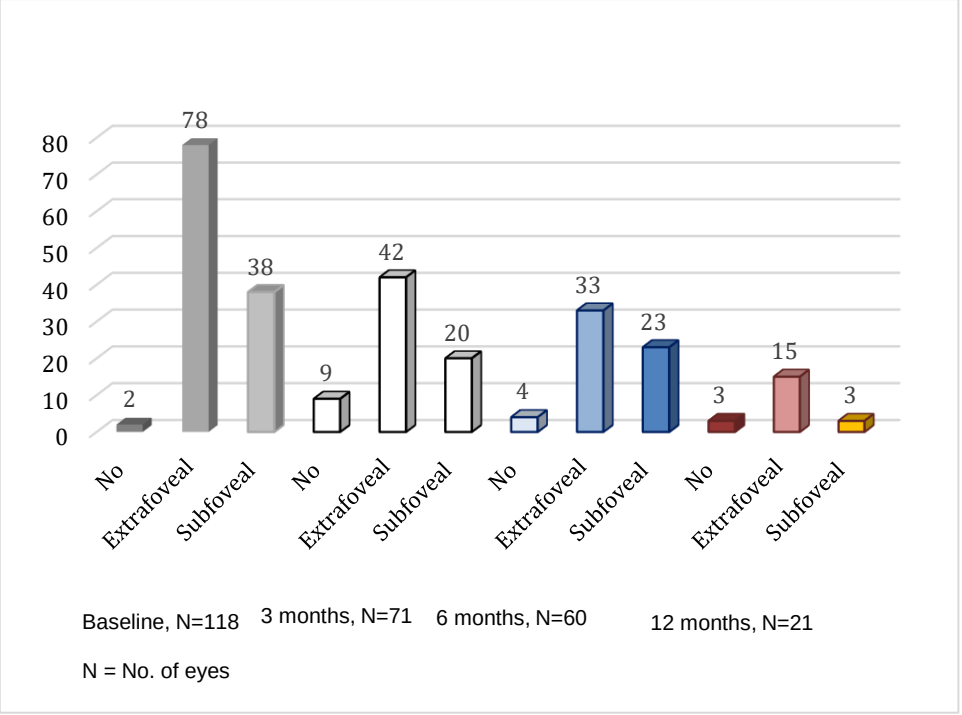

Figure 34- Location of IRF in all eyes observed during study period

3.5.3 Subretinal fluid in all patients

I also looked at the location of the subretinal fluid in all patients at baseline, 3-, 6-, and 12-month visits. In contrast to IRF, SRF presented in a smaller proportion of the study participants. At baseline, 5 eyes (4.23%) had extrafoveal and 22 eyes (18.64%) had subfoveal SRF. At the 3- and 6-month visits, extrafoveal SRF was seen in 2 (2.81%) and 5 (8.33%) eyes respectively. Subfoveal SRF was seen in 8 (11.26%) eyes at 3-month and 7 (11.66%) eyes at 6-month visits. At the 12-month visits, 2 (9.52%) eyes had extrafoveal SRF, and 9 (42.85%) eyes had subfoveal SRF. A summary of the findings is presented in Figure 35.

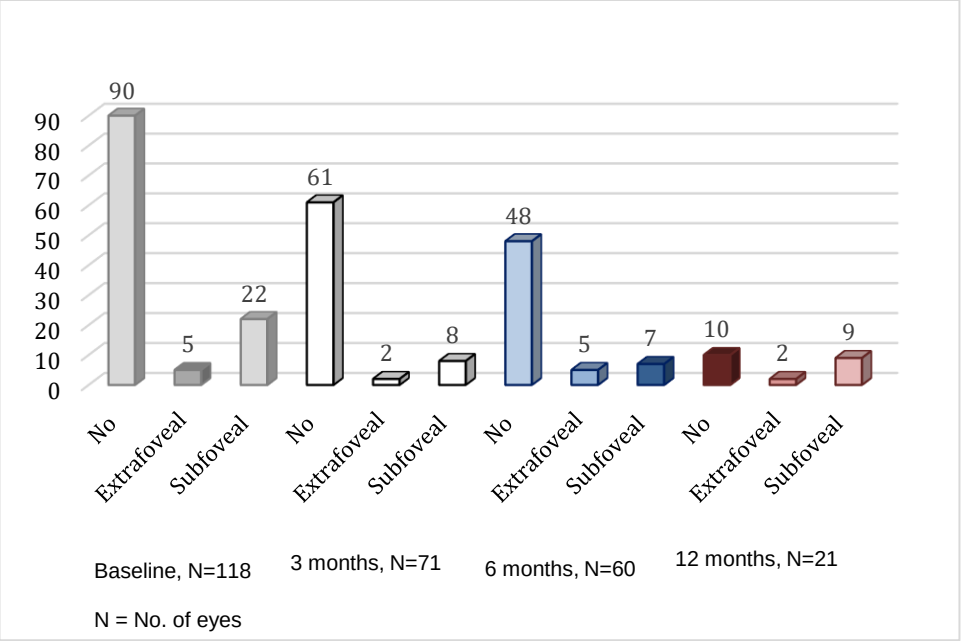

Figure 35- Location of SRF in all eyes observed during study period

3.6 Substantiation of the link between routine clinical and functional tests in patients with macular oedema

In this section, I assess the relationship between the clinical and functional tests. Here I define LogMAR, CMT, and CSRT as routine clinical tests, on the basis that these are regular ophthalmic investigations. I cluster the MS, CZ-MS, and reading speed tests and the VFQ-25 questionnaire as functional vision tests as they determine the functional vision performance. In order to identify the correlation between these measures, Spearman's rho statistical test was used.

3.6.1 VA, CMT, and CSRT correspondence with functional vision tests

Firstly, I examined the correlation between VA and functional test parameters. I used the Spearman's rho test to calculate the correlation between LogMAR and the CMT, CSRT, CZ-MS, MS, and reading speed test results. Although the analysed group includes all patients, the results are presented separately for the two microperimeters.

As shown in Table 18, I found that in all patients tested with the MP-1 device, LogMAR showed moderate correlation with CMT (R = 0.411; p-value < 0.001; N = 84) and CSRT (R = 0.428; p-value < 0.001; N = 84) and strong correlation with CZ-MS (R = -0.577; p-value <

0.001; N = 84), MS (R = -0.530; p-value < 0.001; N = 84), LogMAR at last sentence read (R = 0.695; p-value < 0.001, N = 84), reading acuity in LogMAR (R = 0.654; p-value < 0.001; N = 84), estimated max reading speed (WPM) from the plot (R = -0.453; p-value = 0.032; N = 84) and critical print size in LogMAR (R = 0.632; p-value < 0.001; N = 84).

MP-1									
	LogMAR	**CMT**	**CSRT**	**CZ-MS**	**MS**	**LogMAR at last sentence read**	**Reading acuity in LogMAR**	**Est. max reading speed (WPM)**	**Critical print size in LogMAR**
All	R	0.411	0.428	-0.577	-0.530	0.695	0.652	-0.453	0.632
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.032**	**<0.001**
	N	84	84	84	84	84	84	84	84

Table 18- Correlation between LogMAR vs. CMT, CSRT, CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for all patients tested with the MP-1 device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

I looked at all patients tested with the Optos SLO MP device separately. As shown in Table 19, I found that LogMAR showed moderate correlation with CMT (R = 0.382; p-value = 0.013; N = 34), CSRT (R = 0.372; p-value = 0.011; N = 34), CZ-MS (R = -0.495; p-value = 0.015; N = 34), reading acuity in LogMAR (R = 0.402; p-value = 0.024; N = 34), estimated max reading speed (WPM) from the plot (R = -0.320; p-value = 0.042; N = 34), and critical print size in LogMAR (R = 0.440; p-value = 0.010; N = 34) and strong correlation with the MS (R = -0.505; p-value = 0.020; N = 34) and LogMAR at last sentence read (R = 0.541; value = 0.027; N = 34).

Optos SLO MP									
	LogMAR	**CMT**	**CSRT**	**CZ-MS**	**MS**	**LogMAR at last sentence read**	**Reading acuity in LogMAR**	**Est. max reading speed (WPM)**	**Critical print size in LogMAR**
All	R	0.382	0.372	-0.495	-0.505	0.541	0.402	-0.320	0.440
	p	**0.013**	**0.011**	**0.015**	**0.020**	**0.027**	**0.024**	**0.042**	**0.010**
	N	34	34	34	34	34	34	34	34

Table 19- Correlation between LogMAR vs. CMT, CSRT, CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR , estimated max reading speed (WPM), and critical print size in LogMAR for all patients tested with the Optos SLO device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

I also looked at the correlation between CMT, reading speed, and microperimetry parameters for both MP devices. I found a statistically significant correlation between CMT and CZ-MS (R = -0.253; p-value = 0.023; N = 84), reading acuity in LogMAR (R = -0.335; p-value = 0.042; N = 84), estimated max reading speed (WPM) from the plot (R = -0.335; p-value = 0.047; N = 84), and critical print size in LogMAR (R = 0.475, p-value = 0.006; N = 84) amongst all patients tested with the MP-1 microperimeter (see Table 20). For patients tested with the Optos SLO MP device, I found similar results. As shown in Table 21, there was a statistically significant correlation between CMT and CZ-MS (R = -0.263; p-value = 0.043; N = 34), reading acuity in LogMAR (R = -0.433; p-value = 0.056; N = 34), and critical print size in LogMAR (R = 0.521, p-value = 0.019; N = 34).

MP-1							
	CMT	CZ-MS	LogMAR at last sentence read	Reading acuity in LogMAR	Est. max reading speed (WPM)	Critical print size in LogMAR	MS
All	R	-0.253	0.326	0.365	-0.335	0.475	-0.120
	p	**0.023**	0.052	**0.042**	**0.047**	**0.006**	0.072
	N	84	84	84	84	84	84

Table 20- Correlation between CMT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR in DRP group for the MP-1 device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

Optos SLO MP							
	CMT	CZ-MS	LogMAR at last sentence read	Reading acuity in LogMAR	Est. max reading speed (WPM)	Critical print size in LogMAR	MS
All	R	-0.267	0.378	0.433	-0.411	0.521	-0.131
	p	**0.043**	0.142	**0.056**	0.075	**0.019**	0.117
	N	34	34	34	34	34	34

Table 21- Correlation between CMT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR in DRP group for the Optos SLO MP device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

The CSRT is another clinical parameter widely used to assess the outcomes of the applied treatment for MO. I investigated the correlation between CSRT, reading speed, and microperimeter outcomes. I found that there is correlation between CSRT and CZ-MS (R =

-0.242; p-value = 0.032; N = 84), LogMAR at last sentence read (R = 0.335; p-value = 0.028; N = 84), reading acuity in LogMAR (R = 0.347; p-value = 0.022; N = 84), and critical print size in LogMAR (R = 0.442; p-value = 0.004; N = 84) for patients tested with the MP-1 (see Table 22). For the patients tested with the Optos SLO device, I found similar results (see Table 23). The CSRT showed statistically significant correlation with CZ-MS (R = -0.251; p-value = 0.040; N = 34), LogMAR at last sentence read (R = 0.420; p-value = 0.039; N = 34), reading acuity in LogMAR (R = 0.381; p-value = 0.041; N = 34), and critical print size in LogMAR (R = 0.410; p-value = 0.010; N = 34).

MP-1							
		CSRT	**CZ-MS**	**LogMAR at last sentence read**	**Reading acuity in LogMAR**	**Est. max reading speed (WPM)**	**Critical print size in LogMAR**	**MS**
All	R	-0.242	0.355	0.347	-0.024	0.442	-0.178
	p	**0.032**	**0.028**	**0.022**	**0.520**	**0.004**	0.092
	N	84	84	84	84	84	84

Table 22- Correlation between CSRT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for the MP-1 device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

Optos SLO MP							
		CSRT	CZ-MS	LogMAR at last sentence read	Reading acuity in logMAR	Est. max reading speed (WPM)	Critical print size in LogMAR	MS
All	R	-0.251	0.420	0.381	-0.041	0.410	-0.212
	p	**0.040**	**0.039**	**0.041**	0.82	**0.010**	0.183
	N	34	34	34	34	34	34

Table 23- Correlation between CSRT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for the Optos SLO MP device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

3.6.2 Correlation of microperimetry and reading speed tests

In this section, I investigate whether the microperimetry results correlate with patients' reading speed performance and self-reported vision-related quality of life. I use the MS and CZ-MS from the microperimetry testing for the two MP devices. The Spearman's rho test was used to identify the correlation between CZ-MS and MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM) from the plot, and critical print size in LogMAR. The total number of cases (N), correlation coefficient (R), and p-value are indicated in the table for each group. The results are presented separately for the two MP devices used in this research.

From Table 24 it can be seen that, in all patients tested with the MP-1 device, there was a statistically significant correlation between MS and LogMAR at last sentence read (R = -0.320; p-value = 0.041; N = 84), reading acuity in LogMAR (R = -0.418; p-value = 0.002; N = 84), estimated max reading speed (WPM) from the plot (R = 0.455; p-value = 0.021; N = 84), and critical print size in LogMAR (R = -0.331; p-value = 0.034; N = 84) for patients tested with MP-1 microperimeter. I found similar results for patients tested with the Optos SLO microperimeter. There was statistically significant correlation between MS and LogMAR at

last sentence read (R = -0.287; p-value = 0.041; N = 84), reading acuity in LogMAR (R = -0.418; p-value = 0.002; N = 84), estimated max reading speed (WPM) from the plot (R = 0.455; p-value = 0.021; N = 84), and critical print size in LogMAR (R = -0.332; p-value = 0.034; N = 84).

MP-1					
	MS	**LogMAR at last sentence read**	**Reading acuity in LogMAR**	**Est. max reading speed (WPM)**	**Critical print size in LogMAR**
All	R	-0.320	-0.418	0.455	-0.331
	p	**0.041**	**0.002**	**0.021**	**0.034**
	N	84	84	84	84

Table 24- Correlation between MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for all patients tested with the MP-1 device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

Optos SLO MP					
	MS	LogMAR at last sentence read	Reading acuity in LogMAR	Est. max reading speed (WPM)	Critical print size in LogMAR
All	R	-0.287	-0.381	0.395	-0.322
	p	0.072	**0.021**	**0.041**	**0.068**
	N	34	34	34	34

Table 25- Correlation between MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for all patients tested with the Optos SLO MP device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

I also investigated the correlation between CZ-MS and LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM) from the plot, and critical print size in LogMAR for all patients tested with the MP-1 or the Optos SLO microperimeter. I found a statistically significant correlation between CZ-MS and LogMAR at last sentence read (R = -0.482; p-value = 0.002; N = 84), reading acuity in LogMAR (R = -0.520; p-value = 0.002; N = 84), estimated max reading speed (WPM) from the plot (R = 0.384; p-value = 0.048; N = 84), and critical print size in LogMAR (R = -0.479; p-value = 0.011; N = 84) for all patients tested with the MP-1 device (see Table 26). I found similar results for patients tested with the Optos SLO device. As shown in Table 27, there was a statistically significant correlation between CZ-MS and LogMAR at last sentence read (R = -0.353; p-value = 0.010; N = 84), reading acuity in LogMAR (R = -0.421; p-value = 0.016; N = 84), estimated max reading speed (WPM) from the plot (R = 0.329; p-value = 0.082; N = 84), and critical print size in LogMAR (R = -0.379; p-value = 0.022; N = 84).

MP-1					
	CZ-MS	LogMAR at last sentence read	Reading acuity in logMAR	Est. max reading speed (WPM)	Critical print size in LogMAR
All	R	-0.482	-0.520	0.384	-0.479
	p	**0.002**	**0.002**	**0.048**	**0.011**
	N	84	84	84	84

Table 26- Correlation between CZ-MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for the MP-1 device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

Optos SLO MP					
	CZ-MS	LogMAR at last sentence read	Reading acuity in LogMAR	Est. max reading speed (WPM)	Critical print size in LogMAR
All	R	-0.353	-0.421	0.329	-0.391
	p	**0.010**	**0.016**	**0.082**	**0.022**
	N	84	84	84	84

Table 27- Correlation between CZ-MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for the MP-1 device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

3.6.3 Correspondence between vision-related quality of life (VFQ-25) and VA, CSRT, and CZ-MS

Best corrected visual acuity (BCVA) is an irreplaceable clinical measure in daily eye clinics to assess functionality of the eye system. Yet BCVA does not fully describe all visual function and often does not represent patients' visual experience in daily life. This section presents the

relationship between the participants' self-reported vision-related quality of life and the clinically available assessments. I looked at the VFQ-25 score and the anatomical and functional tests (retinal thickness, MS, CZ-MS, and reading speed).

As Table 28 shows, in all patients with MO, the BCVA (LogMAR) correlated with the scores for general vision (R = -0.483; p-value = 0.012; N = 89), ocular pain (R = -0.219; p-value = 0.040; N = 89), role difficulty (R = -0.114; p-value = 0.021; N = 89), and dependence (R = - 0.324; p-value = 0.039; N = 89).

All	BCVA	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
	R	0.044	-0.483	-0.219	-0.485	-0.387	-0.128	-0.048	-0.114	-0.324	-0.187	-0.082	-0.029
	p	0.691	**0.012**	**0.040**	**0.031**	**0.02**	0.233	0.184	**0.021**	**0.039**	0.067	0.281	0.973
	N	89	89	89	89	89	89	89	89	89	89	89	89

Table 28- Correlation between BCVA and VFQ-25 scores in all patient groups

R = correlation coefficient, N = number of patients, and p-value < 0.05.

I looked at relationship between CSRT and the VFQ-25 to assess whether routinely used OCT parameters (CSRT and CMT) correlated with patients' self-reported vision. As shown in Table 29, I found a statistically significant correlation between CSRT and the scores for general vision score (R = -0.383; p-value = 0.032; N = 89), near vision (R = -0.385; p-value = 0.005; N = 89), role difficulty (R = 0.214; p-value = 0.042; N = 89), and dependence (R = -0.124; p-value = 0.044; N = 89).

	CSRT	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
All	R	0.034	-0.383	0.119	0.385	-0.363	-0.228	-0.028	0.214	-0.124	02187	-0.032	0.059
	p	0.88	**0.032**	0.055	**0.005**	**0.041**	0.121	0.093	**0.042**	**0.044**	0.167	0.451	0.747
	N	89	89	89	89	89	89	89	89	89	89	89	89

Table 29- Correlation between CSRT and VFQ-25 scores in all patient groups

R = correlation coefficient, N = number of patients, and p-value < 0.05.

I also looked at whether testing CZ-MS with the microperimeter could reveal more about patients' functional outcomes. As shown in Table 30, in patients tested with the MP-1, I found a statistically significant correlation between CZ-MS and the scores for general vision (R = 0.533; p-value < 0.001; N = 84), near vision (R = 0.206; p-value = 0.025; N = 84), mental health (R = 0.372; p-value = 0.022; N = 84), role difficulties (R = 0.395; p-value = 0.027; N = 84), dependence (R = 0.273; p-value = 0.033; N = 84), and driving (R = 0.537; p-value = 0.007; N = 84).

For patients tested with Optos SLO, I found similar results (see Table 31). The CZ-MS correlated with the scores for general vision (R = 0.533; p-value < 0.001; N = 84), near vision (R = 0.206; p-value = 0.025; N = 84), mental health (R = 0.372; p-value = 0.022; N = 84), role difficulties (R = 0.395; p-value = 0.027; N = 84), dependence (R = 0.273; p-value = 0.033; N = 84), and driving (R = 0.537; p-value = 0.007; N = 84).

The near vision score did not correlate with the CZ-MS (R = 0.306; p-value = 0.065; N = 37). This was probably due to the small sample size.

MP-1													
	CZ-MS	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
All	**R**	0.344	0.533	0.119	0.206	0.129	0.177	0.372	0.395	0.273	0.537	0.292	0.051
	p	0.088	**<0.001**	0.414	**0.025**	0.136	0.220	**0.022**	**0.027**	**0.033**	**0.007**	0.137	0.771
	N	84	84	84	84	84	84	84	84	84	84	84	84

Table 30- Correlation between CZ-MS and VFQ-25 scores in the all patients group for the MP-1 device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

Optos SLO MP													
Diagnosis Group	CZ-MS	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
All	R	0.285	0.551	0.291	0.282	0.183	0.193	0.392	0.364	0.383	0.432	0.154	0.112
	p	0.116	**0.004**	0.284	**0.045**	0.728	0.446	**0.049**	**0.041**	0.067	**0.026**	0.248	0.822
	N	34	34	34	34	34	34	34	34	34	34	34	34

Table 31- Correlation between CZ-MS and VFQ-25 scores in the all patients group for the Optos SLO MP device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

The CZ-MS correlated with the scores for general vision (R = 0.285; p-value = 0.004; N = 34), near vision (R = 0.282; p-value = 0.045; N = 34), mental health (R = 0.392; p-value =

0.049; N = 34), role difficulties (R = 0.364; p-value = 0.041; N = 34), dependence (R = 0.383; p-value = 0.067; N = 34), and driving (R = 0.432; p-value = 0.026; N = 34).

3.7 Regression models to predict patients' outcomes

Further to the analyses above, I looked at the combined effect of the parameters presented above. The first part of this section presents the results of using a single regression model to identify the relationship between the dependant variable (BCVA) and the independent variables (MS, CZ-MS, CMT, and CSRT). I used regression analysis to understand which amongst the independent variables are related to the dependent variable and to describe the forms of their relationships.

3.7.1 Simple regression model

Simple model regression analysis was used to identify a linear relationship between two variables (LogMAR vs. MS) amongst all study patients. Separate analyses were performed for the MP-1 and Optos SLO devices. Variations in LogMAR were related to variations in MS (p-value < 0.001; R^2 = 0.211), CZ-MS (p-value < 0.001; R^2 = 0.234), CMT (p-value = 0.007; R^2 = 0.088), and CSRT (p-value = 0.004; R^2 = 0.101) in all study patients tested with the MP-1 device (see Table 32).

MP-1 All patients						
Predictors	**Coefficients**	**t**	**p**	**F**	**p**	**R^2**
BCVA (LogMAR)	0.734	10.819	**<0,001**	21.423	**<0.001**	0.211
MS	-0.026	-4.629	**<0,001**			
BCVA (LogMAR)	0.681	12.378	**<0,001**	24.442	**<0.001**	0.234
CZ-MS	-0.028	-4.944	**<0,001**			
BCVA (LogMAR)	0.208	2.192	**0.031**	7.687	**0.007**	0.088
CMT	0.001	2.773	**0.007**			
BCVA (LogMAR)	0.219	2.565	**0.012**	8.984	**0.004**	0.101
CSRT	0.001	2.997	**0.004**			

Table 32- Simple regression model for all patients tested with the MP-1

As shown in Table 33, for all patients tested with the Optos SLO device, I found that variations in LogMAR were related to variations in MS (p-value < 0.001; R^2 = 0.507) and CZ-MS (p-value < 0.001; R^2 = 0.519). For patients tested with the Optos SLO device, I did not observe statistically

significant correlation between BCVA and CSRT (p-value = 0.185; R^2 = 0.051) or CMT (p-value = 0.104; R^2 = 0.076). This could be explained by the small number of patients tested with the Optos SLO (N=17).

Optos SLO All patients						
Predictors	**Coefficients**	**t**	**p**	**F**	**p**	**R^2**
BCVA (LogMAR)	0.879	9.586	**<0.001**	35.034	**<0.001**	0.507
MS	-0.072	-5.919	**<0.001**			
BCVA (LogMAR)	0.818	9.982	**<0.001**	36.629	**<0.001**	0.519
CZ-MS	-0.073	-6.052	**<0.001**			
BCVA (LogMAR)	0.030	0.121	0.905	2.796	0.104	0.076
CMT	0.001	1.672	0.104			
BCVA (LogMAR)	0.007	0.023	0.982	1.831	0.185	0.051
CSRT	0.001	1.353	0.185			

Table 33- Simple regression model for all patients tested with the Optos SLO

3.7.2 Multilinear regression model for LogMAR and its predictors for all patients

Further to the analyses presented above, I used multilinear regression analyses to investigate the effect of two or more clinical measures on variations in VA. I found that, in all the eyes tested with the MP-1 device (see Table 34), 28% of the variations in BCVA were related to combined action of CZ-MS and (p-value < 0.001; R^2 = 0.282).

MP-1 All patients						
Predictors	**Coefficients**	**t**	**p**	**F**	**p**	**R^2**
BCVA (LogMAR)	0.492	5.012	**<0.001**	15.501	**<0.001**	0.282
CZ-MS	-0.025	-4.461	**<0.001**			
CSRT	0.0004	2.293	**0.024**			

Table 34- Multilinear regression model for LogMAR and its predictors for all patients tested with the MP-1

I applied the same model to patients tested with the Optos SLO (see Table 35). I found that 51% of variations in BCVA were related to CZ-MS (p-value < 0.001; R^2 = 0.519).

Optos SLO All patients						
Predictors	**Coefficients**	**t**	**p**	**F**	**p**	**R^2**
BCVA (LogMAR)	0.818	9.982	**<0.001**	36.629	**<0.001**	0.519
CZ-MS	-0.073	-6.052	**<0.001**			

Table 35- Multilinear regression model for LogMAR and its predictors for all patients tested with the Optos SLO

3.8 Discussion

Macular oedema (MO) is a common non-specific sign of several retinal diseases. Typically, it presents as an abnormal presence of fluid in the retinal tissue due to an imbalance in the fluids entering and exiting the retinal layers (Durich et al. 2018). MO can cause reversible visual loss at its early stages and, if left untreated, may cause permanent visual loss at its later stages. In this research project, I observed patients with different stages and causes of MO development. Their treatments varied, including retinal laser photocoagulation, anti-VEGF, and – in some cases – intravitreal steroids. The treatment approach was guided by the currently available NICE clinical guidelines and recommendations. The frequency of the clinical visits was set up to be no more often than what would be routinely required by the treating physician. Overall, I observed 188 eyes (89 patients) for a period of 1 year. Participants' common characteristic at baseline was that they either had newly developed or long-lasting MO. Study participants attended routine clinical visits throughout the 1 year at 3, 6, and 12 months. As shown in Figure 25, the majority of participants did not attend their 6- and 12-month visits; there was a significant drop out in participants attending clinics at the two research hospitals. I explained this with the fact that many patients were referred back to their local clinics for follow up.

From the data acquired, I found a statistically significant change in the BCVA from baseline to the 3-month (p-value = 0.011) and 6-month (p-value = 0.032) visits. Similarly, I found statistically significant improvement in CMT and CSRT from baseline to the 3-month (p-value = 0.035; p-value= 0.032 respectively) and 6-month (p-value = 0.041; p-value=0.039 respectively) visits. I did not observe the same results for patients

who attended their 12-month visit, but this was likely due to the small sample size. These findings are in line with reports published from other researchers (Munk et al. 2013; Nguyen et al. 2012; Okada et al. 2005; Relhan et al. 2017; Qian et al. 2017).

I looked at the change from all reading speed parameters from baseline to 3, 6, and 12 months. I found statistically significant changes in LogMAR at last sentence read at baseline (0.17 ± 0.21 SD) vs. at 3 months (0.12 ± 0.25 SD; p-value= 0.021) and 6 months (0.13 ± 0.19 SD; p-value = 0.025); in total reading errors at baseline (0.03 ± 0.04 SD) vs. at 3 months (0.03 ± 0.04 SD; p-value = 0.032); in reading acuity in LogMAR at baseline (0.31 ± 0.26 SD) vs. at 3 months (0.26 ± 0.28 SD; p-value = 0.015); in reading acuity in LogMAR at baseline (0.31 ± 0.26 SD) vs. at 6 months (0.28 ± 0.26 SD; p-value = 0.038); in estimated smallest print size where reading speed is still close to the maximum at baseline (0.47 ± 0.31 SD) vs. at 3 months (0.44 ± 0.37 SD; p-value= 0.045); and in estimated max reading speed (WPM) from plot at baseline (202.68 ± 54.83 SD) vs. at 3 months (203.70 ± 54.83 SD; p-value = 0.015) and at 6 months (192.84 ± 49.50 SD; p-value = 0.041). Although the sample size for the 12-month visits was too small to test for similar results, I suggest that the reading speed test is a reliable test to assess patients' functional vision. These findings are in line with reports from other researchers (Chong et al. 2014; Frennesson et al. 2010; Kiss et al. 2008).

At the baseline visit, all patients were asked to complete the VFQ-25 questionnaire. I found that in all participants, the most affected scores were for general health (43%), followed by general vision (53%), role difficulties (67%), near vision (70%), mental health (73%) and driving (73%). I also investigated the correlation between the VFQ-25 scores and the BCVA, retinal thickness, and mean sensitivity. I found that the scores which were significantly reduced also showed statistically significant correlation with the scores for general vision, near vision, role difficulties, driving, and mental health (see Tables 28 to 31).

Likewise, I looked at the relationship between VA, anatomical changes, and the functional tests. I found a statistically significant correlation between BCVA (LogMAR) and CMT (R = 0.411; p-value < 0.001; N = 84), CSRT (R = 0.428; p-value < 0.001; N = 84), CZ-MS (R = -0.577; p-value < 0.001; N = 84), MS (R = -0.530; p-value < 0.001; N = 84), LogMAR at last

sentence read (R = 0.695; value < 0.001; N = 84), reading acuity in LogMAR (R = 0.654; p-value < 0.001; N = 84), estimated max reading speed (WPM) from the plot (R = -0.453; p-value = 0.032; N = 84), and critical print size in LogMAR (R = 0.632; p-value < 0.001; N = 84) for all patients tested with the MP-1. I also found similar results for patients tested with the Optos SLO microperimeters: LogMAR showed moderate correlation with CMT (R = 0.382; p-value = 0.013; N = 34), CSRT (R = 0.372; p-value = 0.011; N = 34), CZ-MS (R = -0.495; p-value = 0.015; N = 34), reading acuity in LogMAR (R = 0.402; p-value = 0.024; N = 34), estimated max reading speed (WPM) from the plot (R = -0.320; p-value = 0.042; N = 34), and critical print size in LogMAR (R = 0.440; p-value = 0.010; N = 34), and LogMAR showed strong correlation with the MS (R = -0.505; p-value = 0.020; N = 34) and LogMAR at last sentence read (R = 0.541; p-value = 0.027; N = 34).These findings are similar to those reported by a few other researchers (Frennesson et al. 2010; Munkk et al. 2013; Vijosevic et al. 2006; Pearce et al. 2014).

Measuring retinal thickness is one of the most commonly used techniques to assess the outcome of a treatment in patients with retinal disease. Thus, I looked at the correlation between retinal thickness measures (CMT and CSRT), reading speed, and microperimetry parameters for the two MP devices. I found a statistically significant correlation between CMT and CZ-MS (R = -0.253; p-value = 0.023; N = 84), reading acuity in LogMAR (R = -0.335; p-value = 0.042; N = 84), estimated max reading speed (WPM) from the plot (R = -0.335; p-value = 0.047; N = 84), and critical print size in LogMAR (R = 0.475; p-value = 0.006; N = 84) amongst all patients tested with the MP-1 microperimeter. For patients tested with the Optos SLO MP device, I found similar results. There was a statistically significant correlation between CMT and CZ-MS (R = -0.263; p-value = 0.043; N = 34), reading acuity in LogMAR (R = -0.433; p-value = 0.056; N = 34), and critical print size in LogMAR (R = 0.521; p-value = 0.019; N = 34). For the CSRT, I found significant correlation between CSRT and CZ-MS (R = -0.242; p-value = 0.032; N = 84), LogMAR at last sentence read (R = 0.335; p-value = 0.028; N = 84), reading acuity in LogMAR (R = 0.347; p-value = 0.022; N = 84), and critical print size in LogMAR (R = 0.442; p-value = 0.004; N = 84) for patients tested with the MP-1. For the patients tested with the Optos SLO device, I found similar results. The CSRT showed statistically significant correlation with CZ-MS (R = -0.251; p-value = 0.040; N = 34), LogMAR at last sentence read (R = 0.420; p-value = 0.039; N = 34), reading acuity in LogMAR (R = 0.381; p-value = 0.041; N

= 34), and critical print size in LogMAR (R = 0.410; p-value = 0.010; N = 34). These findings are in line with the clinically proven relationship between VA, retinal thickness, and reading performance in patients with retinal disease.

I also investigated whether microperimetry testing could be informative for patients' reading speed. I found that, amongst all patients tested with the MP-1 device, there was a statistically significant correlation between MS and LogMAR at last sentence read (R = -0.320; p-value = 0.041; N = 84), reading acuity in LogMAR (R = -0.418; p-value = 0.002; N = 84), estimated max reading speed (WPM) from the plot (R = 0.455; p-value = 0.021; N = 84), and critical print size in LogMAR (R = -0.331; p-value = 0.034; N = 84). I found similar results for patients tested with the Optos SLO microperimeter. There was a statistically significant correlation between MS and LogMAR at last sentence read (R = -0.287; p-value = 0.041; N = 84), reading acuity in LogMAR (R = -0.418; p-value = 0.002; N = 84), estimated max reading speed (WPM) from the plot (R = 0.455; p-value = 0.021; N = 84), and critical print size in LogMAR (R = -0.332; p-value = 0.034; N = 84). I also found a statistically significant correlation between CZ-MS and LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM) from the plot, and critical print size in LogMAR for all patients, whether tested with the MP-1 or the Optos SLO microperimeter. I found a statistically significant correlation between CZ-MS and LogMAR at last sentence read (R = -0.482; p-value = 0.002; N = 84), reading acuity in LogMAR (R = -0.520; p-value = 0.002; N = 84), estimated max reading speed (WPM) from the plot (R = 0.384; p-value = 0.048; N = 84), and critical print size in LogMAR (R = -0.479; p-value = 0.011; N = 84) for all patients tested with the MP-1 device. I found similar results for patients tested with the Optos SLO device. There was a statistically significant correlation between CZ-MS and LogMAR at last sentence read (R = -0.353; p-value = 0.010; N = 84), reading acuity in LogMAR (R = -0.421; p-value = 0.016; N = 84), estimated max reading speed (WPM) from the plot (R = 0.329; p-value = 0.082; N = 84), and critical print size in LogMAR (R = -0.379; p-value= 0.022; N = 84). These findings are in line with the reports explaining the relationship between contrast sensitivity and reading speed (Chen et al. 2019; Giacomelli et al. 2013; Edington et al. 2017).

Additionally, I used simple model regression analysis to identify a linear relationship between two variables (LogMAR vs. MS) amongst all study patients. I found that variations in LogMAR were related to variations in MS (p-value < 0.001; R^2 = 0.211), CZ-MS (p-value

< 0.001; R^2 = 0.234), CMT (p-value = 0.007; R^2 = 0.088), and CSRT (p-value = 0.004; R^2 = 0.101) in all study patients tested with the MP-1 device. For all patients tested with the Optos SLO, I found that variations in LogMAR were related to variations in MS (p-value < 0.001; R^2 = 0.507) and CZ-MS (p-value < 0.001; R^2 = 0.519). For this group of participants (Optos SLO), I did not observe statistically significant correlation between BCVA vs. CSRT (p-value = 0.185; R^2 = 0.051) and CMT (p-value = 0.104; R^2 = 0.076). This could be explained by the small number of patients tested with the Optos SLO (N=17).

I used multilinear regression analyses to investigate the effect of two or more clinical measures on variations in VA. I found that of all patients tested with the MP-1, 28% of variations in BCVA were related to combined action of CZ-MS and CSRT (p-value < 0.001; R^2 = 0.282). I applied the same model to patients tested with the Optos SLO. I found that 51% of variations in BCVA are related to CZ-MS (p-value < 0.001; R^2 = 0.519). These methods confirmed the relationship between clinically measured BCVA, retinal structure, and contrast sensitivity described above.

Chapter 4. Functional visual outcomes in patients with diabetic retinopathy

4.1 Introduction

The long-term goal of management of diabetic retinopathy (DRP) is to preserve vision. The current treatment algorithm for diabetic macular oedema (DMO) is laid out in the guidelines developed by the Royal College of Ophthalmologists (December 2012). A variety of treatment approaches and promising therapeutic outcomes are described in the guideline document. Nevertheless, it still not clear how well patients' functional vision is recovering. Chapter 4 presents the results of the research questions related to patients with DRP. Section 4.2 outlines the standard treatment for DRP. Section 4.3 presents the descriptive statistics for routine clinical measures such as VA and retinal thickness (CSRT, CMT). Section 4.4 presents the descriptive analysis for the microperimetry, reading speed, and VFQ-25 outcomes in patients with DRP. Section 4.5 identifies the treatments that the patients with DRP received for the 1-year study period. This section also describes the

anatomical changes in the retina over the course of the treatments. Section 4.6 examines the link between routine clinical and functional tests in the DRP group. Section 4.7 discusses the predictive value of all the clinically examined measures. Section 4.8 summarises the main findings in the DRP group.

4.2 Therapy in diabetic retinopathy

All study participants in the DRP group received standard treatment based on the current NICE and Royal College of Ophthalmologists guidelines (Ghanchi 2012). In the DRP group, 61 eyes from 38 patients were followed up for a period of 1 year. Information was collected about treatment for that period of time: 60.66% (37 eyes) were treated with anti-VEGF and 21.31% (13 eyes) received intravitreal steroid injection. In addition, 47.54% (29 eyes) received retinal photocoagulation as an adjuvant therapy to preserve vision loss in patients with DMO.

4.3 Descriptive statistics

As described in Chapter 2, the data collection took place during the patients' routine examinations in the ophthalmology clinics. The data collected included VA presented as LogMAR and retinal thickness measures such as central subfield retinal thickness (CSRT) and central macular thickness (CMT). At baseline, of the total 118 eyes observed in the study, 61 eyes were diagnosed with DRP. For the following months, the number of observed eyes with DRP fell to 31 eyes at the 3-month visit, 10 eyes at the 6-month visit, and 2 eyes at the 12-month visit. The mean visual acuity amongst observed DRP patients was 0.41 ± 0.37 LogMAR at baseline; 0.44 ± 0.35 LogMAR at the 3-month visit; 0.33 ± 0.41LogMAR at the 6-month visit, and 0.45 ± 0.21 LogMAR at the 12-month visit (see Figure 36). Two measures were used to look at retinal thickness: CSRT and CMT (see Figure 37). The mean CSRT was 371.4 ± 103.45 µm at baseline; 380.23 ± 144.70 µm at the 3-month visit; 380.23 ± 144.72 µm at the 6-month visit; and 357.31 ± 71.44 µm at the 12-month visit. The mean CMT was 374.84 ± 118.41 µm at baseline; 362.53 ± 160.05 µm at the 3-month visit; 348.59 ± 146.13 µm at the 6-month visit; and 333.23 ± 81.65 µm at the 12-month visit (see Figure 37).

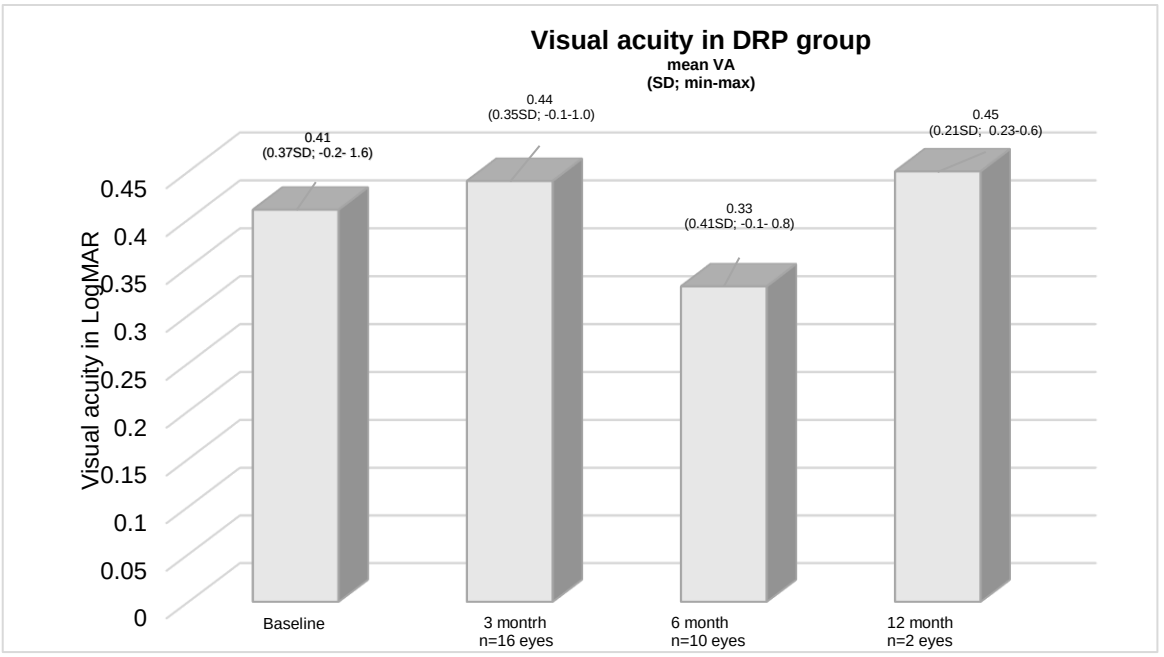

Figure 36- Mean visual acuity at baseline, 3-, 6-, and 12-month visits in the DRP group

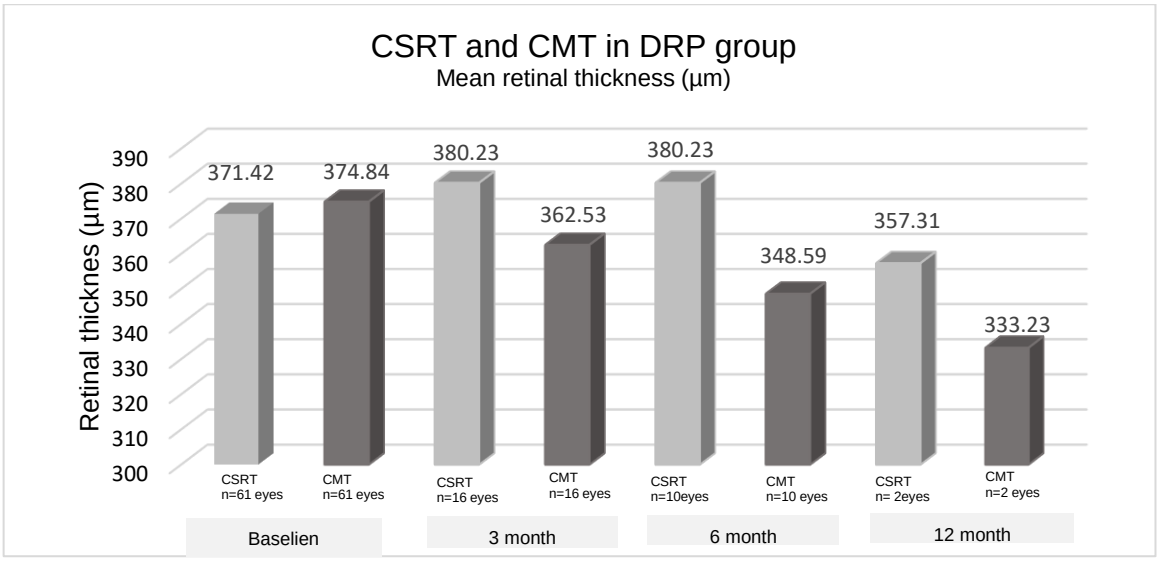

Figure 37- Mean CSRT and CMT at baseline, 3-, 6-, and 12-month visits in the DRP group

The Kolmogorov-Smirnov test showed a non-normal distribution of the data (Appendix III), hence the Wilcoxon Signed Ranks Test was used to calculate the observed change from baseline to 6 and 12 months for LogMAR, CMT, and CSRT. A summary of the results are

presented in Table 36. The table presents number of patients (N), mean, standard deviation (SD), range (Min, Max), percentile 50th (Median), and p-value (significant at p-value < 0.05).

		N	Mean	SD	Min	Max	Percentiles 50th (Median)	p-value
DRP	LogMAR at baseline	10	0.300	0.298	0.000	0.800	0.200	0.236
	LogMAR at 6 months	10	0.390	0.341	-0.100	0.900	0.400	
	LogMAR at baseline	2	0.320	0.326	0.000	0.800	0.200	
	LogMAR at 12 months	2	0.320	0.397	-0.100	0.800	0.250	
	CMT at baseline (μm)	10	285.00	72.661	146	382	301.00	0.333
	CMT at 6 months (μm)	10	342.00	85.514	220	497	315.50	
	CMT at baseline (μm)	2	341.30	90.808	228	571	318.50	
	CMT at 12 months (μm)	2	320.60	81.180	251	514	293.00	
	CSRT at baseline (μm)	10	332.00	52.06	263.00	439.00	331.50	0.333
	CSRT at 6 months (μm)	10	358.50	65.21	267.00	486.00	339.00	
	CSRT at baseline (μm)	2	351.60	115.93	187.00	616.00	350.00	
	CSRT at 12 months (μm)	2	345.50	68.94	279.00	509.00	322.50	

Table 36- Change from baseline to 6- and 12-month visits for LogMAR, CMT, and CSRT in DRP group

4.4 Descriptive statistics of functional vision tests

This section presents the descriptive statistics for the functional vision tests – the microperimetry, reading speed test, and VFQ-25 questionnaire. Due to the reasons explained in the methodology, the microperimetry results are presented separately for each of the two MP devices used in this research.

4.4.1 Microperimetry results

The microperimetry testing was considered as an examination instrument for functional vision testing in this study. The summary of the microperimetric results includes number of total patients tested (N), mean, standard deviation (SD), standard error of the mean (SE), 95% CI, and range (Min, Max). The results are presented in Tables 37 and 38 for the MP-1 and Optos SLO respectively.

MP-1 Device										
Visit		Group	N	Mean	SD	SE	95% CI		Min	Max
Baseline	CZ-MS	DRP	40	10.49	5.34	0.85	8.78	12.20	0.32	19.50
		Total	61	10.88	5.45	0.61	9.68	12.09	0.29	19.57
	MS	DRP	40	9.27	5.41	0.69	7.88	10.65	0.00	19.50
		Total	61	9.35	5.61	0.52	8.33	10.38	0.00	19.57
3 months	CZ-MS	DRP	16	12.23	6.16	1.71	8.51	15.95	2.64	20.00
		Total	31	11.75	5.70	0.94	9.85	13.65	1.00	20.00
	MS	DRP	16	9.75	6.46	1.79	5.85	13.65	0.00	20.00
		Total	31	9.63	5.74	0.94	7.72	11.54	0.00	20.00
6 months	CZ-MS	DRP	16	7.00	7.78	5.50	-62.88	76.88	1.50	14.50
		Total	35	9.62	5.53	1.75	5.67	13.57	0.00	15.75
	MS	DRP	16	9.25	5.41	3.83	-39.36	57.85	5.42	13.07
		Total	35	10.94	4.33	1.37	7.84	14.04	5.28	16.42
12 months	CZ-MS	DRP	3	8.33	8.58	4.95	-12.98	29.64	0.50	17.50
		Total	9	8.85	5.75	1.32	6.08	11.62	0.50	18.00
	MS	DRP	3	12.65	4.01	2.32	2.69	22.61	8.25	16.10
		Total	9	12.54	5.15	1.18	10.06	15.03	1.00	18.21

Table 37- Descriptive statistics of microperimetry outcomes in DRP group at baseline, 3-, 6-, and 12-month visits for patients tested with MP-1 device

Abbreviations: **CZ-MS** = central zone mean sensitivity, **MS** = mean sensitivity

Optos SLO MP Device										
Visit		Group	N	Mean	SD	SE	95% CI		Min	Max
Baseline	CZ-MS	DRP	21	6.45	4.72	1.03	4.30	8.60	0.00	14.50
		Total	61	5.26	4.34	0.72	3.80	6.73	0.00	14.50
	MS	DRP	21	6.94	4.84	1.06	4.74	9.15	0.00	15.60
		Total	61	6.17	4.34	0.72	4.70	7.64	0.00	15.60
3 months	CZ-MS	DRP	15	3.75	4.86	1.98	-1.35	8.85	0.00	11.00
		Total	31	4.75	3.89	1.12	2.28	7.22	0.10	12.70
	MS	DRP	15	4.78	4.01	1.64	0.57	9.00	0.10	9.40
		Total	31	9.63	5.74	0.94	7.72	11.54	0.00	20.00
6 months	CZ-MS	DRP	19	7.53	5.46	1.93	2.96	12.09	0.00	14.50
		Total	35	5.67	5.02	1.39	2.64	8.70	0.00	14.50
	MS	DRP	19	7.70	4.04	1.43	4.32	11.08	0.90	13.00
		Total	35	6.80	3.43	0.95	4.73	8.87	0.90	13.00
12 month	CZ-MS	DRP	7	7.86	6.09	2.30	2.23	13.49	0.00	17.50
		Total	16	6.28	4.73	1.18	3.75	8.80	0.20	13.80
	MS	DRP	6	8.73	4.49	1.70	4.58	12.88	2.10	13.30
		Total	9	12.54	5.15	1.18	10.06	15.03	1.00	18.21

Table 38- Descriptive statistics of microperimetry outcomes in DRP group at baseline, 3-, 6-, and 12-month visits for patients tested with Optos SLO device

Abbreviations: **CZ-MS** = central zone mean sensitivity, **MS** = mean sensitivity

It is noticeable that there is a difference in the MS and CZ-MS values between the two MP devices. Patients tested with the MP-1 device have different results (retinal sensitivity ranging from 7 to 12.65 dB) vs. patients tested with the Optos SLO MP device (retinal sensitivity ranging from 3.75 to 8.73 dB). This difference could be

explained by the fact that the MP-1 and Optos MP use different background luminance, hence the retinal adaptation is different.

The data were not normally distributed. Accordingly, the Wilcoxon Signed Ranks Test was used again to calculate the mean change in MS and CZ-MS from baseline to months 3, 6, and 12. The summary of the results includes the number of total patients tested with the relevant device (N), mean, standard deviation (SD), standard error of the mean (SE), 95% CI, range (Min, Max), percentile 50th (median), and p-value (P) where applicable. The results are presented for the MP-1 and Optos SLO MP devices in Table 39 and 40 respectively.

MP-1								
Diagnosis group		**N**	**Mean**	**Std. Deviation**	**Min**	**Max**	**Percentile 50th (Median)**	**P-value**
DRP	MS at baseline	16	6.72	3.52	0.60	13.10	9.45	0.757
	MS at 3 months	16	7.42	3.65	0.80	14.24	9.25	
	MS at baseline	16	7.67	3.82	0.60	11.70	9.35	0.677
	MS at 6 months	16	8.00	4.04	0.90	13.07	8.90	
	MS at baseline	3	8.39	3.65	0.60	12.00	9.55	n/a
	MCS at 12 months	3	9.90	4.53	2.10	16.10	10.80	
	CZ-MS at baseline	16	7.42	3.45	0.20	14.40	8.80	0.720
	CZ-MS at 3 months	16	7.82	4.25	0.40	16.42	9.25	
	CZ-MS at baseline	16	7.50	3.65	0.50	12.50	7.50	0.596
	CZ- MS at 6 months	16	8.00	6.41	0.00	17.50	7.50 39	
	CZ-MS at baseline	3	7.50	3.65	0.50	12.50	7.50	n/a
	CZ- MS at 12 months	3	8.00	6.41	0.00	17.50	7.50	

Table 39- Mean change in MS and CZ-MS from baseline to 3-, 6-, and 12-month visits in DRP group for MP-1 device

Optos SLO MP								
Diagnosis group		N	Mean	Std. Deviation	Min	Max	Percentile 50th (Median)	P-value
DRP	MS at baseline	15	5.88	3.82	0.60	13.45	8.25	0.672
	MS at 3 months	15	6.02	4.10	0.80	14.56	9.25	
	MS at baseline	19	6.78	4.20	0.80	12.52	8.45	0.722
	MS at 6 months	19	7.82	4.60	0.80	13.26	9.02	
	MS at baseline	6	7.90	3.85	0.60	11.00	9.00	
	MCS at 12 months	6	9.00	4.20	2.40	15.10	12.80	
	CZ-MS at baseline	15	6.65	3.90	0.60	14.25	8.45	0.725
	CZ-MS at 3 months	15	7.25	4.05	0.80	15.10	9.20	
	CZ-MS at baseline	19	6.60	3.26	0.45	11.60	6.50	0.596
	CZ- MS at 6 months	19	8.40	7.10	0.10	17.00	8.10	
	CZ-MS at baseline	6	6.70	4.20	0.50	12.80	6.50	
	CZ- MS at 12 months	6	7.80	6.80	0.20	17.00	7.20	

Table 40- Mean change in MS and CZ-MS from baseline to 3-, 6-, and 12-month visits in DRP group for patients tested with Optos SLO MP

The change observed from the baseline to 6- and 12-month visits was not statistically significant in patients with DRP, whether tested with the MP-1 or Optos SLO MP device. A possible explanation for this is the small sample size that followed up at months 6 and 12.

4.4.2 Reading speed results

The reading speed test was performed as part of the functional vision assessments. In this research project, the MNREAD reading speed test was used. The following parameters were measured in order to describe the outcomes of the MNREAD reading speed test:

- LogMAR at last sentence read
- Total reading errors
- Reading acuity in logMAR
- Estimated max reading speed (WPM) from plot
- Critical print size in LogMAR

Figure 38 summarises the results for reading speed measures at baseline, 3-, 6-, and 12-month visits in the DRP group. The detailed descriptive statistics, namely number (N), mean, standard deviation (SD), standard error of the mean (SE), 95% CI, and range (Min, Max), are presented in Appendix III.

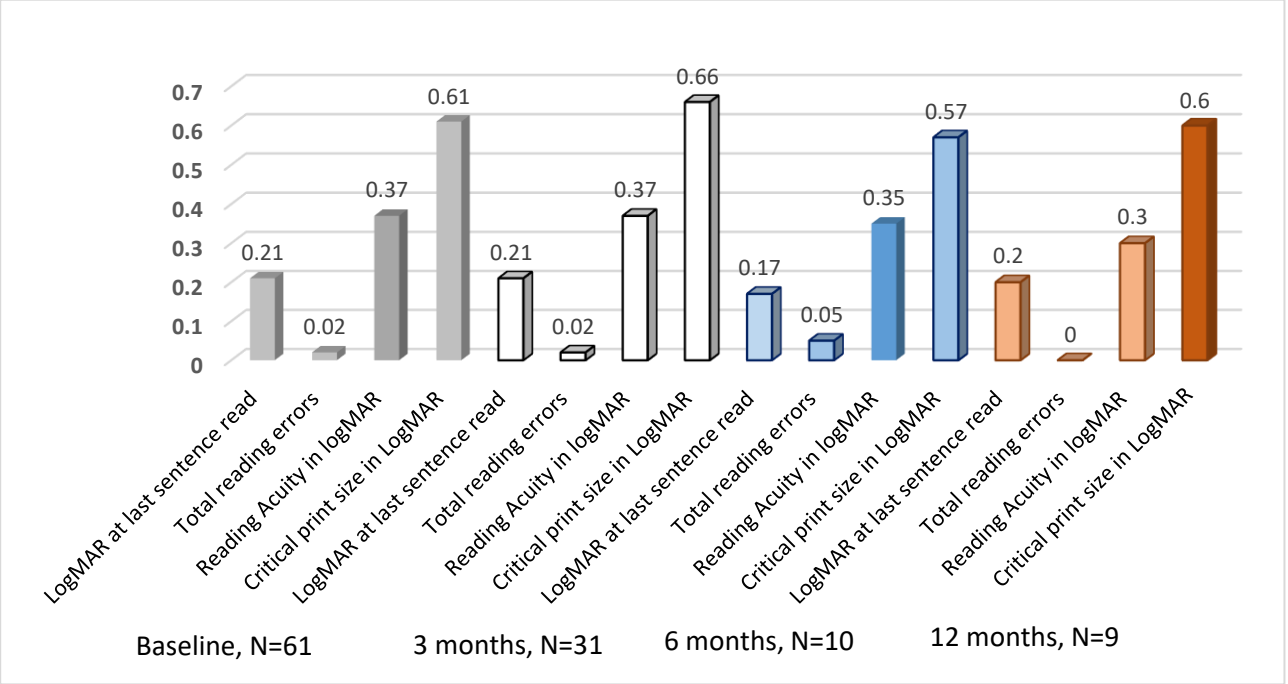

Figure 38- Reading speed results in the DRP group

Diagnosis group		N	Mean	Std. Deviation	Min	Max	Percentile 50th (Median)	P value
DRP	LogMAR at last sentence read at baseline	2	0.20	0.21	0.00	0.50	0.15	
	LogMAR at last sentence read at 12 months	2	0.25	0.12	0.10	0.40	0.20	
	Reading acuity in LogMAR	61	0.33	0.3	-0.1	0.92	0.3	<0,001
	Reading acuity in LogMAR at 3 months	61	0.35	0.31	0	1.29	0.3	
	Reading acuity in LogMAR at baseline	10	0.37	0.31	0.15	0.92	0.235	0.028
	Reading acuity in LogMAR at 6 months	10	0.35	0.15	0.2	0.56	0.3	
	Estimated max reading speed (WPM) from plot at baseline	10	160.20	57.18	60	240	150.00	0.470
	Estimated max reading speed (WPM) from plot at 6 months	10	184.53	69.61	86	300	171.00	
	Critical print size in LogMAR at baseline	10	0.57	0.43	0.00	1.30	0.40	0.66
	Critical print size in LogMAR at 6 months	10	0.61	0.37	0.19	1.70	0.50	
	Critical print size in LogMAR at baseline	9	0.52	0.48	0.10	1.30	0.30	
	Critical print size in LogMAR at 12 months	9	1.77	3.11	0.20	8.10	0.55	

Table 41- Observed change from baseline to 6- and 12-month visits for reading speed parameters in DRP group

In examining the changes in the reading speed measures, I found that the change in the reading acuity in LogMAR from baseline to 3 months (0.35 ± 0.31 LogMAR; p-value <

0.001) and 6 months (0.37 ± 0.31 LogMAR; p-value = 0.028) was statistically significant. This correlation was not observed in any other parameters of the reading speed. A possible explanation for this is the small sample size.

4.4.3 VFQ-25 in the DRP group

In this study, the VFQ-25 questionnaire was provided to all participants at the baseline visit. This tool identified patients' vision-related difficulties in their daily life. Based on the data collected from the VFQ-25, the following scores were calculated. The calculation process is fully described in the VFQ-25 scoring algorithm (Appendix III).

- General Health Score
- General Vision Score
- Ocular Pain Score
- Near Vision Score
- Distance Vision Score
- Social Score
- Mental Health Score
- Role Difficulties Score
- Dependence Score
- Driving Score
- Colour Vision Score
- Peripheral Vision Score

Figure 39 describes the mean VFQ-25 scores achieved in the DRP group. For a full summary of the VFQ-25 scores in the DRP group, including number of patients (n), mean, standard deviation (SD), standard error of the mean (SE), 95% CI, and range (Min, Max), refer to Appendix III.

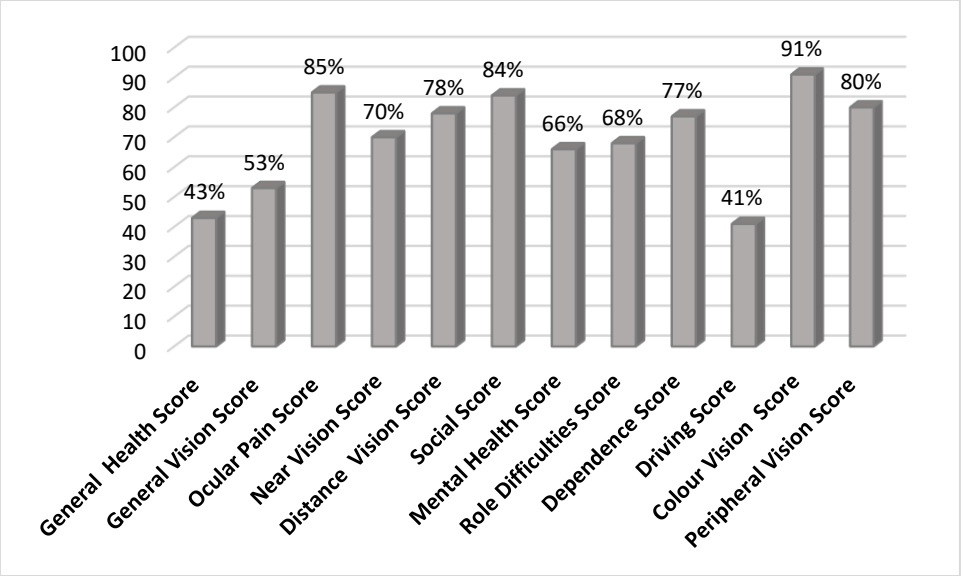

Figure 39- Mean VFQ-25 scores in DRP group

It can be seen that a few scores decreased to 50% from the total possible score of 1.00 achieved in healthy volunteers. These scores were for general health (43% ± 0.23 SD), general vision (53% ± 0.17 SD), and driving (41% ± 0.44 SD). In the DRP group, the distance and near vision scores had relatively good outcomes at 78% ± 2.3 SD and 70% ± 0.24 SD respectively.

4.5 Anatomical response to the therapy

This section describes the outcomes of the routine clinical measures and functional vision tests throughout the study period. I also looked at any changes in retinal anatomy in order to evaluate structural changes in response to the DRP treatment. The following subsections summarise, within the DRP group, the changes in percentage of patients with focal and diffuse macular oedema (MO), intraretinal fluid (IRF), subretinal fluid (SRF), haemorrhages, and exudates.

4.5.1 Focal and diffuse macular oedema in DRP group

At the baseline visit, of the study participants whose MO was due to DRP, 39.3% had focal MO and 57.4% had diffuse MO (see Table 42). In 6 months' time, these results did not show significant change: 40% of the patients had focal MO and 50% had diffuse MO (see Table 43). One explanation for this lack of change could be the drop-out rate, with

patients diagnosed with reabsorbed MO being referred back to the diabetic screening service for follow up.

	Type of macular oedema (MO)		DRP	Total
Baseline	Focal	Count	24	41
		% within Type of MO	58.5%	100.0%
		% within Group	39.3%	34.7%
	Diffuse	Count	35	73
		% within Type of MO	47.9%	100.0%
		% within Group	57.4%	61.9%
	Total	Count	61	118
		% within Type of MO	51.7%	100.0%
		% within Group	100.0%	100.0%
3 months	No	Count	2	10
		% within Type of MO	20.0%	100.0%
		% within Group	6.9%	14.1%
	Focal	Count	9	22
		% within Type of MO	40.9%	100.0%
		% within Group	31.0%	31.0%
	Diffuse	Count	18	39
		% within Type of MO	46.2%	100.0%
		% within Group	62.1%	54.9%
	Total	Count	29	71
		% within Type of MO	40.8%	100.0%
		% within Group	100.0%	100.0%

Table 42- Type of macular oedema in DRP group at baseline and 3-month visits

	Type of macular oedema (MO)		DRP	Total
6 months	No	Count	1	4
		% within Type of MO	25.0%	100.0%
		% within Group	10.0%	11.4%
	Focal	Count	4	14
		% within Type of MO	28.6%	100.0%
		% within Group	40.0%	40.0%
	Diffuse	Count	5	17
		% within Type of MO	29.4%	100.0%
		% within Group	50.0%	48.6%
	Total	Count	10	35
		% within Type of MO	28.6%	100.0%
		% within Group	100.0%	100.0%
12 months	No	Count	1	2
		% within Type of MO	50.0%	100.0%
		% within Group	50.0%	22.2%
	Focal	Count	0	3
		% within Type of MO	0.0%	100.0%
		% within Group	0.0%	33.3%
	Diffuse	Count	1	4
		% within Type of MO	25.0%	100.0%
		% within Group	50.0%	44.4%
	Total	Count	2	9
		% within Type of MO	22.2%	100.0%
		% within Group	100.0%	100.0%

Table 43- Type of macular oedema in DRP group at 6- and 12-month visits

4.5.2 Intraretinal fluid in the DRP group

After identifying the type of MO, I looked at the presence and location of intraretinal fluid among patients with DRP. I found that at the baseline visit, 63.9% of DRP patients had extrafoveal IRF and 34.4% had subfoveal IRF. At the 6-month visits, 60% of the DRP patients had extrafoveal IRF and 30% had subfoveal IRF. Tables 44 and 45 summarise the prevalence of IRF over the 1-year study period.

	Intraretinal fluid (IRF)		DRP	Total
Baseline	No	Count	1	2
		% within IRF	50.0%	100.0%
		% within Group	1.6%	1.7%
	Extrafoveal	Count	39	78
		% within IRF	50.0%	100.0%
		% within Group	63.9%	66.1%
	Subfoveal	Count	21	38
		% within IRF	55.3%	100.0%
		% within Group	34.4%	32.2%
	Total	Count	61	118
		% within IRF	51.7%	100.0%
		% within Group	100.0%	100.0%
3 months	No	Count	2	9
		% within IRF	22.2%	100.0%
		% within Group	6.9%	12.7%
	Extrafoveal	Count	19	42
		% within IRF	45.2%	100.0%
		% within Group	65.5%	59.2%
	Subfoveal	Count	8	20
		% within IRF	40.0%	100.0%
		% within Group	27.6%	28.2%
	Total	Count	29	71
		% within IRF	40.8%	100.0%
		% within Group	100.0%	100.0%

Table 44- Type of IRF at baseline and 3-month visits in DRP group

	Intraretinal fluid (IRF)		DRP	Total
6 months	No	Count	1	4
		% within IRF	25.0%	100.0%
		% within Group	10.0%	11.4%
	Extrafoveal	Count	6	19
		% within IRF	31.6%	100.0%
		% within Group	60.0%	54.3%
	Subfoveal	Count	3	12
		% within IRF	25.0%	100.0%
		% within Group	30.0%	34.3%
	Total	Count	10	35
		% within IRF	28.6%	100.0%
		% within Group	100.0%	100.0%
12 months	No	Count	0	1
		% within IRF	0.0%	100.0%
		% within Group	0.0%	11.1%
	Extrafoveal	Count	1	5
		% within IRF	20.0%	100.0%
		% within Group	50.0%	55.6%
	Subfoveal	Count	1	3
		% within IRF	33.3%	100.0%
		% within Group	50.0%	33.3%
	Total	Count	2	9
		% within IRF	22.2%	100.0%
		% within Group	100.0%	100.0%

Table 45- Type of IRF at 6- and 12-month visits in DRP group

4.5.3 Subretinal fluid in the DRP group

Further to the type of MO and location of IRF, I also looked at the prevalence and location of the subretinal fluid among the DRP patients. I found that at the baseline visit, 86.7% of DRP patients did not have SRF. Thus only a small proportion of DRP patients did have SRF: subfoveal SRF was observed in 10% of DRP patients and extrafoveal SRF was observed in 3.3%. Over the study period, I found that at the 6-month visit, 100% of the DRP group showed no signs of SRF. An outline of SRF prevalence in the DRP group at baseline and 3 months and then at 6 and 12 months is presented in Tables 46 and 47 respectively.

	Subretinal fluid (SRF)		DRP	Total
Baseline	No	Count	52	90
		% within SRF	57.8%	100.0%
		% within Group	86.7%	76.9%
	Extrafoveal	Count	2	5
		% within SRF	40.0%	100.0%
		% within Group	3.3%	4.3%
	Subfoveal	Count	6	22
		% within SRF	27.3%	100.0%
		% within Group	10.0%	18.8%
	Total	Count	60	117
		% within SRF	51.3%	100.0%
		% within Group	100.0%	100.0%
3 months	No	Count	52	61
		% within SRF	57.8%	100.0%
		% within Group	86.7%	85.9%
	Extrafoveal	Count	2	2
		% within SRF	40.0%	100.0%
		% within Group	3.3%	2.8%
	Subfoveal	Count	6	8
		% within SRF	27.3%	100.0%
		% within Group	10.0%	11.3%
	Total	Count	60	71
		% within SRF	51.3%	100.0%
		% within Group	100.0%	100.0%

Table 46- Type of IRF at baseline and 3-month visits in DRP group

	Subretinal fluid (SRF)		DRP	Total
6 months	No	Count	10	30
		% within SRF	33.3%	100.0%
		% within Group	100.0%	85.7%
	Extrafoveal	Count	0	1
		% within SRF	0.0%	100.0%
		% within Group	0.0%	2.9%
	Subfoveal	Count	0	4
		% within SRF	0.0%	100.0%
		% within Group	0.0%	11.4%
	Total	Count	10	35
		% within SRF	28.6%	100.0%
		% within Group	100.0%	100.0%
12 months	No	Count	2	8
		% within SRF	25.0%	100.0%
		% within Group	100.0%	88.9%
	Extrafoveal	Count	0	1
		% within SRF	0.0%	100.0%
		% within Group	0.0%	11.1%
	Subfoveal	Count	2	9
		% within SRF	22.2%	100.0%
		% within Group	100.0%	100.0%
	Total	Count	9	9
		% within SRF	33.3%	100.0%
		% within Group	100.0%	85.7%

Table 47- Type of SRF at 6- and 12-month visits in DRP group

4.6 Substantiation of the link between routine clinical and functional tests in the DRP group

This section presents the assessment results on the relationship between the clinical and functional tests in the DRP group. As mentioned several times prior, LogMAR, CMT, and CSRT were defined as part of the routine clinical testing, on the basis of the fact that these are regular ophthalmic investigations. The MS, CZ-MS, reading speed tests and the VFQ-25 questionnaire were defined as the functional vision tests as they determine the functional vision performance. In order to identify the correlation between these two groups of measures, Spearman's rho statistical test was used. Total number of cases (N),

correlation coefficient (R), and p-value (p) are indicated in the tables shown for each test group.

4.6.1 VA, CMT, and CSRT correspondence with functional vision tests

In this study, I looked at the correlation between VA and the routine clinical tests of CSRT and CMT. The Spearman's rho test was used to calculate the correlation with LogMAR. Tables 48 and 49 present the results for the DRP group participants tested with the MP-1 and Optos SLO MP devices respectively.

MP-1									
Diagnosis group	LogMAR	CMT	CSRT	CZ-MS	MS	**Lo**gMAR at last sentence read	**R**eading acuityin LogMAR	**Esti**mated reading speed from the **plot**	Critical print size in LogMAR
DRP	R	0.318	0.318	-0.547	-0.480	0.569	0.555	-0.303	0.511
	p-value	0.013	0.012	<0.001	<0.001	<0.001	<0.001	0.069	<0.001
	N	40	40	40	40	40	40	40	40

Table 48- Correlation between LogMAR vs. CMT, CSRT, CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR in DRP group for MP-1 device

As shown in Table 48, I found that in the DRP group, for patients tested with the MP-1 device, LogMAR showed moderate correlation with CMT (R = 0.318; p-value = 0.013; N = 40) and CSRT (R = 0.318; p-value = 0.012; N = 40) and strong correlation with CZ-MS (R = -0.547; p-value < 0.001; N = 40), MS (R = 0.480; p-value < 0.001; N = 40), LogMAR at last sentence read (R = 0.569; value < 0.001; N = 40), reading acuity in

LogMAR (R = 0.569; p-value < 0.001; N = 40), and critical print size in LogMAR (R = 0.511; p-value < 0.001; N = 40).

Optos SLO MP									
Diagnosis	LogMAR	CMT	CSRT	CZ-MS	MS	LogMAR at last sentence read	Reading acuity in LogMAR	Estimated max reading speed WPM from plot	Critical print size in LogMAR
DRP	R	0.351	0.327	-0.493	-0.463	0.492	0.451	-0.342	0.473
	P-value	0.021	0.023	0.013	0.016	0.031	0.027	0.074	0,011
	N	21	21	21	21	21	21	21	21

Table 49- Correlation between LogMAR vs. CMT, CSRT, MS, CZ-MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR in DRP group for Optos SLO MP device

Similar results were observed in the DRP patients tested with the Optos SLO MP device (see Table 49). For this patient group, LogMAR had moderate correlation with CMT (R = 0.351; p-value = 0.021; N = 21), and CSRT (R = 0.327; p-value = 0.023; N = 21) and a strong correlation with CZ-MS (R = -0.493; p-value = 0.013; N = 21), MS (R = -0.463; p-value = 0.016; N = 21), LogMAR at last sentence read (R = 0.492; p-value = 0.031; N = 21), reading acuity in LogMAR (R = 0.451; p-value = 0.027; N = 21), and critical print size in LogMAR (R = 0.473; p-value = 0.011; N = 21).

MP-1							
Diagnosis	CMT	Central Zone MS	LogMAR at last sentence read	Reading Acuity in logMAR	Estimated max reading speed WPM from plot	Critical print size in LogMAR	MS
DRP	R	-0.175	0.283	0.329	-0.306	0.440	-0.069
	p	0.177	0.090	0.047	0.066	0.006	0.599
	N	40	40	40	40	40	40

Table 50- Correlation between CMT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), critical print size in LogMAR in DRP group for MP-1 device

There was a statistically significant correlation between CMT and reading acuity in LogMAR (R = 0.329; p-value = 0.047; N = 40) and critical print size in LogMAR (R = 0.440; p-value = 0.006; N = 40) amongst DRP patients tested with the MP-1 microperimeter.

Optos SLO MP							
Diagnosis	CMT	Central Zone MS	LogMAR at last sentence read	Reading Acuity in logMAR	Estimated max reading speed WPM from plot	Critical print size in LogMAR	MS
DRP	R	-0.192	0.311	0.331	-0.326	0.462	-0.073
	p	0.193	0.142	0.056	0.075	0.012	0.614
	N	21	21	21	21	21	21

Table 51- Correlation between CMT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR in DRP group for Optos SLO MP device

In DRP patients tested with the Optos SLO MP device, I found that there was a statistically significant correlation between CMT and critical print size in LogMAR (R = 0.462; p-value = 0.012; N = 21). The correlation between CMT and reading acuity in LogMAR was not statistically significant (R = 0.331; p-value = 0.056; N = 21) in this group. A possible explanation for this might be the smaller number of patients tested with the Optos MP device (N = 21) in contrast to those tested with the MP-1 device (N = 40). This is also reflected in my sample size calculation.

Besides the CMT, the CSRT is commonly used as a key measure to assess the therapeutic response in patients with diabetic MO. I found a significant correlation between CSRT and LogMAR at last sentence read (R = 0.035; p-value = 0.031; N = 40), reading acuity in LogMAR (R = 0.347; p-value = 0.032; N = 40), and critical print size in LogMAR (R = 0.442; p-value = 0.006; N = 40) for patients tested with the MP-1 (see Table 52). The correlation between CSRT and CZ-MS is below the significance level of the p-value < 0.5 (R = -0.242; p-value = 0.060; N = 40) in the DRP group.

MP-1							
Diagnosis		CSRT	CZ-MS	LogMAR at last sentence read	Reading Acuity in logMAR	Estimated max reading speed WPM from plot	Critical print size in LogMAR	MS
DRP	R	-0.242	0.355	0.347	-0.024	0.442	-0.178
	p	0.060	0.035	0.032	0.89	0.006	0.17
	N	40	40	40	40	40	40

Table 52- Correlation between CSRT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR in DRP group for MP-1 device

Optos SLO MP							
Diagnosis	CSRT	CZ-MS	LogMAR at last sentence read	Reading Acuity in logMAR	Estimated max reading speed WPM from plot	Critical print size in LogMAR	MS
DRP	R	-0.32	0.475	0.431	-0.04	0.543	-0.21
	p	0.08	0.042	0.044	0.93	0.011	0.23
	N	21	21	21	21	21	21

Table 53- Correlation between CSRT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR in DRP group for Optos SLO MP device

As shown in Table 53, for patients tested with the Optos SLO MP, there was a correlation between CSRT and LogMAR at last sentence read (R = 0.475; p-value = 0.042; N = 21), reading acuity in LogMAR (R = 0.431; p-value = 0.044; N = 21), and critical print size in LogMAR (R = 0.543; p-value = 0.011; N = 21).

4.6.2 Correlation of microperimetry and reading speed outcomes

The purpose of this section is to investigate whether the microperimetry results correlate with patients' reading speed performance and self-reported vision-related quality of life. As previously described in Chapter 2 of this thesis, the MP outcomes are presented by using MS and CZ-MS. The Spearman's rho test was used to identify the correlation between CZ-MS and MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM) from the plot, and critical print size in LogMAR. The total number of cases (N), correlation coefficient (R), and p-value (p) are indicated in the tables in this section for each group. The results are presented separately for the two MP devices used in this research.

As Table 54 shows, in the DRP group, there was a statistically significant correlation between MS and estimated max reading speed (WPM) from the plot (R = -0.363; p-value = 0.027; N = 40) and critical print size in LogMAR (R = -0.341; p-value = 0.039; N = 40) for patients tested with the MP-1 microperimeter.

MP-1					
Diagnosis	MS	LogMAR at last sentence read	Reading Acuity in LogMAR	Estimated max reading speed WPM from plot	Critical print size in LogMAR
DRP	R	-0.296	-0.315	0.363	-0.341
	p	0.075	0.058	0.027	0.039
	N	40	40	40	40

Table 54- Correlation between MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR in DRP group for MP-1 device

Amongst the participants in the DRP group tested with the Optos SLO MP device, there is a statistically significant correlation between MS and estimated max reading speed (WPM) from plot (R = -0.381; p-value = 0.031; N = 21) and critical print size in LogMAR (R = -0.351; p-value = 0.041; N = 21).

Optos SLO MP					
Diagnosis group	MS	LogMAR at last sentence read	Reading Acuity in LogMAR	Estimate max reading speed WPM from plot	Critical print size in LogMAR
DRP	R	-0.257	-0.301	0.381	-0.351
	p	0.083	0.061	0.031	0.041
	N	21	21	21	21

Table 55- Correlation between MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR in DRP group for Optos SLO MP device

I also investigated the correlation between CZ-MS and LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM) from the plot, and critical print size in LogMAR. The Spearman's rho test was used for the analysis. The total number of cases (N), correlation coefficient (R), and p-value for the DRP group are indicated in Tables 56 and 57 for the MP-1 and Optos SLO MP devices respectively.

MP-1					
Diagnosis group	CZ-MS	LogMAR at last sentence read	Reading Acuity in logMAR	Estimate max reading speed WPM from plot	Critical print size in LogMAR
DRP	R	-0.346	-0.359	0.334	-0.409
	p	0.036	0.029	0.044	0.012
	N	40	40	40	40

Table 56- Correlation between CZ-MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR in DRP group for MP-1 device

As shown in Table 56, in the DRP group, for participants tested with the MP-1 device, I found a statistically significant correlation between CZ-MS and LogMAR at last sentence read (R = -0.346; p-value = 0.036; N = 40), reading acuity in LogMAR (R = -0.359; p-value = 0.029; N = 40), estimated max reading speed (WPM) from plot (R = 0.334; p-value = 0.044; N = 40), and critical print size in LogMAR (R = -0.409; p-value = 0.012; N = 40).

Optos SLO MP					
Diagnosis group	CZ- MS	LogMAR at last sentence read	Reading Acuity in logMAR	Estimated max reading speed WPM from plot	Critical print size in LogMAR
DRP	R	-0.293	-0.301	0.329	-0.396
	p	0.045	0.036	0.048	0.021
	N	21	21	21	21

Table 57- Correlation between CZ-MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR in DRP group for Optos SLO MP device

For patients tested with Optos SLO MP microperimeter, the results were similar (see Table 57). There was a correlation between CZ-MS and LogMAR at last sentence read (R = -0.293; p-value = 0.045; N = 21), reading acuity in logMAR (R = -0.301; p-value = 0.036; N = 21), estimated max reading speed WPM from plot (R = 0.329; p-value = 0.048; N = 21), and critical print size in LogMAR (R = -0.396; p-value = 0.021; N = 21).

4.6.3 Correspondence between vision-related quality of life (VFQ-25) and VA, CSRT, and CZ-MS

This section of the thesis presents the relationship between patients' self-reported vision-related quality of life and clinically available assessments. I looked at the VFQ-25 score and four anatomical and functional tests: retinal thickness, MS, CZ-MS, and reading speed tests.

The reason for investigating the relationship between the VFQ-25 questionnaire and VA was that BCVA assessment is an irreplaceable measurement in routine ophthalmic practice. Per Table 58, in the DRP group, the VA (LogMAR) correlated with the scores for general vision (R = -0.561; p-value < 0.001; N = 37), mental health (R = -0.42; p-value = 0.001; N = 37), role difficulty (R = -0.523; p-value < 0.001; N = 37), dependence (R = - 0.468; p-value = 0.003; N = 37), and driving (R = -0.392; p-value = 0.016; N = 37).

I looked at the relationship between CSRT and the VFQ-25 to assess whether this routinely used anatomical parameter correlates with patients' self-reported vision. There was a statistically significant correlation between CSRT and the general vision score (R = -0.353; p-value = 0.032; N = 37).

	CSRT	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
DRP	R	0.004	-0.353	0.069	-0.185	-0.163	-0.028	-0.028	0.004	-0.124	-0.187	-0.032	0.159
	p	0.98	0.032	0.684	0.274	0.334	0.869	0.093	0.979	0.466	0.267	0.851	0.347
	N	37	37	37	37	37	37	37	37	37	37	37	37

Table 58- Correlation between CSRT and VFQ-25 scores in DRP group

MP-1													
	CZ-MS	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
DRP	R	0.304	0.544	0.209	0.306	0.163	0.169	0.382	0.345	0.373	0.437	0.162	0.05
	p	0.068	<0.001	0.214	0.065	0.336	0.316	0.022	0.037	0.023	0.008	0.337	0.77
	N		40	40	40	40	40	40	40	40	40	40	40

Table 59- Correlation between CZ-MS and VFQ-25 scores in DRP group for MP-1 device

Similar results were observed in the DRP patients tested with the Optos SLO microperimeter (see Table 60). CZ-MS correlated with the scores for general vision (R = 0.582; p-value = 0.002; N = 21), mental health (R = 0.382; p-value = 0.029; N = 21), role difficulties (R = 0.354; p-value = 0.041; N = 21), dependence (R = 0.383; p-value = 0.032; N = 21), and driving (R= 0.432; p-value = 0.006; N = 37).

Optos SLO MP													
Diagnosis Group	CZ-MCS	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Menthal Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Periferal Vision Score
DRP	R	0.295	0.582	0.291	0.302	0.183	0.193	0.382	0.354	0.383	0.432	0.164	0.102
	p	0.078	0.002	0.254	0.085	0.363	0.346	0.029	0.041	0.032	0.006	0.348	0.822
	N	21	21	21	21	21	21	21	21	21	21	21	21

Table 60- Correlation between CZ-MS and VFQ-25 scores in DRP group for Optos SLO MP device

4.7 Regression models to predict patient outcomes

This section presents the results of my assessment of the combined effect of the values presented above. The first subsection presents the results of using a single regression model to identify the relationship between the dependant variable (BCVA) and the independent variables (MS, CZ-MS, CMT, and CSRT). The second subsection presents the results of using regression analysis to understand which amongst the independent variables were related to the dependent variable and the forms of those relationships.

4.7.1 Simple linear regression model

Simple model regression analysis was used to identify a linear relationship between two variables (LogMAR vs. MS) amongst the DRP group. Separate analyses were performed for the MP-1 and Optos SLO MP devices. Variations in LogMAR were related to variations in MS (p-value < 0.001; $R^2 = 0.244$), CZ-MS (p-value = 0.002; $R^2 = 0.232$), CMT (p-value = 0.004; $R^2 = 0.198$), and CSRT (p-value < 0.001; $R^2 = 0.330$) in DRP patients tested with the MP-1 device (see Table 61).

MP-1							
Single linear model Y=b0+b1*X1							
Group	Predictors	Coefficients	t	p	F	p	R^2
DRP N=40 eyes	LogMAR MS	0.775 -0.031	7.528 -3.504	<0,001 0.001	12.275	**<0.001**	0.244
	LogMAR CMT	0.013 0.001	0.089 3.066	0.929 0.004	9.398	**0.004**	0.198
	LogMAR CSRT	-0.096 0.002	-0.718 4.329	0.477 <0,001	18.738	**<0.001**	0.330
	LogMAR CZ-MS	0.676 -0.028	8.367 -3.388	<0,001 0.002	11.481	**0.002**	0.232

Table 61- Simple linear regression model of LogMAR vs. MS, CZ-MS, CSRT, and CMT in DRP patients tested with MP-1 microperimeter

As shown in Table 62, for patients with DRP tested on the Optos SLO MP device, I found that variations in LogMAR were related to variations in MS (p-value < 0.001; $R^2 = 0.538$) and CZ-MS (p-value < 0.001; $R^2 = 0.590$). There was no relationship between LogMAR and retinal thickness (CMT, CSRT) for patients tested with the Optos SLO microperimeter. This was probably due to the small sample size in this group.

Optos SLO MP							
Single linear model Y=b0+b1*X1							
Group	Predictors	Coefficients	t	p	F	p	R^2
DRP N=21eyes	LogMAR MS	0.796 -0.067	6.693 -4.705	<0,001 <0,001	22.137	**<0,001**	0.538
	LogMAR CMT	0.942 -0.002	1.570 -1.028	0.133 0.317	1.056	0.317	0.053
	LogMAR CSRT	0.340 0.000	0.650 -0.012	0.524 0.991	0.000	0.991	0.000
	LogMAR CZ-MS	0.795 -0.072	7.323 -5.224	<0,001 <0,001	27.293	**<0,001**	0.590

Table 62- Simple linear regression model of LogMAR vs. MS, CZ-MS, CSRT, and CMT in DRP patients tested with Optos SLO MP device

4.7.2 Multiple linear regression model of LogMAR and its predictors for the DRP group

Further analysis was undertaken to investigate the effect of two or more clinical measures on variations in VA using a multilinear regression analysis. In the DRP group tested with the MP-1 device, I found that up to 41% of variation of LogMAR was related to combined action of CZ-MS and CSRT (p-value < 0.001; $R^2 = 0.413$). Regrettably, this model could not be applied to the patients tested with the Optos SLO MP device as the sample size was not large enough.

MP-1							
Multilinear model - $Y=b_0+b_1*X_1+b_2*X_2$							
Group	Predictors	Coefficients	t	p	F	p	R^2
DRP	Constant V	0.159	0.955	0.346	18.738	<0,001	0.418
N=40 eyes	CZ- MS	-0.019	-2.363	0.023			
	CSRT	0.001	3.440	0.001			

Table 63- Multiple linear regression model of LogMAR and its predictors for DRP patients tested with MP-1 device

4.8 Discussion

Macular oedema (MO) is a leading cause for blindness amongst diabetic retinopathy (DRPDespite several available therapeutic options, macular oedema remains as one of the most common causes for vision loss (Coscas 2010). Based on the latest NICE clinical guidelines recommendation, the first-line treatment for patients with diabetic macular oedema (DMO) is anti-VEGFs (ranibizumab, aflibercept, bevacizumab). When intravitreal injections are not suitable, it is recommended to treat patients with laser. The patients in the study were treated based on the NICE clinical guidelines' recommendations. The 61 eyes in the DRP group received anti-VEGF treatment with either ranibizumab or aflibercept during the 1-year period of the study. In addition, 29 patients (47.54%) completed the study with either panretinal or focal retinal photocoagulation treatments. It was also observed that 13 (21.31%) patients with diabetic maculopathy received local steroids as well. This treatment approach was recommended by the NICE clinical guidelines for DRP treatment ("Diabetic Retinopathy Guidelines" 2013). Most of the diabetic patients had lived with diabetes for many years, so different treatment approaches had been used prior to entering into the study. Hence, a combination of anti-VEGF, retinal laser photocoagulation, and intravitreal triamcinolone had already been established as treatments at the study baseline. As a result, I was not able to assess the functional outcomes of a single therapeutic approach. The research project also observed

patients within a normal clinical setting, so randomisation and consecutively assessing the therapeutic effect of different treatments was not possible either.

The major question in this research project was to explore visual outcomes in patients with MO. The majority of published studies have set BCVA as their primary end point. Figure 40 presents a summary of the most recent randomised controlled studies and the BCVA gain, which varies from 6.8 to 12.5 letters, in patients with DMO.

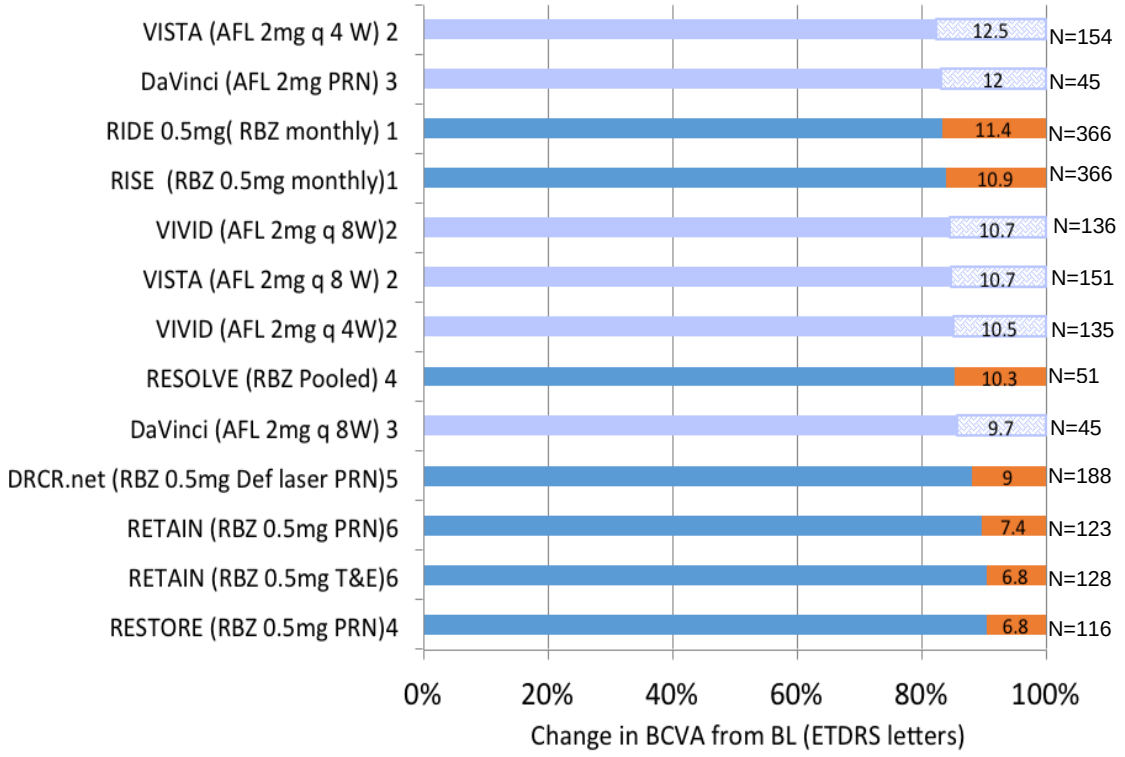

Figure 40- Summary of clinical trials on DMO presenting main VA gain from baseline

These findings are in contrast with the findings of this study, wherein no significant change in the visual acuity (VA) was observed. This contrast is probably due to the small sample size in the DRP group compared with the sample sizes in the studies listed above. Another explanation is the fact that observational studies like the present study tend to have relatively relaxed inclusion/exclusion criteria and do not apply strict treatment algorithms. Thus, the observed changes in VA in a real-world setting often differ from the observed values in randomised, controlled clinical trials.

The majority of the clinical trials were set up to investigate changes in retinal thickness alongside VA. Fewer studies have looked at the functional changes in patients with DRP. I designed this research project to examine the functional vision in DRP patients and the best way to measure it. From the findings presented earlier in this chapter, I can propose that microperimetry testing (MS, CZ-MS) and reading speed testing can be used as sufficient indicators for patients' clinically measured VA outcome. Further, I found that microperimetry results can statistically correlate with reading speed performance. In another aspect of functional vision assessment, I looked at the VFQ-25 scores and their relationship to the routine clinical and functional vision measures. In the DRP study group, I found that there is statistically significant correlation between LogMAR, CZ-MS, and the following VFQ-25 scores:

- General vision
- Mental health
- Dependence
- Driving

Therefore, I could confirm that patients' self-reported functional vision is also informative about their visual ability.

As a final step for this research, I looked at the VA predictive factors and their combined action. By using multiregression model analysis, I found that in the DRP group, CZ-MS and CSRT can be used as reliable predictors of patients' visual outcomes.

Chapter 5. Functional visual outcomes in patients with macular oedema caused by retinal vein occlusion

5.1 Introduction

Macula oedema (MO) is one of the major complications and reasons for vision loss amongst patients with retinal vein occlusion (RVO) (McIntosh et al. 2010). The present treatment algorithm for patients with RVO is based on the Royal College of Ophthalmologists guidelines and the NICE clinical guidelines. Many clinical trials have shown good visual recovery reached by different therapeutic approaches. Yet the recovery of functional vision in patients with MO due to RVO is still not well understood. In Chapter 5, I focus on the research questions about MO caused by RVO. Section 5.2 describes the treatment procedures that participants with RVO received for the 1-year study period. Section 5.3 presents the descriptive statistics for the routine clinical measures of VA and retinal thickness (CSRT, CMT), and Section 5.4 presents the functional vision measures of microperimetry, reading speed, and the VFQ-25. Section 5.5 examines the predictive value of all clinically examined measures. Section 5.6 summarises the main findings for the RVO group.

5.2 Therapy of retinal vein occlusion

In the RVO group, 26 eyes from 26 patients were recruited. During the study period, equal numbers of patients were treated with anti-VEGF intravitreal injections and intravitreal corticosteroids (14 eyes, 53.85%). Additionally, 6 eyes (23.08%) had retinal laser photocoagulation as further treatment.

5.3 Description of routine clinical tests in the RVO group

For the RVO group, the setup of data collection was identical to that for the DRP group. Information related to VA (LogMAR) and retinal thickness (CMT, CSRT) was collected as part of the routine clinical visits. The number of patients attending routine clinical appointments declined over the observation period. This drop out meant that at the 3-

month visits, only 16 eyes (16 patients) were seen. At the 6-month visits, 9 eyes (9 patients) were seen again, and only 3 eyes (3 patients) were seen at the 12-month visit. A summary of the mean VA, CSRT, and CMT for each study visit is presented in Figure 41.

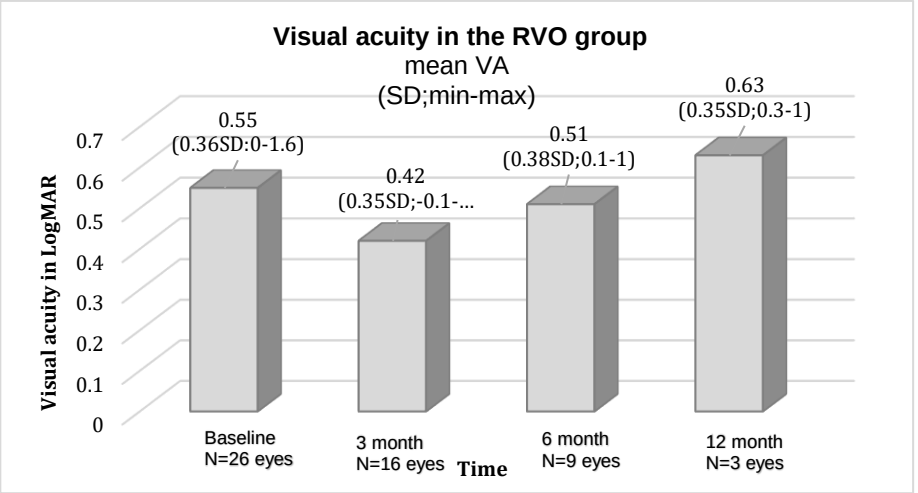

Figure 41- Mean VA at baseline, 3-, 6-, and 12-month visits in RVO group

The mean VA amongst observed RVO patients was 0.55 ± 0.36 LogMAR at baseline; 0.42 ± 0.35 LogMAR at the 3-month visit; 0.51 ± 0.38 LogMAR at the 6-month visit; and 0.63 ± 0.35 LogMAR at the 12-month visit.

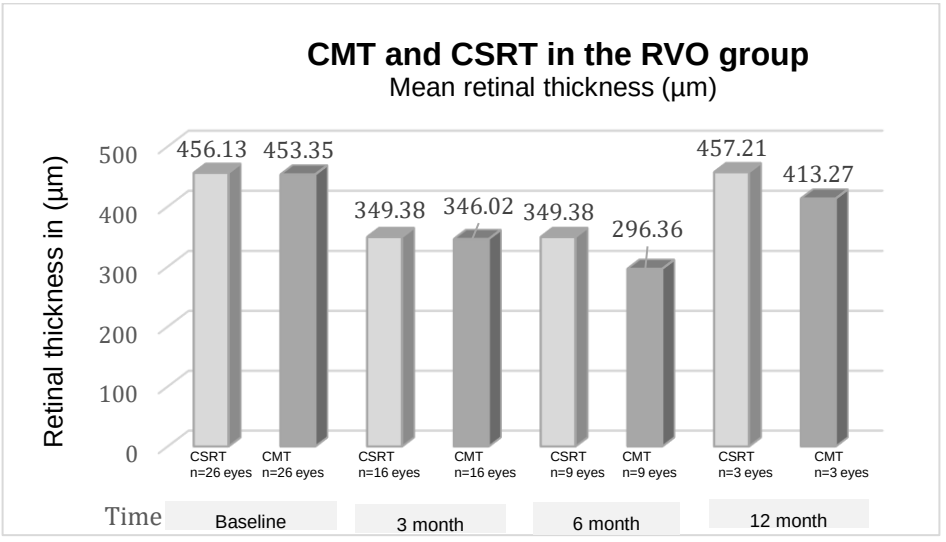

Figure 42- Mean CMT and CSRT at baseline, 3-, 6-, and 12-month visits in RVO group

CSRT and CMT were used to look at retinal thickness. The mean CSRT was 456.13 ± 163.05 µm at the baseline visit; 349.38 ± 144.36 µm at the 3-month visit; 349.38 ± 144.36 µm at the 6-month visit; and 457.21 ± 147.04 µm at the 12-month visit. The mean CMT was 453.35 ± 151.86 µm at baseline; 346.02 ± 167.87 µm at the 3-month visit; 296.36 ± 66.35 µm at the 6-month visit; and 413.27 ± 148.09 µm at the 12-month visit.

The Kolmogorov-Smirnov test showed a non-normal distribution of the data, hence the Wilcoxon Signed Ranks Test was used to calculate the observed change from baseline to 6 and 12 months for LogMAR, CMT, and CSRT. Due to the small number of patients observed from baseline to months 6 and 12, the p-value was not generated. A summary of results is presented in Table 64.

		N	Mean	SD	Minimum	Maximum	Percentiles 50th (Median)
RVO	LogMAR at baseline	9	0.400	0.187	0.200	0.600	0.500
	LogMAR at 6 months	9	0.320	0.179	0.200	0.600	0.200
	LogMAR at baseline	3	0.533	0.312	0.200	1.000	0.500
	LogMAR at 12 months	3	0.578	0.367	0.100	1.000	0.600
	CMT at baseline	9	394.20	166.941	247	655	345.00
	CMT at 6 months	9	267.60	51.150	183	304	292.00
	CMT at baseline	3	366.11	137.994	246	655	315.00
	CMT at 12 months	3	396.00	153.015	246	708	347.00
	CSRT at baseline	9	390.00	162.35	182.00	594.00	349.00
	CSRT at 6 months	9	350.20	108.50	242.00	499.00	331.00
	CSRT at baseline	3	370.67	140.08	182.00	594.00	349.00
	CSRT at 12 months	3	445.11	147.11	274.00	662.00	447.00

Table 64- Change from baseline to 6- and 12-month visits for LogMAR, CMT, and CSRT in RVO group

Number (n), Mean, Standard Deviation (SD), 95% CI, Range (Min, Max),

5.4 Description of functional vision test in the RVO group

This section presents the results of the functional vision tests for the RVO group. These tests include microperimetry, the reading speed test, and the VFQ-25 questionnaire.

5.4.1 Microperimetry results

The results for the central zone mean sensitivity (CZ-MS) and the mean sensitivity (MS) are presented for the RVO patients tested with the MP-1 and Optos SLO MP devices in Tables 65 and 66 respectively. The two tables show number of patients in the RVO group and in total (N), mean, standard deviation (SD), standard error of the mean (SE), 95% CI, and range (Min, Max).

MP- 1										
Visit		Group	N	Mean	SD	SE	95% CI		Min	Max
Baseline	CZ-MS	RVO	16	6.25	5.11	1.00	4.19	8.31	0.00	17.00
		Total	26	7.24	5.27	0.49	6.28	8.20	0.00	19.00
	MS	RVO	16	9.46	5.91	1.16	7.08	11.85	0.00	19.42
		Total	26	9.35	5.61	0.52	8.33	10.38	0.00	19.57
3 months	CZ-MS	RVO	9	6.43	4.79	1.33	3.53	9.32	0.00	14.50
		Total	16	7.91	6.03	0.85	6.19	9.62	0.00	20.00
	MS	RVO	9	9.33	5.58	1.40	6.35	12.30	0.00	15.71
		Total	16	9.34	5.65	0.67	8.00	10.67	0.00	20.00
6 months	CZ-MS	RVO	3	9.14	6.55	2.93	1.00	17.28	1.00	15.75
		Total	9	7.39	5.50	1.15	5.01	9.76	0.00	15.75
	MS	RVO	3	9.11	6.19	2.06	4.35	13.87	0.60	16.42
		Total	9	9.11	5.88	0.99	7.09	11.13	0.20	18.21
12 months	CZ-MS	RVO	2	7.07	4.90	1.63	3.30	10.83	0.00	14.50
		Total	3	7.34	5.65	0.96	5.40	9.28	0.00	18.00
	MS	RVO	2	10.48	6.42	3.71	-5.46	26.43	3.10	14.75
		Total	3	8.78	6.05	2.02	4.14	13.43	1.70	16.35

Table 65- Descriptive statistics of microperimetry outcomes at baseline, 3-, 6-, and 12-month visits for RVO patients tested with MP-1 device

Optos SLO MP										
Visit		Group	N	Mean	SD	SE	95% CI		Min	Max
Baseline	CZ-MS	RVO	10	4.15	3.11	0.92	2.21	6.21	0.00	14.00
		Total	26	7.24	5.27	0.49	6.28	8.20	0.00	19.00
	MS	RVO	10	7.26	3.82	1.0	5.28	9.25	0.00	16.32
		Total	26	9.35	5.61	0.52	8.33	10.38	0.00	19.57
3 months	CZ-MS	RVO	7	4.33	3.34	1.13	2.23	8.42	0.00	12.20
		Total	16	7.91	6.03	0.85	6.19	9.62	0.00	20.00
	MS	RVO	7	6.82	3.88	1.22	4.45	10.10	0.00	13.41
		Total	16	9.34	5.65	0.67	8.00	10.67	0.00	20.00
6 months	CZ-MS	RVO	6	6.10	4.24	1.81	1.25	15.25	1.00	12.55
		Total	9	7.39	5.50	1.15	5.01	9.76	0.00	15.75
	MS	RVO	6	6.08	4.16	2.00	2.45	10.25	0.40	10.22
		Total	9	9.11	5.88	0.99	7.09	11.13	0.20	18.21
12 months	CZ-MS	RVO	1	5.00	n/a					
		Total	3	7.34	5.65	0.96	5.40	9.28	0.00	18.00
	MS	RVO	1	8.50	n/a					
		Total	3	8.78	6.05	2.02	4.14	13.43	1.70	16.35

Table 66- Descriptive statistics of microperimetry outcomes at baseline, 3-, 6-, and 12-month visits for RVO patients tested with Optos SLO MP device

In the RVO group, I also observed that patients tested with the MP-1 device had different results (retinal sensitivity ranging from 6.25 to 10.48 dB) vs. patients tested with the Optos SLO MP device (retinal sensitivity ranging from 4.15 to 9.34 dB). An explanation for this is that retinal adaptation is different for the two MP devices.

The data were not normally distributed; accordingly, the Wilcoxon Signed Ranks Test was used again to calculate the mean change in MS and CZ-MS from baseline to months 6 and 12. Due to the small number of patients observed at the 6- and 12-month visits, the p-value was not generated. A summary of the results for the RVO patients tested with the MP-1 and Optos SLO MP devices is given in Tables 67 and 68 respectively. The tables show

number of eyes in the RVO group (N), mean, standard deviation (SD), range (Min, Max), and percentile 50th (Median).

MP-1							
Diagnosis group		N	Mean	SD	Min	Max	Percentile 50th (Median)
RVO	MS at baseline	3	11.28	5.3	5.50	17.07	12.29
	MS at 6 months	3	10.82	6.52	3.30	16.42	15.03
	MS at baseline	2	8.35	5.44	0.50	17.07	6.00
	MS at 12 months	2	8.76	5.74	0.60	15.32	7.10
	CZ-MS at baseline	3	5.78	5.67	0.00	16.50	4.00
	CZ-MS at 6 months	3	7.07	4.90	0.00	14.50	6.90
	CZ-MS at baseline	2	5.78	5.67	0.00	16.50	4.00
	CZ-MS at 12 months	2	7.07	4.90	0.00	14.50	6.90

Table 67- Mean change in MS and CZ-MS from baseline to 6- and 12-month visits in RVO patients tested with MP-1 device

Optos SLO MP								
Diagnosis group		N	Mean	SD	Min	Max	Percentile 50th (Median)	P-value
RVO	MS at baseline	6	11.28	5.3	5.50	17.07	12.29	n/a
	MS at 6 months	6	10.82	6.52	3.30	16.42	15.03	
	MS at baseline	1	8.35	5.44	0.50	17.07	6.00	n/a
	MS at 12 months	1	8.76	5.74	0.60	15.32	7.10	
	CZ-MS at baseline	3	5.78	5.67	0.00	16.50	4.00	n/a
	CZ-MS at 6 months	3	7.07	4.90	0.00	14.50	6.90	
	CZ-MS at baseline	1	5.78	5.67	0.00	16.50	4.00	n/a
	CZ-MS at 12 months	1	7.07	4.90	0.00	14.50	6.90	

Table 68- Mean change in MS and CZ-MS from baseline to 6- and 12-month visits in RVO patients tested with Optos SLO MP device

5.4.2 Reading speed

For the RVO group, the reading speed was examined using the same MNREAD test. As with the DRP group, the following parameters of the MNREAD test were examined:

- LogMAR at last sentence read
- Total reading errors
- Reading acuity in logMAR
- Estimated max reading speed (WPM) from plot

Figure 43 shows reading speed measures at the baseline, 3-, 6-, and 12-month visits. For all examined parameters, the detailed descriptive statistics are presented in Appendix III.

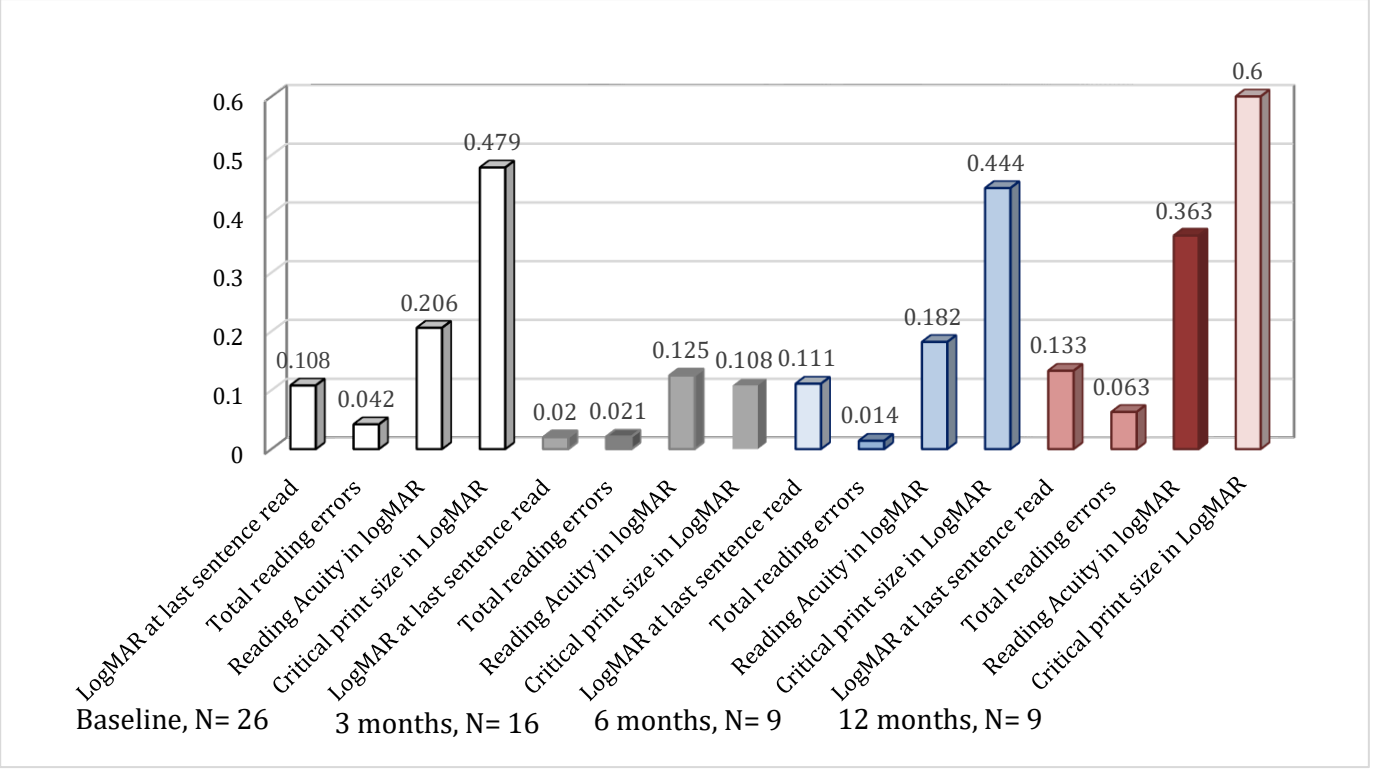

Figure 43- Reading speed measures at baseline, 3-, 6-, and 12-month visits in RVO group

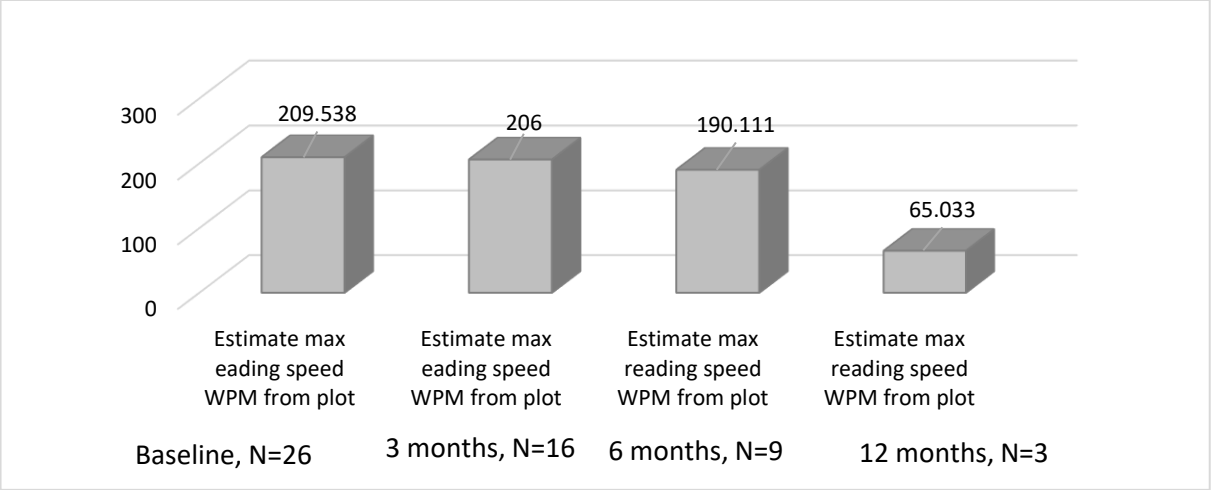

Figure 44- Estimated max reading speed (WPM) from the plot in RVO group

I looked at the change in reading speed measures and found that the change in the reading acuity in LogMAR from baseline to 3 months (0.25 ± 0.24 LogMAR; p-value<0.001) was statistically significant. This correlation was not observed in any other parameters of the reading speed. A possible explanation for this is the small sample size. Table 69 presents the number of RVO patients (N), mean, standard deviation (SD), range (Min, Max), percentile 50th (Median), and p-value.

		N	Mean	SD	Min	Max	Percentile 50th (Median)	P-value
RVO	LogMAR at last sentence read at baseline	3	0.13	0.17	-0.10	0.50	0.10	
	LogMAR at last sentence read at 12 months	3	0.03	0.16	-0.30	0.30	0.00	
	Reading acuity in LogMAR at baseline	16	0.25	0.24	-0.01	1	0.17	**<0,001**
	Reading acuity in LogMAR at 3 months	16	0.16	0.2	-0.1	0.6	0.14	
	Reading acuity in LogMAR at baseline	9	0.24	0.18	-0.01	0.61	0.19	
	Reading acuity in LogMAR at 6 months	9	0.20	0.26	-0.3	0.61	0.175	
	Estimated max reading speed (WPM) from plot at baseline	9	199.35	57.92	133	375	188.00	
	Estimated max reading speed (WPM) from plot at 6 months	9	199.76	40.40	133	273	188.00	
	Critical print size in LogMAR at baseline	9	0.47	0.28	0.10	1.10	0.40	
	Critical print size in LogMAR at 6 months	9	0.36	0.32	0.00	1.10	0.250	
	Critical print size in LogMAR at baseline	3	0.48	0.25	0.20	1.00	0.45	
	Critical print size in LogMAR at 12 months	3	0.39	0.33	0.00	1.10	0.25	

Table 69- Observed change from baseline to 6- and 12-month visits for reading speed parameters in the RVO group

5.4.3 VFQ-25 in the RVO group

As described in the methodology section, the VFQ-25 questionnaire was administered at the baseline visit for all participants. Data collected by the VFQ-25 survey were used to calculate the following VFQ-25 scores:

- General Health Score
- General Vision Score
- Ocular Pain Score
- Near Vision Score
- Distance Vision Score

- Social Score
- Mental Health Score
- Role Difficulties Score
- Dependence Score
- Driving Score
- Colour Vision Score
- Peripheral Vision Score

A summary of the VFQ-25 results in the RVO group (N=26) are presented in Figure 45. The percentages represent the achieved percentage of the total possible score. A full description of the VFQ-25 results for the RVO group can be found in in Appendix III.

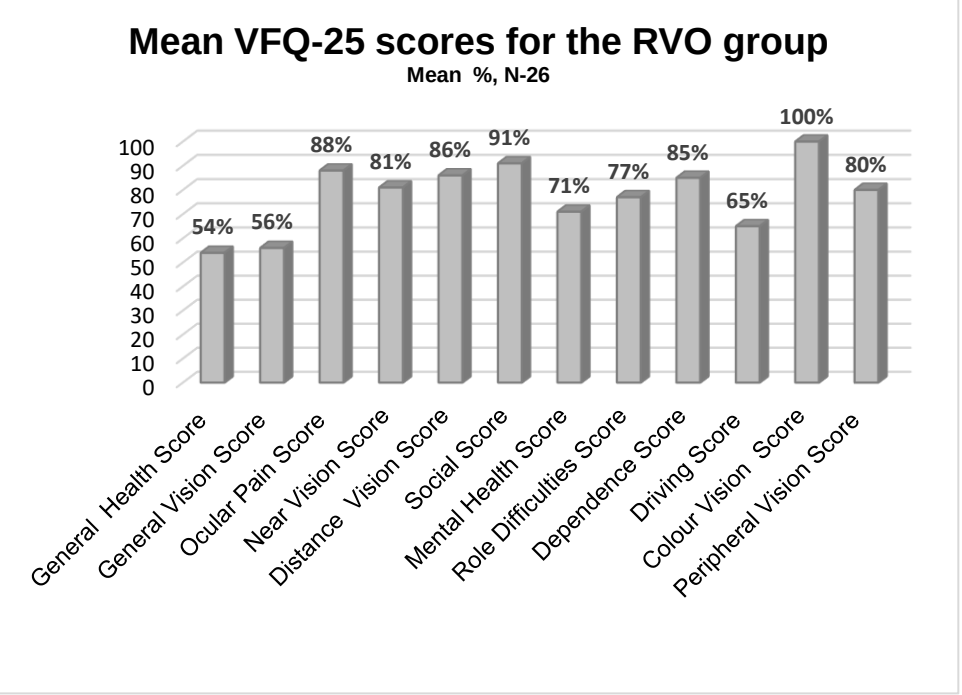

Figure 45- Mean VFQ-25 scores in RVO group

5.5 Anatomical response to the therapy

In order to assess the therapeutic responses to the RVO treatment, I also looked at any changes in the anatomical structure of the retina, focusing on the type of MO, IRF, and SRF location. This section provides information about the anatomical response to the treatment.

5.5.1 Focal and diffuse macular oedema in the RVO group

To assess the prevalence of focal and diffuse MO in the RVO group, I used Fisher's exact test. At baseline, 23.1% of the RVO patients had focal MO and 69.2% had diffuse MO. At the 6-month visits, the percentage with diffuse MO had reduced to 43.8%, but the percentage with focal MO had risen to 44.4% of RVO patients. This shift could be explained by the therapeutic response, which leads to reduction of the fluid and transition to focal MO. A summary of the observed results at the baseline and 3-month and then 6- and 12-month visits is presented in Tables 70 and 71 respectively.

	Type of macular oedema (MO)		RVO	Total
Baseline	Focal	Count	6	41
		% within Type of MO	14.6%	100.0%
		% within Group	23.1%	34.7%
	Diffuse	Count	18	73
		% within Type of MO	24.7%	100.0%
		% within Group	69.2%	61.9%
	Total	Count	26	118
		% within Type of MO	22.0%	100.0%
		% within Group	100.0%	100.0%
3 months	No	Count	3	10
		% within Type of MO	30.0%	100.0%
		% within Group	16.7%	14.1%
	Focal	Count	8	22
		% within Type of MO	36.4%	100.0%
		% within Group	44.4%	31.0%
	Diffuse	Count	7	39
		% within Type of MO	17.9%	100.0%
		% within Group	38.9%	54.9%
	Total	Count	18	71
		% within Type of MO	25.4%	100.0%
		% within Group	100.0%	100.0%

Table 70- Type of macular oedema in RVO group at baseline and 3-month visits

	Type of macular oedema (MO)		RVO	Total
6 months	No	Count	0	4
		% within Type of MO	0.0%	100.0%
		% within Group	0.0%	11.4%
	Focal	Count	4	14
		% within Type of MO	28.6%	100.0%
		% within Group	44.4%	40.0%
	Diffuse	Count	5	17
		% within Type of MO	29.4%	100.0%
		% within Group	55.6%	48.6%
	Total	Count	9	35
		% within Type of MO	25.7%	100.0%
		% within Group	100.0%	100.0%
12 months	No	Count	0	2
		% within Type of MO	0.0%	100.0%
		% within Group	0.0%	22.2%
	Focal	Count	2	3
		% within Type of MO	66.7%	100.0%
		% within Group	66.7%	33.3%
	Diffuse	Count	1	4
		% within Type of MO	25.0%	100.0%
		% within Group	33.3%	44.4%
	Total	Count	3	9
		% within Type of MO	33.3%	100.0%
		% within Group	100.0%	100.0%

Table 71- Type of macular oedema in RVO group at 6- and 12-month visits

5.5.2 Intraretinal fluid in the RVO group

I also looked at the prevalence of IRF amongst RVO patients during the study period. Fishers' exact test was used to describe IRF at each study visit. At the baseline visit, 65.5% of the RVO patients had extrafoveal and 30.8% had subfoveal IRF. At the 6-month visit, the proportion of patients with extrafoveal IRF had dropped to 55.6%, and the proportion with subfoveal IRF had increased to 44.4%.

This can be explained by the fact that localised extrafoveal IRF, which generally does not impact vision, is often observed and not treated if vision is not deteriorated. A summary of

the results at the baseline and 3-month and then 6- and 12-month visits is presented in Tables 72 and 73 respectively.

	Intraretinal fluid (IRF)		RVO	Total
Baseline	No	Count	1	2
		% within IRF	50.0%	100.0%
		% within Group	3.8%	1.7%
	Extrafoveal	Count	17	78
		% within IRF	21.8%	100.0%
		% within Group	65.4%	66.1%
	Subfoveal	Count	8	38
		% within IRF	21.1%	100.0%
		% within Group	30.8%	32.2%
	Total	Count	26	118
		% within IRF	22.0%	100.0%
		% within Group	100.0%	100.0%
3 months	No	Count	3	9
		% within IRF	33.3%	100.0%
		% within Group	16.7%	12.7%
	Extrafoveal	Count	10	42
		% within IRF	23.8%	100.0%
		% within Group	55.6%	59.2%
	Subfoveal	Count	5	20
		% within IRF	25.0%	100.0%
		% within Group	27.8%	28.2%
	Total	Count	18	71
		% within IRF	25.4%	100.0%
		% within Group	100.0%	100.0%

Table 72- Type of IRF in RVO group at baseline and 3-month visits

	Intraretinal fluid (IRF)		RVO	Total
6 months	No	Count	0	4
		% within IRF	0.0%	100.0%
		% within Group	0.0%	11.4%
	Extrafoveal	Count	5	19
		% within IRF	26.3%	100.0%
		% within Group	55.6%	54.3%
	Subfoveal	Count	4	12
		% within IRF	33.3%	100.0%
		% within Group	44.4%	34.3%
	Total	Count	9	35
		% within IRF	25.7%	100.0%
		% within Group	100.0%	100.0%
12 months	No	Count	0	1
		% within IRF	0.0%	100.0%
		% within Group	0.0%	11.1%
	Extrafoveal	Count	2	5
		% within IRF	40.0%	100.0%
		% within Group	66.7%	55.6%
	Subfoveal	Count	1	3
		% within IRF	33.3%	100.0%
		% within Group	33.3%	33.3%
	Total	Count	3	9
		% within IRF	33.3%	100.0%
		% within Group	100.0%	100.0%

Table 73- Type of IRF in RVO group at 6- and 12-month visits

5.5.3 Subretinal fluid in the RVO group

After describing the type of MO and location of IRF, I also looked at the prevalence of SRF. I used Fishers' exact test to describe SRF at each study visit. At baseline, 7.7% of the RVO patients had extrafoveal SRF, and 30.8% had subfoveal SRF. At the 6-month visits, the proportion of extrafoveal SRF dropped to 11.1%, and subfoveal SRF was observed in 22.2% of RVO patients. The prevalence and location of SRF in the RVO group at the baseline and 3-month and then 6- and 12-month visits is presented in Tables 74 and 75 respectively.

	Subretinal fluid (SRF)		RVO	Total
Baseline	No	Count	16	90
		% within SRF	17.8%	100.0%
		% within Group	61.5%	76.9%
	Extrafoveal	Count	2	5
		% within SRF	40.0%	100.0%
		% within Group	7.7%	4.3%
	Subfoveal	Count	8	22
		% within SRF	36.4%	100.0%
		% within Group	30.8%	18.8%
	Total	Count	26	117
		% within SRF	22.2%	100.0%
		% within Group	100.0%	100.0%
3 month	No	Count	16	61
		% within SRF	26.2%	100.0%
		% within Group	88.9%	85.9%
	Extrafoveal	Count	0	2
		% within SRF	0.0%	100.0%
		% within Group	0.0%	2.8%
	Subfoveal	Count	2	8
		% within SRF	25.0%	100.0%
		% within Group	11.1%	11.3%
	Total	Count	18	71
		% within SRF	25.4%	100.0%
		% within Group	100.0%	100.0%

Table 74- Type of SRF in RVO group at baseline and 3-month visits

	Subretinal fluid (SRF)		RVO	Total
6 month	No	Count	6	30
		% within IRF	20.0%	100.0%
		% within Group	66.7%	85.7%
	Extrafoveal	Count	1	1
		% within IRF	100.0%	100.0%
		% within Group	11.1%	2.9%
	Subfoveal	Count	2	4
		% within IRF	50.0%	100.0%
		% within Group	22.2%	11.4%
	Total	Count	9	35
		% within IRF	25.7%	100.0%
		% within Group	100.0%	100.0%
12 month	No	Count	2	8
		% within IRF	25.0%	100.0%
		% within Group	66.7%	88.9%
	Extrafoveal	Count	1	1
		% within IRF	100.0%	100.0%
		% within Group	33.3%	11.1%
	Subfoveal	Count	3	9
		% within IRF	33.3%	100.0%
		% within Group	100.0%	100.0%
	Total	Count	6	30
		% within IRF	20.0%	100.0%
		% within Group	66.7%	85.7%

Table 75- Type of SRF in RVO group at 6- and 12-month visits

5.6 Substantiation of the link between routine clinical and functional tests in the RVO group

This section examines the relationships between the clinical and functional vision tests in the RVO group. In order to identify the correlation between these measures, the Correlations Spearman's rho and Wilcoxon Signed Ranks Test statistical tests were used. In the tables in this section, the total number of cases (N), correlation coefficient (R), and p-value (P) are indicated for each of the test groups.

5.6.1 VA, CMT, and CSRT correspondence with functional vision tests in the RVO group

In this study, I looked at the correlation between VA and other routine clinical measurements such as CSRT and CMT. Spearman's rho test was used to calculate the correlation between LogMAR and retinal thickness, macular contrast sensitivity, and reading speed in patients with MO due to RVO. Tables 76 and 77 present the results for the RVO patients measured with the MP-1 and Optos SLO MP devices respectively.

MP-1											
Diagnosis group	LogMAR	CMT	CSRT	CZ-MS	MS	LogMAR at last Senten read		Reading Acuity LogMAR	Estimate max re speed from the (WPM)	Critical print size in LogMAR	
RVO	R	0.153	0.238	-0.654	-0.720	0.205		0.192	-0.196	0.132	
	p-value	0.454	0.241	**<0.001**	**<0.001**	0.315		0.347	0.336	0.520	
	N	16	16	16	16	16		16	16	16	

Table 76- Correlation between LogMAR vs. CMT, CSRT, CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for RVO patients tested with MP-1 device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

Optos SLO MP									
Diagnosis group	LogMAR	CMT	CSRT	CZ-MS	MS	LogMAR at last sentence read	Reading Acuity in LogMAR	Estimate max reading speed from the plot (WPM)	Critical print size in LogMAR
RVO	R	0.123	0.201	-0.436	-0.520	0.235	0.175	-0.147	0.153
	p-value	0.536	0.325			0.471	0.368	0.371	0.582
	N	10	10	10	10	10	10	10	10

Table 77- Correlation between LogMAR vs. CMT, CSRT, CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for RVO patients tested with Optos SLO MP device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

Amongst the RVO patients tested with the MP-1 microperimeter, I found a statistically significant correlation between LogMAR and CZ-MS (R = -0.654; p-value < 0.001, N = 16) and MS (R = -0.720; p-value < 0.001; N = 16). I did not observe any correlation between VA and reading speed performance in this group. Patients tested with the Optos SLO MP showed similar results. There was a statistically significant correlation between VA (LogMAR) and CZ-MS (R = -0.436; p-value = 0.015; N = 10) and MS (R = -0.520; p-value = 0.016; N = 10). The results in the RVO group did not show the correlations observed in the DRP group in this particular analysis. A possible explanation for this difference is the small number of patients observed in the RVO group.

Further analysis to identify the relationship between retinal thickness and functional vision tests were conducted. Tables 78–81 present the correlation coefficients for retinal thickness (CMT, CSRT) vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM) from plot, and critical print size in LogMAR. Tables 78 and 79 present the coefficients for CMT for RVO patients tested with the MP-1 and Optos

SLO MP devices respectively. Tables 80 and 81 present the coefficients for CSRT for RVO patients tested with the MP-1 and Optos SLO MP devices respectively. In all four tables, the total number of cases (N), correlation coefficient (R), and p-value (p) are indicated.

MP-1							
Diagnosis	CMT	Central Zone MS	LogMAR at last sentence read	Reading Acuity in logMAR	Estimate max reading speed WPM from plot	Critical print size in LogMAR	MS
RVO	R	0.046	0.163	0.085	0.112	-0.093	0.156
	p	0.822	0.428	0.680	0.586	0.652	0.448
	N	16	16	16	16	16	16

Table 78- Correlation between CMT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for RVO patients tested with MP-1 device

Optos SLO MP							
Diagnosis	CMT	Central Zone MS	LogMAR at last sentence read	Reading Acuity in logMAR	Estimate max reading speed WPM from plot	Critical print size in LogMAR	MS
RVO	R	0.066	0.184	0.076	0.144	-0.086	0.172
	p	0.792	0.538	0.713	0.596	0.741	0.658
	N	10	10	10	10	10	10

Table 79- Correlation between CMT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for RVO patients tested with Optos SLO MP

In contrast with the findings for the DRP group, the findings for the RVO group did not show a statistically significant correlation between CMT, MS, and reading speed. This applied for all RVO patients whether tested with the MP-1 or Optos SLO MP device.

In addition to CMT, I examined CSRT to see if a positive relationship could be observed. A summary of the findings for patients tested with the MP-1 and Optos SLO MP devices is presented in Tables 80 and 81 respectively. The tables present the correlation coefficients (R); number of eyes (N); and p-value (p), which is significant at p-value < 0.05

MP-1							
Diagnosis group	CSRT	CZ-MS	LogMAR at last sentence read	Reading Acuity in logMAR	Estimate max reading speed WPM from plot	Critical print size in LogMAR	MS
RVO	R	-0.081	0.219	0.184	0.052	-0.053	0.039
	p	0.694	0.282	0.370	0.802	0.797	0.849
	N	16	16	16	16	16	16

Table 80- Correlation between CSRT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for RVO patients tested with MP-1 device

Optos SLO MP							
Diagnosis group	CSRT	CZ-MS	LogMAR at last sentence read	Reading Acuity in logMAR	Estimate max reading speed WPM from plot	Critical print size in LogMAR	MS
RVO	R	0.041	0.116	0.137	0.049	0.033	0.057
	p	0.714	0.371	0.422	0.917	0.894	0.799
	N	10	10	10	10	10	10

Table 81- Correlation between CSRT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for RVO patients tested with Optos SLO MP device

In contrast with the findings in the DRP group, the findings for the RVO group did not show a statistically significant correlation between retinal thickness (CMT, CSRT) and functional tests (reading speed and microperimeter). A possible explanation for this is the small sample size in the RVO group compared with the DRP group.

5.6.2 Correlation of microperimetry and reading speed outcomes in the RVO group

I also explored whether the microperimetry results linked better with patients' reading speed performance and self-reported vision-related quality of life. For the analysis, I used the Spearman's rho test. The results for correlation between MS and reading speed performance are presented in Tables 82 and 83 for patients tested with the MP-1 and Optos SLO MP devices respectively. The tables present the correlation coefficients (R); number of eyes (N); and p-value (p), which is significant at p-value < 0.05.

MP-1					
	MS	**LogMAR at last sentence read**	**Reading acuity in logMAR**	**Est. max reading speed (WPM)**	**Critical print size in LogMAR**
RVO	R	-0.338	-0.354	0.20	-0.195
	p	0.091	0.076	0.327	0.34
	N	16	16	16	16

Table 82- Correlation between MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for RVO patients tested with MP-1 device

	Optos SLO MP				
	MS	LogMAR at last s read	Reading acuity in LogMAR	Est. max reading (WPM)	Critical print size in LogMAR
RVO	R	-0.345	-0.426	0.197	-0.201
	p	0.141	0.166	0.484	0.398
	N	10	10	10	10

Table 83- Correlation between MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for RVO patients tested with Optos SLO MP device

Unfortunately, due to the small sample size, I was not able to establish a statistically significant correlation between MS and reading speed performance in patients with MO due to RVO who were tested with the MP-1 and the Optos SLO MP devices.

In addition, I looked at whether CZ-MS could better present changes in the reading speed. I used the Spearman's rho test for this analysis. Total number of eyes tested (N), correlation coefficient (R), and p-value (significant at p-value <0.05) are indicated in Tables 84 and 85 for the RVO patients tested with the MP-1 and Optos SLO MP devices respectively.

MP-1					
Diagnosis group	Central Zone MS	LogMAR at last sentence read	Reading Acuity in logMAR	Estimate max reading speed WPM from plot	Critical print size in LogMAR
RVO	R	-0.378	-0.396	0.338	-0.036
	p	0.057	0.045	0.092	0.860
	N	16	16	16	16

Table 84- Correlation between CZ-MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for RVO patients tested with MP-1 device

Optos SLO MP					
Diagnosis group	Central Zone MS	LogMAR at last sentence read	Reading Acuity in logMAR	Estimate max reading speed WPM from plot	Critical print size in LogMAR
RVO	R	-0.298	-0.453	0.401	-0.020
	p	0.069	**0.049**	0.112	0.960
	N	10	10	10	10

Table 85- Correlation between CZ-MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for RVO patients tested with Optos SLO MP device

In the RVO group, I found a statistically significant correlation between CZ-MS and reading acuity in LogMAR (R = -0.396; p-value = 0.045; N = 16) for patients tested with the MP-1 device. The results for patients tested with the Optos SLO MP device also showed a statistically significant correlation between CZ-MS and reading acuity in LogMAR (R = -0.453; p-value = 0.049; N = 10). Due to the small sample size in both subgroups (in the

RVO group, 16 patients were tested with the MP-1, and 10 were tested with the Optos SLO MP), correlation between CZ-MS and reading speed parameters was not observed either.

5.6.3 Correspondence between vision-related quality of life (VFQ-25) and VA, CSRT, and CZ-MS in the RVO group

In this section, I investigate the relationship between patient self-reported functional vision (VFQ-25) and VA (LogMAR), CSRT, and CZ-MS. Table 86 summarises the main findings.

		General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
RVO	LogMAR												
	R	-0.234	-0.002	-0.383	-0.212	-0.417	-0.288	-0.189	-0.371	- 0.283	-0.281	-0.197	-0.257
	p	0.260	0.992	0.059	0.308	0.038	0.163	0.365	0.068	0.170	0.174	0.346	0.215
	N	26	26	26	26	26	26	26	26	26	26	26	26

Table 86- Correlation between LogMAR and VFQ-25 scores in RVO group

R = correlation coefficient, N = number of patients, and p-value < 0.05.

In the RVO group, I found that VA (LogMAR) significantly correlated only with the distance vision score (R = -0.417; p-value = 0.038; N = 26). The remaining results were in contrast with the findings for the DRP group. A possible explanation is the small sample size in the RVO group.

In regards to the relationship between CSRT and the VFQ-25 scores, I found a statistically significant correlation with the scores for general vision (R = -0.513; p-value = 0.009; N = 26), mental health (R = -0.404; p-value = 0.045; N = 26), and role difficulties (R = -0.471; p value = 0.017; N = 26). Table 87 summarises these findings. Similar correlations were observed in the DRP group.

	CSRT	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
RVO	R	-0.169	-0.513	0.081	-0.300	-0.391	-0.140	-0.404	-0.471	-0.047	0.045	0.130	-0.324
	p	0.420	0.009	0.699	0.147	0.053	0.504	0.045	0.017	0.823	0.832	0.535	0.115
	N	26	26	26	26	26	26	26	26	26	26	26	26

Table 87- Correlation between CSRT and VFQ-25 scores in RVO group

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

Finally, I also looked at the correlation between CZ-MS and the VFQ-25 score. The results for the MP-1 and Optos SLO MP devices are presented in Tables 88 and 89 respectively.

MP-1													
	CZ-MS	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
RVO	R	0.107	-0.172	0.387	0.215	0.355	0.307	0.193	0.312	0.225	0.356	0.332	0.107
	p	0.609	0.411	0.056	0.303	0.081	0.136	0.354	0.128	0.280	0.080	0.105	0.609
	N	16	16	16	16	16	16	16	16	16	16	16	16

Table 88- Correlation between CZ-MS and VFQ-25 scores for RVO patients tested with MP-1 device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

Optos SLO MP													
	CZ-MS	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
RVO	R	0.125	-0.194	0.392	0.202	0.361	0.387	0.152	0.367	0.191	0.368	0.252	0.057
	p	0.703	0.432	0.062	0.393	0.094	0.148	0.366	0.282	0.320	0.091	0.127	0.759
	N	10	10	10	10	10	10	10	10	10	10	10	10

Table 89- Correlation between CZ-MS and VFQ-25 scores for RVO patients tested with Optos SLO MP device

R = correlation coefficient, N = number of eyes, and p-value < 0.05.

I found that there was no statistically significant correlation between CZ-MS and any of the VFQ-25 scores. These findings are in contrast to the findings for the DRP group, where CZ-MS showed a correlation with the scores for general vision, mental health, role difficulties, dependence, and driving. A possible explanation for this is the small sample size observed.

5.7 Regression models to predict patient outcomes in the RVO group

In this section, I present the results from the regression model analysis for the RVO group. The aim of using this model was to explore the predictive value of each measure in assessing patients' outcomes. First, I used a single regression model to identify the relation between the dependant variable (VA) and the independent variables (MS, CZ-MS, CMT, CSRT). Second, I looked at the potential combining effect of different variables and their role in explaining changes in the patients' outcomes. Regrettably, the statistical program used was not able to generate multiple linear regression models for the RVO group due to the small sample size in the RVO group.

5.7.1 Simple linear regression model in the RVO group

In order to identify the linear relationship between two variables, I used simple linear regression model analysis. The results for the RVO patients tested with the MP-1 and Optos SLO MP devices are shown in Tables 90 and 91 respectively.

MP-1							
Group	Predictors	Coefficients	t	p	F	p	R^2
RVO	LogMAR	0.858	6.830	<0,001	13.742	0.002	0.478
	MS	-0.035	-3.707	0.002			
	LogMAR	0.321	1.859	0.083	0.532	0.477	0.034
	CMT	0.000	0.730	0.477			
	LogMAR	0.222	1.130	0.276	1.341	0.265	0.082
	CSRT	0.000	1.158	0.265			
	LogMAR	0.716	6.750	<0,001	9.800	**0.007**	0.395
	CZ-MS	-0.035	-3.131	0.007			

Table 90- Simple linear regression model of LogMAR vs. MS, CZ-MS, CSRT, and CMT for RVO patients tested with MP-1 device

Optos SLO MP							
Group	Predictors	Coefficients	t	p	F	p	R^2
RVO	LogMAR	1.226	5.523	0.001	5.776	0.047	0.452
	MS	-0.098	-2.403	0.047			
	LogMAR	0.571	1.201	0.269	0.164	0.698	0.023
	CMT	0.000	0.405	0.698			
	LogMAR	0.395	0.603	0.565	0.319	0.590	0.044
	CSRT	0.001	0.565	0.590			
	LogMAR	0.955	5.215	0.001	2.181	0.183	0.238
	CZ-MS	-0.068	-1.477	0.183			

Table 91- Simple linear regression model of LogMAR vs. MS, CZ-MS, CSRT, and CMT for RVO patients tested with Optos SLO MP device

In the RVO group, I found that variations in LogMAR are related to variations in MS (p-value = 0.002; R^2 = 0.475) and CZ-MS (p-value = 0.007; R^2 = 0.395), but not to variations in CMT (p-value = 0.477; R^2 = 0.034) and CSRT (p-value = 0.265; R^2 = 0.082) for patients tested with the MP-1 device. For patients tested with the Optos SLO MP device, I found a statistically significant correlation only between VA (LogMAR) and MS (p-value = 0.047; R^2 = 0.452). The difference in the results between the two microperimeters could be explained by the small sample size in the group tested with the Optos SLO MP device. Overall, the findings in this group are in contrast with the results observed for the DRP group. The findings are also different from those in the current practice for management of MO caused by RVO, wherein retinal thickness reduction is considered a key marker for good therapeutic response.

5.8 Discussion

Macular oedema (MO) is a serious complication of retinal vein occlusion (RVO). MO can lead to severe and chronic visual impairment. Recently, clinical trials on RVO have shown significant improvement in visual acuity (VA). A summary of these trials are presented in Table 92.

Study name	Sample size, N	Reported Change from baseline in the BCVA (letters gain)
BRAVO 12 months	397	+18.4
CRUISE 12 months	392	+14.9
HORIZON	600	+17.5 BRVO/ +12.0 CRVO
SHORE	175	+18.0 CRVO/ +23.3 BRVO
Galileo	177	+16.9
Copernicus	188	+16.1
VIBRANT	183	+17.0

Table 92- Summary of clinical trials on RVO and reported VA improvement

In this study, I was not able to identify significant improvement in VA. One possible explanation is the small sample size and high drop-out rate of the study participants. A significant amount of study participants were lost during follow up due to participants being referred to local treatment centres. Another possible explanation for the study's results could be the level of ischaemia in the macula, which further contributes to visual

deterioration. Unfortunately, the severity of the ischaemia was not examined; it is considered as a topic for possible further research.

The purpose of this chapter was to establish functional vision change amongst patients with MO due to RVO. Accordingly, I examined the functionality of the eyesight in the RVO patients by using the same reading speed test (MNREAD) and microperimeters as used for the DMO group. The findings for the RVO group differed from the results observed for the DRP group. In the RVO group, I was not able to identify any link between VA and macular contrast sensitivity (MS, CZ-MS). Also, there was no correlation between retinal thickness, MS, CZ-MS, and reading speed parameters. There were discrepancies in the findings related to the VFQ-25. I found that in the RVO group, LogMAR correlated with the scores for distance vision, ocular pain, and role difficulties. In addition, CSRT correlated with the mental health score. In the DRP group, I found a statistically significant correlation between LogMAR and the scores for general vision, mental health, dependence, and driving. This was another point of contrast between patients with MO caused by DRP versus RVO.

In order to evaluate the treatment response in RVO patients, it is common practice to report the retinal thickness change. At baseline, I found mean CMT was 453.35 ± 151.66 μm and CSRT was 456.13 ± 163.05 μm. At months 3, 6, and 12, the means for CSRT were 349.38 ± 144.70 μm (n = 13), 349.38 ± 144.36 μm (n = 13), and 357.31 ± 147.04 μm (n=9) respectively for the RVO group. At the same time, the mean CMT was 346.02 ± 167.87 μm (n = 13), 296.36 ± 66.35 μm (n = 13), and 413.27 ± 148.09 μm (n = 9) for months 3, 6, and 12 correspondingly. In this study, neither CMT nor the CSRT showed improvement in the RVO group. Thus CMT increased +47.7 μm (p-value = 0.88) and CSRT increased +57.0 μm (p = 0.40) from baseline. The results observed in this research project are in contrast to the outcomes reported by several clinical trials.

Study name	Sample size	Follow-up time	Reported change from baseline in retinal thickness
BRAVO	397	12 months	-347.4 µm
CRUISE	392	12 months	-462.1 µm
HORIZON	600	12 months	-330.6 µm BRVO/ -412.2 µm CRVO
SHORE	175	15 months	-247.8 µm
Galileo	177	52 weeks	-423.5 µm
Copernicus	188	100 weeks	-413.0 µm
COMRAD-B	126	6 months	-275 µm

Table 93- Summary of clinical trials on RVO and reported changes in retinal thickness improvement

As final step of the analysis in the RVO group, by using a simple regression model, I found that changes in vision could be explained by variations in CZ-MS and MS, but not by variations in CMT or CSRT.

Chapter 6. Functional visual outcomes in patients with uveitic macular oedema

6.1 Introduction

Macular oedema (MO) is a common accompaniment of severe intraocular inflammation. Uveitic macular oedema (UMO) can be temporary or chronic, and it requires regular follow ups. Although there are no established guidelines for management of uveitis, the ISUN group provides guidance on therapeutic approach, which depends on the initial cause triggering the inflammatory process in the eye. The treatment itself varies from local non-steroidal anti-inflammatory medications to intravitreal corticosteroid or immunosuppressants. For severe and chronic cases, systemic treatment includes corticosteroids with or without a combination of immunosuppressive drugs. In other words,

although a wide range of treatment approaches and promising therapeutic outcomes are available, it is not known what the functional vision outcomes are in patients with UMO.

In Chapter 6, I present the results from this research project investigating functional vision in the study participants with UMO. Section 6.2 presents the main characteristics of the patients enrolled in the UMO group with regard to routine clinical measures. Sections 5.3 and 5.4 present descriptive analyses for the microperimetry, reading speed, and VFQ-25 outcomes in patients with UMO. The predictive value of clinically examined measures is presented in Section 5.7. Section 5.8 summarises the main findings in the UMO group.

6.2 Therapy in uveitic macular oedema

Due to the fact that there is no existing recommendation from NICE or the Royal College of Ophthalmologists about treatment for uveitis, the study participants had received management of treatment based on the ISUN group's recommendations. In the UMO group, 25 patients (31 eyes) were enrolled in the study at the baseline visit. Of the observed patients, 95.24% received local steroid treatment, and 33.33% received anti-VEGF intravitreal injections to control the complications of uveitis. In the DRP and RVO groups, the treatment was mainly local for the eye conditions. In contrast, in the UMO group, 76.19% of the eyes (23.81% of patients) were treated with systemic corticosteroids, and 33.33% of the eyes (23.81% patients) received immunosuppressant therapy.

6.3 Descriptive statistics of routine clinical tests in the UMO group

The data collection process for the UMO group took place only at Moorfields Eye Hospital NHS Trust in a single routine uveitis clinic. The data collected included VA (LogMAR) and retinal thickness (CMT, CSRT). There were 31 eyes diagnosed with UMO at baseline. The number of patients returning for follow-up, however, declined over the study period: 19 patients (24 eyes) were seen at the 3-month visit, 13 patients (16 eyes) at the 6-month visit, and only 5 patients (9 eyes) at the 12-month visit. This high drop-out rate was triggered by the disease activity and patients' need for monitoring, which led the patients to be referred to local clinics instead. For the UMO group, Figure 46 presents the mean values of VA, and Figure 47 presents the mean values of CMT and CSRT.

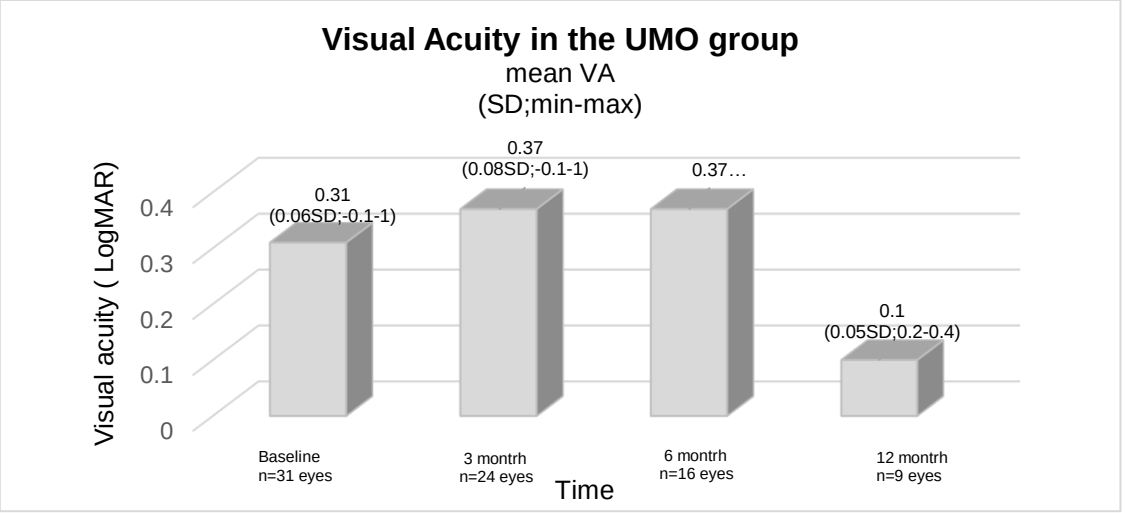

Figure 46- Visual acuity in UMO group over 12-month study period

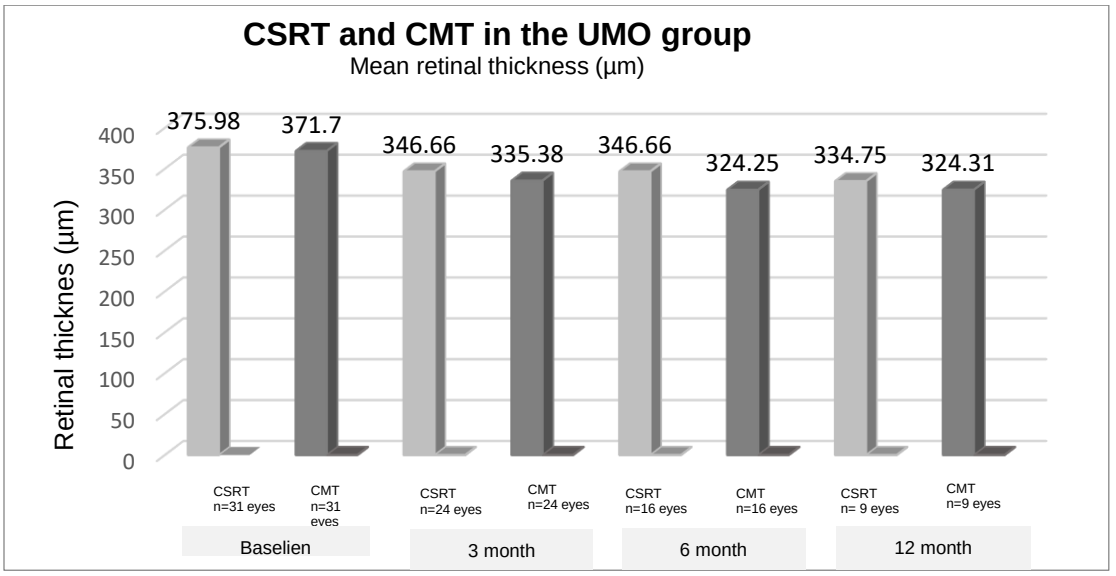

Figure 47- CSRT and CMT in UMO group over 12-month study period

The Kolmogorov-Smirnov test showed a non-normal distribution of the data, hence the Wilcoxon Signed Ranks Test was used to calculate the observed change from baseline to 3-, 6-, and 12-month visits for LogMAR, CMT, and CSRT. A summary of the results is presented in Table 94. The table presents number of eyes (N), mean, standard deviation (SD), range (Min, Max), percentiles 50th (Median), and p-value (significance at p-value <0.05).

	N	Mean	SD	Min	Max	Percentiles 50th (Median)	P-value
LogMAR at baseline	16	0.400	0.338	-0.100	0.800	0.400	0.326
LogMAR at 6 month	16	0.488	0.323	0.000	1.000	0.500	
LogMAR at baseline	9	0.488	0.350	-0.100	1.000	0.500	
LogMAR at1 2 month	9	0.481	0.347	0.000	1.000	0.350	
CMT at baseline	16	342.50	110.05	204	517	333.50	0.251
CMT at 6 month	16	324.25	88.87	182	441	335.50	
CMT at baseline	9	361.75	108.69	233	570	345.50	
CMT at 12 month	9	324.31	72.20	230	485	310.50	
CSRT at baseline	16	352.50	121.78	189.00	514.00	376.00	0.572
CSRT at 6 months	16	343.75	68.78	243.00	426.00	356.00	
CSRT at baseline	9	351.88	124.14	179.00	547.00	360.00	
CSRT at 12 months	9	334.75	68.69	240.00	479.00	328.00	

Table 94- Change from baseline to 6- and 12-month visits for LogMAR, CMT, and CSRT in UMO group

6.4 Descriptive statistics of functional vision tests

This section presents the descriptive statistics for the functional vision tests – microperimetry, the reading speed test, and the VFQ-25 questionnaire. All patients in the UMO group were recruited from one site (Moorfields Eye Hospital), hence their microperimeter testing was conducted only with the MP-1 device. The Optos SLO MP device was not available at Moorfields Eye Hospital during the research project.

6.4.1 Microperimetry results

Similarly to the DRP and RVO groups, the UMO group underwent microperimetry testing at the baseline, 3-, 6-, and 12-month visits. Table 95 summarises these results including number of eyes (N), mean, standard deviation (SD), standard error of the mean (SE), 95% CI, and range (Min, Max).

MP-1									
Visit		Group	N	Mean	SD	SE	95% CI		Min	Max
Baseline	CZ-MS	Uveitis	31	7.73	5.31	0.95	5.78	9.68	0.00	19.00
		Total	118	7.24	5.27	0.49	6.28	8.20	0.00	19.00
	MS	Uveitis	31	9.42	5.91	1.06	7.26	11.59	0.20	19.57
		Total	118	9.35	5.61	0.52	8.33	10.38	0.00	19.57
3 months	CZ-MS	Uveitis	24	9.03	6.36	1.50	5.87	12.19	0.50	20.00
		Total	71	7.91	6.03	0.85	6.19	9.62	0.00	20.00
	MS	Uveitis	24	9.58	5.82	1.19	7.12	12.03	0.70	20.00
		Total	71	9.34	5.65	0.67	8.00	10.67	0.00	20.00
6 months	CZ-MS	Uveitis	16	6.25	5.32	1.88	1.80	10.70	0.00	14.50
		Total	35	7.39	5.50	1.15	5.01	9.76	0.00	15.75
	MS	Uveitis	16	8.94	6.63	1.66	5.41	12.47	0.20	18.21
		Total	35	9.11	5.88	0.99	7.09	11.13	0.20	18.21
12 months	CZ-MS	Uveitis	9	7.08	5.87	1.47	3.95	10.21	0.50	18.00
		Total	14	7.34	5.65	0.96	5.40	9.28	0.00	18.00
	MS	Uveitis	9	8.65	7.48	3.74	-3.25	20.55	1.70	16.35
		Total	14	8.78	6.05	2.02	4.14	13.43	1.70	16.35

Table 95- Descriptive statistics of microperimetry outcomes in UMO group at baseline, 3-, 6-, and 12-month visits for patients tested with the MP-1 device

Abbreviations: **CZ-MS** = central zone mean sensitivity; **MS** = mean sensitivity

In order to calculate the mean change in MS and CZ-MS from the baseline to 6- and 12-month visits, the Wilcoxon Signed Ranks Test was used. An overview of the findings are presented in Table 96, which includes number of eyes (N), mean, standard deviation (SD), range (Min, Max), percentile 50th (Median), and p-value (significant at p-value < 0.05).

MP-1								
Diagnosis group		N	Mean	Std. Deviation	Min	Max	Percentile 50th (Median)	P-value
UMO	MS at baseline	13	6.14	4.95	.20	15.57	6.93	0.537
	MS at 6 month	13	7.95	2.88	5.28	14.25	7.07	
	MS at baseline	9	9.09	6.12	.20	17.79	7.80	
	MS at 12 month	9	10.05	6.81	.20	18.21	12.00	
	CZ-MS at baseline	13	6.97	4.76	0.00	13.75	7.00	0.67
	CZ- MS at 6 month	13	7.08	5.87	0.50	18.00	5.50	
	CZ-MS at baseline	9	6.97	4.76	0.00	13.75	7.00	
	CZ- MS at 12 month	9	7.08	5.87	0.50	18.00	5.50	

Table 96- Change from baseline to 6- and 12 month visits for MS and CZ-MS in UMO group tested with MP-1

6.4.2 Reading speed results

As with the DRP and RVO groups, the reading speed assessment for the UMO group was performed at the baseline, 3-, 6-, and 12-month visits by using the same MNREAD test. The key measures for the reading speed assessment were identical to those described in the DRP and the RVO groups: LogMAR at last sentence real, total reading errors, reading acuity in logMAR, and estimated max reading speed (WPM) from plot. An outline of the reading speed results over the 1-year period of observational are presented in Figure 48. The detailed descriptive statistics of the reading speed in the UMO group are presented in Appendix III.

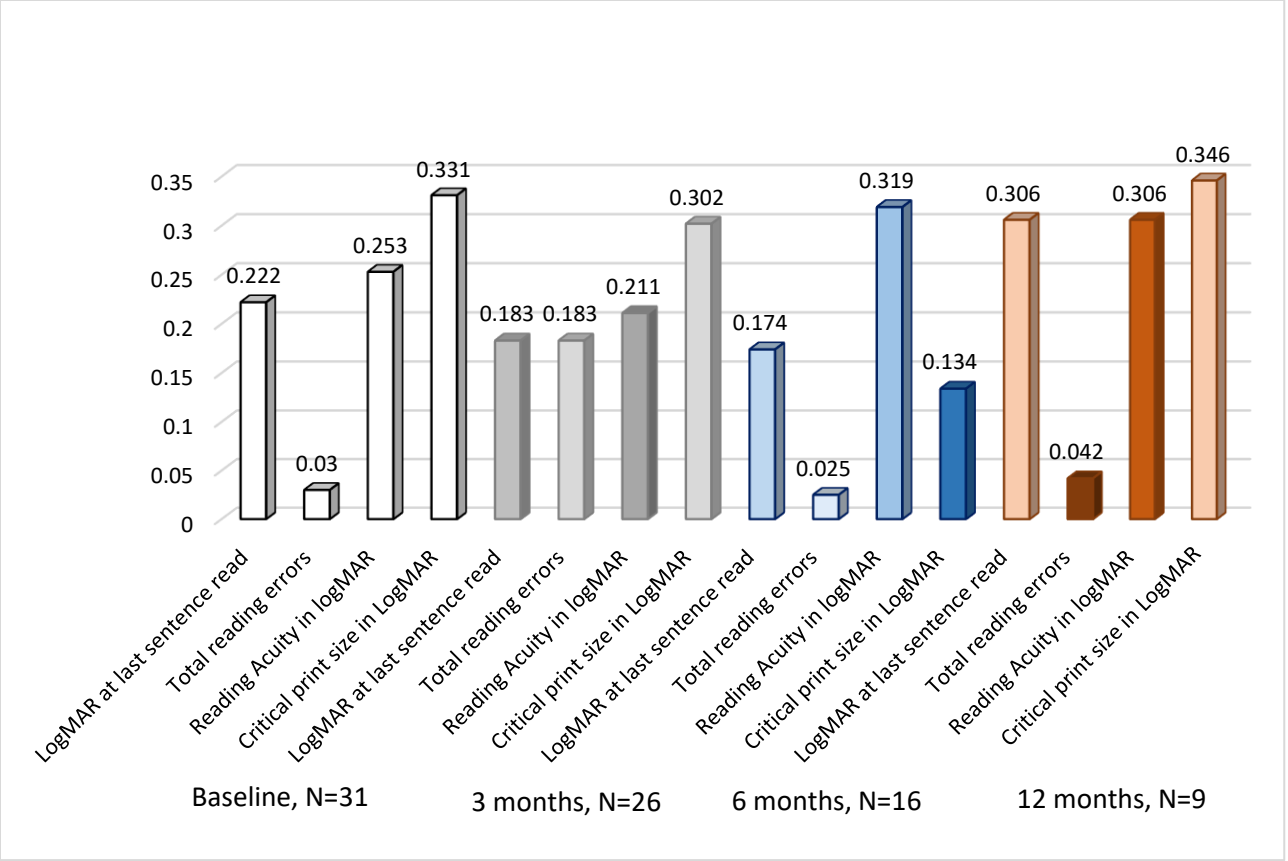

Figure 48- Reading speed results in UMO group

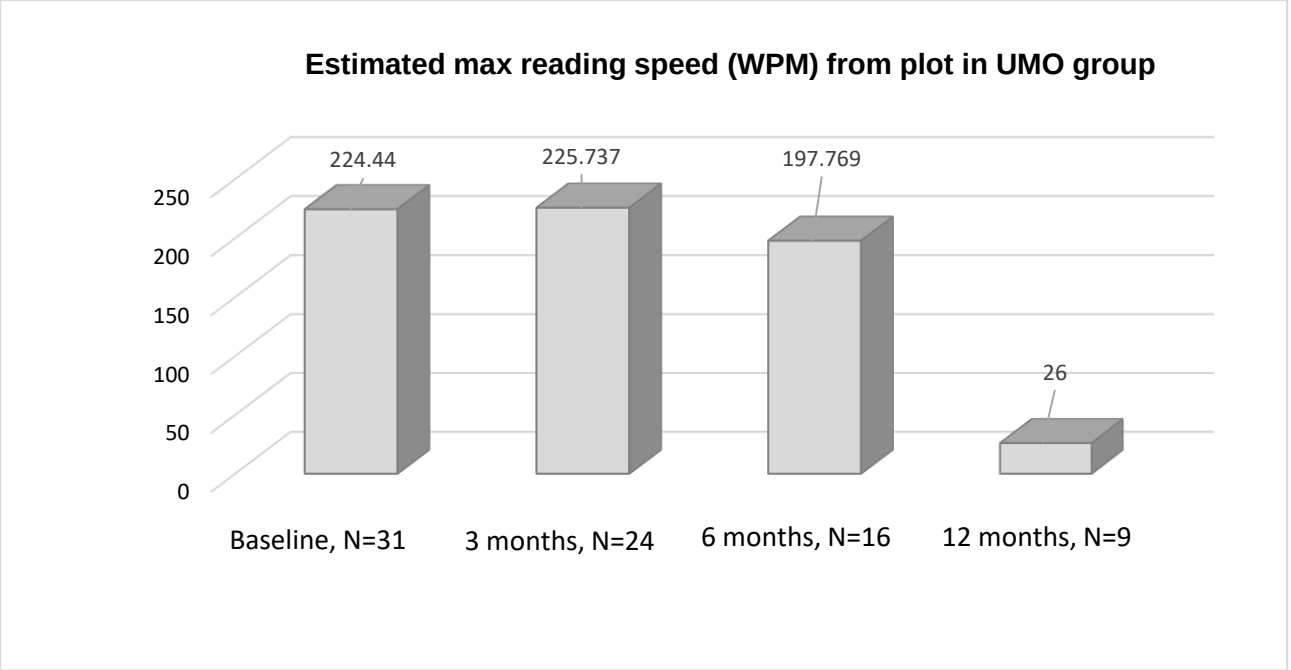

Figure 49- Estimated max reading speed (WPM) from the plot in the UMO group

The change from baseline to months 3, 6, and 12 was also calculated for the reading speed outcomes in the UMO group. I found that the change in the reading acuity in LogMAR from baseline to 3 months (p-value < 0.001) and 6 months (p-value = 0.002) was statistically significant. This correlation was not observed in any other parameters of the reading speed. One possible explanation could be the small number of observed patients in each of the groups over the 1-year period.

Diagnosis group		N	Mean	SD	Min	Max	Percentile 50th (Median)	P-value
UMO	LogMAR at last sentence read at baseline	9	0.26	0.19	-0.10	0.60	0.25	n/a
	LogMAR at last sentence read at 12 months	9	0.12	0.22	-0.20	0.70	0.05	
	Reading acuity in LogMAR at baseline	24	0.34	0.27	0.01	0.98	0.31	<0,001
	Reading acuity in LogMAR at 3 months	24	0.27	0.17	0	0.61	0.29	
	Reading acuity in LogMAR at baseline	16	0.40	0.26	0.06	0.98	0.39	
	Reading acuity in LogMAR at 6 months	16	0.30	0.38	-0.02	1.14	0.2	0.002
	Estimated max reading speed (WPM) from plot at baseline	16	221.89	44.44	171	333	214.00	0.081
	Estimated max reading speed (WPM) from plot at 6 months	16	196.47	47.39	107	273	214.00	
	Estimated max reading speed (WPM) from plot at baseline	9	231.50	49.84	171	333	227.00	n/a
	Estimated max reading speed (WPM) from plot at 12 months	9	163.16	52.08	24.0	240.0	179.50	
	Critical print size in LogMAR at baseline	16	0.51	0.33	0.00	1.30	0.50	0.60
	Critical print size in LogMAR at 6 months	16	0.57	0.26	0.10	1.10	0.60	
	Critical print size in LogMAR at baseline	9	0.56	0.23	0.20	1.00	0.55	n/a
	Critical print size in LogMAR at 12 months	9	0.58	0.46	0.10	1.40	0.35	

Table 97- Observed change from baseline to 6- and 12-month visits for reading speed parameters in UMO group

6.4.3 VFQ-25

Patients in the UMO group were also asked to complete the VFQ-25 questionnaire at their baseline visit. The following scores were calculated:

- General Health Score
- General Vision Score
- Ocular Pain Score
- Near Vision Score
- Distance Vision Score
- Social Score
- Mental Health Score

- Role Difficulties Score
- Dependence Score
- Driving Score
- Colour Vision Score
- Peripheral Vision Score

The mean percentage of the VFQ-25 score for the UMO group is presented in Figure 50. Detailed descriptive statistics including number (N), mean, standard deviation (SD), standard error of the mean (SE), 95% CI, and range (Min, Max) are available in Appendix III.

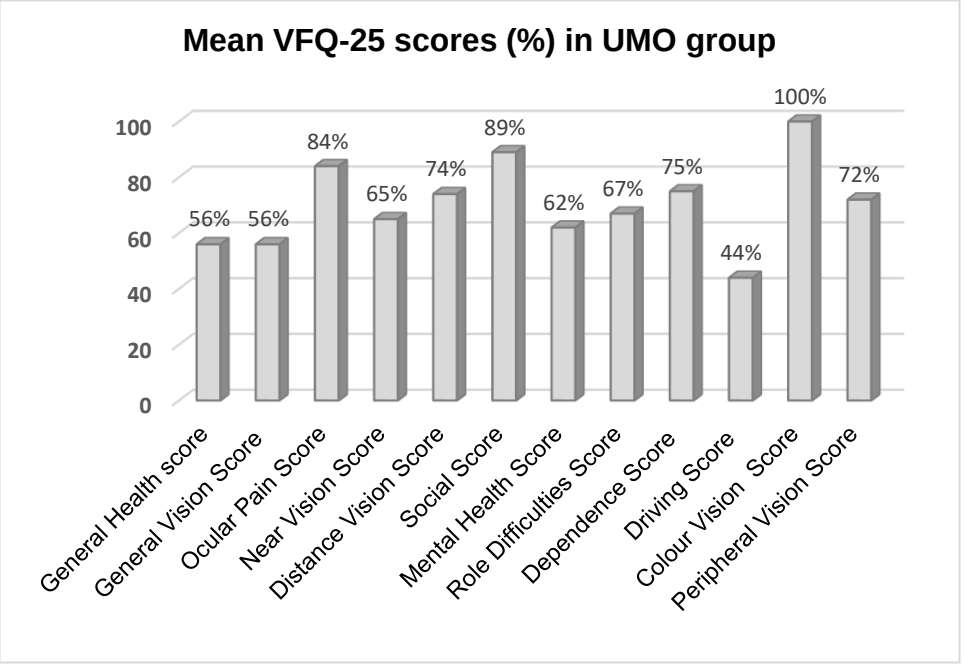

Figure 50- Mean VFQ-25 scores in UMO group

In the UMO group, a significant reduction occurred in the scores for general health, general vision, near vision, mental health, role difficulties, and driving.

6.5 Anatomical response to the therapy

In this section, I present the results for anatomical changes in the retina for the UMO group. The anatomical response to the treatment is summarised by type of MO and presence and location of intraretinal fluid (IRF) and subretinal fluid (SRF).

6.5.1 Focal and diffuse macular oedema in the UMO group

In the UMO group, at baseline, 26.6% of the patients had focal and 27.4% had diffuse MO. At the 6-month visit, these percentages were 37.5% with focal and 43.8% with diffuse MO. A possible explanation for this observation could be the fact that patients with active uveitis are seen more often in the clinic. A summary of the results for the baseline and 3-month and then 6- and 12-month visits are presented in Tables 98 and 99 respectively.

	Type of macular oedema		UMO	Total
Baseline	Focal	Count	0	41
		% within Type of MO	0.0%	100.0%
		% within Group	0.0%	34.7%
	Diffuse	Count	11	73
		% within Type of MO	26.8%	100.0%
		% within Group	35.5%	61.9%
	Total	Count	20	118
		% within Type of MO	27.4%	100.0%
		% within Group	64.5%	100.0%
3 months	No	Count	31	10
		% within Type of MO	26.3%	100.0%
		% within Group	100.0%	14.1%
	Focal	Count	5	22
		% within Type of MO	50.0%	100.0%
		% within Group	20.8%	31.0%
	Diffuse	Count	5	39
		% within Type of MO	22.7%	100.0%
		% within Group	20.8%	54.9%
	Total	Count	14	71
		% within Type of MO	35.9%	100.0%
		% within Group	58.3%	100.0%

Table 98- Type of macular oedema in UMO group at baseline and 3-month visits

	Type of macular oedema		UMO	Total
6 months	No	Count	3	4
		% within Type of MO	75.0%	100.0%
		% within Group	18.8%	11.4%
	Focal	Count	6	14
		% within Type of MO	42.9%	100.0%
		% within Group	37.5%	40.0%
	Diffuse	Count	7	17
		% within Type of MO	41.2%	100.0%
		% within Group	43.8%	48.6%
	Total	Count	16	35
		% within Type of MO	45.7%	100.0%
		% within Group	100.0%	100.0%
12 months	No	Count	1	2
		% within Type of MO	50.0%	100.0%
		% within Group	25.0%	22.2%
	Focal	Count	1	3
		% within Type of MO	33.3%	100.0%
		% within Group	25.0%	33.3%
	Diffuse	Count	2	4
		% within Type of MO	50.0%	100.0%
		% within Group	50.0%	44.4%
	Total	Count	4	9
		% within Type of MO	44.4%	100.0%
		% within Group	100.0%	100.0%

Table 99- Type of macular oedema in UMO group at 6- and 12-month visits

6.5.2 Intraretinal fluid in the UMO group

In addition to the type of MO, I looked at the presence and location of IRF amongst patients with UMO. At the baseline visit, 54.2% of the observed patients had extrafoveal IRF and 29.2% had subfoveal IRF. At the 6-month visits, 50% had extrafoveal IRF and 31.3% had subfoveal IRF. An overview of the results at the baseline and 3-month and then at the 6- and 12-month visits are presented in Tables100 and 101 respectively.

	Intraretinal fluid (IRF)		UMO	Total
Baseline	No	Count	0	2
		% within IRF	0.0%	100.0%
		% within Group	0.0%	1.7%
	Extrafoveal	Count	22	78
		% within IRF	28.2%	100.0%
		% within Group	71.0%	66.1%
	Subfoveal	Count	9	38
		% within IRF	23.7%	100.0%
		% within Group	29.0%	32.2%
	Total	Count	31	118
		% within IRF	26.3%	100.0%
		% within Group	100.0%	100.0%
3 months	No	Count	4	9
		% within IRF	44.4%	100.0%
		% within Group	16.7%	12.7%
	Extrafoveal	Count	13	42
		% within IRF	31.0%	100.0%
		% within Group	54.2%	59.2%
	Subfoveal	Count	7	20
		% within IRF	35.0%	100.0%
		% within Group	29.2%	28.2%
	Total	Count	24	71
		% within IRF	33.8%	100.0%
		% within Group	100.0%	100.0%

Table 100- Type of IRF in UMO group at baseline and 3-month visits

	Intraretinal fluid (IRF)		UMO	Total
6 months	`No	Count	3	4
		% within IRF	75.0%	100.0%
		% within Group	18.8%	11.4%
	Extrafoveal	Count	8	19
		% within IRF	42.1%	100.0%
		% within Group	50.0%	54.3%
	Subfoveal	Count	5	12
		% within IRF	41.7%	100.0%
		% within Group	31.3%	34.3%
	Total	Count	16	35
		% within IRF	45.7%	100.0%
		% within Group	100.0%	100.0%
12 months	No	Count	1	1
		% within IRF	100.0%	100.0%
		% within Group	25.0%	11.1%
	Extrafoveal	Count	2	5
		% within IRF	40.0%	100.0%
		% within Group	50.0%	55.6%
	Subfoveal	Count	1	3
		% within IRF	33.3%	100.0%
		% within Group	25.0%	33.3%
	Total	Count	4	9
		% within IRF	44.4%	100.0%
		% within Group	100.0%	100.0%

Table 101- Type of IRF in UMO group at 6- and 12-month visits

6.5.3 Subretinal fluid in the UMO group

As SRF is one of the key factors for visual loss in patients with MO, I looked at its location with respect to the fovea. I found that, at the baseline visit, 3.3% of the UMO patients had extrafoveal SRF and 25.8% had subfoveal SRF. At the 6-month visit, no patients had extrafoveal SRF, and the percentage of patients with subfoveal SRF had decreased to 12.5%. A summary of the results at the baseline and 3-month and then at the 6- and 12-month visits is presented in Tables 102 and 103.

	Subretinal fluid (SRF)		UMO	Total
Baseline	No	Count	22	90
		% within SRF	24.4%	100.0%
		% within Group	71.0%	76.9%
	Extrafoveal	Count	1	5
		% within SRF	20.0%	100.0%
		% within Group	3.2%	4.3%
	Subfoveal	Count	8	22
		% within SRF	36.4%	100.0%
		% within Group	25.8%	18.8%
	Total	Count	31	117
		% within SRF	26.5%	100.0%
		% within Group	100.0%	100.0%
3 months	No	Count	20	61
		% within SRF	32.8%	100.0%
		% within Group	83.3%	85.9%
	Extrafoveal	Count	1	2
		% within SRF	50.0%	100.0%
		% within Group	4.2%	2.8%
	Subfoveal	Count	3	8
		% within SRF	37.5%	100.0%
		% within Group	12.5%	11.3%
	Total	Count	24	71
		% within SRF	33.8%	100.0%
		% within Group	100.0%	100.0%

Table 102- Type of SRF in UMO group at baseline and 3-month visits

	Subretinal fluid (SRF)		UMO	Total
6 months	No	Count	14	30
		% within SRF	46.7%	100.0%
		% within Group	87.5%	85.7%
	Extrafoveal	Count	0	1
		% within SRF	0.0%	100.0%
		% within Group	0.0%	2.9%
	Subfoveal	Count	2	4
		% within SRF	50.0%	100.0%
		% within Group	12.5%	11.4%
	Total	Count	16	35
		% within SRF	45.7%	100.0%
		% within Group	100.0%	100.0%
12 months	No	Count	4	8
		% within SRF	50.0%	100.0%
		% within Group	100.0%	88.9%
	Extrafoveal	Count	0	1
		% within SRF	0.0%	100.0%
		% within Group	0.0%	11.1%
	Subfoveal	Count	4	9
		% within SRF	44.4%	100.0%
		% within Group	100.0%	100.0%
	Total	Count	14	30
		% within SRF	46.7%	100.0%
		% within Group	87.5%	85.7%

Table 103- Type of SRF in UMO group at 6- and 12-month visits

6.6 Substantiation of the link between routine clinical and functional tests in the UMO group

In this section, I investigate the correlation between VA and retinal thickness measures (CSRT,CMT) and the correlation of MS and CZ-MS with reading speed in the UMO group.

6.6.1 VA, CMT, and CSRT correspondence with functional vision tests in the UMO group

For the UMO group, I looked at the correlation between VA and retinal thickness (CSRT and CMT), contrast sensitivity in the macula, and reading speed performance. For the purpose of this analysis, Spearman's rho test was used.

	MP-1								
Diagnosis	LogMAR	CMT	CSRT	CZ-MS	MS	LogMAR at last Sentence read	Reading acuity in LogMAR	Est. max reading speed (WPM)	Critical print size in LogMAR
	R	0.098	0.196	-0.302	-0.2	0.352	0.347	0.110	0.367
	p-value	0.601	0.292	0.099	0.25	0.085	0.090	0.600	0.071
	N	31	31	31	31	31	31	31	31

Table 104- Correlation between LogMAR vs. CMT, CSRT, CZ-MS, LogMAR at last sentence read, reading acuity in LogMAR , estimated max reading speed (WPM), and critical print size in LogMAR in the UMO group for the MP-1

R = correlation coefficient, N = number of eyes, and significance is at p-value < 0.05.

In the UMO group, I was not able to detect correlation with statistical significance set at the level of p-value < 0.05. These findings are in contrast with the findings in the DRP and the RVO groups. Notably, I was also unable to observe any correlation between VA and retinal thickness. One probable explanation could be that active uveitis patients have severe inflammation, which significantly affects patients' VA. The observed highly likely correlation between VA and CZ-MS and reading speed performance can support this possible explanation.

Further, I investigated the correlation between retinal thickness, reading speed performance, and macular contrast sensitivity in the UMO patients. I used Spearman's rho correlation test for the purpose of this analysis. The results for CMT and CSRT are summarised in Tables 105 and 106 respectively. The tables present the correlation coefficient (R), the number of eyes (N), and p-value (p), with significance set at p-value < 0.05.

	MP-1						
	CMT	CZ-MS	LogMAR at last sentence read	Reading acuity in logMAR	Est. max reading speed (WPM)	Critical print size in LogMAR	MS
UMO	R	0.001	-0.189	-0.187	0.211	0.037	0.023
	p	0.988	0.492	0.367	0.364	0.877	0.953
	N	31	31	31	31	31	31

Table 105- Correlation between CMT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for UMO patients tested with MP-1 device

MP-1							
	CSRT	CZ-MS	LogMAR at last sentence read	Reading acuity in logMAR	Est. max reading speed (WPM)	Critical print size in LogMAR	MS
UMO	R	-0.046	-0.070	-0.083	-0.027	0.144	-0.092
	p	0.824	0.735	0.721	0.895	0.577	0.651
	N	31	31	31	31	31	31

Table 106- Correlation between CSRT vs. CZ-MS, MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for UMO patients tested with MP-1 device

In the UMO group, I was not able to identify any link between CMT, CSRT, and the functional test results for contrast sensitivity and reading speed.

6.6.2 Correlation of microperimetry and reading speed outcomes in the UMO group

Further to the analysis described above, I looked at whether microperimetry results showed a significant link with reading speed outcomes in the UMO group. The correlation between MS and CZ-MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM) from the plot, and critical print size in LogMAR was assessed by the Spearman's rho test. An outline of the findings for MS and CZ-MS are presented in Tables 107 and 108 respectively. The tables present correlation coefficient (R); number of eyes (N); and p-value (p), with significance at p-value < 0.05.

	MP-1				
	MS	LogMAR at last sentence read	Reading acuity in LogMAR	Est. max reading speed (WPM)	Critical print size in LogMAR
UMO	R	-0.462	-0.247	0.139	-0.120
	p	0.028	0.233	0.515	0.576
	N	31	31	31	31

Table 107- Correlation between MS vs. LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for UMO patients tested with MP-1 device

	MP-1				
	CZ-MS	LogMAR at last sentence read	Reading acuity in logMAR	Est. max reading speed (WPM)	Critical print size in LogMAR
UMO	R	-0.291	-0.167	0.215	-0.131
	p	0.172	0.441	0.292	0.538
	N	31	31	31	31

Table 108- Correlation between CZ-MS, LogMAR at last sentence read, reading acuity in LogMAR, estimated max reading speed (WPM), and critical print size in LogMAR for UMO patients tested with MP-1 devices

In the UMO group, I found a statistically significant correlation between MS and LogMAR at last sentence read (R = -0.462; p-value = 0.028; N = 31). This finding can be explained by the fact that in UMO patients, the diffuse inflammatory process affects MS rather than CZ-MS. This finding supports the previous statement that UMO patients' visual outcome is affected predominantly by the severity of the inflammation.

6.6.3 Correspondence between vision-related quality of life (VFQ-25) and VA, CSRT, and CZ-MS in the UMO group

In this section, I look at which of the self-reported visual disability scores correlate better with clinically measured VA, retinal thickness (CSRT), and macular contrast sensitivity (CZ-MS) amongst the patients with UMO. A summary of the main findings for VA (LogMAR), CSRT, and CZ-MS are presented in Tables 109, 110, and 111 respectively.

	LogMAR	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
UMO	R	0.149	0.072	0.087	-0.080	0.142	-0.081	-0.183	-0.116	-0.138	-0.187	0.099	0.149
	p	0.476	0.734	0.680	0.704	0.499	0.699	0.380	0.580	0.512	0.370	0.636	0.476
	N	25	25	25	25	25	25	25	25	25	25	25	25

Table 109- Correlation between LogMAR and VFQ-25 scores in UMO group

In contrast to the findings observed in the DRP and the RVO groups, in the UMO group, LogMAR did not show a significant link with any of the VFQ-25 scores.

	CSRT	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
UMO	R	-0.038	-0.081	-0.203	-0.250	-0.077	0.16 6	-0.204	-0.367	-0.245	-0.276	-0.208	0.032
	p	0.856	0.701	0.331	0.229	0.715	0.427	0.328	0.071	0.238	0.182	0.318	0.880
	N	25	25	25	25	25	25	25	25	25	25	25	25

Table 110- Correlation between CSRT and the VFQ-26 scores in UMO group

None of the VFQ-25 scores showed correlation with CSRT in the UMO group.

MP-1													
	CZ-MS	General Health Score	General Vision Score	Ocular Pain Score	Near Vision Score	Distance Vision Score	Social Score	Mental Health Score	Role Difficulty Score	Dependence Score	Driving Score	Colour Vision Score	Peripheral Vision Score
UMO	R	-0.323	0.208	-0.220	0.155	0.012	0.353	0.380	-0.058	-0.020	-0.031	-0.336	-0.323
	p	0.116	0.318	0.292	0.460	0.954	0.083	0.061	0.782	0.926	0.884	0.101	0.116
	N	23	23	23	23	23	23	23	23	23	23	23	23

Table 111- Correlation between CZ-MS and VFQ-26 scores in the UMO group.

The CZ-MS showed no correlation with any of the VFQ-25 scores.

The reason for the observed discrepancy with the UMO group may be its smaller number of patients.

6.7 Regression models to predict patient outcomes in the UMO group

I used regression models in order to identify the relationship between two or more variables for which I hypothesised that one variable was dependent on another. In the UMO group, I was able to generate only simple linear regression models. The smaller number of eyes in the UMO group may have prevented the statistics program from calculating results.

6.7.1 Simple linear regression models in the UMO group

In the UMO group, a simple linear regression model was calculated for LogMAR, MS, CZ-MS, CMT, and CSRT. A summary of the results is presented in Table 112.

MP-1							
Group	Predictors	Coefficients	t	p	F	p	R^2
UMO	LogMAR	0.619	4.929	<0,001	1.791	0.194	0.072
	MS	-0.014	-1.338	0.194			
	LogMAR	0.365	2.183	0.039	0.481	0.495	0.020
	CMT	0.000	0.693	0.495			
	LogMAR	0.358	2.350	0.028	0.672	0.421	0.028
	CSRT	0.000	0.820	0.421			
	LogMAR	0.671	6.150	<0,001	4.622	**0.042**	0.167
	CZ-MS	-0.023	-2.150	0.042			

Table 112- Simple linear regression model of LogMAR vs. MS, CZ-MS, CSRT, and CMT for UMO patients tested with MP-1 device

I found a statistically significant correlation between LogMAR and CZ-MS (p-value = 0.042; $R^2 = 0.167$) in the UMO group.

6.8 Discussion

Macular oedema (MO) is one of the most common complications of uveitis causing long-lasting vision loss. The majority of patients with uveitic macular oedema (UMO) have recurrent episodes of flare up which often leads to increased fluid accumulation in the retina. Hence, uveitis patients often require regular lifelong observation and treatment to control the inflammation. As discussed earlier in the thesis, clinicians are currently tasked with balancing lower episodes of uveitis activation with the effects of long-term immunosuppressive treatment in order to maintain the patients' quality of life.

In this chapter, I investigated the functional visual outcomes of uveitis treatment. Besides standard VA and retinal thickness measurements, I explored patients' contrast sensitivity, reading speed, and vision-related quality of life in order to uncover better predictors for functional vision amongst the UMO group. Several researchers have reported a correlation between VA, retinal thickness, and retinal contrast sensitivity in patients with MO caused by uveitis (Roesel et al. 2011; Niederer et al. 2017). In contrast to these reports, however, I was not able to identify a relationship between VA, CMT, and CSRT in the UMO group. One possible explanation could be that uveitis is a long-lasting

disease with multiple reactivation periods. The nature of uveitis consecutively leads to improvement in the short term, but questionable long-term outcomes. In another research project, Lahpamer et al. (2016) reported that 74% of the observed patients (N = 75) with some SRF observed at baseline showed improved retina thickness after 3 months of treatment with corticosteroids. In the present research, I found improvement in retinal thickness from baseline to 6- and 12-month visits amongst patients with UMO; however, these results were not associated with visual function improvement. One possible explanation is the fact that uveitis patients often complain of visual disturbance due to inflammation in the vitreous, which is not always present with MO. I observed statistically significant correlation between VA and reading speed measures (reading acuity in LogMAR, LogMAR at last sentence read, and critical print size in LogMAR). These findings suggest that measuring reading speed could be a good approach to examining functional vision amongst patients with UMO. The UMO group did not show significant improvement in their VA during the observation period, but very few patients were observed until the end of the study due to the high drop-out rate. Thus a larger sample size with a longer observation period may be a better approach to establishing the VA change in UMO patients.

Contrast sensitivity, in comparison, was highly affected in the UMO group in this study. Often it was not possible to have microperimetry testing completed, and many treatments were required. That was due to the severity of the inflammation in the vitreous, which affected the quality of the fundus image and the functioning of the eye-tracking option in the microperimeter device. Regrettably, I did not assess the impact of the severity of the intraocular inflammation on the functional vision testing with the microperimeter. In the observed UMO group, I identified minor changes in the MS and CZ-MS over the study period. However, I also noticed that repeated inflammatory attacks often did cumulative damage to the retinal sensitivity. Henceforward, longer and more detailed investigation of the mean macular contrast sensitivity in uveitis patients with recurrent MO is necessary.

In order to define vision-related difficulties in performing daily tasks, I asked all participants in the UMO group to complete the VFQ-25 questionnaire. The NEI VFQ-25 helped to identify the dimension of self-reported vision-related health status in patients with chronic conditions requiring long follow up such as uveitis. Although the near vision and colour vision scores are considered as the most sensitive scores for patients with

MO, I found no statistically significant correlation between them and VA, retinal thickness (CSRT), or macular contrast sensitivity (MS, CZ-MS). The only score close to statistical significance (set at p-value < 0.05) was the mental health score. This could be explained by the fact that uveitis often has high-frequency relapses and is associated with general health problems. Thus, the effect on the patients' mental health is expected and should be investigated further with a larger sample size to establish the relationship.

In summary, I can suggest that the severe inflammation in uveitis may impact functional vision due to floaters and fogginess rather than due to increased retinal thickness. As stated above, amongst patients with MO due to uveitis, there is a tendency for diffuse reduction of the contrast sensitivity caused by the inflammatory reaction in the vitreous. This finding is in contrast with the pattern I observed in the RVO and DMO groups, wherein local MS reduction was more common and linked to localised pathological changes in the retina. Also in contrast to the findings for the RVO and DRP groups, the findings for the UMO group indicated that visual function disability seemed to be mainly due to the severity of the inflammation rather than to structural changes. In UMO, anatomical deviations in the retina occur later in the disease progression, causing local changes in the MS detected by MP. Further research is required to investigate the effect of the relapses and inflammation.

Chapter 7. Conclusions

Macular oedema (MO) is described as an accumulation of fluid in the outer plexiform and inner nuclear layer of the retina, leading to the swelling of Müller cells. It is a common cause of the sudden or chronic decrease in vision that occurs in many retinal diseases such as diabetic retinopathy (DRP), retinal vein occlusion (RVO), uveitic macular oedema (UMO), and inherited retinal dystrophies and in issues such as trauma, age-related macular degeneration, medication complications, vitreo-retinal tractions, and post phacoemulsification. Hence, MO is a non-specific sign of retinal disfunction. MO is developed due to a variety of etiologies and complex pathophysiological mechanisms. In this research project, I focused on the three most common causes of MO: DRP, RVO, and UMO. The research aimed to investigate not only the prevalence of MO in these three diseases but also the functional outcomes of current clinical treatment approaches.

As discussed at the beginning of this thesis, the pathophysiological mechanism of MO development for these three types of retinal disease is quite similar. Hence, the ischaemia, inflammation, and vascular components are observed in different degrees of severity in these diseases. Consequently, the treatment approaches employed vary as well. For example, anti-VEGFs are used for MO treatment in DRP, RVO, and some cases of UMO associated with neovascular development. At the same time, emerging literature has shown favourable therapeutic effect in patients with MO treated with intravitreal corticosteroids. These recent findings have led to discussions regarding what should be the first-line treatment choice for MO. While some patients do not benefit from anti-VEGF and/or intravitreal corticosteroid treatment, others show significant improvement in VA. In addition, in some cases retinal laser photocoagulation seems to be the only therapeutic option, but this treatment leads to irreversible retinal damage and visual field loss. Therefore, vital questions around the best treatment algorithm and visual improvement in patients with MO have emerged.

In the present study, although I observed improved retinal anatomy, patients often reported lack of VA improvement. In addition, the clinicians often observed improved anatomical structure without functional improvement. The findings of the present study support further researching another set of unanswered questions about assessing patients' vision-related disability and quality of life, calling into question the currently used

techniques for measuring VA. Indeed, an increasing amount of research is focusing on identifying new biomarkers to better predict patients' VA outcomes and on how to use a personalised approach in setting up therapeutic algorithms and improving vision-related quality of life.

Currently, the therapeutic approach to treating MO due to DRP, RVO and uveitis is based mainly on the amount of retinal thickness reduction and on underestimating the functionality of the ocular system. In this research project, I reviewed widely used techniques for eye assessment in ophthalmology clinics in the UK and explored the potential of using additional methods that could perhaps be integrated into clinical practice. Namely, I investigated the possibility of using microperimetry and reading speed tests, assessing their potential to predict the amount of visual disturbance in patients with MO caused by DRP, RVO, and uveitis.

In the DRP group, I followed 61 eyes for a period of 1 year. Patients were seen as part of a routine clinical visit. Due to the high drop-out rate, I was not able to collect data on all patients throughout the study period. Often, patients were referred to local primary care centres, so observation for a long period was not possible. Nonetheless, a few key findings arose for in this group. For patients tested with the MP-1 and Optos SLO MP devices, I found a statistically significant correlation between VA (LogMAR) and retinal thickness (CMT, CSRT), mean retinal sensitivity, and reading speed (LogMAR at last sentence read, reading acuity in LogMAR, estimated reading speed (WPM) from the plot, and critical print size in LogMAR). In addition, retinal thickness (CMT, CSRT) showed a statistically significant correlation with three reading speed parameters (LogMAR at last sentence read, reading acuity in LogMAR, and critical print size in LogMAR). Regarding the microperimetry testing in the DRP group, I found a statistically significant correlation between CZ-MS and reading speed (LogMAR at last sentence read, reading acuity in LogMAR, estimated reading speed (WPM) from the plot, and critical print size in LogMAR). I applied a multilinear regression model to explore the synergic effect of two or more variables on visual acuity. I found a statistically significant correlation between VA and MS, CZ-MS, CMT, and CSRT in the DRP group. The stepwise process used by the multilinear regression model did not identify any of the reading speed parameters to be of statistical significance. One possible explanation is the small sample size in the observed groups.

The RVO group included 26 patients. During the observation period, many of these patients were again referred to local clinics for treatment, so only 3 patients attended the 12-month follow-up visit. Nevertheless, there are a few important findings for this group. I found a statistically significant correlation between VA (LogMAR) and CZ-MS and MS for patients tested with the MP-1 and Optos SLO MP devices. In contrast to the findings in the DRP group, I did not find a statistically significant correlation between VA, retinal thickness (CMT, CSRT), and reading speed parameters in the RVO group. This was probably due to the small sample size. Distinctive in the RVO group is the observed statistically significant correlation between MS, CZ-MS, and reading speed measure of reading acuity in LogMAR. As for the DRP group, I used a regression model to explore the predictive value of the assessed parameters. In the RVO group, only a simple linear regression model could be built due to the small sample size. Similarly to the DRP group, I found a statistically significant correlation between VA and retinal thickness (CMT, CSRT) and microperimetry outcomes (CZ-MS, MS). It was not possible to build a multilinear regression model for the RVO group. For the RVO group, I suggest that there are additional co-factors contributing towards patient VA outcome, and further research is needed to identify them.

The last section of this thesis focused on investigating functional outcomes in the UMO group. An essential finding for this group was the lack of any statistically significant correlation of MP testing and reading speed with VA. This finding was due to the small sample size; research with a large observation group may be able to identify specific relationship between these parameters in patients with UMO. Another possible explanation to identify the correlations observed in RVO and DMO groups is related to the severity of the inflammation in these patients. Severe intraocular inflammation makes macular contrast sensitivity examination difficult to carry out. On the other hand, patients with active uveitis can experience temporary visual loss due to the activity of the disease. These factors make the microperimetry test applicable only for a very small group of uveitis patients. The reading speed test may be a better functional vision assessment method for uveitis patients, allowing detection of small variations in visual performance. At the same time, as with the DMO and RVO group, a simple linear regression model was used in the UMO group. Using this model, I found a statistically significant correlation between LogMAR and CZ-MS for the MP-1 microperimeter.

Another important part of the research was to assess the changes observed over the treatment period of 1 year amongst the three study groups. Figures 51–54 show the observed changes in VA, retinal thickness (CMT), and retinal mean sensitivity (MS) in patients tested with the MP-1 and Optos SLO respectively.

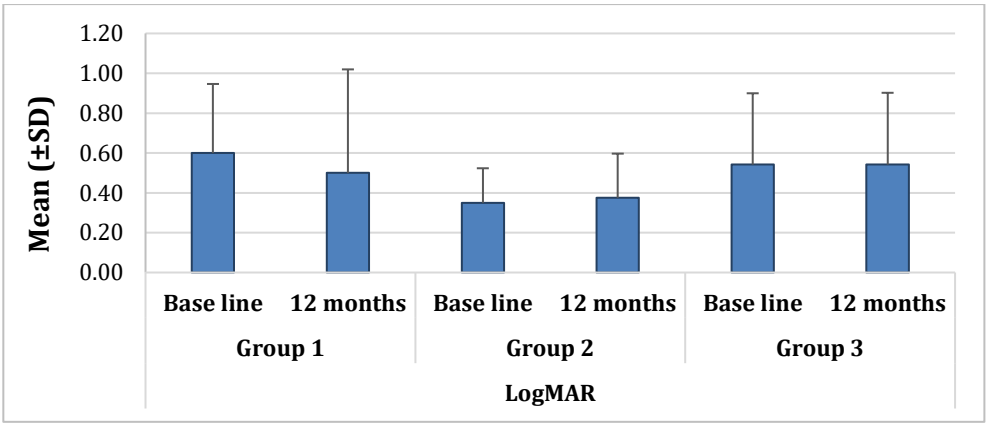

Figure 51- Changes in visual acuity in all three study groups (DRP, RVO, UMO)

Group 1 –DRP; Group 2-RVO; Group 3- UMO

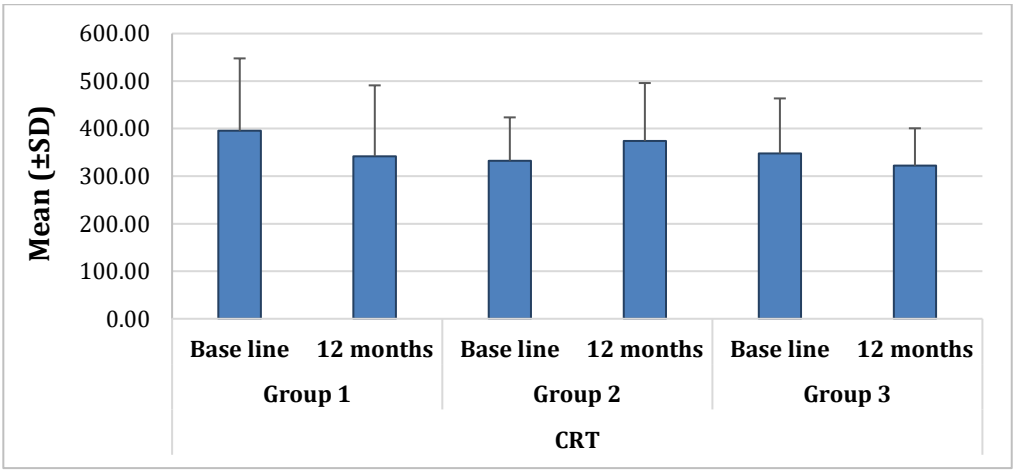

Figure 52- Change in CMT in all three study groups

Group 1 –DRP; Group 2-RVO; Group 3- UMO

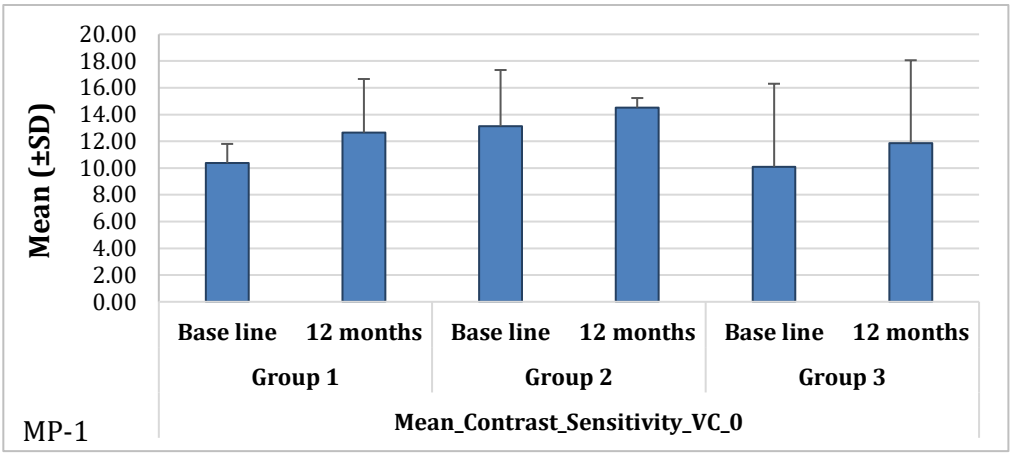

Figure 53- Change in MS in the three study group tested with the MP-1 microperimeter

Group 1 –DRP; Group 2-RVO; Group 3- UMO

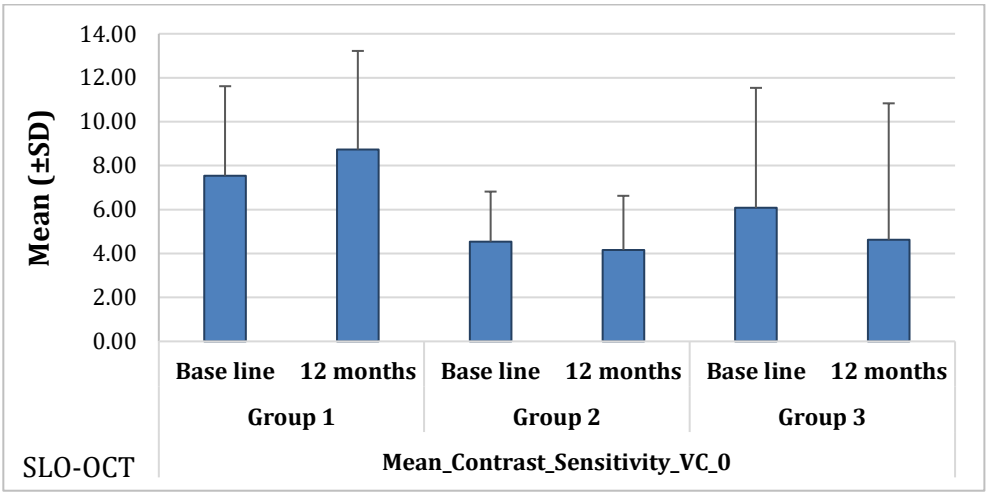

Figure 54- Change in Mean sensitivity in the three study group tested with the Optos SLO microperimeter

Group 1 –DRP; Group 2-RVO; Group 3- UMO

I suggest that macular contrast sensitivity testing and reading speed tests can be of help in current practice for assessing variations in the therapeutic response and potentially improving eye care. Reading speed has always been a major complaint amongst patients visiting ophthalmology clinics. Reading ability affects a person's ability to function at work and at home, thus affects quality of

life (Elliott et al., 1997; Mangione et al., 1998). Differences in clinical signs and symptoms should therefore be taken into consideration when choosing the most appropriate assessment technique.

7.1 Limitations of the study

Alongside its strengths, this research project has its limitations. Regrettably, due to the character of the clinics, the majority of the patients were referred to local eye clinics for further follow up and treatment before the conclusion of the 1-year study period. Hence long-term observation was difficult to achieve. Furthermore, this work was limited in part because of the inability to control participants' compliance in attending their routine clinical visit. A significant drop-out of study participants occurred in each of the three groups during the observational period. This high drop-out rate severely limited the opportunity to follow all participants for a period of 12 months. Thus, the majority of patients were effectively followed only up to the 6-month point. This limitation reflected on the analyses presented in this thesis where a p-value could not be generated.

In addition, I did not have the opportunity to assess all patients using both microperimeters. The MP-1 was only available at Moorfields Eye Hospital, and the Optos SLO was only available at Royal County Surrey Hospital. Due to the difference in the illuminance, the retinal status for the two microperimeters was not identical. Hence, results from the two devices were not comparable. For future research projects, it would be crucial to test all study participants using the same microperimeter device.

Another limitation of the study was the fact that the design of the VFQ-25 questionnaire is not sensitive to patients with minor functional vision disability levels. This fact was identified during the completion of the survey and via feedback by study participants with minor chronic MO. Hence, this study was not able to examine individual adaptation to minor visual impairment. Another limitation related to the assessment instruments used in this study was the lack of any colour vision examination. This is a gap for this particular research project that the design of future projects could address. Another weakness identified during this study was related to the reading speed test performance. Though I used an examination tool which better expresses functionality of the macula, the tool requires fluency in English.

A further limitation regarding the reading speed test used is that I did not take into consideration the effects of aging and cognitive variations on reading speed. Currently available reading speed tests have been used to show age-dependant variation in reading speed where adult patients often report reading difficulties (McGowan et al. 2014). A number of studies have shown an age-related decline in reading speed (Rayner et al. 2004, 2006; Calabrese et al. 2016; Chen et al. 2019). Most recently, Chen et al. (2019) reported reduction in reading speed of about 9% in WPM in adults vs. young individuals. Chen et al.'s research also suggested that this decrement is related to a combination of age-related decline in contrast sensitivity, age-related deficit in eye movement control, a defective transient system in older patients with prolonged visual-neural processing time, and a decline in cognitive function. Further research could focus on incorporating age-related adjustments into the reading speed assessment.

In summary, I would like to point out a few key facts for any future similar research projects. First, it is crucial to plan for a longer duration of the follow-up periods and to collaborate with other healthcare professionals involved in the management of the study patients. I believe these actions will improve data collections for such projects. With regards to the functional vision examination, it could potentially be beneficial to involve practical examination techniques instead of relying on patients' self-reporting. Further investigation of the functionality of the system, such as colour vision and ability to adapt, can be considered as anticipated areas for future research to explore. With respect to patients' self-report tools, I found the VFQ-25 to reflect mainly moderate to severe levels of visual impairment. Thus, revision of the existing VFQ-25 questionnaire may provide further understanding of patients' self-reported vision specifically for mild functional vision disabilities.

Conclusively, I believe this research project has shed light on several important aspects of functional vision testing in patients with MO and provides useful guidance for future researchers.

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Appendix II Trial documents

A. Cover letter ethics committe

11th December 2012

Dear Ethics Committee

Name of study: Functional visual outcome of retinal oedema and its standard management

Please accept my application to you to undertake this study. It is timely as the treatments for retinal oedema have all been approved on the basis of letters gained by reading a vision chart in a clinic setting. No functional vision testing has been undertaken and the clinic environment is very artificial.

We are interested in the patients perception of their vision and its impact on them, hence the questionnaires and the vision that we measure, letters read on reading a vision chart in the clinic but also on what they can do with their vision, functional vision testing. The questionnaires, visual acuity testing and the functional vision testing have all been validated and are in clinical use.

There are no interventions as part of this study. The treatment given to a patient is determined by NICE and we are looking at the outcomes of these only – we initiate no treatment in the study. Many patients will have had retinal laser treatment which is the gold standard and we would like to know if the micro - scotomas induced by this type of laser in their central visual field actually are now disadvantageous as compared to the effects of the new treatments.

Please contact me if you require further information. The study was approved to go to Ethics by the R and D Department at the Royal Surrey Hospital on Wednesday November 28th 2012.

Yours faithfully

Professor Sue Lightman FRCP PhD FRCOphth

Consultant Ophthalmologist

Principal Investigator

B. GP information letter on headed paper from Royal Surrey County Hospital

Royal Surrey County Hospital NHS
NHS Foundation Trust

GP name and address

15th November 2012

Dear GP

Re: Patient details

This is to let you know that your patient has agreed to be been enrolled in a study entitled "Functional visual outcomes of retinal oedema and its standard management".

This is a clinic based study looking at functional visual outcome from the treatments they have had for their retinal oedema. No treatment interventions are part of this study and no extra clinic visits are required. The study lasts 1 years and the study questionnaires and visual function assessments will take place at the clinic visits at baseline,3, 6 and 12 months.

Yours sincerely

Professor Sue Lightman FRCP PhD FRCOphth

Consultant Ophthalmologist and Principal Investigator

C. GP information letter on Moorfileds Eye Hospital headed paper

Moorfields Eye Hospital NHS
NHS Foundation Trust

GP name and address
15th November 2012
Dear GP

Re: Patient details

This is to let you know that your patient has agreed to be been enrolled in a study entitled "Functional visual outcomes of retinal oedema and its standard management ".

This is a clinic based study looking at functional visual outcome from the treatments they have had for their retinal oedema. No treatment interventions are part of this study and no extra clinic visits are required. The study lasts 1 years and the study questionnaires and visual function assessments will take place at the clinic visits at baseline, 3, 6, and 12 months.

Yours sincerely

Professor Sue Lightman FRCP PhD FRCOphth

Consultant Ophthalmologist and Principal Investigator

D. Research and development approval for Moorfields Eye Hospital

Joint Research Office

UCLH NHS Foundation Trust

1't Floor Maple House (Suite B)

149 Tottenham Court Road, London WlT 7DN

E-mail ncharm@uclh.nhs.uk

NHS PERMISSION FOR RESEARCH (R&D Approval)

01/04/2014

Dear Colleague/s

IRAS ID:

REC Ref: 128193 (Please quote in all correspondence)

Study Title: 13/L0/1005

Functional visual outcomes of retinal oedema and its standard management

1

NHS permission for the above research has been granted for the following NHS Trusts:

Trust	Name of PI	Date of Permission
Moorfields Eye Hospital NHS Foundation Trust	Professor Susan Lightman	1st April 2014

Permission/Assurance is based on the REC favourable opinion given on d 23/07/2013 and the most recent amendments submitted with REC favourable opinion on date 12/11/2013 and 30/12/2013wlth REC acknowledgment

19 1° 3 1 2014

Permission is granted on the understanding that the study is conducted in accordance with the Research Governance Framework, ICH GCP,and the policies and procedures of the Trust/s http://www.crncc.nihr.ac.uk /about us/ccrn/celondon/corporate /constituent.

Permission is only granted for the activities for which a favourable opinion has been given by the REC [and which have been authorised by the MHRA].

Specific Conditions of Permission (If applicable) none

If you are the Chief Investigator/Sponsor of this study, please ensure that all amendments are notified to your Lead [1]

CLRN via IRAS

Please also ensure that this office is notified of any unexpected changes in status to the project, for example if the site closes before the stated end date, and any urgent safety measures enacted.

Yours sincerely,

[redacted]

Monty Mythen

Director of Research and Development

UCL/UCLH/Royal Free Joint Research Office

Cc: LCRN Core team; Chief Investigator,Sponsor Contact, Research Site R&D Office/s;Pharmacy/Medical Exposure

Review Coordinators

E. Consent form on a headed paper from Royal Surrey County Hospital

Royal Surrey County Hospital NHS
NHS Foundation Trust

CONSENT FORM

Title of Project: Functional visual outcomes of retinal oedema and its standard management

Name of Researcher: **Professor Sue Lightman** Please initial all boxes

1. I confirm that I have read and understand the information sheet dated [15/11/12 (version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the Royal Surrey County Hospital Research Team from regulatory authorities or from the NHS Trust, 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 agree to my GP being informed of my participation in the study. ☐
5. I agree to take part in the above study.

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

F. Participants connect form on a headed paper from Moorfields Eye Hospital

Moorfields Eye Hospital NHS
NHS Foundation Trust

CONSENT FORM

Title of Project: Functional visual outcomes of retinal oedema and its standard management

Name of Researcher: **Professor Sue Lightman** Please initial all boxes

6. I confirm that I have read and understand the information sheet dated [15/11/12 (version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

7. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

8. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the Royal Surrey County ☐ Hospital Research Team from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

9. I agree to my GP being informed of my participation in the study. ☐

10. I agree to take part in the above study.

_____ _____

Name of Participant Date Signature

_____

Name of Person taking consent Date Signature

G. Participants iformation leaflet – Royals Surrey County Hospital

Royal Surrey County Hospital NHS
NHS Foundation Trust

Patient information Sheet

Name of study: Functional visual outcome of retinal oedema and its standard management

Why are we doing this study?

You have been diagnosed with an eye problem in which there is swelling of the retina at the back of your eye causing your vision to become affected. In some of you this may affect just one eye or both eyes may be involved. We have treatments for this which your clinic doctor will discuss with you.

In addition to treating you we would like to ask your help in a study designed to help determine the effect of treatment on how your vision recovers to help you do tasks of daily life such as reading, putting in PIN numbers, playing cards. Involvement in the study has no affect on the treatment that is offered to you. To do this we would like to ask you to do some extra tests over the next 2 years at your clinic visits – at every 6 months appointment for 2 years although you may come to the eye clinic more frequently than this. This will add a short time to your clinic visit (you will seen in the clinic by the nursing and medical staff in the usual way) and the tests are easy to do. There is a quality of life questionnaire which looks at how your vision is affecting your life which we can help you do if you need assistance to read the questions. We will then run tests with you using your vision such as how fast you can read, can you identify coins or playing cards, can you put a key in a lock or punch in a PIN number?

The aim of this is to see if your perception of how good or bad your vision is , is the same as the vision we measure in the clinic as often patients say to us that although the

vision may appear better, the quality is affected. This is important information for us to know so that we can help improve treatments for patients like yourself in the future.

As part of your normal clinic visit you are likely to have an eyescan known as an OCT. These will be done as usual but we would add an additional test on the same machine which asks you to press a button when you see a flashing light. This will only add a few minutes to the time it takes to do the scan – this is called microperimetry.

The information about your condition and tests will be recorded on a data sheet and then kept in a locked cabinet. Only doctors/nurses involved in the study will have access to it so it remains confidential at all times. To put your data together with other patients' data to look at the results of the study, we give you a study number and only that number is then used on a computer for data analysis and you cannot be identified.

Please discuss this with your friends/family GP as you like and we will discuss this again with you at your next clinic visit. If you are happy to take part in the study, we will ask you to sign a consent form so that we can collect your information. If you wish to withdraw from the Study at any time during the 2 years you are at liberty to do this.

Do I have to take part?

No you do not and taking part is purely voluntary. If you do not take part, your care in the clinic will not be affected in any way.

Will my information be kept confidential?

Yes it will as the data about you is kept in a locked filing cabinet in the research office [0] which is locked. From then on you have a study number which does not identify you in any way and all the data collected as part of the study will have this number on it. If during the study you are no longer able to take part or lose the capacity to consent, we will retain the data we have collected with you and keep it confidential in the same way.

What if something goes wrong or I wish to complain?

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff you may have experienced due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you. Please ask your research doctor if you would like more information on this. In the unlikely event that you are harmed by taking part in this study, compensation may be available to you. If you suspect that the harm is the result of the Sponsor's (University College London) or the hospital's negligence then you may be able to claim compensation. After discussing with your research doctor, please make the claim in writing to the Professor Sue Lightman who is the Chief

Investigator for the research and is based at UCL Institute of Ophthalmology and the Royal Surrey County Hospital. She will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this. NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm.

The Principal Investigator of the Study is Professor Sue Lightman who is a Consultant Ophthalmologist at the Royal Surrey County Hospital and others doctors involved in the research include Mr Simon Taylor (Consultant Ophthalmologist), Dr Filis Ismetova

(ophthalmologist), Mr Oren Tomkins (ophthalmologist), Mr Albert Lula, (research assistant).

We appreciate your attention

With best wishes

[redacted]

Professor Sue Lightman

Consultant Ophthalmologist and Study Lead 14th April 2013

H. Participants iformation leaflet – Moorfields Eye Hospital Hospital

Moorfields Eye Hospital NHS
NHS Foundation Trust

Patient information Sheet

Name of study: Functional visual outcome of retinal oedema and its standard management

Why are we doing this study?

You have been diagnosed with an eye problem in which there is swelling of the retina at the back of your eye causing your vision to become affected. In some of you this may affect just one eye or both eyes may be involved. We have treatments for this which your clinic doctor will discuss with you.

In addition to treating you we would like to ask your help in a study designed to help determine the effect of treatment on how your vision recovers to help you do tasks of daily life such as reading, putting in PIN numbers, playing cards. Involvement in the study has no affect on the treatment that is offered to you. To do this we would like to ask you to do some extra tests over the next 2 years at your clinic visits – at every 6 months appointment for 2 years although you may come to the eye clinic more frequently than this. This will add a short time to your clinic visit (you will seen in the clinic by the nursing and medical staff in the usual way) and the tests are easy to do. There is a quality of life questionnaire which looks at how your vision is affecting your life which we can help you do if you need assistance to read the questions. We will then run tests with you using your vision such as how fast you can read, can you identify coins or playing cards, can you put a key in a lock or punch in a PIN number?

The aim of this is to see if your perception of how good or bad your vision is , is the same as the vision we measure in the clinic as often patients say to us that although the vision may appear better, the quality is affected. This is important information for us to know so that we can help improve treatments for patients like yourself in the future.

As part of your normal clinic visit you are likely to have an eyescan known as an OCT. These will be done as usual but we would add an additional test on the same machine

which asks you to press a button when you see a flashing light. This will only add a few minutes to the time it takes to do the scan – this is called microperimetry.

The information about your condition and tests will be recorded on a data sheet and then kept in a locked cabinet. Only doctors/nurses involved in the study will have access to it so it remains confidential at all times. To put your data together with other patients' data to look at the results of the study, we give you a study number and only that number is then used on a computer for data analysis and you cannot be identified.

Please discuss this with your friends/family GP as you like and we will discuss this again with you at your next clinic visit. If you are happy to take part in the study, we will ask you to sign a consent form so that we can collect your information. If you wish to withdraw from the Study at any time during the 2 years you are at liberty to do this.

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No you do not and taking part is purely voluntary. If you do not take part, your care in the clinic will not be affected in any way.

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What if something goes wrong or I wish to complain?

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff you may have experienced due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you. Please ask your research doctor if you would like more information on this. In the unlikely event that you are harmed by taking part in this study, compensation may be available to you. If you suspect that the harm is the result of the Sponsor's (University College London) or the hospital's negligence then you may be able to claim compensation. After discussing with your research doctor, please make the claim in writing to the Professor Sue Lightman who is the Chief

Investigator for the research and is based at UCL Institute of Ophthalmology and the Royal Surrey County Hospital. She will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this. NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm.

The Principal Investigator of the Study is Professor Sue Lightman who is a Consultant Ophthalmologist at the Royal Surrey County Hospital and others doctors involved in the research include Mr Simon Taylor (Consultant Ophthalmologist), Dr Filis Ismetova

(ophthalmologist), Mr Oren Tomkins (ophthalmologist), Mr Albert Lula, (research assistant).

We appreciate your attention

With best wishes

Professor Sue Lightman

Consultant Ophthalmologist and Study Lead 14th April 2013

I. Research protocol

Royal Surrey County Hospital NHS
NHS Foundation Trust

PROTOCOL

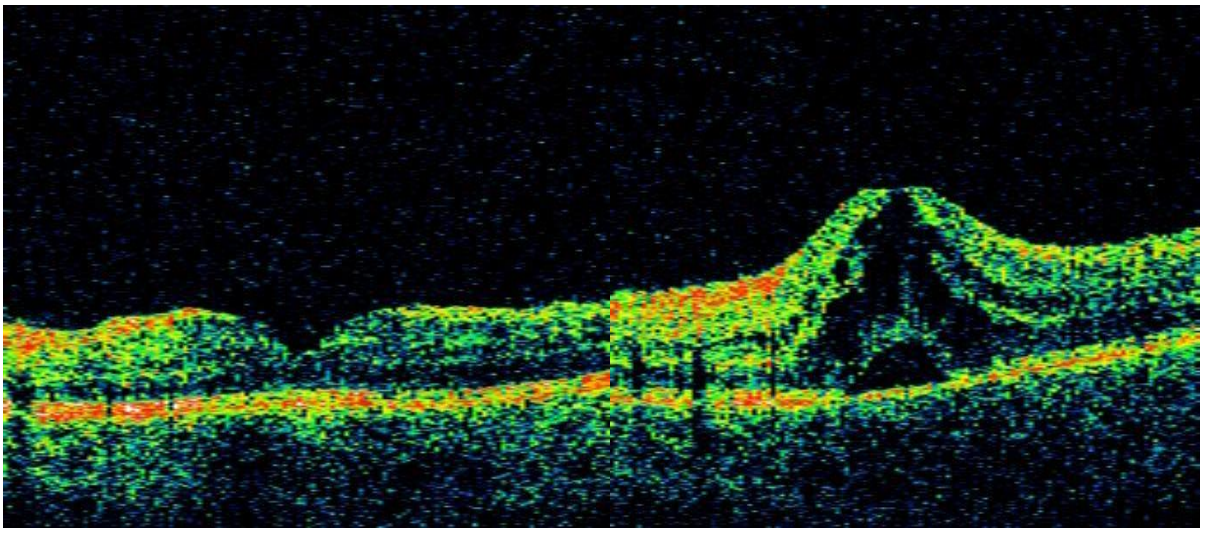
Title: Functional visual outcomes of retinal oedema and its standard management

Aims of study:

1. To determine whether clinic measured visual acuity correlates well with functional visual performance assessments in patients with retinal oedema treated as per NICE/clinic protocols
2. 2. To determine whether laser treatment at any stage has a beneficial role or not in patients receiving intraocular therapy for macular oedema

Background: Macular oedema is a major cause of visual loss in many retinal disorders – the commonest being retinal vein occlusions, diabetic retinopathy and uveitis (intraocular inflammation). Macular oedema is swelling of the retina in the macular region which is the central area of the retina required for good visual acuity. The presence of fluid there means that the retina is swollen and as a consequence it does not function well and vision, both for distance and for near is reduced.

OCT pictures of normal eye and eye with macular oedema



Normal macula contour on OCT Macular oedema showing fluid on OCT

Up until 3 years ago laser treatment was the only major treatment option and patients were offered this to try and stabilize their vision rather than try and improve it. Laser to the oedematous area (either focal treatment to leaking spots or application of grid with the laser for diffuse leakage) could be repeated if vision continued to fall because of increasing amounts of fluid but was not successful in most patients at significantly reducing the amount of fluid or in improving vision. Over the last 3 years drugs injected into the eye have been shown to reduce the amount of fluid quite dramatically and improve vision [references?]. Treatment options include 4-6 weekly injections with either bevacizumab (Avastin) or ranibizumab (Lucentis) or a dexamethasone corticosteroid implant injection (Ozurdex) every 5 months. Patients with macular oedema and uveitis do not have laser treatment as it is ineffective [references?]. Treatment is either on drugs given orally (systemic steroids) or by injections of steroid given in or around the eye. The resolution of oedema is associated with improved vision in most patients [references?].

Guidelines from NICE for treatment of macular oedema due to retinal vein occlusions include the following: the steroid implant is given as many times as required but usually every 5 months. Laser treatment is recommended as a first line option when possible, but is not used when there is significant haemorrhage in the macular region because the blood prevents uptake of laser energy by retinal tissue. It is certainly possible that

laser treatment may be of no additional benefit – the clinical trial data data not show an effect up to 12 months - and may in fact be deleterious in the long run as the laser burns produces small blanks (scotomas) in the vision which are very likely to interfere with fine visual function. For patients with diabetic retinopathy, the PCT approved the use of bevacizumab in patients in whom laser treatment had been unsuccessful; we have run one of the few diabetic treatment clinics for this in the UK. Since February 2013, NICE has said that ranibizumab may be given for this condition as a monthly intraocular injection but only when the macular thickness is >400u. The clinical trials with ranibizumab show no additional benefit over 2 years of additional laser treatment compared with the injections alone. However, many ophthalmologists feel that laser treatment may stabilize the situation or reduce the number of injections required. Again, it is not known whether additional laser treatment will in fact be deleterious to fine visual function as compared to those in which it is not used. Patients with vein occlusions have predominately unilateral eye problems whereas diabetics and uveitis patients often have bilateral eye involvement. This study will evaluate whether the functional effect of laser treatment on both eyes may be greater in those who have had bilateral treatment. We will also be able to evaluate uveitis patients (who are not treated with laser) as a control group, although many patients often say the quality of their vision is reduced and we will be able to test that in this study .

In the clinical setting, visual acuity is measured by reading letters on a chart at a set distance, which may be a poor predictor of actual visual function. It is possible that visual acuity may improve with the use of laser in addition to intravitreal injections but visual function will be impaired due to the small scotomata the laser induces. This study will assess both visual acuity and visual function, using standardised questionnaires for quality of life that have been validated for eye diseases and are used in the major eye treatment trials [references] to assess a patient's perception of the quality of their life as well as visual function. Longstanding fluid in the eye (macular oedema) and laser burns may both reduce visual function, but the types of visual compromise may be different. We will monitor the amount of fluid in the retina in the standard way with the use of optical coherence tomography (OCT). We will also use the microperimeter we have purchased to map fine visual acuity over the oedematous area to determine if retinal tissue treated with laser burns is associated with focal visual impairment. Both the OCT and microperimetry are brief, noninvasive tests.

Functional vision is tested by the use of specially designed tasks such as placing keys in locks, identifying coins, identifying playing cards, entering PIN codes into keypads, and reading speed. These have been used in several studies of patients with eye diseases [references?], allowing researchers to correlate subjective patient complaints of difficulty performing practical, everyday tasks with objective assessment of visual function. We aim to repeat these tests at 6-month intervals over 2 years to determine if the effects of treatment can be predicted and whether the effects of laser are better or worse with time.

Inclusion Criteria: All patients with macular oedema who are willing and able to participate over 18 years old

Exclusion criteria: Medial opacities making measurement of retinal fluid impossible

Patients not wishing to take part

Patients under 18 years old

Patients not able to give consent

Patients with no retinal oedema

Clinic visits

Routine eye clinic : Patients with retinal oedema identified and approached to take part in the Study by one of our Clinical Research Staff by information given about the study. The patient information sheet given and patients are given 2 weeks to their next clinic visit (at which visit treatment options are discussed) to decide whether or not they wish to participate. Informed consent is taken and patient enrolled in the study.

Baseline: Patient attends clinic and macular oedema from a retinal disorder is diagnosed

Underlying cause identified: central retinal vein occlusion central (CRVO) or branch retinal vein occlusion (BRVO), diabetic retinopathy, uveitis, and other retinal conditions such as macular telangectasias.

Relevant history of condition and previous treatment is obtained.

Vision measured - with refraction (using both a Snellen Chart and ETRDS vision chart).

Other tests such as visual fields if clinically required (e.g., patient has glaucoma).

Quality of life questionnaire undertaken (with assistance if required).

Functional assessment tests - worse eye first , then better eye, then with both eyes open

Intraocular pressure measured on slit lamp

Patient's pupils dilated with 1% tropicamide and 2.5% phenylephrine

Clinical examination - biomicroscopy with retinal examination

OCT with microperimetry - done on same machine at same time

Other tests as clinically indicated (e.g., fluorescein angiography), blood tests

Treatment as clinically indicated (e.g., observation, laser (diabetics and vein occlusions), intravitreal injections of bevacizumab or ranibizumab (diabetics), dexamethasone intraocular implant (vein occlusions), uveitis (local or systemic steroids)).

Patients with BRVO have treatment as per NICE Guidelines - laser as required every 3 months and ozurdex injections as required every 5 months

Clinic follow up as required and any further treatment as required - usually 2 - 3 monthly visits

Study follow up visits at 6 months 12 months 18 months and 24 months - run at same time as clinic visits – no additional clinic visits required

Data collection: Specific data collection sheets for each visit will be completed and the data entered into a database. The data collection sheets will have a trail number on them and further patient identification details will not be used. These data sheets will be kept in a locked filing cabinet in the Clinical Research Office in the Ophthalmology Department. Five data collection points will be recorded - baseline, 6, 12 , 18, and 24 months, after which the patient will exit the study. The database will be analysed to look for the effects of disease and treatment on functional vision outcome using a multivariate analysis.

Insurance

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Reporting Serious Unexpected Adverse Events

All Serious Unexpected Adverse Events to a research subject in the study must be reported immediately to the sponsor using the following email address research-incidents@ucl.ac.uk.

A Serious Adverse Event

- Results in death
- Is life Threatening
- Requires Hospitalisation or prolongation of hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congential anomaly or birth defect
- Any other serious medical occurrence

Serious Adverse Events will be documented from the point of enrolment until the patient is exited from study. Information recorded and reported shall include

- A description of the event
- the date of event onset
- The relatedness of the event to the procedure
- The expectedness of the event
- The outcome of the event
- The date the event was first noticed by, or reported to the investigator

All ongoing Serious Adverse Events will be followed-up until the last study visit.

Reporting Incidents

All incidents must be reported through the appropriate Trust incidents reporting system. Where no Trust is involved the incident should be reported by completing form at http://www.ucl.ac.uk/jro/postapproval

Where the study is being conducted at UCLH then the incidents should be reported through Datix.

An incident in a research study is

- Something that should not have happened OR
- Something that should have happened but didn't
- which significantly effects any of the following
- the rights and well being of the research subject
- the scientific value of the study
- the compliance of the study with all relevant legal rules or ethics guidance including the Data Protection Act and the Human Tissue Act.
- The reputation of UCL

This includes a requirement to report all serious breaches of protocol or GCP (if applicable).

Archiving

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study master file at UCL for 20 years from the study end. The Principal Investigator at each participating site agrees to archive his/her respective site's study documents for 5 years from the study end.

Intellectual Property Rights

All background intellectual property rights (including licences) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights.

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCL. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to UCL. and to disclose all such know-how to UCL.

Each participating site agrees to, at the request and expense of UCL, execute all such documents and do all acts necessary to fully vest the IPR in UCL.

Nothing in this section shall be construed so as to prevent or hinder the participating site from using knowhow gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of UCL. This does not permit the disclosure of any of the results of the study, all of which remain confidential.

Data transfer (handling, processing and storage)

In the study, [Description of type of patient data or reference to description of the patient data from a previous protocol section, to be inserted] will be collected from patients in

accordance with the patient consent form, patient information sheet and sections [To be inserted] of this protocol.

The [Description of patient data to be inserted] will be appropriately sent to [Full name and address of party handling the patient data to be inserted] for [Description of use/processing to be inserted – e.g. “for statistical analysis”], and [To be inserted] will act as the data controller of such data for the study [NOTE: In most cases, it may be that UCL, as the study sponsor, is the data controller].

[Full name and address of party handling the patient data to be inserted] will process, store and dispose of

[Description of patient data to be inserted] in accordance with all applicable legal and regulatory requirements, including the Data Protection Act 1998 and any amendments thereto. [More details regarding actual storage may be inserted here – e.g. “patient data will be stored centrally at the Rayne Institute in a locked filing cabinet controlled by the Chief Investigator”

Professor Sue Lightman

Consultant Ophthalmologist

Principal Investigator 14th April 2013

Flow chart

Patient attends eye clinic and diagnosed with retinal oedema

Routine investigations organised and patients returns 2 weeks later for discussion of treatment options Discussion of clinical study and patient information sheet given

Routine clinical exam and additional clinical tests as required

Plus refraction

Quality of life questionnaires

OCT with Microperimetry

Functional vision testing

Treatment options discussed and treatment booked

[no treatment, laser, Oxurdex,

Lucentis/avastin]

Clinic visits and treatment as required usually 2-3 monthly over 2+ years

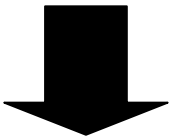
Clinic visits at 6,12,18,24 months - Routine clinical exam, additional clinical tests and treatment as required

Plus refraction

Quality of life questionnaires

OCT with Microperimetry

Functional vision testing



At 2 years patient exits the study but clinic visits continue as required

Red colour indicates tests as part of the study over and above routine clinic visit – it is anticipated it will add 40 mins to each clinic visit

J. Research review - 1

From: Peter McCluskey

[peter.mccluskey@sydney.edu.au]

Sent: 16 November 2012 20:56

To: Lightman, Susan

Subject: Research Review

Follow Up Flag: Flag for follow up

Flag Status: Flagged

To whom it may concern:

I have been asked to comment on this research proposal that aims to determine the effect on the quality of life of patients affected by common diseases (diabetic retinopathy, retinal vein occlusion and uveitis) characterised by macular oedema. We are aware that the reduced vision caused by macular oedema affects quality of life but there are very very few studies that have sought to measure this accurately and importantly whether different treatments (in this study, antiVEGF injections, laser and steroids) improve quality of life by different amounts or are in fact deleterious.The study uses standard clinical tests such as OCT and microperimetry to document macular structure and function, and validated quality of life questionnaires and tests to measure the effect on patients quality of life. It aims to follow patients for 2 years to document the effects of treatment which is essential as macular oedema resolves slowly and the effects of treatment such as laser have delayed effects on vision.This is critical information that will change what treatment we offer patients with different diseases. Studies to date have used visual acuity and macular thickness as the outcome measures of effectiveness and have not used quality of life measures.

In conclusion, this is an extremely useful study that is focused on a practical problem for patients. The study will produce important data that is likely to change how we manage patients.

Please contact me if you require additional information

Peter McCluskey

Director Save Sight Institute

Professor of Ophthalmology

Sydney Medical School

University of Sydney

Phone: +612 9382 7300

Fax: +612 9382 7372

Email: pmccluskey@med.usyd.edu.au peter.mccluskey@sydney.edu.au

K. Research review – 2

From: JP Dunn [jpdunn@jhmi.edu]

Sent: 21 November 2012 13:55

To: Lightman, Susan

Subject: RE: rapid revie

Sue-

Thanks for letting me look at the protocol for the visual function assessment for patients treated for macular edema. I think this is an excellent idea and I hope the project can move forward promptly. As you point out, the primary outcome in clinical trials of treatments such as grid laser, intravitreal steroids, or anti-VEGF injections has generally been visual acuity (either by Snellen or ETDRS testing), and clearly central visual acuity may not correlate well with tests of visual function and assessment of quality of life. With the Multicenter Uveitis Steroid Trial (MUST) as an example, uveitis trials should now be routinely assessing visual function and quality of life as part of their outcomes measures. Studies such as yours should have a major impact on the field as regards both the development of future clinical trials protocols and establishing a "real world" means of assessing just how truly effective our treatments for macular edema are. Good luck with the study; I look forward to seeing the outcomes in a few years!

J.P. Dunn, M.D.

Associate Professor of Ophthalmology

Division of Ocular Immunology

The Wilmer Eye Institute

The Johns Hopkins School of Medicine

Baltimore, MD 21287 USA jpdunn@jhmi.edu

L. Validated questionnaire – VFQ25

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is*:

(Circle One)

READ CATEGORIES:	
	Excellent 1
	Very Good 2
	Good 3
	Fair 4
	Poor 5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

READ CATEGORIES:	
	Excellent 1
	Good 2
	Fair 3
	Poor 4
	Very Poor 5
	Completely Blind 6

* Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0

3. How much of the time do you worry about your eyesight?

(Circle One)

READ CATEGORIES:

None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

READ CATEGORIES:

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. **How much difficulty do you have doing work or hobbies that require you to <u>see well up close</u>, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this 6

7. **Because of your eyesight, how much difficulty do you have <u>finding something on a crowded shelf</u>?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this 6

8. **How much difficulty do you have <u>reading street signs or the names of stores</u>?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this 6

9. **Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. **Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. **Because of your eyesight, how much difficulty do you have seeing how people react to things you say?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. **Because of your eyesight, how much difficulty do you have <u>picking out and matching your own clothes</u>?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

13. **Because of your eyesight, how much difficulty do you have <u>visiting with people in their homes, at parties, or in restaurants</u>?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

14. **Because of your eyesight, how much difficulty do you have <u>going out to see movies, plays, or sports events</u>?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 *Skip To Q 15c*

No 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove ..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ..... 1 *Skip To Part 3, Q 17*

Mainly other reasons ..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons ... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4

16. How much difficulty do you have driving at night? Would you say you have: (READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight	**5**
Have you stopped doing this for other reasons or are you not interested in doing this	**6**

16a. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight	**5**
Have you stopped doing this for other reasons or are you not interested in doing this	**6**

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.....	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.....	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me..	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.....	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.....	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your <u>overall health</u>, on a scale where zero is <u>as bad as death</u> and 10 is <u>best</u> possible health?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										**Best**

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										**Best**

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have <u>reading the small print in a telephone book, on a medicine bottle, or on legal forms</u>? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A7. Because of your eyesight, how much difficulty do you have <u>taking part in active sports or other outdoor activities that you enjoy</u> (like golf, bowling, jogging, or walking)?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A8. Because of your eyesight, how much difficulty do you have <u>seeing and enjoying programs on TV</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have <u>entertaining friends and family in your home</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

SUBSCALE: DRIVING

A10. [This items, "driving in difficult conditions", has been included as item 16a as part of the base set of 25 vision-targeted items.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.
(READ CATEGORIES AS NEEDED)

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.	**1**	**2**	**3**	**4**	**5**
A13. I don't go out of my home alone, because of my eyesight.....	**1**	**2**	**3**	**4**	**5**

M. Health Research Authoroty amendment approval letter

National Research Ethics Service

NRES Committee London - Fulham HRA NRES Centre Manchester Barlow House

3rd Floor, 4 Minshull Street Manchester M1 3DZ

Telephone: 0161 625 7821

Facsimile: 0161 625 7299

12 November 2013

Miss Suzanne Binks

Joint Research Office

Universtiy College London, Gower Street

London

WC1E 6BT

Dear Miss Binks

Study title:	Functional visual outcomes of retinal oedema and its standard management
REC reference:	13/LO/1005
Amendment number:	**1**
Amendment date:	15 October 2013
IRAS project ID:	128193

The amendment proposed:

- Reduce the sample size from 200 to 100
- Add Moorefield's Eye Hospital as a participating site

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMPs)	1	15 October 2013

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet. **R&D approval**

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

/LO/1005:	Please quote this number on all correspondence

Yours sincerely

Dr Charles Mackworth-Young Chair

E-mail: nrescommittee.london-fulham@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Ms Cathy Mayes, R and D Department

Professor Sue Lightman, Royal Surrey County Hospital NHS Foundation Trust/ UCL

NRES Committee London - Fulham

Attendance at Sub-Committee of the REC meeting on 08 November 2013

Name	Profession	Capacity
Dr Charles Mackworth-Young	Physician (Chairman)	Expert
Dr Frank Miskelly	Physician (Vice-Chairman)	Expert

N. Health Research Authority approval letter

Health Research Authority

National Research Ethics Service

NRES Committee London - Fulham HRA NRES Centre Manchester Barlow House

3rd Floor, 4 Minshull Street Manchester M1 3DZ

Telephone: 0161 625 7821

Facsimile: 0161 625 7299

23 July 2013

Professor Sue Lightman

Chief Investigator/ Academic Supervisor

Royal Surrey County Hospital NHS Foundation Trust/ UCL

Egerton Road

Guildford

GU2 7XX

Dear Professor Lightman

Study title:	Functional visual outcomes of retinal oedema and its stan management
REC reference:	13/LO/1005

IRAS project ID: 128193

The Research Ethics Committee reviewed the above application at the meeting held on 15 July 2013. Thank you for attending to discuss the application along with Dr Filis Ismetova

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator, Miss Shehnaz Ishaq, nrescommittee.london-fulham@nhs.net

Ethical opinion

1. The Committee commended you both on such a well written application and confirmed that they did not have any ethical issues with the research. The Committee confirmed that you will receive a letter within 10 working days with a positive result.

You were both thanked for attending and left the meeting room.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see“Conditions of the favourable opinion” below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission (“R&D approval”) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites (“participant identification centre”), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were

Document	Version	Date
Covering Letter		
REC application	3.5	12 June 2013
Protocol	1.1	14 April 2013
Investigator CV	Dr Sue Lightman	
Participant Information Sheet	1.1	14 April 2013
Participant Consent Form	1.0	15 November 2012
GP/Consultant Information Sheets	1.0	14 March 2013
Referees or other scientific critique report	1.0	14 March 2013
Investigator CV	Fills Ismetova	
Evidence of insurance or indemnity	Institution sponsored interventional study agreement	22 March 2012
Referees or other scientific critique report	2.0	14 March 2013
Questionnaire: EuroQol Questionnaire		
Questionnaire: Visual Functioning Questionnaire - 25		
Investigator CV	Simon Taylor	13 August 2012

Other: UCL agreement between UCL and Allergan Limited

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/LO/1005 Please quote this number on all correspondence

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project. Yours sincerely

[redacted]

Signed on behalf:

Dr Charles Mackworth-Young Chairman

Email: nrescommittee.london-fulham@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: Miss Suzanne Binks (randd@uclh.nhs.uk) Ms Cathy Mayes, R and D Department (c.mayes@nhs.net)

NRES Committee London - Fulham

Attendance at Committee meeting on 15 July 2013

Committee Members:

Name	Profession	Present	Notes
Prof Alison Crombie	Anthropologist Nurse	Yes	
Dr Kanagasabai	Retired Scientist	Yes	
GDra nSehsahuang uruGrit	Director of Communications and Public Affairs – H Tissue	No	
The Rev'd Nigel Griffin	AHoutshpoitrality C h	No	
Dr Akil Jackson	Physician	Yes	
Mr David Leonard	Pharmacist	Yes	
Dr Charles Mackworth-You	Physician (Chairman	Yes	
Dr Colin Michie	Paediatrician	Yes	
Dr Frank Miskelly	Physician (Vice-	Yes	
Dr Shirlony Morgan	ChaPsycirhmiatranis	Yes	
Professor Sandra Oliver	Retired Organisation Psychologist	No	
Lady Alexandra Roche	Lay Member	Yes	
Mrs Gillian Sichau	Occupational Therap	Yes	
Mrs Katie Wilkinson	Clinical Trials Centre Manager	Yes	
Mrs Margaret Anne William	Lay Member	No	
Dr Ruth Williamson	Radiologist	Yes	

Also in attendance:

Name	Position (or reason for attending)
Mr Noel Graham	Centre Manager - HRA NRES Centre Manchester
Miss Shehnaz Ishaq	Committee Co-ordinator
Ms Monsey McLeod	Pharmacist
Mrs Ann Tunley	Regional Manager (North)

O. Case report form

CRF V 2.1

Date _____ Study Number _____/ RE LE

Past Ocular History (type, since when): Past Medical History (since when):

Right Eye

1- Mild NPDRP; 2- moderate NPDRP; 3-severe NPDRP; 4-PDRP;5-BRVO; 6-i-CRVO; 7-non-i-CRVO; 8- Anterior Uveitis; 9-Intermediate Uveitis; 10- Posterior Uveitis; 11- Others_____

Left Eye

1- Mild NPDRP; 2- moderate NPDRP; 3-severe NPDRP; 4-PDRP;5-BRVO; 6-i-CRVO; 7-non-i-CRVO; 8- Anterior Uveitis; 9-Intermediate Uveitis; 10- Posterior Uveitis; 11- Others_____

Present systemic medication: **Present Ocular Treatment:**

Past Ocular Treatment:

Right Eye 1- PRP; 2- Macula Grid; 3- IVTA; 4-Ozurdex; 5-Avastin; 6-Lucentis; 7-Eylea; 8-Others.....

Left Eye 1-PRP; 2- Macula Grid; 3- IVTA; 4-Ozurdex; 5-Avastin; 6-Lucentis; 7-Eylea; 8-Others.....

Other Comments (number and dates of IV treatments):

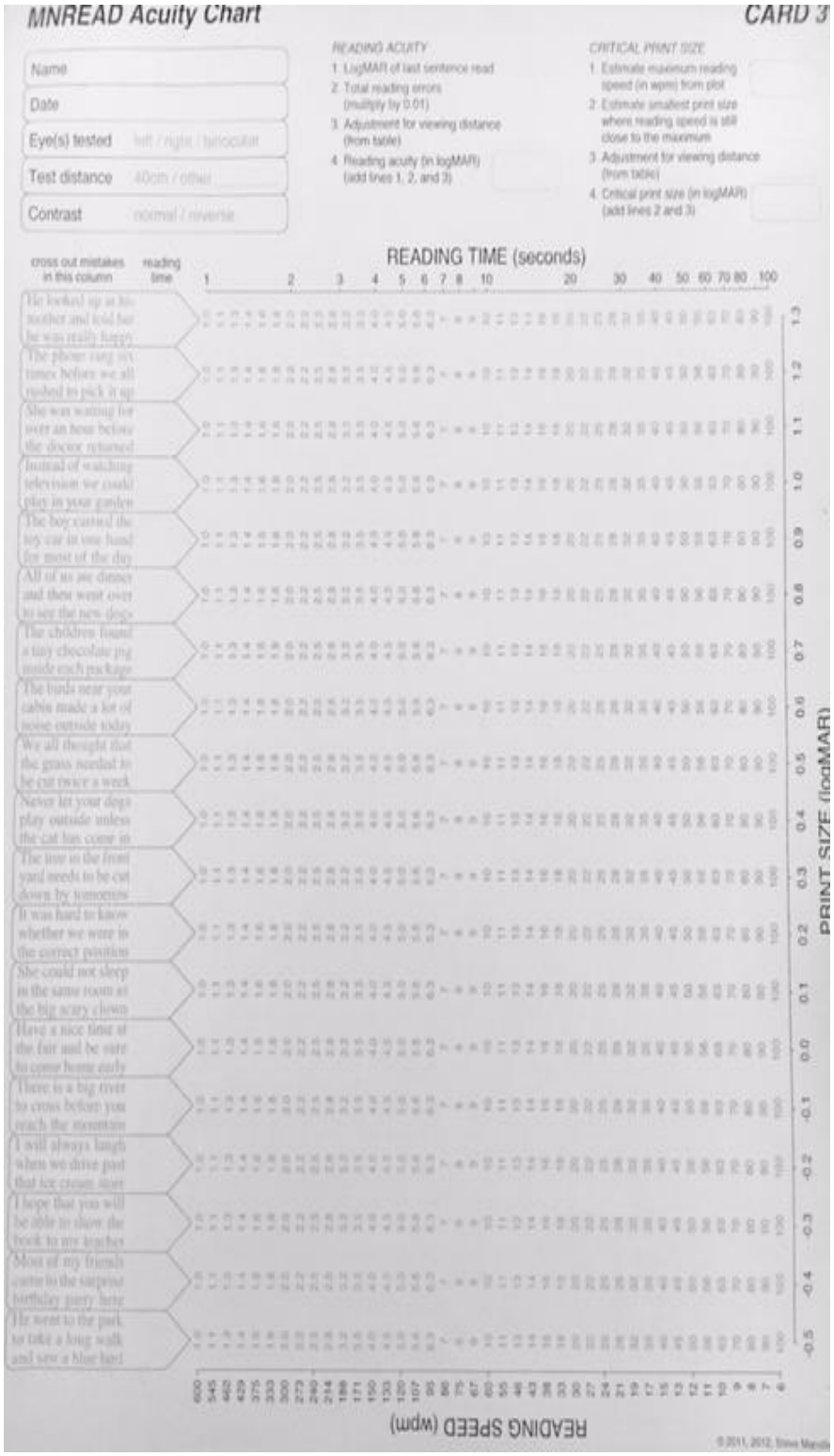
Vision	Right Eye	Left Eye
Total EDTRS letters		
LogMAR		
Snellen Chart		
Reading Speed performed	YES / NO	YES / NO

CRF V 2.1

	Right Eye	Left Eye
Cornea	1-clear, 2-corneal opacification	1-clear, 2-corneal opacification
AC	Cells grade 0,1,2,3,4, Others 5_____	Cells grade 0,1,2,3,4, Others 5_____
IOP		
Iris	1- Normal 2- Abnormal(posterior synechia)	1- Normal 2- Abnormal(posterior synechia)
Lens	1. Normal or trivial opacities 2. Nuclear sclerosis 3. Cortical changes 4. Posterior subcapsular opacities 5. Pseudophakic 6. Aphakic	1. Normal or trivial opacities 2. Nuclear sclerosis 3. Cortical changes 4. Posterior subcapsular opacities 5. Pseudophakic 6. Aphakic
Vitreous	Cells 0, 0.5+, 1+, 2+, 3+, 4+ Haze 0, 1+, 2+, 3+, 4+	Cells 0, 0.5+, 1+, 2+, 3+, 4+ Haze 0, 1+, 2+, 3+, 4+
OCT Topcon/ Heidelberg Microperimetry test	CRT_____/ Volume_____ Mean Contrast Sensitivity_____dB Eye movement 2^0 _____% Eye Movement 4^0 _____%	CRT_____/Volume_____ Mean Contrast Sensitivity_____dB Eye movement 20 _____% Eye Movement 40 _____%

Haemorrhage?	Pre-	Intra-	Subretinal	No	Pre-	Intra-	Subretinal	No
Haemorrhage at fovea?	Yes		No		Yes		No	
Ischemia at the fovea?	Yes		No		Yes		No	
FAZ zone grade	0, 1, 2, 3, 4				0, 1, 2, 3, 4			
Exudates?	Yes		No		Yes		No	
NVD	Yes		No		Yes		No	
NVE	Yes		No		Yes		No	
IRMA	Yes		No		Yes		No	
Retinal atrophy?	Extrafoveal	Subfoveal	No		Extrafoveal	Subfoveal	No	
Type of macular oedema	Focal	Diffuse	No		Focal	Diffuse	No	
PED	Serous	Fibrovascular	No		Serous	Fibrovascular	No	
IRF	Extrafoveal	Subfoveal	No		Extrafoveal	Subfoveal	No	
SRF	Extrafoveal	Subfoveal	No		Extrafoveal	Subfoveal	No	
ERM	Significant with VRT (vessels tortuosity)	Mild with no VRT (cellophane reflex)	No		Significant with VRT (vessels tortuosity)	Mild with no VRT (cellophane reflex)	No	
Treatment Plan / Comments								

P. MNREAD visual acuity card



R. VFQ-25 scorring algorithm

Version 2000

The National Eye Institute 25-Item

Visual Function Questionnaire (VFQ-25)

Version 2000

This final version of the VFQ-25 differs from the previous version in that it includes an extra driving item from the appendix of supplementary questions as part of the base set of items. Also, the revised scoring algorithm excludes the single-item general health rating question from the calculation of the visiontargeted composite score. Because of these changes, the base set of items actually includes 26 questions, however, only 25 are vision-targeted and included in the composite score. Please see the "Frequently Asked Questions" or FAQ section for additional clarifications of these changes.

Background

The National Eye Institute (NEI) sponsored the development of the VFQ-25 with the goal of creating a survey that would measure the dimensions of self-reported vision-targeted health status that are most important for persons who have chronic eye diseases. Because of this goal, the survey measures the influence of visual disability and visual symptoms on generic health domains such as emotional wellbeing and social functioning, in addition to taskoriented domains related to daily visual functioning. Questions included in the VFQ-25 represent the content identified during a series of condition-specific focus groups with patients who had age-related cataracts, glaucoma, age-related macular degeneration, diabetic retinopathy, or

CMV retinitis. [1]

The VFQ-25 is the product of an item-reduction analysis of the longer field test version of the survey called the 51-item National Eye Institute Vision Function Questionnaire (NEI-VFQ).[2]

The longer version contains 51 questions which represent 13 different sub-scales. The NEI- VFQ Field Test Study collected the data needed to examine the reliability and validity of the survey across all of the above-mentioned ocular diseases.

Also, reliability and validity was assessed in a heterogeneous group of patients with low vision from any cause and a group of age-matched persons with normal vision. A published report describes the psychometric properties of the longer field test version of the survey. [3] Additional a number of clinical studies have used either the 51 or the 25- item version of the NEI-VFQ across a number of chronic ocular conditions. [4-8] Despite the success of the longer field test version and its continued use, to enhance feasibility a short-form version was planned since the earliest developmental phase.

The VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. The VFQ-25 also includes an appendix of additional items from the 51-item version that researchers can use to expand the scales up to 39 total items. All items in the VFQ-25 are from the 51-item field test version; no new items were developed for use in the VFQ-25. Unless otherwise specified, the remainder of this document will use the term VFQ-25 to refer to the base set of items.

The VFQ-25 takes approximately 10 minutes on average to administer in the interviewer format. There is also a self-administered version of the survey, however, psychometric testing of the self- administered version has not been done. The VFQ- 25 generates the following vision-targeted sub- scales: global vision rating (1), difficulty with near vision activities (3), difficulty with distance vision activities (3), limitations in social functioning due to vision (2), role limitations due to vision (2), dependency on others due to vision (3), mental health symptoms due to vision (4), driving difficulties (3), limitations with peripheral (1) and color vision (1), and ocular pain (2). Additionally,

the VFQ-25 contains the single general health rating question which has been shown to be a robust predictor of future health and mortality in populationbased studies. Please see the FAQ section for more information about the general health rating question.

Development of the NEI VFQ-25

The guiding principles for the selection of the short-form items included: 1) low item-level missing data rates; 2) normal distribution of response choices; and 3) retention of items that explained the greatest proportion of variance in the 51-item sub-scales. The items retained in the VFQ-25 and the optional items (provided in the appendix to the survey) are listed on Table 1. A report describing the performance of the VFQ-25 relative to the Field Test version is currently under review. [2] The reliability and validity of the VFQ-25 is similar to that observed for the 51item version of the survey. On average, each VFQ-25 sub-scale predicts 92% of the variance in the corresponding 51-item sub- scale score.

Optional Items

Appendix 1 consists of additional questions that users may add to a specific sub-scale. Inclusion of these may be helpful if a particular sub-scale represents the primary domain of vision-targeted HRQOL that is felt to be most important for the condition under study. For example, if a user is testing a new treatment for macular degeneration, by adding near vision questions A3, A4, and A5 to VFQ-25 questions 5, 6, and 7, the investigator would have a six-item near vision scale rather than a three-item scale. The addition of these items would enhance the reliability of the near vision sub-scale and is likely to improve the responsiveness of the sub-scale to the intervention over time (Table 6). If items from the appendix are used, the VFQ-25 developers would encourage users to incorporate all optional items for a given sub-scale. This strategy will enhance the comparability of results across studies.

Scoring

Scoring VFQ-25 with or without optional items is a two-step process:

First, original numeric values from the survey are recoded following the scoring rules outlined in Table

2. All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format scores represent the achieved percentage of the total possible score, e.g. a score of 50 represents 50% of the highest possible score.

In step 2, items within each sub-scale are averaged together to create the 12 sub-scale scores. Table 3 indicates which items contribute to each specific sub-scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the sub- scale that the respondent answered.

Composite Score Calculation

To calculate an overall composite score for the VFQ-25, simply average the vision-targeted sub- scale scores, excluding the general health rating question. By averaging the sub-scale scores rather than the individual items we have given equal weight to each sub-scale, whereas averaging the items would give more weight to scales with more items.

Table 1. Item Number Translation from the 51-Item Field Test Version to the VFQ 25

S = retained in the VFQ-25, A = retained in the appendix should be used for the VFQ-39, --- = deleted from the VFQ-25 & VFQ-39

Field Test Version Ques.#	Sub-scale	Status	VFQ-25 Que	Field Test Version Ques.#	Sub-scale	Status	VFQ-25 Que
1	general health	S	**1**	29	social fx	---	---
2	general health	A	A1	30	social fx	A	A9
3	general vision	S	**2**	31	social fx	S	13
4	expectations	---	---	32	distance vision	A	A8
5	well-being/ distress	S	**3**	33	distance vision	A	A7
6	well-being/ distress	---	---	34	distance vision	S	14
7	ocular pain	S	19	35	driving (filter item)	S	15
8	expectations	---	---	35a	driving (filter item)	S	15a
9	expectations	---	---	35b	driving (filter item)	S	15b
10	expectations	---	---	35c	driving	S	15c
11	well-being/ distress	S	25	36	driving	---	---
12	ocular pain	S	**4**	37	driving	S	16
13	well-being/ distress	---	---	38	driving	S	16a *

14	general vision	A	A2	39a	role limitations	S	17
15	near vision	S	**5**	39b	role limitations	A	A11a
16	near vision	A	A3	39c	well-being/ distress	---	---
17	near vision	S	**6**	39d	role limitations	---	---
18	near vision	---	---	39e	role limitations	A	A11b
19	near vision	S	**7**	39f	role limitations	S	18
20	distance vision	S	**8**	40	well-being/ distress	A	A12
21	distance vision	---	---	41	dependency	S	20
22	distance vision	S	**9**	42	well-being/ distress	S	21
23	peripheral visic	S	10	43	well-being/ distress	S	22
24	distance vision	A	A6	44	dependency	---	---
25	social fx	S	11	45	dependency	A	A13
26	near vision	A	A4	46	dependency	S	23
27	color vision	S	12	47	dependency	S	24
28	near vision	A	A5				

* VFQ-25 item 16a was listed in previous versions as part of the appendix of supplemental items (#A10).

Table 2. Scoring Key: Recoding of Items

Item Numbers	Change original response category [a]	To recoded value of:
1,3,4,15c[b]	1	100
		2 75
		3 50
		4 25 5 0
2	1	100
		2 80
		3 60
		4 40
		5 20
		6 0
5,6,7,8,9,10,11,12,13,14,16,16a	1	100 A3,A4,A5,A6,A7,A8,A9[c] 2 75
		3 50
		4 25 5 0 6 *
17,18,19,20,21,22,23,24,25,	1	0
A11a,A11b,A12,A13	2	25
		3 50
		4 75
		5 100

A1,A2	0 0 to	to
	10	100

[a] Precoded response choices as printed in the questionnaire.

[b] Item 15c has four-response levels, but is expanded to a five-levels using item 15b.

Note: If 15b=1, then 15c should be recoded to “0” If 15b=2, then 15c should be recoded to missing. If 15b=3, then 15c should be recoded to missing.

[c] “A” before the item number indicates that this item is an optional item from the Appendix. If optional items are used, the NEI-VFQ developers encourage users to use <u>all</u> items for a given sub-scale. This will greatly enhance the comparability of sub-scale scores across studies.

* Response choice "6" indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing."

Table 3. Step 2: Averaging of Items to Generate VFQ-25 Sub-Scales

Scale	Number of items	Items to be averaged (after recoding per Table 2)

General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Table 4. Step 2: Averaging of Items to Generate VFQ-39 Sub-Scales (VFQ-25 + Optional Items)

Scale	Number of items	Items to be averaged (after recoding per Table 2)
General Health	2	1, A1
General Vision	2	2, A2
Ocular Pain	2	4, 19
Near Activities	6	5, 6, 7, A3, A4, A5
Distance Activities	6	8, 9, 14, A6, A7, A8
Vision Specific:		
Social Functioning	3	11, 13, A9
Mental Health	5	3, 21, 22, 25, A12
Role Difficulties	4	17, 18, A11a, A11b
Dependency	4	20, 23, 24, A13
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Figure 1. Example of VFQ-25 Scoring Algorithm for Near Activities Sub-Scale

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

No difficulty at all..... 1

A little difficulty 2

Moderate difficulty 3

Extreme difficulty ..... (4)

Stopped doing this because of your eyesight 5

Stopped doing this for other reasons or not

interested in doing this..... 6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing . . . ? Would you say you have:

No difficulty at all..... (1)

A little difficulty 2

Moderate difficulty 3

Extreme difficulty 4

Stopped doing this because of your eyesight 5

Stopped doing this for other reasons or not

interested in doing this..... 6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf? Would you say you have:

No difficulty at all..... 1

A little difficulty 2

Moderate difficulty 3

Extreme difficulty ..... (4)

Stopped doing this because of your eyesight 5

Stopped doing this for other reasons or not

interested in doing this..... 6

Scoring example - Figure 1

Items 5, 6, and 7 are used to generate the near activities sub-scale score (Table 3). Each of the items has 6 response choices. Response choice 6 indicates that the respondent does not perform the activity because of reasons that are unrelated to vision. If a respondent selects this choice, the answer is treated as missing and an average of the remaining items is calculated. Response choice 5 indicates that an activity is so difficult that the participant no longer performs the

Formula:

activity. This extremely poor near vision response choice is recoded to “0” points before taking an average of all three items. To score all items in the same direction, Table 2 shows that responses 1 through 5 for items 5, 6, and 7 should be recoded to values of 100, 75, 50, 25, and 0 respectively. If the respondent is missing one of the items, the person's score will be equal to the average of the two non-missing items.

Mean = (Score for each item with a non-missing answer) Total number of items with non-missing answers *Example:*

With responses converted: = (25 + 100 + 25) = 50

3

Note: 100 = Best, 0 = Worst possible score.

Psychometric properties of

VFQ-25 sub-scales

Psychometric data for VFQ-25 reported in the earlier pre-publication version of the scoring manual have been updated and submitted for peer-reviewed publication.[2] The values reported in this document are identical to those reported in the future publication and should be used when citing the performance characteristics of the VFQ-25.

Statistical Power Calculations

Tables 8, 9, and 10 are provided to estimate statistical power when using the VFQ-25 and VFQ-39. These tables estimate the number of subjects needed per group to attain 80% power (alpha = 0.05, two-tailed) depending on the anticipated difference in scores between groups. Table 8 contains power calculations for changes over time between two experimental (i.e. randomized) groups using a repeated-measures design. For example, if one were interested in being able to detect a 5-point difference for the VFQ-25 General Vision sub-scale, one would need 271 subjects per group. Table 9 shows power calculations for two experimental groups using a single, post-intervention measurement design. Such a design is not as precise as a design that uses a baseline and post-intervention measurement points (i.e., more subjects are needed per group to detect the same difference). Table 10 provides corresponding sample size information for a non-experimental (i.e. non- randomized) repeated-measures design where subjects self-select into the two groups. One sees that the number of subjects needed per group is more than that needed for a randomized experiment (Table 8) and less than the number needed for a randomized, post-intervention-only measurement design (Table 9).

Table 8. Sample sizes needed per group to detect differences in *change over time* between two experimental groups for the VFQ-25, repeated measures design

		Number of Points Difference			
Scale Name	SD	2	5	10	20
VFQ-25:					
General Health	26.00	1696	271	68	17
General Vision	21.00	1106	177	44	11
Ocular Pain	17.00	725	116	29	7
Near Activities	29.00	2110	338	84	21
Distance Activities	29.00	2110	338	84	21
Social Functioning	27.00	1829	293	73	18
Mental Health	27.00	1829	293	73	18
Role Difficulties	29.00	2110	338	84	21
Dependency	28.00	1967	315	79	20
Driving	35.00	3073	492	123	31
Color Vision	23.00	1327	212	53	13
Peripheral Vision	27.00	1829	293	73	18
VFQ-25 Composite	20.00	1004	161	40	10
VFQ-39:		1106			
General Health	21.00		177	44	11
General Vision	19.00	906	145	36	9

Ocular Pain	17.00	725	116	29	7
Near Activities	28.00	1967	315	79	20
Distance Activities	26.00	1696	271	68	17
Social Functioning	25.00	1568	251	63	16
Mental Health	26.00	1696	271	68	17
Role Difficulties	28.00	1967	315	79	20
Dependency	27.00	1829	293	73	18
Driving	35.00	3073	492	123	31
Color Vision	23.00	1327	212	53	13
Peripheral Vision	27.00	1829	293	73	18
VFQ-39 Composite	21.00	1106	177	44	11

Note: Scales are all scored on 0-100 possible range. Estimates assume alpha = 0.05, two-tailed t-test, power = 80%, and an inter-temporal correlation between scores of 0.60.

forTabl thee VFQ9. Sampl-25, *pos*e size*t-intervention*s needed per *measures*group to detec*only*. t differences between two experimental groups

Number of Points Difference

Scale Name	SD	2	5	10	20
VFQ-25:					
General Health	26.00	2650	424	106	26
General Vision	21.00	1729	277	69	17
Ocular Pain	17.00	1133	181	45	11

Near Activities	29.00	3297	527	132	33
Distance Activities	29.00	3297	527	132	33
Social Functioning	27.00	2858	457	114	29
Mental Health	27.00	2858	457	114	29
Role Difficulties	29.00	3297	527	132	33
Dependency	28.00	3073	492	123	31
Driving	35.00	4802	768	192	48
Color Vision	23.00	2074	332	83	21
Peripheral Vision	27.00	2858	457	114	29
VFQ-25 Composite	20.00	1568	251	63	16
VFQ-39:		1729			
General Health	21.00		277	69	17
General Vision	19.00	1415	226	57	14
Ocular Pain	17.00	1133	181	45	11
Near Activities	28.00	3073	492	123	31
Distance Activities	26.00	2650	424	106	26
Social Functioning	25.00	2450	392	98	25
Mental Health	26.00	2650	424	106	26
Role Difficulties	28.00	3073	492	123	31
Dependency	27.00	2858	457	114	29
Driving	35.00	4802	768	192	48
Color Vision	23.00	2074	332	83	21

Peripheral Vision	27.00	2858	457	114	29
VFQ-39 Composite	21.00	1729	277	69	17

Note: Scales are all scored on 0-100 possible range. Estimates assume alpha = 0.05, two-tailed t-test, and power = 80%.

Table 10. Sample sizes needed per group to detect differences between two *self-selected groups* for the VFQ-25, repeated measures design

	Number of Points Difference				
Scale Name	SD	2	5	10	20
VFQ-25:					
General Health	26.00	2120	339	85	21
General Vision	21.00	1383	221	55	14
Ocular Pain	17.00	906	145	36	9
Near Activities	29.00	2637	422	105	26
Distance Activities	29.00	2637	422	105	26
Social Functioning	27.00	2286	366	91	23
Mental Health	27.00	2286	366	91	23
Role Difficulties	29.00	2637	422	105	26
Dependency	28.00	2459	393	98	25
Driving	35.00	3842	615	154	38
Color Vision	23.00	1659	265	66	17
Peripheral Vision	27.00	2286	366	91	23

VFQ-25 Composite	20.00	1254	201	50	13
VFQ-39:		1383			
General Health	21.00		221	55	14
General Vision	19.00	1132	181	45	11
Ocular Pain	17.00	906	145	36	9
Near Activities	28.00	2459	393	98	25
Distance Activities	26.00	2120	339	85	21
Social Functioning	25.00	1960	314	78	20
Mental Health	26.00	2120	339	85	21
Role Difficulties	28.00	2459	393	98	25
Dependency	27.00	2286	366	91	23
Driving	35.00	3842	615	154	38
Color Vision	23.00	1659	265	66	17
Peripheral	27.00	2286	366	91	23
VFQ-39 Composite	21.00	1383	221	55	14

Note: Scales are all scored on 0-100 possible range.Estimates assume alpha = 0.05, two-tailed t-test, power = 80%, and an inter-temporal correlation between scores of 0.60.

Q. What kind of permissions are required to use the VFQ-25 in a research study?

Frequently Asked Questions (FAQ)

The VFQ-25 is a public document available without charge for all researchers to use provided they

identify the measure as such in all publications and cite the appropriate developmental papers. Users do not need to notify the developers or the NEI that they intend to use the measure. However, there are some specific permissions for using the VFQ-25 that are detailed on the cover page of the questionnaire itself. These include acknowledging in all publications that the VFQ25 was developed by RAND and funded by the NEI, and that any changes made to the measure for your particular study will be identified as such.

Q. Can I change the format of the VFQ-25 to suit my study?

Any change to the wording or order of the items would constitute a change to the measure and should be specified as such in any published papers. Other than this, it is expected that researchers may need to change the format or appearance of items to suit their purposes.

As of August 2000, to our knowledge no studies have reported on the effect of item order on responses to VFQ-25 or other similar vision- targeted surveys. That is, whether responses change depending where particular items appear in the questionnaire. However, to ensure the comparability of scores across studies, it is our position that the order of items should not be changed.

Q. Has the VFQ-25 been translated into any other languages?

As of August 2000, the developers are aware of translation into approximately 9 languages. For the cost of distribution, a Spanish language version for Mexican-American populations is available from the UCLA and RAND based developers. The developers will provide researchers with the names of other persons to contact for other language translations. Should researchers wish to translate the VFQ-25, the same permissions apply, with the additional requirement that all publications specify responsibility for the translation along with instructions for obtaining a copy of the translated version.

Q. Do you have any additional normative information for specific populations?

The developers currently are not conducting studies for the express purpose of further investigating the psychometric properties of the VFQ-25 or producing normative data. However, many researchers are

currently using the VFQ-25 as an endpoint or outcome in a number of health services and clinical studies. It is likely that as these studies are completed, results that are relevant to better understanding the performance of the VFQ-25 will accompany the main results of each study. The developers and staff at the NEI are aware of other researchers who are collecting condition-specific normative data on population-based samples with the VFQ-25 and when possible will provide contact information for these investigators to new users.

Q. How relevant is the normative data provided in the scoring manual to my sample?

The means, standard deviations, and statistical power values shown in this document were estimated using cross-sectional data from the Field Test Study. Participants recruited for the Field Test were not randomly sampled, but rather were identified for enrollment based on clinical criteria biased towards persons with moderate to severe forms of each target disease. Further, because it was our desire to enroll a broad spectrum of patients based on disease severity, we did not take into consideration treatment status. Please see references #3 for a full description of the NEI-VFQ field test study sample.

Q. Why is a single-item general health item included in the VFQ-25?

During the developmental phase of the NEI-VFQ, vision-targeted health-related quality of life (HRQOL) was a relatively new concept. For this reason, we included this question to insure that researchers had a minimal amount of information about a person's general health status to use as a benchmark against other published samples or cohorts.

This general health rating question has been widely used in studies and is a robust predictor of future health and mortality. However, to fully measure generic HRQOL, many quality of life measurement experts recommend including a separate generic measure of HRQOL such as the SF-36 or SF-12.[9] In such a situation the single- item VFQ-25 general health rating question is not needed because the identical question is asked as part of these surveys.[10, 11]

Q. Should we be looking at the sub-scales or the composite score?

The VFQ-25 sub-scales are grouped by theme or domain. So, for example, items having to do with

near vision are differentiated from items having to do with other vision activities like distance vision or ocular pain. This does not mean that the items are not highly correlated or that they are psychometrically distinct. What it does mean is that researchers should beforehand carefully consider which vision-specific domains are most likely to be influenced by a particular disease and/or treatment and then focus on the results from those sub-scales to support their findings.

The composite score is best used in situations where an overall measure of vision-targeted health related quality of life is desired. For example, in studies where it is not clear what the specific impact of ocular disease or a new treatment might be. Also, in situations where differences can be hypothesized between groups

beforehand across multiple sub-scales but the overall sample size of the study is relatively small, because it is likely that the error term for the composite score is likely to be smaller than for any given sub-scale, it may be more efficient to represent these differences as a single score.

Q. What benefit is there to using the VFQ-25 over a measure more specific to a particular disease, like the Activity of Daily Vision Scale (ADVS)[10] for persons with age-related cataracts?

The VFQ-25 contains items that are very similar to items found in other vision-targeted measure like the ADVS that are more task oriented. However, whereas the ADVS was designed specifically to assess a set of activities most relevant to patients undergoing cataract surgery, the VFQ-25 expands the range of activities to measure the impact of ocular disease on broader domains of health such as social and emotional well-being. Serious ocular diseases that lead to irreversible loss of vision are likely to impact dimensions of a person's life beyond simple tasks such as driving or reading the newspaper, and similarly, by preserving vision, many successful interventions also will impact persons' lives at this more global level. Especially in these situations, use of the VFQ-25 should be considered.

Q. Why does the response to item 15b, "stopped driving due to vision and other reasons", generate a missing score for the subsequent driving items?

Driving items 15, 15a, and 15b are filter questions designed to specify whether a person has ever driven a car, and if so, whether they are currently driving or if they have stopped. If people have never driven a car, then, of course, their answers should be set to missing for all driving items. Similarly, this also applies to people who

have stopped driving for other reasons not due to vision. However, in the course of pilot testing the field test participants wanted this additional mixed response option. It was our decision that although persons did indeed report not driving due to vision, it was not clear how much of a role the “other” reason also played in this decision. Therefore, we set the scoring criteria for this response to be missing for all subsequent driving items to be absolutely sure that all driving responses reflected only problems with vision. Should researchers wish to change this response option to allow persons to answer subsequent driving items (currently there is a skip to item #17), this change should be noted in subsequent publications.

References

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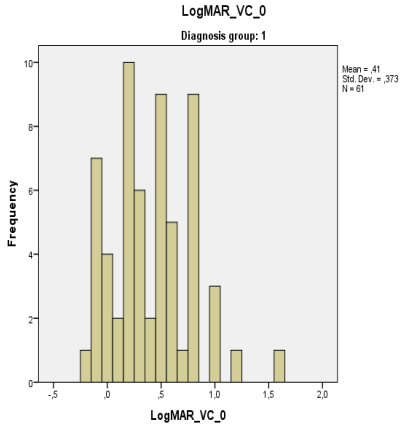
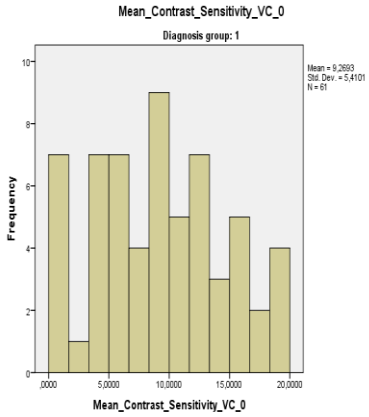
Attachments include:

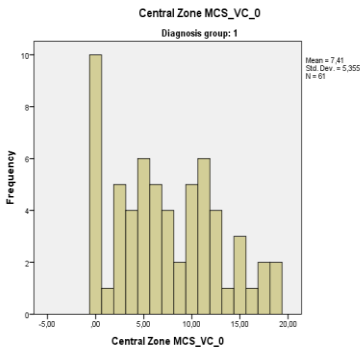
NEI VFQ-25 (IA = Interviewer-Administered format) (SA = Self-Administered format)

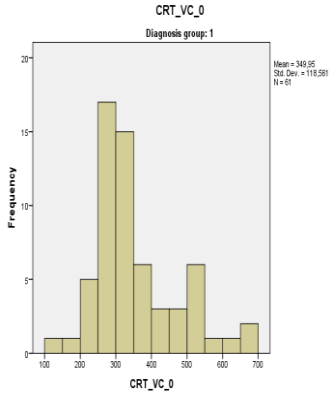
Appendix III -Normality distribution histograms

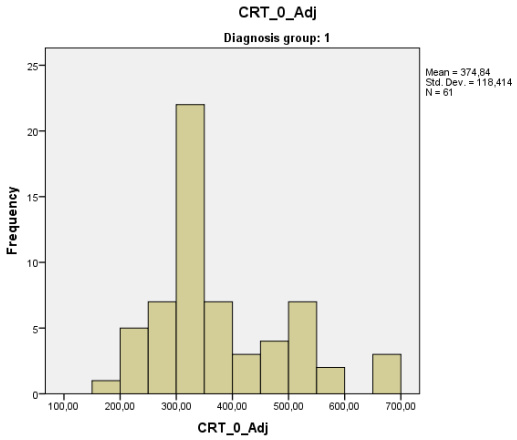
Histogram







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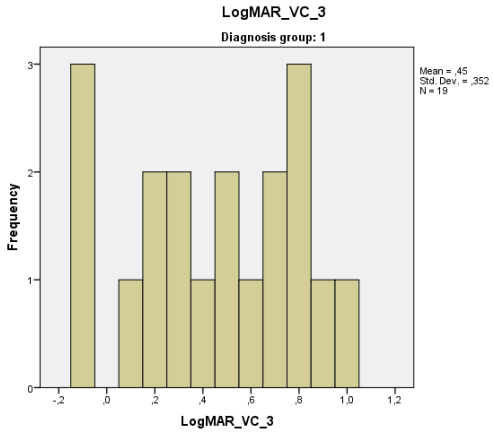
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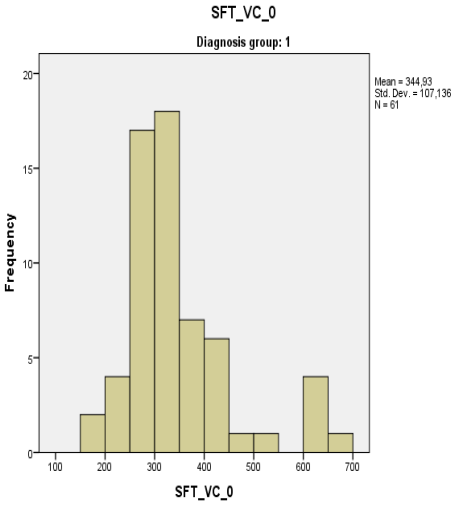
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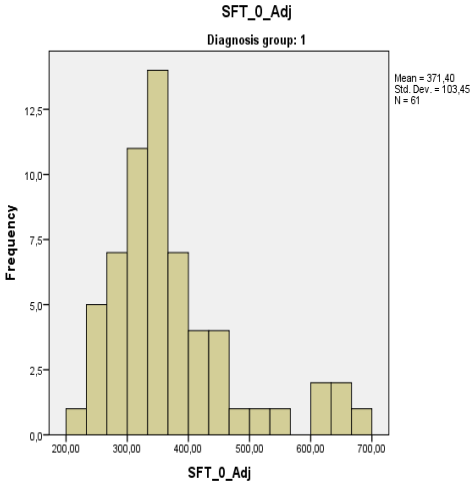
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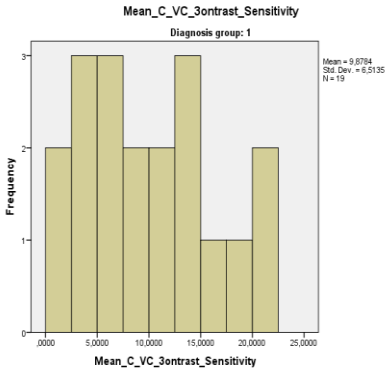
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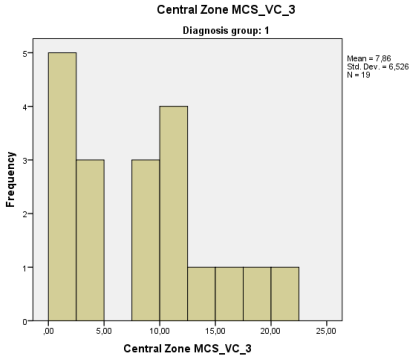
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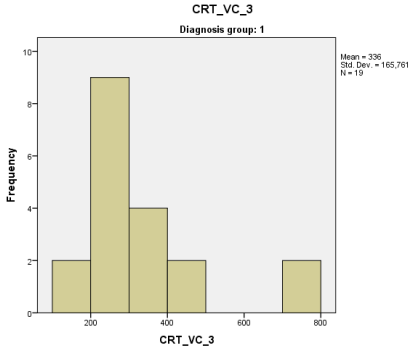
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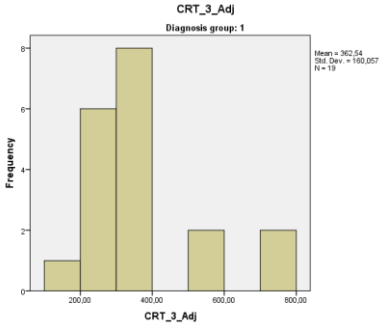
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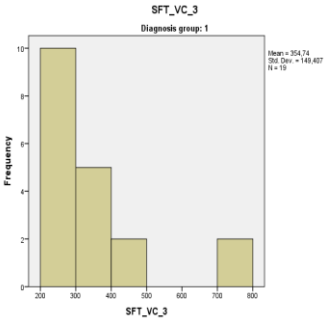
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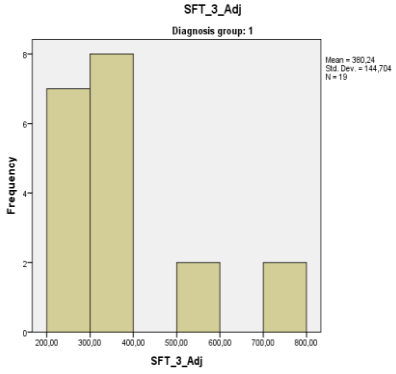
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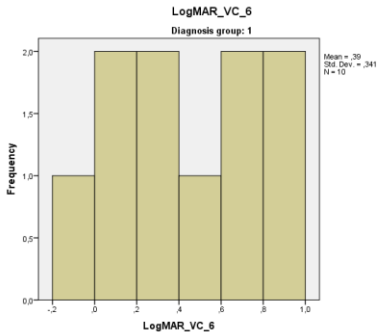
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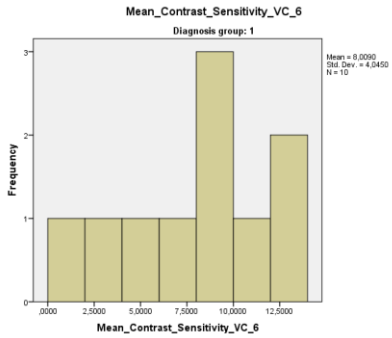
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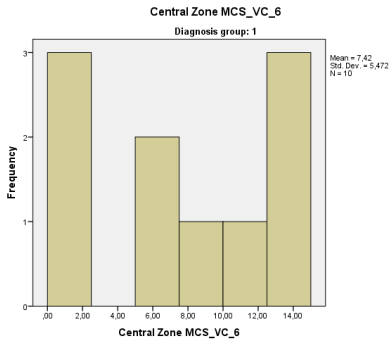
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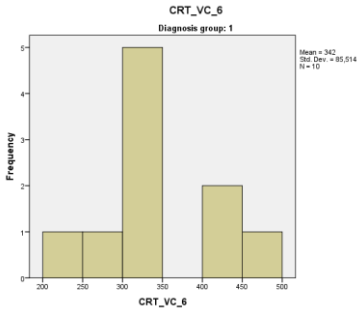
Central Zone MCS_VC_6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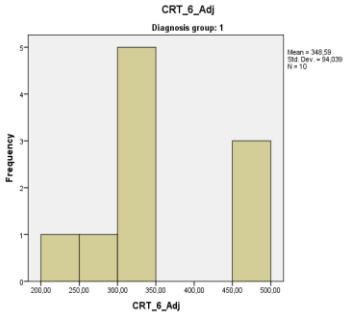
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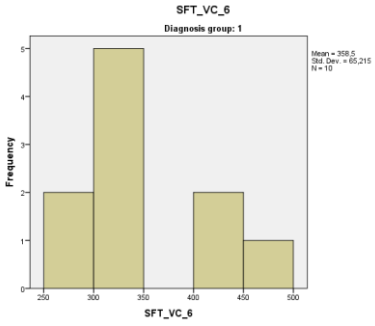
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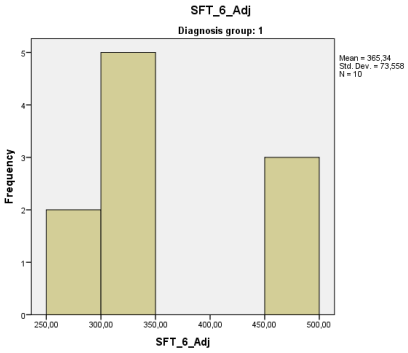
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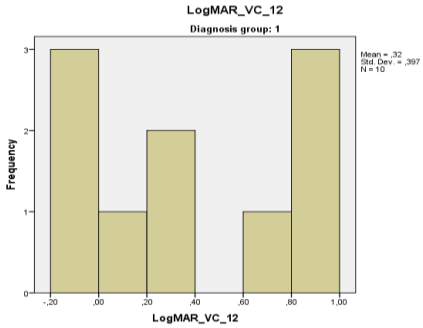
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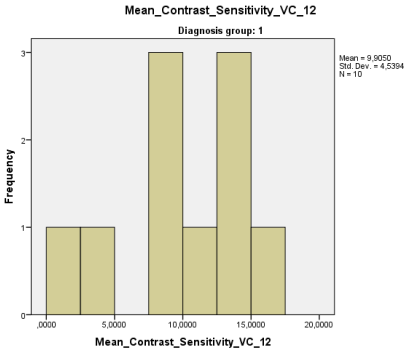
LogMAR_VC_12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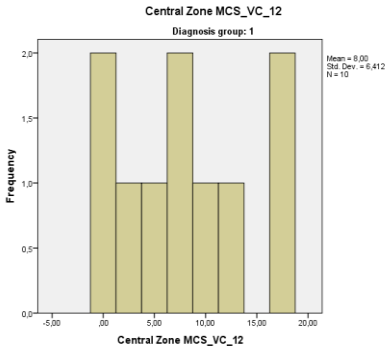
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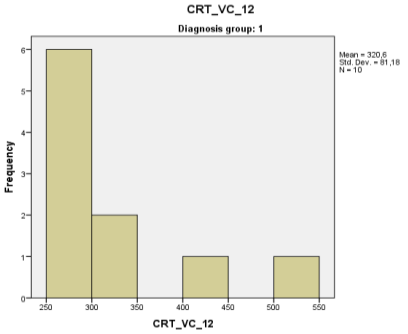
Frequency
Central Zone MCS_VC_12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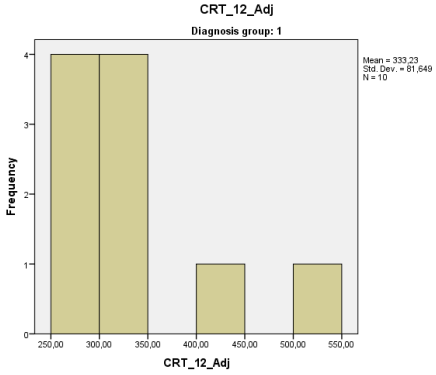
Frequency
CRT_VC_12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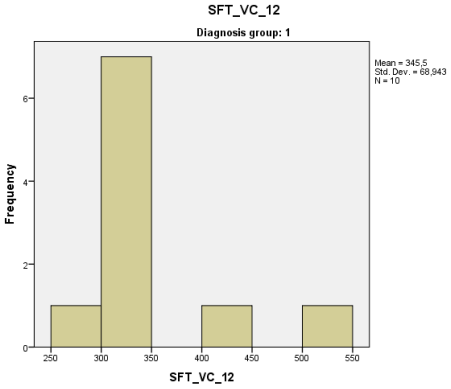
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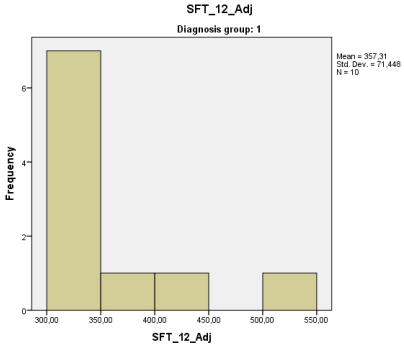
SFT_VC_12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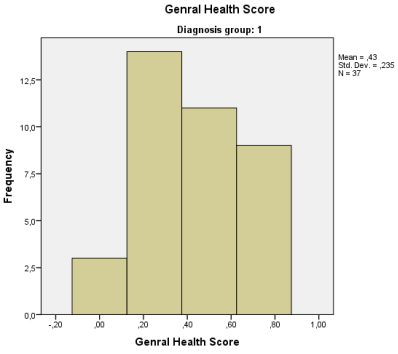
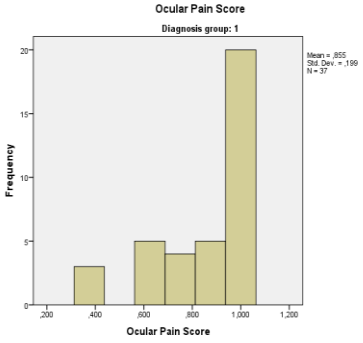
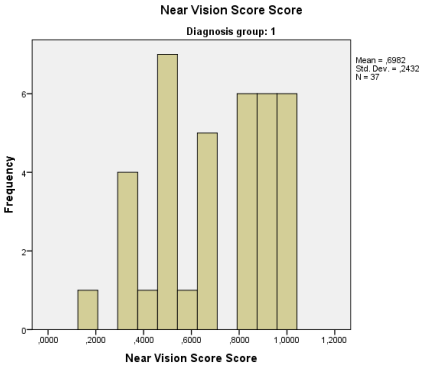
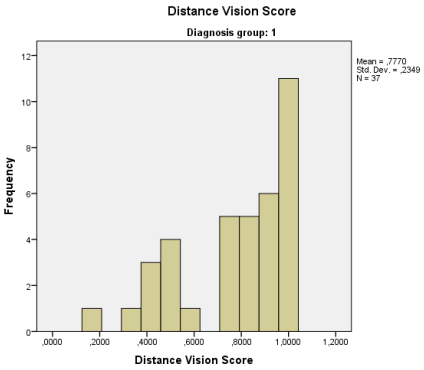
Frequency
SFT_12_Adj


Genral Health Score
Diagnosis group: 1
Mean = ,43
Std. Dev. = ,235
N = 37
Frequency
Genral Health Score

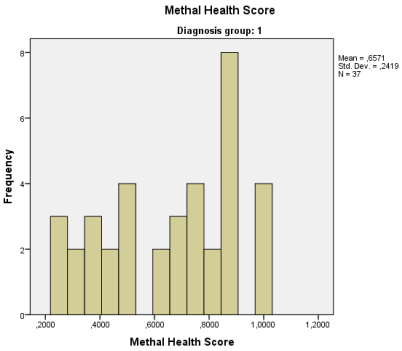

General Vision Score
Diagnosis group: 1
Mean = ,53
Std. Dev. = ,175
N = 37
Frequency
General Vision Score

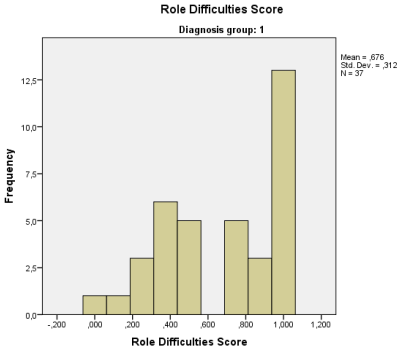

Ocular Pain Score
Diagnosis group: 1
Mean = ,855
Std. Dev. = ,199
N = 37
Frequency
Ocular Pain Score

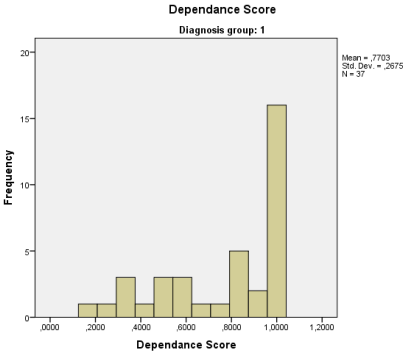

Near Vision Score Score
Diagnosis group: 1
Mean = ,6982
Std. Dev. = ,2432
N = 37
Frequency
Near Vision Score Score

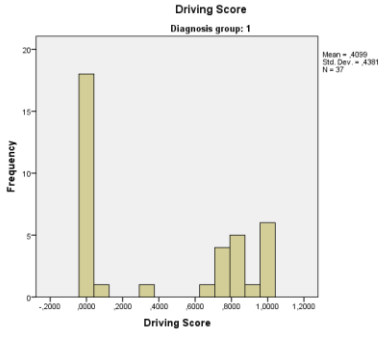

Distance Vision Score
Diagnosis group: 1
Mean = ,7770
Std. Dev. = ,2349
N = 37
Frequency
Distance Vision Score

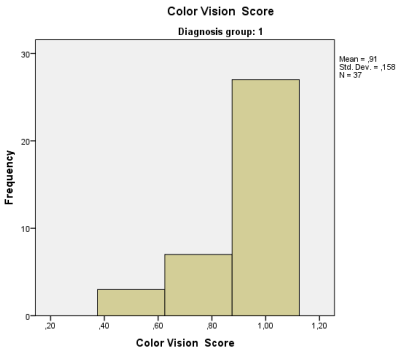

Score Social Score
Diagnosis group: 1
Mean = ,845
Std. Dev. = ,203
N = 37
Frequency
Score Social Score

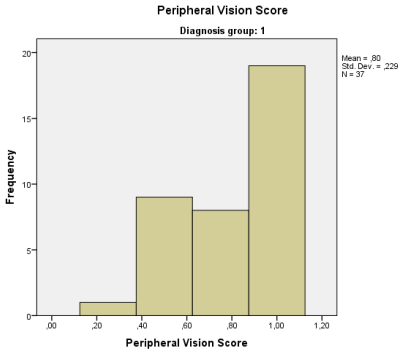

Methal Health Score
Diagnosis group: 1
Mean = ,8571
Std. Dev. = ,2419
N = 37
Frequency
Methal Health Score

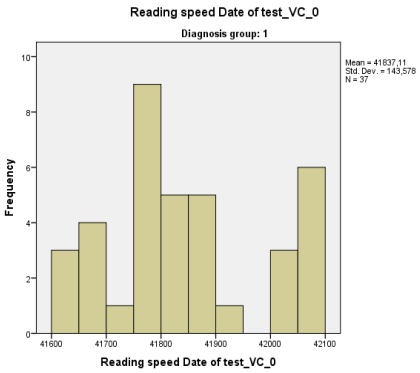

Role Difficulties Score
Diagnosis group: 1
Mean = ,676
Std. Dev. = ,312
N = 37
Frequency
Role Difficulties Score

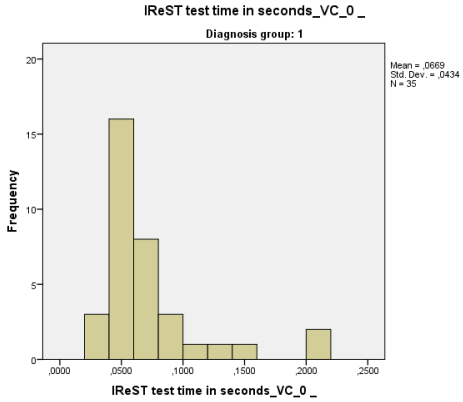

Dependance Score
Diagnosis group: 1
Mean = ,7703
Std. Dev. = ,2675
N = 37
Frequency
Dependance Score

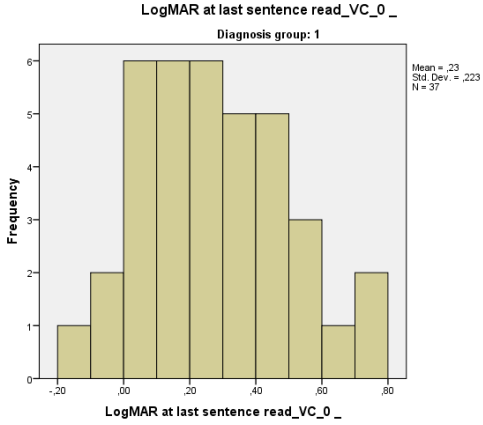

Driving Score
Diagnosis group: 1
Mean = ,4099
Std. Dev. = ,4381
N = 37
Frequency
Driving Score

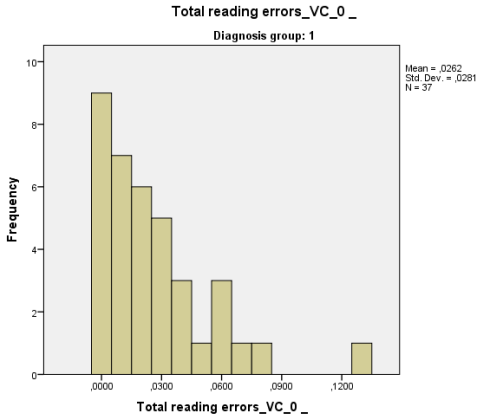

Color Vision Score
Diagnosis group: 1
Mean = ,91
Std. Dev. = ,158
N = 37
Frequency
Color Vision Score

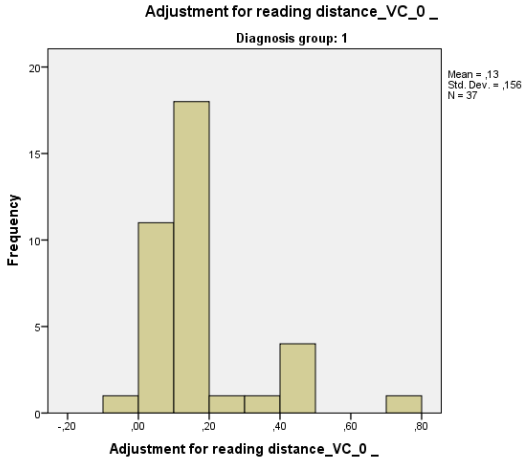

Peripheral Vision Score
Diagnosis group: 1
Mean = ,80
Std. Dev. = ,229
N = 37
Frequency
Peripheral Vision Score

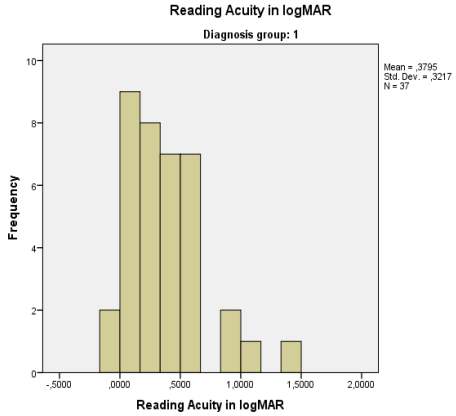

Reading speed Date of test_VC_0
Diagnosis group: 1
Mean = 41837,11
Std. Dev. = 143,578
N = 37
Frequency
Reading speed Date of test_VC_0

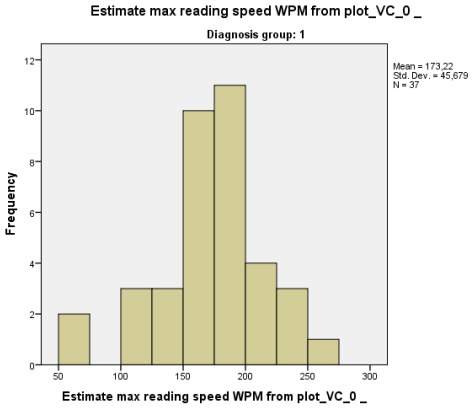

IReST test time in seconds_VC_0 _
Diagnosis group: 1
Mean = ,0669
Std. Dev. = ,0434
N = 35
Frequency
IReST test time in seconds_VC_0 _

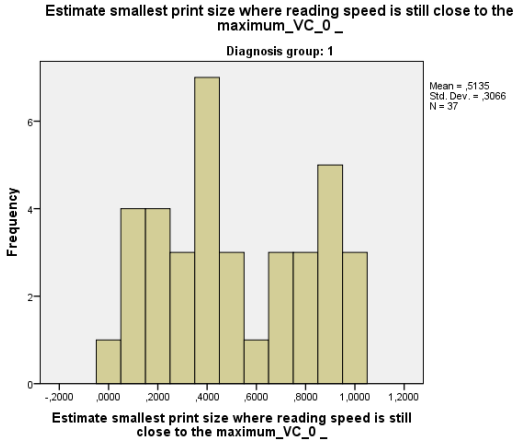

LogMAR at last sentence read_VC_0 _
Diagnosis group: 1
Mean = ,23
Std. Dev. = ,223
N = 37
Frequency
LogMAR at last sentence read_VC_0 _

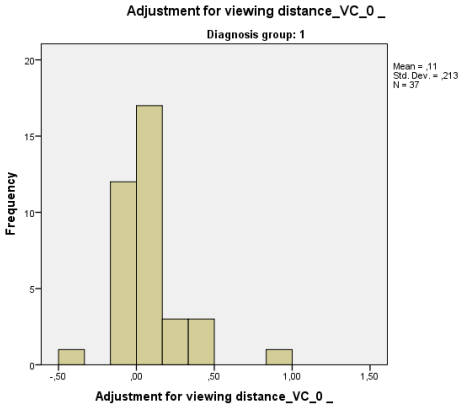

Total reading errors_VC_0 _
Diagnosis group: 1
Mean = ,0262
Std. Dev. = ,0281
N = 37
Frequency
Total reading errors_VC_0 _

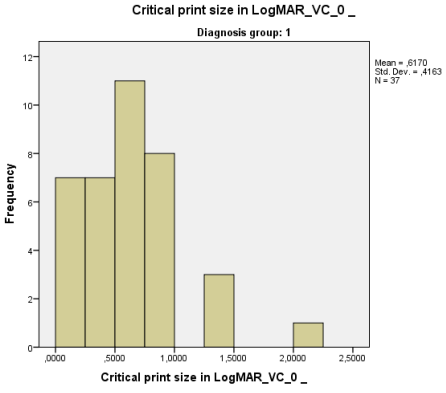

Adjustment for reading distance_VC_0 _
Diagnosis group: 1
Mean = ,13
Std. Dev. = ,156
N = 37
Frequency
Adjustment for reading distance_VC_0 _

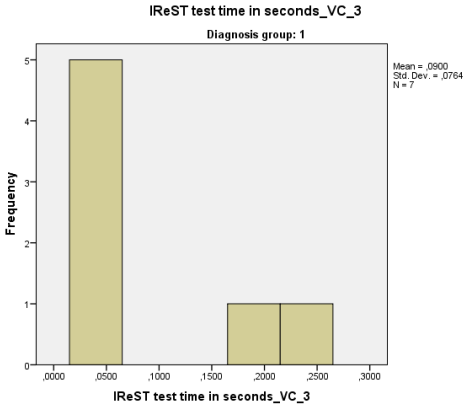

Reading Acuity in logMAR
Diagnosis group: 1
Mean = ,3795
Std. Dev. = ,3217
N = 37
Frequency
Reading Acuity in logMAR

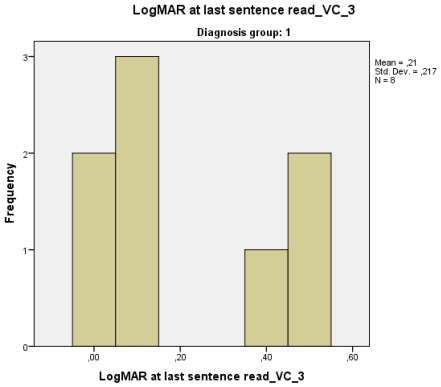

Estimate max reading speed WPM from plot_VC_0 _
Diagnosis group: 1
Mean = 173,22
Std. Dev. = 45,679
N = 37
Frequency
Estimate max reading speed WPM from plot_VC_0 _

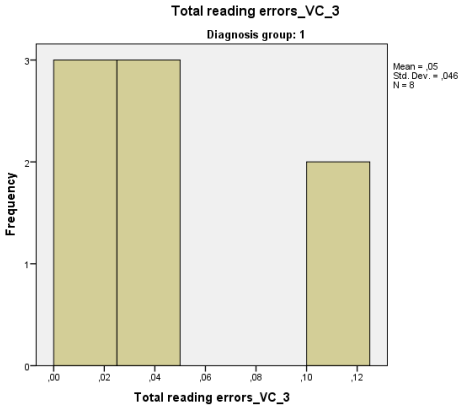

Estimate smallest print size where reading speed is still close to the maximum_VC_0 _
Diagnosis group: 1
Mean = ,5135
Std. Dev. = ,3066
N = 37
Frequency
Estimate smallest print size where reading speed is still close to the maximum_VC_0 _

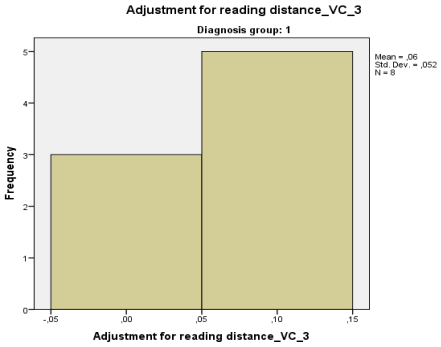

Adjustment for viewing distance_VC_0 _
Diagnosis group: 1
Mean = ,11
Std. Dev. = ,213
N = 37
Frequency
Adjustment for viewing distance_VC_0 _

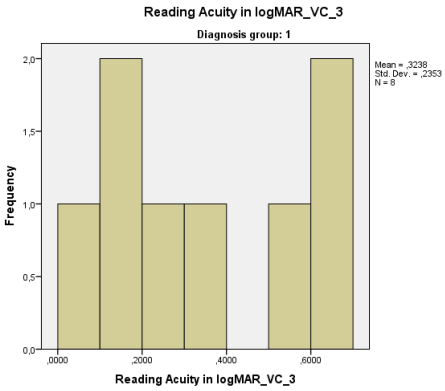

Critical print size in LogMAR_VC_0 _
Diagnosis group: 1
Mean = ,6170
Std. Dev. = ,4163
N = 37
Frequency
Critical print size in LogMAR_VC_0 _

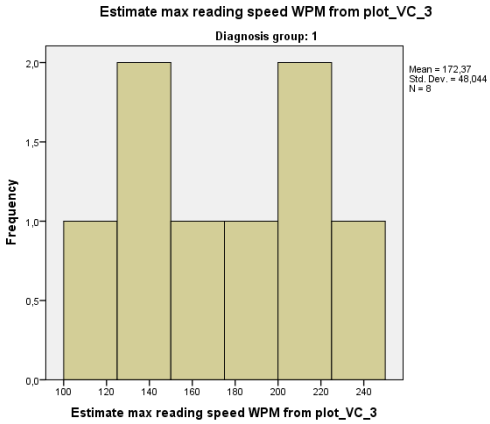

IReST test time in seconds_VC_3
Diagnosis group: 1
Mean = ,0900
Std. Dev. = ,0764
N = 7
Frequency
IReST test time in seconds_VC_3

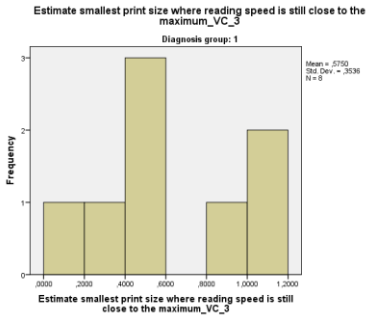

LogMAR at last sentence read_VC_3
Diagnosis group: 1
Mean = ,21
Std. Dev. = ,217
N = 8
Frequency
LogMAR at last sentence read_VC_3

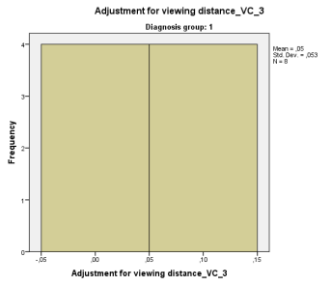

Total reading errors_VC_3
Diagnosis group: 1
Mean = ,05
Std. Dev. = ,046
N = 8
Frequency
Total reading errors_VC_3

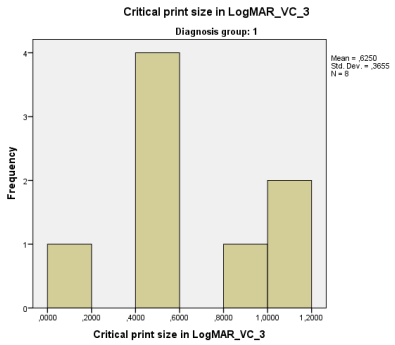

Adjustment for reading distance_VC_3
Diagnosis group: 1
Mean = ,06
Std. Dev. = ,052
N = 8
Frequency
Adjustment for reading distance_VC_3

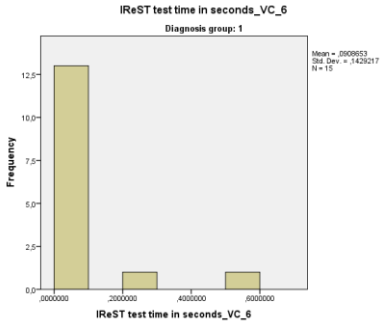

Reading Acuity in logMAR_VC_3
Diagnosis group: 1
Mean = ,3238
Std. Dev. = ,2353
N = 8
Frequency
Reading Acuity in logMAR_VC_3

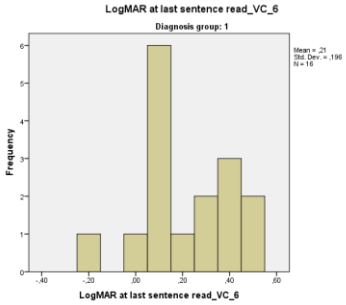

Estimate max reading speed WPM from plot_VC_3
Diagnosis group: 1
Mean = 172,37
Std. Dev. = 48,044
N = 8
Frequency
Estimate max reading speed WPM from plot_VC_3

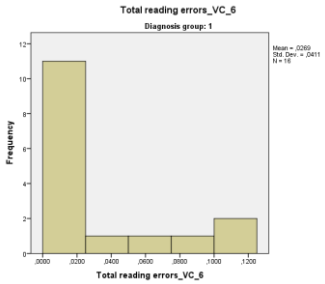

Estimate smallest print size where reading speed is still close to the maximum_VC_3
Diagnosis group: 1
Mean = .5750
Std. Dev. = .3536
N = 8
Frequency
Estimate smallest print size where reading speed is still close to the maximum_VC_3

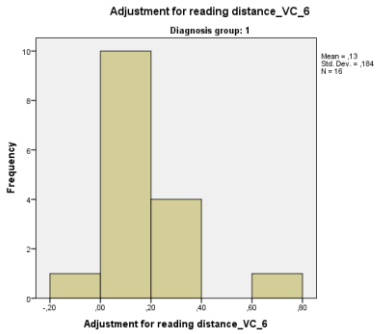

Adjustment for viewing distance_VC_3
Diagnosis group: 1
Mean = .05
Std. Dev. = .053
N = 8
Frequency
Adjustment for viewing distance_VC_3

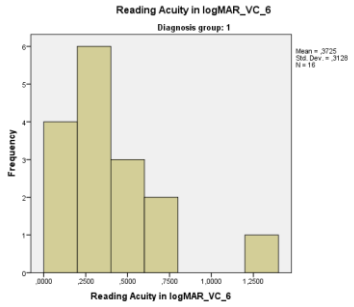

Critical print size in LogMAR_VC_3
Diagnosis group: 1
Mean = .6250
Std. Dev. = .3655
N = 8
Frequency
Critical print size in LogMAR_VC_3

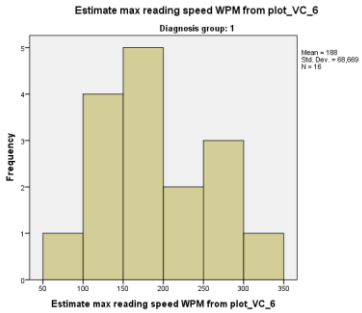

IReST test time in seconds_VC_6
Diagnosis group: 1
Mean = .0909853
Std. Dev. = .1429217
N = 15
Frequency
IReST test time in seconds_VC_6

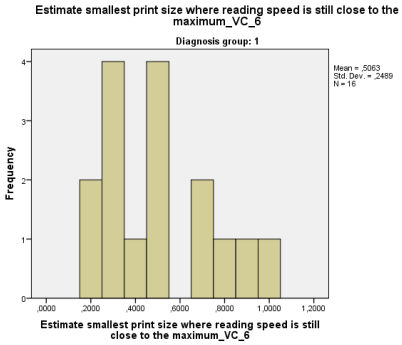

LogMAR at last sentence read_VC_6
Diagnosis group: 1
Mean = .21
Std. Dev. = .196
N = 16
Frequency
LogMAR at last sentence read_VC_6

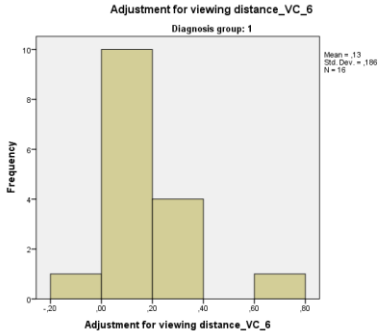

Total reading errors_VC_6
Diagnosis group: 1
Mean = .0269
Std. Dev. = .0411
N = 16
Frequency
Total reading errors_VC_6

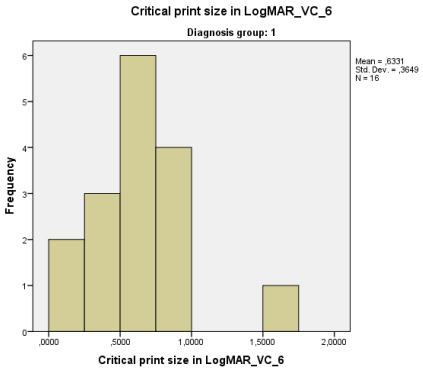

Adjustment for reading distance_VC_6
Diagnosis group: 1
Mean = ,13
Std. Dev. = ,184
N = 16
Frequency
Adjustment for reading distance_VC_6

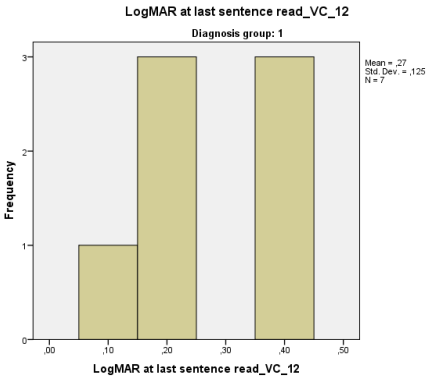

Reading Acuity in logMAR_VC_6
Diagnosis group: 1
Mean = ,3725
Std. Dev. = ,3128
N = 16
Frequency
Reading Acuity in logMAR_VC_6

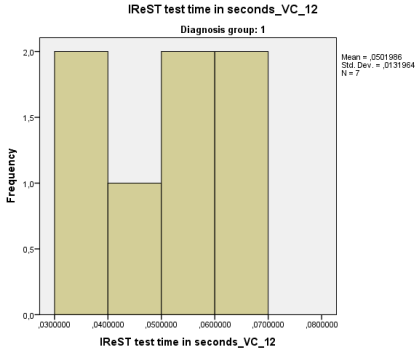

Estimate max reading speed WPM from plot_VC_6
Diagnosis group: 1
Mean = 198
Std. Dev. = 68,669
N = 16
Frequency
Estimate max reading speed WPM from plot_VC_6

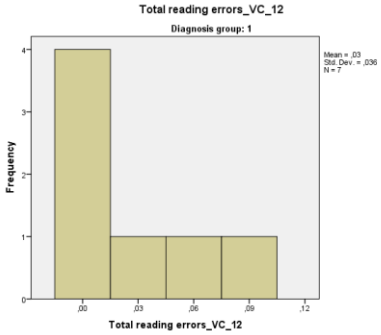

Estimate smallest print size where reading speed is still close to the maximum_VC_6
Diagnosis group: 1
Mean = ,5063
Std. Dev. = ,2489
N = 16
Frequency
Estimate smallest print size where reading speed is still close to the maximum_VC_6

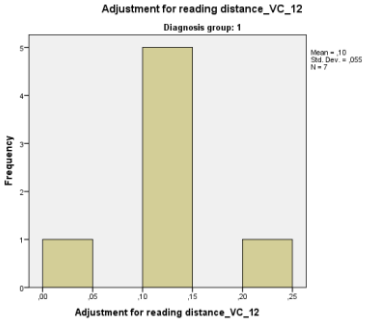

Adjustment for viewing distance_VC_6
Diagnosis group: 1
Mean = ,13
Std. Dev. = ,186
N = 16
Frequency
Adjustment for viewing distance_VC_6

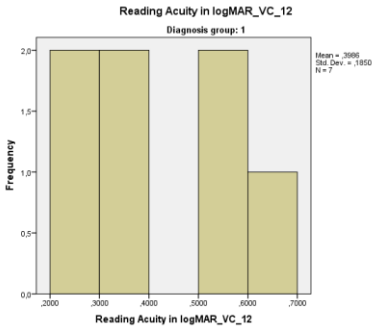

Critical print size in LogMAR_VC_6
Diagnosis group: 1
Mean = ,6331
Std. Dev. = ,3649
N = 16
Frequency
Critical print size in LogMAR_VC_6

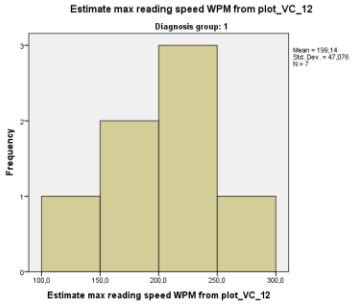

LogMAR at last sentence read_VC_12
Diagnosis group: 1
Mean = ,27
Std. Dev. = ,125
N = 7
Frequency
LogMAR at last sentence read_VC_12

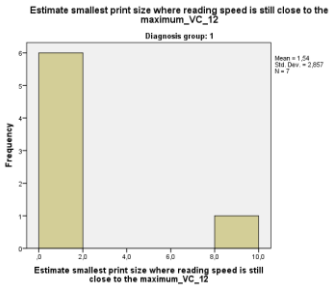

IReST test time in seconds_VC_12
Diagnosis group: 1
Mean = ,0501986
Std. Dev. = ,0131964
N = 7
Frequency
IReST test time in seconds_VC_12

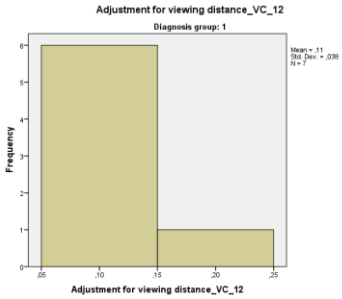

Total reading errors_VC_12
Diagnosis group: 1
Mean = ,03
Std. Dev. = ,036
N = 7
Frequency
Total reading errors_VC_12

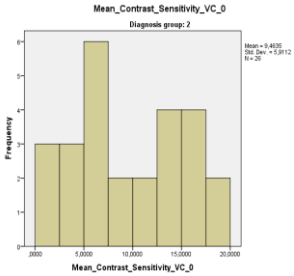

Adjustment for reading distance_VC_12
Diagnosis group: 1
Mean = ,10
Std. Dev. = ,055
N = 7
Frequency
Adjustment for reading distance_VC_12

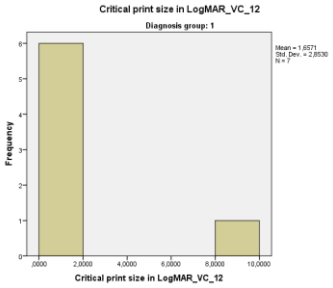

Reading Acuity in logMAR_VC_12
Diagnosis group: 1
Mean = ,3986
Std. Dev. = ,1850
N = 7
Frequency
Reading Acuity in logMAR_VC_12

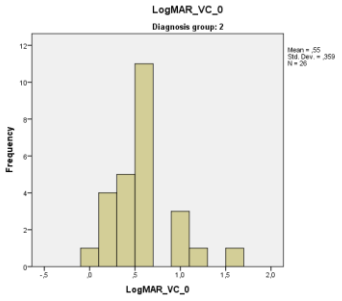

Estimate max reading speed WPM from plot_VC_12
Diagnosis group: 1
Mean = 199,14
Std. Dev. = 47,076
N = 7
Frequency
Estimate max reading speed WPM from plot_VC_12

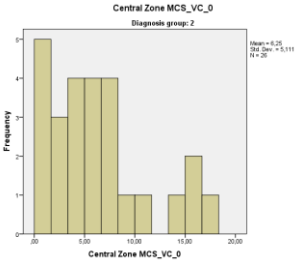

Estimate smallest print size where reading speed is still close to the maximum_VC_12
Diagnosis group: 1
Mean = 1.54
Std. Dev. = 2.857
N = 7
Frequency
Estimate smallest print size where reading speed is still close to the maximum_VC_12

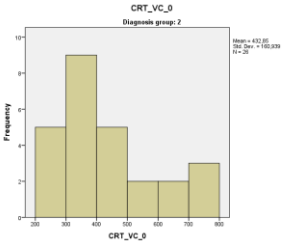

Adjustment for viewing distance_VC_12
Diagnosis group: 1
Mean = .11
Std. Dev. = .038
N = 7
Frequency
Adjustment for viewing distance_VC_12

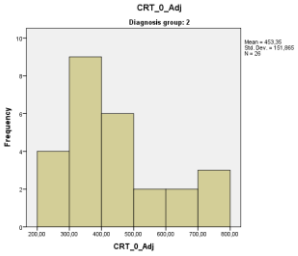

Mean_Contrast_Sensitivity_VC_0
Diagnosis group: 2
Mean = 9.4635
Std. Dev. = 5.9112
N = 26
Frequency
Mean_Contrast_Sensitivity_VC_0

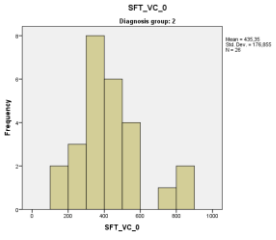

Critical print size in LogMAR_VC_12
Diagnosis group: 1
Mean = 1.6571
Std. Dev. = 2.8530
N = 7
Frequency
Critical print size in LogMAR_VC_12

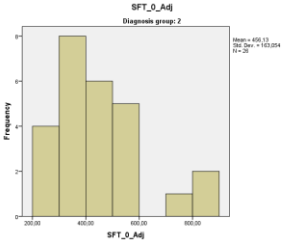

LogMAR_VC_0
Diagnosis group: 2
Mean = .55
Std. Dev. = .359
N = 26
Frequency
LogMAR_VC_0

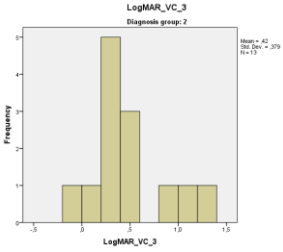

Central Zone MCS_VC_0
Diagnosis group: 2
Mean = 6.25
Std. Dev. = 5.111
N = 26
Frequency
Central Zone MCS_VC_0

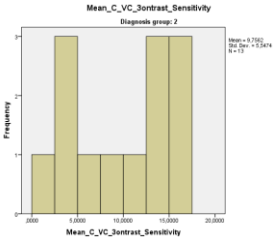

CRT_VC_0
Diagnosis group: 2
Mean = 432.85
Std. Dev. = 160.939
N = 26
Frequency
CRT_VC_0

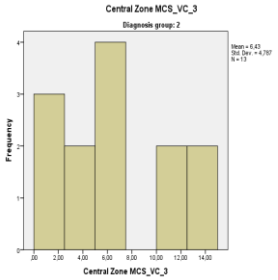

CRT_0_Adj
Diagnosis group: 2
Mean = 453.35
Std. Dev. = 151.865
N = 26
Frequency
CRT_0_Adj

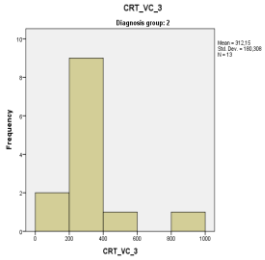

SFT_VC_0
Diagnosis group: 2
Mean = 436.35
Std. Dev. = 176.855
N = 26
Frequency
SFT_VC_0

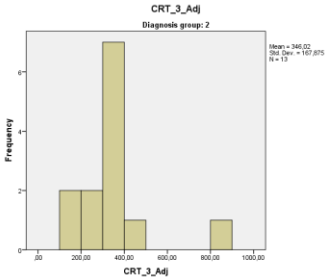

SFT_0_Adj
Diagnosis group: 2
Mean = 459.13
Std. Dev. = 163.054
N = 26
Frequency
SFT_0_Adj

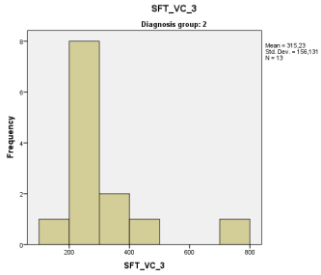

LogMAR_VC_3
Diagnosis group: 2
Mean = .42
Std. Dev. = .379
N = 13
Frequency
LogMAR_VC_3

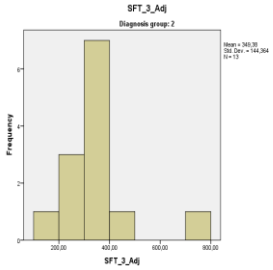

Mean_C_VC_3ontrast_Sensitivity
Diagnosis group: 2
Mean = 9.7582
Std. Dev. = 5.5474
N = 13
Frequency
Mean_C_VC_3ontrast_Sensitivity

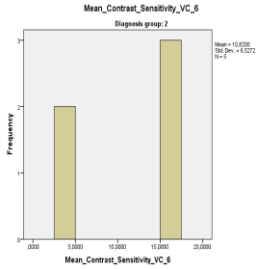

Central Zone MCS_VC_3
Diagnosis group: 2
Frequency
Central Zone MCS_VC_3

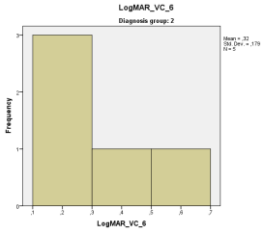

CRT_VC_3
Diagnosis group: 2
Frequency
CRT_VC_3

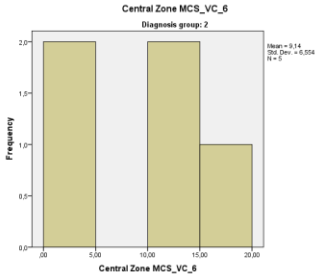

CRT_3_Adj
Diagnosis group: 2
Frequency
CRT_3_Adj

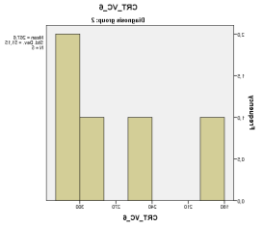

SFT_VC_3
Diagnosis group: 2
Frequency
SFT_VC_3

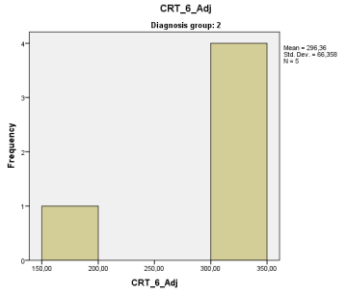

SFT_3_Adj
Diagnosis group: 2
Frequency
SFT_3_Adj

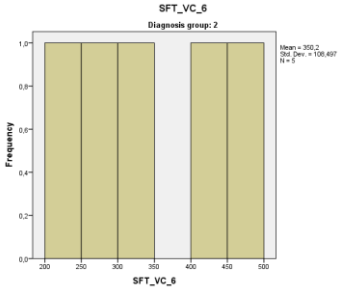

Mean_Contrast_Sensitivity_VC_6
Diagnosis group: 2
Frequency
Mean_Contrast_Sensitivity_VC_6

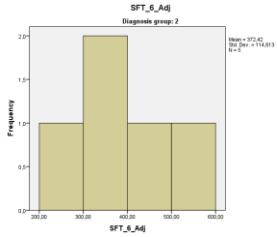

LogMAR_VC_6
Diagnosis group: 2
Frequency
LogMAR_VC_6

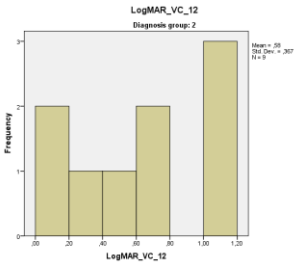

Central Zone MCS_VC_6
Diagnosis group: 2
Frequency
Central Zone MCS_VC_6

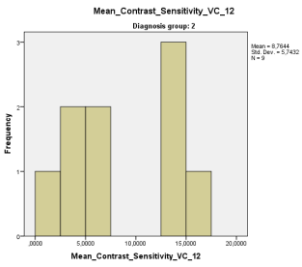


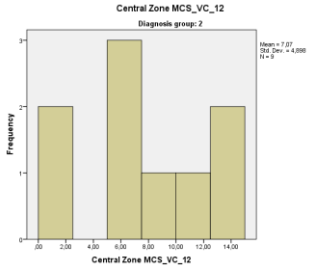

CRT_6_Adj
Diagnosis group: 2
Frequency
CRT_6_Adj

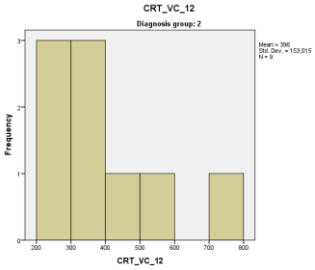

SFT_VC_6
Diagnosis group: 2
Frequency
SFT_VC_6

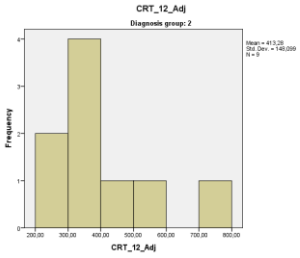

SFT_6_Adj
Diagnosis group: 2
Frequency
SFT_6_Adj

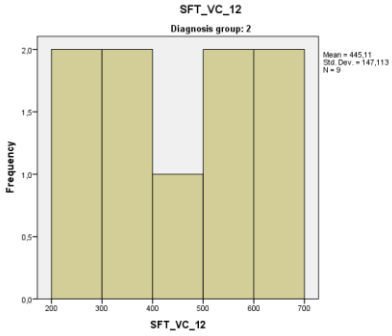

LogMAR_VC_12
Diagnosis group: 2
Frequency
LogMAR_VC_12

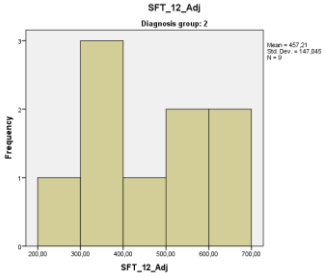

Mean_Contrast_Sensitivity_VC_12
Diagnosis group: 2
Frequency
Mean_Contrast_Sensitivity_VC_12


Central Zone MCS_VC_12
Diagnosis group: 2
Frequency
Central Zone MCS_VC_12


CRT_VC_12
Diagnosis group: 2
Frequency
CRT_VC_12

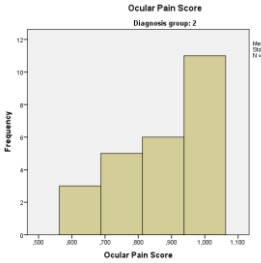

CRT_12_Adj
Diagnosis group: 2
Frequency
CRT_12_Adj

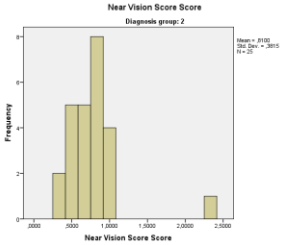

SFT_VC_12
Diagnosis group: 2
Frequency
SFT_VC_12

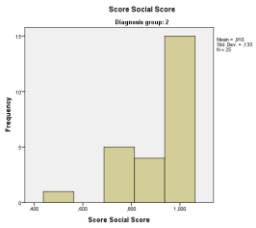

SFT_12_Adj
Diagnosis group: 2
Frequency
SFT_12_Adj


Genral Health Score
Diagnosis group: 2
Frequency
Genral Health Score

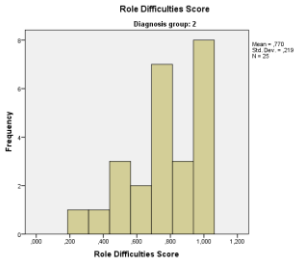

General Vision Score
Diagnosis group: 2
Frequency
General Vision Score

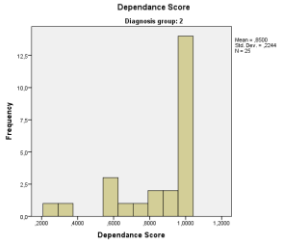

Ocular Pain Score
Diagnosis group: 2
Frequency
Ocular Pain Score

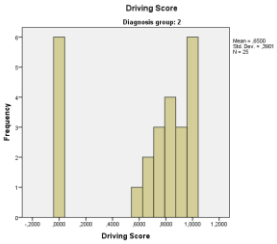

Near Vision Score Score
Diagnosis group: 2
Frequency
Near Vision Score Score

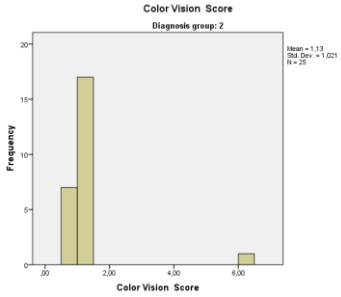

Score Social Score
Diagnosis group: 2
Frequency
Score Social Score

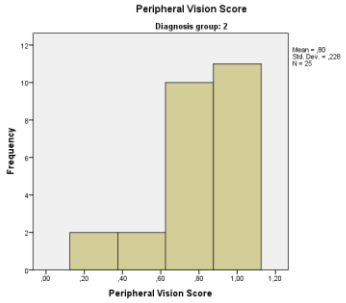

Methal Health Score
Diagnosis group: 2
Mean = .7100
Std. Dev. = .2157
N = 25
Frequency
Methal Health Score

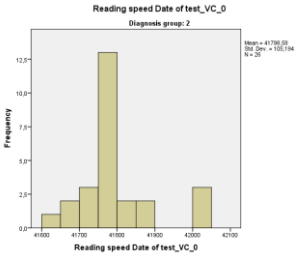

Role Difficulties Score
Diagnosis group: 2
Mean = .770
Std. Dev. = .219
N = 25
Frequency
Role Difficulties Score

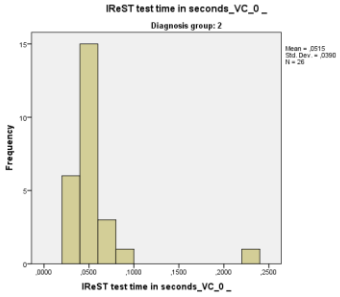

Dependance Score
Diagnosis group: 2
Mean = .8000
Std. Dev. = .2244
N = 25
Frequency
Dependance Score

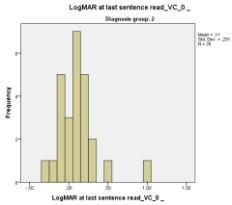

Driving Score
Diagnosis group: 2
Mean = .6500
Std. Dev. = .3661
N = 25
Frequency
Driving Score

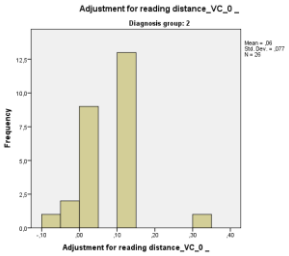

Color Vision Score
Diagnosis group: 2
Mean = 1.13
Std. Dev. = 1.021
N = 25
Frequency
Color Vision Score

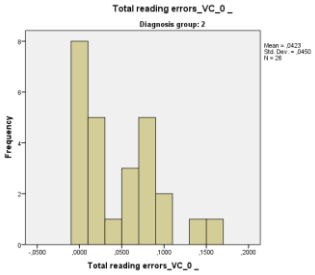

Peripheral Vision Score
Diagnosis group: 2
Mean = .80
Std. Dev. = .228
N = 25
Frequency
Peripheral Vision Score

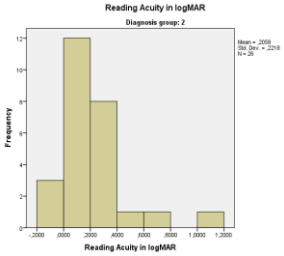

Reading speed Date of test_VC_0
Diagnosis group: 2
Mean = 41796.08
Std. Dev. = 105.194
N = 26
Frequency
Reading speed Date of test_VC_0

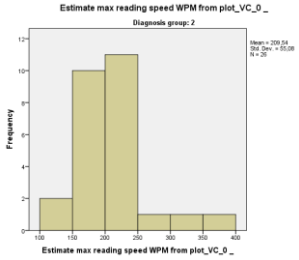

IReST test time in seconds_VC_0 _
Diagnosis group: 2
Mean = .0515
Std. Dev. = .03990
N = 26
Frequency
IReST test time in seconds_VC_0 _

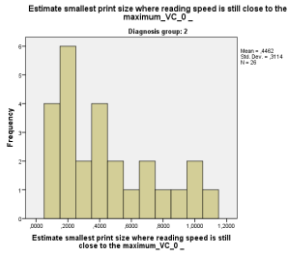

LogMAR at last sentence read_VC_0 _
Diagnosis group: 2
Frequency
LogMAR at last sentence read_VC_0 _

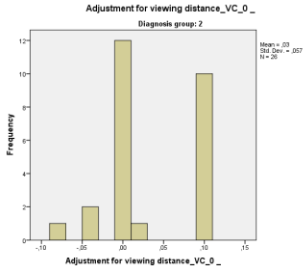

Adjustment for reading distance_VC_0 _
Diagnosis group: 2
Mean = .06
Std. Dev. = .077
N = 26
Frequency
Adjustment for reading distance_VC_0 _

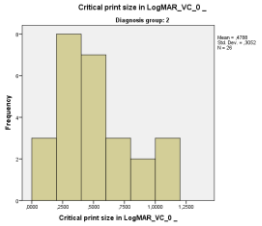

Total reading errors_VC_0 _
Diagnosis group: 2
Mean = .0423
Std. Dev. = .0450
N = 26
Frequency
Total reading errors_VC_0 _


Reading Acuity in logMAR
Diagnosis group: 2
Mean = .2000
Std. Dev. = .2218
N = 26
Frequency
Reading Acuity in logMAR

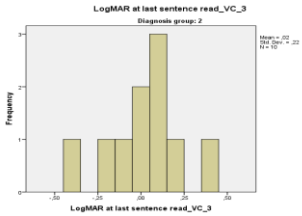

Estimate max reading speed WPM from plot_VC_0 _
Diagnosis group: 2
Frequency
Estimate max reading speed WPM from plot_VC_0 _

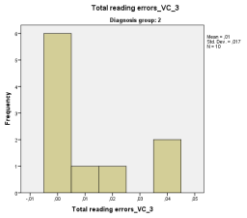

Estimate smallest print size where reading speed is still close to the maximum_VC_0 _
Diagnosis group: 2
Frequency
Estimate smallest print size where reading speed is still close to the maximum_VC_0 _

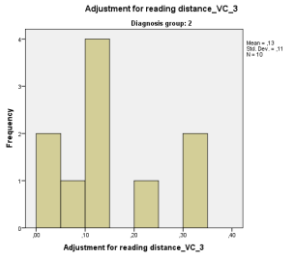

Adjustment for viewing distance_VC_0 _
Diagnosis group: 2
Frequency
Adjustment for viewing distance_VC_0 _

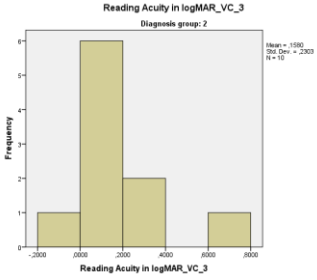

Critical print size in LogMAR_VC_0 _
Diagnosis group: 2
Frequency
Critical print size in LogMAR_VC_0 _

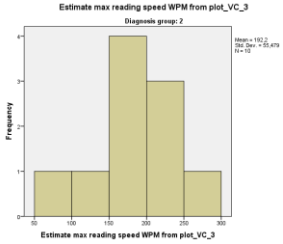

IReST test time in seconds_VC_3
Diagnosis group: 2
Frequency
IReST test time in seconds_VC_3

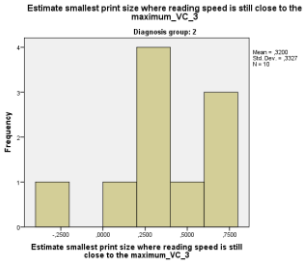

LogMAR at last sentence read_VC_3
Diagnosis group: 2
Frequency
LogMAR at last sentence read_VC_3

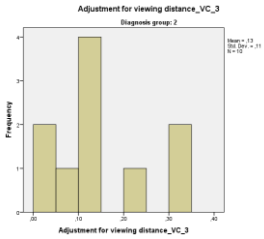

Total reading errors_VC_3
Diagnosis group: 2
Frequency
Total reading errors_VC_3

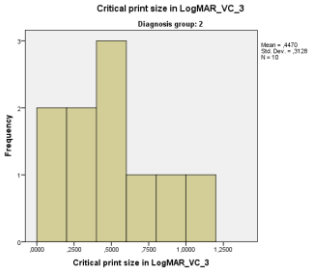

Adjustment for reading distance_VC_3
Diagnosis group: 2
Frequency
Adjustment for reading distance_VC_3

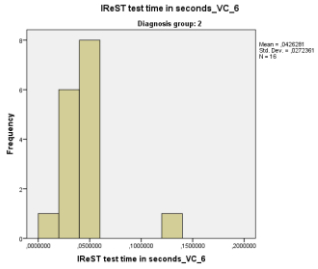

Reading Acuity in logMAR_VC_3
Diagnosis group: 2
Frequency
Reading Acuity in logMAR_VC_3

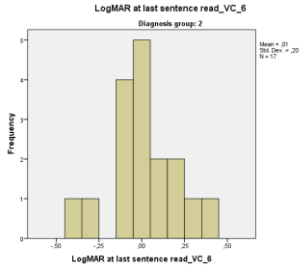

Estimate max reading speed WPM from plot_VC_3
Diagnosis group: 2
Frequency
Estimate max reading speed WPM from plot_VC_3

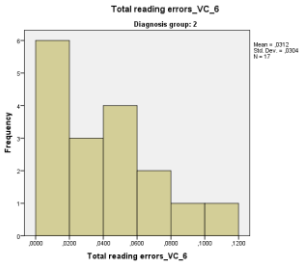

Estimate smallest print size where reading speed is still close to the maximum_VC_3
Diagnosis group: 2
Frequency
Estimate smallest print size where reading speed is still close to the maximum_VC_3

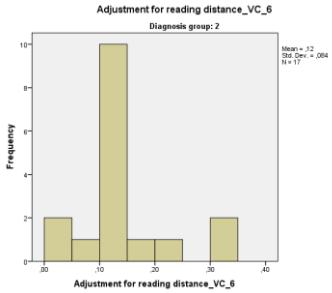

Adjustment for viewing distance_VC_3
Diagnosis group: 2
Frequency
Adjustment for viewing distance_VC_3

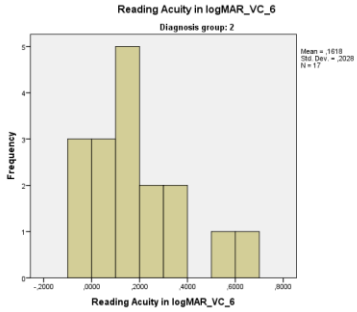

Critical print size in LogMAR_VC_3
Diagnosis group: 2
Mean = .4470
Std. Dev. = .3128
N = 10
Frequency
Critical print size in LogMAR_VC_3

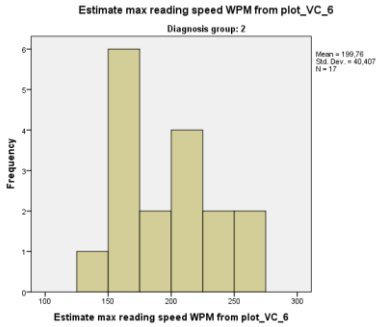

IReST test time in seconds_VC_6
Diagnosis group: 2
Mean = .0426281
Std. Dev. = .0272361
N = 10
Frequency
IReST test time in seconds_VC_6

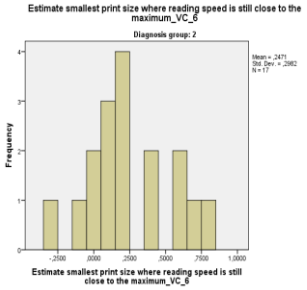

LogMAR at last sentence read_VC_6
Diagnosis group: 2
Mean = .01
Std. Dev. = .20
N = 17
Frequency
LogMAR at last sentence read_VC_6

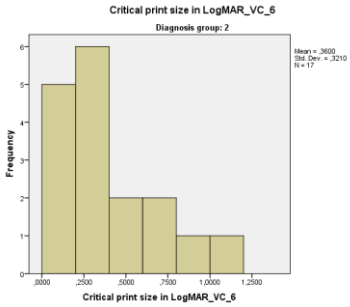

Total reading errors_VC_6
Diagnosis group: 2
Mean = .0312
Std. Dev. = .0304
N = 17
Frequency
Total reading errors_VC_6

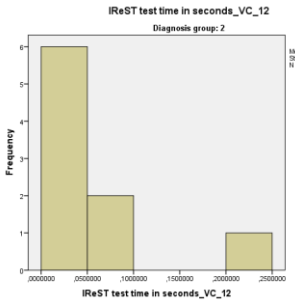

Adjustment for reading distance_VC_6
Diagnosis group: 2
Mean = .12
Std. Dev. = .084
N = 17
Frequency
Adjustment for reading distance_VC_6

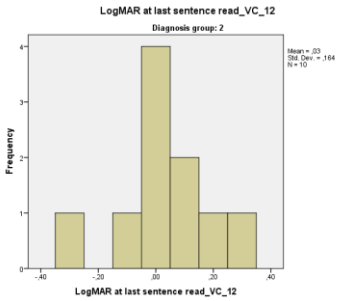

Reading Acuity in logMAR_VC_6
Diagnosis group: 2
Mean = .1618
Std. Dev. = .2028
N = 17
Frequency
Reading Acuity in logMAR_VC_6

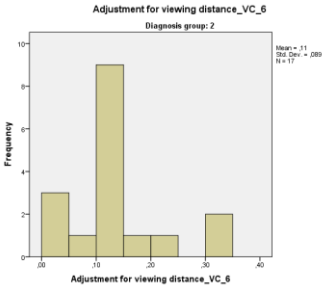

Estimate max reading speed WPM from plot_VC_6
Diagnosis group: 2
Mean = 199.76
Std. Dev. = 40.407
N = 17
Frequency
Estimate max reading speed WPM from plot_VC_6

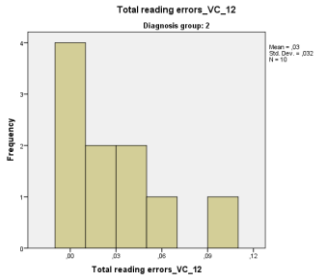

Estimate smallest print size where reading speed is still close to the maximum_VC_6
Diagnosis group: 2
Mean = .2471
Std. Dev. = .2882
N = 17
Frequency
Estimate smallest print size where reading speed is still close to the maximum_VC_6

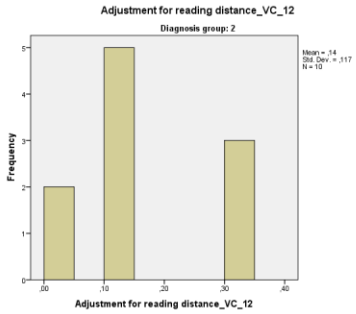

Critical print size in LogMAR_VC_6
Diagnosis group: 2
Mean = .3600
Std. Dev. = .3210
N = 17
Frequency
Critical print size in LogMAR_VC_6

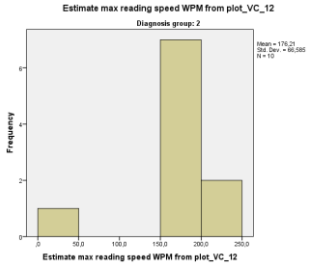

IReST test time in seconds_VC_12
Diagnosis group: 2
Mean = .0608820
Std. Dev. = .0636652
N = 9
Frequency
IReST test time in seconds_VC_12

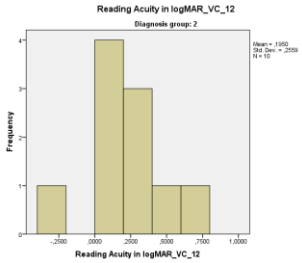

LogMAR at last sentence read_VC_12
Diagnosis group: 2
Mean = .03
Std. Dev. = .164
N = 10
Frequency
LogMAR at last sentence read_VC_12

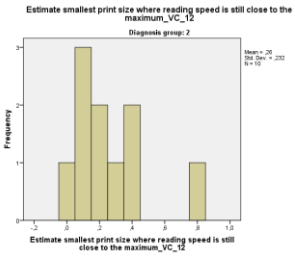

Adjustment for viewing distance_VC_6
Diagnosis group: 2
Mean = .11
Std. Dev. = .089
N = 17
Frequency
Adjustment for viewing distance_VC_6

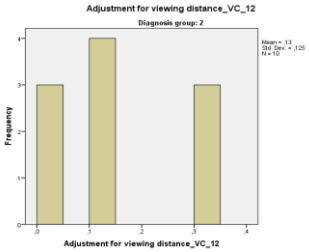

Total reading errors_VC_12
Diagnosis group: 2
Mean = .03
Std. Dev. = .032
N = 10
Frequency
Total reading errors_VC_12

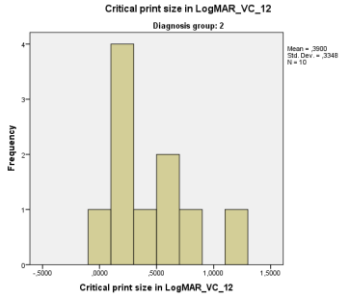

Adjustment for reading distance_VC_12
Diagnosis group: 2
Mean = .14
Std. Dev. = .117
N = 10
Frequency
Adjustment for reading distance_VC_12

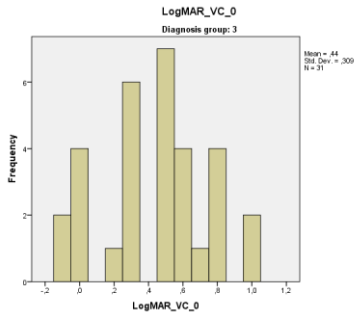

Estimate max reading speed WPM from plot_VC_12
Diagnosis group: 2
Mean = 176.21
Std. Dev. = 66.585
N = 10
Frequency
Estimate max reading speed WPM from plot_VC_12

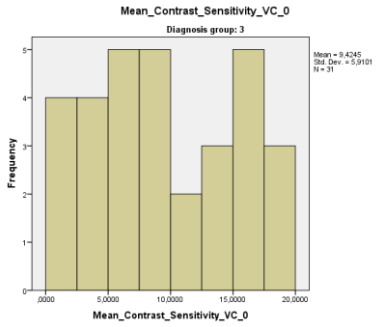

Reading Acuity in logMAR_VC_12
Diagnosis group: 2
Mean = .1950
Std. Dev. = .2559
N = 10
Frequency
Reading Acuity in logMAR_VC_12

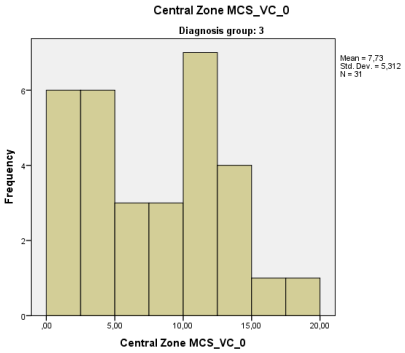

Estimate smallest print size where reading speed is still close to the maximum_VC_12
Diagnosis group: 2
Mean = .26
Std. Dev. = .232
N = 10
Frequency
Estimate smallest print size where reading speed is still close to the maximum_VC_12

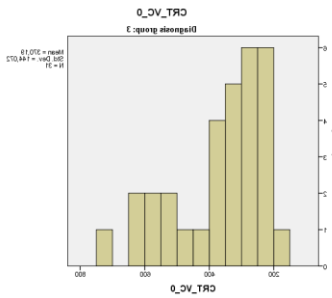

Adjustment for viewing distance_VC_12
Diagnosis group: 2
Mean = .13
Std. Dev. = .125
N = 10
Frequency
Adjustment for viewing distance_VC_12

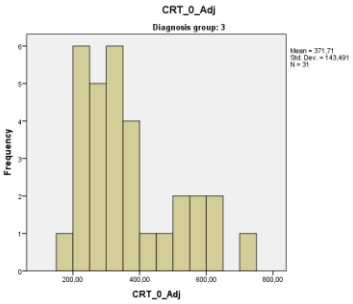

Critical print size in LogMAR_VC_12
Diagnosis group: 2
Mean = .3800
Std. Dev. = .3348
N = 10
Frequency
Critical print size in LogMAR_VC_12

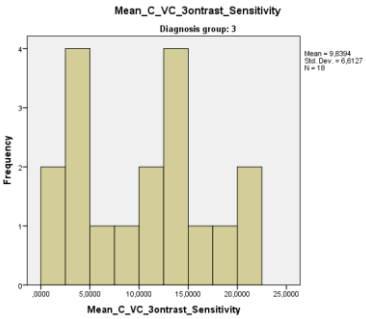

LogMAR_VC_0
Diagnosis group: 3
Mean = .44
Std. Dev. = .309
N = 31
Frequency
LogMAR_VC_0

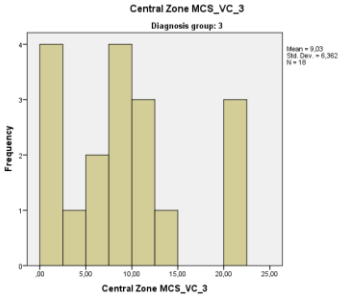

Mean_Contrast_Sensitivity_VC_0
Diagnosis group: 3
Mean = 9.4245
Std. Dev. = 5.9101
N = 31
Frequency
Mean_Contrast_Sensitivity_VC_0

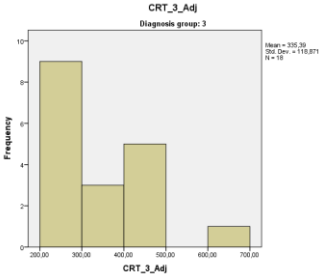

Central Zone MCS_VC_0
Diagnosis group: 3
Mean = 7,73
Std. Dev. = 5,312
N = 31
Frequency
Central Zone MCS_VC_0

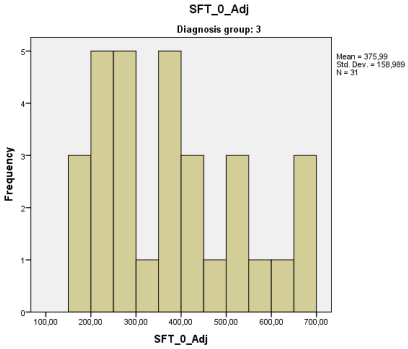


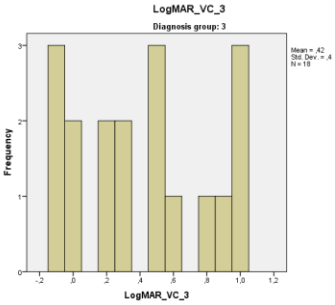

CRT_0_Adj
Diagnosis group: 3
Frequency
CRT_0_Adj

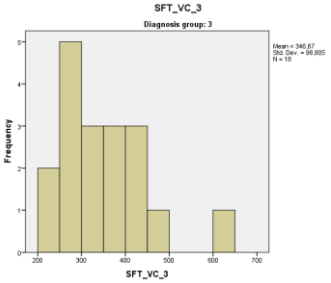

Mean_C_VC_3ontrast_Sensitivity
Diagnosis group: 3
Frequency
Mean_C_VC_3ontrast_Sensitivity

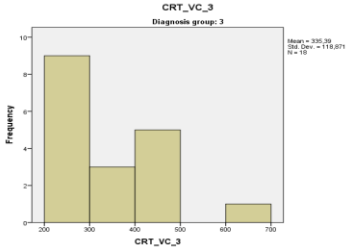

Central Zone MCS_VC_3
Diagnosis group: 3
Frequency
Central Zone MCS_VC_3

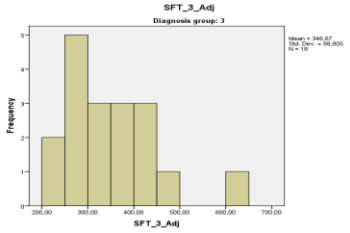

CRT_3_Adj
Diagnosis group: 3
Frequency
CRT_3_Adj

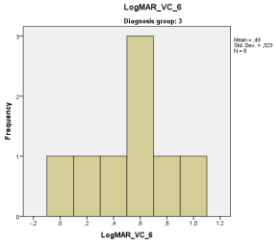

SFT_0_Adj
Diagnosis group: 3
Mean = 375,99
Std. Dev. = 156,989
N = 31
Frequency
SFT_0_Adj

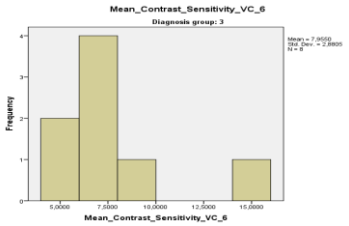

LogMAR_VC_3
Diagnosis group: 3
Frequency
LogMAR_VC_3

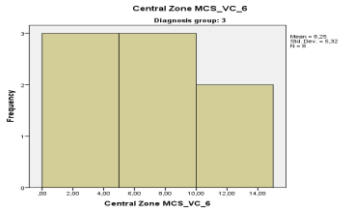

SFT_VC_3
Diagnosis group: 3
Frequency
SFT_VC_3

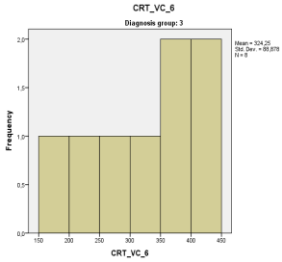

CRT_VC_3
Diagnosis group: 3
Frequency
CRT_VC_3

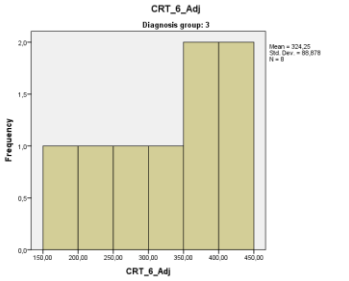

SFT_3_Adj
Diagnosis group: 3
Frequency
SFT_3_Adj

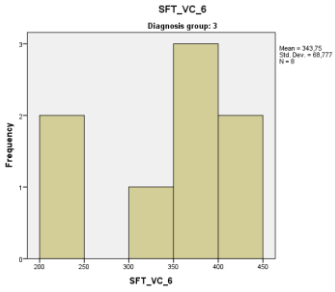

LogMAR_VC_6
Diagnosis group: 3
Frequency
LogMAR_VC_6

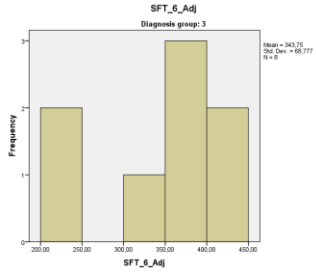

Mean_Contrast_Sensitivity_VC_6
Diagnosis group: 3
Frequency
Mean_Contrast_Sensitivity_VC_6

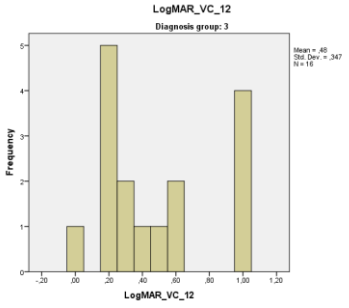

Central Zone MCS_VC_6
Diagnosis group: 3
Frequency
Central Zone MCS_VC_6

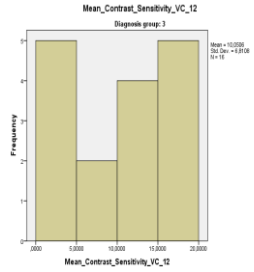

CRT_VC_6
Diagnosis group: 3
Frequency
CRT_VC_6

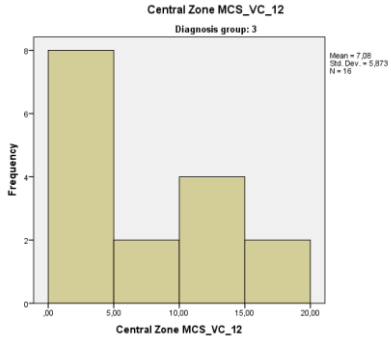

CRT_6_Adj
Diagnosis group: 3
Frequency
CRT_6_Adj

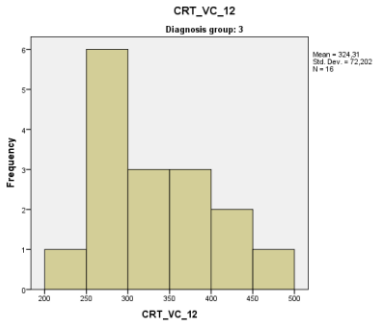

SFT_VC_6
Diagnosis group: 3
Frequency
SFT_VC_6

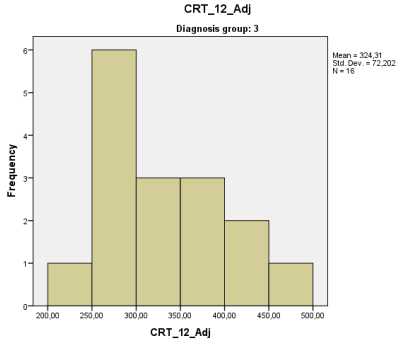

SFT_6_Adj
Diagnosis group: 3
Frequency
SFT_6_Adj

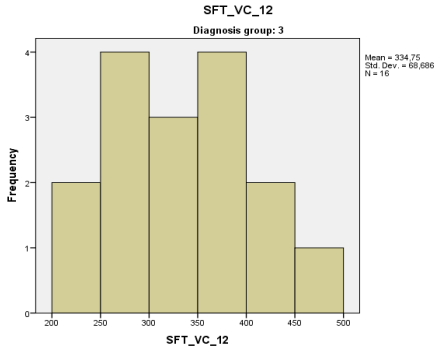

LogMAR_VC_12
Diagnosis group: 3
Frequency
LogMAR_VC_12

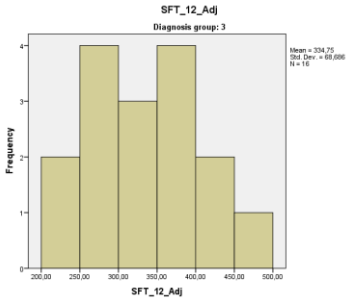

Mean_Contrast_Sensitivity_VC_12
Diagnosis group: 3
Frequency
Mean_Contrast_Sensitivity_VC_12

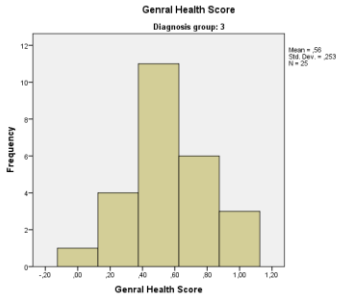

Central Zone MCS_VC_12
Diagnosis group: 3
Frequency
Central Zone MCS_VC_12

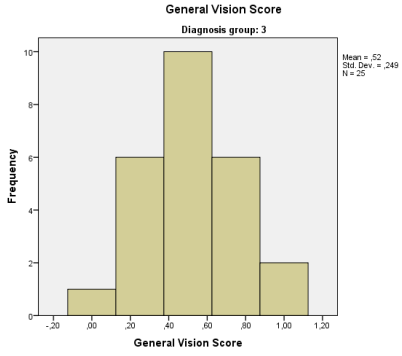

CRT_VC_12
Diagnosis group: 3
Mean = 324,31
Std. Dev. = 72,202
N = 16
Frequency
CRT_VC_12

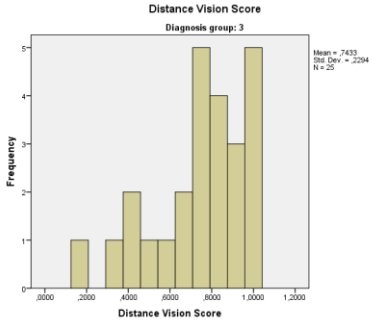

CRT_12_Adj
Diagnosis group: 3
Mean = 324,31
Std. Dev. = 72,202
N = 16
Frequency
CRT_12_Adj

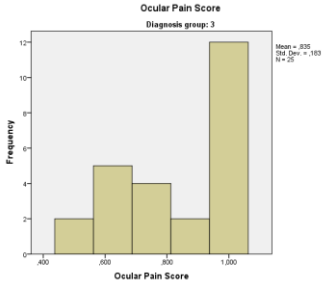

SFT_VC_12
Diagnosis group: 3
Mean = 334,75
Std. Dev. = 68,686
N = 16
Frequency
SFT_VC_12

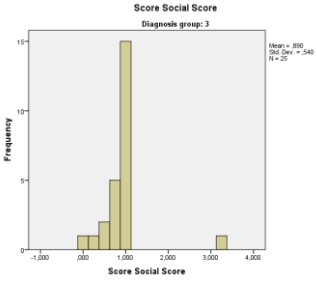

SFT_12_Adj
Diagnosis group: 3
Mean = 334,75
Std. Dev. = 68,686
N = 16
Frequency
SFT_12_Adj

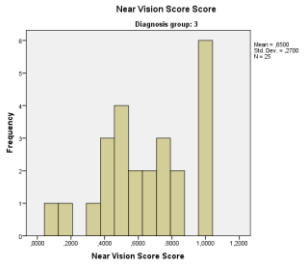

Genral Health Score
Diagnosis group: 3
Mean = ,56
Std. Dev. = ,253
N = 25
Frequency
Genral Health Score

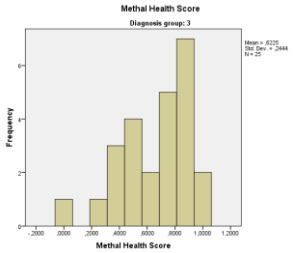

General Vision Score
Diagnosis group: 3
Mean = ,52
Std. Dev. = ,249
N = 25
Frequency
General Vision Score

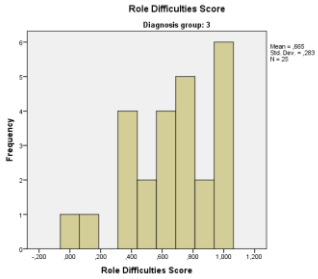

Distance Vision Score
Diagnosis group: 3
Mean = ,7433
Std. Dev. = ,2294
N = 25
Frequency
Distance Vision Score

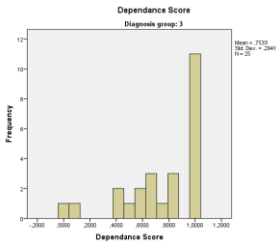

Ocular Pain Score
Diagnosis group: 3
Mean = ,835
Std. Dev. = ,183
N = 25
Frequency
Ocular Pain Score

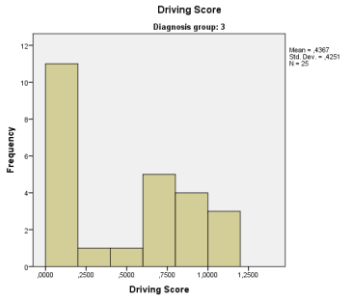

Score Social Score
Diagnosis group: 3
Mean = ,890
Std. Dev. = ,540
N = 25
Frequency
Score Social Score

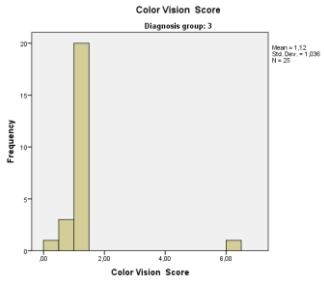

Near Vision Score Score
Diagnosis group: 3
Frequency
Near Vision Score Score

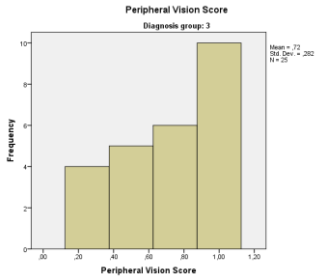

Methal Health Score
Diagnosis group: 3
Frequency
Methal Health Score

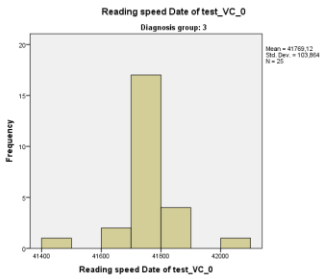

Role Difficulties Score
Diagnosis group: 3
Frequency
Role Difficulties Score

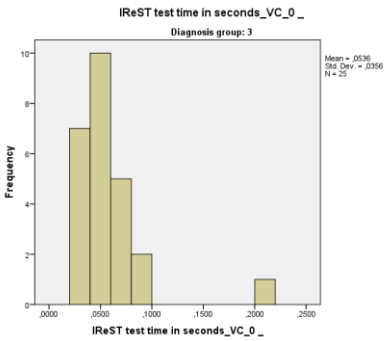

Dependance Score
Diagnosis group: 3
Frequency
Dependance Score

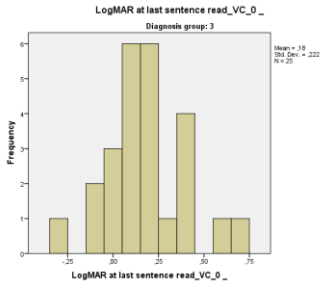

Driving Score
Diagnosis group: 3
Frequency
Driving Score

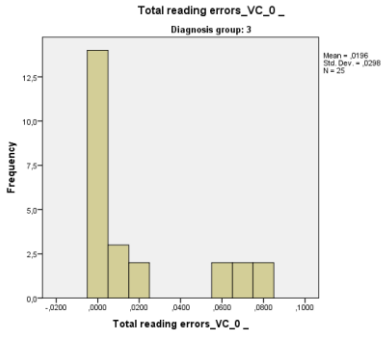

Color Vision Score
Diagnosis group: 3
Frequency
Color Vision Score

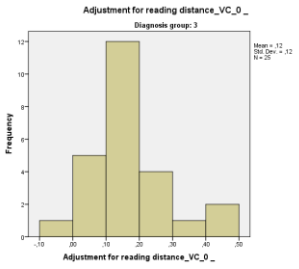

Peripheral Vision Score
Diagnosis group: 3
Frequency
Peripheral Vision Score

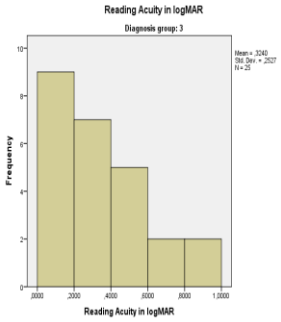

Reading speed Date of test_VC_0
Diagnosis group: 3
Frequency
Reading speed Date of test_VC_0

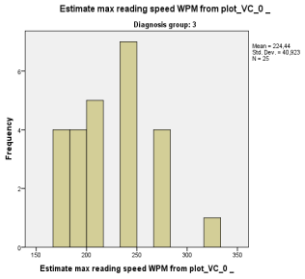

IReST test time in seconds_VC_0 _
Diagnosis group: 3
Frequency
IReST test time in seconds_VC_0 _

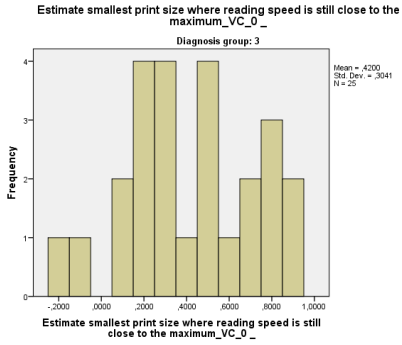

LogMAR at last sentence read_VC_0 _
Diagnosis group: 3
Frequency
LogMAR at last sentence read_VC_0 _

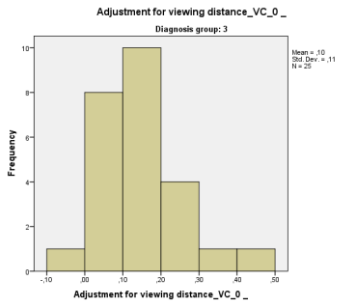

Total reading errors_VC_0 _
Diagnosis group: 3
Frequency
Total reading errors_VC_0 _

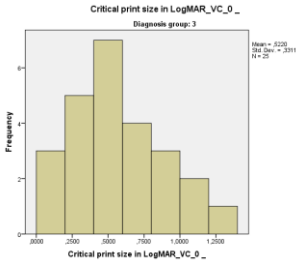

Adjustment for reading distance_VC_0 _
Diagnosis group: 3
Frequency
Adjustment for reading distance_VC_0 _

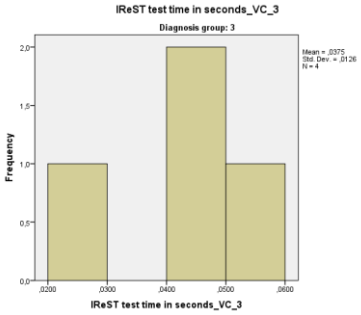

Reading Acuity in logMAR
Diagnosis group: 3
Mean = .3240
Std. Dev. = .2527
N = 25
Frequency
Reading Acuity in logMAR

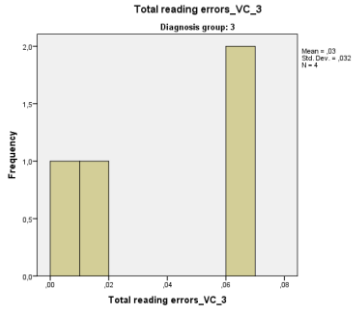

Estimate max reading speed WPM from plot_VC_0 _
Diagnosis group: 3
Mean = 224.44
Std. Dev. = 48.823
N = 25
Frequency
Estimate max reading speed WPM from plot_VC_0 _

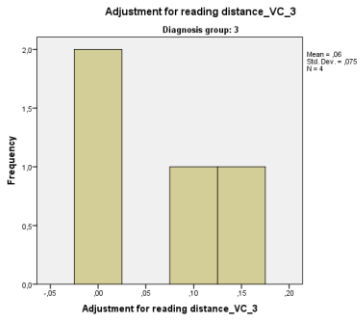

Estimate smallest print size where reading speed is still close to the maximum_VC_0 _
Diagnosis group: 3
Mean = .4200
Std. Dev. = .3041
N = 25
Frequency
Estimate smallest print size where reading speed is still close to the maximum_VC_0 _

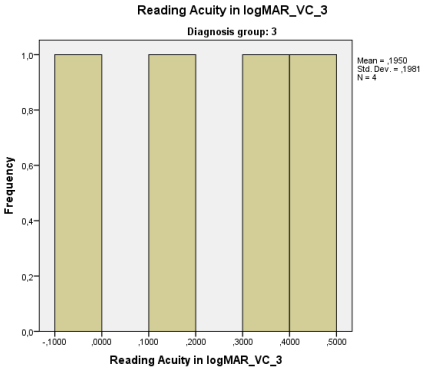

Adjustment for viewing distance_VC_0 _
Diagnosis group: 3
Mean = .10
Std. Dev. = .11
N = 25
Frequency
Adjustment for viewing distance_VC_0 _

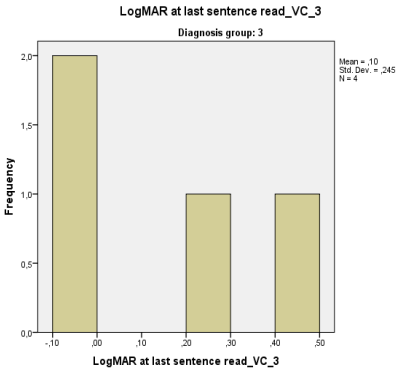

Critical print size in LogMAR_VC_0 _
Diagnosis group: 3
Mean = .5220
Std. Dev. = .3311
N = 25
Frequency
Critical print size in LogMAR_VC_0 _

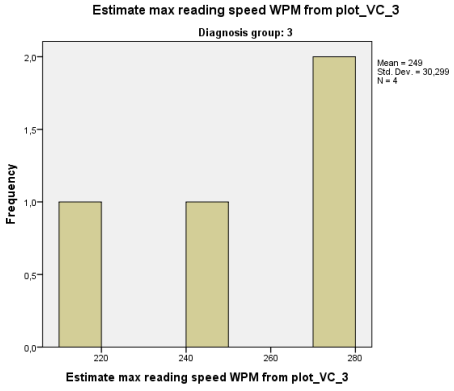

IReST test time in seconds_VC_3
Diagnosis group: 3
Mean = .0375
Std. Dev. = .0126
N = 4
Frequency
IReST test time in seconds_VC_3

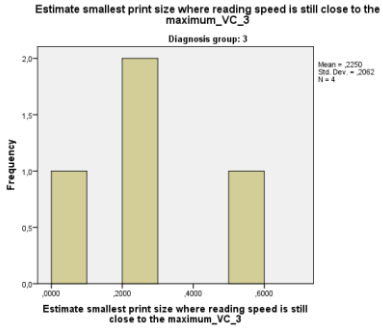

Total reading errors_VC_3
Diagnosis group: 3
Mean = .03
Std. Dev. = .032
N = 4
Frequency
Total reading errors_VC_3

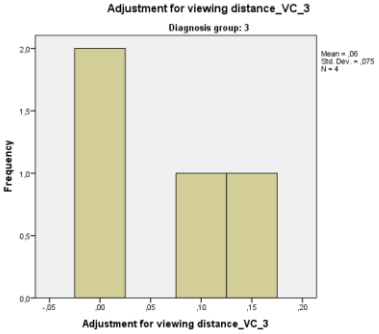

Adjustment for reading distance_VC_3
Diagnosis group: 3
Mean = .06
Std. Dev. = .075
N = 4
Frequency
Adjustment for reading distance_VC_3

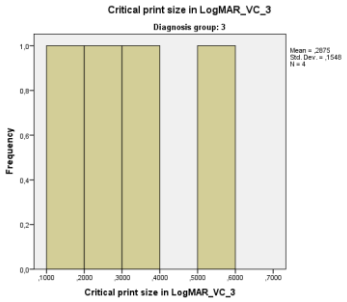

Reading Acuity in logMAR_VC_3
Diagnosis group: 3
Mean = .1950
Std. Dev. = .1981
N = 4
Frequency
Reading Acuity in logMAR_VC_3

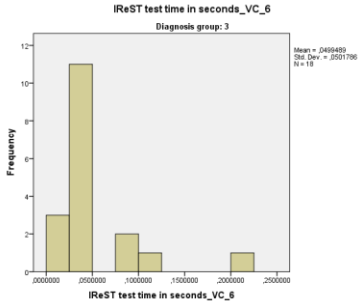

LogMAR at last sentence read_VC_3
Diagnosis group: 3
Mean = ,10
Std. Dev. = ,245
N = 4
Frequency
LogMAR at last sentence read_VC_3

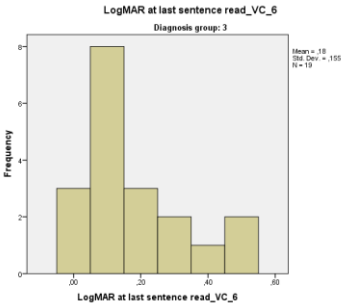

Estimate max reading speed WPM from plot_VC_3
Diagnosis group: 3
Mean = 249
Std. Dev. = 30,299
N = 4
Frequency
Estimate max reading speed WPM from plot_VC_3

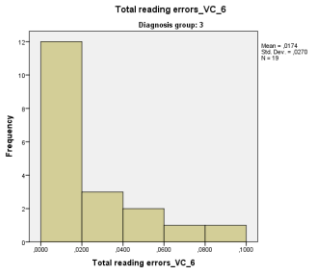

Estimate smallest print size where reading speed is still close to the maximum_VC_3
Diagnosis group: 3
Mean = ,2250
Std. Dev. = ,2062
N = 4
Frequency
Estimate smallest print size where reading speed is still close to the maximum_VC_3

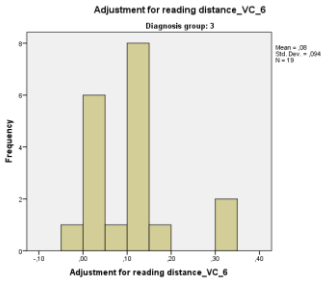

Adjustment for viewing distance_VC_3
Diagnosis group: 3
Mean = ,06
Std. Dev. = ,075
N = 4
Frequency
Adjustment for viewing distance_VC_3

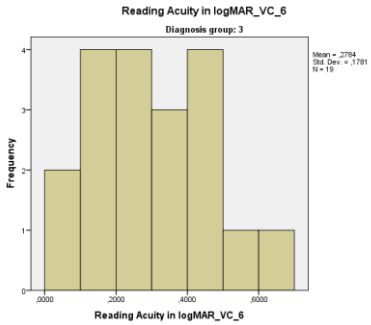

Critical print size in LogMAR_VC_3
Diagnosis group: 3
Mean = ,2875
Std. Dev. = ,1548
N = 4
Frequency
Critical print size in LogMAR_VC_3

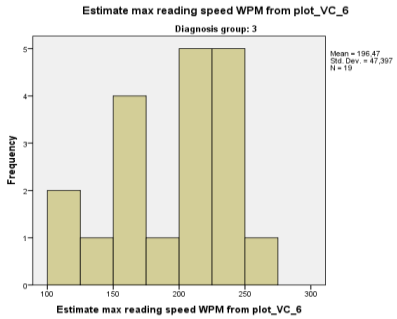

IReST test time in seconds_VC_6
Diagnosis group: 3
Mean = ,0499489
Std. Dev. = ,0501786
N = 19
Frequency
IReST test time in seconds_VC_6

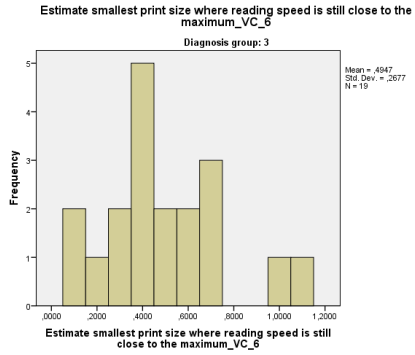

LogMAR at last sentence read_VC_6
Diagnosis group: 3
Mean = ,18
Std. Dev. = ,155
N = 19
Frequency
LogMAR at last sentence read_VC_6

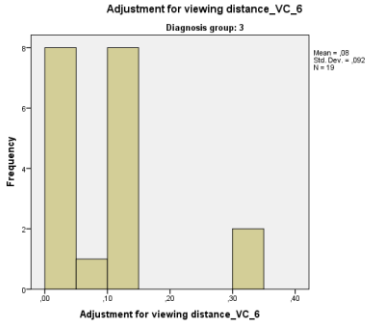

Total reading errors_VC_6
Diagnosis group: 3
Mean = ,0174
Std. Dev. = ,0270
N = 19
Frequency
Total reading errors_VC_6

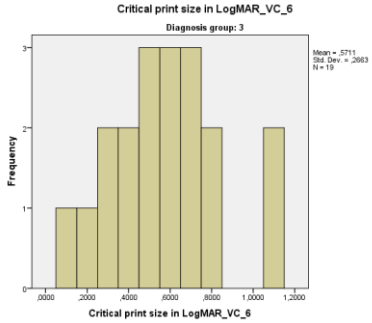

Adjustment for reading distance_VC_6
Diagnosis group: 3
Mean = ,06
Std. Dev. = ,094
N = 19
Frequency
Adjustment for reading distance_VC_6

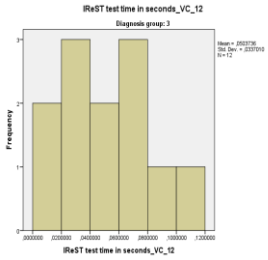

Reading Acuity in logMAR_VC_6
Diagnosis group: 3
Mean = ,2784
Std. Dev. = ,1781
N = 19
Frequency
Reading Acuity in logMAR_VC_6

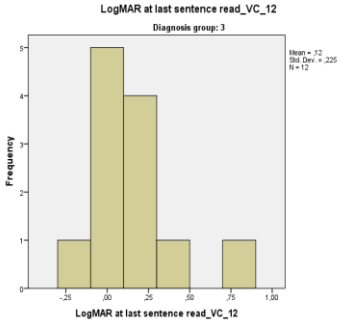

Estimate max reading speed WPM from plot_VC_6
Diagnosis group: 3
Mean = 196,47
Std. Dev. = 47,397
N = 19
Frequency
Estimate max reading speed WPM from plot_VC_6

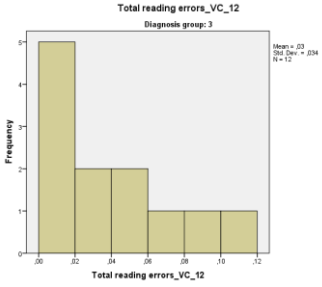

Estimate smallest print size where reading speed is still close to the maximum_VC_6
Diagnosis group: 3
Mean = ,4947
Std. Dev. = ,2677
N = 19
Frequency
Estimate smallest print size where reading speed is still close to the maximum_VC_6

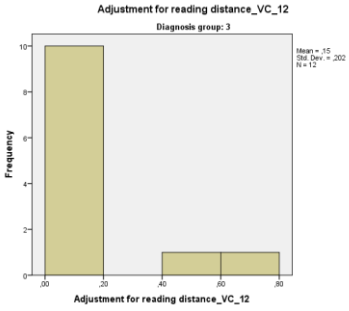

Adjustment for viewing distance_VC_6
Diagnosis group: 3
Mean = ,08
Std. Dev. = ,092
N = 19
Frequency
Adjustment for viewing distance_VC_6

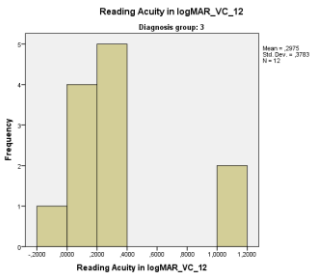

Critical print size in LogMAR_VC_6
Diagnosis group: 3
Mean = ,5711
Std. Dev. = ,2663
N = 19
Frequency
Critical print size in LogMAR_VC_6

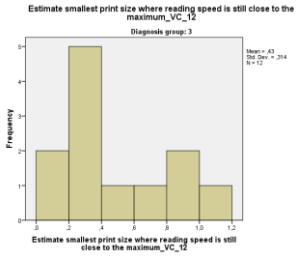

IReST test time in seconds_VC_12
Diagnosis group: 3
Frequency
IReST test time in seconds_VC_12

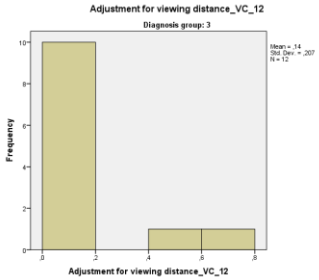

LogMAR at last sentence read_VC_12
Diagnosis group: 3
Mean = ,12
Std. Dev. = ,225
N = 12
Frequency
LogMAR at last sentence read_VC_12

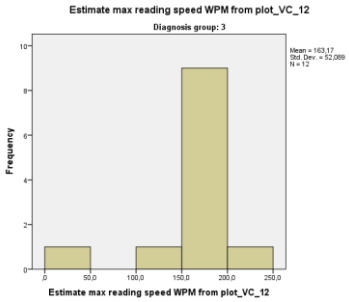

Total reading errors_VC_12
Diagnosis group: 3
Mean = ,03
Std. Dev. = ,034
N = 12
Frequency
Total reading errors_VC_12

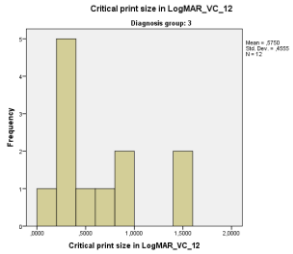

Adjustment for reading distance_VC_12
Diagnosis group: 3
Mean = ,15
Std. Dev. = ,202
N = 12
Frequency
Adjustment for reading distance_VC_12


Reading Acuity in logMAR_VC_12
Diagnosis group: 3
Mean = .2975
Std. Dev. = .3783
N = 12
Frequency
Reading Acuity in logMAR_VC_12


Estimate smallest print size where reading speed is still close to the maximum_VC_12
Diagnosis group: 3
Mean = .43
Std. Dev. = .314
N = 12
Frequency
Estimate smallest print size where reading speed is still close to the maximum_VC_12


Adjustment for viewing distance_VC_12
Diagnosis group: 3
Mean = .14
Std. Dev. = .207
N = 12
Frequency
Adjustment for viewing distance_VC_12


Estimate max reading speed WPM from plot_VC_12
Diagnosis group: 3
Mean = 163.17
Std. Dev. = 82.089
N = 12
Frequency
Estimate max reading speed WPM from plot_VC_12


Critical print size in LogMAR_VC_12
Diagnosis group: 3
Mean = .5750
Std. Dev. = .4555
N = 12
Frequency
Critical print size in LogMAR_VC_12