MIRROR

Efficacy of the Telescopic Mirror Implant for Age-related Macular Degeneration: The MIRROR Trial (acronym MIRROR). A Multicentre Randomised Controlled Clinical Trial

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Chief Investigator:	Miss Giuliana Silvestri Consultant Ophthalmic Surgeon Department of Ophthalmology The Royal Group of Hospitals Grosvenor Road Belfast BT12 6BA

PROTOCOL AUTHORISATION

Protocol Title	Efficacy of the Telescopic Mirror Implant for Age-related Macular Degeneration: The MIRROR Trial
Protocol Acronym (if applicable)	MIRROR
Protocol Number	15113GS-AS
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A review of the protocol has been completed and is understood and approved by the following:

		DD / MM / YYYY
Chief Investigator Name	Signature	Date
		DD / MM / YYYY
Statistician	Signature	Date

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LIST OF ABBREVIATIONS

Abbreviation / Acronym	Full Wording
AE	Adverse Event
AMD	Age-related macular degeneration
BCDVA	Best corrected distance visual acuity
BCNVA	Best corrected near visual acuity
BHSCT	Belfast Health and Social Care Trust
CEAC	Cost Effectiveness Acceptability Curve
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQoL-5 Dimension Questionnaire (5 level version)
EME	Efficacy and Mechanism Evaluation
ETDRS	Early Treatment Diabetic Retinopathy Study
EudraCT	European Clinical Trials Database
FFA	Fundus Fluorescein Angiography
GA	Geographic atrophy
GCP	Good Clinical Practice
GP	General Practitioner
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMT	Intraocular Miniaturised Telescope
IOL-VIP	Intraocular Lens for Visually Impaired Persons
IOP	Intraocular Pressure
ISRCTN	International Standard Randomised Controlled Trial Number Register
IVI	Impact of Vision Impairment Profile
JLA	James Lind Alliance
LMI	Lipshitz Macular Implant
LMI-SI	Lipshitz Macular Implant- Secondary Implant
LVAs	Low vision aids
MHRA	Medicine and Healthcare Products Regulatory Agency
MIPFG	MIRROR Participant Forum Group
Nd:YAG	Neodymium-doped yttrium aluminium garnet
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute for Health Research
OCT	Optical Coherence Tomography
PCO	Posterior Capsular Opacification
PI	Principal Investigator
PIL	Participant Information Leaflet
PRL	Preferred Retinal Locus

PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOPs	Standard Operating Procedures
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	Visual analogue scale
WTP	Willingness-to-pay

1 STUDY SUMMARY

Scientific title	Efficacy of the Telescopic Mirror Implant for Age-related Macular Degeneration: The MIRROR Trial
Public title	How well does the OriLens (Hubble-type) implant work in improving vision in age-related macular degeneration?
Health condition(s) or problem(s) studied	Visual loss due to age-related macular degeneration (AMD)
Study Design	(i) Interventional randomised controlled trial (ii) The trial design will be a multicentre randomised controlled trial that seeks to evaluate the efficacy, safety and cost-effectiveness of a novel intraocular telescopic lens (OriLens) in improving visual function and quality of life in participants with advanced AMD, measured against "standard of care" (conventional low vision training). All participants will undergo Nd: YAG laser treatment (capsulotomy) to the study eye unless this has already been carried out. Participants will be randomised equally to one of two groups. Group 1 will undergo implantation of the magnifying device (OriLens) as a secondary surgical procedure, have refraction, be provided with any necessary supplementary spectacles and low vision aids (LVAs), and have three sessions of low vision training. Group 2 will undergo refraction, be provided with any necessary spectacles and LVAs, and have three sessions of low vision training. -Method of allocation: Eligible participants will be randomised equally to each ARM (stratified by site). -Masking: Due to the surgical procedure it will not be possible to mask the participants. Also as the device is easily visible with the naked eye due to the reflections from the mirror, it will not be possible to mask the observers. However the final assessment for the primary outcome i.e., best corrected distance visual acuity (BCDVA), will be duplicated by an independent observer who will be asked not to discuss the trial with the participant and not to examine the participant's eyes. -Assignment (double arm, single randomisation)
Study Aim and Objectives	The main goal of the study is to investigate the effectiveness, safety, and mechanisms of action of a novel implantable intraocular telescopic device in advanced AMD. We will also conduct a cost-effectiveness analysis. The specific objectives are to compare the effect of the telescopic implant at 12 months in terms of: • Best corrected distance visual acuity • Other measures of visual function such as near acuity, reading speed and contrast sensitivity • Health-related and visual-related quality of life • Safety

	• Costs and cost-effectiveness • To explore whether patient ocular parameters such as scar size, and volume at site are associated with visual outcome • To assess the importance of Preferred Retinal Locus (PRL) and ocular dominance on outcomes. • To evaluate the role of binocularity and visual summation on outcomes
Study Intervention	(i) Interventional ARM: LMI-SI Lipshitz Macular Implant-Secondary Implant (OriLens) with tailored Low Vision Training (ii) Control ARM: Conventional Low vision training
Primary Outcome	Change in best corrected distance visual acuity (BCDVA) using number of letters improvement on Early Treatment Diabetic Retinopathy Study (ETDRS) Chart at 12 months
Key Secondary Outcomes	Change in best corrected near visual acuity (BCNVA) and reading speed at 12 months Vision-specific quality of life measured using the Impact of Vision Impairment Profile (IVI) at randomisation, and months six and 12 Health related quality of life status (EQ-5D-5L) at randomisation, months six and 12 Health service use and associated costs at months six and 12. Safety of device assessed by surgical complications at day 1, day 7, months one, three, six and 12 and endothelial cell density at baseline and at month 12.
Key Inclusion and Exclusion Criteria	(i) Inclusion criteria • Age 55 years or above • Bilateral stable advanced AMD either neovascular (required to be stable for at least 12 months after last treatment) or atrophic AMD • Bilateral uncomplicated cataract surgery with unifocal intraocular lenses • Bilateral best-corrected distance visual acuity of 6/38-6/240 (LogMAR 0.80 to 1.60) • Must demonstrate a 10-letter improvement in BCDVA (ETDRS chart) with the external x2.5 telescope in the eye for implantation • Must have had experience of using low vision aids • Have an endothelial cell density within normal limits for age • Be willing to undergo laser capsulotomy in the eligible eye prior to randomisation (if required) • Must be three months or more following any intraocular surgical or laser procedure • Must be in good general health with every likelihood of involvement in the trial for the duration of the study and be able to physically or verbally complete the questionnaires • Only one eye per participant will be included in the

	study. (ii) Exclusion criteria • Cataract surgery with multifocal intraocular lenses • A history of glaucoma or of being on anti-glaucomatous medication • Any other retinal condition • Lack of clear view of the retina • Abnormal or de-centred pupil • Endothelial cell density <1500 cells/mm^2 • History of ocular inflammatory disease • Zonular instability or instability of existing intraocular lens • BCDVA of better than 6/38 (0.80 LogMAR) or worse than 6/240 (1.60 LogMAR) in either eye • Participants unable to provide informed consent • Be in poor general health that could compromise attending follow-up assessments • Difficulties with balance • Not fluent in English
Countries of Recruitment	United Kingdom
Study Setting	NHS Hospitals with retinal specialists
Target Sample Size	132
Study Duration	42 months

2 STUDY TEAM

Chief Investigator	Miss Giuliana Silvestri MD FRCP FRCSEd FRCOphth Consultant Ophthalmic Surgeon Ground Floor Eye & Ear Clinic Royal Hospitals Grosvenor Road Belfast BT12 6BA Tel: 028 9063 3690 julie.silvestri@belfasttrust.hscni.net
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3 FUNDING

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4 ROLES AND RESPONSIBILITIES

4.1 Contributorship

GS conceived the study. The grant holders GS, AAB, Lynn Murphy, Evie Gardner, AA, MW, GR, MMcK, BD, JJ, JEM, alongside the Trial Manager contributed to the design of the study. EG provided statistical expertise in clinical trial design and MN is conducting the statistical analysis. AA provided health economics expertise in clinical trial design and is conducting the primary health economics analysis. All investigators and the Trial Management Group contributed to the refinement of the study protocol and approved the final manuscript. AA(2) provided comment in his capacity as Lay Advisor.

4.2 Sponsor and Funder

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the Chief Investigator (CI) will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor, CI and each organisation who will undertake Sponsor-delegated duties in relation to the management of the study.

4.3 Committees

The CI will have overall responsibility for the conduct of the study. The Clinical Trials Unit (CTU) will undertake trial management including preparing clinical trial applications (Research Ethics Committee (REC) and research governance), site initiation/training, monitoring, analysis, and reporting. The Trial Manager will be responsible on a day-to-day basis for overseeing and co-ordinating the work of the multi-disciplinary trial team. Additional trial specific oversight committees will be convened for the trial, these will include a Trial Management Group (TMG), Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committee (TSC). The CTU will facilitate in the setting-up and the co-ordination of these trial committees. As expertise is required in selecting the best eye for implantation of the device, a small Eye Selection Committee (ESC) will be formed for this purpose.

4.3.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be established and Chaired by the CI. The TMG will have representation from the CTU and other investigators/collaborators who are involved in the study and provide trial specific expertise (e.g. trial statistician). This group will have responsibility for the day to day operational management of the trial, and regular meetings of the TMG will be held to discuss and monitor progress. The discussions of the TMG will be formally minuted and a record kept in the TMF.

The TMG Charter will detail the terms of reference of the TMG including membership and roles/responsibilities.

4.3.2 Trial Steering Committee (TSC)

The TSC will oversee the progress of the trial on behalf of the trial funder and sponsor. The TSC will provide overall supervision of the trial and provide advice through the Chair to the CI, Sponsor, Funder and host institution on all appropriate aspects of the trial. The TSC will concentrate on the progress of the trial, adherence to protocol, participant safety, new information of relevance to the research question, the rights, safety and wellbeing of trial participants and ensure appropriate approvals are obtained in line with the project plan. The TSC will agree proposals for substantial amendments and provide advice to the sponsor and funder regarding approvals of such amendments.

Membership of the TSC will comprise of an independent chair, the CI (or designee), independent clinicians with relevant expertise, independent statisticians/epidemiologists/diagnosticians with relevant expertise and at least one participant/public representative. The TSC will meet at least annually and will have a minimum of 75% independent members. The NIHR HTA Programme Director will vet nominees and appoint the chair and members.

The TSC charter will detail the terms of reference of the TSC including membership and roles/responsibilities.

4.3.3 Data Monitoring Ethics Committee

The role of the DMEC is to safeguard the rights, safety and wellbeing of trial participants, monitor data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue, and monitor the overall conduct of the study to ensure the validity and integrity of the study findings.

Membership of the DMEC will be completely independent and comprise experts in the field e.g. a clinician with relevant experience and a statistician. The DMEC will meet at least annually. The NIHR HTA Programme Director will vet nominees and appoint the chair and members.

The DMEC charter will detail the terms of reference of the DMEC including membership and roles/responsibilities. A DMEC report, written by the trial statistician, will include information on any adverse events (AEs), recruitment, outcomes and any other data requested by the committee.

4.3.4 User Involvement or any other relevant committees

This study will address a key priority identified for Age-Related Macular Degeneration Research through participant consultation by the James Lind Alliance (JLA), i.e., “Are there ways of restoring sight loss for people with AMD?". The JLA is a non-profit priority-setting initiative, established in 2004 which brings **patients**, **carers** and **clinicians** together to identify and prioritise the **top 10** 'unanswered questions' in a disease area. In 2007, the applicant was the Chief Investigator in a UK commercial clinical trial on the miniaturised intraocular magnifying telescope (IMT). Eight participants were recruited in Belfast and at the end of the trial a participant support group was established to develop a support mechanism for the use of the device. The trial participants provided valuable insights for the design of this current trial. One member (IM), who was one of the most successful users of the IMT device, has been particularly instrumental in articulating the benefits and difficulties of the previous implant. The difficulties included the importance of participants understanding the need for lifelong practice with these devices which was not always

fully appreciated by all participants. IM also highlighted the importance of managing expectations pre-implantation so that participants understand clearly that the procedure is likely to help but will most definitely NOT restore normal vision. IM has agreed to be part of the MIRROR Participant Forum Group (MIPFG) for this study. The role of the MIPFG will be in advising on clarity of Participant Information Leaflets (PILs), Consent Forms and in providing support to participants if required. IM has indicated that she would be happy to speak to participants by telephone as she has experience in this area. Two other participants (RH) and (AA2) have also agreed to join the MIPFG. AA2 has also agreed to sit on the Trial Steering Committee. AA2 has been involved in reviewing the Plain Word Summary and has discussed the trial design with the Chief Investigator. The MIPFG will contribute to the development of the study protocol, participant information documents, consent forms and any other outputs relevant to participants, their families or the public. They will assist with the dissemination of the research findings by making these more accessible and comprehensible to participants and the public.

GJ in her role as local PPI Adviser to the Public Health Authority has also advised on the project.

4.3.5 Eye Selection Committee

GS or her designee from the Eye Selection Committee (AJJ and Lisa Kelly) will propose the study eye based on the criteria set out below. This selection will be confirmed by IL (Isaac Lipshitz) or designee. The selection of the eye will occur before randomisation and therefore the involvement of the CI or the manufacturer in the process will not cause bias. This process will also ensure that the individual sites, which will be implanting the device, will not bias the outcome and will ensure consistent decision making for all participants which is critical for the validity of the study. The study eye selection criteria are described below.

Eye Selection: As there is little evidence to indicate whether implantation should be in the dominant or non-dominant eye, eye selection will be based on the eye achieving the best visual acuity. It is important that post-operatively, the eye implanted has better acuity than the non-implanted eye, otherwise the eye with the device is likely to be ignored or suppressed. In the event that visual acuity is equal in both eyes, then the study site will be instructed to select the non-dominant eye.

5 BACKGROUND AND RATIONALE

5.1 **Background Information**

This study seeks to investigate the efficacy, safety and cost-effectiveness of a novel implantable intraocular telescopic device in advanced age-related macular degeneration (AMD). AMD is the most common cause of visual impairment in the elderly (1). Data from 2010 for the United Kingdom show that over 500,000 persons are estimated to have AMD with over 220,000 suffering sight loss (1). AMD can be either wet (neovascular) or atrophic (geographic atrophy (GA)) both of which cause loss of vision. Over the past five years anti-VEGF therapies have made a significant impact on reduction of visual loss in wet AMD, however no therapy exists for the atrophic form of the disease. In addition, a substantial proportion of patients with wet AMD still lose vision either because of late diagnosis or lack of effect of current treatments. The only treatment option for these individuals is the enhancement of vision through the use of external low vision aids. These devices are variably accepted but use can be tedious as the field of vision is small and tracking can be difficult (2).

A novel concept is the use of implantable intraocular magnifying telescopes. A number of new intraocular technologies have been developed with the aim of improving residual vision in those who are in the advanced stage of the disease. These technologies aim to allow improved visual acuity by implanting a magnifying system within the eye either at the time of cataract surgery or at a subsequent time, thereby improving visual acuity and reducing the requirement for high powered external low visual aids. If successful, these devices could improve the quality of life and reduce dependency thereby potentially reducing the costs associated with caring for visually impaired individuals. Three devices are currently available: the Intraocular Miniaturised Telescope (IMT, Centrasight, VisionCare Ophthalmic Technologies, Inc.), the Intraocular Lens for Visually Impaired Persons (IOL-VIP, Tanner Eyes) and the Lipshitz Macular Implant (LMI)/OriLens (OptoLight Vision Technologies) but none have been extensively studied and information on the usefulness of these devices remains limited. The most extensive information available is on the IMT device with some small case series published on the IOL-VIP (3-5). Data on the LMI is limited to a case series and little is available on the newer OriLens device (6).

The benefits of cataract surgery in the general population are well established, with 91% of eyes achieving a best corrected visual acuity of 6/12 or better (7). The presence of AMD as a comorbidity has been highlighted as a risk factor for poor visual outcome following cataract surgery. Individuals with “no AMD” gained a mean of 8.36 letters, those with “mild AMD” 6.13 letters, those with “intermediate AMD” 3.92 letters and those with “advanced AMD” 1.94 letters (95% CI: 0.05-3.82) (8). Despite the small improvement in vision in these participants, most studies demonstrate that the majority of individuals found that cataract surgery improved quality of life (9-10).

This proposal seeks to study whether the addition of the LMI-SI Lipshitz secondary IOL (OriLens) telescopic device following cataract surgery could augment the improvement in vision in participants with advanced AMD and therefore further reduce the burden of blindness and its consequences for this population and their carers. The OriLens offers x2.5 magnification and is based on “Cassegrain” (mirrored) telescopic principles. This has facilitated the design of a telescope with several advantages. These include reduced device thickness: 1.25mm versus 4mm (Centrasight) which allows a reduction in wound size, shorter recovery time and less reduction of visual field (6). The size of the surgical incision required is 5.5 to 6 mms and the device is surgeon-friendly enabling a short learning curve. Due to the small size in terms of thickness, the device sits completely behind the iris and is placed in the sulcus thereby reducing the potential for corneal endothelial cell damage. Figure 1a shows the position of the OriLens in the eye. The device appearance is shown in Figure 1b. A further potential advantage is that the OriLens is reported to cause less restriction of the peripheral visual field (Figure 1c). The central image is magnified x2.5 while the peripheral image stays

unchanged in size and contrast. This feature is unique to the OriLens. The existence and size of the peripheral vision is pupil dependent. There is a mechanism incorporated in the device that equalizes the contrast of the central to the peripheral vision. Figure 1c. demonstrates the different magnifications and visual field changes in three devices.

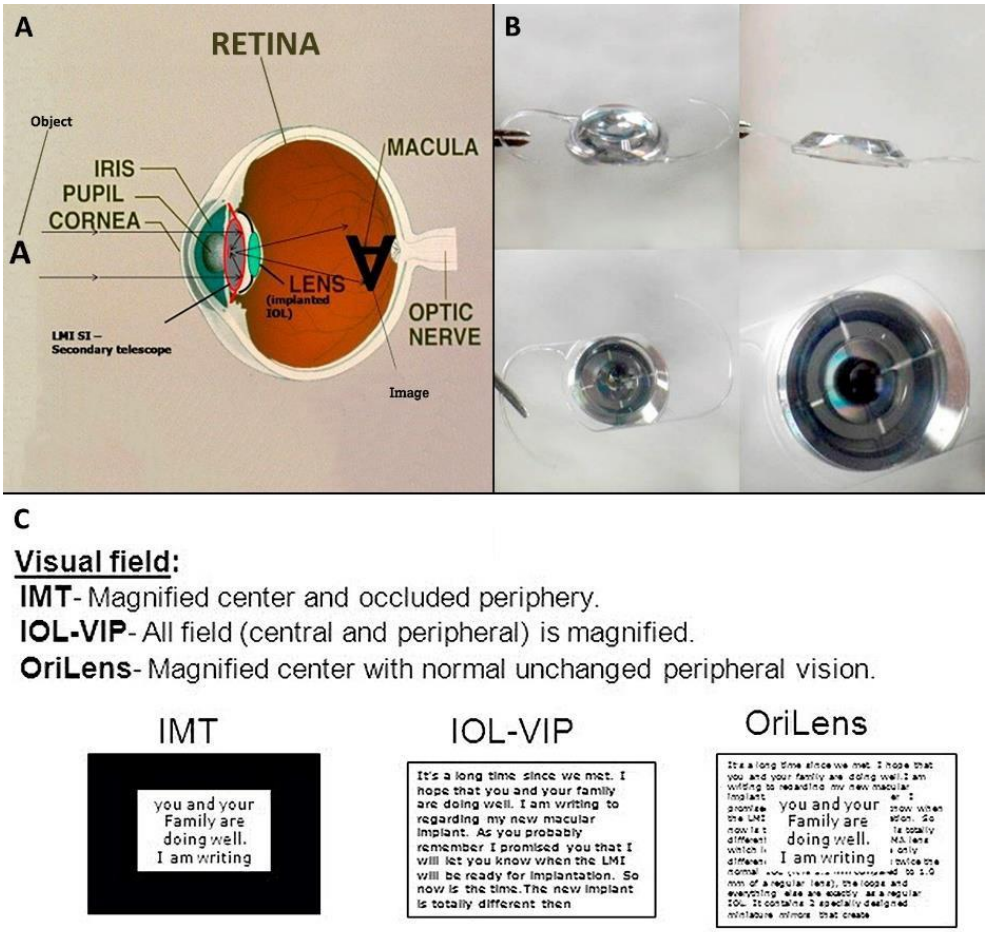


Figure 1. a. The position of the OriLens in the eye and resultant magnification of image. b.OriLens device both in profile and en–face. c. Comparison of magnification and visual field restriction with IMT, IOL-VIP and OriLens (Images reproduced with permission from OptoLight Technologies).

Name and description of device used in the trial

The LMI-SI Lipshitz Macular Implant- Secondary Implant (OriLens), which is an intraocular magnifying device designed and manufactured by OptoLight Vision Technologies, has recently become available. The device is CE marked for use in patients with advanced AMD and is described above.

5.2 Rationale for the Study

This trial will evaluate the efficacy and safety of a new intraocular implantable device (OriLens) to improve vision in participants with severe AMD. In advanced AMD, there are no effective treatments to improve vision. Visual aids such as hand-held magnifiers or external telescopic lenses may provide modest visual improvement to some participants and only for some specific tasks. Patients with AMD often have co-existing cataract, but it remains uncertain whether surgery is useful as visual improvement after cataract surgery is very limited. Despite this, many patients are keen to undergo cataract surgery as they are anxious for any possible improvement, no matter how small.

Intraocular telescopic or magnifying devices have been tried in people with advanced AMD, and several uncontrolled reports have described improvement in visual function. However, evidence from randomised trials is not available. The OriLens has recently become available (6) offering a number of features, which would seem to be advantageous in comparison to other implants regarding their efficacy and safety. Intraocular magnifying devices were reviewed by NICE in 2008 (IPG272, 11). The appraisal concluded that these devices should be used under "Special Arrangements". A further planned NICE appraisal review in 2011 was abandoned due to lack of further evidence. The aim of this project is to investigate the efficacy, safety and cost-effectiveness of this device.

Although significant improvements in visual acuity in participants with intraocular magnifying devices have been reported, a number of participants remain unhappy with the device, in spite of measured improvement in visual acuity. The study also seeks to investigate participant ocular parameters which may impact on the outcome, either positively or negatively, of the implantation of these devices. We propose a number of research questions to try to understand this with a view to optimising participant selection, procedures and outcomes.

5.3 **Rationale for the Intervention**

The choice of the intervention with this device is as follows. The OriLens (intraocular magnifying device) from OptoLight Vision Technologies has recently become available (6) and offers a number of features such as better magnification and smaller surgical incision, which would seem to be advantageous in comparison to other implants regarding their efficacy and safety (NICE, 2008). Both best-corrected distance and near visual acuity showed a statistically significant improvement six months post-operatively and improvements in quality of life were also observed in a small case series. In addition, endothelial cell loss was reportedly smaller than that observed with other devices. Little evidence is currently available on the efficacy and safety of this device, therefore further study is warranted. The device has also been tested for MRI compatibility. Testing was conducted in an MRI machine manufactured by Bruker, the magnetic power of which was seven Tesla (4-5 times higher than that currently used in medical MRI machines). The tests concluded that the MRI magnetic field has no effect on the implant and it is safe for patients with these implants to undergo MRI testing under seven Tesla.

5.4 **Rationale for Comparator**

The comparator is the usual standard of care for this participant population i.e., conventional low vision training with low visual aids. As the amount and type of training given conventionally may vary between centres, a Standardized Operating Procedure (SOP) will be established to ensure that participants in both groups and across all sites receive the same training during the study.

6 STUDY AIM AND OBJECTIVES

6.1 **Research Hypotheses**

Efficacy Evaluation: Implantation of the OriLens, a novel intraocular telescopic lens, will improve visual function and quality of life in participants with advanced AMD.

Mechanistic Evaluation: 1. To explore whether participant ocular parameters such as scar size, volume at site are associated with visual outcome and to assess the importance of Preferred Retinal Locus (PRL) and ocular dominance on outcomes. 2. To evaluate the role of binocularity and visual summation on participant-reported outcomes.

6.2 Study Aim

To investigate the effectiveness and safety of a novel implantable intraocular telescopic device (OriLens) in advanced AMD. In addition, cost-effectiveness, and a number of participant parameters will also be investigated to assess their impact on the outcomes.

6.3 Study Objectives

6.3.1 Primary objective

The primary objective is to compare the effect of the OriLens telescopic implant to conventional Low Vision Training in terms of best corrected distance visual acuity (BCDVA). The outcome measure will be recorded as count of letters in Early Treatment Diabetic Retinopathy Study (ETDRS) Chart at 12 months.

6.3.2 Secondary objectives

- To evaluate the effect of the device on other participant-important measures of visual function such as near acuity, reading speed and contrast sensitivity
- To assess the health-related and visual-related quality of life of participants
- To assess the safety of the device
- To estimate health service use and associated costs
- To estimate the cost-effectiveness of the intervention compared to usual care
- To explore whether participant ocular parameters such as scar size, volume at site are associated with visual outcome, and assess the importance of Preferred Retinal Locus (PRL) and ocular dominance on outcomes.
- To evaluate the role of binocularity and visual summation on participant-reported outcomes

7 STUDY DESIGN

7.1 **Study Design**

The project will be a multicentre randomised controlled trial which will evaluate the efficacy, safety and cost-effectiveness of a novel intraocular telescopic lens (OriLens). We will enrol participants with bilateral advanced stable AMD who have had previous cataract surgery (bilateral pseudophakia). Surgical implantation of the OriLens will be carried out within eight weeks of randomisation. Primary and secondary outcomes will be assessed at one, three, six and 12 months post randomisation.

Those who fulfil the inclusion criteria will be randomised equally (stratified by site) to one of two groups: Group One (Surgical Intervention) will undergo implantation of the OriLens device as a secondary surgical procedure in addition to usual standard of care; Group Two (Conventional Intervention- Control) will receive usual standard of care.

In addition, a number of participant specific parameters will be evaluated to assess the impact of these factors on participant outcomes. Specifically, the study will evaluate the following using data collected during the study.

1. Does the type, size and location of the scar/atrophy or the preferred retinal locus (PRL) have an impact on visual outcome?
2. Does implantation in the aiming dominant/non-dominant eye produce a better outcome?
3. Do participants who have good binocular function pre-operatively, find use of the telescopic device more difficult?
4. Do pre-operative binocular vision abnormalities impact on acceptance and use of the device?
5. Does implantation of the device cause a change in visual summation and does this impact on the tolerability of the device?

Although the OriLens is suitable for implantation both at the time of cataract surgery and in eyes that have had previous cataract surgery, it is the opinion of the investigators that the best trial design is to carry out the study in eyes that have had previous cataract surgery (pseudophakic eyes). The main reason for this is that a proportion of eyes which have had cataract extraction will develop posterior capsular opacification (PCO). PCO causes reduction in vision and often requires treatment by laser (neodymium-doped yttrium aluminium garnet (Nd:YAG)) capsulotomy. Nd:YAG capsulotomy is however contraindicated following OriLens implantation as laser energy could cause damage to the device. It is therefore important to avoid the need for Nd:YAG capsulotomy after OriLens implantation, thus the current study design includes a Nd:YAG capsulotomy for all participants. All participants will undergo Nd:YAG capsulotomy (unless already carried out) prior to randomisation. Nd:YAG capsulotomy is a routine procedure in many pseudophakic patients and the risk has been shown to be negligible. In a study of over 12,000 consecutive cataract surgeries, a number of factors were associated with retinal detachment post cataract surgery however Nd:YAG capsulotomy was not (12). A second and important reason in terms of efficacy, is that that cataract surgery alone will in itself give an improvement in various aspects of visual function, not just acuity, and as such removal of the cataract could be the reason for improvement in visual function. The current methodology takes this variable out of the equation.

7.2 **Study Timeline**

Year		1				2				3				4	
Quarter		1	2	3	4	1	2	3	4	1	2	3	4	1	2
Project- months	Pre-grant start	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Trial Stage	Using Enabling Grant Award	Set up		Recruitment and Follow-up						Follow-up				Analysis and Reporting	
Pilot study with implantation of 4 OriLens devices	X														
Identification of six potential sites	X														
Protocol Development and finalising of Trial Manual after trial of four participants	X														
Training Pack development and collation including surgical movie	X														
R&D Approvals		X	X												
Site Training		X	X	X											
Main Study					X	X	X	X	X						
Number of sites open			5	8	10	10	10	10	10	10	10	10	10		
Participant Recruitment				10	20	40	80	120	132						
Participant Follow up				X	X	X	X	X	X	X	X	X	X		
Interim Analysis							X								
stop & go POINT (safety)							X								
Data Collection (including HRQoL)			X	X	X	X	X	X	X	X	X	X	X		
Management Meetings		XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
DMEC		X		X			X		X				X		X
TSC		X		X			X		X				X		X
Trial Close Down (sites)														X	X
Data Analysis														X	X
Health Economics Analysis														X	X
Trial Report														X	X
Dissemination															X

Table 1: MIRROR STUDY TIMELINE

7.3 **Project Milestones**

The duration of the study will be 42 months. A maximum of 10 centres will be required for the study with each site recruiting approximately 13-14 participants. As training will be required in participant selection, visual function testing, surgical implantation, and the use of the telescope, the study investigators would prefer to open eight sites only. However, if recruitment is not progressing to target, consideration will be given to opening new sites. The first six months will be spent on study setup, recruitment of staff, and in the initiation of surgical and low vision training of staff at all sites. A period of 18 months has been allocated for the recruitment phase (months seven to 24). Twelve months follow-up will be required after recruitment of the last subject and six months for analysis of data and dissemination of results including report writing and submission of papers. Project recruitment will be measured to determine that the target sample of 132 is achievable with the number of recruiting sites indicated.

8 Methods: participants, interventions, and outcomes

8.1 **Study Setting**

Participants will be recruited from a maximum of 10 NHS/Foundation Trusts with retinal specialist clinics across the UK. A list of study sites will be maintained in the TMF and can be obtained from the NICTU.

8.2 **Eligibility Criteria**

8.2.1 Selection of Subjects

Individuals with bilateral stable advanced AMD (neovascular or atrophic) who have had uncomplicated bilateral cataract surgery with visual acuity of 6/38-6/240 (LogMAR 0.80 to 1.60) will be screened according to the protocol.

8.2.2 Inclusion Criteria

- Age 55 years or above
- Bilateral stable advanced AMD either neovascular (required to be stable for at least 12 months after last treatment) or atrophic AMD
- Bilateral uncomplicated cataract surgery with unifocal intraocular lenses
- Bilateral BCDVA of 6/38- 6/240 (LogMAR 0.80 to 1.60) and above
- Must demonstrate a 10-letter (0.20 LogMAR) improvement in BCDVA (ETDRS chart) with the external x2.5 telescope in the eye for implantation
- Must have had experience of using low vision aids
- Have an endothelial cell density appropriate for age as detailed in Appendix I
- Be willing to undergo laser capsulotomy in the eligible eye prior to randomisation (if required)
- Must be three months or more following any intraocular surgical or laser procedure
- Must be in good general health with every likelihood of involvement in the trial for the duration of the study and be able to physically or verbally complete the questionnaires
- Only one eye per participant will be included in the study.

8.2.3 Exclusion Criteria

- Cataract surgery with multifocal intraocular lenses
- A history of glaucoma or of being on anti-glaucomatous medication
- Any other retinal condition
- Lack of clear view of the retina
- Abnormal or de-centred pupil
- Endothelial cell density <1500 cells/mm^2
- History of ocular inflammatory disease
- Zonular instability or instability of existing intraocular lens
- BCDVA of better than 6/38 (0.80 LogMAR) or worse than 6/240 (1.60 LogMAR) in either eye
- Participants unable to provide informed consent
- Be in poor general health that could compromise attending follow-up assessments
- Difficulties with balance
- Not fluent in English*

* Fluency in English is required due to the complexity of screening examinations (reading speed is tested), the detailed explanations given for examinations and interventions, and the type of rehabilitation required.

8.2.4 Selection of Study Eye

As there is little evidence to indicate whether implantation should be in the dominant or non-dominant eye, eye selection will be based on the eye achieving the best visual acuity. Ocular dominance will be recorded and analysed as an independent factor but will not be used as a parameter in eye selection unless, as indicated below, the visual acuity with the external simulator is equal in both eyes. The overriding important factor in eye selection is that the eye selected for study should have better distance acuity with the external simulator than the non-study eye with best spectacle correction, otherwise the device is likely to be ignored/suppressed. If the visual acuity is equal in both eyes, then the device will be implanted in the non-dominant eye. The study eye will be proposed by the Eye Selection Committee and confirmed by the manufacturer prior to randomisation. Manufacturer advisement on eye selection is standard clinical practice.

8.2.5 Co-enrolment guidelines

Participants currently enrolled in any other study, which involves the delivery of any investigational medicinal product (IMP) or device intraocularly, will be excluded. Participants currently enrolled in any observational study are potentially eligible for co-enrollment in the current study. This will be decided on a case by case basis by the PI. The CTU should be informed if co-enrollment is being considered and it should be documented in the CRF.

8.2.6 Trial Site requirements

The trial will take place in a maximum of 10 NHS/Foundation Trusts with retinal specialist clinics across the UK. Preference will be given to those sites with experience in the delivery of ophthalmology clinical trials and access to this patient population with sufficient infrastructure support to screen, recruit, consent and randomise participants. The study requires that sites have access to the following equipment and services:

- ETDRS Visual acuity charts and illuminated box
- Reading acuity and reading speed tests (Pelli Robson CS test, Bailey Lovie word reading charts and MN Read reading charts)
- Standard equipment for refraction
- Standard equipment for orthoptic examination
- Slit lamp
- Colour fundus camera with FFA capability
- Optical Coherence Tomography
- Endothelial cell analyser (contact or non-contact)
- Low Vision Service providing low vision aids suitable for distant and near vision tasks

Preference will be given to sites which also have:

- Microperimeter

Equipment which will be provided:

- External x2.5 telescope
- MARS chart for contrast sensitivity (The Mars Perceptrix Corporation)

8.2.7 Research Team Requirements

Staff must demonstrate and document a willingness to comply with the protocol, SOPs, trial specific procedures, the principles of International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP) and regulatory requirements and be prepared to participate in locally-delivered trial-specific training. In particular, the site must have access to the following team members:

- Research nurses
- Research accredited optometrists
- Ophthalmic imaging technicians
- Orthoptist
- Additional masked assessor for BCDVA at 12 month follow-up

8.3 Interventions

The planned interventions will be posterior Nd:YAG capsulotomy in the study eye (if not already done) for all eligible participants followed by: Group 1- implantation of the OriLens device plus three sessions of low vision training; Group 2- three sessions of low vision training. In order to minimise the possibility of a placebo effect an equal number of low vision sessions will be given in each Group.

8.3.1 Intervention description

Group 1: Intervention
The implantation of the OriLens device will be carried out as a secondary surgical procedure no more than eight weeks post randomisation. Participating surgeons will be trained in the surgical procedure for implantation at the beginning of the trial: an instructional video developed by the research team will be available and the CI may observe the first procedure at each site at the request of the PI. The degree of difficulty of this intervention is considered to be small for experienced cataract surgeons. The pupil will be dilated. Local anaesthetic will be used according to the individual surgeon's preference. A minimal incision of 5.5 millimetres is recommended. The wound can either be a scleral flap or tunnel according to the surgeon's preference. The anterior chamber will be filled with viscoelastic and the implant will also be covered in viscoelastic material before insertion. It is important that the optic does not come into contact with the forceps. The orientation of the device should be checked: the lens should vault backwards and the end of the superior haptic should point to the right. Both loops of the device are to be placed in the sulcus. Implantation should not proceed if there is evidence of zonular or existing intraocular lens instability. All viscoelastic will be removed at the end of the surgery. Closure of the incision will be according to surgeon's preference. A peripheral iridotomy is not a routine requirement but may be carried out at the surgeon's discretion. An intracameral injection of antibiotics and a subconjunctival injection of steroids will be administered according to the surgeon's preference. Post-operative management is similar to phacoemulsification surgery and is according to the surgeon's preference. Participants will be prescribed combined steroid/antibiotic drops for use four weeks post-operatively. A standard surgical report documenting the details above will be completed post-operatively.

If the pupil is <2.5 mm in diameter, small sphincterotomies should be performed at the time of implantation of the device. Recording of concomitant medications during medical history is required to determine presence of such which may have an effect on pupil size.

Refraction, spectacle prescription and provision and three 45 minute sessions of low vision training as per the trial manual will follow post-operatively as per section 10.2.

Group 2: Control

Participants will receive refraction, spectacle prescription and low vision aid provision and three 45 minute sessions of low vision training as per the trial manual.

8.3.2 Intervention adherence

Participants will be required to attend the low vision training sessions in order to adapt to the device. Adherence will be monitored by attendance at all low vision training sessions for both groups.

8.3.3 Intervention discontinuation

Implantation of the OriLens device may not proceed if the participant has zonular instability or for any other reasons deemed appropriate by the surgeon. This will be at the surgeon's discretion.

The OriLens may be removed if required post-operatively. Removal of the OriLens is at the surgeon's discretion and may be requested by the participant.

8.4 Outcomes

8.4.1 Primary Outcome

The primary outcome is change in BCDVA at 12 months after randomisation using number of letters improvement on ETDRS as measured by a masked independent assessor. Visual acuity will be assessed as indicated in the Trial Manual. BCDVA can be a variable endpoint depending on the assessor. In order to reduce variability, participants can be encouraged to read to achieve their best visual acuity. BCDVA at the 12 month time point will initially be measured by the optometrist on the research team. An independent assessor will then repeat the BCDVA at the 12-month time point and this measurement will be used for the primary analysis. Refraction will be carried out by the optometrist on the research team prior to the independent assessment and the independent assessor will be instructed not to look directly into the participant's eyes. As an additional measure, the trial frames will be placed on the participant by the research optometrist, which will aid masking.

8.4.2 Secondary Outcomes

- **Clinical outcomes**:
  1. Change in best-corrected near visual acuity (BCNVA), reading speed and contrast sensitivity from baseline.

- **Health Economic Outcomes:**
  1. Health related quality of life measured using EQ-5D-5L at randomisation, six and 12 months (17)
  2. Vision-specific quality of life measured using Impact of Vision Profile (IVI) at randomisation, six and 12 months (18)
  3. Health service use and associated costs measured at six months and 12 months
  4. Participant out-of-pocket costs measured at six months and 12 months.

- **Safety of the device:** The safety of device will be assessed postoperatively by noting any surgical complications during or after surgery and at each subsequent visit, including any reduction in visual acuity, position of the device, and corneal clarity. The endothelial cell density will be assessed at baseline and at 12 months (13-16).

- **Mechanistic evaluation:**
  1. Correlation of participant ocular parameters such as scar size and volume with outcomes
  2. Correlation of Preferred Retinal Locus (PRL) and ocular dominance with outcomes
  3. Evaluation of the role of binocularity and visual summation on outcomes.

8.5 Participant Timeline

Eligibility will be determined at the screening visits. Surgery in Group 1 will take place at Day 0 with surgical review on days one and seven and study visits for both Groups at months one, three, six and 12. As the presence of the device is obvious to the casual observer, it will not be possible to mask assessors. Participants can also not be masked to the intervention. However, the final BCDVA measurement at 12 months will be duplicated by an additional observer independent to the trial and this measurement will be used for the primary analysis. BCDVA (primary outcome) will be measured with 4-meter ETDRS charts. Assessment at screening will include medical history, ophthalmic examination, confrontation visual field testing, visual acuity, reading speed, refraction, contrast sensitivity, assessment with x2.5 external telescope for distance and near vision, assessment for ocular dominance, binocular visual function, endothelial cell density, ocular coherence tomography (OCT) with volume scan, colour fundus photography, IVI, and EQ-5D-5L. Fundus fluorescein angiography (FFA) will be carried out in addition to OCT at baseline and only subsequently if clinically indicated as OCT cannot be performed post implantation of the device. The order of screening examinations will follow as per Figures 3 and 4, however, this may vary at site depending on the location of equipment. The detailed schedule is shown below in Table 2.

If all inclusion criteria are met at both screening visits, participants will be enrolled into the study. The required clinical information will be returned to the lead site (NICTU) and the study eye will be selected. The participant will be informed within 72 hours regarding which eye has been selected as the study eye and will be provided with a date to attend for Nd:YAG capsulotomy in the study eye, if not already done. After the participant has undergone the laser treatment, the Principal Investigator (PI) or designee will contact the CTU to determine group allocation. The participant will then be notified within 72 hours post laser treatment regarding group allocation.

Group 1 Care Pathway:

- Day 0: Surgery (surgical implantation of OriLens device)
- Day 1: Surgical review
- Day 7: Surgical review
- Assessments will be carried out at Months 1, 3, 6 and 12
- Low vision training at months 1, 3 and 12

Group 2 Care Pathway

- Day 0: No procedure
- Assessments will be carried out at Months 1, 3, 6 and 12 (beginning approximately six weeks post randomisation)
- Low vision training at months 1, 3 and 12

Figure 2. Study Schematic Diagram

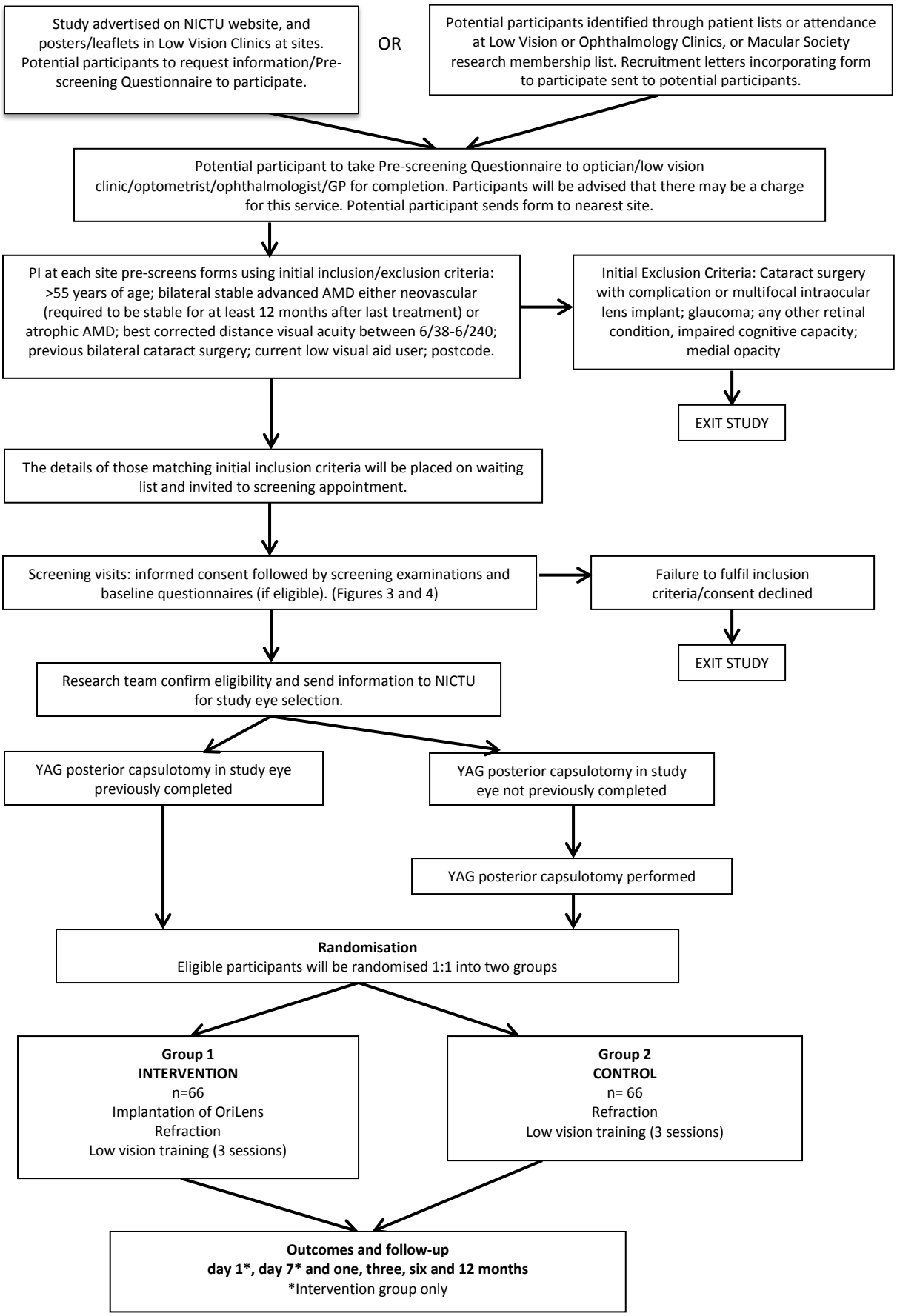


Table 2. Schedule of enrolment, interventions and assessments

TIMEPOINT	Screening			Day -20 to -7	Day -7 to -1	**Day 0**	Day 1	Day 7	Month 1*	Month 3*	Month 6*	Month 12*
	Pre-screen	Screening 1 Day -45 to -20	Screening 2 Day -45 to -20									
Pre-screening Questionnaire	**X**											
Informed consent		**X**										
Medical History†		**X**			**XX**		**XX**	**XX**	**X**	**X**	**X**	**X**
Ophthalmic Examination‡		**X**			**XX**		**XX**	**XX**	**X**	**X**	**X**	**X**
Visual field by confrontation		**X**										
Visual Acuity (Distance)		**X**			**XX**		**XX**	**XX**	**X**	**X**	**X**	**X**
Visual Acuity (near), reading speed		**X**						**XX**	**X**	**X**	**X**	**X**
Refraction, contrast sensitivity		**X**						**XX**	**X**	**X**	**X**	**X**
Testing with external telescope		**X**										
Fundus photography		**X**										**X**
OCT		**X**										
FFA		**X**										
Specular microscopy			**X**									**X**
Microperimetry			**X**									
Assessment of PRL			**X**									
Orthoptic assessment #			**X**									
EQ-5D-5L			**X**								**X**	**X**
IVI			**X**								**X**	**X**
Health service use questionnaire											**X**	**X**
Eye Selection confirmation				**X**								
Nd:YAG Capsulotomy (if required)				**X**								
Randomisation				**X**								
Informed consent for surgery					**XX**							
Surgical procedure ∞						**XX**						
Spectacle prescription & voucher for glasses									**X**		**X**	**
Visual Rehabilitation Training									**X**	**X**		**X**
Adverse Events Check							**XX**	**XX**	**X**	**X**	**X**	**X**

X: Both groups; XX: Intervention group; **: Spectacles dispensed at participants own cost; *: Control group Month 1- Approximately 6 to 8 weeks post randomisation, month 3- 14 weeks post randomisation, month 6- 6 to 7 months post randomisation, month 12- 12 to 13 months post randomisation; †: Medical history will include general medical history, ophthalmic medical history, blood pressure measurement and concomitant medication; ‡: Ophthalmic examination will include slit lamp assessment, pupillary assessment, intraocular pressure measurement and fundoscopy; #: Orthoptic assessment will include history of binocular vision anomalies, cover test, record of ocular movements, prism cover test, Bagolini glasses assessment, near point of convergence (NPC) assessment, measurement of horizontal fusional reserves and assessment of ocular dominance; ∞: standard surgical report will be completed immediately post-op.

8.6 Sample Size

As little information is available on improvement with secondary telescopic implants in pseudophakic eyes, the power calculations were based on improvements in BCDVA in participants with advanced AMD undergoing cataract surgery. Assuming from the previous IMT study that the telescope is capable of providing a 10 letter improvement for BCDVA from baseline and that standard care i.e., cataract surgery without the magnifying device will improve visual acuity by a mean (SD) of 1.94 (13.4) letters, 59 participants in each group would be required to detect a 8.06 letter difference between the two groups at 90% power, giving 66 per group accounting for 10 attrition (3, 8).

The power for the study is based on a minimum improvement of 10 letters expected from the telescope. This is in keeping with other studies such as the FDA-approved IMT study (3). However, as this is a comparative study with comparison to standard care i.e., cataract surgery with routine type IOL insertion, the difference expected will be eight letters. The choice of an eight letter difference is justified as follows:

An improvement of eight letters is clinically significant. Many studies in AMD use a 15 ETDRS letter change, which is doubling the visual angle, to assess the efficacy of interventions. It is proposed that half of this change is also clinically significant, according to the clinical experts in the team. It is certain that changes of less than five letters are not clinically significant, and this level of improvement is also considered not to be clinically significant by NICE. Data from previous studies confirm that the minimum number of letters required for repeatability of testing in normally-sighted individuals varies between 8-10 letters (19-21). In addition, Reeves et al (2009) have demonstrated that in vertepoforin photodynamic therapy, in participants with AMD, a five letter change in BCVA was associated with appreciable changes in vision-related and health-related QoL (HRQoL) (22). A difference of eight letters is also comparable to the range of improvement gained by participants with wet AMD during anti-VEGF treatment trials. Bressler et al (2010) report that in the landmark studies (MARINA and ANCHOR), an average improvement of 5-6 letters results in a detectable change in vision-related QoL (23). Although the mean improvement in BCVA following standard cataract surgery in participants with Advanced AMD has been shown to be 1.94 letters by Forooghian et al (2009) in the largest series, standard deviation is large at 13.4 letters (8). This large standard deviation is confirmed in fellow eyes which had intra-study cataract surgery in the IMT trial where the standard deviation was 13.5 letters (3). Given the large standard deviation in visual acuity outcomes following routine cataract surgery in this population, the least number of letters which gives test repeatability and that has been associated with an improvement in vision-related QoL has been selected as the primary endpoint in order to ensure that the trial is sufficiently powered.

8.7 Recruitment

8.7.1 Recruitment strategy

The study will be advertised on the NICTU website as well as on posters and flyers in Low Vision Clinics and Ophthalmology Clinics at each study site. The study email address, a contact telephone number, and details for the Research Nurse at each site will be provided for participants who would like more information. Upon request of information, potential participants will be sent a Research Ethics Committee (REC) approved Participant Information Leaflet (PIL), Information about NICE interventional procedure guidance (IPG) 272 and Pre-screening Questionnaire via email or post. In addition, the Macular Society will review the list of members who are on their research database to identify potential participants. The PI will also review the patient lists in the Low Vision Clinics. Potential participants will be contacted via mail to inform them of the study, invite them to

participate and provide them with the REC approved PIL, Information about NICE IPG 272 and pre-screening questionnaire.

The recruitment period will last approximately 21 months with an initial lag time of three months. It is expected that 10 participants will be recruited in the first six months across all study sites with an increase in the number recruited per six-month block during the study period (see Study Timelines, table 1). It is anticipated that approximately 14 participants would be recruited at each study site, with the potential of generating a waiting list in the event of recruitment of higher than anticipated numbers. Recruitment progress will be monitored by the TMG.

8.7.2 Screening procedure

Potential participants will undergo a pre-screen to determine general suitability for the study. This will entail completion of a pre-screening questionnaire by an optometrist, ophthalmologist or General Practitioner (GP) of the potential participant's choosing. The completed pre-screening questionnaire will be sent by the potential participant to their nearest site and will subsequently be screened by the PI or delegated clinician as per the inclusion/exclusion criteria defined in the protocol. Potential participants will be sent a standard letter informing them that they may or may not be eligible for the study, dependant on further tests, and that the site will be in contact with them to arrange a suitable time to attend a screening appointment. Those who do not meet the initial inclusion criteria will be sent a standard letter to inform them of this.

Due to the number of screening examinations, two screening visits are required so as not to over burden the participant. The participant will not be expected to continue with screening if they do not meet the eligibility criteria as a result of any screening examination. It is anticipated that screening Visit 1 will last up to three hours and screening Visit 2, up to two hours. Those participants who meet the inclusion criteria and are enrolled into the study will receive reimbursement for their travel expenses at the end of the second screening visit. This will be a set amount for all participants.

Upon attending the first face-to-face screening appointment, the PI or designee will ask the potential participant whether they have any questions and whether they are still willing to participate in the study. If the patient agrees to participate, the PI or designee will obtain written informed consent prior to conducting screening tests. The following examinations will be conducted during the screening visits in the order as shown in Figures 2 and 3 as per the trial manual. However, the order may vary depending on the location of instruments at site.

1. Medical History[†] and ophthalmic examination[‡]
2. Visual field by confrontation
3. Visual Acuity (distance and near), reading speed, refraction, contrast sensitivity
4. Testing with external telescope
5. Fundus photography
6. Ocular Coherence Tomography (OCT)
7. Fundus Fluorescein Angiography (FFA)
8. Specular microscopy
9. Microperimetry with assessment of PRL (sites with equipment available only)
10. Orthoptic assessment[#] and assessment of ocular dominance

[†]: Medical history will include general medical history, ophthalmic medical history, blood pressure measurement and recording of concomitant medication. [‡]: Ophthalmic examination will include slit lamp assessment, pupillary assessment, intraocular pressure measurement and fundoscopy. [#]: Orthoptic assessment will include history of binocular vision anomalies, cover test, record of ocular

movements, prism cover test, Bagolini glasses assessment, near point of convergence (NPC) assessment, measurement of horizontal fusional reserves and assessment of ocular dominance.

Eligibility may be determined at any of points 1-8 above based on the inclusion/exclusion criteria as specified in the protocol. Points 9-10 will provide information for the mechanistic evaluation but will not form part of the eligibility criteria. Data will be recorded on paper CRFs and the PI will confirm eligibility using an eligibility checklist. The PI will notify the NICTU of a new eligible participant.

A screening log will be maintained by the PI or designee at each site which will include data on the numbers of potential participants meeting initial eligibility for the trial but not entered into the trial. A fully anonymised minimal dataset will be recorded on these potential participants (screening number, age, gender, type of AMD (GA or wet) and reason for non-enrolment).

Figure 3. Flowchart of Screening Procedures: Screening visit 1

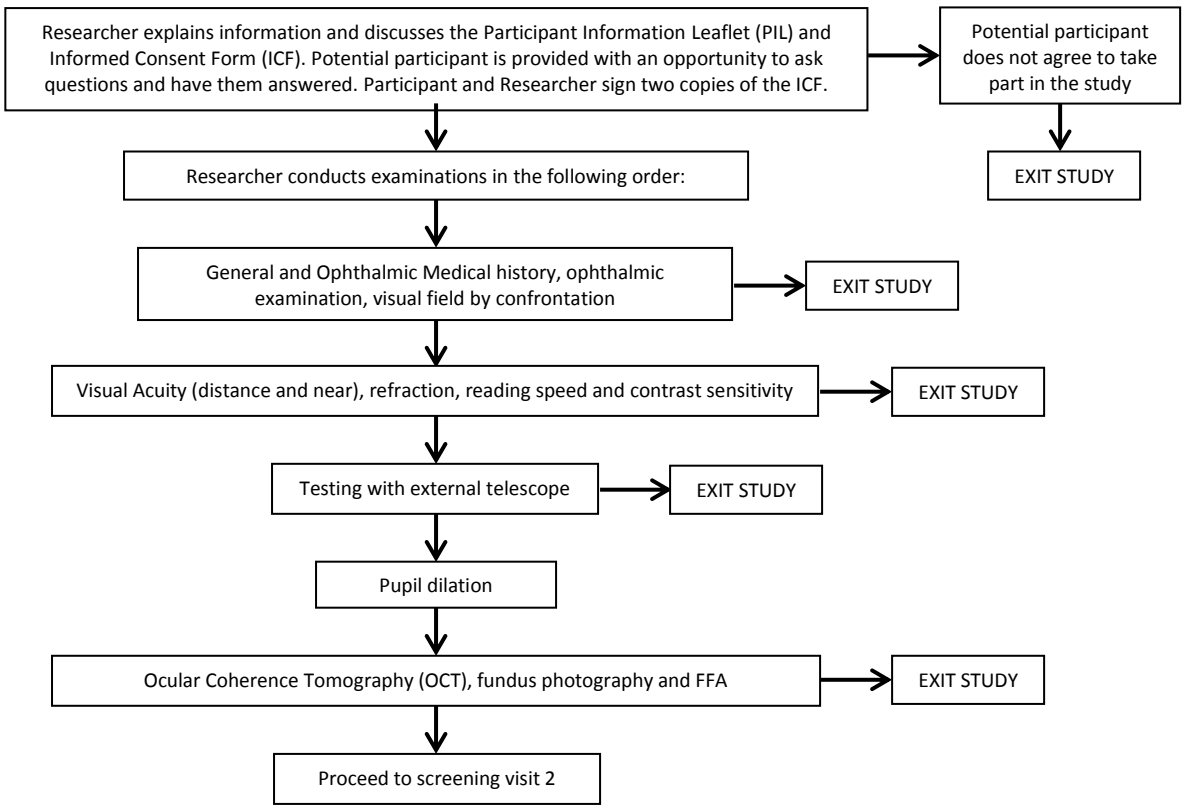
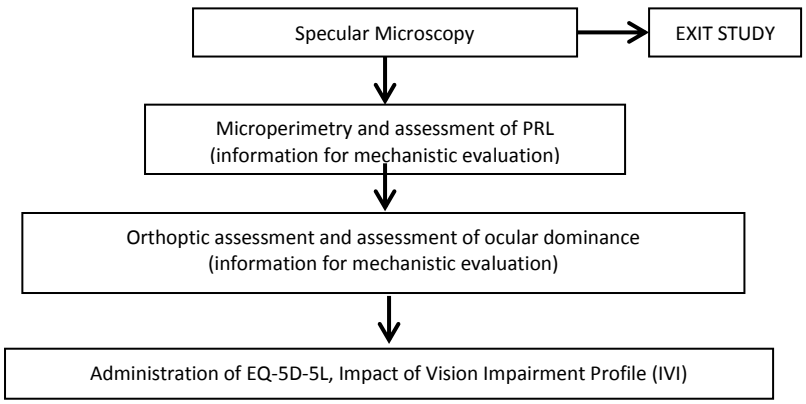


Figure 4. Flowchart of Screening Procedures: Screening visit 2



8.7.3 Informed consent procedure

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Eligible patients may only be included in the trial after written informed consent is obtained. Informed consent must be obtained prior to conducting any trial specific procedures and the process for obtaining informed consent must be documented in the participant's medical records (source documents will be reviewed at the time of on-site monitoring visits).

Informed Consent Forms (ICF) approved by the REC will be provided by the CTU. The PI or designee is responsible for ensuring that informed consent for trial participation is given by each participant prior to any trial treatment being administered. This requires that the ICF be signed and personally dated by the participant prior to any trial treatment proceeding. If no consent is given, a patient cannot be recruited into the trial.

The CTU will provide the PIL approved by the REC. The PI or designee is responsible for ensuring that all patients are given a copy of the PIL and are allowed adequate time to review this and have had the opportunity to ask any study related questions. All participants should have the capacity to self-consent; this should be judged by the PI or the designated member of the study team who will have the responsibility for taking consent. The PI (or designee) taking informed consent must be GCP trained, suitably qualified and experienced, and have been delegated this duty by the PI on the delegation log. Two copies of the ICF must be signed and personally dated by the participant and the individual taking consent. A copy of the signed ICF will be filed in the participant's medical records, whilst the originals will be retained by the participant and by the PI in the Investigator Site File (ISF).

The participant's medical notes will be annotated by the PI to confirm that the participant has provided written informed consent and has been recruited onto the study.

Following the recruitment of a participant onto the study, the PI or designee will issue a letter to the participant's GP to inform them that their patient is participating in the MIRROR trial. The participant will be advised of this contact with their GP on the REC approved PIL. If the recruited participant is not already a registered patient, a referral letter will be requested from their GP.

Surgical consent will also be sought from those participants randomly allocated to the intervention group. This is per standard NHS/Trust guidelines and will be conducted at the pre-operative visit. A full discussion of both the laser procedure, if needed, and the surgical procedure will be carried out by the operating surgeon or their designee. A copy of the surgical consent will be retained in the CRF and the participant's medical notes.

8.7.4 Withdrawal of consent

Participants may withdraw or be withdrawn from the trial at any time without prejudice. In the event of consent withdrawal, participants will be asked for their permission to use the data already collected to date. If this permission is declined, any data collected to date on that participant will not be entered into the trial analysis. A withdrawal of consent form will be completed in the CRF defining further use of data.

All study investigators will be informed of the participant's withdrawal and they will not be contacted again with regards to the study. If the participant requests removal of the OriLens device, an appointment will be provided by the operating surgeon and the participant will be given the

opportunity to discuss the request for removal. The consultation will include discussion on reason for the request to have the device removed and the potential risks and benefits of removing the device. If removal goes ahead, the participant will revert to standard care treatment.

Withdrawal of consent, participant/PI request not to proceed with implantation of the OriLens, or participant/PI request to have the OriLens removed will be recorded on the CRF.

9 Methods: Assignment of interventions

9.1 Sequence Generation

Eligible participants will be allocated to either implantation of the OriLens device with three sessions of low vision training or to standard of care with three sessions of low vision training. The randomisation will use a 1:1 allocation ratio between treatments. The randomisation will be stratified by site.

The randomisation sequence will be saved in a restricted area of the TMF which will only be able to be accessed by statisticians and not those who enrol or assign interventions.

9.2 Allocation Concealment Mechanism

The randomisation sequence will be concealed using a number of measures including:

i) Using a central telephone randomisation service provided by NICTU
ii) Restricting access to the randomisation sequence

9.3 Allocation Implementation

The randomisation sequence will be generated by a statistician from NICTU as per the departmental SOPs.

When the research team at each study site identifies a patient suitable for enrolment, they will obtain informed consent for participation in the trial. After laser treatment, the PI or designee will phone the central telephone randomisation service provided by NICTU to randomise the participant. The research team will notify the participant within 72 hours regarding the group to which they have been allocated.

9.4 Masking

Due to the surgical procedure, it will not be possible to mask the participants. As the device is easily visible with the naked eye due to the reflections from the mirror, it will not be possible to mask the observers however the final assessment for the primary outcome will be measured by an independent observer who will be asked not to discuss the trial with the participant (See Section 8.4.1).

10 METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

10.1 Data Quality

The CI and CTU will provide training to site staff on trial processes and procedures including CRF completion and data collection. Within the CTU, the clinical data management process is governed by Standard Operating Procedures (SOPs) which help ensure standardisation and adherence to ICH-GCP guidelines and regulatory requirements.

On-site monitoring visits during the trial will check the accuracy of entries on CRF, the adherence to the protocol, trial specific procedures and Good Clinical Practice (GCP). This monitoring will be carried out as per the trial specific monitoring plan. Changes to data will be recorded and fully auditable. Data errors will be documented and corrective actions implemented.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify data that may be out of range, inconsistent or protocol deviations based on data validation checks programmed into the clinical trial database.

A Data Monitoring & Ethics Committee (DMEC) will be convened for the study to carry out reviews of the study data at intervals during the study.

10.2 Data Collection

10.2.1 Screening/Baseline Visit and Procedures

The screening tests will be conducted as per Section 8.7.2 above during two screening visits. The following baseline questionnaires will be administered at the end of the second screening visit:

- Health related quality of life (EQ-5D-5L)
- Vision-related quality of life (IVI)

10.2.2 Study Visits and Procedures

Pre-randomisation (Day -20 to -7) (Both groups)
Nd: YAG Capsulotomy in study eye (if not already done)

Pre-operative (Day -7 to -1) (Intervention group only)
Pre-op medical history assessment
Visual acuity (distance only) and ophthalmic examination
Informed consent for surgical procedure

Day 0 (Intervention group only)
Surgical procedure
Standard surgical report (post-operatively)

Day 1 Post-operative (Intervention group only)
Medical history, ophthalmic examination
Visual acuity (Distance only)
Adverse events check

Day 7 Post-operative (Intervention group only)
Medical history, ophthalmic examination

Visual acuity (distance and near), reading speed, refraction, and contrast sensitivity
Adverse events check

1 Month (approximately 6-8 weeks post randomisation) (Both groups)
Medical history, ophthalmic examination
Visual Acuity (distance and near), reading speed, refraction, and contrast sensitivity
Spectacle prescription dispensing and voucher for glasses
Visual Rehabilitation training
Adverse events check

3 months (approximately 14 weeks post randomisation) (Both groups)
Medical history, ophthalmic examination
Visual Acuity (distance and near), reading speed, refraction, and contrast sensitivity
Visual Rehabilitation training
Adverse events check

6 months (approximately 6-7 months post randomisation) (Both groups)
Medical history, ophthalmic examination
Visual Acuity (distance and near), reading speed, refraction, and contrast sensitivity
Health related quality of life (EQ-5D-5L)
Vision-related quality of life (IVI)
Health service use questionnaire
Spectacle prescription dispensing and voucher for glasses
Adverse events check

12 months (approximately 12-13 months post randomisation) (Both groups)
Medical history, ophthalmic examination
Visual Acuity (distance and near), reading speed, refraction, and contrast sensitivity
Fundus photography
Specular microscopy
Health related quality of life (EQ-5D-5L)
Vision-related quality of life (IVI)
Health service use questionnaire
Spectacle prescription dispensing
Visual Rehabilitation training
Adverse events check

10.3 Study Instruments

Best corrected distance visual acuity (BCDVA) will be obtained in both eyes by an optometrist trained in research studies using the ETDRS charts at screening visit one and months one, three, six and 12. Additionally, BCDVA will be obtained pre-operatively and on days one and seven post-operatively in the intervention group. BCDVA can be a variable endpoint depending on the assessor. In order to reduce variability, participants can be encouraged to read to achieve their best visual acuity. Furthermore, an additional independent assessor will repeat the BCDVA at the 12-month time point. Refraction will be prepared by the optometrist on the research team prior to the assessment and the independent assessor will be instructed not to look directly at the participant's eyes. As an additional measure to aid masking, the trial frames will be placed on the participant by the research optometrist.

Vision-related quality of life will be measured using the IVI (18). The IVI has been validated in AMD and the subscales of IVI (reading and assessing information, mobility and independence, and

emotional well-being) have been demonstrated to have superior-quality psychometric properties and validity (22, 23). It will be administered at baseline, and six and 12 months post-randomisation.

Health related quality of life will be measured using the EQ-5D-5L (17). The EQ-5D-5L is a generic preference-based instrument which provides a description of health using five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each with five levels of severity. Responses are converted to an overall utility score which will be used for the calculation of quality adjusted life years (QALYs). Respondents are also asked to place their health on a visual analogue scale (VAS) where 0 represents the worst imaginable health state and 100 the best imaginable health state. It is recommended by NICE (24) for use in economic evaluations. It will be administered at baseline, and six and 12 months post-randomisation.

A resource use questionnaire has been developed specifically for the MIRROR study. It will measure participants' use of health services (community, social, hospital and care services) up to 12 months post-randomisation. It will also measure participants' use of privately purchased vision aids and the costs of these. It will be administered at six and 12 months post-randomisation.

10.4 Participant Retention and Follow-up

Participants in the intervention arm will be advised that low vision training is required to fully adapt to the device. Participants in the control group will be attending low vision training which is in addition to their usual standard of care.

Participants who do not attend follow up visits will be contacted to determine if they still consent to remain in the study and permission will be sought for use of data collected to date.

10.5 Data Management

Trial data, including the CRF and questionnaires, will be entered onto a web-based Clinical Trial Database (MACRO) by CTU personnel and processed electronically as per CTU Standard Operating Procedures (SOPs) and the study specific Data Management Plan (DMP). Data queries will be 'raised' electronically. Where clarification from site staff is required for data validations or missing data, site staff will respond to email queries to enable amendments, where applicable, to be made to the Clinical Trial Database.

Ophthalmic images will be anonymised and uploaded electronically by the PI or designee at site to the Central Angiographic Resource Facility (CARF). CARF is only accessible by a username/password combination unique to the site. Once uploaded, the images will be downloaded by CARF personnel and stored on secure servers housed by Queen's University Belfast.

All essential documentation and trial records will be stored securely and access will be restricted to authorised personnel. All study documentation (including participant medical records) and data will be archived as per regulatory requirements and those responsible for archiving will be noted on the sponsor delegation framework.

10.6 Data Analysis

10.6.1 Analysis population

In the efficacy evaluation, the primary analysis will be conducted on an intention to treat basis, that is, on all outcome data obtained from all participants as randomised and regardless of protocol

adherence. Per-protocol analysis will also be conducted which will involve a comparison of treatment groups that includes only those participants who completed the treatment originally allocated. In the mechanistic evaluation, the analysis will be performed only on the subjects who were randomised to the intervention arm and who received the treatment originally allocated.

10.6.2 Statistical methods

The primary endpoint is the change from baseline of BCDVA at the 12-month time point in the study eye. The treatments will initially be compared using the independent t-test followed by a repeated measures analysis of covariance, adjusting for site, baseline BCDVA as a covariate and other covariates/factors where appropriate. Possible covariates/ factors will be discussed in the Statistical Analysis Plan (SAP) and may include size of scar, thickness of scar, and ocular dominance. Statistical diagnostic methods will be used to check for violations of the model assumptions and data transformations or non-parametric equivalents such as Mann-Whitney may be performed as appropriate. The primary data at 12 months are the BCDVA measurements by the independent assessor. The 12 month BCDVA data measured by the optometrist on the research team will be analysed as part of a sensitivity analysis.

The continuous secondary endpoints will be analysed in the same manner as the primary endpoint with an endpoint specific baseline covariate term included.

Analyses will be two-sided and tested at an a priori significance level of p=0.05. The primary time point has been defined as the 12-month time point. There is no adjustment for multiple testing at the different time points, as the primary outcome has been defined and prioritised.

For the mechanistic evaluation, descriptive statistics will be used to present the results. Also, the relationship between visual outcome and several factors (as discussed in Section 7.1) will be investigated using the independent t-test, 1-way analysis of variance, Pearson's correlation coefficient or non-parametric equivalents as appropriate depending on the scale of measurement of the factors.

Inter-rater reliability between the independent assessor and the optometrist on the research team will be tested for BCDVA at 12 months using the intra-class correlation coefficient.

Baseline characteristics, follow-up measurements and safety data will be described graphically and in tabular format using appropriate descriptive summary measures depending on the scale of measurement and distribution.

A detailed SAP will be written by the trial statistician prior to the final analysis.

10.6.3 Health economic evaluation

A within-trial economic evaluation in the form of a cost-utility analysis will be undertaken to measure the cost-effectiveness of the intervention compared with standard care. A National Health Service (NHS) and personal social services (PSS) perspective will be adopted for the analysis as recommended by the National Institute for Health and Clinical Excellence (NICE, 25). The incremental cost-effectiveness ratio (ICER) for the analysis will be the cost per Quality Adjusted Life Year (QALY) gained at 12 months. Utilities for the calculation of QALYs will be measured using the EQ-5D-5L administered at baseline, and six and 12 months post-randomisation. Participant level resource use will be combined with unit costs to estimate total costs for each participant in the trial. Unit costs will be obtained from publicly available sources, for example, the NHS reference costs (25) and the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care (26).

Costs will include those associated with the implantation of the device (cost of device, cost of surgery, surgery review appointments) and those associated with participants' use of the health service over the study period. Costs associated with low vision training will not be included in the analysis as these are research costs and common to both arms. Health service use will be collected at six and 12 months post-randomisation using the Health Service Use Questionnaire. A secondary analysis will explore participants' out-of-pocket expenses associated with participants' own purchase of visual aids.

Multiple regression methods will be used to estimate incremental (differential) costs and QALYs with and without adjustment for participant baseline characteristics. Standard methods will be used to explore and display uncertainty in the cost-effectiveness data including a scatterplot on the cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC). The curve will show the probability of the intervention being more cost-effective than standard care at different threshold levels of willingness-to-pay (WTP) per QALY gained. Sensitivity analysis will be performed to assess the robustness of the cost-effectiveness results to changes in key parameters. Since the time horizon of the analysis is one year, it will not be necessary to discount costs and effects. Details of the analysis will be incorporated in to the SAP.

10.6.4 Additional analyses

Planned additional analyses will be described in the SAP.

10.6.5 Missing data

Every effort will be made to minimise missing baseline and outcome data in this trial. The level and pattern of the missing data in the baseline variables and outcomes will be established by forming appropriate tables and the likely causes of any missing data will be investigated. This information will be used to determine whether the level and type of missing data has the potential to introduce bias into the analysis results for the proposed statistical methods, or substantially reduce the precision of estimates related to treatment effects. If necessary, sensitivity analyses will be performed using multiple imputation or Bayesian Methods for missing data as appropriate.

10.6.6 End of Study

The end of trial will be when database lock occurs for the final study analysis. The study will be stopped early if;

1. Mandated by the research ethics committee
2. Mandated by Sponsor
3. Mandated by regulatory authorities
4. Recommended by the TSC
5. If funding ceases

11 METHODS: MONITORING

b.4 **Assessment of safety**

The safety of device will be assessed at each visit by noting any surgical complications during or after surgery, including visual acuity, position and clarity of the device and corneal clarity. From previous studies it is known that loss of corneal endothelial cells following implantation of devices such as this is often biphasic i.e., there is an initial decrease following surgery then a continued loss for some months but at a lower rate. Stabilisation usually occurs at 12 months (13-16). The corneal endothelial count will therefore be repeated at month 12. It is not anticipated that the device itself will cause any systemic adverse events. A record will be kept of all Serious Adverse Events (SAEs). The CI will be responsible for informing the Sponsor, the Research Ethics Committee and all study sites about any SAEs. The DMEC will provide information on all SAEs on a routine basis.

b.4.1 **Analysis of safety data**

Adverse events (AEs, SAEs) will be listed and summarised by treatment. Incidents will be listed and summarised by treatment. Responses to the recent falls question will be tabulated. Endothelial cell densities will be listed.

11.2 Interim analyses

In order to assess recruitment progress, an internal pilot study will be undertaken to assess feasibility which will run until month six of the recruitment period (month 12). By this time, it is anticipated that 20 participants will have been recruited and all sites will have been opened.

At the end of the pilot, the following analysis will be completed:

- Recruitment rate: % recruited versus target recruitment number
- % randomised based on total number screened

Recruitment feasibility milestones will be as follows: If recruitment rates achieve 75-100%, the trial will progress. If only 50-75% recruitment is achieved, the trial will progress following review of screening logs and the protocol and once barriers to achieve adequate recruitment are addressed. If 25-50% of the required number are recruited, the trial will progress only after screening logs and the protocol are reviewed and once, following approval by NIHR-EME, additional sites are opened. Should recruitment be <25%, it is not expected that the trial will progress; this decision will be made by the TSC.

An interim analysis will also be conducted to analyse efficacy and safety parameters. In relation to efficacy, an independent t-test will be applied with a p value <0.001 according to the Haybittle-Peto stopping rule. For safety, intraoperative complications are not anticipated to be significant. There is a potential risk of corneal endothelial cell damager in those who have been implanted with the device. Therefore, corneal clarity will be assessed at each clinic visit.

11.3 Definition of Adverse Events

As the current study is not investigating medical products, adverse event reporting will follow the Health Research Authority guidelines on safety reporting in non CTIMP studies. The PI or designee will make an assessment of seriousness as per the definitions below:

An **adverse event (AE)** is defined as any untoward medical occurrence in a participant in a research study, including occurrences which are not necessarily caused by or related to the study.

A **serious adverse event (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.

*Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

b.4 Anticipated adverse events due to implantation of the OriLens

Below is a list of potential or anticipated Adverse Events based on prior IMT clinical trials or known to be occasionally associated with similar types of anterior segment surgery. This list should not be considered comprehensive, but rather identifies events which can be reasonably anticipated.

- Acute corneal decompensation
- Anterior segment neovascularizion
- Choroidal detachment
- Corneal oedema
- Cystoid macular oedema
- Endophthalmitis
- Fibrin in the anterior chamber
- Hyphema
- PC IOL dislocation
- OriLens device dislocation
- Inflammatory deposits on OriLens device
- Intraocular inflammation
- Iris transillumination defects
- Optic atrophy
- Posterior synechiae
- Removal of OriLens device
- Repositioning of OriLens device
- Retinal vascular occlusion
- Anterior chamber cells
- Anterior synechiae
- Corneal transplant
- Cyclitic membrane
- Distorted pupil
- Epithelial heaping
- Flat anterior chamber
- Hypopyon
- Increased IOP requiring treatment
- Iris atrophy
- Iritis
- Pigment deposits on OriLens device
- Pupillary block
- Requirement for iridectomy/iridotomy
- Retinal detachment
- Secondary glaucoma

11.5 Eliciting Adverse Event Information

The PI or designee will record all directly observed AEs and all AEs spontaneously reported by the participant that are not related to underlying medical conditions. In addition, the participant will be asked about AEs at day one, day seven, and months one, three, six and 12 following implantation of the device.

11.6 Recording of Adverse Events

All AEs will be assessed for seriousness, expectedness and relatedness by the PI or designee, recorded in the CRF and notified to the CI/trial manager once the PI becomes aware of the AE. All AEs will also be recorded in the participant's medical notes.

11.7 Adverse Event Reporting

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

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

Reports of related and unexpected SAEs will be submitted to REC within 15 days of the CI becoming aware of the event, using the SAE report form for non-CTIMPs published on the HRA website available at: http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/. The CI will include a report on the safety of participants in the annual progress report.

11.8 Follow-up of Adverse Events

The AE reporting period for the trial begins upon enrolment of a participant into the trial and ends at month 12. All AEs assessed by the PI or designee as being related and unexpected will be followed until they are resolved or are clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es). The CRF should be updated with the date and time of resolution or confirmation that the event is due to the participant's illness as soon as this information becomes available.

11.9 Urgent Safety Measures

The PI or designee may take appropriate urgent safety measures in order to protect participants from any immediate hazards to their health or safety. The main REC will be notified by telephone immediately and in writing within three working days (by the CI or sponsor). The written notification should set out the reasons for the urgent safety measures and the plan for further action.

11.10 Data Monitoring

11.10.1 Data access

Prior to commencement of the study, the PI at each site will give permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Consent from participants for direct access to data will also be obtained. The participants' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.10.2 Monitoring arrangements

The CTU will be responsible for trial monitoring. On-site monitoring visits will be conducted in accordance with the trial monitoring plan. On-site monitoring will be an on-going activity from the time of initiation until trial close-out and will comply with the principles of Good Clinical Practice (GCP). The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor.

Before the trial starts at a participating site, a site initiation process will be completed to ensure that all relevant essential documents and trial supplies are in place and that site staff are fully aware of

the trial protocol and procedures. On-site monitoring visits during the trial will check the accuracy of entries on CRF's against the source documents, the adherence to the protocol, procedures and GCP, and the progress of participant recruitment and follow up.

The PI or designee should ensure that access to all trial related documents including source documents (to confirm their consistency with CRF entries) are available during monitoring visits. The extent of source data verification (SDV) will be documented in the monitoring plan.

The close out procedure at each site will commence once the final participant enrolled has completed all follow-up required by the protocol.

12 REGULATIONS, ETHICS AND GOVERNANCE

The trial will comply with the principles of GCP and the Research Governance Framework.

12.1 Sponsorship

The BHSCT will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor, CI and each organisation who will undertake Sponsor delegation duties in relation to the management of the study.

12.2 Regulatory and Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee.

12.3 Protocol Amendments

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee. Changes to the protocol may require ethics committee approval/favourable opinion prior to implementation, except when modification is needed to eliminate an immediate hazard(s) to participants. The CTU in collaboration with the CI and sponsor will submit all protocol modifications to the research ethics committees for review in accordance with the governing regulations. Amendments to protocol will be communicated to sites by the CTU in collaboration with the CI. Protocol compliance will be monitored by the CTU who will undertake monitoring visits to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRF's, participant consent) is being completed appropriately.

12.4 Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org). All members of the trial team will be required to have GCP training.

12.5 Protocol Compliance

A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented on the protocol deviation form in the CRF. A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The PI or designee is responsible for ensuring that serious breaches are reported directly to the Sponsor within one working day of becoming aware of the breach. Protocol compliance will be monitored by the CTU who will undertake site visits to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRF's, participant consent) is being completed appropriately.

12.6 Participant Confidentiality

In order to maintain confidentiality, all CRF's, questionnaires, study reports and communication regarding the study will identify the participants by the assigned unique trial identifier only. Databases where information will be stored will be password protected. Participant confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.7 Post-trial Care

There are no specific post-trial provisions for participants.

12.8 Indemnity

The BHSCT will provide indemnity for any negligent harm caused to participants by the design of the research protocol through the Clinical Negligence Fund in Northern Ireland.

12.9 Data Access

Following the publication of the primary and secondary study outcomes, there may be scope for the CI in the study to conduct additional analyses on the data collected. In such instances the CI will discuss this with the TMG. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission. Authorship will need to take the format of "[name] on behalf of the MIRROR Clinical Trial Group" or something similar which will be agreed by the TMG.

12.10 Record Retention

Archiving of essential documents will take place as outlined in the Sponsor delegation framework. The PI will be provided with an ISF by the CTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The PI is responsible for archiving of essential documents at local sites in accordance with the requirements of the Sponsor and local policies. The PI has a responsibility to allow Sponsor access to archived data and can be audited by the Sponsor or competent authority on request. The Trial Master File (TMF) will be held by the CTU within the BHSCT and the essential documents that make up the TMF are listed in an SOP. On completion of the trial, the TMF and study data will be archived by the CTU according to the applicable regulatory requirements and for up to five years as required by the BHSCT Sponsor. Following confirmation from the Sponsor, the CTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the CTU and Sponsor. Images stored in CARF will be archived according to the applicable regulatory requirements at the request of the CI.

12.11 Competing Interests

The research costs including the cost of the intervention were funded by NIHR EME. The CI and members of the TMG have no financial or non-financial competing interests and the members of the DMEC/TSC will be asked to confirm that they have no conflict of interest. In the event that a DMEC/TSC member reports a conflict of interest, advice will be sought from the Sponsor.

13 DISSEMINATION/PUBLICATIONS

13.1 Publication Policy

The final study report will be provided by the Trial Statistician; it is anticipated that the study findings will be published in national and international peer review journals which will be led by the CI. Publications will be discussed at the TMG and will be considered on a case by case basis. This will secure a searchable compendium of these publications and make the results readily accessible to the public and health care professionals. In addition, study findings may be presented at both national and international meetings and also to appropriate participant groups. NIHR will be acknowledged as the funder in research publications and a copy of papers will be sent to the relevant co-ordinating centre 28 days before publication.

Due to limited resources, it will not be possible to provide each participant with a personal copy of the results of the trial. However upon request, participants involved in the trial will be provided with a lay summary of the principal study findings. The most significant results will be communicated to the public through press releases. An on-going update of the trial will also be provided on the NICTU website.

The project will have a dedicated website providing details on the study and the research team members will provide regular updates on study progress. We plan to publish our trial protocol in accordance with the open access policies proposed by the NIHR and we aim to publish the findings in high quality peer-reviewed open access (via Pubmed) journals. This will secure a searchable compendium of these publications and make the results readily accessible to the public, health care professionals and scientists. A final report will also be published in the NIHR EME journal.

The results of the study will also be disseminated through conferences at national and international ophthalmic meetings. As part of our commitment to PPI, we will hold a seminar for PPI representatives and other stakeholders to present the study findings. A lay person's summary will also be sent to patient support groups e.g. the Macular Society. This may be published in the Macular Society quarterly publication for the Lay Public. Following peer-reviewed publication, appropriate key findings, presentations and summaries will be made available on the study website. The Royal National Institute for the Blind (RNIB) Northern Ireland Branch has also indicated it's support for the study (personal communication with Mr David Galloway, Chief Executive) and will publicise the study to their membership and partner branches in England, Scotland and Wales. With agreement of the funder, appropriate press releases will be prepared by institutional press offices and members of the research team.

13.2 Authorship Policy

An author will be considered to be someone who has made a substantive intellectual contribution to the study. All investigators, Trial Statistician and relevant members of the Trial Management Group will potentially be co-authors. Collaborators will be acknowledged.

13.3 Trial Registration

The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) register.

13.4 Data Sharing Statement

Requests for data sharing will be reviewed on an individual basis by the CI and TMG.

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14 APPENDICES

14.1 Appendix I: Endothelial Cell Density Reference Table

There is substantive evidence in the literature identifying the fact that in an otherwise healthy adult human eye, the minimum endothelial cell density required to sustain normal physiological functions and thus corneal transparency, is between 400 and 500 c/mm2. If we establish an arbitrary safety limit of acceptable loss down to a figure of three times this value (1500cells/mm^2), then the maximum % cell loss that would be tolerable in all four age groups identified above would be: 40%, 38%, 32% and 21%. There is also now ample evidence in the literature that phaco-assisted cataract surgery with a PC implant results in less than 5% cell loss at the one year post op period. Results in the literature for predicted cell loss after implantation of telescopic implants has improved significantly as devices have evolved. Current estimates are now running at 20%. This being the case, we believe that by setting age related endothelial cell density to minimal pre implantation of device safety levels of 2600 (50-59 years of age), 2500 (60-69 years of age), 2300 (70-79 years of age) and 2000 (80-89 years of age) (within the upper third of the normative range) we will provide a safety margin that will protect against decompensation both at time of surgery and into older life.

Age (Yrs)	**50-59**	**60-69**	**70-79**	**80-89**
EC Density (Range) (cells/mm^2)	2100-2900	2000-2800	1800-2600	1500-2300
EC Density (Mean) (cells/mm^2)	2500	2400	2200	1900

Adapted from: Ostern AE and Drolsum L. Corneal endothelial cells 6–7 years following cataract surgery in patients with pseudoexfoliation syndrome. Acta Ophthalmologica. 2012;90(5):408-411.