Macular Hole: Imaging and Post Operative Positioning

Studies

MD(Res) Thesis

by

Saruban Pasu BSc MBBS FRCOphth

UCL Institute of Ophthalmology

University College London
Declaration

“I, Saruban Pasu 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.”
Abstract

Since 1991 when Kelly and Wendel published the first case series of a surgical technique to repair macular holes, both the closure rates and functional outcomes have improved.

The four novel studies presented in this thesis all have the subject of macular hole as a common theme running throughout.

A comprehensive review of the pathophysiology, imaging and surgical reparative techniques is described in Chapter 1 which concludes with the results of a Cochrane review undertaken to determine the value of post-operative face down positioning.

Chapter 2 focuses on a previously unreported method of imaging a macular hole using the Shadowgram overlay tool on the Topcon 3D – OCT 2000 (Topcon, Tokyo, Japan). This technique while offering no significant benefit over traditional linear OCT measurements may be of interest in other causes of macula pathology.

Another aspect of macula imaging is explored in Chapter 3, which concentrates on assessing the reproducibility and reliability of the caliper tool on three different OCT devices. This original piece of work is the first of its kind to look in detail at the varies aspects of macular hole geometry.

Chapters 4 and 5 offer an extensive explanation of the PIMS (positioning in macular hole study) trial. This NIHR funded trail is to date the largest multi-centre randomised controlled trial to determine whether advice to position face down improves the surgical success rate of closure of large (≥400 μm) macular holes.
Impact Statement

The work published herein has already begun to have a scientific impact by contributing to the published literature on macular holes. I have had 2 manuscripts published, 1 international and 2 national presentations. It is my hope that a further 3 manuscripts will be published.

A total of four original bodies of work have been described in this thesis, and I believe the impact of this work is not only within academia but also to the public at large.

Currently OCT (optical coherence tomography) is the gold standard imaging technique used to assess the macular. The caliper tool on the OCT device is not only regularly used in the clinical setting but also in academia for research purposes. Chapter 3 provides details of the first study of its kind to report on the reproducibility and reliability of the caliper tool when measuring dimensions of macular hole geometry.

The NIHR funded PIMS trial (See Chapter 4 and 5) is unique in not only being the largest trial to date determining whether advice to position face down improves the surgical success rate of closure of large (≥400 μm) macular holes, but also used a patient and public advisory group to inform on aspects of study design in order to maximise recruitment. The advisory group are also in the process of reviewing the final manuscript of the PIMS trial which will be submitted to a high impact journal for publication. I believe that by engaging with patients and the wider public in study design has helped make this body of work clinically relevant and will help patients make informed decisions alongside their clinician.
Acknowledgements

I would like to sincerely thank my research supervisors - Professor James Bainbridge and Professor Michel Michaelides, for their professional guidance, support and encouragement in the preparation of this body of work.

I offer my sincere gratitude to the Pragmatic Clinical Trials Unit, Queen Mary University of London, who were instrumental in helping move my research forwards in a timely and seamless manner.

I would like to thank the staff of the Moorfields Clinical Research Facility, all of the Investigators and trial coordinators involved in the PIMS trial, Catey Bunce for her statistical input and all the study subjects for their participation. A special thank you to the PIMS trial Patient advisory group for their insightful comments.

This thesis is dedicated to my wife Victoria and two children, Ishaan and Ammaiayar, who over the last few years have provided invaluable support to enable me to complete this work.
List of Tables & Figures

Table 1: Gass classification of macular hole
Table 2: Demographic data
Table 3: OCT based parameters
Table 4: Shadowgram based parameters
Table 5: Correlations between OCT and shadowgram parameters
Table 6: Correlations between OCT dimensions/ shadowgram areas and visual acuity
Table 7: Means and standard deviations for the first measurements from grader 1
Table 8: Means and standard deviations for the second measurements from grader 1 two weeks after the first
Table 9: Means and standard deviations of measurements take from grader 2 (EC) and grader 3 (NK)
Table 10: Intrgrader measurement analysis for all three OCT devices
Table 11: Intergrader measurement analysis for all three OCT devices
Table 12: Number of measured parameters that had an absolute value of limit of agreement more than 50 microns
Table 13: Baseline characteristics, by randomised group
Table 14: Main results for primary outcome
Table 15: Main results for untransformed secondary outcomes
Table 16: Main results for transformed continuous secondary outcomes
Table 17: Main results for dichotomous secondary outcomes

Figure 1: Spectral domain OCT image of ELM, EZ, IZ and RPE
Figure 2: AO-SLO photoreceptor mosaics of the same location in a normal eye
Figure 3: Topcon OCT of macular hole and shadowgram overlay
Figure 4: Full thickness macular hole with the six measured parameters

Figure 5: Column bar graph showing means and standard deviations of all 6 Spectralis measurements from all graders

Figure 6: Column bar graph showing means and standard deviations of all 6 Topcon measurements from all graders

Figure 7: Column bar graph showing means and standard deviations of all 6 Stratus measurements from all graders

Figure 8: Intragrader Spectralis measurement of Base diameter

Figure 9: Intragrader Spectralis measurement of Inner Opening

Figure 10: Intragrader Spectralis measurement of Minimum linear diameter

Figure 11: Intragrader Spectralis measurement of Height

Figure 12: Intragrader Spectralis measurement of Left side

Figure 13: Intragrader Spectralis measurement of Right side

Figure 14: Intragrader Topcon measurement of Base diameter

Figure 15: Intragrader Topcon measurement of Inner Opening

Figure 16: Intragrader Topcon measurement of Minimum linear diameter

Figure 17: Intragrader Topcon measurement of Height

Figure 18: Intragrader Topcon measurement of Left side

Figure 19: Intragrader Topcon measurement of Right side

Figure 20: Intragrader Stratus measurement of Base diameter

Figure 21: Intragrader Stratus measurement of Inner opening

Figure 22: Intragrader Stratus measurement of Minimum linear diameter

Figure 23: Intragrader Stratus measurement of Height

Figure 24: Intragrader Stratus measurement of Left side

Figure 25: Intragrader Stratus measurement of Right side

Figure 26: Intergrader Spectralis measurement of Base diameter

Figure 27: Intergrader Spectralis measurement of Inner opening
Figure 28: Intergrader Spectralis measurement of Minimum linear diameter
Figure 29: Intergrader Spectralis measurement of Height
Figure 30: Intergrader Spectralis measurement of Left side
Figure 31: Intergrader Spectralis measurement of Right side
Figure 32: Intergrader Topcon measurement of Base diameter
Figure 33: Intergrader Topcon measurement of Inner opening
Figure 34: Intergrader Topcon measurement of Minimum linear diameter
Figure 35: Intergrader Topcon measurement of Height
Figure 36: Intergrader Topcon measurement of Left side
Figure 37: Intergrader Topcon measurement of Right side
Figure 38: Intergrader Stratus measurement of Base diameter
Figure 39: Intergrader Stratus measurement of Inner opening
Figure 40: Intergrader Stratus measurement of Minimum linear diameter
Figure 41: Intergrader Stratus measurement of Height
Figure 42: Intergrader Stratus measurement of Left side
Figure 43: Intergrader Stratus measurement of Right side
Figure 44: CONSORT diagram
# Table of Contents

**DECLARATION** 2  
**ABSTRACT** 3  
**ACKNOWLEDGEMENTS** 5  
**LIST OF TABLES & FIGURES** 6  

## 1.0 INTRODUCTION  
1.1 Retinal Anatomy and Function 12  
1.2 The Macula 13  
1.3 The Vitreous 13  
1.4 Posterior Vitreous Detachment 14  
1.5 Macular Hole 15  
1.5.1 Classification 15  
1.5.2 Epidemiology 17  
1.5.3 Pathogenesis 17  
1.5.4 Vitreomacular Adhesion (VMA) 18  
1.5.5 Vitreomacular Traction (VMT) 19  
1.5.6 OCT 19  
1.5.7 Ellipsoid Zone in Macular Hole 22  
1.5.8 Adaptive Optics 26  
1.5.9 Preoperative Predictive Factors 30  
1.5.10 Macular Hole Parameters and Indices 32  
1.5.11 History of Surgical Technique to Close Macular Holes 35  
1.5.12 Post-operative Positioning Review 38  
1.5.13 Cochrane Review 38  

## 2.0 Using the Shadowgram Overlay Tool to Assess Macular Hole Geometry on Topcon OCT 43  
2.1 Introduction 43  
2.2 Methods 44  
2.3 Shadowgram Results 46  
2.3.1 Summary of Data 46  
2.3.2 Parameter Measurements 47  
2.4 Shadowgram Discussion 50  

## 3.0 Reproducibility and Reliability for Measurements of Macular Hole Geometry using the Caliper Tool on Three Different Optical Coherence Tomography Devices 52  
3.1 Introduction 52  
3.2 Methods 54  
3.3 Results 56  
3.4 Discussion 67  

## 4.0 BEAVRS Survey and PPI (Patient & Public Involvement) 69  
4.1 Introduction 69  
4.2 Methods 70  
4.3 Results 71
1.0 Introduction

1.1 Retinal anatomy and function

The eye is responsible for focusing and transforming light stimuli into nerve signals that are processed in the brain for visual perception. The retina comprises complex neural circuitry that converts the graded electrical activity of photoreceptors into action potentials that travel to the brain via axons in the optic nerve.

Although it has the same types of functional elements and neurotransmitters found in other parts of the central nervous system, the retina comprises five types of neurons: photoreceptors, bipolar cells, ganglion cells, horizontal cells and amacrine cells. The cell bodies and processes of these neurons are stacked in five alternating layers, with the cell bodies located in the inner nuclear, outer nuclear, and ganglion cell layers, and the processes and synaptic contacts located in the inner plexiform and outer plexiform layers. A direct three neuron chain (photoreceptor cell to bipolar cell to ganglion cell) is the major route of information flow from photoreceptors to the optic nerve.

Rods and cones are the two types of light sensitive cells in the retina, collectively called photoreceptors. Both types of photoreceptor have an outer segment that is composed of membranous disks that contain photopigment and lies adjacent to the retinal pigment epithelial (RPE) layer, and an inner segment that contains the cell nucleus and gives rise to synaptic terminals that contact bipolar or horizontal cells. Absorption of light by the photopigment in the outer segment of the photoreceptors initiates a cascade of events that changes the membrane potential of the receptor, and therefore the amount of neurotransmitter released by the photoreceptor synapses onto the cells they contact. The synapses between photoreceptor terminals and bipolar cells (and horizontal cells) occur in
the outer plexiform layer; more specifically, the cell bodies of photoreceptors make up the outer nuclear layer, whereas the cell bodies of bipolar cells lie in the inner nuclear layer. The short axonal processes of bipolar cells make synaptic contacts in turn on the dendritic processes of ganglion cells in the inner plexiform layer. The much larger axons of the ganglion cells form the optic nerve and carry information about retinal stimulation to the rest of the central nervous system.

1.2 The Macula

The retina is divided into the macula area within the central posterior pole and the peripheral fundus. Anatomically the macula (macula lutea or central retina) is defined as the portion of the posterior retina that contains xanthophyll and two or more layers of ganglion cells. It measures approximately 5.5mm in diameter and is centered approximately 4mm temporal to and 0.8mm inferior to the center of the optic disc [1]. On the basis of microscopic anatomy, the macula area can be further subdivided into the umbo, foveola, fovea, parafovea, and perifoveal areas. The umbo is the center of the fovea.

1.3 The Vitreous

The vitreous gel is composed mainly of type 2 collagen fibres running in an anterior-posterior direction through the vitreous centre, convening in the anterior vitreous base, and inserting into the posterior vitreous cortex [2]. The protein opticin and the glycosaminoglycan chondroitin sulphate maintain the spaces between the collagen fibrils [3]. Water (98% of the vitreous gel component) and hyaluronic acid, provide the gel-like consistency of the vitreous. The vitreoretinal interface is a complex anatomical structure composed by the union between the retina and the vitreous [4]. Densely packed collagen fibrils of the posterior
vitreous cortex (100–300 μm in thickness) lie over the macula and superficially insert into the internal limiting membrane (ILM) of the retina by means of adhesion molecules, such as laminin, fibronectin, and proteoglycans, which interact with opticin in the vitreous gel [3]. Adherences are more firmly attached to the retina at the vitreous base, optic disc, and fovea, as well as along the major retinal blood vessels. The vitreomacular junction has an annular shape, with a diameter of 3-4 mm. The vitreous gel is constructed to resist both tractional and compressive forces [5].

Age related physiological changes in the vitreous gel begin with progressive liquefaction (at the age of 80, around 50% of the vitreous gel has been liquefied) and gradual destruction of the collagen-hyaluronic acid network [6]. The vitreous changes occur as a result of the development of fluid-filled pockets in front of the macula, which over the time coalesce and enlarge, resulting in a weakened adhesion between the vitreous and the retina. This gradually predisposes to posterior vitreous detachment (PVD), defined as separation of the posterior cortex from the ILM of the retina, which represents the final step of the normal vitreous aging process [7]. The process of PVD is asymptomatic, until vitreous separation from the optic disc occurs [7]. Symptoms of complete (acute) PVD include light flashes and floaters. Light flashes are caused by vitreous traction on the peripheral retina, while floaters may be due to blood, condensations of vitreous collagen, or glial tissue torn from the optic nerve.

1.4 Posterior vitreous detachment

Focal peri-foveal PVD can occur in around 50% at ages 30–39 years, whereas complete PVD is observed in 50% or more of individuals aged 70 years or older [8, 9]. PVD is significantly more common in postmenopausal women than men; this is thought to be due to
the effects of decreased oestrogen on connective tissues such as those within the vitreous gel [10, 11]. The presence of myopia is also associated with a three- to fourfold increased risk of PVD compared with absence of myopia [11].

The normal process of PVD due to vitreous aging may be complicated by the presence of vitreomacular adhesions between the cortex and the macula area, resulting from vitreous syneresis [12]. These adherences may be focal or extensive, affecting the foveola only or a wide region of the macular area and the optic disc. Simple vitreomacular adhesion (VMA) is not associated with distortion of macular architecture. However, these adherences may exert tractional forces on the macula resulting in vitreomacular traction (VMT) causing retinal distortion and foveal detachment.

1.5 Macular hole

Idiopathic macular holes are round full-thickness vertical retinal defects in the foveal neurosensory retina.

1.5.1 Classification

For decades, macular holes have been classified by fundus biomicroscopy in four stages, as first described by Donald Gass in 1988 [13]. The Gass classification is based on the fovea appearance, the estimated size of the hole, and whether or not the posterior vitreous is separated (Table 1). Confirmation of full-thickness macular holes (FTMH) can be performed with further clinical investigations such as Amsler grid assessment, the Watzke-Allen sign, or the laser aiming beam test [14].
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Yellow spot with loss of foveal depression, no vitreous separation</td>
</tr>
<tr>
<td>1b</td>
<td>Yellow ring with loss of foveal depression, no vitreous separation</td>
</tr>
<tr>
<td>2</td>
<td>Small full-thickness macular hole &lt;400 microns</td>
</tr>
<tr>
<td>3</td>
<td>Full-thickness maculae hole &gt;400 microns, no vitreous separation</td>
</tr>
<tr>
<td>4</td>
<td>Full-thickness macular hole &gt;400 microns, complete vitreous separation</td>
</tr>
</tbody>
</table>

Table 1: Gass classification of macular hole

The earliest stage, according to Gass, is an impending hole, characterised by a yellow spot (stage 1a) or a yellow ring (stage 1b) in the fovea. Stage 1 macular holes are difficult to diagnose bio-microscopically and even experienced observers disagree about the diagnosis in many cases [15]. In stage 2 macular holes, there is a foveal full thickness defect less than 400 microns in diameter; these holes can be round, ovoid or slit-like in shape. The fully developed, stage 3 macular hole appears as a round, full thickness defect larger than 400 microns in diameter. Stage 4 macular holes appear similar to stage 3 holes except that in stage 4 holes there is complete posterior vitreous detachment, as frequently evidenced by a visible Weiss ring.
1.5.2 Epidemiology

Idiopathic macular holes (MH) have an annual incidence of 8 per 100,000 individuals [16], and prevalence of 0.2 [17] to 3.3 [18] per 1000 individuals with visual impairment. The condition occurs more frequently in women and adults aged 75 years or older [19] and is unilateral in around 80% of cases [20]. A number of factors have been suggested to increase the risk of MH development, such as elevated plasma fibrinogen [21] while in women, use of oestrogen-replacement therapy is associated with a reduced risk of MH. In individuals with severe myopia (−14 to −32 dioptres), the prevalence of MH has been reported to be as high as 6% [22]. Notably, the risk of MH development in fellow eyes without manifest vitreous separation has been estimated at around 7–12% after 5 years and 17% at 10 years [23].

1.5.3 Pathogenesis

A degenerative process possibly due to vascular insufficiency was an early theory on MH pathogenesis [24]. The role of the vitreous in macular hole formation was suggested by Gass. He hypothesized that tangential traction, possibly caused by Müller cell proliferation and subsequent contraction in the vitreoretinal interface, was the prime factor in the pathogenesis of macular holes [25]. The low frequency of macular holes in eyes with complete posterior vitreous detachment, also supports the theory that the vitreous must be play a key role in the pathogenesis [26, 27]. The presence of a posterior vitreous detachment at the time of diagnosis allows the macular hole to be less prone to enlargement, with consequent better preservation of vision [28].
Reports from histopathological examination of surgically removed operculae in cases of macular hole have shown cases confirming glial elements only, while others have shown cone photoreceptors within the operculae [27, 29, 30]. Jensen et al developed a technique whereby local retinal photoreceptor displacement could be accurately assessed. Differential perimetry in patients with idiopathic macular holes clearly documented radial centrifugal photoreceptor displacement away from the centre of the retina in 8 of 10 patients. They concluded that most idiopathic macular holes are formed by neuroretinal tissue dehiscence at the umbo and gradual distention without significant loss of tissue [31].

More recent research (using ultrasound and optical coherence tomography) has elucidated that MHs are initiated during perifoveal PVD as a consequence of anteroposterior and dynamic vitreomacular traction [20, 32, 33].

1.5.4 Vitreomacular adhesion (VMA)

VMA represents a specific stage of partial vitreous detachment in the perifoveal area without retinal abnormalities. VMA is characterized by elevation of the cortical vitreous above the retinal surface, with the vitreous remaining attached within a 3 mm radius of the fovea (as defined arbitrarily). The angle between the vitreous and the inner retinal surface is acute, and the retina displays no abnormalities in contour or morphological features on OCT. VMA is not accompanied by visual impairment and may be considered a normal finding in the natural course of PVD. Also, VMA may be sub-classified by the size of the adhesion into focal (≤1500 μm) or broad (>1500 μm). The cutoff of 1500 μm corresponds to the area of increased vitreous adhesion to the fovea. VMA usually resolves spontaneously as part of the normal process of PVD, although it may progress to VMT [34].
1.5.5 Vitreomacular traction (VMT)

Vitreomacular adhesions may exert tractional forces on the macula, increased during ocular saccades, causing retinal distortion and disruption [35]. VMT can be classified as focal (less than or equal to 1500 µm) or broad (more than 1500 µm) depending on the width of the vitreous attachment. Distortion of the foveal profile, formation of intraretinal cysts, intraretinal cavitation, subretinal fluid, and, even, RPE detachment can be observed. In symptomatic patients, enzymatic vitreolysis [36] or vitrectomy may be indicated.

1.5.6 OCT

Optical coherence tomography (OCT) is capable of providing high-resolution tomographic images of the posterior vitreous, retina and choroid [37].

OCT has become the gold standard for the diagnosis of macular hole and for confirming anatomic closure after surgery. OCT imaging is analogous to ultrasound imaging except that OCT performs imaging by measuring the echo time delay and magnitude of back reflected or back scattered light. A light beam is incident on the retina, and the echo time delay and magnitude of back reflected or back-scattered light are measured to generate an axial scan similar to an A-scan in ultrasound. The light beam is scanned across the retina, and A-scans are measured at a series of different transvers positions. The resulting data are displayed as a false colour or grey scale image, similar to a B-mode image in ultrasound. The OCT image represents a cross-sectional view of tissue, where the contrast in the image is produced by differences in back scattering or back reflection between different tissues. Because echoes of light are too fast to be measured directly by electronics, in OCT measurements of light echoes are performed using a technique known as low-coherence interferometry. Light back
reflected from the eye (one arm of the interferometer) is correlated with light that has a known delay (from the second, reference arm of the interferometer).

Since the 1990s, time-domain optical coherence tomography (TD-OCT) – having axial resolution of 15μm and scanning speed of 400 A-scans per second – has been widely used to image the vitreomacular interface. In the last few years, OCT techniques have evolved to spectral-domain OCT (SD-OCT), which features a higher speed and improved resolution, presenting an axial resolution of 3–7μm and a scanning speed of up to 40,000 A-scans per second in commercially available systems [38-40].

This well-established diagnostic imaging technique provides both qualitative (morphology and reflectivity) and quantitative (thickness, mapping and volume) analyses of the retinal architecture. Correlations between anatomy on OCT and visual function have been investigated in a number of retinal diseases [41-46].

In 2014 an, international panel of OCT experts came to a consensus on the most appropriate terminology for the retinal layers as visualized on OCT, and this terminology is currently commonly used among experts in the field. The term “zone” was used to define anatomical regions without recognised histopathological correlation to a specific retinal layer. The recent nomenclature of the outer retinal bands and their anatomical feature attributions are described below (Figure 1), from the innermost to the outermost [47].
The external limiting membrane (ELM) is located at the boundary between the cell bodies (nuclei) and the inner segments of the photoreceptors, and comprises clusters of junctional complexes between the Müller cells and the photoreceptors.

The ellipsoid zone (EZ), which was previously referred as the photoreceptor inner segment/outer segment (IS/OS) junction, is now thought to be formed mainly by mitochondria within the ellipsoid layer of the outer portion of the inner segments of the photoreceptors. In a normal fovea, the distance from the EZ line to the ELM is shorter than that from the EZ line to the RPE.

The interdigitation zone (IZ) corresponds to the contact cylinder represented by the apices of the RPE cells that encase part of the cone outer segments. This layer was previously referred to as cone outer segment tips (COST) or rod outer segment tips (ROST), and it is not always distinguishable from the underlying RPE layer, even in normal subjects.
The retinal pigment epithelial band is formed by the RPE and Bruch’s membrane (indistinguishable from each other in a normal state using current SD-OCT systems). In the fovea, this band is thicker, which indicates that choroidal structures may also contribute to the hyper-reflectivity of the RPE band at this location.

The application of SD-OCT imaging to macular holes augments clinical staging by enabling visualisation of the foveal and vitreous microstructure and tractional relationships and by calculating size measurements of hole architecture. SD-OCT allows for manual quantification of the width and height of the macular hole and identifies perifoveal cystoid oedema, vitreomacular traction, and perifoveal ellipsoid zone integrity.

1.5.7 Ellipsoid zone in macular hole

It is widely believed that damage or disruption of the photoreceptors can be visualized on OCT as loss of integrity of the ELM, EZ and IZ bands [48, 49]. Attenuation, discontinuity or disruption of these bands have been reported as likely hallmarks of photoreceptor dysfunction or damage in a variety of retinal diseases [44, 49].

These changes are better assessed in the absence of features that could weaken the signal intensity of the outer retinal layers, such as retinal oedema, hemorrhage or media opacity.

Various stages of photoreceptor damage over time have still not been clearly correlated histopathologically with OCT findings. However, OCT of retinal degenerative diseases over time has demonstrated that ELM, EZ and IZ lengths are highly correlated with each other, and dis-organisation seems to occur in a stepwise order: first at the IZ, followed by the EZ and finally the ELM line [49-51].
The hypothesis that the photoreceptor outer segment layer is the first one to be affected in degenerative conditions, followed by damage of photoreceptor cell bodies occurring later in the process, is supported by histopathological evidence of decrease in outer segment length after retinal detachment [52] and shortening of cone outer segments and death of neighboring cones following rod cell death in eyes with retinitis pigmentosa [53].

On the other hand, photoreceptor restoration as observed after macular surgery seems to occur in the opposite order. The ELM zone has been reported as the first structure to recover after macular hole closure, and its recovery has been considered a sign of intact photoreceptor cell bodies and Müller cells [54]. Additionally, OCT findings showed that EZ recovery is restricted to areas with intact ELM, and IZ recovery is observed only in eyes with an intact EZ and ELM line after macular hole and epiretinal membrane surgeries [55, 56].

These findings suggest that an intact ELM at the fovea is necessary to complete restoration of the other photoreceptor microstructures. The integrity of the ELM has been reported to be an important characteristic in the photoreceptor layer that accounts for visual recovery in patients with successful repair of macular-involved retinal detachments [51].

Chang et al [57] assessed the long term dynamic healing process of outer retinal changes for 1 year in patients who underwent macular hole repair. They found that the ELM was restored much earlier than the EZ and showed that the ELM gradually regains its continuity and is well correlated with BCVA postoperatively. Of the 60 eyes retrospectively studied, there were no eyes with a disrupted ELM in the presence of an intact EZ. The eyes with intact ELM and/or intact EZ showed better BCVA than eyes with defects in ELM or EZ.
Ko et al [58] found that the highly visible IS/OS (inner segment/outer segment) line may be used to detect the integrity of the photoreceptor outer segments. They note that diminishment of the highly reflecting IS/OS in the region of detachment (due to macular hole), may be attributed to the altered orientation of the photoreceptor segments caused by the lifting away of the photoreceptors from the RPE. They showed that following successful repair of macular holes, the ELM layer and IS/OS can reappear on OCT. The reflectivity of the usually highly reflective IS/OS line is diminished. There are also small discontinuities of the IS/OS in the region of the repaired hole, suggesting that small residual photoreceptor impairments may still be present. This may account for the lack of full VA recovery postoperatively. Surgery can re-attach the intact photoreceptors back to their normal anatomical position against the RPE and facilitate the recovery of visual function.

Kitaya et al [59] found that the regular reflex from the photoreceptor layer on OCT was associated with good postoperative visual acuity. An irregular reflex from the photoreceptor layer may represent damaged photoreceptors, resulting in limited visual recovery.

Drexler and colleagues [60] imaged the macula with ultrahigh resolution OCT showing that the ELM as well as the transition zone between the inner and outer segments of the photoreceptors could be visualized. This IS/OS junction can be easily identified as a thin hyper-reflective band above the bright highly reflective broader band representing the retinal pigment epithelium-Bruchs choriocapillaris. The integrity of this layer may be a better predictor of good visual outcome.

Villate et al [61] in their retrospective review of patients with closed macular holes, found that photoreceptor outer segment thickness significantly correlated with postoperative BCVA. This study suggests that the physical integrity of the photoreceptor layer is important for visual function. They comment that the outer retina may be more important than the inner
retina in terms of restoring optimal postoperative VA, while the inner retina is likely more important to induce anatomic closure.

Itoh et al [62] hypothesized that postoperative recovery of visual acuity is dependent on the restoration of the foveal COST line. They concluded that eyes with an irregular COST line had significantly better BCVA than eyes with an absent COST line at 3, 6, and 9 months. Eyes with distinct COST line had significantly better BCVA than eyes with an irregular or absent COST line at 12 months after surgery.

Oh et al [63] set out to standardise measurements of the IS/OS and to investigate the relationship of the IS/OS defect to visual acuity outcomes in patients before and after macular hole surgery. A specific question was whether the area of the IS/OS defect correlates better than linear measurements. They found that poorer preoperative BCVA correlated with larger preoperative IS/OS defect diameter area and larger basal hole area, and that better BCVA improvement correlated with larger preoperative IS/OS defect area.

Inoue et al [64] found that length and area of IS/OS junction defect, both exhibited significant negative correlations with postoperative BCVA. They quantitatively measured the IS/OS junction and investigated the correlation between junction defect and visual recovery.

The ability to visualize the ELM and the IS/OS is an important indicator of photoreceptor integrity. The ability to visualize and track photoreceptor morphology associated with macular hole formation and repair may play a role in further understanding the process of macular hole formation and may be useful in predicting and assessing the potential outcome of macular hole surgery.
1.5.8 Adaptive Optics

Structural changes in the photoreceptor layers of eyes with surgically closed MH, such as varying degrees of disruption of the junction between the photoreceptor inner segment and outer segment (IS/OS) and of the external limiting membrane, have been identified using time-domain OCT, ultra-high resolution OCT and spectral domain OCT. These imaging methods have not provided sufficiently clear images of individual photoreceptor cells for identifying specific microstructural abnormalities that might explain visual disturbance in eyes with closed macular holes. This failure results primarily from aberrations in ocular optics. These aberrations can be compensated for by using imaging systems that incorporate Adaptive Optics (AO).

An AO system consists of a wavefront sensor (a Shack Hartmann sensor) that measures aberrations of the entire eye and a deformable mirror or a spatial light modulator that compensates for these aberrations in living eyes. The instrument in question is a custom built adaptive optics equipped scanning light ophthalmoscope (AO-SLO). It is based on the commonly used ophthalmic imaging scheme of scanning ophthalmoscopy. The instrument uses 840nm light for wavefront sensing and a mix of chromatic and infrared lights for imaging (currently 790nm, 680nm and 488nm). The specific device has been used at Moorfields Eye Hospital for 18 months (at the time of writing this thesis) for other studies, with 162 unique patients having been imaged during ~250 imaging sessions. The device is an exact replica of systems at the Medical College of Wisconsin (4 years and 2200 patients) and University of Rochester (6 years, 700 patients). Given that the lights used for imaging are at least an order of magnitude below the maximal permissible exposure limit, and below most commonly used clinical instruments there have been no adverse effects to imaging at any site. The purpose of the device is for imaging individual cells in the living human eye.
Lateral resolutions in the order of 2 microns can be achieved, thereby allowing for the visualization of individual cone photoreceptors [65].

AO-SLO can implement multiple detectors to produce confocal images (Figure 2A), and more recently, split-detection images (Figure 2B) [66].

Figure 2: AO-SLO photoreceptor mosaics of the same location in a normal eye. (A) Confocal AO-SLO image. The large hyperreflective circular structures surrounded by a dark ring are cones. (B) Corresponding split-detection AO-SLO image. The circular structures are cones.

Confocal AO requires relatively intact and correctly oriented photoreceptor outer segments to visualize individual photoreceptors [66, 67]. Confocal images of a healthy photoreceptor mosaic show individual photoreceptors as round bright spots due to the wave guiding of light by the photoreceptor inner segment into the outer segment. The bright spots appear regularly spaced in a hexagonal array, with the reflectance varying topographically and over time. Conversely, the split-detector AO technique visualizes photoreceptor inner segments.
This is valuable in diseases where outer segments are not intact. In macular holes, for instance, the photoreceptor orientation may be impaired and confocal images cannot be interpreted without uncertainty. Split-detection allows for the visualization of the inner segment mosaic regardless of the integrity of the outer segments and provides an enhanced illustration of cones.

The ability of AO-SLO to provide in vivo images of the photoreceptor mosaic allows for a quantitative assessment of photoreceptor numerosity and density and to potentially be able to describe progression over time on a cellular basis.

Many studies using conventional time domain or SD OCT have reported a possible association between the integrity of the photoreceptor layer and visual improvement after successful MH repair. Several investigators have reported that a disrupted photoreceptor IS/OS junction, a disrupted ELM, or both may be associated closely with postoperative visual impairment. However, these studies could not ascertain how the individual photoreceptors are damaged after successful MH repair or how these damages are correlated with decreased visual function.

Ooto et al [68] used AO-SLO and SD-OCT to assess photoreceptor structure in surgical closed macular holes. After macular hole repair, AO-SLO revealed the presence of dark areas totaling 0.004 to 0.754mm2 in the foveae of all treated eyes. This was true even in eyes for which postoperative SD OCT did not reveal any visible defect in the IS/OS junction. Mean cone density in eyes with surgically closed macular holes was 19650 cones/mm2, which was significantly lower than that of normal eyes (p=0.003). Preoperative logMAR visual acuity was correlated with postoperative cone density. After surgery, lower cone density correlated with poorer logMAR visual acuity, lower mean foveal sensitivity (as measured by microperimetry), and thinner inner and outer segments at the foveal centre.
Cone density was significantly lower after surgery in eyes that had preoperative OS defects in the fluid cuff. The size of the dark areas was correlated positively with symptom duration before surgery and after surgery with poorer logMAR visual acuity, lower mean foveal sensitivity, thinner inner and outer segments at the centre of the fovea, and larger IS/OS junction decreased reflectivity size.

This study provides evidence that structural damage to large areas of photoreceptors correlated with greater decreases in visual function in eyes with surgical closed MH. They comment that dark areas of the cone mosaic on AO-SLO are likely to represent loss of the cone photoreceptor cells. Dark areas on the AO-SLO correlated positively with the areas of disruption in the IS/OS junction on SD OCT images. In cases where the IS/OS junction appeared intact on SDOCT, there were actually micro-abnormalities in the IS/OS junction that could not be seen on SD-OCT because of its lower resolution. Cone density was significantly lower, and dark area was significantly larger, when an OS defect in the fluid cuff was present before surgery. This finding suggests that when an MH forms, cone photoreceptors are pulled out of the RPE as a result of AP traction on the photoreceptor layer caused by detachment of the perifoveal posterior vitreous.

In keeping with other studies, these findings suggest that functional impairment may be associated closely with foveal photoreceptor alterations in eyes with closed MH.

Yokata et al [69] used AO-SLO to investigate the microstructure of eyes with surgically closed MHs. They found dark regions on the AO-SLO were confined to the preoperative macular hole area. These dark areas corresponded to areas of IS/OS junction disruption, or to areas where the IS/OS line was almost intact but the COST line was disrupted as seen on post operative SD-OCT. They found cone loss ratio in the foveola correlated with
postoperative logMAR visual acuity and mean foveal sensitivity. They concluded that cone damage in the foveola may account for visual disturbance after macular hole surgery.

Hansen et al [70] conducted a pilot study using AOSLO to examine foveal photoreceptor structure in patients after surgery for macular holes and compared these findings with those from SD-OCT. They successfully demonstrated recovery of cone photoreceptor structure over time using longitudinal imaging. This finding corroborates prior studies of visual function where delayed recovery of visual acuity can occur over extended periods of time, in some cases for as long as 2–3 years [71]. They comment that the improvements in foveal photoreceptor mosaic observed here are likely due to recovery of cones within the area of disruption as opposed to "shifting" of neighboring cells given the stability of serial cone density measurements in areas of retina adjacent to these disruptions. Although structural recovery has been documented with SD-OCT [54, 72, 73] the resolution of commercial SD-OCT is not sufficient to resolve individual photoreceptors, and consequently is limited in its ability to analyze the relationship between cone structure and visual function.

1.5.9 Preoperative predictive factors

A number of possible prognostic factors such as the duration of symptoms, preoperative macular hole size, preoperative visual acuity, axial length, age, and sex have been reported [74-76]

Kang et al [19] conducted a meta-analysis of 36 studies reporting the outcome of surgery for macular hole. Eleven studies were entered in the meta-analysis on the basis of the availability of case-specific data points. The authors found that a postoperative visual acuity of 6/12 or better was achieved in 65.9% of the stage 2 MH group. This
figure is significantly higher than in the stage 3 and 4 MH group (15.0%). A multiple regression analysis using the RCT data of the Moorfields Macular Hole Study also concluded that the advanced stages had a worse visual outcome[77].

The duration of symptom is a possible prognostic factor in idiopathic macular hole surgery. While several reports revealed that the shorter duration of symptoms was correlated with better postoperative visual improvement [78-81] other reports did not [76, 82]. However, an important point regarding this issue is that many patients who suffered from macular hole cannot remember exactly the onset of symptoms especially in elderly patients with a healthy contralateral eye. Several lines of evidence have shown that the chance of recovering good visual acuity following MH surgery is decreased if the duration of symptoms is longer than 12 months [83-86].

Kang et al [19] reported the percentage of cases with a postoperative visual acuity of 6/12 or better was significantly higher in the cases with a preoperative visual acuity greater than 6/60, and the rate of 2 or more lines of improvement in visual acuity was significantly higher in the cases with a preoperative visual acuity of 6/60 or worse.

The preoperative size of the MH is known to be inversely correlated with visual outcomes: eyes with a larger diameter hole had worse visual outcomes[77]. In the investigation of 91 eyes enrolled in The Vitrectomy for Macular Hole Study Group, stepwise regression analysis revealed that the preoperative hole size was the only predictor of postoperative visual acuity.
1.5.10 Macular hole parameters and Indices

Numerous attempts have been made to utilise the optical coherence tomography (OCT) parameters obtained from MH eyes to predict visual outcomes. In 2002, Ip et al [80] used OCT to quantify MH size as the shortest distance across the full-thickness defect. This definition of MH size is referred to as the minimum linear diameter (MLD). In their retrospective study of 40 eyes, a trend was found that greater visual acuity improvement was achieved in MHs with an MLD smaller than 400μm. Moreover, in a prospective study of 94 eyes, MH size measured by OCT was identified as being negatively correlated with postoperative visual acuity [74]. Gupta et al [87] also reported that OCT-based preoperative MH size is a significant predictor of visual success. This retrospective study of 132 eyes, found the predicted probability of visual success (better than 20/40) was 93% in patients less than 60 years of age with a MLD <350 μm and a preoperative logMAR visual acuity ≥0.6.

The basal hole diameter is a linear dimension of MH at the level of the retinal pigment epithelium (RPE) layer. Studies have provided conflicting reports as to the predictive trend of the basal hole diameter for visual outcomes. Wakely et al concluded that the smaller the basal hole diameter becomes, the better the postoperative visual acuity is. In their retrospective study of 50 eyes, the odds of visual success (postoperative visual acuity ≥6/12) decreased by 10% for every 26-μm increase in the basal hole diameter[88].However, in a retrospective case series of 38 eyes that were followed up for at least 5 years after surgery, the minimum diameter showed a significant correlation with the final visual acuity, whereas the basal hole diameter did not [89]. In a case series of 21 eyes that underwent MH surgery with C₃F₈ gas tamponade and autologous platelet injection, no correlation was found between the minimum diameter and the visual acuity or visual improvement at 6 postoperative months [90].
The hole height is another preoperative OCT parameter, defined as the greatest distance between the retinal pigment epithelium layer and the vitreoretinal interface. Previous studies concluded that there is no significant relationship between the hole height and postoperative visual outcomes with the exception of one retrospective study showing a negative correlation between the hole height and visual acuity more than 5 years after MH surgery [91].

The photoreceptor inner segment/outer segment (IS/OS) junction line can be better recognised as a hyperreflective band by spectral domain OCT imaging, and the relationship between the length of the IS/OS junction defect and visual outcomes has been investigated. The predictive performance of the IS/OS junction defect length for visual outcomes varies across the studies [55, 63, 72, 92-94]. There are studies reporting that the preoperative IS/OS junction defect length is associated with the postoperative macular sensitivity and visual acuity [55, 93]. However, in a retrospective case series of 51 eyes, no significant correlation was found between the preoperative IS/OS junction defect length and visual acuity up to 12 postoperative months [72]. Matsumiya et al investigated 50 MH eyes and proved that the preoperative IS/OS defect length can predict visual success (visual acuity ≥20/28) at 6 postoperative months. With a cut-off value of 1,500 μm, the specificity and sensitivity were 76 and 64%, respectively [92].

The hole form factor (HFF) was the first calculated OCT index used as a prognostic factor [95]. HFF is the summation of the left and right arm lengths divided by the basal hole diameter. The original case series found that HFF was associated significantly with the probability of anatomic success. Form factors greater than 0.9 had a greater than
80% chance of closure whereas form factors of less than 0.5 predicted a success rate of less than 25%. Form factors between 0.5 and 0.9 did not produce decisive prediction. The HFF is reported to be positively correlated with the postoperative visual acuity, but the correlation is weaker than those for the minimum linear diameter and the basal hole diameter [74, 91].

First reported by Kusuhara et al, the macular hole index (MHI) is defined as the ratio of the hole height to the basal hole diameter[96] They found that eyes with an MHI value ≥0.5 had better post-operative visual acuity than those with an MHI value <0.5. Several studies have reported MHI to be positively correlated to the postoperative visual acuity [88, 89].

The tractional hole index (THI), defined as the ratio of the hole height to the minimum diameter, is another OCT index tested as a predictor for visual outcome. Ruiz-Moreno et al.[89] evaluated preoperative OCT findings as predictive factors for macular hole surgery outcomes. Of the 46 eyes involved in the study, BCVA improvement was observed in 69.6% at 3 months, no change in 26.1% and acuity decreased by one line or more in 4.4%. MHI and THI correlated significantly with postoperative vision at 3 months. Base diameter and minimum diameter showed a significant linear relationship with postoperative BCVA. A better visual result was observed in patients with larger THI values (stronger anteroposterior vitreomacular traction and weaker tangential traction) and larger MHI values. They concluded that minimum diameter and the THI are fair predictors of a gain of two or more lines of decimal BCVA after surgery. A good visual prognosis can be expected for a macular hole with a minimum diameter <311 microns and a THI > 1.41 after surgery. Later studies failed to prove the significant predictive performance of the THI[88, 92].
Wakely et al [88] compared several methods of macular hole measurement using OCT and assessed their predictive capability against anatomical and visual outcomes in a single cohort of patients. They reported that base diameter, macular hole inner opening and minimum linear diameter and MHI were significantly associated with anatomical success, and could be used as effective predictors of anatomical success. The same parameters including THI, were also significantly associated with visual success.

1.5.11 History of surgical technique to close macular holes

Kelly & Wendel [97] developed the modern day concept of macular hole surgery and showed that it was possible to close established full thickness macular holes. Closure of the hole was defined as the flattening of the edges and disappearance of the cuff of subretinal fluid around the hole.

Their procedure included a vitrectomy with a complete posterior vitreous separation, peeling of eventual epiretinal membranes in the macula, tamponade with long-acting gas, and positioning of the patient strictly face-down for the first postoperative week. In their initial report of macular hole surgery in 52 patients, they were able to achieve visual improvement of two or more Snellen lines in 42% and closure of the macular hole in 73% of their patients. Several subsequent case series confirmed the feasibility and good anatomical and functional results of macular hole surgery, especially if the hole was stage 2 or had developed recently (i.e. within 6 months prior to surgery) [81, 98].

We know both from ultrasound and OCT imaging that firm vitreoretinal adhesion is an important risk factor in macular hole formation. Several theories have suggested that traction at this interface is a major factor in their pathogenesis resulting in the initial intrafoveolar split or foveolar detachment. At birth, the posterior vitreous face is attached to the inner most
retinal layers; this attachment is particularly strong at the centre of the macular. With increasing age the vitreous gel gradually degenerates, resulting in anteroposterior (AP) vitreoretinal tractional forces [99]. Glial remodelling in the outer retina may result in tangential traction within the vitreofoveal plane [100]. Both AP traction and tangential forces, or infact a combination, cause separation and splitting of the retinal layers at the fovea, and the development of an intraretinal cyst. This cyst can lose both its inner retinal wall and outer retinal walls leading to the development of a full thickness macular hole. Fluid from the degenerative vitreous gains access to the potential subretinal space, elevating the edges of the retinal hole [101].

The surgical objective is to relieve tractional forces to achieve anatomical closure of the macular hole. Indirectly surgery also activates reparative healing mechanisms. The success rates after a single operation has risen to above 90%. Surgery is associated with an increase in the visual quality of life despite good visual acuity in the fellow eye [102]. A standard operation involves a three-port pars plana vitrectomy, removal of cortical vitreous, removal of epiretinal membrane or internal limiting membrane (ILM), gas fill for endotamponade, and face down positioning for a variable duration.

ILM peeling to relieve tangential forces on the fovea can improve the closure of macular holes after surgery [103]. In addition, its removal will also necessarily injur muller cell footplates and trigger reparative gliosis. Anatomical closure is thought to require chorioretinal adhesion between the edges of the neurosensory retina and between the retina and retinal pigment epithelium.

As mentioned earlier intraocular gas fill is a step widely used in modern day macular hole surgery. Following surgery, face down positioning for a variable period may be advised with
the aim of improving outcome by maintaining contact of the intraocular gas bubble with the macular.

The mechanism by which the tamponade agent facilitates hole closure is subject to debate. The gas is believed to encourage the re-apposition of the edges of the macular hole and to provide a smooth scaffold for the migration of glial cells, principally composed of Muller cells and fibrous astrocytes, that promote and maintain hole closure [104]. Tornambe’s “waterproofing” theory suggests the gas isolates the macular hole from the vitreous fluid to keep it dry. Fluid contact during the postoperative period may interfere with the bridging between glial cells and prevent sealing of the edges of the hole and adhesion with the RPE. Tornambe suggests that a larger gas fill will ensure the macular remains dry with less dependence on positioning [101]. The “floatation force” concept holds that gas bubbles exert an upwards force at their apex, at the point of contact with retina, and face down positioning therefore helps to maintain the bubble in the optimal position for bubble buoyancy forces to be applied to the macular [105]. The buoyancy force arises due to differences in the specific gravities between intraocular fluid and gas. The gas-retina contact also serves to hold the macular hole edges against the RPE and helps to displace subretinal fluid away from the macular. It has also been suggested the gas provides mechanical counter pressure against tractional vectors [105].

After vitrectomy, 75% will develop visually significant cataracts within 1 year and 95% within 2 years and require subsequent cataract surgery ([106]. Some centres advocate combining cataract removal and macular hole repair (phacovitrectomy) as one procedure whereas others prefer a sequential technique, only addressing the cataract if visually significant.
1.5.12 Post-operative positioning review

Following on from Kelly and Wendels landmark pilot study, empirical observations led to the conclusion that face down positioning improved the success rates. Face down positioning is still considered essential to success of macular hole surgery, although this has never been proven in a controlled trial.

The process of face down positioning is not without risk, and as mentioned earlier is unproven. Maintaining this posture can be more difficult in the elderly with an increased prevalence of cervical and lower back problems [107]. Ulnar nerve palsies, ulnar decubitis [108] and angle closure glaucoma [109] have been reported as potential complications of maintaining this posture. There also is an increased risk of thromboembolism as reported by Au Eong and colleagues [110]. Face down positioning is an arduous task and the prospect can be a significant deterrent to surgery for some people [111]. It is disabling, delays rehabilitation and in some instances is wholly unfeasible even with the aid of specially designed supports. The majority of patients in one study described face down positioning as difficult or very difficult [112] with another study reporting compliance with positioning averaged only 38% of the prescribed time [113].

1.5.13 Cochrane Review

A recently published Cochrane review [114] aimed to evaluate the evidence of the impact of post-operative face down positioning on the outcome of surgery for macular hole. The review concluded that there is currently insufficient evidence from which to draw firm conclusions about the impact of postoperative face-down positioning on the outcome of surgery for macular hole
Three randomised controlled trials [115-117] were included from the 266 records identified electronically. Randomisation of participant allocation to treatment groups was managed independently of study investigators in all three randomised studies with concealment of allocation from investigators and participants until surgery.

Guillaubey et al [115] compared outcomes following five days of 8 hours per day face down positioning, and five days of seated postoperative positioning. 150 eyes (78 in face down group) of 144 participants with stage 2 to 4 idiopathic macular holes were included. All participants underwent vitrectomy or phacovitrectomy involving ILM peeling. For macular holes less than 500 microns SF6 gas was used, holes between 500 to 800 microns C2F6 was used and for holes larger than 800 microns C3F8 was used. Masking of the investigators assessing the outcome was not reported in this study.

The intervention of face down positioning was associated with improved macular hole closure rates (RR 1.10, 95% CI 1.00 – 1.20, P=0.05). The outcome following phacovitrectomy was similar but not statistically significant (RR 1.11, 95% CI 0.97 – 1.27).

For holes less than 500 microns: RR 1.03, 95% CI 0.97 – 1.15.

Holes larger than 500 microns: RR 1.19, 95% CI 0.94 – 1.51.

Holes larger than 800 microns: RR 1.33, 95% CI 0.54 to 3.32.

For the above sub-groups the effect did not reach statistical significance. There was no reported significant effect of posturing in either vitrectomy or phacovitrecomy groups in holes less than 400 microns: RR 1.03, 95% CI 0.95 – 1.12. In holes greater than 400 microns, posturing significantly improved the rates of successful hole closure RR 1.20, 95% CI 1.01 – 1.42 P=0.04. No adverse events of posturing were reported.

Tadayoni et al [117] compared outcomes following 10 days of 22 hours per day face down positioning (with compliance assessed through participant diaries), with no positioning for
participants with small macular holes measuring less than 400 microns in diameter. 69 eyes (34 in face down group) from 69 participants with stage 2 to 4 idiopathic macular holes were included. All participants underwent vitrectomy with C2F6 gas but ILM peeling was not undertaken. Although there was no formal masking, process investigators were asked to keep themselves masked to patient allocation where possible.

Face down positioning of 10 days was associated with an increased success rate of closure following vitrectomy without ILM peel, but this was not statistically significant (RR 1.03, CI 0.90 to 1.17).

One of the 35 participants (3%) developed brachial plexopathy following 10 days of positioning.

Lange et al [116] compared outcomes following 10 days of face down positioning for 50 minutes in every hour, with no positioning. 30 eyes (15 in the face down group) from 30 participants with stage 2 to 4 idiopathic macular holes were included. All participants underwent vitrectomy with ILM peel and C3F8 fluid-gas exchange. Hole closure on OCT was determined by assessors masked to treatment allocation.

They found face down positioning was associated with an improvement in success rates of closure following vitrectomy with ILM peel (RR 1.58, 95% CI 1.00 – 2.50, P=0.01).

For holes less than 400 microns there was no reported significant effect of face down positioning following vitrectomy with ILM peel and 10 days of positioning (RR 1.00, 95% CI 0.68 – 1.46).

For holes larger than 400 microns, face down positioning significantly improved rates of hole closure (RR 2.27, 95% CI 1.04 – 4.97, P=0.04).

The Cochrane review concluded that the three randomised controlled studies identified were consistent in their findings of the effect of positioning on hole closure but heterogeneous.
study design prevented a more robust meta-analysis of their findings. Estimated effects were in favour of posturing but estimates were not statistically significant for small hole sizes.

There is currently insufficient evidence from which to draw firm conclusions about the impact of postoperative face-down positioning on the outcome of surgery for macular hole. Of three RCTs, two suggested a benefit in larger holes but none demonstrated evidence of a benefit in smaller holes.

A meta-analysis by Tatham and Banerjee [118] also concluded that there is insufficient evidence to allow firm conclusions as to whether face down posturing following macular hole surgery influences hole closure rates. They included nine studies in their meta-analysis. Studies were divided into two groups depending on the duration of face down posturing investigated. The meta-analysis revealed a relative risk on anatomical failure of 1.34 (95% CI 0.66 – 2.72) with face down posturing for 24 hours or less compared with face down posturing for 5 – 10 days, but this was not statistically significant (p=0.42).

There are currently five non-randomised comparative studies [104, 119-122] in the published literature investigating face down posturing following macular hole surgery. All are consistent in showing a lack of significant effect of face down positioning on successful hole closure.

Alberti M et al [123] published their results of a randomised controlled trial to determine whether non-supine positioning (NSP) is non-inferior to face-down positioning (FDP) in full-thickness macular hole (FTMH) surgery. Patients in the FDP group were instructed to maintain a face-down position for 10 hours/day for three full days. Those in the NSP group were instructed to maintain a forward or slightly downward gaze. All patients were asked to avoid looking up during the daytime and avoid the supine position at night. After three postoperative days (72 hours), patient positioning was no longer required. A total of 34 patients were in each of the two groups. Final analysis of 68 patients demonstrated equal
closure rates in the FDP and NSP groups, 33 closed FTMHs out of 34 (97.1%, 95% CI: 84.7-99.9) and confirmed their hypothesis that NSP is non-inferior compared with FDP.

The same group a year earlier had the results of a retrospective study published also suggesting similar closure rates, 95.5% and 96.4% in the FDP group and the NSP group, respectively.[124]

Two other retrospective studies recently published have also indicated that non supine positioning may be as effective as face down positioning. Forsaa et al [125] compared the efficacy of short - term non - supine positioning (NSP) and strict face - down positioning (FDP) in the repair of macular hole. The closure rates following a single operation were 30/33 (90.9%) in the FDP group, and 31/34 (91.2%) in the NSP group, respectively (p=0.97). Feist et al [126] also found the anatomical success rates were similar between the two groups with 96% of final hole closure (55/57) in the face-down group versus 100% (25/25) in the non-supine group.

Essex et al [127] in their nonrandomized, observational cohort study found that withholding face-down positioning was non-inferior to face down-positioning in holes ≤400 μm in diameter. In holes >400 μm in diameter, non-inferiority of withholding face-down positioning could not be concluded.
2.0 Using the Shadowgram overlay tool to assess macular hole geometry on Topcon OCT

2.1 Introduction

Several authors have described different methods of macular hole measurement using OCT scans, including minimum linear dimension [96], base hole diameter [80], hole height [28], IS/OS junction line [30], hole form factor (HFF) [86], macular hole index (MHI) [96], diameter hole index (DHI) [87] and tractional hole index (THI) [87].

The previously mentioned parameters were all measured from single B-scan images generated from a number of single A-scans. The measured parameters depend on correct centering of the OCT scan and are conventionally described in terms of linear measurements in a single cross-sectional plane. This approach makes the assumption that the hole has similar dimensions in all planes and fails to take into account possible irregularities.

The shadowgram function is an overlay tool available on Topcon OCT (Topcon Medical Systems Inc., Oakland, CA, USA) for the fundus image. It is the OCT signal reflection from a coronal or Z plane of the most reflective component of the retina, the RPE. It is useful clinically as it can sometimes explain appearances on the B-scan and en face image, such as reduced signal which can be down to opacities, or vitreous floaters which the shadowgram would clearly illustrate. With respect to macular hole imaging the ‘shadowgram’ function presents the hole in a compressed en-face image which by accounting for any irregularity may offer more accurate measurement in terms of 2-dimensional areas. Our study aimed to determine the anatomical significance of the features of the shadowgram by comparison with OCT parameters.
We set out to compare the shadowgram areas defined by a freehand circle with those defined by an automated circle, and compared the correlation of linear dimensions on OCT and areas on the shadowgram.

This study aimed to compare some of these methods of macular hole measurement and regress them against anatomical and visual outcomes in a single cohort of patients.

2.2 Methods

We retrospectively collected data from 50 patients diagnosed with idiopathic macular hole who had surgery to promote closure. Demographic data is showed in Table 1. Preoperative vision and post-operative final vision was recorded, as was whether the hole had closed or not following surgery. Pre- and post-operative lens status of the patients was also recorded. The preoperative Topcon OCT images were analysed. The caliper function was used on the B-scan image to measure the minimum linear diameter (MLD), inner opening diameter (IOD), ellipsoid zone defect (EZD) across the hole and the base diameter (BD).

The shadowgram overlay tool (Figure 3) was then applied to the fundus image. This image was then exported to ImageJ (U. S. National Institutes of Health, Bethesda, Maryland, USA, https://imagej.nih.gov/ij/, 1997-2016). The horizontal length of the outer ring, middle ring and inner ring was then measured. A free hand circle and an automated circle was drawn around the outer and inner rings. All imageJ measurements were converted from pixles to microns for comparison with measurements in microns taken from the Bscan image.
Holes were considered closed, indicating anatomical success, if there was complete circumferential hole rim reattachment without foveal neurosensory retinal defect demonstrated on OCT. This was taken as the primary outcome measure. A secondary outcome measure of ‘visual success’ was defined as a postoperative visual acuity of 0.3 logMAR or less (better than or equal to 6/12,) at up to a year postoperatively, in order to remain consistent with other UK studies [86].

Figure 3: Top image – Single Bscan image from Topcon OCT scan showing full thickness macular hole; Bottom image – shadowgram overlay; Purple horizontal arrow – Horizontal length of EZ defect; Red circle/arrows – Outer ring corresponding to EZ defect; Yellow
circle/arrows – Middle ring corresponding to BD; White circle/arrows – Inner ring corresponding to MLD

2.3 Shadowgram results

2.3.1 Summary of data

Fifty Topcon OCT images were reviewed. The mean age was 68.7, with 19 males and 31 female patients. 37 patients were Caucasian, 7 Asian and 5 Afro-Caribbean. Twenty two were right eyes and 28 were left (Table 2).

<table>
<thead>
<tr>
<th>Number of eyes</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>68.7</td>
</tr>
<tr>
<td>Sex</td>
<td>19 Male, 31 Female</td>
</tr>
<tr>
<td>Laterality</td>
<td>22 right, 28 left</td>
</tr>
</tbody>
</table>

Table 2: Demographic data

Mean preop LogMAR visual acuity was 0.90. Mean final LogMAR was 0.56. 20/50 (40%) eyes achieved ‘visual success’ with a post op acuity of 0.3 logMAR or less. The mean improvement in VA was 0.32 logMAR units.

Forty-three out of 50 (86%) macular holes closed following primary surgery. Six holes had secondary surgery to close the hole with 5/6 achieving anatomical closure. One patient did not want further surgery following unsuccessful primary repair.

Twenty-four out of 50 (48%) eyes had holes larger than or equal to 400 μm. Eighteen (75%) of 24 eyes with an idiopathic macular hole larger than or equal to 400 μm achieved
anatomical closure after primary repair. For the group of macular holes measuring less than 400 μm, closure was observed in 25 (96%) of 26 eyes.

All 50 patients were phakic pre-operatively. Two patients had simultaneous cataract surgery and macular hole repair. At final follow up 36/50 (72%) patients were pseudophakic.

2.3.2 Parameter measurements

The mean base diameter measured on the OCT was 876.92μm, minimum linear diameter was 427.20μm, and mean EZ defect 2372.66μm (Table 3).

<table>
<thead>
<tr>
<th>OCT dimension</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean EZ defect</td>
<td>2372.66 μm (SD 447.5)</td>
</tr>
<tr>
<td>Mean Base diameter</td>
<td>876.92 μm (SD 313.4)</td>
</tr>
<tr>
<td>Mean Minimum linear diameter</td>
<td>427.20 μm (SD 174.7)</td>
</tr>
</tbody>
</table>

Table 3: OCT based parameters

<table>
<thead>
<tr>
<th>Shadowgram dimension</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Outer ring diameter</td>
<td>2422.67 μm (SD 472.2)</td>
</tr>
<tr>
<td>Mean Middle ring diameter</td>
<td>801.80 μm (SD 301.3)</td>
</tr>
<tr>
<td>Mean inner ring diameter</td>
<td>418.80 μm (SD 173.4)</td>
</tr>
</tbody>
</table>

Table 4: Shadowgram based parameters

The mean outer ring horizontal length of the shadowgram was 2422.67 μm, mean middle ring horizontal length 801.80 μm and mean inner ring horizontal length 418.80 μm (Table 4).
The measurements taken from the shadowgram were all highly correlated with their OCT counterparts (Table 5).

<table>
<thead>
<tr>
<th>OCT parameter</th>
<th>Shadowgram parameter</th>
<th>Pearsons correlation (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum liner diameter</td>
<td>Inner ring diameter</td>
<td>0.98 (p&lt;0.0001)</td>
</tr>
<tr>
<td>Base diameter</td>
<td>Middle ring diameter</td>
<td>0.91 (p&lt;0.0001)</td>
</tr>
<tr>
<td>EZ defect length</td>
<td>Outer ring diameter</td>
<td>0.87 (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

Table 5: Correlations between OCT and shadowgram parameters

The mean outer ring area measured by freehand was $183540.87 \, \mu m^2$ (SD 61882) and measured by automated circle was $190147.08 \, \mu m^2$ (SD 70535).

The mean middle ring area measured by freehand was $144061.98 \, \mu m^2$ (SD 69413) and measured by automated circle was $149031.72 \, \mu m^2$ (SD 72458).

The mean inner ring area measured by freehand was $9668.96 \, \mu m^2$ (SD 7553), and measured by automated circle was $9195.67 \, \mu m^2$ (SD 6885).

The freehand and automated circle measurements were also well correlated, outer ring ($r=0.954$, $p<0.0001$), middle ring ($r=0.943$, $p<0.0001$) and inner ring ($r=0.980$, $p<0.0001$)

Eyes with a MLD larger than or equal to 400 μm had poorer preoperative visual acuity (mean 1.02) than eyes with macular holes smaller than 400um (mean 0.78, $p = 0.003$)

Eyes with a MLD larger than or equal to 400 μm had poorer post-operative visual acuity (mean 0.65) than eyes with macular holes smaller than 400 μm (mean 0.48, $p = 0.027$)
Weak to moderate correlation was found between MLD and the size of the EZ defect ($r = 0.351$, Pearson Correlation).

The measured OCT parameters (MLD, EZ and BD) and the corresponding shadowgram areas showed varying levels of correlation with pre-operative and final visual acuity in the cohort of 50 eyes (Table 6).

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Correlation coefficient for Pre op VA</th>
<th>Correlation coefficient for Final VA</th>
<th>Correlation coefficient for Final VA (pseudophakes/closed holes only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT EZ defect</td>
<td>0.24 (p=0.09)</td>
<td>0.11 (p=0.441)</td>
<td>0.26 (p=0.310)</td>
</tr>
<tr>
<td>Free hand outer ring area</td>
<td>0.21 (p=0.143)</td>
<td>0.20 (p=0.169)</td>
<td>0.31 (p=0.247)</td>
</tr>
<tr>
<td>Automated circle outer ring area</td>
<td>0.20 (p=0.157)</td>
<td>0.20 (p=0.640)</td>
<td>0.34 (p=0.166)</td>
</tr>
<tr>
<td>OCT Base diameter length</td>
<td>0.29 (p=0.04)</td>
<td>0.06 (p=0.700)</td>
<td>0.10 (p=0.521)</td>
</tr>
<tr>
<td>Free hand middle ring area</td>
<td>0.22 (p=0.150)</td>
<td>0.20 (p=0.235)</td>
<td>0.19 (p=0.211)</td>
</tr>
</tbody>
</table>
### Table 6: Correlations between OCT dimensions/shadowgram areas and visual acuity

<table>
<thead>
<tr>
<th></th>
<th>0.22 (p=0.132)</th>
<th>0.21 (p=0.192)</th>
<th>0.21 (p=0.189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automated circle area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>middle ring area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.42(p=0.002)</td>
<td>0.32 (p=0.022)</td>
<td>0.36 (p=0.030)</td>
</tr>
<tr>
<td>OCT MLD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free hand Inner ring area</td>
<td>0.15 (p=0.293)</td>
<td>0.17 (p=0.226)</td>
<td>0.12 (p=0.263)</td>
</tr>
<tr>
<td>Automated circle inner</td>
<td>0.22 (p=0.125)</td>
<td>0.20 (p=0.155)</td>
<td>0.14 (p=0.175)</td>
</tr>
<tr>
<td>ring area</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.4 Shadowgram discussion

The mean preoperative visual acuity and mean improvement of visual acuity in this cohort of 50 eyes is in keeping with other studies [128]. 86% of holes closed after primary repair. Eyes with a minimum linear diameter larger than or equal to 400 μm had both a preoperative and postoperative worse visual acuity than holes with a MLD less than or equal to 400 μm.

The minimum linear diameter, base diameter and EZ defect length showed a very strong correlation with their shadowgram counterparts (inner, middle and outer rings respectively).
A positive correlation coefficient indicates a positive linear relationship between vision and the 3 linear OCT measurements and the shadowgram areas. The strength of this relationships ranged from very mild to moderate (see Table 5). The linear measurement of minimum linear diameter (MLD) on OCT showed the greatest correlation with vision (0.418 for baseline vision and 0.361 for final vision) and was statistically significant.

As previously mentioned the MLD and inner ring diameter showed a strong correlation (0.975), so one would think the inner ring area would have shown a better correlation with vision but this was not the case (see Table 5).

Free hand and automated circle measurements of the shadowgram correlated very closely, indicating that the configuration of a macular hole is highly regular.

From a clinical perspective, the parameters of minimum linear diameter, base diameter and ellipsoid zone length have all been shown to provide some prognostic indicators of anatomical and functional success following macular hole repair ([55, 80, 88, 93]. Several authors have used a combination of parameters to provide prognostic information: namely the hole form factor ([95] which is the summation of the left and right arm lengths divided by the basal hole diameter, the macular hole index (hole height divided by the base diameter) [96] and the tractional hole index (hole height divided by minimum linear diameter) [89].

The shadowgram function on Topcon OCT provides an alternative method of imaging the macular. The results of this study conclude that the shadowgram offers no significant advantage over linear based OCT measurements of macular holes. Further investigations of shadowgram macular imaging may be of interest.
This project was financed by the Special Trustees – a Moorfields Charity, and the NIHR BRC at Moorfields Eye Hospital.

3.0 Reproducibility and reliability for measurements of macular hole geometry using the caliper tool on three different Optical Coherence Tomography devices

3.1 Introduction

Macular holes are full thickness defects in neurosensory retina at the fovea from the internal limiting membrane to the outer segment of the photoreceptors. Recently we have been paying more attention into classifying which holes are more likely to close than others and lateral measurement of the size of the hole is a well documented prognostic factor [74].

Optical coherence tomography (OCT) provides high resolution cross sectional images of the layers of the retina. Most modern spectral domain OCT (SD-OCT) scanners provide a caliper function, which clinicians use and rely on to provide prognostic indicators of the likelihood of success of macular hole surgery and eligibility for surgery. There is however scant evidence behind the repeatability and reproducibility of lateral SD-OCT scan measurements in humans [129, 130]. We have extrapolated reproducibility from few studies, one of which used a model eye [131]. This paper looked at lateral and axial measurements from a human retina phantom on two instruments each from four spectral-domain optical coherence tomography instruments. A total of 80 images were assessed. They found lateral and axial manual measurements have greater variance across different SDOCT platforms than between instruments from the same platform. Conversion factors for measurements from different platforms can produce normalized values for patient care and clinical studies. Another looked at the reproducibility of manual sub-foveal choroidal
thickness measurements compared to automated measurements in 44 patients with neovascular age related macular degeneration [132]. They concluded that the automated algorithm generally yielded smaller choroidal thickness than the raters with a moderate level of agreement. However, its repeat scan measurement repeatability was comparable to that of the manual measurements.

Furthermore, variability of vertical measurements between machines has been documented. Variability is determined by technical factors including the scan protocol used, which segmentation algorithms are used in the machines software, the resolution of the machine and the fixation of the individual, as well as anatomical factors of the patient, including axial length and curvature of the retina [133-136]. The technical factors vary between manufacturers so direct comparison between the different machines is problematic [131, 137]. It has been shown that variability between machines using the same platform is less than the variability between machines across different platforms – this is to be expected statistically since one source of variability (platform) has been removed in the former comparison.

The final consideration when looking for reliability and reproducibility of measurements is the investigator themselves. Pierro et al provided estimates of inter operator variability in the measurements of foveal thickness [136], but the same for lateral measurements has not been shown.

Although all of the published literature used OCT measured preoperative macular hole geometry to predict visual outcomes following surgery, the results are variable [55, 63, 74, 88, 89, 96, 138-140]. This variability may be attributed to the somewhat poor reproducibility and reliability of OCT measurements. It is important that researchers be explicit in describing
what instruments and software versions they have used. The OCT parameters that were assessed in previous studies were either measured manually or calculated based on manual measurements, which raised doubts about the accuracy of the OCT parameter measurements.

For the benefits of this study the term reliability is used when the same measurement is made on the same subject under identical conditions, and reproducibility is used when there are changing conditions (e.g. different graders).

The purpose of this current study is to determine the intragrader reliability and intergrader reproducibility of various parameters of a macular hole on three different OCT devices; Stratus OCT (Carl Zeiss Meditec, Inc. Dublin, CA), Spectralis HRA+OCT (Heidelberg Engineering, Inc., Heidelberg, Germany) and Topcon 3D – OCT 2000 (Topcon, Tokyo, Japan) using the inbuilt calliper tool on each of the devices.

3.2 Methods

The study included analysis of single B scan images of 100 full thickness macular holes on the Status OCT, 100 images on the Topcon OCT and 50 images on the Spectralis OCT. These images were all taken from patients attending retina clinics at Moorfields Eye Hospital, London.

Built-in software callipers were used to perform manual measurements of the following parameters on each device: Base diameter (BD), Inner opening (IO), Minimum linear diameter (MLD), Hole height (HH), Left side elevation (LE) and Right side elevation (RE) (Figure 4).
Figure 4: Full thickness macular hole with the six measured parameters - Base diameter - BD (a), Minimum linear diameter - MLD (b), Left arm (c), Right arm (d) Height (e), inner opening - IO (f) (Image reference: [88])

Grader 1 (SP) measured the dimensions once and then again two weeks later after the study images were randomly shuffled. This was done for the images on each device to assess intragrader reliability. Two weeks was deemed long enough for the observer to have forgotten their previous measurement particularly after random reshuffle.

Grader 2 (EC) measured the images from the Topcon OCT once.
Grader 3 (NK) measured the images from the Stratus and Spectralis OCT.

Reliability was assessed by comparing the first and second measurements made by grader 1 on all three instruments. Reproducibility was assessed by comparing the first measurement made by observer 1 against a second grader (either EC or NK).

All statistical tests were performed by using GraphPad Prism software (GraphPad Software, San Diego, California). All Values presented are in microns. Bland-Altman plots (BA plot) and histograms were constructed for each of the measured parameters for both the intra and inter grader groups.
Statistical significance was accepted at \( P < 0.05 \).

### 3.3 Results

A total of 100 images of macular hole taken on Stratus OCT, 100 from Topcon OCT and 50 from Spectralis OCT were assessed. The means and standard deviations for Grader 1 measurements (Table 7) and then 2 weeks later (Table 8) are shown below.

Table 9 shows the means and standard deviations from the other two graders.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spectralis</th>
<th>Topcon</th>
<th>Stratus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>BD</td>
<td>955.8</td>
<td>295.1</td>
<td>907.2</td>
</tr>
<tr>
<td>IO</td>
<td>589</td>
<td>176</td>
<td>707.9</td>
</tr>
<tr>
<td>MLD</td>
<td>425.2</td>
<td>159</td>
<td>445.7</td>
</tr>
<tr>
<td>Height</td>
<td>433.3</td>
<td>67.38</td>
<td>409.5</td>
</tr>
<tr>
<td>Left</td>
<td>295.7</td>
<td>114.6</td>
<td>296.6</td>
</tr>
<tr>
<td>Right</td>
<td>270.2</td>
<td>100.6</td>
<td>294.6</td>
</tr>
</tbody>
</table>

Table 7: Means and standard deviations for the first measurements from grader 1 (SP)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spectralis</th>
<th>Topcon</th>
<th>Stratus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>BD</td>
<td>952.9</td>
<td>289.3</td>
<td>891.9</td>
</tr>
<tr>
<td>IO</td>
<td>585.6</td>
<td>172.3</td>
<td>707.5</td>
</tr>
<tr>
<td>MLD</td>
<td>425.6</td>
<td>159.5</td>
<td>435.2</td>
</tr>
<tr>
<td>Height</td>
<td>436.1</td>
<td>66.26</td>
<td>412</td>
</tr>
<tr>
<td>Left</td>
<td>298.7</td>
<td>116.4</td>
<td>295.2</td>
</tr>
<tr>
<td>Right</td>
<td>272</td>
<td>102.1</td>
<td>294.8</td>
</tr>
</tbody>
</table>

Table 8: Means and standard deviations for the second measurements from grader 1 two weeks after the first.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spectralis (NK)</th>
<th>Mean</th>
<th>SD</th>
<th>Topcon (EC)</th>
<th>Mean</th>
<th>SD</th>
<th>Stratus (NK)</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD</td>
<td>974.1</td>
<td>294.1</td>
<td></td>
<td>924.3</td>
<td>351.7</td>
<td></td>
<td>921.5</td>
<td>453.3</td>
<td></td>
</tr>
<tr>
<td>IO</td>
<td>492.8</td>
<td>176.7</td>
<td></td>
<td>489.1</td>
<td>165.1</td>
<td></td>
<td>442.9</td>
<td>229</td>
<td></td>
</tr>
<tr>
<td>MLD</td>
<td>432</td>
<td>175.5</td>
<td></td>
<td>432.9</td>
<td>174.7</td>
<td></td>
<td>420.2</td>
<td>229.4</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>436.3</td>
<td>62.21</td>
<td></td>
<td>432.1</td>
<td>64.83</td>
<td></td>
<td>395.2</td>
<td>75.2</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>293.5</td>
<td>107.4</td>
<td></td>
<td>287.2</td>
<td>119.6</td>
<td></td>
<td>333.6</td>
<td>243.9</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>258.2</td>
<td>96.01</td>
<td></td>
<td>297.2</td>
<td>141</td>
<td></td>
<td>309.3</td>
<td>220.4</td>
<td></td>
</tr>
</tbody>
</table>

Table 9: Means and standard deviations of measurements take from grader 2 (EC) and grader 3 (NK).
Figure 5: Column bar graph showing means and standard deviations of all 6 Spectralis measurements from all graders.
Figure 6: Column bar graph showing means and standard deviations of all 6 Topcon measurements from all graders.
Figure 7: Column bar graph showing means and standard deviations of all 6 Stratus measurements from all graders.
The means and standard deviations are represented graphically in Figures 5, 6 and 7 for Spectralis, Topcon and Stratus respectively.

Tables 10 and 11 show the data from the intragradr and intergrader measurements respectively. Bias, 95% confidence intervals for the bias, standard deviation of the bias, p value and 95% limits of agreement were calculated for each measurement.

Appendix 9.4 shows Figures 8-25 the Bland-Altman plots and histograms for the intragradr measurements with Figures 26-43 for the intergrader measurements.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bias</th>
<th>95% CI for bias</th>
<th>SD of the differences</th>
<th>Paired t-test (p value)</th>
<th>Limits of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spectralis - BD</strong></td>
<td>2.84</td>
<td>-7.07, 12.75</td>
<td>35.75</td>
<td>0.58</td>
<td>-67.23, 72.91</td>
</tr>
<tr>
<td>IO</td>
<td>3.42</td>
<td>-2.19, 9.03</td>
<td>20.23</td>
<td>0.24</td>
<td>-36.23, 43.07</td>
</tr>
<tr>
<td>MLD</td>
<td>-0.44</td>
<td>-4.99, 4.11</td>
<td>16.42</td>
<td>0.85</td>
<td>-32.61, 31.73</td>
</tr>
<tr>
<td>Height</td>
<td>2.8</td>
<td>-0.65, 6.25</td>
<td>12.45</td>
<td>0.12</td>
<td>-21.6, 27.2</td>
</tr>
<tr>
<td>Left</td>
<td>2.94</td>
<td>-4.77, 7.71</td>
<td>17.2</td>
<td>0.23</td>
<td>-30.77, 36.65</td>
</tr>
<tr>
<td>Right</td>
<td>-1.74</td>
<td>-6.61, 3.13</td>
<td>17.55</td>
<td>0.49</td>
<td>-36.13, 32.65</td>
</tr>
<tr>
<td><strong>Topcon - BD</strong></td>
<td>15.29</td>
<td>8.29, 22.29</td>
<td>35.7</td>
<td>&lt;0.0001</td>
<td>-54.67, 85.25</td>
</tr>
<tr>
<td>IO</td>
<td>0.45</td>
<td>-6.30, 7.20</td>
<td>34.46</td>
<td>0.9</td>
<td>-67.09, 67.99</td>
</tr>
<tr>
<td>MLD</td>
<td>10.54</td>
<td>5.70, 15.38</td>
<td>24.69</td>
<td>&lt;0.0001</td>
<td>-37.85, 58.93</td>
</tr>
<tr>
<td>Height</td>
<td>-2.53</td>
<td>-5.03, -0.03</td>
<td>12.77</td>
<td>0.05</td>
<td>-27.56, 22.50</td>
</tr>
<tr>
<td>Left</td>
<td>1.41</td>
<td>-3.51, 6.33</td>
<td>25.08</td>
<td>0.58</td>
<td>-47.75, 50.57</td>
</tr>
<tr>
<td>Right</td>
<td>-0.19</td>
<td>-4.12, 3.74</td>
<td>20.06</td>
<td>0.92</td>
<td>-39.51, 39.13</td>
</tr>
<tr>
<td><strong>Stratus - BD</strong></td>
<td>1.54</td>
<td>-8.60, 11.68</td>
<td>51.76</td>
<td>0.77</td>
<td>-99.92, 103</td>
</tr>
<tr>
<td>IO</td>
<td>11.42</td>
<td>2.44, 20.40</td>
<td>45.83</td>
<td>0.01</td>
<td>-78.4, 101.2</td>
</tr>
<tr>
<td>MLD</td>
<td>1.97</td>
<td>-6.36, 10.30</td>
<td>42.5</td>
<td>0.64</td>
<td>-81.33, 85.27</td>
</tr>
<tr>
<td>Height</td>
<td>0.05</td>
<td>-3.63, 3.73</td>
<td>18.76</td>
<td>0.98</td>
<td>-36.72, 36.82</td>
</tr>
<tr>
<td>Left</td>
<td>8.29</td>
<td>1.78, 14.80</td>
<td>33.21</td>
<td>0.01</td>
<td>-56.8, 7.38</td>
</tr>
<tr>
<td>Right</td>
<td>1.28</td>
<td>-3.16, 5.72</td>
<td>22.64</td>
<td>0.57</td>
<td>-43.09, 45.65</td>
</tr>
</tbody>
</table>

Table 10: Intragradr measurement analysis for all three OCT devices
**Reliability**

**Intragrader Spectralis results**

The measurement with the smallest bias was the minimum linear diameter (0.44, p=0.85). Inner opening showed the greatest bias of all the measurements (3.42, p=0.24). The base diameter measurement had the largest width of limits of agreement (SD 35.75) and the height measurement had the narrowest limits of agreement (SD 12.45).

The Bland-Altman plot (BA plot) for base diameter measurement, inner opening, minimum linear diameter, height, left side and right side suggests no trend and that the variability seems to be consistent. The histogram suggests a normal distribution to the data (Appendix 9.4: Figure 8-13).

**Intragrader Topcon results**

The measurement with the smallest bias was that of the right side (0.19, p=0.92), while the greatest bias was for the base diameter measurement (15.29, p<0.0001). The base diameter measurement had the largest width of limits of agreement (SD 35.70) and the height measurement had the narrowest limits of agreement (SD 12.77)

The BA plots and histograms for the minimum linear diameter, height, left and right sides suggest variability to be consistent and the data to be normally distributed (Appendix 9.4: Figure 16,17,18,19). The BA plots for base diameter and inner opening suggest that the difference between measurements increases up to a cut off of approximately 1500 and 1000 microns
respectively (Appendix 9.4: Figure 14,15). The histogram for base diameter shows a normal distribution, but for inner opening this was not the case.

**Intragrader Stratus results**

The measurement with the smallest bias was the height (0.05, p=0.98). Inner opening measurement had the greatest bias (11.42, p=0.01). Base diameter had the largest width of limits of agreement (SD 51.76), and the height measurement had the narrowest width of limits of agreement (SD 18.76).

The BA plots and histograms for base diameter, inner opening, minimum linear diameter, height and left side suggest consistent variability and that the data is not normally distributed (Figures 20,21,22,23,24). The BA plot for the right side measurement suggests that the difference between measurements increases to a cut off of approximately 400 microns (Appendix 9.4: Figure 25).
Reproducibility

**Intergrader Spectralis results**

The measurement with the smallest bias was the left side (2.26, \(p=0.78\)) while the greatest bias was for the inner opening (96.22, \(p<0.0001\)). Inner opening measurement had the largest width.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bias</th>
<th>95% CI for bias</th>
<th>SD of the differences</th>
<th>Paired t-test (p value)</th>
<th>Limits of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spectralis - BD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BD</td>
<td>-18.28</td>
<td>-33.09, -3.48</td>
<td>53.42</td>
<td>0.02</td>
<td>-123, 86.42</td>
</tr>
<tr>
<td>IO</td>
<td>96.22</td>
<td>66.89, 125.55</td>
<td>105.8</td>
<td>&lt;0.0001</td>
<td>-111.2, 303.7</td>
</tr>
<tr>
<td>MLD</td>
<td>-6.8</td>
<td>-30.56, 16.96</td>
<td>85.71</td>
<td>0.68</td>
<td>-174.8, 161.2</td>
</tr>
<tr>
<td>Height</td>
<td>-2.98</td>
<td>-10.77, 4.81</td>
<td>28.1</td>
<td>0.46</td>
<td>-58.06, 52.1</td>
</tr>
<tr>
<td>Left</td>
<td>2.26</td>
<td>-13.29, 17.81</td>
<td>56.1</td>
<td>0.78</td>
<td>-107.7, 112.2</td>
</tr>
<tr>
<td>Right</td>
<td>12</td>
<td>-1.11, 25.11</td>
<td>47.3</td>
<td>0.08</td>
<td>-80.71, 104.7</td>
</tr>
<tr>
<td><strong>Topcon - BD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IO</td>
<td>17.07</td>
<td>6.73, 27.41</td>
<td>52.78</td>
<td>0.002</td>
<td>-120.5, 86.38</td>
</tr>
<tr>
<td>MLD</td>
<td>218.8</td>
<td>181.68, 428.85</td>
<td>189.4</td>
<td>&lt;0.0001</td>
<td>-152.4, 589.9</td>
</tr>
<tr>
<td>Height</td>
<td>12.84</td>
<td>-4.56, 27.24</td>
<td>88.8</td>
<td>0.15</td>
<td>-161.2, 186.9</td>
</tr>
<tr>
<td>Left</td>
<td>-22.58</td>
<td>-25.99, -19.17</td>
<td>17.41</td>
<td>&lt;0.0001</td>
<td>-56.71, 11.55</td>
</tr>
<tr>
<td>Right</td>
<td>9.37</td>
<td>-0.73, 19.47</td>
<td>51.55</td>
<td>0.07</td>
<td>-91.67, 110.4</td>
</tr>
<tr>
<td><strong>Stratus - BD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IO</td>
<td>-64.66</td>
<td>-95.02, -34.30</td>
<td>154.9</td>
<td>&lt;0.0001</td>
<td>-368.3, 239</td>
</tr>
<tr>
<td>MLD</td>
<td>61.59</td>
<td>23.47, 99.71</td>
<td>194.5</td>
<td>0.002</td>
<td>-319.6, 442.8</td>
</tr>
<tr>
<td>Height</td>
<td>-40.99</td>
<td>-62.82, -19.16</td>
<td>111.4</td>
<td>0.0004</td>
<td>-249.5, 177.4</td>
</tr>
<tr>
<td>Left</td>
<td>2.38</td>
<td>-5.59, 10.35</td>
<td>40.65</td>
<td>0.56</td>
<td>-77.29, 82.05</td>
</tr>
<tr>
<td>Right</td>
<td>-38.15</td>
<td>-65.35, -12.24</td>
<td>135.3</td>
<td>0.005</td>
<td>-303.9, 226.4</td>
</tr>
</tbody>
</table>

Table 11: Intergrader measurement analysis for all three OCT devices
of limits of agreement (SD 105.8), while height measurement had the narrowest limits of agreement (SD 28.1).

The BA plots for inner opening, minimum linear diameter and right side showed consistent variability, with only the right side measurement having a normal distribution. The base diameter and height BA plots suggested the difference between intergrader measurements increased as the average value increased, with the former having a cut of at approximately 1000 microns (Appendix 9.4: Figures 26-31).

**Intergrader Topcon results**

The right side measurement had the smallest bias (2.53, p=0.58), while the inner opening has the greatest bias (218.8, p<0.0001). The inner opening had the widest limits of agreement (SD 189.4) and the narrowest limits of agreement were for height measurement (SD 17.41).

The BA plots for all measurements except inner opening suggested consistent variability. There seemed to be an increase in measurement difference as the average of the inner opening measurement increased. All the data except inner opening and minimum linear diameter seem to be normally distributed.
**Intergrader Stratus results**

The height measurement had the smallest bias (2.38, p=0.56), while the base diameter had the largest bias (64.66, p<0.0001). The inner opening had the widest limits of agreement (SD 194.5) with the narrowest limits of agreement for the height measurement (SD 40.65),

The BA plots for all except base diameter suggested consistent variability. The difference between measurements seemed to increase as the base diameter value increased. All the data was normally distributed except minimum linear diameter and height measurements.

<table>
<thead>
<tr>
<th>OCT device</th>
<th>Larger absolute value of limit of agreement for intragradar measurements &gt;50 microns</th>
<th>Larger absolute value of limit of agreement for intergrader measurements &gt;50 microns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectralis</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Topcon</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Stratus</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 12: Number of measured parameters that had an absolute value of limit of agreement more than 50 microns.
3.4 Discussion

From a surgical point of view the size of the macular hole is an important consideration before deciding on the most suitable treatment. With this in mind numerous authors have set out to analyse the geometry of a macular hole and determine any prognostic indicators for anatomical and functional success post operatively.

Spectral domain OCT scanners have replaced time domain OCT scanners due to their improved quality of images, and the speed of image acquisition. SD-OCT scanners use a spectrometer and Fourier transformation rather than a moving mirror of the time domain machines.

The Heidelberg Spectralis machine has an axial resolution of 7 microns, and scans at 40,000 A-scans per second. It combines a scanning laser ophthalmoscope with OCT and through software optimization it claims a digital resolution of 3.5 microns. The SLO provide real time eye tracking and allows serial comparison of the same points in a scan[141].

Cirrus OCT (Carl Zeiss Meditec) has an axial resolution of 5 microns and scans at 27,000 A-scans per second. Its predecessor, Stratus OCT, has resolution of 8-10 microns and a scanning speed 70 times slower than the Cirrus OCT[142]. The Cirrus OCT allows the operator to move the scanning zone without adjusting patient fixation [141].

Studies between Cirrus and Stratus machines do show variable correlation in eyes with retinal pathology, and the automatic depth readings are different as the Cirrus software includes the region from the Ellipsoid zone to the RPE in depth measurements [133, 143-145].
The Topcon OCT system has a 6 micron axial resolution and scans at 18000 A-scans per second. It has integrated software designed to reduce artifacts from movement and allows manual registration of chosen points of a scan to allow sequential images to be compared over time.

This current study is the first to determine the intra and inter grader reliability of such measurements and to do so on three different OCT devices.

The Bland-Altman method was used for statistical analysis to check there is no relationship between the magnitude of the measurement and the difference between the measurements.

For almost all six measurements (base diameter, inner opening, minimum linear diameter, height, left side and right side) across all three OCT devices the level of bias was more for the intergrader measurement than for the intragrader.

The mean bias within the intragrader measurement was 2.37, 5.06, 4.09 and for the intergrader measurement 23.09, 47.19 and 41.09 on the Spectralis, Topcon and Stratus devices respectively. The level of systematic bias within the intragrader group on all three devices was clinically acceptable (range 0.05 – 15.29). However, for the intergrader measurements on each of the devices there were levels of bias that would be deemed clinically unacceptable (range 2.38 – 218.8).

Using 50 microns as an arbitrary value whereby this difference in measurement would be clinically unacceptable, the intragrader measurements faired much better than the intergrader measurements (Table 12).
In clinical practice the MLD and base diameter parameters are the more commonly used by clinicians, and this study shows that the reliability of these measurements is good on all three OCT devices. The Spectralis and Topcon devices show a good level of reproducibility, whereas on the Stratus devices reproducibility was less.

The major limiting factor in the design of this current study was that the same macular hole was not imaged on each of the three devices. Unlike the intraocular pressure measured in glaucoma patients, or the axial length measurement obtained in biometry, the precise value of macular hole size is only of real importance if used to determine prognostic factors or for research purposes. This study has shown the in-built caliper tool on three different OCT devices showed clinically acceptable levels of systematic bias for intragrader measurements but not for intergrader measurements. The caliper tool seems to provide reliable measurements of macular hole geometry but moderate reproducibility.

4.0 BEAVRS Survey and PPI (Patient & Public Involvement)

4.1 Introduction

An anonymous, online survey of current macular hole management with members of the British and Eire Association of Vitreoretinal Surgeons (BEAVRS) was carried out to gauge the opinion regarding involvement in a randomised controlled trial that aimed to address the issue of postoperative face-down positioning. A total of 42 out of 142 members replied to the survey.
4.2 Methods

The following questions were asked:

1. Would you be willing to participate in a multi-centre RCT of positioning following surgery for full-thickness macular holes, in which your patients were randomised to either face-down positioning or non-positioning arms?

2. Which stains would you be prepared to use for ILM peeling?

3. Which gases would you be prepared to use for tamponade?

4. With respect to the management of the lens, which of the following techniques would you be prepared to perform – combined or sequential cataract surgery?

5. What gauge of instrumentation do you normally use for macular hole surgery?

6. Do you normally peel the ILM?

7. How do you normally advise your patients to position postoperatively following surgery for a SMALL (less than 400 microns in diameter) full thickness macular hole?

8. How do you normally advise your patients to position postoperatively following surgery for a LARGE (400 microns or greater) full thickness macular hole?
4.3 Results

The survey highlighted variability in current practice and a great willingness to participate in a potential RCT that would provide a greater body of evidence from which to work from.

65.9% (27/41) of the surgeons surveyed answered yes when asked whether they would be willing to participate in a multicentre RCT of positioning following surgery for full-thickness macular holes, in which patients were randomised to either face-down positioning or non-positioning arms.

In designing this study we aimed to remove as many potential sources of error / bias as possible. With this in mind we wanted to gauge current surgical practice to ensure that all participating centres were using the same standardised surgical technique in repairing macular holes.

86.5% (32/37) were prepared to use brilliant blue dye to stain the ILM pre-peeling. 81.6% (31/38) were prepared to use C3F8 as the intraocular gas.

84.2% (32/38) were prepared to perform phacovitrectomies, while a similar number 76.3% (29/38) preferred sequential surgery.

64.8% (26/38) currently mainly use size 23 gauge instruments when repairing macular holes.

97.4% (37/38) normally peel the ILM.

The greatest variation in responses came from questioning about post operative positioning.

When asked how surgeons advise patients to posture after repair of small (less than 400 microns) macular holes, 15.8% (6/38) gave no posture advice, 21.2% (8/38) told patients to avoid the face up position, 23.7% (9/38) advised face down for up to 5 days, while 13.2% (5/38)
advised face down for more than 5 days. Three advised overnight face down positioning for the first night only.

Post-operative advice following surgery for large (greater than 400 microns) macular holes was as follows: 10.3% (4/39) gave no posture advice, 10.3% (4/39) told patients to avoid the face up position, 30.8% (12/39) advised face down for up to 5 days, while 20.5% (8/39) advised face down for more than 5 days.

4.4 Patient and Public Involvement

Thanks to financial support from the Enabling Involvement Fund (awarded by the Research Design Service (RDS) London) patients have both informed and influenced the design of our proposed randomised controlled trial.

A Patient and Public Involvement (PPI) meeting was held in March 2013 at Moorfields Eye Hospital with patients who had themselves had macular hole surgery; all had experience of posturing and a number had participated in a pilot study [116] for this trial. During the meeting, several topics were discussed including:

- Patient experience of posturing
- Trial design
- Practical trial details and patient information
- Plans for patient involvement as the project progresses
It became very clear that the patients were keen to establish a strong scientific basis for guidance on postoperative posturing and were supportive of this research proposal. Having discussed with patients the practical challenges of face-down posturing it was apparent how very onerous a task it presents; patients had to devise their own ways of coping with posturing, for example by wearing loose clothing, eating only small meals, and by positioning reading material and screens on the floor. Patients would be willing to posture if it would benefit their sight. When discussing the trial design the patients described the particular challenge of maintaining face-down posture at night; for this reason, it was agreed that the trial would involve posturing during the day only. They suggested that clear practical information on posturing be provided to trial participants; which become part of the patient information sheets. The patients suggested the inclusion of qualitative measures of outcome as well as clinical measures, and these have been incorporated accordingly with the inclusion of a quality of life questionnaire (National Eye Institute Visual Function Questionnaire (VFQ-25). The patients attending were keen to form a Patient Advisory Panel (PAP) for the duration of the project. The trial team has experience of collaborative research with the Royal National Institute for Blind People (RNIB); the proposal has been reviewed by the RNIB’s Head of Evidence who has committed to helping disseminate the research findings.

5.0 Positioning in Macular Hole Surgery (PIMS) Trial

5.1 Introduction

5.1.1 Aim

To address the limitations in the evidence a multi-centre interventional, comparative randomised controlled clinical trial was designed to determine whether advice to position face down
improves the surgical success rate of closure of large (≥400 μm) macular holes, and thereby reduces the need for further surgery.

Nine hospitals across the UK took part in the trial: Bristol Eye Hospital, Gartnavel General Hospital, Ipswich Hospital, Maidstone Hospital, Manchester Royal Eye Hospital, Moorfields Eye Hospital, Southend Hospital, Sunderland Royal Hospital and Whipps Cross Hospital.

This research project was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the UK’s main research and ethics committee (NRES Committee London – Westminster) and the local Moorfields Eye Hospital Research Management Committee (REC reference 14/LO/2061). The clinical trial was prospectively registered on the UK Clinical Research Network (UKCRN: 17966).

5.2 Methods

5.2.1 Study design and outcome measures

The primary outcome of the study was the anatomical closure of the macular hole at 3 months post surgery.

Successful closure of the macular hole was determined by OCT scans. The scans were anonymised and sent to two independent retinal surgeons who independently graded the macular hole as closed; ‘open and flat’ (without a cuff of subretinal fluid); or ‘open and elevated’ (with cuff of subretinal fluid). The readers were masked to the identity and allocated treatment of the subject. In the event of any disparity in grading, a third independent retinal surgeon, also masked to identify and treatment allocation, would arbitrate.
The categories ‘open and flat’ (without a cuff of subretinal fluid), or ‘open and elevated’ (with a cuff of subretinal fluid) were pooled into one category of ‘open’ for the purpose of analysis.

Secondary outcomes at 3 months post surgery were:

- Further surgery for macular hole, performed or planned (yes/no)
- Best-corrected visual acuity (BCVA) measured using a Snellen chart at a standard distance of 6 m
- Patient-reported experience of positioning on a scale from 0 (very difficult) to 10 (very easy)
- Patient-reported health and quality of life assessed using the National Eye Institute Visual Function Questionnaire (VFQ-25) from 0 (worst health and quality of life) to 100 (best health and quality of life)
- Patient-reported outcome ‘Given what you now know, would you still have elected to have the operation?’ with responses Yes, No or Don’t Know

5.2.3 Inclusion criteria

- Presence of an idiopathic full-thickness macular hole, greater than or equal to 400 μm (minimum linear diameter) as measured by optical coherence tomography (OCT).

- Patients electing to have surgery for a macular hole, with or without simultaneous phacoemulsification and intra-ocular lens implant.

- Ability and willingness to position face down or in an inactive face-forward position.
5.2.4 Exclusion criteria

- Age-related macular degeneration; glaucoma; diabetic retinopathy; retinal degeneration; amblyopia; previous vitrectomy surgery (refractive error, lens opacity and previous use of ocriplasmin are not exclusion criteria).

- Traumatic macular hole.

- History of visual loss suggesting macular hole duration longer than 12 months.

- Presence of a retinal tear identified during surgery for which postoperative positioning is advised.

5.2.5 Unit of analysis

All ocular assessments relate to the study eye. In the event that a subject was having surgery for bilateral macular holes (which are not operated on simultaneously), the first eye to be operated on during the trial was the study eye.

Pre-operative data collection included demographic data (age, sex, ethnicity), laterality, duration of symptoms, BCVA measured using Snellen charts at a standard distance of 6 meters of the affected and unaffected eye, OCT with recording of minimal hole diameter, lens status and the VFQ-25 questionnaire.
Data collected from the surgery itself included presence or absence of vitreofoveal attachment, complications and whether simultaneous cataract surgery with intraocular lens insertion was performed.

Post-operative data collected at 3 months included BCVA measured using Snellen charts at a standard distance of 6 meters of the affected and unaffected eye, lens status, macular hole status (closed, open and flat, open and elevated), whether further surgical repair either had been performed or was being planned, and patient-reported experience of positioning.

5.2.6 Informed consent

Eligible candidates were approached at their baseline visit by the clinical team, provided with information about the trial and invited to participate. They were given time to consider their decision and the opportunity to ask questions. Investigators ensured that information about equipoise is provided impartially so as to avoid potential bias by influencing compliance with advice to position. Consent was obtained at the time of listing for surgery (see Appendix).

5.2.7 Surgery

The surgery was standardised across all participating sites. Subjects underwent vitrectomy (using instruments of any gauge), internal limiting membrane (ILM) peeling (with or without staining by a vital dye), fluid-air exchange and injection of octafluoropropane (C3F8) 14 % gas. Simultaneous phacoemulsification and intra-ocular lens implant was allowed as per the surgeons decision.
5.2.8 Intervention

The intervention was advice to adopt face down positioning. Subjects were advised to maintain a face down position for a total of at least 8 consecutive or non-consecutive hours a day for 5 days following surgery.

The comparator was advice to adopt face forward positioning. Subjects were advised to maintain a face forward position, inactive, for at least 8 consecutive or non-consecutive hours a day for 5 days following surgery.

Subjects in either group were allowed a 15-minute break (every hour) from their allocated position. In the position-free-time we advised subjects to avoid the face up position.

Face down or face forward positioning was advised during waking hours only, not during sleep. We advised subjects to avoid the face-up position during sleep.

5.2.9 Screening

The PIMS trial did not collect data on the number of participants screened for eligibility. The reason for this omission is that the proportion of patients with macular holes ≥400 μm in size is a small minority of the overall number of patients presenting with macular holes. For some hospital sites, the data collection of the number of patients screened for eligibility was considered unfeasible given their current resources.
5.2.10 Randomisation

At the conclusion of standardised surgery across all sites, participants still eligible for inclusion were allocated randomly 1:1 to one of the 2 treatment arms stratified by site.

Randomisation was performed using a secure bespoke online randomisation service implemented by the PCTU (Pragmatic Clinical Trials Unit, Queen Mary University of London). Each site was provided with a unique login username and password to access the service. Online randomisation was available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance. Access to the service was restricted to staff as delegated by the Principal Investigator (PI). Participant ID and details required for randomisation were inputted, and staff were presented with immediate on-screen randomisation. The randomisation system had built-in checks to check that (1) the participant ID was not a duplicate, and (2) the date of birth was within the eligible age set in the protocol.

Once the subject was randomised, the enrolment of this subject was documented on the enrolment log. An email was automatically generated to notify the Chief Investigator’s (CIs) team and PCTU of all participants randomised to the trial.

5.2.11 Follow-up

Subjects attended for follow-up assessment as part of the trial at 3 months following surgery. Their surgical teams managed their routine postoperative clinical care in the meantime.

5.2.12 Sample size and power calculation

Clinical consensus was that face down positioning would be recommended if there were a difference of 15% in success rates. This was the smallest clinically relevant treatment
difference that we wished to detect. Previous studies[115] indicated that successful closure of
large macular holes without advice to position face down is 80%. A study with 86 patients per
group has 85 % power to detect a difference between 80 % in the face-forward positioning arm
and 95 % in the face down positioning arm. With a 10 % loss to follow-up, we aimed to recruit
96 patients in each arm.

5.2.13 Statistical Analysis

Baseline characteristics were tabulated in the two treatment arms.

Proportions of macular hole closures at 3 months were compared between treatment arms
using logistic regression adjusting for age and sex, with site as a random effect.

Visual acuity at baseline and 3 months was compared using linear regression adjusting for age,
sex, and baseline visual acuity, with site as a random effect. We adjusted for surgery type in the
logistic regression analysis. Questionnaire scores assessed at baseline and 3 months was
compared using linear regression adjusting for age and sex, with site as a random effect.

The numbers of participants who withdraw or were lost to follow-up were recorded in a
Consolidated Standards of Reporting Trials (CONSORT) flow-chart.

The primary analysis for each outcome was by intention-to-treat, meaning that all patients on
whom an outcome was available were included in the analysis, and were analysed according to
the treatment group to which they were randomised.
Through vigilance and careful planning, the PIMS trial management team aimed to achieve complete capture of all data from all patients, including patients who did not adhere to the protocol or patients who withdrew from the trial.

The PCTU were responsible for all the trial statistical analysis.

5.2.14 Interim analyses

The PIMS Trial Steering Committee was made up of a chair, a second clinician, an independent statistician, and a lay member. There was no Data Monitoring Committee (DMC) nor any planned interim analyses for this trial due to the relatively short time span of follow-up, and minimal clinical risks.

5.2.15 Safety considerations

Random allocation to the alternatives of face-down and face-forward positioning presents a possible safety issue because of the uncertainty over which is more effective, and the known adverse effects of prolonged face-down positioning. We addressed these risks by advising a minimum of inactive face-forward positioning for all subjects, and only an 8-hour total minimum period of face-down positioning.

5.2.16 Data handling and record keeping

- Confidentiality -
  Information related to participants were kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee (REC) approval.
• Record retention and archiving -

All study documents will be retained for a period of 5 years following conclusion of the study. Following the submission of the end of study report the sponsor arranged for archiving of the Trial Master File in accordance with the sponsor’s process. The sponsor will also notify the local PIs that the Investigator Site Files (ISFs) may be archived. The ISFs will be retained and archived at site in accordance with the Trusts’ procedures.

Following the end of the retention period the sponsor will notify the PIs in writing that the required retention period has completed and that documents can be destroyed. A copy of the instruction to the Trust Archivist to destroy the ISF will be requested.

5.2.17 Devices

Spectral domain ocular coherence tomography (SD-OCT) was used at the various sites to determine the preoperative size of the macular hole, and whether surgery has been successful in terms of hole closure at 3 months.

The size of the macular hole was defined as its minimum horizontal diameter. This is its linear width measured using the OCT calliper function along a line that bisects the hole in the horizontal meridian and is parallel to the retinal pigment epithelium (see Appendix).

5.2.18 Tools

The VFQ-25 is a reliable and valid 25-item version of the 51-item National Eye Institute Visual Function Questionnaire (NEI-VFQ).
5.2.19 Adverse event (AE)

Safety reporting adhered to the sponsor’s standard operating procedures. If the AE was not defined as serious, it was recorded in the study file and the participant was followed-up by the research team. The AE was documented in the participants’ medical notes.

5.2.20 Serious adverse event (SAE)

A SAE is defined as an untoward occurrence that:

(a) Results in death;

(b) Is life-threatening;

(c) Requires hospitalisation or prolongation of existing hospitalisation;

(d) Results in persistent or significant disability or incapacity;

(e) Consists of a congenital anomaly or birth defect; or

(f) Is otherwise considered medically significant by the investigator.

Any SAE occurring to a research participant was reported to the main REC where in the opinion of the CI the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

Expected AEs include the following:

- Ocular discomfort; epiphora; periocular swelling; diplopia; ptosis
- Subconjunctival or intra-ocular haemorrhage
- Corneal abrasion
- Retinal or choroidal tear or detachment
• Wound leak
• Ocular hypotony or raised intra-ocular pressure/glaucoma
• Overfill or underfill of intra-ocular gas tamponade
• Intra-ocular or extra-ocular inflammation or infection
• Intra-ocular neovascularisation
• Lens opacity, subluxation or dislocation of lens or lens implant
• Persistent or recurrent macular hole
• Visual field defect or other disturbance of sight
• Discomfort of joints, neck, back or limbs

SAEs that were considered to be ‘related’ and ‘unexpected’ were reported to the sponsor within 24 hours of learning of the event using the following Email address: pharmacovigilance@moorfields.nhs.uk and to the main REC within 15 days, in line with the required timeframe. SAEs were documented in the participants’ medical notes and the Case Report Form (CRF).

5.2.21 Urgent safety measures

The CI was able to make urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. In this instance, the approval of the REC prior to implementing these safety measures was not required. However, it was the responsibility of the CI to inform the sponsor and main REC (via telephone) of this event immediately.

The CI had an obligation to inform both the main REC in writing within 3 days, in the form of a substantial amendment.
5.2.22 Annual safety reporting

The CI was responsible for sending the Annual Progress Report to the main REC using the National Research Ethics Service (NRES) template (the anniversary date is the date on the ‘favourable opinion’ letter from the REC) and to the sponsor.

5.2.23 Overview of the safety reporting responsibilities

The CI had the overall safety oversight responsibility and ensured that safety monitoring and reporting was conducted in accordance with the sponsor’s requirements.

5.2.24 Monitoring and auditing

The study was monitored in line with the study monitoring plan, written by the PCTU quality assurance (QA) manager and agreed by the study sponsor. The PCTU had provisionally identified this study as being medium risk.

5.2.25 Finance and funding

The trial was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Research for Patient Benefit scheme.

5.2.26 Indemnity

The sponsor was Moorfields Eye Hospital (MEH) NHS Foundation Trust, which participates in the Clinical Negligence Scheme for Trusts (CNST), run by the NHS Litigation Authority, which pools the risk of clinical negligence claims. NHS indemnity (for negligent harm) covered MEH employees, both substantive and honorary, who worked in the course of their NHS employment and in respect of conducting research projects, which must have received NHS Permission.
MEH did not accept liability for any activity that had not been properly registered and Trust approved.

5.2.27 Ethics

Random allocation to the alternatives of face-down or face-forward positioning presents a possible ethical issue because of the uncertainty over which is safer and more effective. In particular, there is some concern that individuals with large holes randomised to non-positioning may be less likely to benefit from hole-closure. We have addressed this concern by ensuring that subjects not allocated to face-down positioning are advised to maintain an inactive face-forward position, which has been an acceptable standard for previous trials. If the results demonstrate that positioning face-down is more effective than positioning inactively face-forward we can conclude that it is also likely to be more effective than not positioning at all.

Applications to the UK’s main REC (NRES Committee London – Westminster) and the local Moorfields Research Management Committee received favourable opinion (REC reference 14/LO/2061).

The study was performed in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments.

5.3 PIMS Results

5.3.1 Summary of data

A total of 206 participants were enrolled in the study (Figure 44). 22 withdrew prior to randomisation because they no longer met the inclusion criteria or no longer wished to participate. 184 participants were randomised, of whom 3 participants from each group were
excluded following randomisation because they were found to be ineligible owing to macular
hole dimension of less than 400 μm minimum linear diameter. No participants were lost to follow
up. The group advised to position face-down included a greater number of participants of black
ethnicity and fewer participants of Asian ethnicity, and had a slightly smaller median macular
hole diameter. The baseline characteristics (Table 13) of the 2 groups were otherwise very
similar.
Figure 44: CONSORT diagram

- Informed Consent given and Enrolled in the trial (N=206)
  - Withdrew after surgery but before randomisation (N=22)
    - Patient no longer met entrance criteria (n=6)
    - Patient no longer willing to participate (n=13)
    - Other (n=3)
- Randomised (N=184)
- Allocation
  - Allocation to face-down positioning
    - Follow up
      - Lost to follow up (n=0)
  - Allocation to face-forward positioning
    - Follow up
      - Lost to follow up (n=0)
- Analysis
  - Analysed (n=88)
  - Excluded from analyses (n=3)
    - Protocol violation (n=3)
  - Analysed (n=90)
  - Excluded from analyses (n=3)
    - Protocol violation (n=3)
Table 13: Baseline characteristics, by randomised group

<table>
<thead>
<tr>
<th></th>
<th>Face-forward positioning</th>
<th>Face-down positioning</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=90</td>
<td>N=88</td>
</tr>
<tr>
<td>Age (years) – median (IQR)</td>
<td>69 (64,73)</td>
<td>69 (64,73)</td>
</tr>
<tr>
<td>Male – n (%)</td>
<td>22 (24.4)</td>
<td>23 (26.1)</td>
</tr>
<tr>
<td>Ethnicity – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>78 (86.7)</td>
<td>78 (88.6)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (2.2)</td>
<td>7 (8.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (8.9)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Mixed</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Laterality – Left Side – n (%)</td>
<td>47 (52.2)</td>
<td>49 (55.7)</td>
</tr>
<tr>
<td>Duration of symptoms (months) – median (IQR)</td>
<td>5 (3,7)</td>
<td>5 (4,7)</td>
</tr>
<tr>
<td>BCVA (Best-Corrected Visual Acuity) – median (IQR)</td>
<td>6/60 (6/36,6/60)</td>
<td>6/60 (6/36,6/60)</td>
</tr>
<tr>
<td>Lens Status – Phakic – n (%)</td>
<td>78 (86.7)</td>
<td>72 (81.8)</td>
</tr>
<tr>
<td>Cataract surgery performed – Yes – n (%)</td>
<td>44 (48.9)</td>
<td>45 (51.1)</td>
</tr>
<tr>
<td>Macular hole diameter on OCT – median (IQR)</td>
<td>517 (460,588)</td>
<td>480 (446,557)</td>
</tr>
<tr>
<td>Quality of life VFQ-25 – mean (sd)</td>
<td>77.1 (17.4)</td>
<td>76.4 (17.9)</td>
</tr>
<tr>
<td>Vitreo-foveal Detachment present – n (%)</td>
<td>32 (35.6)</td>
<td>33 (37.5)</td>
</tr>
</tbody>
</table>
5.3.2 Primary Outcome results

Grading of macular hole status on OCT scans at 3 months was consistent between the 2 masked graders in every instance. Anatomical macular hole closure was observed in 85.6% of those advised to position face-forward and in 95.5% of participants advised to position face-down (adjusted odds ratio 3.15; 95% CI 0.87, 11.41; p=0.081) (Table 14). At the median macular hole size (488.5µm) the odds ratio of 3.15 corresponded to an absolute risk difference of 4.1% (95% confidence interval -0.8% to 9.1%), or a number needed to treat of 24.
Table 14: Main results for primary outcome

<table>
<thead>
<tr>
<th>Successful closure of macular hole - n (%)</th>
<th>Face-forward positioning (N=90)</th>
<th>Face-down positioning (N=88)</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful closure of macular hole</td>
<td>77 (85.6)</td>
<td>84 (95.5)</td>
<td>3.15 (0.87,11.41)</td>
<td>0.0810</td>
</tr>
</tbody>
</table>

The primary outcome was defined as the anatomical closure of the macular hole at 3 months post surgery.

<table>
<thead>
<tr>
<th>Macular Hole Size</th>
<th>μm:</th>
<th>Successful closure of macular hole Absolute risk difference (95% CI)</th>
<th>P-value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum value</td>
<td>400</td>
<td>0.018 (-0.008, 0.044)</td>
<td>0.179</td>
<td>55</td>
</tr>
<tr>
<td>Lower Quartile</td>
<td>450</td>
<td>0.029 (-0.009, 0.067)</td>
<td>0.131</td>
<td>34</td>
</tr>
<tr>
<td>Median</td>
<td>488.5</td>
<td>0.041 (-0.008, 0.091)</td>
<td>0.100</td>
<td>24</td>
</tr>
<tr>
<td>Upper Quartile</td>
<td>578</td>
<td>0.089 (-0.004, 0.182)</td>
<td>0.061</td>
<td>11</td>
</tr>
<tr>
<td>Maximum value</td>
<td>854</td>
<td>0.273 (-0.039, 0.586)</td>
<td>0.086</td>
<td>4</td>
</tr>
</tbody>
</table>
5.3.3 Secondary outcome results

The median best-corrected Snellen visual acuity at 3 months was 6/36 in the face-forward group and 6/24 in the face-down group (Table 15). The mean logMAR converted best-corrected visual acuity at 3 months was 0.87 in the face-forward group and 0.68 in the face-down group (adjusted mean difference -0.15; 95% CI -0.29, -0.01; p=0.031) (Table 16).

Table 15: Main results for untransformed secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Face-forward positioning (N=90)</th>
<th>Face-down positioning (N=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best-corrected Visual Acuity (BCVA) using standard Snellen chart at 6m at 3 months - median (IQR)</td>
<td>6/36 (6/24,3/60)</td>
<td>6/24 (6/12,6/60)</td>
</tr>
<tr>
<td>Patient-reported health and quality of life as assessed at 3 months using National Eye Institute Visual Function Questionnaire (VFQ-25) – median (IQR)</td>
<td>87 (73,93)</td>
<td>89 (76,94)</td>
</tr>
<tr>
<td>Patient-reported experience of positioning at 3 months- median (IQR)</td>
<td>9 (7,10)</td>
<td>6 (4,8)</td>
</tr>
</tbody>
</table>

The median participant-reported ease-of-positioning score (using a 10-point scale where 0 was very difficult and 10 was very easy) was 9 in the face-forward group and 6 in the face-down...
group (Table 15). The proportion of participants reporting a score ≥5 was 92.7% in the face-forward group and 56.1% in the face-down group (adjusted odds ratio 0.10; 95% CI 0.04, 0.27; p<0.001) (Table 17). The proportion of participants reporting at 3 months that, given their experience, they would still have elected to have the operation was 90.5% in the face-forward group and 90.4% in the face-down group (adjusted odds ratio 1.01, 95% CI 0.36, 2.88; p=0.98). The median VFQ-25 score was 87 in the face-forward group and 89 in the face-down group (adjusted mean difference on a logistic scale 0.02; 95% CI -0.03, 0.07; p=0.41).

5.4 PIMS Discussion

Surgical techniques for macular hole repair have key common steps but also include variations that can confound the interpretation of outcomes unless appropriately controlled. Our trial was designed to determine the impact of positioning as it is commonly advised by many UK retina surgeons, taking into account their preferred practice as determined by a survey of members of the British and Eire Association of Vitreoretinal Surgeons and their opinions on clinical equipoise. In this way we could ensure efficient recruitment to the trial, and results that would be relevant to common practice. Our findings are relevant specifically to surgery for macular holes at least 400 μm minimum linear diameter with the use of C3F8 14% gas and positioning face-down 8 hours daily for 5 days, and are not directly relevant to the use of alternative gases or positioning regimens. We chose to compare face-down positioning not with free positioning but with seated face-forward positioning, so as to mitigate concerns regarding a perceived risk of harm from physical overactivity; the seated position may reduce shear stress associated with intraocular fluid currents induced by physical activity in gas-filled eyes [146] and should be regarded as a positioning regimen, albeit less onerous than face-down positioning.
Table 16: Main results for transformed continuous secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Face-forward positioning (N=90)</th>
<th>Face-down positioning (N=88)</th>
<th>Regression coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LogMAR conversion of Best corrected visual acuity (BCVA) using standard Snellen chart at 6m at 3 months - mean (sd)</td>
<td>0.87 (0.57)</td>
<td>0.68 (0.39)</td>
<td>0.15 (0.01,0.29)</td>
<td>0.0308</td>
</tr>
<tr>
<td>Logistic transformation of Patient-reported health and quality of life as assessed at 3 months using National Eye Institute Visual Function Questionnaire (VFQ-25) – mean (sd)</td>
<td>4.4 (0.2)</td>
<td>4.4 (0.2)</td>
<td>-0.02 (-0.07,0.03)</td>
<td>0.4097</td>
</tr>
</tbody>
</table>
Table 17: Main results for dichotomous secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Face-forward positioning (N=90)</th>
<th>Face-down positioning (N=88)</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further surgery for macular holes, performed or</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>planned, of those with unsuccessful closure of</td>
<td>10 (76.9)</td>
<td>4 (100.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>macular hole* – n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dichotomised Patient-reported experience of</td>
<td>76 (92.7)</td>
<td>46 (56.1)</td>
<td>9.75 (3.76, 25.30)</td>
<td>0.0000</td>
</tr>
<tr>
<td>positioning at 3 months**- n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient reported outcome, if they would still have</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elected to have the operation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes – n (%)</td>
<td>76 (90.5)</td>
<td>75 (90.4)</td>
<td>0.99 (0.35, 2.81)</td>
<td>0.9802</td>
</tr>
<tr>
<td>Yes/Don’t know (sensitivity analysis) – n (%)</td>
<td>79 (94.0)</td>
<td>78 (94.0)</td>
<td>1.01 (0.28, 3.71)</td>
<td>0.9869</td>
</tr>
</tbody>
</table>

* Face-forward positioning N=13, Face-down positioning N=4

**Patient-reported outcome was dichotomised as Negative for answers (0-5) and Positive for answers (6-10) after analysis of blinded results through a histogram as per analysis plan.
In designing the study we sought the involvement of people with personal experience of macular hole surgery. Our lay advisory group specifically requested that the intervention be termed ‘positioning’ instead of ‘posturing’ because they judged this term more appropriate. They also selected anatomical hole closure as the primary outcome because of anxiety about the prospect of further intervention that might be necessary to close a macular hole that was persistently open despite surgery. They considered that face-down positioning for 8 hours daily for 5 days was achievable but cautioned against advice to position face-down while sleeping because they judged this to be unfeasible for most people. We chose not to estimate adherence of participants with the advice to position postoperatively because such measurement is of unknown reliability and could influence behaviour artificially. Instead we sought pragmatically to determine the impact of the advice to position as described.

On the evidence of our findings, people with macular holes of diameter 400 μm or greater can be informed that surgery using the technique described and positioning face-forward offers an estimated 86% likelihood of hole closure. We found no clear evidence that advice to position face-down improved the likelihood of closure; this was achieved in 95.5% with an adjusted odds ratio of 3.15 but the confidence interval was wide (0.87 to 11.41) and the overall effect was not statistically significant. Any difference in absolute risk is unlikely to exceed 10%. Some participants reported difficulty in positioning face-down but not to an extent that it would have deterred them from surgery. Face-down positioning led to a modest benefit to visual acuity at 3 months but no benefit to participant-reported quality of life 3 months following surgery. For people with macular holes of diameter 400 μm or greater the results of this trial provide evidence to predict the likely outcome of surgery and to guide their choice of positioning postoperatively.
6.0 Final discussion

The previous five chapters have concentrated on the sight limiting disease known as a macular hole. While its exact mechanism may never be truly understood, we live in an era where thankfully a surgical technique is available which can improve the eyesight of these patients. Surgical instruments and techniques are in a constant state of flux and I am sure that within the next 5-10 years the current landscape with its limitations would have evolved [147]. Supra-human precision has already been demonstrated through robot assisted retinal surgery [148].

The Cochrane review [114] on post-operative position concluded that there was currently insufficient evidence from which to draw firm conclusions about the impact of postoperative face-down positioning on the outcome of surgery for macular hole. To address this lack of evidence the PIMS trial was setup to help clinicians and patients alike to be better informed on best practice. We found no clear evidence that advice to position face-down improved the likelihood of closure; this was achieved in 95.5% with an adjusted odds ratio of 3.15 but the confidence interval was wide (0.87 to 11.41) and the overall effect was not statistically significant. As Table 14 shows, 85.6% of patients in the face-forward position group achieved anatomical closure at 3 months after surgery. Having worked closely with patients on setting up and running the PIMS trial, a common real life concern patients had was what was the evidence for and against adopting a certain position after surgery. They wanted this evidence to be from a robust source and I feel that this trial has done its best to provide high quality results from which patients and clinicians can use to make better informed decisions.

Several authors have described different methods of macular hole measurement using OCT scans, including minimum linear dimension [96], base hole diameter [80], hole height [28], IS/OS junction line [30], hole form factor (HFF) [86], macular hole index (MHI) [96], diameter hole index (DHI) [87] and tractional hole index (THI) [87].
The Shadowgram study described in Chapter 2 showed a high degree of correlation between linear horizontal OCT parameters and the linear horizontal shadowgram parameters. The measured OCT parameters (MLD, EZ and BD) and the corresponding shadowgram rings showed poor correlation with pre-operative or final visual acuity in the cohort of 50 eyes. The linear measurement of minimum linear diameter (MLD) on OCT showed the greatest correlation with vision (0.418 for baseline vision and 0.361 for final vision) and was statistically significant. As per other reports, the clinical usefulness of the minimum linear diameter measurement was confirmed with this study. The results of the study described in Chapter 3 showed that the MLD and base diameter measurements were reliable on each of the three different OCT devices but were less reproducible on the Stratus device. The caliper tool seems to provide reliable measurements of macular hole geometry but moderate reproducibility.
7.0 References


8.0 Presentations & Publications

- European Society for Low Vision Research and Rehabilitation, Keble College, University of Oxford - 25th - 27th September 2015
- NIHR BRC Moorfields Eye Hospital Retina Day - October 2015
- EURetina 2018, Vienna – 20th Sept 2018
STUDY PROTOCOL

PIMS (Positioning In Macular hole Surgery) trial – a multicentre interventional comparative randomised controlled clinical trial comparing face-down positioning, with an inactive face-forward position on the outcome of surgery for large macular holes: study protocol for a randomised controlled trial

Saruban Pasu¹,²*, Catey Bunce¹,², Richard Hooper³, Ann Thomson³ and James Bainbridge¹,²

Abstract

Background: Idiopathic macular holes are an important cause of blindness. They have an annual incidence of 8 per 100,000 individuals, and prevalence of 0.2 to 3.3 per 1000 individuals with visual impairment. The condition occurs more frequently in adults aged 75 years or older. Macular holes can be repaired by surgery in which the causative tractional forces in the eye are released and a temporary bubble of gas is injected. To promote successful hole closure individuals may be advised to maintain a face-down position for up to 10 days following surgery. The aim of this study is to determine whether advice to position face-down improves the surgical success rate of closure of large (>400 µm) macular holes, and thereby reduces the need for further surgery.

Methods/Design: This will be a multicentre interventional, comparative randomised controlled clinical trial comparing face-down positioning with face-forward positioning.

At the conclusion of standardised surgery across all sites, participants still eligible for inclusion will be allocated randomly 1:1 to 1 of the 2 treatment arms stratified by site, using random permuted blocks of size 4 or 6 in equal proportions. We will recruit 192 participants having surgery for large macular holes (>400 µm); 96 in each of the 2 arms of the study. The primary objective is to determine the impact of face-down positioning on the likelihood of closure of large (>400 µm) full-thickness macular holes following surgery.

Discussion: This will be the first multicentre randomised control trial to investigate the value of face-down positioning following macular hole standardised surgery.

Trial registration: UK CRN: 17966 (date of registration 26 November 2014).

* Correspondence: sarubanp@gmail.com
¹ Moorfields Eye Hospital NHS Foundation Trust, City Road, EC1V 2PD
² London, UK
³ NH Biomedical Research Centre (BRC) at Moorfields Eye Hospital NHS Foundation Trust and UCL, Institute of Ophthalmology, London, UK

© 2015 Pasu et al. Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Introduction

Background
Idiopathic macular holes are an important cause of blindness. They have an annual incidence of 8 per 100,000 individuals [1], and a prevalence of 0.2% [2] to 3.3% [3] per 1000 individuals with visual impairment. The condition occurs more frequently in adults aged 75 years or older [2]. Macular holes can have a devastating impact on quality of life and independence but can be repaired by surgery in which the causative tractional forces in the eye are released and a temporary bubble of gas is injected. To promote successful hole closure individuals may be advised to maintain a face-down position for up to 10 days following surgery. However, face-down positioning can be arduous [4] and associated with significant adverse effects [5], and evidence of its value is lacking. A recent Cochrane review [6] highlighted the need for an appropriately designed, adequately powered randomised controlled clinical trial to determine with confidence its value. The review reported that estimated effects were in favour of positioning but differences were not statistically significant for smaller macular holes. It concluded that face-down positioning may improve the likelihood of successful surgery for large macular holes (400 μm or greater in diameter) and highlighted the need for an appropriately designed, adequately powered randomised controlled clinical trial to determine with confidence the value of advice to position face-down.

Rationale
The benefit of face-down positioning to the success of surgery is proven; evidence to guide individuals on its impact is lacking and advice offered by clinicians varies widely. The current lack of evidence with which to guide patients has led to a lack of consensus among clinicians and wide variation in clinical practice.

To address the limitations in the evidence we will perform a trial to determine whether advice to position face-down, as opposed to face-forward, improves the probability of macular hole closure at 3 months after surgery, and so reduces the need for further surgery. We will test whether advice to position face-down results in a better outcome than an inactive face-forward position following surgery for large macular holes (≥400 μm).

A previous pilot randomised controlled trial (RCT) [7] has demonstrated the feasibility of this definitive RCT.

We have chosen to include only large macular holes (≥400 μm) because the available evidence suggests that face-down positioning is of more relevance to larger holes than for smaller macular holes [7–9]. In addition, the role of surgery in the management of smaller macular holes may be influenced in the future by the introduction of enzymatic vitreolysis techniques; intraocular injection of ocirplasmin can help induce closure in up to 40% of smaller macular holes [10]. However, this approach is not designed for larger holes, the management of which is likely to involve surgery for the foreseeable future.

The proposed trial has been designed taking into account the views of individuals with macular holes and clinicians. The pilot study suggested a benefit of positioning following surgery for large macular holes. Previous pilot study subjects were invited to form a Patient Advisory Panel to advise on the design and methodology of this new RCT. Both patients and clinicians indicated that randomisation to either face-down positioning for as long as 10 days, or conversely to no positioning at all, would adversely affect recruitment to the trial because these alternatives are typically considered too arduous or would present too high a risk of non-compliance, respectively. Instead, we have reached a consensus, based on the approach used by Guillaubey et al. [8], on the alternatives of 5 days positioning either face-down or in an inactive face-forward position.

For the primary outcome we have chosen successful closure of the macular hole because, according to our Patient Advisory Panel, this is directly relevant to patients; hole closure is essential for a favourable impact on sight and determines whether further surgery is required. Although visual acuity is a relevant measure of functional outcome, its validity is limited to some extent in the short term by the confounding influence of secondary lens opacity and does not directly determine the need for further surgery.

We have chosen not to attempt to measure objectively the compliance of subjects with positioning. This is because self-reported compliance is of unknown reliability, and objective monitoring risks influencing behaviour artificially and unpredictably. Instead, we have taken the pragmatic approach to determine the value of the advice to patients regarding position. However, following the period of positioning we will ask subjects to say retrospectively how easy they found it to maintain their allocated position (on a scale of 0 (very difficult) to 10 (very easy). We will also assess their quality of life using the National Eye Institute Visual Function Questionnaire (VFQ-25).

The trial will benefit patients by providing reliable information on the value of positioning following surgery for large macular holes, thereby enabling them to make an appropriately informed choice about the management of their condition.

The research will benefit the National Health Service (NHS) because by determining the value of face-down positioning we can expect to improve the likelihood of prompt successful surgery and hence reduce the amount of additional resource required for further clinical management and associated costs.
Objectives
The aim is to determine whether advice to position face-down improves the surgical success rate of closure of large (≥400 μm) macular holes, and thereby reduces the need for further surgery.

Primary objective
The primary objective is to determine the impact of face-down positioning on the likelihood of closure of large (≥400 μm) full-thickness macular holes following surgery.

Secondary objective
The secondary objective is to determine the impact of face-down positioning on sight, quality of life and wellbeing.

Methods/Design
This will be a multicentre interventional, comparative randomised controlled clinical trial comparing face-down positioning with face-forward positioning.

We will recruit 192 participants having surgery for large macular holes (≥400 μm); 96 in each of the 2 arms of the study.

Inclusion criteria
1. Presence of an idiopathic full-thickness macular hole, greater than or equal to 400 μm in diameter as measured by optical coherence tomography (OCT).
2. Patients electing to have surgery for a macular hole, with or without simultaneous phacoemulsification and intra-ocular lens implant.
3. Ability and willingness to position face-down or in an inactive face-forward position.

Exclusion criteria
1. Age-related macular degeneration; glaucoma; diabetic retinopathy; retinal degeneration; amblyopia; previous vitrectomy surgery (refractive error, lens opacity and previous use of ocriplasmin are not exclusion criteria).
2. Traumatic macular hole.
3. History of visual loss suggesting macular hole duration longer than 12 months.
4. Presence of a retinal tear identified during surgery for which postoperative positioning is advised.

Informed consent
Eligible candidates will be approached at their baseline visit by the clinical team, provided with information about the trial and invited to participate. They will be given time to consider their decision and the opportunity to ask questions. Investigators will ensure that information about equipoise is provided impartially so as to avoid potential bias by influencing compliance with advice to position. Should candidates elect to participate, informed consent will be obtained (see Additional file 1) at the time of listing for surgery. Candidates will understand that although consenting to participate in the trial, they will be formally enrolled only if the inclusion and exclusion criteria are still met following surgery.

We will not be recruiting/consenting subjects who we feel lack capacity.

The surgery will involve vitrectomy (using instruments of any gauge), internal limiting membrane (ILM) peeling (with or without staining by a vital dye), fluid-air exchange and injection of octafluoropropane (C3F8) 14 % gas. Vitrectomy may be combined with phacoemulsification and intra-ocular lens implant.

Subjects will be randomised immediately following surgery, unless exclusion criteria are met during surgery.

Intervention
The intervention is advice to adopt face-down positioning (see Additional file 2); subjects will be advised to maintain a face-down position for a total of at least 8 consecutive or non-consecutive hours a day for 5 days following surgery.

The comparator is advice to adopt face-forward positioning (see Additional file 3); subjects will be advised to maintain a face-forward position, inactive, for at least 8 consecutive or non-consecutive hours a day for 5 days following surgery.

Subjects in either group will be allowed a 15-minute break (every hour) from their allocated position. In the position-free-time we will advise subjects to avoid the face-up position.

Face-down or face-forward positioning will be advised during waking hours only, not during sleep. We will advise subjects to avoid the face-up position during sleep.

Investigators will explain positioning to candidates prior to surgery, providing written instructions with diagrams.

Randomisation
Eligible candidates will be invited to participate and to sign the consent form prior to surgery.

At the conclusion of standardised surgery across all sites, participants still eligible for inclusion will be allocated randomly 1:1 to one of the 2 treatment arms (refer to the flow diagram in Additional file 4) stratified by site, using random permuted blocks of size 4 or 6 in equal proportions.

Randomisation will be performed using a secure bespoke online randomisation service implemented by the PCTU (Pragmatic Clinical Trials Unit). Each site will be provided with a unique log-in username and password to access the service. Online randomisation will be
available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance. Access to the service will be restricted to staff as delegated by the Principal Investigator (PI). They will input the participant ID and details required for randomisation, and then will be presented with immediate on-screen randomisation. The randomisation system will have built-in checks to check that (1) the participant ID is not a duplicate, and (2) the date of birth is within the eligible age set in the protocol.

Once the subject has been randomised, the enrolment of this subject will be documented on the enrolment log. An Email will be automatically generated to notify the Chief Investigator's (CIs) team and PCTU of all participants randomised to the trial.

**Masking**

Subjects and clinicians will be unmasked to treatment allocation.

Investigators assessing the primary endpoint by grading of OCT scans will be masked to treatment allocation. This will be achieved by electronic capture of OCT images which are presented anonymously to the grading clinicians. Each clinician will be masked to their colleague's grading. Postoperative hole closure will be determined according to the presence (open) or absence (closed) of any gap between the opposing edges of the hole. No measurement is involved. In the event of disagreement between clinicians, the opinion of a third clinician (also masked) will be sought.

**Follow-up**

Subjects will attend for follow-up assessment as part of the trial at 3 months following surgery. Their surgical teams will manage their routine postoperative clinical care in the meantime.

The primary outcome, macular hole closure, will be determined by masked assessment of OCT scans acquired at 3 months.

**Unit of analysis**

All ocular assessments relate to the study eye. In the event that a subject is having surgery for bilateral macular holes (which are not operated on simultaneously), the first eye to be operated on during the trial will be the study eye.

**Data collection**

Table 1 shows the schedule of assessments.

Pre-operative data collection:

- Demographic data (age, sex, ethnicity)
- Laterality
- Duration of symptoms

### Table 1 Schedule of assessments

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Preoperative</th>
<th>Surgery</th>
<th>3 months postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laterality</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCVA</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Lens status, phakic/pseudophakic</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macular hole diameter on OCT</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macular hole status (closed; open flat open elevated)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QoL-WFQ-25 questionnaire</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject-reported experience of positioning</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If primary repair of macular hole failed, second operation performed/planned</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BCVA best-corrected visual acuity, OCT optical coherence tomography, QoL quality of life, WFQ-25 Visual Functional Questionnaire

- Best-corrected visual acuity (BCVA) measured using Snellen charts at a standard distance of 6 metres
- OCT with recording of minimal hole diameter (see Additional file 5)

**Outcome measures**

**Primary outcome**

The primary outcome will be anatomical closure of the macular hole, determined at 3 months after surgery by masked assessment of OCT scans.

**Secondary outcomes**

- Further surgery for macular hole, performed or planned
- BCVA using standard Snellen chart at 6 metres
- Patient-reported experience of positioning at 3 months
- Patient-reported health and quality of life as assessed at baseline and at 3 months using the National Eye Institute Visual Function Questionnaire (VFQ-25)

**End of study definition**

The end of the study will be at the final assessment of the final subject.
Statistical considerations

Sample size and power calculation

Clinical consensus is that face-down positioning would be recommended if there were a difference of 15% in success rates. This is the smallest clinically relevant treatment difference that we wish to detect. Previous studies [8] indicate that successful closure of large macular holes without advice to position face-down is 80%. A study with 86 patients per group has 85% power to detect a difference between 80% in the face-forward positioning arm and 95% in the face-down positioning arm. With a 10% loss to follow-up, we are aiming to recruit 96 patients in each arm.

Analysis

Baseline characteristics will be tabulated in the two treatment arms.

Proportions of macular hole closures at 3 months will be compared between treatment arms using logistic regression adjusting for age and sex, with site as a random effect.

Visual acuity at 3 months will be compared using linear regression adjusting for age, sex, and baseline visual acuity, with site as a random effect. We will also adjust for surgery type in the logistic regression analysis. Questionnaire scores assessed at 3 months will be compared using linear regression adjusting for age and sex, with site as a random effect.

The numbers of participants who decline to participate, fall screening, or withdraw or are lost to follow-up will be recorded in a Consolidated Standards of Reporting Trials (CONSORT) flow-chart.

The analyses will be on an intention-to-treat basis, and every effort will be made to collect complete data. If any outcome data are missing we will analyse available subjects only (this is unbiased under a missing-at-random assumption where missingness depends only on variables adjusted for in the analysis), but we will also perform secondary analyses investigating the missing-at-random assumption and involving further baseline covariates if necessary.

OCT scans will be anonymised and sent to two independent retinal surgeons who will grade the macular hole as closed, open and flat (without a cuff of subretinal fluid), open and elevated (with a cuff of subretinal fluid). The readers will be masked to the identity and treatment allocation of the subject. In the event of any disparity in grading, a third independent retinal surgeon, also masked to identity and treatment allocation, will arbitrate.

A formal statistical analysis plan will be signed off by the Trial Steering Committee prior to analysis.

Safety considerations

Random allocation to the alternatives of face-down and face-forward positioning presents a possible safety issue because of the uncertainty over which is more effective, and the known adverse effects of prolonged face-down positioning. We have addressed these risks by advising a minimum of inactive face-forward positioning for all subjects, and only an 8-hour total minimum period of face-down positioning.

Data handling and record keeping

- Confidentiality
  Information related to participants should be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee (REC) approval.

- Record retention and archiving
  All study documents are to be retained for a period of 5 years following conclusion of the study. Following the submission of the end of study report the sponsor will arrange for archiving of the Trial Master File in accordance with the sponsor’s process. The sponsor will also notify the local PIs that the Investigator Site Files (ISFs) may be archived. The ISFs will be retained and archived at site in accordance with the Trusts’ procedures. Following the end of the retention period the sponsor will notify the PIs in writing that the required retention period has completed and that documents can be destroyed. A copy of the instruction to the Trust Archivist to destroy the ISF will be requested.

Products, devices, techniques and tools

Devices

Spectral domain ocular coherence tomography (SD-OCT) will be used at the various sites to determine the preoperative size of the macular hole, and whether surgery has been successful in terms of hole closure at 3 months.

The size of the macular hole is defined as its minimum horizontal diameter. This is its linear width measured using the OCT caliper function along a line that bisects the hole in the horizontal meridian and is parallel to the retinal pigment epithelium (see Additional file 5).

Tools

The VFQ-25 is a reliable and valid 25-item version of the 51-item National Eye Institute Visual Function Questionnaire (NEI-VFQ).

Safety reporting

Adverse event (AE)

Safety reporting will adhere to the sponsor’s standard operating procedures. If the AE is not defined as serious,
it will be recorded in the study file and the participant will be followed-up by the research team. The AE will be documented in the participants’ medical notes.

**Serious adverse event (SAE)**

A SAE is defined as an untoward occurrence that:

(a) Results in death;
(b) Is life-threatening;
(c) Requires hospitalisation or prolongation of existing hospitalisation;
(d) Results in persistent or significant disability or incapacity;
(e) Consists of a congenital anomaly or birth defect; or
(f) Is otherwise considered medically significant by the investigator.

An SAE occurring to a research participant will be reported to the main REC where in the opinion of the CI the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

Expected AEs include the following:

- Ocular discomfort; epiphora; periocular swelling; diplopia; ptosis
- Subconjunctival or intra-ocular hemorrhage
- Corneal abrasion
- Retinal or choroidal tear or detachment
- Wound leak
- Ocular hypotony or raised intra-ocular pressure/glaucoma
- Overfill or underfill of intra-ocular gas tamponade
- Intra-ocular or extra-ocular inflammation or infection
- Intra-ocular neovascularisation
- Lens opacity, subluxation or dislocation of lens or lens implant
- Persistent or recurrent macular hole
- Visual field defect or other disturbance of sight
-Discomfort of joints, neck, back or limbs

SAEs that are considered to be ‘related’ and ‘unexpected’ are to be reported to the sponsor within 24 hours of learning of the event using the following Email address: pharmacovigilance@moorfields.nhs.uk and to the main REC within 15 days, in line with the required timeframe. SAEs will be documented in the participants’ medical notes and the Case Report Form (CRF).

**Urgent safety measures**

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and main REC (via telephone) of this event immediately.

The CI has an obligation to inform both the main REC in writing within 3 days, in the form of a substantial amendment. The sponsor must be sent a copy of the correspondence with regards to this matter.

**Annual safety reporting**

The CI will send the Annual Progress Report to the main REC using the National Research Ethics Service (NRES) template (the anniversary date is the date on the ‘favourable opinion’ letter from the REC) and to the sponsor.

**Overview of the safety reporting responsibilities**

The CI has the overall safety oversight responsibility and will ensure that safety monitoring and reporting is conducted in accordance with the sponsor’s requirements.

**Monitoring and auditing**

The study will be monitored in line with the study monitoring plan, written by the PCTU quality assurance (QA) manager and agreed by the study sponsor. The PCTU has provisionally identified this study as being medium risk.

**Trial organisation**

**Trial management committee**

James Bainbridge: Chief Investigator, Moorfields Eye Hospital, London, UK

Saruban Pasu: Co-investigator, NIHR Biomedical Research Centre (BRC) at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK

Catey Bunce: Co-investigator and statistician, Moorfields Eye Hospital, London, UK

Ann Thomson: Senior Trial Manager, Pragmatic Clinical Trials Unit, London, UK

Irene Simmonds: Trial Co-ordinator, Pragmatic Clinical Trials Unit, London, UK

Richard Hooper: Statistician, Pragmatic Clinical Trials Unit, London, UK

Mike Waring: Data Manager, Pragmatic Clinical Trials Unit, London, UK
**Trial steering committee**
Noemi Lois: Consultant Ophthalmic Surgeon, Belfast Health and Social Care Trust, Belfast, Northern Ireland, UK.
Simon Skene: Senior Statistician, University College London, London, UK.
Roy Smith: Lay Person, UK.
This team will also perform the duties of a data management committee.

**Finance and funding**
The trial is funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Research for Patient Benefit scheme.

**Indemnity**
The sponsor is Moorfields Eye Hospital (MEH) NHS Foundation Trust, which participates in the Clinical Negligence Scheme for Trusts (CNST), run by the NHS Litigation Authority, which pools the risk of clinical negligence claims. NHS indemnity (for negligent harm) will cover MEH employees, both substantive and honorary, who are working in the course of their NHS employment and in respect of conducting research projects, which must have received NHS permission. MEH will not accept liability for any activity that has not been properly registered and Trust approved.

**Ethics**
Random allocation to the alternatives of face-down or face-forward positioning presents a possible ethical issue because of the uncertainty over which is safer and more effective. In particular, there is some concern that individuals with large holes randomised to non-positioning may be less likely to benefit from hole-closure. We have addressed this concern by ensuring that subjects not allocated to face-down positioning are advised to maintain an inactive face-forward position, which has been an acceptable standard for previous trials. If the results demonstrate that positioning face-down is more effective than positioning inactively face-forward we can conclude that it is also likely to be more effective than not positioning at all.

Applications to the UK’s main REC (NRES Committee London – Westminster) and the local Moorfields Research Management Committee have received favourable opinion (REC reference 14/LO/2061).

We will perform the study in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments.

**Dissemination of research findings**
The results will be disseminated at clinical meetings, and by publication in a peer-reviewed journal.

**Discussion**
The research team combines the strengths of experienced eye specialists with the expertise of the PCTU, and the active involvement of patients to ensure that the trial addresses their needs. The trial will benefit patients by providing reliable information on the value of posturing following surgery for large macular holes, thereby enabling them to make an appropriately informed choice about the management of their condition.

**Trial status**
The authors confirm that the trial will start recruiting from May 2015 onwards.

**Additional files**
- Additional file 1: Consent form. (DOCX 38 kb)
- Additional file 2: Examples of face-down seated and face-down lying. (DOCX 446 kb)
- Additional file 3: Examples of face-forward reading and face-forward watching TV. (DOCX 414 kb)
- Additional file 4: Flow diagram of PIMS trial. (DOCX 39 kb)
- Additional file 5: OCT image of macular hole. (DOCX 627 kb)

**Abbreviations**
AE: adverse event; BRC: Biomedical Research Centre; BCVA: best-corrected visual acuity; CNST: Clinical Negligence Scheme for Trusts; CONSORT: Consolidated Standards of Reporting Trials; CI: Chief Investigator; CRF: Case Report Form; HTA: Health Technology Assessment; IAR: internal limiting membrane; IFS: Investigator Site Files; NIHR: National Institute for Health Research; NRES: National Research Ethics Service; OCT: optical coherence tomography; PCTU: Pragmatic Clinical Trials Unit; PI: Principal Investigator; QA: quality assurance; RCT: randomised controlled trial; RIEC: Research Ethics Committee; SAR: serious adverse event; SD-OCT: spectral domain optical coherence tomography; VFD: Visual Functional Questionnaire.

**Competing interests**
The authors declare that they have no competing interests.

**Authors' contributions**
SP participated in development of the trial protocol, gained regulatory authority approvals, prepared study documentation and drafted the manuscript. CB, RH, AT participated in development of the trial protocol, standard operating procedures, study documentation and contributed to drafting the manuscript. JB conceived and designed the trial, secured trial funding, prepared the trial set-up, prepared the standard operating procedures, study documentation and contributed to drafting the manuscript. All authors read and approved the final manuscript.

**Acknowledgments**
The authors wish to acknowledge the NIHR Research for Patient Benefit scheme for funding the study. Written informed consent was obtained from the individual in Additional files 2 and 3 for publication of this manuscript and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.
References
Positioning In Macular hole Surgery (PIMS): statistical analysis plan for a randomised controlled trial

Lauren Bell1,5*, Richard Hooper1,5, Catey Bunce2,3,6, Saruban Pasu3,4,7 and James Bainbridge3,4,7

Abstract

**Background:** The treatment of idiopathic full-thickness macular holes involves surgery to close the hole. Some surgeons advise patients to adopt a face-down position to increase the likelihood of successful macular hole closure. However, patients often find the face-down positioning arduous. There is a lack of conclusive evidence that face-down positioning improves the outcome. The “Positioning In Macular hole Surgery” (PIMS) trial will assess whether advice to position face-down after surgery improves the surgical success rate for the closure of large (≥400 μm) macular holes.

**Methods/design:** The PIMS trial is a multicentre, parallel-group, superiority clinical trial with 1:1 randomisation. Patients (n = 192) with macular holes (≥400 μm) will be randomised after surgery to either face-down positioning or face-forward positioning for at least 8 h (which can be either consecutive or nonconsecutive) a day, for 5 days following surgery. Inclusion criteria are: presence of an idiopathic full-thickness macular hole ≥400 μm in diameter, as measured by optical coherence tomography (OCT) scans, on either or both eyes; patients electing to have surgery for a macular hole, with or without simultaneous phacoemulsification and intraocular lens implant; ability and willingness to position face-down or in an inactive face-forward position; a history of visual loss suggesting a macular hole of 12 months’ or less duration. The primary outcome is successful macular hole closure at 3 months post surgery. The treatment effect will be reported as an odds ratio with 95% confidence interval, adjusted for size of macular hole and phakic lens status at baseline. Secondary outcome measures at 3 months are further surgery for macular holes performed or planned (of those with unsuccessful closure); patient-reported experience of positioning: whether patients report they would still have elected to have the operation given what they know at follow-up: best-corrected visual acuity (BCVA) measured using Snellen charts at a standard distance of 6 m; patient-reported health and quality of life assessed using the National Eye Institute Visual Function Questionnaire (VFQ-25).

**Discussion:** The PIMS trial is the first multicentre randomised control trial to investigate the value of face-down positioning following macular hole standardised surgery.

**Trial registration:** International Standard Randomised Controlled Trials Number registry, ID: ISRCTN12410596. Registered on 11 February 2015.


**Keywords:** Statistical analysis plan, Idiopathic macular holes, Surgery, Positioning, Recovery

*Correspondence: l.bell@qmul.ac.uk
1Pragmatic Clinical Trial Unit, Queen Mary University of London, London, UK
2Blistar Institute, Barts and The London School of Medicine and Dentistry, 4 Newark Street, London E1 2AT, UK
Full list of author information is available at the end of the article
Overview

Purpose and scope of statistical analysis plan (SAP)
The aim of this paper is to report, in detail, the planned analyses that were approved by the Trial Steering Committee for the principal research for the PIMS (Positioning In Macular hole Surgery) trial, a multicentre, interventional, comparative, randomised controlled clinical trial comparing face-down with face-forward positioning on the outcome for surgery for large macular holes. The PIMS trial is registered with ISRCTN, number 12410596 and the UKCRN portfolio, number 17966. The pilot study preceding PIMS was published in *Eye*, 2011 [1]. This pilot randomised controlled trial (RCT) explored the feasibility of a definitive trial to determine the value of face-down positioning following vitrectomy, internal limiting membrane (ILM) peeling, and C3F8 gas tamponade for full-thickness macular holes, without simultaneous phacoemulsification. The PIMS study protocol was published in *Trials*, 2015 [2]. We aim to maximise transparency of the planned analysis with the intention of eradicating misreporting or selective reporting of the trial data. We have also considered any contingencies, with regards to specifying alternative analysis plans if statistical models fail to converge.

This analysis plan was written, reviewed and signed off prior to database lock, and prior to any member of the trial team having access to unmasked trial data.

Changes from the published protocol
The protocol published in *Trials* stated that the analysis for the primary outcome would be adjusted for age and sex as fixed effects, and site as a random effect [2].

Opinion leaders questioned whether age and sex were associated with successful macular hole closure. A brief literature review highlighted a relevant study which did not find a significant association between age or sex and successful macular hole closure [3].

At the suggestion of the independent Trial Steering Committee (TSC) the PIMS management team decided to remove age and sex as covariates and to specify instead that the primary outcome would be adjusted for macular hole size (µm) and phakic lens status, with site as a random effect.

Background and trial design
Further details of the rationale, treatment policies and design of the PIMS study are given in the study protocol.

In summary, idiopathic macular holes (macular holes) cause patients’ central vision to be blurred or distorted. Macular holes have an estimated annual incidence of 8 per 1000 individuals per year [4].

Macular holes can be treated surgically by removing the vitreous gel from the eye (vitrectomy), peeling off the ILM and then injection of a temporary gas bubble into the back of the eye. Surgery is deemed successful when the macular hole is fully closed. The current lack of evidence with which to guide patients has led to a lack of consensus among clinicians and wide variation in clinical practice. Patients are understandably confused and distressed by uncertainty and inconsistent advice.

Some surgeons advise patients to adopt a face-down position for a period immediately following surgery with the aim of improving the outcome by maintaining contact of the gas bubble with the macular hole. The duration of the face-down position varies among surgeons. However, maintaining the face-down position can be arduous for patients [5] and is associated with serious adverse events. Furthermore, evidence that face-down position treatment policy increases the closure rates of macular holes is lacking.

Main objectives
The PIMS trial aims to determine whether the advice to position face-down improves the surgical success rate for closure of large (≥400 µm) macular holes, and thereby reduces the need for further surgery. This trial will benefit patients by providing robust evidence on the value of posturing following surgery for large macular holes, and enable health care providers and patients to make an informed choice for the best positioning to adopt after surgery.

Trial design
The PIMS trial is a multicentre, parallel-group, superiority clinical trial with 1:1 randomisation. The trial will recruit 192 participants having surgery for large macular holes (≥400 µm), who will be randomly allocated into one of the two treatment arms:

1. Face-down positioning: subjects will be advised to maintain a face-down position for a total of at least eight consecutive or nonconsecutive hours a day for 5 days following surgery
2. Face-forward positioning: subjects will be advised to maintain a face-forward position, inactive, for at least eight consecutive or nonconsecutive hours a day for 5 days following surgery

Participants
The PIMS trial is being conducted at nine hospitals in the UK.
Patients are deemed eligible to participate in the study if they meet the following inclusion criteria:

1. The presence of idiopathic full-thickness macular hole, ≥400 µm in diameter as measured by optical
coherence tomography (OCT) scans, on either or both eyes
2. Patients electing to have surgery for macular hole, with or without simultaneous phacoemulsification and intraocular lens implant
3. Ability and willingness to position face-down or in an inactive face-forward position
4. Patients with a history of visual loss suggesting a macular hole of 12 months’ or less duration

Patients are deemed ineligible to participate in the study if they meet one or more of the following exclusion criteria:

1. Age-related macular degeneration, glaucoma, diabetic retinopathy, retinal degeneration; amblyopia; previous vitrectomy surgery (refractive error, lens opacity, and previous use of ocuplasmin are not exclusion criteria)
2. Traumatic macular hole
3. History of visual loss suggesting macular hole duration longer than 12 months
4. The presence of retinal tear identified during surgery for which postoperative positioning is advised

Outcome measures

The primary outcome of the study is the anatomical closure of the macular hole at 3 months post surgery.

Successful closure of the macular hole will be determined by OCT scans. The scans will be anonymised and sent to two independent retinal surgeons who will independently grade the macular hole as closed; ‘open and flat’ (without a cuff of subretinal fluid); or ‘open and elevated’ (with cuff of subretinal fluid). The readers will be masked to the identity and allocated treatment of the subject. In the event of any disparity in grading, a third independent retinal surgeon, also masked to identity and treatment allocation, will arbitrate.

The categories ‘open and flat’ (without a cuff of subretinal fluid), or ‘open and elevated’ (with a cuff of subretinal fluid) will be pooled into one category of ‘open’ for the purpose of analysis.

Secondary outcomes at 3 months post surgery are:

- Patient-reported outcome ‘Given what you now know, would you still have elected to have the operation?’ with responses Yes, No or Don’t Know

Sample size and randomisation

Unit of analysis

All ocular assessments relate to the study eye. In the event that a subject is having surgery for bilateral macular holes (which are not operated on simultaneously), the first eye to be operated on during the trial will be the study eye.

Sample size

Clinical consensus is that face-down positioning would be recommended if there were a difference of 15% in success rates. This is the smallest clinically relevant treatment difference that we wish to detect. Previous research [6] indicates that successful closure of large macular holes without advice to position face-down occurs in 80% of cases. A study with 86 patients per group has 85% power and 95% confidence to detect a difference in outcome rate of 80% in the face-forward positioning arm versus 95% in the face-down positioning arm. With an anticipated 10% loss to follow-up, we are aiming to recruit 96 patients in each arm.

Screening

The PIMS trial did not collect data on the number of participants screened for eligibility. The reason for this omission is that the proportion of patients with macular holes ≥400 μm in size is a small minority of the overall number of patients presenting with macular holes. For some hospital sites, the data collection of the number of patients screened for eligibility was considered unfeasible given their current resources.

Randomisation and masking

Patients are randomised in a 1:1 ratio to follow either a face-forward positioning or a face-down positioning. Randomisation is stratified by site, using random permuted blocks of size 4 or 6 in equal proportions. A secure bespoke online randomisation service implemented by the Pragmatic Clinical Trials Unit performs the randomisation. Randomisation is conducted post surgery to ensure masking the surgeon to the treatment allocated. Post surgery, trial staff input the patient’s ID and details for immediate on-screen randomisation. Randomisation is provided 7 days a week, 24 h a day. Each site is provided with a unique log-in username and password to access the service. Due to the open-label nature of the treatment, postoperative clinical staff and patients are unmasked to the treatment allocation.

Investigators assessing the primary endpoint by grading of the OCT scans are masked to the treatment allocation.
In the event of any disagreement between the two clinician grades, a third independent retinal surgeon, who is also masked to the treatment allocation, will arbitrate.

**Analysis methods**

**General analysis principles**

The primary analysis for each outcome will be by intention-to-treat, meaning that all patients on whom an outcome is available will be included in the analysis, and will be analysed according to the treatment group to which they were randomised.

Through vigilance and careful planning, the PIMS trial management team aim to achieve complete capture of all data from all patients, including patients who do not adhere to the protocol or patients who withdraw from the trial. We acknowledge that despite our best efforts, some patients may have missing data. In accordance with the intention-to-treat principle and to avoid concerns over data-driven selection methods, we state the plan for dealing with missing data here.

Missing data is a potential source of bias, and the extent and pattern of missing data can influence the interpretation of the trial. The sample size for the PIMS trial allows for a 10% loss of follow-up, and in our results we will provide a full listing of all the reasons for patients' withdrawal of the study. This list will be helpful in justifying the assumptions that we make in regards to missing data; however, we cannot be certain that there is a relationship between observed covariates and missing outcome data, and cannot exclude the possibility of some data missing not at random.

We will analyse the data without undertaking any sensitivity analysis if the primary outcome is missing in fewer than 5% of cases (nine patients or less). If more than nine patients' primary outcome is missing, we will undertake sensitivity analysis to test if the missing at random assumptions are appropriate. We will use a pattern-mixture approach to model the consequences of a systematic difference between missing and nonmissing values, to see if the conclusions drawn from the PIMS study are affected when the missing-at-random assumption is violated.

All analyses will be performed using Stata (Stata Corporation, College Station, TX, USA).

**Variables measured and schedule of assessments**

- The variables measured preoperatively are age, sex, ethnicity, laterality, duration of symptoms, BCVA (Best-corrected Visual Acuity), lens status (either phakic or pseudophakic), macular hole diameter on OCT scans and the Quality of Life VFQ-25 questionnaire.

- The variables measured at 3 months postoperatively are BCVA, macular hole status (closed, open flat or open elevated), the Quality of Life VFQ-25 questionnaire, subject-reported experience of positioning and, if primary repair of a macular hole failed, was a second operation performed or planned?

For each comparison of outcomes according to positioning policy, the following summaries will be provided (see templates for tables in Additional file 1):

- The number of patients in each positioning policy group who are included in the analysis.
- A summary measure of the outcome, by positioning policy group (mean and standard deviation (SD) for continuous outcomes; number and percentage in each category for categorical outcomes). The treatment effect (difference in means for continuous outcomes; odds ratio for binary outcomes) with its 95% confidence interval (95% CI) and p value.

All comparisons will adjust for linear effect of macular hole size (µm) at baseline, phakic lens status at baseline, and a random effect of site (hospital). We will anonymise data reported by hospital site. Outcomes which are also assessed at baseline (BCVA and quality of life) will be analysed adjusting also for a linear effect of the baseline measurement.

Patients have a 2-week postoperative appointment, at which time clinicians may be able to identify that the macular hole closure was unsuccessful, meaning that a second operation to close the hole is required. The outcome of any participant who had a second surgery after randomisation but before the 3-month visit will be imputed as open, as it is most unlikely that the hole will close without further treatment by 3 months. These patients will not be completing secondary questionnaires.

**Participants**

We will report numbers of participants consented, randomised, and followed up in a Consolidated Standards of Reporting Trials (CONSORT) flowchart (Fig. 1). At the time of writing this SAP, recruitment of patients is on-going, and the trial teams remain unmasked; therefore, the aggregated values for the CONSORT flowchart are not provided here.

Baseline characteristics (variables measured preoperatively) will be summarised by positioning policy group. For continuous variables, we will examine the distribution of the data for symmetry, and report either the mean and SD, or the median and interquartile range (IQR) values. For categorical variables we will report the number and percentage in each category for categorical
variables, with a note of numbers with missing data if any (see Additional file 1: Table S1).

Analysis of primary outcome
This will be analysed using mixed-effects logistic regression. This analysis will be performed by the command *xtlogit* in Stata 14:

```
xtset site
xtlogit machole randgrp machsize i.lenstat, re
```

If the mixed regression model fails to converge, we will model site as a fixed effect rather than a random effect with the following command:

```
xtlogit machole randgrp machsize i.lenstat, fe
```

We will ensure that the quadrature approximation in our model is adequate and stable. First, we will run the command *quadchk* to test if our model is sensitive to changes in the number of adaptive points [7]. If the relative differences in our coefficients change by more than 1%, we will improve the quadrature approximation by increasing the number of integration points until this difference in coefficients is less than 1%. If this approach is not successful in achieving stable quadrature approximation, we will consider the command *gllamm* [8] which allows for adaptive quadrature numerical integration with the following command:

```
gllamm machole randgrp machsize i.lenstat, i(site) family(binom) link(logit) adapt
```

Analyses of secondary outcomes
For the analysis of further surgery for macular holes, performed or planned, we will use logistic regression (*xtlogit*). Best-corrected visual acuity (BCVA), measured using Snellen charts at a standard distance of 6 m, will be transformed to a LogMAR scale with two decimal places [9], and then analysed using linear regression (*xtreg*). Measurements of BCVA corresponding to count fingers (CF), hand movements (HM), perception of light (PL), and no perception of light (NPL) will be replaced with values of 2.10, 2.40, 2.70, and 3.00, respectively. The number of patients in each BCVA category and
their corresponding numerical values will be tabulated by treatment arm. For the patient-reported experience of positioning at 3 months, which is on the scale 0 (very difficult) to 10 (very easy) we will remain masked to treatment arm and consider an applicable cut-off value to dichotomise this variable and then use logistic regression (xtologit). For the patient-reported outcome ‘Given what you know now, would you still have elected to have the operation?’ we will pool the responses ‘Don’t know’ and ‘No’ into one category, and use logistic regression (xtologit). If the proportion of ‘Don’t know’ responses exceeds 10% (19 patients) we will undertake a sensitivity analysis by pooling the ‘Don’t know’ with ‘Yes’ responses and compare how this alternative pooling affects the odds ratio estimate. The Complications of Age-related Macular Degeneration Prevention Trial Research Group [10] observed a skewed distribution of the VFQ-25 score; therefore, we will assume that our results will be similarly skewed, and perform a logistic transformation (log(x/(100 - x))) of the VFQ-25 scores, and with this transformed outcome use linear regression (xtreg). When adjusting analyses of BCVA and VFQ-25 for their respective baselines we will use the same normalising transformation for the baseline measurement as for the follow-up measurement.

Interim analyses
The PIMS Trial Steering Committee is made up of a chair, a second clinician, an independent statistician, and a lay member. There is no Data Monitoring Committee (DMC) nor any planned interim analyses for this trial due to the relatively short time span of follow-up, and minimal clinical risks. Following the guidance in the MRC’s updated terms of reference for Trial Steering Committees [11], if circumstance arise that concern the TSC, an emergency DMC, made up of independent members, will convene to review the unblinded data and advise the TSC.

Serious adverse events
Serious adverse events (SAE), as defined in the protocol, will be tabulated and reported. The chief investigator will class the SAE as Related, which is resulting from administration of any research procedures, and/or Unexpected, that is not listed in the protocol as an expected occurrence.

Trial status
Recruitment began in May 2015, with nine UK hospitals participating in the trial. At the time of manuscript submission, November 2016, the PIMS trial is open to recruitment.

Additional file

**Additional file 1:** Templates for PIMS results tables (PDF 391 kb)

Abbreviations
95% CI: 95% confidence interval; BCVA: Best-corrected visual acuity; CONSORT: Consolidated Standards of Reporting Trials; ILM: Internal limiting membrane; IQR: Interquartile range; RCT: Randomised Controlled Trial; VCN: International Standard Randomised Controlled Trial Number registry; OCT: Optical coherence tomography; PIMS: Positioning in Macular hole Surgery trial; RCT: Randomised controlled trial; SAP: Statistical analysis plan; SD: Standard deviation; TSC: Trial Steering Committee; UKCTN: UK Clinical Research Network; VFQ-25: National Eye Institute Visual Function

Acknowledgements
Not applicable.

Funding
The PIMS trial is funded by the UK National Institute for Health Research (NHSR) through its Research for Patient Benefit scheme (grant number PB-PG-0213-30083).

Availability of data and materials
Not applicable.

Authors’ contributions
LB drafted the SAP, RH and CB provided guidance on the methods. SP led the development of the trial protocol and gained regulatory authority approvals. LB, RH, CB, SP, and JB contributed to the development of the protocol and other study documentation. JB conceived and designed the trial and secured trial funding. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Informed consent has been obtained from all participants. This study was approved by the Research Ethics Committee NRES Committee London – Westminster who provided approval for all the participating sites in the study. The REC Reference Number is 14/LD/0261.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
1Pragmatic Clinical Trial Unit, Queen Mary University of London, London, UK
2Department of Primary Care and Public Health Sciences, King’s College London, London, UK
3NIHR Biomedical Research Centre (BRC) at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK
4Moorfields Eye Hospital NHS Foundation Trust, London, UK
5BاBizard Institute, Barts and The London School of Medicine and Dentistry, 4 Newbattle Street, London E1 2AT, UK
64th Floor House, 4th Floor, Addison House, Guy’s Campus, London SE1 9UL, UK
7Mile End Hospital, Bancroft Road, London E1 4DG, UK

Received: 28 November 2016 Accepted: 25 May 2017
Published online: 13 June 2017

References
2. Pala S, et al. PIMS-Positioning in Macular hole Surgery trial—a multicentre interventional comparative randomised controlled clinical trial comparing face-down positioning, with an inactive face-forward position on the
outcome of surgery for large macular holes: study protocol for a randomized controlled trial. Trials. 2015;16:527.
7. StataCorp. Stata Statistical Software: Release 14. College Station, TX, USA.

Submit your next manuscript to BioMed Central and we will help you at every step:
- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at www.biomedcentral.com/submit
9.0 Appendix

9.1 Standard operating procedures (SOP) for PIMS trial

9.1.1 Informed Consent

<table>
<thead>
<tr>
<th>Standard Operating Procedures (SOP) for: Informed Consent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOP Number:</strong> 1</td>
</tr>
<tr>
<td><strong>Effective Date:</strong></td>
</tr>
<tr>
<td><strong>Author:</strong> Irene Simmonds</td>
</tr>
<tr>
<td><strong>Authorisation:</strong></td>
</tr>
<tr>
<td><strong>Name / Position</strong> J. Bainbridge, Chief Investigator</td>
</tr>
<tr>
<td><strong>Signature</strong></td>
</tr>
<tr>
<td><strong>Date</strong></td>
</tr>
</tbody>
</table>

**Purpose and Objective:**
This document describes the procedure for taking informed consent from study participants involved in the PIMS trial.


**SOP Text**

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Principle investigator.</td>
<td>Complete the delegation log</td>
</tr>
<tr>
<td></td>
<td>Please ensure any individual who will be taking consent has received appropriate training, as outlined by the training SOP, before signing the PIMS delegation log.</td>
</tr>
<tr>
<td></td>
<td>Only clinically trained individuals, for example nursing staff, can be delegated to take consent.</td>
</tr>
<tr>
<td>2. Principle investigator, staff delegated to take consent on the delegation log.</td>
<td>Local versions of the PIS and consent forms</td>
</tr>
<tr>
<td></td>
<td>The PIS, ICF and GP Letters should be printed on local headed paper. Please ensure that the PIS has the correct patient advice and liaisons service (PALS) details for your site.</td>
</tr>
<tr>
<td>Principle investigator, staff delegated to take consent on the delegation log.</td>
<td>Please make every effort to use the correct version of the documents, as any patients consented to the wrong version of the forms will need to be reconsented at a later date.</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3.</td>
<td>PIS given at the pre-operative consultation&lt;br&gt;The patient information sheet should be given to the patient at the pre-operative consultation. The patient should be talked through the PIS and given the opportunity to ask questions. The patient should be given as long as they require to make a decision, and under no circumstances should be pressured to give consent, or pressurized to make a decision. It should be made very clear to the patient that their care will not be impacted by refusing to take part in the trial, and that they can withdraw consent at any time.</td>
</tr>
<tr>
<td>4.</td>
<td>Taking informed consent&lt;br&gt;The patient should be given a copy of the patient information sheet, and the person taking consent should be satisfied that they have understood this document before signing the consent form.&lt;br&gt;The clinician taking consent should witness the participant signing the consent form. Ask the patient to initial all the boxes on the form adjacent to the consent statements. The participant should then print and sign their name, and date the consent form. The study participant must do this for themselves, the person taking consent cannot complete any section of the consent form designed to be completed by the participant.&lt;br&gt;The consent form is then countersigned and dated by the delegated member of the research team taking consent.</td>
</tr>
<tr>
<td>5.</td>
<td>Filing the consent form in the medical notes&lt;br&gt;A total of three copies of the consent form will be required.&lt;br&gt;One copy should be given to the patient for their reference.&lt;br&gt;A second copy should be filed by the study team in the patient identifiable information folder. This copy should be retained as evidence that consent was taken.&lt;br&gt;A third copy of the consent form should be put in the patient’s medical notes, along with a copy of the PIS and the GP letter, to indicate that the patient has been involved in the PIMS study.</td>
</tr>
</tbody>
</table>
6. Principle investigator, staff delegated to take consent on the delegation log.

Pre-operative questionnaire

The pre-operative questionnaire should not be completed until after the patient has been consented. The pre-op questionnaire should therefore not be given to the patient until after the consent procedure has been completed.

References:

<table>
<thead>
<tr>
<th>Version</th>
<th>Reason for Change</th>
<th>Author of change</th>
<th>Date Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>Clarify the effective date.</td>
<td>Simmonds</td>
<td>14th July</td>
</tr>
</tbody>
</table>

9.1.2 Data management and image transfer

Standard Operating Procedures (SOP) for: Data Management and OCT Image Transfer

SOP Number: 2   Version Number: 2.0
Effective Date:   Review Date:

Author: Irene Simmonds
Reviewed by: Saruban Pasu

Authorisation:
Name / Position: J. Bainbridge, Chief Investigator
Signature: 
Date: 

Purpose and Objective:
To describe the data management procedures for the PIMS study.

SOP Text

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chief Investigator, Principle Investigator, Research Team</td>
<td>Data Protection</td>
</tr>
</tbody>
</table>

Patient confidentiality must be maintained at all times. Study records should be pseudonymised using a Unique Trial Identification Number (UTIN.) All study data will be stored in a secure location and in compliance with the terms of the Data Protection Act 1998.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Personal identifiable information will not under any circumstances leave the hospital site.</th>
</tr>
</thead>
</table>
| 3. | Principle Investigator, Research Team | **Screening, Enrolment and Patient Identification Logs**<br>A screening log is not required for the PIMS study. To test fidelity to the exclusion criteria, it may be requested that a screening log is kept for one week only for a given week during the duration of the study.  

**Enrolment log**<br>All patients who give consent will be included on an enrolment log. This log will document patient name, NHS number, inclusion and exclusion criteria, the date upon which consent was given, date of randomisation, and the UTIN.  
Approximately 7% of patients will experience surgical complications which mean they no longer meet the inclusion criteria for the PIMS study as they will be required to position. These patients should be withdrawn from the trial. This information should be recorded on the withdrawal form and on the enrolment log.  

**Patient identification log**<br>The enrolment log includes the patients name and NHS number. The NHS number can be used to link the patient to other identifying information, such as their address and contact details.  
Contact information could be required in the event that the subject suffered an SAE. As the PIMS study is necessarily unblinded, a separate patient identification log has not been deemed necessary. Instead, all staff will follow a localized procedure to use the NHS number to access patient contact details. This procedure will be detailed on a file note in the ISF. |
| 4. | Principal Investigator/ delegated staff, as documented on delegation log | **CRF Completion**<br>**Pre and post-operative questionnaires**<br>Sites will offer the questionnaires to patients, and should encourage subjects to fill in the questionnaires in the waiting area or a quiet room. Since these patients will have had |
their pupils dilated, reading the questionnaire may be difficult. It is advisable that the patient is given all the necessary help to complete the questionnaire. Returned questionnaires can then be stored in a returns/ballot box in the reception area before being posted to **Emilia Gnat, R&D Corridor, 2nd Floor, NIHR Clinical Research Facility, Moorfields Eye Hospital, 162 City Road, EC1V 2PD**

The pre and post-operative questionnaires offered to enrolled trial participants will be entered onto the database centrally, by staff based at Moorfields Eye Hospital.

**E-CRF**

Some limited data about the subject’s macular hole will need to be uploaded to the PIMS database. Access is via a web application hosted in open clinica. Access is available to trained, delegated individuals only.

All data will be pseudonymised using a UTIN, and no patient identifiable data will be entered onto the main study database.

In the event that the database is temporarily unavailable, the information should be uploaded at a later date.

The test database can be accessed at: [https://oc.pctu.qmul.ac.uk/OpenClinica_test](https://oc.pctu.qmul.ac.uk/OpenClinica_test)

The live database can be found at: [https://oc.pctu.qmul.ac.uk/OpenClinica/MainMenu](https://oc.pctu.qmul.ac.uk/OpenClinica/MainMenu)

Detailed instructions for how to enter data can be found in the Open Clinica User Guide PIMS 22nd April 2015.

**OCT images**

The pre and post-operative OCT image should be generated in accordance with PIMS SOP 7a, 7b and 7c, depending on the imaging machine in use at each site. Each image should be marked with the subject UTIN number and the label ‘pre-op’ or ‘post-op’. The image should be uploaded to the PIMS online database, and the trial coordinator or data assistant will then forward the images onto the masked graders, using an nhs.net e-mail account.
5. **Ensuring data quality**  
Trial coordinator, data assistant, delegated site staff  
After data has been input into the database, the data assistant will run checks to ensure the data is of a sufficiently good quality. If any errors or queries are found, they will be communicated to the research team at the site who will advise on whether any amendment is necessary.

6. **Data archiving**  
Trial coordinator, QA assistant  
On completion of the study, all CRF will be archived for five years in accordance with the sponsor policy, and following guidance in PCTU SOP TC_02. Electronic data will be saved in password-protected files on external HDD/DVD or other appropriate media, and these will be kept in a secure environment, with an authorisation log to identify those who are permitted access to the data.

**References:**

<table>
<thead>
<tr>
<th>Version</th>
<th>Reason for Change</th>
<th>Author of change</th>
<th>Date Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>Removed reference to a screening log, clarified the effective date</td>
<td>Simmonds</td>
<td>14th July 2015</td>
</tr>
</tbody>
</table>

9.1.3 Study monitoring

<table>
<thead>
<tr>
<th><strong>Standard Operating Procedures (SOP) for: Study Monitoring</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOP Number:</strong> 3</td>
</tr>
<tr>
<td><strong>Effective Date:</strong></td>
</tr>
<tr>
<td>Author: Irene Simmonds</td>
</tr>
<tr>
<td>Reviewed by: Saruban Pasu</td>
</tr>
</tbody>
</table>

**Authorisation:**

**Name / Position:** J. Bainbridge, Chief Investigator

**Signature**

**Date**

**Purpose and Objective:**

To outline the monitoring procedure for the PIMS study
<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Quality Assurance Manager</td>
<td>Risk assessment and monitoring schedule</td>
</tr>
<tr>
<td></td>
<td>The study sponsor, Moorfields Eye Hospital, has risk assessed the study and concluded that it represents a low risk.</td>
</tr>
<tr>
<td></td>
<td>As a result of this, the study will receive two on-site monitoring visits. One of these will be a site initiation visit, the second will be a visit from the PCTU monitor during the recruitment period.</td>
</tr>
<tr>
<td></td>
<td>Subsequent to this, self-monitoring will be scheduled every six months from the date of first patient being recruited.</td>
</tr>
<tr>
<td>2. Trial Coordinator</td>
<td>Site Initiation Visit</td>
</tr>
<tr>
<td></td>
<td>The purpose of the SIV is to ensure that:</td>
</tr>
<tr>
<td></td>
<td>The site has received training in the protocol and any study related procedures,</td>
</tr>
<tr>
<td></td>
<td>The site has received RGF training where site staff do not have a GCP certificate</td>
</tr>
<tr>
<td></td>
<td>The site has all essential documents in place before recruitment begins</td>
</tr>
<tr>
<td></td>
<td>The SIV will be made by the trial coordinator, and the visit will be made in person. Site initiation visits will be documented on the site initiation checklist, given to sites at the end of the visit.</td>
</tr>
<tr>
<td>3. PCTU monitor, study team</td>
<td>Monitoring Visit</td>
</tr>
<tr>
<td></td>
<td>At least one monitoring visit will be conducted at each site by the PCTU monitor during the recruitment and follow up period.</td>
</tr>
<tr>
<td></td>
<td>Four weeks before the proposed date, the monitor will e-mail the site to introduce themselves, explain the purpose of the visit and arrange a mutually convenient date and time. A request will be made for medical notes to be made available on the day, so that source document verification can be performed.</td>
</tr>
<tr>
<td></td>
<td>During the visit, the PCTU monitor will review the ISF and carry out source document verification, checking the patient medical notes against the database. At the end of the visit,</td>
</tr>
</tbody>
</table>
the monitor will go over any findings with the team, and explain possible means of resolution.

A report of the visit will be written up and returned to the study team, with details of any findings and a proposed timescale for resolution. Any findings classed as ‘critical’ will require immediate corrective action, (critical findings may also require reporting as a serious breach of protocol, if applicable.)

Any findings classed as “urgent” should have a corrective action plan put in place within a week.

Any findings classed as “significant” should have a corrective action plan put in place within two weeks.

Any findings classed as “minor” should have a corrective action plan put in place within four weeks.

The study team should remain in communication with the monitor, and confirm with the PCTU when all findings have been resolved.

<table>
<thead>
<tr>
<th>4.</th>
<th>PCTU monitor, trial coordinator, study team</th>
<th>Self-Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>‘Self-monitoring’ refers to the sites monitoring themselves, making checks on their own files and previous actions. This is done using a preformatted questionnaire provided by the PCTU QA team.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The study coordinator will provide the self-monitoring form, and completed forms should be returned to both the study coordinator and the PCTU monitor. The study coordinator will then check the template document and help the site follow up and resolve any findings.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All findings will be graded as minor, significant, urgent and critical as with the monitoring visit, and in exceptional circumstances critical findings may trigger an audit.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5.</th>
<th>QA manager, trial coordinator</th>
<th>Triggered Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>If concerns are raised for any reason by a study site, a monitoring visit or an audit can be arranged.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6.</th>
<th>PCTU monitor, trial coordinator, study team</th>
<th>Site Close-Out Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before archiving, the site will receive a close out visit to ensure that essential documentation has all been correctly completed and that the trial is ready to be reconciled.</td>
</tr>
</tbody>
</table>
The close out visit may be made in person by the trial coordinator, or via teleconference. After the visit, findings will be discussed and when satisfactorily resolved, the site may proceed to archiving.

References:

<table>
<thead>
<tr>
<th>Version</th>
<th>Reason for Change</th>
<th>Author of change</th>
<th>Date Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>Clarify the effective date</td>
<td>Simmonds</td>
<td>14\textsuperscript{th} July 2015</td>
</tr>
</tbody>
</table>

9.1.4 Training

**Standard Operating Procedures (SOP) for: Training**

<table>
<thead>
<tr>
<th>SOP Number:</th>
<th>4</th>
<th>Version Number:</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Date:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review Date:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Author:** Irene Simmonds

**Reviewed by:** Saruban Pasu

**Authorisation:**

Name / Position | J. Bainbridge, Chief Investigator
Signature        | |
Date             |   |

**Purpose and Objective:**

To outline the training that will be given to investigators and research staff. Training should allow study teams to carry out their roles and responsibilities in compliance with the Research Governance Framework (2005) and the EU Clinical Trials Directive 2004. It is a requirement of both these articles of legislation that staff involved in research should have the training and experience to effectively carry out their roles.

**SOP Text**

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Trial coordinator, individual</td>
<td>Good Clinical Practice</td>
</tr>
</tbody>
</table>

Good Clinical Practice (GCP) is the gold standard for carrying out research. It follows the International...
Conference on Harmonisation (ICH) guidelines and enforces strong ethical standards in clinical research. High standards are required in terms of comprehensive documentation for the clinical protocol, record keeping and training. Quality assurance ensures these standards are achieved. GCP aims to ensure that the rights of the study participant are respected, and that the data generated by the trial is reliable.

A GCP certificate is the minimum requirement to work on a trial involving medicinal products, and it is the gold standard for all trials. As the PIMS study is funded by the National Institute for Health Research, GCP training can be accessed online through their website at: [http://www.crn.nihr.ac.uk/learning-development/good-clinical-practice/](http://www.crn.nihr.ac.uk/learning-development/good-clinical-practice/)

It is strongly preferable that all researchers working on the PIMS study have undertaken this free course, to make themselves familiar with the basic concepts underlying Good Clinical Practice. A copy of the researchers GCP certificate, along with a signed CV, should be filed in the Investigators site file (ISF) to evidence GCP training.

<table>
<thead>
<tr>
<th>2.</th>
<th><strong>Trial coordinator, individual researcher</strong></th>
<th><strong>Research Governance Framework</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The Research Governance Framework represents the minimum standard required of a health or social care study being carried out under the remit of the Department of Health. It takes a largely broader brushstroke approach than GCP, and is therefore less robust in guaranteeing individual aspects of the study.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To ensure that the PIMS study meets all training requirements, Research Governance Framework training will be given at the site initiation visit, with training documented in the visit report. This will be delivered unless everyone at the site initiation visit already has a valid GCP certificate taken within the last two years, and evidence of this present in the investigators site file.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anyone subsequently being added to the delegation log, who did not attend the site initiation visit, should undertake either Research Governance Framework training or Good Clinical Practice training. A training pack for RGF will be provided by the study coordinator, or the NIHR GCP course is available online free.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Again, it should be stressed that the GCP course is strongly preferred to RGF training: the GCP course is provided in a convenient online format, is free, and represents a higher</td>
<td></td>
</tr>
</tbody>
</table>
standard that will allow staff to work on trials involving medicinal products in the future. There are no benefits to undertaking RGF training instead of Good Clinical Practice certification.

3. **Trial coordinator, individual researcher**

**PIMS study specific training**

Study specific training will be given at the site initiation visit. This training will cover the protocol and the information contained in the standard operating procedures, relevant to the day to day running of the trial.

Anyone subsequently joining the trial team should be supplied with a brief pack of study specific training materials and given training by an existing member of the study team. There should be adequate opportunity to ask questions at any point, and ongoing support should be given.

The standard operating procedures should contain enough detail that someone joining the trial could refer back to these documents and understand how to perform any given trial related task. The SOP have been provided as reference documents, and the study team should be familiar with their content.

### References:

<table>
<thead>
<tr>
<th>Version</th>
<th>Reason for Change</th>
<th>Author of change</th>
<th>Date Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>Clarify the effective date</td>
<td>Simmonds</td>
<td>14th July 2015</td>
</tr>
</tbody>
</table>

#### 9.1.5 Randomisation

**Standard Operating Procedures (SOP) for: Randomisation**

<table>
<thead>
<tr>
<th>SOP Number:</th>
<th>5</th>
<th>Version Number:</th>
<th>2.0</th>
</tr>
</thead>
</table>

**Effective Date:**

**Review Date:**

**Author:** Irene Simmonds

**Reviewed by:** Saruban Pasu

**Authorisation:**

**Name / Position** | J. Bainbridge, Chief Investigator
### Purpose and Objective:
This document outlines the procedure for randomising patients to the PIMS study.

### SOP Text

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delegated member of staff</td>
<td><strong>Randomisation</strong> Enrolled subjects are randomised into the PIMS study only after their surgery. This is to maintain blinding, otherwise a more conservative surgery may be given to subjects allocated to one or the other arm of the trial. After surgery, the eligibility criteria should be checked and only eligible participants should be randomised. It is possible some subjects will not be eligible for the PIMS study after surgery, for example if it becomes necessary for the subject to face-down position for clinical reasons. These patients should be withdrawn from the PIMS study.</td>
</tr>
</tbody>
</table>
| Delegated member of staff | **Logging in to the randomisation system** A test version of the PIMS randomisation system can be found at: 

http://138.37.129.230/randomise

Username: Pims01
Password: Test

The liver version of the randomisation system is available at:

https://trials.pctu.qmul.ac.uk/randomise/

Passwords and usernames for the live system will be supplied by the trial coordinator prior to the start of recruitment. |
| Delegated member | **Randomising Patients** The Unique Trial Identifying Number (UTIN) issued to |
of staff

patients when they are enrolled in the PIMS study should be used as the randomisation code. This number is manually entered into the randomisation system.

Please be aware when randomising patients, that the result (face-down or face-forward) cannot be re-accessed through the randomisation system. It is advised to take a print-screen of the result.

Delegated member of staff

Positioning Booklet

After surgery and after randomisation, the patient should be informed of their allocation. Please take this opportunity to give the patient a positioning booklet. These booklets have been developed with the PIMS Patient and Public Involvement Group, but individuals who have previously been required to position, and offer practical advice about how to position.

Any patient expressing unwillingness to follow the positioning advice should be withdrawn from the study.

References:

<table>
<thead>
<tr>
<th>Version</th>
<th>Reason for Change</th>
<th>Author of change</th>
<th>Date Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9.1.6 Safety and adverse events reporting

Standard Operating Procedures (SOP) for: Safety and Adverse Events Reporting

<table>
<thead>
<tr>
<th>SOP Number:</th>
<th>Version Number:</th>
<th>Effective Date:</th>
<th>Review Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>2.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author:</th>
<th>Reviewed by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irene Simmonds</td>
<td>Saruban Pasu</td>
</tr>
</tbody>
</table>
Purpose and Objective:

To describe the safety reporting responsibilities and procedures for the PIMS study.

Glossary of terms: 
- **AE** – Adverse event
- **CI** – Chief Investigator
- **Non-CTIMP** – Non Clinical Trial of Investigational Medicinal Product (i.e. non-drug trial)
- **PCTU** – Pragmatic Clinical Trials Unit
- **PI** – Principal Investigator
- **SAE** – Significant Adverse Event
- **SAR** – Significant Adverse Reaction
- **SUSAR** – Suspected Unexpected Significant Adverse Reaction

SOP Text

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Chief investigator/ Principle Investigator</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><strong>Principle</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Investigator

The SAE should also be recorded on the sites own SAE log, a copy of which can be found towards the back of the Investigators Site File.

The CI can upgrade but not downgrade an SAE, and this should be considered if an event escalates in seriousness.

Only SAE that are unexpected and related to the clinical trial (SUSAR) will require further reporting by the Chief Investigator. Any SUSAR will be forwarded to the PCTU, Sponsor and Ethics Committee.

References:

<table>
<thead>
<tr>
<th>Version</th>
<th>Reason for Change</th>
<th>Author of change</th>
<th>Date Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>Clarify the effective date</td>
<td>Simmonds</td>
<td>14th July 2015</td>
</tr>
</tbody>
</table>

9.1.7 Cirrus OCT imaging

Standard Operating Procedures (SOP) for: Cirrus OCT Imaging

<table>
<thead>
<tr>
<th>SOP Number:</th>
<th>Version Number:</th>
<th>Effective Date:</th>
<th>Review Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>2.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Author: Edward White
Reviewed by: Irene Simmonds

Authorisation:
Name / Position: J. Bainbridge, Chief Investigator

Purpose and Objective:
Outlines how to make and save an image using the Cirrus imaging machine.
### SOP Text

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scan Required</strong></td>
<td>Macular Cube 512x128 (Study Eye) x 1</td>
</tr>
</tbody>
</table>

### Patient Information Entry

Click the middle tab “Add New Patient” and use the following protocol:

- **Last Name:** enter ‘**StudyName**’
- **First Name:** enter participant’s **Subject ID Number**
- **Date of Birth:** enter the **Patients Date of Birth**
- **Gender:** must be checked.

Disregard all the other fields for study patient entry. Click ‘OK’ then click “Save.” Next click “Acquire”

---

### Acquiring Scans

On the acquisition screen select Macular Cube 512x128

1. Make sure the OCT image is centre on the screen
2. Click **Auto Focus** the image to increase the intensity of the scan
3. Click **Capture**
4. If scan signal strength is less than 5, click “Try Again” or else “Save”
5. Click **Finish**

### Measuring Scans

![Image of OCT scan](image)  

*a = base diameter*
b = minimum linear dimensions

1. Open the images for analysis and select the Macular thickness analysis option.

2. Using the mouse wheel scroll through the images until you find the cross-sectional scan through the macula which shows the greatest distance at the base diameter (see Fig 1, arrow a) using the upper temporal to nasal image as your reference.

3. Select the ruler icon, click on the image and drag the mouse to create a measurement.

4. Double click on the image to enlarge the graphic. Adjust the two measure markers (plus signs) on the image to the correct placement (as per figure 1, arrow b).

Exporting Scans

Right click on the enlarged image and select “save as.” Save and name the image file with the words ‘pre-op’ or ‘post-op’ (depending on whether the image was generated before or after surgery,) and the subject's study ID.

References:

<table>
<thead>
<tr>
<th>Version</th>
<th>Reason for Change</th>
<th>Author of change</th>
<th>Date Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>Clarify the effective date</td>
<td>I.Simmonds</td>
<td>14th July 2015</td>
</tr>
</tbody>
</table>

9.1.8 Spectralis OCT imaging

**Standard Operating Procedures (SOP) for: Spectralis OCT Imaging**

<table>
<thead>
<tr>
<th>SOP Number:</th>
<th>7b</th>
<th>Version Number:</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Date:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review Date:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Author:** Edward White

**Reviewed by:** Irene Simmonds

**Authorisation:**

**Name / Position** | J. Bainbridge, Chief Investigator
**Purpose and Objective:**
Outlines how to make and save an image using the Spectralis imaging machine.

**SOP Text**

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Scan Required</strong></td>
</tr>
<tr>
<td></td>
<td>Volume Scan (37 sections, 20”x15”) ART 15 High Res Study Eye x 1</td>
</tr>
<tr>
<td>2</td>
<td><strong>Patient Information Entry</strong></td>
</tr>
<tr>
<td></td>
<td>1. Click on the ‘new patient’ icon. Complete using the following protocol:</td>
</tr>
<tr>
<td></td>
<td>a) <strong>Last Name:</strong> enter ‘<strong>StudyName</strong>’</td>
</tr>
<tr>
<td></td>
<td>b) <strong>First Name:</strong> enter the participant’s <strong>Subject ID Number</strong></td>
</tr>
<tr>
<td></td>
<td>c) <strong>Date of Birth:</strong> enter <strong>Patient’s Date of Birth</strong></td>
</tr>
<tr>
<td></td>
<td>d) <strong>Gender:</strong> must be checked.</td>
</tr>
<tr>
<td></td>
<td>Disregard all the other fields for study patient entry. Click ‘OK’</td>
</tr>
<tr>
<td></td>
<td>In the next dialogue box, “Examination Data” select:</td>
</tr>
<tr>
<td></td>
<td>Device Type: Spectralis</td>
</tr>
<tr>
<td></td>
<td>Operator: Select from the drop down list</td>
</tr>
<tr>
<td></td>
<td>Study: Select from the drop down list or add new study</td>
</tr>
<tr>
<td>3</td>
<td><strong>Acquiring Scans</strong></td>
</tr>
<tr>
<td></td>
<td><em>Working on the touch panel</em></td>
</tr>
<tr>
<td></td>
<td>1. Touch the yellow start button then:</td>
</tr>
<tr>
<td></td>
<td>Select OCT</td>
</tr>
<tr>
<td></td>
<td>Select IR&amp;OCT</td>
</tr>
<tr>
<td></td>
<td>Select section</td>
</tr>
<tr>
<td></td>
<td>Touch “More”</td>
</tr>
<tr>
<td></td>
<td>Touch “High Res”</td>
</tr>
<tr>
<td></td>
<td><em>Working on the screen</em></td>
</tr>
</tbody>
</table>
2. In the “Scan Area”
   Click on the Volume icon
   Set Art to 15
   Angle to 0°
   Volume size to 20°x15°
   Sections to 37

3. Align the camera on the patient’s eye ensuring good even illumination on the Spectralis image and push forward until the OCT image is at the top of the preview window.

4. Looking at the OCT image, adjust the focus using the focus knob and the brightness by rotating the “Sensitivity/ART button” on the touch panel.

5. Push the “Sensitivity/ART button” on the touch panel to activate the ART function.

6. Wait until 15 ART frames have been recorded

7. Touch the Acquire button on the panel to start the acquisition of the scans.

8. Save images and exit.

---

4

**Measuring Scans**

![Image of OCT scan]

\[ a = \text{base diameter} \]
\[ b = \text{minimum linear dimensions} \]

1. After the image has been acquired and saved double click on the thumbnail to open the image.

2. Select the “display tab” on the upper left hand side of the screen.

3. Using the mouse wheel scroll through the images until you find the cross-sectional scan through the macula which shows the greatest distance at the base diameter (see Fig
1. Adjust the vertical scale to a horizontal scale by switching from 1:1 pixel to 1:1 µm by selecting the option directly under the image. Zoom in if necessary using the magnifying glass icon.

5. Use the callipers option (first blue measurement icon below near bottom of frame) to measure the minimum linear dimension (see Fig 1, arrow b). Please move the numerical measurement figure to the centre of the image so it is clearly legible.

5 Exporting Scans

1. After the measurement have been completed, from the menu bar at the top of the screen select “Image” → ”Export as Picture”.

2. Save the image as a JPEG file with JPEG quality at 100% (best) and name the file with the words ‘pre-op’ or ‘post-op’ (depending on whether the image was generated before or after surgery,) and the subject’s study ID.

References:

<table>
<thead>
<tr>
<th>Version</th>
<th>Reason for Change</th>
<th>Author of change</th>
<th>Date Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>Clarify the effective date</td>
<td>Simmonds</td>
<td>14th July 2015</td>
</tr>
</tbody>
</table>

9.1.9 Topcon OCT imaging

Standard Operating Procedures (SOP) for: Topcon OCT Imaging

<table>
<thead>
<tr>
<th>SOP Number: 7c</th>
<th>Version Number: 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Date:</td>
<td>Review Date:</td>
</tr>
</tbody>
</table>

Author: Edward White
Saruban Pasu

Reviewed by: Irene Simmonds

Authorisation:
Name / Position: J. Bainbridge, Chief Investigator
Purpose and Objective:
Outlines how to make and save an image using the Topcon imaging machine.

SOP Text

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Scan Required</td>
</tr>
<tr>
<td></td>
<td>3D Scan, 6x6mm, 512x128, (Study Eye) x 1</td>
</tr>
<tr>
<td>2</td>
<td>Patient Information Entry</td>
</tr>
<tr>
<td></td>
<td>1. Click Camera Icon</td>
</tr>
<tr>
<td></td>
<td>2. 'Register Patient' dialogue box appears (similar to ImageNet Dialogue). Use the following protocol to enter a new patient or search for existing patient:</td>
</tr>
<tr>
<td></td>
<td>a) Last Name: enter 'StudyName'</td>
</tr>
<tr>
<td></td>
<td>b) First Name: enter participant's Subject ID Number</td>
</tr>
<tr>
<td></td>
<td>c) Date of Birth: enter the Patient's Date of Birth</td>
</tr>
<tr>
<td></td>
<td>d) Gender: must be checked.</td>
</tr>
<tr>
<td></td>
<td>Disregard all other fields for study patient entry. Click OK</td>
</tr>
<tr>
<td>3</td>
<td>Acquiring Scans</td>
</tr>
<tr>
<td></td>
<td>On the acquisition screen there are several tabs to check:</td>
</tr>
<tr>
<td></td>
<td>1. Scan parameter - set as follows: Scan mode 3D Scan, 6x6mm, 512x128</td>
</tr>
<tr>
<td></td>
<td>2. Fixation set to Macula</td>
</tr>
<tr>
<td></td>
<td>3. After positioning the patient, line the OCT on the pupil and drive the camera forward</td>
</tr>
<tr>
<td></td>
<td>4. Focus on the retina</td>
</tr>
<tr>
<td></td>
<td>5. Press the AZ button to optimize the scan signal</td>
</tr>
<tr>
<td></td>
<td>6. Make sure the OCT image is centre on the screen</td>
</tr>
<tr>
<td></td>
<td>7. Press the button to capture the OCT scan</td>
</tr>
<tr>
<td></td>
<td>8. Click save, then Analyse</td>
</tr>
<tr>
<td>4</td>
<td>Measuring Scans</td>
</tr>
</tbody>
</table>
Figure 1: OCT image of macular hole
a = base diameter
b = minimum linear diameter

1. Open the image and select the “white on black” viewing option near the bottom left hand corner of the image.

2. Using the mouse wheel scroll through the images until you find the cross-sectional scan through the macula which shows the greatest distance at the base diameter (see Fig 1, arrow a)

3. Select the calliper from the options in the top left of the image.

4. Click and drag the callipers to measure the minimum linear dimension (see Fig 1, arrow b). This is the minimum linear width along a line that bisects the hole in the horizontal meridian and is parallel to the retinal pigment epithelium.

Exporting Scans

Select “export” from menu bar → “B scan image” → “save as”. Save and name the image file with the words ‘pre-op’ or ‘post-op’ (depending on whether the image was generated before or after surgery,) and the subject’s study ID. Figure 2 is an example of the exported image with the calliper measurement on.
Figure 2: Oct image showing macular hole with MLD of 710 microns.

References:

<table>
<thead>
<tr>
<th>Version</th>
<th>Reason for Change</th>
<th>Author of change</th>
<th>Date Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>Clarify the effective date</td>
<td>Simmonds</td>
<td>14th July 2015</td>
</tr>
</tbody>
</table>
9.2 Consent forms for PIMS trial

PATIENT ID NUMBER:

PARTICIPANT CONSENT FORM

PIMS trial: Positioning in Macular Hole Surgery Trial

Please initial box to indicate agreement

1. I confirm I have read and understood Patient Information Sheet v2.1 13\textsuperscript{th} March 2015 for the above study. I have had the opportunity to consider the information, ask questions and these questions have been 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 responsible individuals from the study team, regulatory authorities or by individuals delegated by the Sponsor, Moorfields Eye Hospital NHS Foundation Trust, where it is relevant to the 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 the clinical data generated by this study being used for other research purposes in the future, after being appropriately anonymised.

6. I agree to take part in the above study.

You will be provided with a signed copy of this consent form.

________________________  __________________________  
Print name of participant    Signature     Date

_________________________  __________________________  
Print name of person taking consent     Date
PIMS trial: Positioning in Macular Hole Surgery Trial

We would like to invite you to take part in a research study. Before you decide to participate it is important for you to understand why the research is being done and what it will involve for you. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information and feel free to talk to others about the study if you would like. Take as much time as you want to decide whether or not you wish to take part.

What is the purpose of this study?
The purpose of this study is to determine whether positioning face down or face forward for a period of time following surgery for macular hole improves the likelihood of success.

Why have you been invited for this study?
You have been invited because you have a macular hole, and you have chosen to have an operation to repair the hole.

Participation is entirely voluntary. If you do decide to take part you will be given this information sheet to keep and you will be asked to sign a consent form. You are still free to withdraw at any time, without giving a reason. Withdrawing from the study, or deciding not to take part, would not affect the standard of care you receive.

What will happen if I decide to take part?
If you agree to participate there will be no change in what happens to you before or during the operation, and no change to which surgeon operates on your eyes.

You will be asked to fill in a questionnaire about your eyesight before your surgery. After your operation you will be randomly allocated to one of two positions. There is an equal chance that you could be allocated to either position. You will be advised to maintain either a face-down or an inactive face-forward position for a total of at least 8 consecutive or non-consecutive hours a day for 5 days. You will be allowed a 15 min break in each hour from your allocated position. During your position free time we ask that you keep activity to a minimum (although washing, light meals and taking of medication are advised) and avoid the face up position. You will not need to maintain the allocated position at night, but we advise avoiding the face up position while you sleep.

Face-down positioning: We suggest that you make arrangements at home as though you were going to be advised to position face-down. If advised to position face-down, you will maintain this position for at least eight consecutive or non-consecutive hours a day for five days. You may find you are able to read or watch television during this time; the medical and nursing staff will be able to provide information and advice on how to manage with the least discomfort and disruption. An image showing the face-down position can be seen below.
FACE-DOWN SEATED

FACE-DOWN LYING (for resting – not necessary during night time sleeping)

**Face forward positioning:** If advised to position face-forward, you may maintain an inactive face-forward position for a total of at least eight hours a day for five days. You will be allowed a 15 minute break in each hour from your allocated position. You may undertake reading or watching television but should refrain from more physical activity.

Whether asked to position face-down or face-forward, you should avoid a face up position at any time for five days following surgery.
FACE-FORWARD READING

FACE-FORWARD WATCHING TELEVISION
# An example of a possible eight-hour schedule of positioning face-down or face-forward

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Break</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00 – 9:45</td>
<td>Maintain allocated position</td>
<td>1st hour (with 15 min break)</td>
</tr>
<tr>
<td>10:00 – 10:45</td>
<td>Maintain allocated position</td>
<td>2nd hour (with 15 min break)</td>
</tr>
<tr>
<td>11:00 – 11:45</td>
<td>Maintain allocated position</td>
<td>3rd hour (with 15 min break)</td>
</tr>
<tr>
<td>11:45 – 14:00</td>
<td>FREE POSITION</td>
<td>BREAK</td>
</tr>
<tr>
<td>14:00 – 14:45</td>
<td>Maintain allocated position</td>
<td>4th hour (with 15 min break)</td>
</tr>
<tr>
<td>15:00 – 15:45</td>
<td>Maintain allocated position</td>
<td>5th hour (with 15 min break)</td>
</tr>
<tr>
<td>16:00 – 16:45</td>
<td>Maintain allocated position</td>
<td>6th hour (with 15 min break)</td>
</tr>
<tr>
<td>16:45 – 17:15</td>
<td>FREE POSITION</td>
<td>BREAK</td>
</tr>
<tr>
<td>17:15 – 18:00</td>
<td>Maintain allocated position</td>
<td>7th hour (with 15 min break)</td>
</tr>
<tr>
<td>18:00 – 20:00</td>
<td>FREE POSITION</td>
<td>BREAK</td>
</tr>
<tr>
<td>20:00 – 20:45</td>
<td>Maintain allocated position</td>
<td>8th hour (with 15 min break)</td>
</tr>
</tbody>
</table>

You will be asked to return for a routine follow-up appointment after your surgery. There will be no additional visits, procedures, or restrictions other than those that would normally apply after this type of surgery. At the three month follow up visit, you will be asked to complete another questionnaire about your vision. If you don’t return this questionnaire, we may call you once to remind you about it.

## What are the possible benefits or risks of taking part?

Your participation will help us understand the possible value of positioning on the outcome of surgery. This information will be invaluable in helping other people with the same condition.

You may be asked to maintain a face-forward position following surgery; this may be more comfortable than a face-down position. However, keep in mind you may be asked to maintain a face-down position, and this may be less comfortable than the face-forward position.
What if there is a problem?

If you have any concerns about any part of this study, you can talk to the researchers involved who will do their best to answer your questions. If you remain unhappy and wish to complain you should contact the Patient Advice and Liaison Service (PALS) <insert local PALS contact here>

Will my taking part in this study be kept confidential?

All information collected during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

Your own GP (general practitioner) will be notified of your involvement in this trial together with the standard information that is sent to them about your treatment. Please tell the doctor who obtains your consent if you do not wish your GP to know about your participation in this trial.

What will happen to the results of the research study?

The results of this study will be communicated through national and international meetings and through publication in scientific journals.
9.4 Bland Altman Plots

**Figure 8: Intragrader Spectralis measurement of Base diameter**

Bland-Altman of Intragrader measurement of Base Diameter on Spectralis OCT

Histogram of Intragrader Base Diameter measurement on Spectralis OCT
Figure 9: Intragrader Spectralis measurement of Inner Opening

Bland-Altman of Intragrader measurement of Inner Opening on Spectralis OCT

Histogram of Intragrader Inner Opening measurement differences on Spectralis OCT
Figure 10: Intrgrader Spectralis measurement of Minimum linear diameter

Bland-Altman of Intrgrader measurement of Minimum Linear Diameter on Spectralis OCT

Histogram of Intrgrader Minimum Linear Diameter measurement differences on Spectralis OCT
Figure 11: Intragrader Spectralis measurement of Height

Bland-Altman of Intragrader measurement of Height on Spectralis OCT

Histogram of Height measurement differences on Spectralis OCT
Figure 12: Intragrader Spectralis measurement of Left side

Bland-Altman of Intragrader measurement of left side on Spectralis OCT

Histogram of Intragrader Left side measurement differences on Spectralis OCT
Figure 13: Intragrader Spectralis measurement of Right side

Bland-Altman of Intragrader measurement of Right side on Spectralis OCT

Histogram of Intragrader Right side measurement differences on Spectralis OCT
Figure 14: Intragrader Topcon measurement of Base diameter

Bland-Altman of Intragrader measurement of base diameter on Topcon OCT

Histogram of Intragrader Base Diameter measurement differences on Topcon OCT
Figure 15: Intragrader Topcon measurement of Inner Opening

Bland-Altman of Intragrader measurement of Inner Opening on Topcon OCT

Histogram of Intragrader Inner Opening measurement differences on Topcon OCT
Figure 16: Intragrader Topcon measurement of Minimum linear diameter

Bland-Altman of Intragrader measurement of Minimum Linear Diameter on Topcon OCT

Histogram of Intragrader Minimum Linear Diameter measurement differences on Topcon OCT
Figure 17: Intragrader Topcon measurement of Height

Bland-Altman of Intragrader measurement of Height on Topcon OCT

Histogram of Intragrader Height measurement differences on Topcon OCT
Figure 18: Intragrader Topcon measurement of Left side

Bland-Altman of Intragrader measurement of left side on Topcon OCT

Histogram of Intragrader Left side measurement differences on Topcon OCT
Figure 19: Intragrader Topcon measurement of Right side

Bland-Altman of Intragrader measurement of Right side on Topcon OCT

Histogram of Intragrader Right side measurement differences on Topcon OCT
Figure 20: Intragrader Stratus measurement of Base diameter

Bland-Altman of Intragrader measurement of Base Diameter on Stratus OCT

Histogram of Intragrader Base Diameter measurement differences on Stratus OCT
Figure 21: Intragrader Stratus measurement of Inner opening

Bland-Altman of Intragrader measurement of Inner Opening on Stratus OCT

Histogram of Intragrader Inner Opening measurement differences on Stratus OCT
Figure 22: Intragrader Stratus measurement of Minimum linear diameter

Bland-Altman of Intragrader measurement of Minimum Linear Diameter on Stratus OCT

Histogram of Intragrader Minimum Linear Diameter measurement differences on Stratus OCT
Figure 23: Intragrader Stratus measurement of Height

Bland-Altman of Intragrader measurement of Height on Stratus OCT

Histogram of Intragrader Height measurement differences on Stratus OCT
Figure 24: Intragrader Stratus measurement of Left side

Bland-Altman of Intragrader measurement of Left side on Stratus OCT

Histogram of Intragrader Left side measurement differences on Stratus OCT
Figure 25: Intragrader Stratus measurement of Right side

Bland-Altman of Intragrader measurement of right side on Stratus OCT

Histogram of Intragrader Right side measurement differences on Stratus OCT
Figure 26: Intergrader Spectralis measurement of Base diameter

Bland-Altman of Intergrader measurement of Base Diameter on Spectralis OCT

Histogram of Intergrader Base Diameter measurement differences on Spectralis OCT
Figure 27: Intergrader Spectralis measurement of Inner opening

Bland-Altman of Intergrader measurement of Inner Opening on Spectralis OCT

Histogram of Intergrader Inner Opening measurement differences on Spectralis OCT
Figure 28: Intergrader Spectralis measurement of Minimum linear diameter

Bland-Altman of Intergrader measurement of Minimum Linear Diameter on Spectralis OCT

Histogram of Intergrader Minimum Linear Diameter measurement differences on Spectralis OCT
Figure 29: Intergrader Spectralis measurement of Height

Bland-Altman of Intergrader measurement of Height on Spectralis OCT

Histogram of Intergrader Height measurement differences on Spectralis OCT
Figure 30: Intergrader Spectralis measurement of Left side

Bland-Altman of Intergrader measurement of Left side on Spectralis OCT

Histogram of Intergrader Left side measurement differences on Spectralis OCT
Figure 31: Intergrader Spectralis measurement of Right side

Bland-Altman of Intergrader measurement of Right side on Spectralis OCT

Histogram of Intergrader Right side measurement differences on Spectralis OCT
Figure 32: Intergrader Topcon measurement of Base diameter

Bland-Altman of Intergrader Base Diameter measurement on Topcon OCT

Histogram of Intergrader Base Diameter measurement differences on Topcon OCT
Figure 33: Intergrader Topcon measurement of Inner opening

Bland-Altman of Intergrader Inner Opening measurement on Topcon OCT

Histogram of Intergrader Inner Opening measurement differences on Topcon OCT
Figure 34: Intergrader Topcon measurement of Minimum linear diameter

Bland-Altman of Intergrader measurement of Minimum Linear Diameter on Topcon OCT

Histogram of Intergrader Minimum Linear Diameter measurement differences on Topcon OCT
Figure 35: Intergrader Topcon measurement of Height

Bland-Altman of Intergrader measurement of Height on Topcon OCT

Histogram of Intergrader Height measurement differences on Topcon OCT
Figure 36: Intergrader Topcon measurement of Left side

Bland-Altman of Intergrader measurement of Left side on Topcon OCT

Histogram of Intergrader Left side measurement differences on Topcon OCT
Figure 37: Intergrader Topcon measurement of Right side

Bland-Altman of Intergrader measurement of Right side on Topcon OCT

Histogram of Intergrader Right side measurement differences on Topcon OCT
Figure 38: Intergrader Stratus measurement of Base diameter

Bland-Altman of Intergrader measurement of Base Diameter on Stratus OCT

Histogram of Intergrader Base Diameter measurement differences on Stratus OCT
Figure 39: Intergrader Stratus measurement of Inner opening

Bland-Altman of Intergrader Inner Opening measurement on Stratus OCT

Histogram of Intergrader Inner Opening measurement differences on Stratus OCT
Figure 40: Intergrader Stratus measurement of Minimum linear diameter

Bland-Altman of Intergrader measurement of Minimum Linear Diameter on Stratus OCT

Histogram of Intergrader Minimum Linear Diameter measurement differences on Stratus OCT
Figure 41: Intergrader Stratus measurement of Height

Bland-Altman of Intergrader Height measurement on Stratus OCT

Histogram of Intergrader Height measurement differences on Stratus OCT
Figure 42: Intergrader Stratus measurement of Left side

Bland-Altman of Intergrader measurement of Left side on Stratus OCT

Histogram of Intergrader Left side measurement differences on Stratus OCT
Figure 43: Intergrader Stratus measurement of Right side

Bland-Altman of Intergrader measurement of Right side on Stratus OCT

Histogram of Intergrader Right side measurement differences on Stratus OCT