

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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PROTOCOL AUTHORISATION

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A review of the protocol has been completed and is understood and approved by the following:

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

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LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Full Wording
ACD	Anterior chamber depth
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
CARF	Central Angiographic Resource Facility
CEAC	Cost Effectiveness Acceptability Curve
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical trials of investigational medicinal products
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
FDA	Food and Drug Administration
FFA	Fundus Fluorescein Angiography
GA	Geographic atrophy
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
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	Intraocular Lens
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
LogMAR	Logarithm of the Minimum Angle of Resolution
LMI	Lipshitz Macular Implant
LMI-SI	Lipshitz Macular Implant- Secondary Implant
LVA's	Low vision aids
MIPFG	MIRROR Participant Forum Group
MRI	Magnetic resonance imaging
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
SD	Standard Deviation
SDV	Source Data Verification
SOPs	Standard Operating Procedures
TMF	Trial Master File
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	<p>(i) Interventional randomised controlled trial</p> <p>(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 optimised “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.</p> <p>-Method of allocation: Eligible participants will be randomised equally to each ARM (stratified by site).</p> <p>-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.</p> <p>-Assignment (double arm, single randomisation)</p>
Study Aim and Objectives	<p>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:</p> <ul style="list-style-type: none"> • 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

	<p>as scar size, and volume at site are associated with visual outcome</p> <ul style="list-style-type: none"> • 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	<p>(i) Interventional ARM: LMI-SI Lipshitz Macular Implant-Secondary Implant (OriLens) with tailored low vision training</p> <p>(ii) Control ARM: Optimised conventional low vision training</p>
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	<p>Change in BCDVA at one, three, and six months</p> <p>Change in best corrected near visual acuity (BCNVA), reading speed and contrast sensitivity at 12 months</p> <p>Vision-specific quality of life measured using the Impact of Vision Impairment Profile (IVI) at randomisation, and months six and 12</p> <p>Health related quality of life status (EQ-5D-5L) at randomisation and months six and 12</p> <p>Health service use and associated costs at months six and 12</p> <p>Safety of device assessed by surgical complications at day one, day seven, months one, three, six and 12 and endothelial cell density at baseline and at month 12</p>
Key Inclusion and Exclusion Criteria	<p>(i) Inclusion criteria</p> <ul style="list-style-type: none"> • 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 lens positioned within the capsular bag • 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 • Must have an anterior chamber depth (ACD) of ≥ 3mm in both eyes • Must have a pupil size ≥ 3mm in diameter in both eyes • Must have an endothelial cell density within normal limits for age (see appendix 1) • Must be willing to undergo laser capsulotomy in the eligible eye prior to randomisation (if not already done) • Must be three months or more following any

	<p>intraocular surgical procedure and one month following YAG capsulotomy</p> <ul style="list-style-type: none"> • 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 <p>(ii) Exclusion criteria</p> <ul style="list-style-type: none"> • Cataract surgery with multifocal intraocular lenses • A history of glaucoma or of being on anti-glaucomatous medication • Any other retinal condition which may require treatment • Lack of clear view of the retina • Abnormal or de-centred pupil • Anterior chamber depth (ACD) of <3mm in both eyes • Pupil size of <3mm in diameter in both eyes • Endothelial cell density outside normal limits for age (see appendix 1) • History of ocular inflammatory disease • Zonular instability or instability of existing intraocular lens or intraocular lens not within the capsular bag • 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 sufficiently fluent in English i.e. a friend/relative/translator is needed when taking consent
Countries of Recruitment	United Kingdom
Study Setting	NHS Hospitals with retinal specialists
Target Sample Size	132
Study Duration	42 months

2 STUDY TEAM

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Secondary/Co-sponsor (delete as appropriate)	Not applicable
Secondary/co-sponsor's reference (if applicable)	Not applicable
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3 FUNDING

This study is funded by the National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme. This funding covers staff costs, travel, consumables, equipment, training, trial registration fees, software licences, conference fees and open access publication fees. This study is funded for a period of 42 months from 1st November 2015.

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 (TMG) 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 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, although there may be periods when more frequent meetings are necessary. In addition, the TSC will have a minimum of 75% independent members. Membership of the TSC should be limited and include an independent Chair, at least two other independent members, one or two principal investigators and, where possible, a consumer representative. Involvement of independent members provides protection for both Trial Participants and the Principal Investigator(s) (PIs). Representatives of the Trial Sponsor and the Trial Funder should be invited to all TSC meetings. Responsibility for calling and organising TSC meetings lie with the Chief Investigator, in association with the Chair.

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 EME 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 (18 in total in the UK) 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 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.

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 vision 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, Veni-Vide /Optegra) 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.

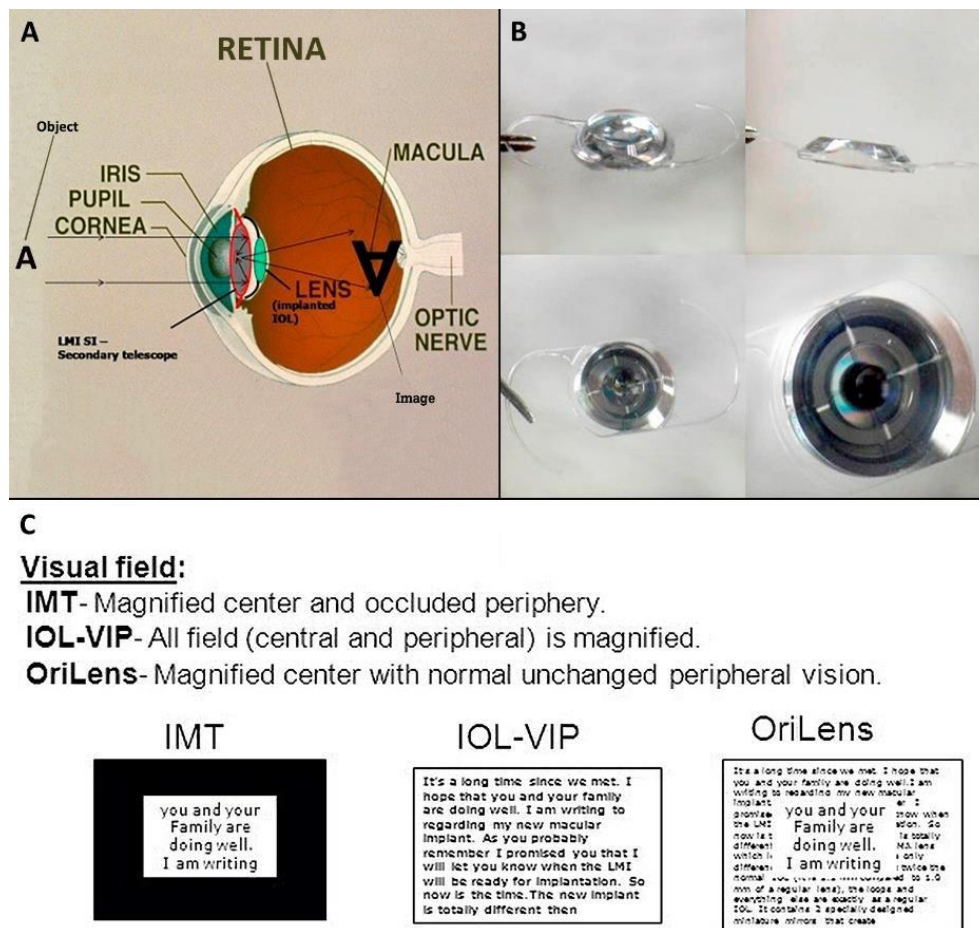


Figure 1. a. The position of the OriLens in the eye and resultant magnification of image. b. OriLens device both in profile and en-face. c. Comparison of magnification and visual field restriction with IMT, IOL-VIP and OriLens (Images reproduced with permission from OptoLight Technologies).

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 optimised usual standard of care for this participant population i.e., conventional low vision training with low visual aids. Individuals in the control arm will be offered the opportunity to try external telescopes for everyday tasks. An assessment will be made regarding frequency of use and participants' perceived usefulness for everyday tasks such as TV viewing, facial recognition and distance viewing for example seeing bus numbers. As the amount and type of training given conventionally may vary between centres, a guideline 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. If YAG capsulotomy is required as part of the trial, a minimum of 1 month will elapse between YAG capsulotomy and surgical implantation of the device. 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 optimised 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 in the study eye (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 Project Milestones/Study Timeline

The duration of the study will be 42 months. It is anticipated that 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 will open ten sites. A waiting list of potentially interested sites will be retained if further interest is expressed. The first nine 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 approximately 15 months has been allocated for the recruitment phase. 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 10 NHS/Foundation Trusts with retinal specialist clinics across the UK. If the PI at the site is not a cataract surgeon, the PI will nominate a cataract surgeon for their site. 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
- Intraocular lens must be stable and in the capsular bag
- Bilateral BCDVA of 6/38- 6/240 (LogMAR 0.80 to 1.60)
- 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 an anterior chamber depth (ACD) of ≥ 3 mm in both eyes
- Must have a pupil size ≥ 3 mm in diameter in both eyes
- 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 procedure or 1 month after any YAG capsulotomy.
- 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

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 outside normal limits for age (see appendix 1)
- History of ocular inflammatory disease
- Zonular instability or instability of existing intraocular lens
- Intraocular lens not within the capsular bag
- ACD of < 3 mm in both eyes
- Pupil size of < 3 mm in diameter in both eyes
- 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 sufficiently fluent in English i.e. a friend/relative/translator is needed when taking consent**

** 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 this is an efficacy and safety study the eye selected for implantation will be the poorer seeing eye. Only one eye per participant will be included in the study. This follows guidelines issued by the Food and Drug Administration (FDA) for the safety and efficacy trial for the IMT-001 study. This decision has also been endorsed by the Patient Representative.

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.

8.2.5 Eligibility on visual parameters

To be eligible for the trial the participant must demonstrate at least a 10-letter improvement in best corrected distance visual acuity (ETDRS chart) with the external x2.5 telescope in the eye for implantation, which will be the poorer seeing eye.

As there is little evidence to indicate whether implantation should be in the dominant or non-dominant eye, eye selection will not be based on dominance. Ocular dominance will be recorded and analysed as an independent factor but will not be used as a parameter in eye selection unless the visual acuity with the external simulator is equal in both eyes. If the visual acuity is equal in both eyes, then the device will be implanted in the non-dominant eye.

8.2.6 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 Case Report Form (CRF).

8.2.7 Trial Site requirements

The trial will take place in approximately 10 NHS/Foundation Trusts with retinal specialist clinics across the UK. Where the PI at a site does not perform cataract surgery, the PI will nominate a cataract surgeon at the site to implant the devices. 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, reading speed and contrast sensitivity tests (MN Read reading charts & MARS Charts)
- Bailey Lovie word reading charts (visual rehabilitation only)
- Standard equipment for refraction
- Standard equipment for orthoptic examination
- Slit lamp
- Colour fundus camera with Fundus Fluorescein Angiography (FFA) capability
- Optical Coherence Tomography (OCT)
- 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)
- Pin hole occluder (for pupil size measurement)

8.2.8 Research Team Requirements

Staff must demonstrate and document a willingness to comply with the protocol, Standard Operating Procedures (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 (trained in LogMAR visual acuity testing)

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 optimised low vision training with the opportunity to try external telescopes for day-to-day tasks. 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. Where a YAG capsulotomy has been carried out as part of the trial, a minimum of one month will elapse before implantation of the device. 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 before implantation. The OriLens should be soaked in sterile balanced salt solution. There is no set time for the lens to be soaked. The OriLens should be covered in viscoelastic material before insertion. It is important that the optic does not come into contact with the forceps. 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. Rotation of the device should be carried out using the carrier and not the central device. All viscoelastic will be removed at the end of the surgery. Intraocular Miochol®-E (acetylcholine chloride intraocular solution) or similar substance is optional but recommended. A peripheral iridotomy is not a routine requirement but may be carried out at the surgeon's discretion. Closure of the incision will be according to surgeon's preference. 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 again according to the surgeon's preference. Participants will be prescribed combined steroid/antibiotic drops for use four weeks post-operatively. Post-operative dilatation is at the surgeon's discretion. A device card with contact details for further information will be given to each participant. A standard surgical report documenting the details above will be completed post-operatively.

Refraction, spectacle prescription 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. Participants will be offered a trial of external telescopes for use with everyday tasks thereby optimising standard care.

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 both recording attendance at all low vision training sessions for both groups and by recording if each specified task has been completed and to which percentage i.e. 25%, 50%, 75%, or 100%.

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 BCDVA at one, three, and six months
 2. Change in best-corrected near visual acuity (BCNVA), reading speed and contrast sensitivity at 12 months 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 1 and 7 and study visits for both Groups at months 1, 3 6 and 12. Both groups will be assessed at Day -7 to -1 to assess medical history, visual acuity (distance), visual acuity (near), reading speed, contrast sensitivity, testing with external telescope and for ophthalmic assessment after YAG capsulotomy. 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, distance and near visual acuity, reading speed, refraction, contrast sensitivity, assessment with x2.5 external telescope for distance and near vision, orthoptic assessment, microperimetry, assessment of PRL, biometry, 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 and can be carried out at the discretion of the PI. 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

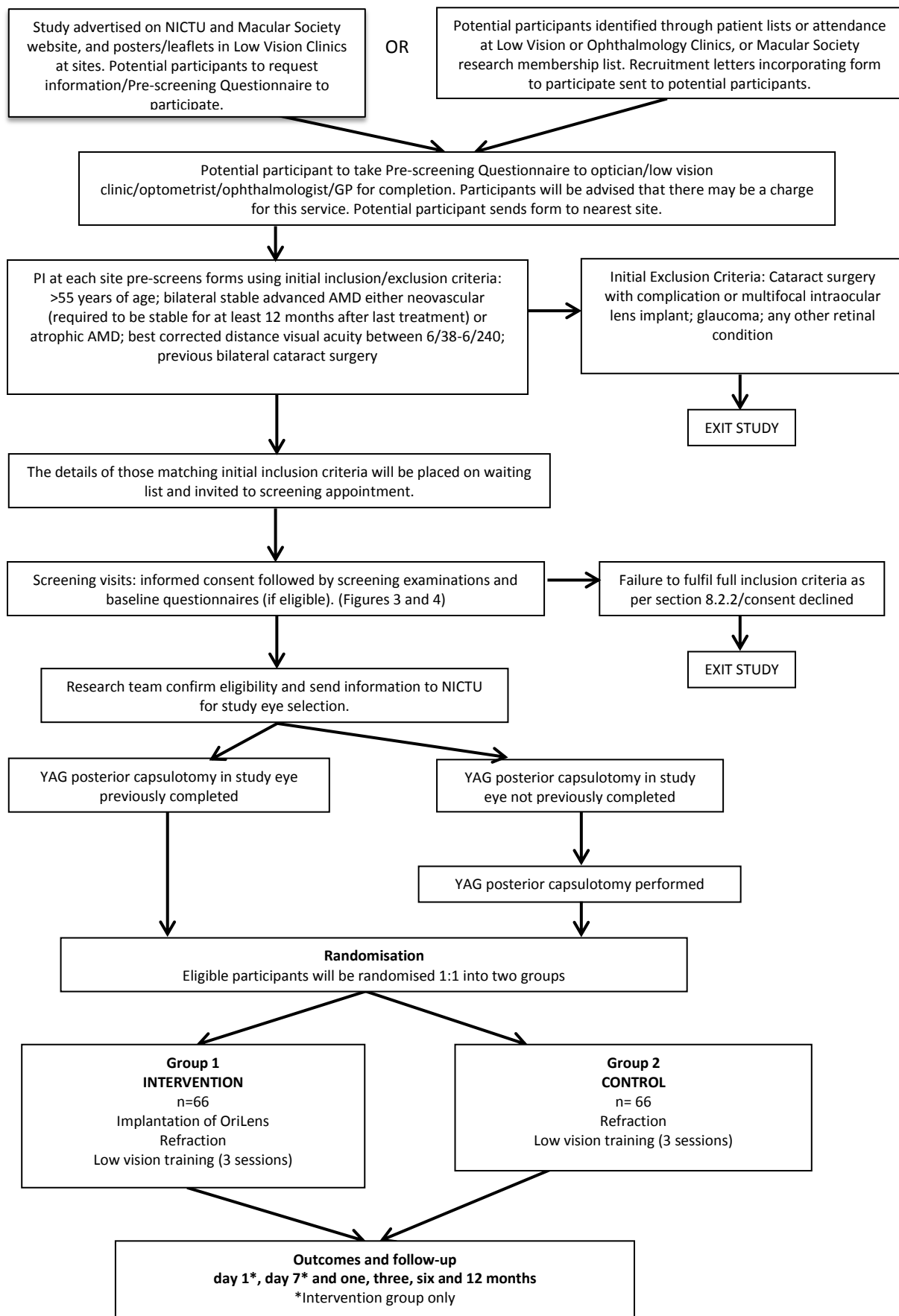


Table 2. Schedule of enrolment, interventions and assessments

TIMEPOINT	Screening			Day -35 to -30	Day -30 to -7	Day -7 to -1	Day 0	Day 1 (+1 day)	Day 7 (+/-1 day)	Month 1* (+/-3 days)	Month 3* (+/-3 days)	Month 6* (+/-3 days)	Month 12* (+/-3 days)
	Pre-screen	Screening 1 Day -60 to -35	Screening 2 Day -60 to -35										
Pre-screening Questionnaire	X												
Informed consent		X											
Medical History†		X				X		XX	XX	X	X	X	X
Ophthalmic Examination‡		X				X^		XX	XX	X	X	X	X
Visual Acuity (Distance)		X				X^		XX	XX	X	X	X	X
Visual Acuity (near), reading speedπ		X				X^			XX	X	X	X	X
Refraction		X							XX	X	X	X	X
Contrast sensitivity		X				X^			XX	X	X	X	X
Testing with external telescope		X				X^							
Biometry ~		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	X	X
Visual Rehabilitation Training										X	X		X
Adverse Events Check								XX	XX	X	X	X	X

X: Both groups; XX: Intervention group; **: Control group participants will be eligible for one voucher for glasses to a value of £50, intervention group participants will be eligible for two vouchers to a total value of £100; *: Control group Month 1- Approximately 6 to 8 weeks post randomisation, month 3- 14 to 16 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, smoking status and concomitant medication including nutritional supplements; ‡: Ophthalmic examination will include slit lamp assessment, pupillary assessment, intraocular pressure measurement, visual field by confrontation 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. ^: Test only repeated for intervention group and control group who had undergone YAG procedure. ~: Order of tests can be carried out at discretion of PI; **: Timeframe subject to surgery scheduling times; π: Testing at baseline with glasses and x2.5 telescope and at month 12 with glasses and habitual low vision aids.

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 verteporfin 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 and Macular Society websites 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 15 months. 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 optician, low vision clinic, 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 overburden 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 of £100 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 3 and 4 as per the trial manual. However, the order may vary depending on the location of instruments at site and can be carried out at the discretion of the PI.

1. Medical History[†] and ophthalmic examination[‡]
2. Visual Acuity (distance and near), reading speed, refraction, contrast sensitivity
3. Testing with external telescope
4. Biometry to determine ACD and Keratometry readings
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, smoking status and recording of concomitant medication including nutritional supplements. [‡]: Ophthalmic examination will include slit lamp assessment, pupillary assessment, intraocular pressure measurement, visual field by confrontation, 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 1-9 above based on the inclusion/exclusion criteria as specified in the protocol. Points 10-11 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

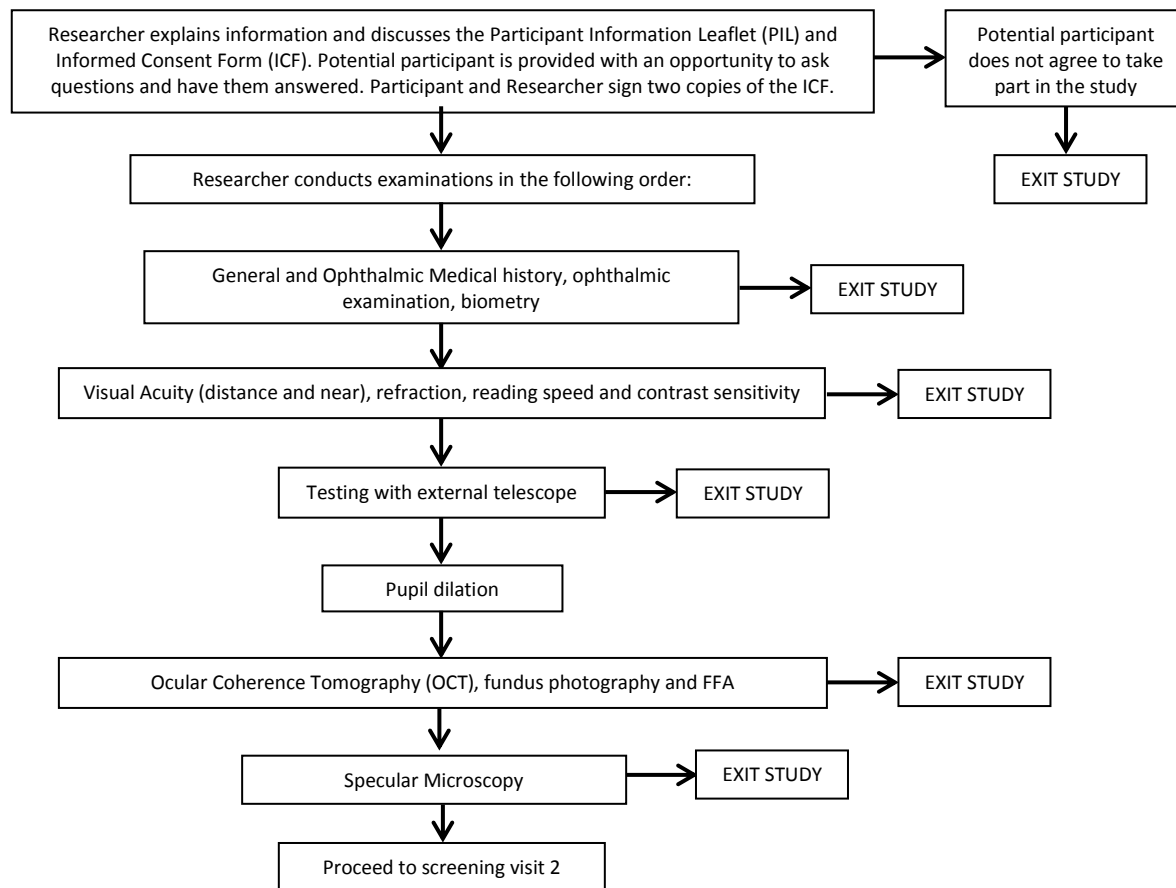
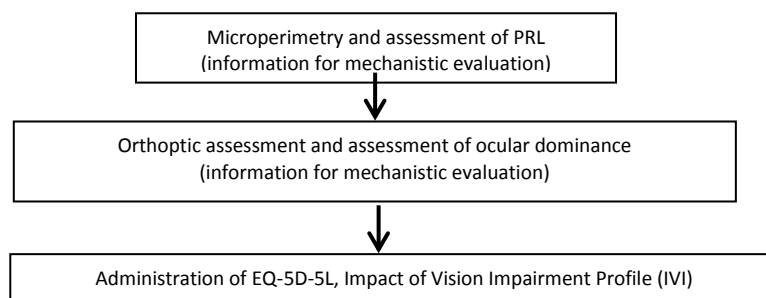


Figure 4. Flowchart of Screening Procedures: Screening visit 2



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 filed in the participant's medical notes. A patient information leaflet on "Aftercare Following Surgery" will be provided to those participants undergoing the implantation procedure.

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 withdraws from the study pre-insertion of the OriLens telescope, they will not be contacted again about the study and will be returned to standard care.

If the participant withdraws after laser capsulotomy but before insertion of the OriLens telescope, they will not be contacted again about the study. They will be advised to visit their optometrist and will receive standard care for their condition.

If the participant withdraws from the study post-insertion of the OriLens telescope, they will be followed up by the operating surgeon and at the Low Vision Clinic as part of their standard care independent of the study.

If the participant withdraws from the study post-insertion of the OriLens telescope and wishes to have the OriLens device removed, an appointment will be arranged with the operating surgeon to

discuss the 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.

If the participant wishes to have the OriLens device removed but remain in the study they will be followed up as per the study schedule.

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 optimised 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 (Days -60 to -35)

The screening tests will be conducted as per Section 8.7.2 above during two screening visits. The following baseline questionnaires will be administered by a designated member of the site research team 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

The following assessments of each participant will be undertaken by a designated member of the site research team.

Pre-randomisation (Day -35 to -30) (Both groups)

Eye Selection confirmation

Nd: YAG Capsulotomy in study eye (if not already done)

Randomisation (Day -30 to -7)

Pre-operative (Day -7 to -1) (Both Groups)

Pre-op medical history assessment

Ophthalmic examination

Visual acuity (distance only)

Visual Acuity (near), reading speed

Contrast sensitivity

Testing with external telescope

Informed consent for surgical procedure (Intervention Group only)

Day 0 (Intervention group only)

Surgical procedure

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 (if required). Please note participants will be provided with a letter with their prescription to take their optician
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
Spectacle prescription dispensing (if required)
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 (if required)
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 (if required)
Visual Rehabilitation training
Adverse events check

Please note: Control group participants will be eligible for one voucher for glasses to a value of £50, intervention group participants will be eligible for two vouchers to a total value of £100

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, day -7 to -1, and months 1, 3, 6 and 12. Additionally, BCDVA will be obtained pre-operatively (both groups) 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. Participants who are in the intervention ARM and who have had the device implanted, will be followed up by the operating surgeon and through their usual Low Vision Service.

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. The results of the microperimetry testing will also be uploaded as an image file to CARF.

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 a modified intention to treat basis, that is, on all outcome data obtained from all participants as randomised and regardless of protocol adherence. The modified intention-to-treat population will consist of randomised participants that have data from at least one post baseline efficacy assessment. 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

11.1 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.

11.1.1 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

11.2.1 Early safety report

A brief report will be submitted to the DMEC (concerning SAEs) after 10 participants have been recruited (or earlier in the event of 2 SAEs).

11.2.2 Internal pilot study assessing feasibility

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.

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
- Summary of screen failures

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 is 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% against target, it is not expected that the trial will progress; this decision will be made by the TSC.

11.2.3 Full interim analysis

After the first 50 participants have completed the three month follow-up period, an interim analysis will be conducted with a main focus on safety parameters (endothelial cell counts, IOP, early post-operative complications, corneal clarity, removal of device by surgeon and early visual acuity (BCDVA at 3 months to assess if any reduction in vision). For safety, intraoperative complications are not anticipated to be significant. There is a potential risk of corneal endothelial cell damage in those who have been implanted with the device. Therefore, corneal clarity will be assessed at each clinic visit. In addition, efficacy will also be analysed. In relation to efficacy, an independent t-test will be applied with a p value <0.001 according to the Haybittle-Peto stopping rule.

The DMEC will then decide whether further interim analyses are required.

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.

11.4 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 | ▪ Retinal vascular occlusion |
| ▪ Anterior segment neovascularization | ▪ Anterior chamber cells |
| ▪ Choroidal detachment | ▪ Anterior synechiae |
| ▪ Corneal oedema | ▪ Corneal transplant |
| ▪ Cystoid macular oedema | ▪ Cyclitic membrane |
| ▪ Endophthalmitis | ▪ Distorted pupil |
| ▪ Fibrin in the anterior chamber | ▪ Epithelial heaping |
| ▪ Hyphema | ▪ Flat anterior chamber |
| ▪ PC IOL dislocation | ▪ Hypopyon |
| ▪ OriLens device dislocation | ▪ Increased IOP requiring treatment |
| ▪ Inflammatory deposits on OriLens device | ▪ Iris atrophy |
| ▪ Intraocular inflammation | ▪ Iritis |
| ▪ Iris transillumination defects | ▪ Pigment deposits on OriLens device |
| ▪ Optic atrophy | ▪ Pupillary block |
| ▪ Posterior synechiae | ▪ Requirement for iridectomy/iridotomy |
| ▪ Removal of OriLens device | ▪ Retinal detachment |
| ▪ Repositioning of OriLens device | ▪ 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 BHSCCT 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 BHSCCT 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 BHSCCT 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/Macular Society 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 its 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.

14 REFERENCES

1. Owens C. Do we know how many people have age-related macular degeneration (AMD) in the UK? MDS Digest. 2011(Sept):38-43.
2. Margrain TH. Helping blind and partially sighted people to read: the effectiveness of low vision aids. Br J Ophthalmol. 2000;84(8):919-21. Epub 2000/07/25.
3. Hudson HL, Stulting RD, Heier JS, Lane SS, Chang DF, Singerman LJ, et al. Implantable telescope for end-stage age-related macular degeneration: long-term visual acuity and safety outcomes. American journal of ophthalmology. 2008;146(5):664-73. Epub 2008/09/02.
4. Khoramnia R, von Mohrenfels CW, Salgado JP, Schweiger B, Engel M, Hader J, et al. [The IOL-Vip system : Principles and clinical application]. Ophthalmologe. 2010;107(3):274, 6-80. Epub 2010/02/27. Das IOL-Vip System : Grundlagen und klinische Anwendung.
5. Singer MA, Amir N, Herro A, Porbandarwalla SS, Pollard J. Improving quality of life in patients with end-stage age-related macular degeneration: focus on miniature ocular implants. Clin Ophthalmol. 2012;6:33-9. Epub 2012/01/20.
6. Agarwal A, Lipshitz I, Jacob S, Lamba M, Tiwari R, Kumar DA. Mirror telescopic intraocular lens for age-related macular degeneration: design and preliminary clinical results of the Lipshitz macular implant. Journal of cataract and refractive surgery. 2008;34(1):87-94. Epub 2008/01/01.
7. Sparrow JM, Taylor H, Qureshi K, Smith R, Birnie K, Johnston RL. The Cataract National Dataset electronic multi-centre audit of 55,567 operations: risk indicators for monocular visual acuity outcomes. Eye (Lond). 2012;26(6):821-6. Epub 2012/03/24.
8. Forooghian F, Agron E, Clemons TE, Ferris FL, 3rd, Chew EY. Visual acuity outcomes after cataract surgery in patients with age-related macular degeneration: age-related eye disease study report no. 27. Ophthalmology. 2009;116(11):2093-100. Epub 2009/08/25.
9. Armbricht AM, Findlay C, Kaushal S, Aspinall P, Hill AR, Dhillon B. Is cataract surgery justified in patients with age related macular degeneration? A visual function and quality of life assessment. Br J Ophthalmol. 2000;84(12):1343-8. Epub 2000/11/25.
10. Lundstrom M, Brege KG, Floren I, Lundh B, Stenevi U, Thorburn W. Cataract surgery and quality of life in patients with age related macular degeneration. Br J Ophthalmol. 2002;86(12):1330-5. Epub 2002/11/26.
11. NICE. Implantation of minature lens systems for advanced age-related macular degeneration. <http://www.nice.org.uk/guidance/ipg272/resources/implantation-of-miniature-lens-systems-for-advanced-agerelated-macular-degeneration-1899865574485189>
12. Olsen T, Jeppesen P. The incidence of retinal detachment after cataract surgery. The open ophthalmology journal. 2012;6:79-82. Epub 2012/09/25.
13. Yee RW, Matsuda M, Schultz RO, Edelhauser HF. Changes in the normal corneal endothelial cellular pattern as a function of age. Current eye research. 1985;4(6):671-8. Epub 1985/06/01.
14. Bourne WM, Nelson LR, Hodge DO. Central corneal endothelial cell changes over a ten-year period. Investigative ophthalmology & visual science. 1997;38(3):779-82. Epub 1997/03/01.
15. Doughty MJ, Muller A, Zaman ML. Assessment of the reliability of human corneal endothelial cell-density estimates using a noncontact specular microscope. Cornea. 2000;19(2):148-58. Epub 2000/04/04.
16. Walkow T, Anders N, Klebe S. Endothelial cell loss after phacoemulsification: relation to preoperative and intraoperative parameters. Journal of cataract and refractive surgery. 2000;26(5):727-32. Epub 2000/06/01.
17. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2011;20(10):1727-36. Epub 2011/04/12.

18. Lamoureux EL, Pallant JF, Pesudovs K, Tennant A, Rees G, O'Connor PM, et al. Assessing participation in daily living and the effectiveness of rehabilitation in age related macular degeneration participants using the impact of vision impairment scale. *Ophthalmic epidemiology*. 2008;15(2):105-13. Epub 2008/04/25.
19. Rosser DA, Cousens SN, Murdoch IE, Fitzke FW, Laidlaw DA. How sensitive to clinical change are ETDRS logMAR visual acuity measurements? *Investigative ophthalmology & visual science*. 2003;44(8):3278-81. Epub 2003/07/29.
20. Lovie-Kitchin JE. Validity and reliability of visual acuity measurements. *Ophthalmic Physiol Opt*. 1988;8(4):363-70. Epub 1988/01/01.
21. Bailey IL, Bullimore MA, Raasch TW, Taylor HR. Clinical grading and the effects of scaling. *Investigative ophthalmology & visual science*. 1991;32(2):
22. Reeves BC, Langham J, Walker J, Grieve R, Chakravarthy U, Tomlin K, et al. Verteporfin photodynamic therapy cohort study: report 2: clinical measures of vision and health-related quality of life. *Ophthalmology*. 2009;116(12):2463-70. Epub 2009/12/02.
23. Bressler NM, Chang TS, Suner IJ, Fine JT, Dolan CM, Ward J, et al. Vision-related function after ranibizumab treatment by better- or worse-seeing eye: clinical trial results from MARINA and ANCHOR. *Ophthalmology*. 2010;117(4):747-56 e4. Epub 2010/03/02.
24. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. NICE: London. 2013.
25. Department of Health. NHS reference costs 2014–15. London: Department of Health, 2014.
26. Curtis L and Burns A. Unit costs of health and social care 2015. Canterbury: University of Kent: Personal Social Services Research Unit, 2015.

15 APPENDICES

15.1 Appendix I: Endothelial Cell Density Reference Table

In the adult human cornea, the corneal endothelial monolayer is essentially amitotic with the result that age related cell loss causes the corneal endothelial cell density (ECD) to diminish slowly throughout life. Whereas in childhood the normal corneal endothelial cell density is in the region of 3000 cells per mm^2 , in older adults it ranges from 1500 to 2500 cells per mm^2 . There is however 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 cells/ mm^2 . Evidence further suggests that whereas the majority of eyes develop some corneal guttata, in older age only those eyes with substantive corneal guttata are more at risk of corneal endothelial decompensation when compared to those that are guttata free.

Intra ocular surgery involving the anterior chamber will invariably result in some endothelial cell loss, the impact of a very wide range of cataract surgical techniques and intraocular lens types having been extensively evaluated over a 35 year period. There is now ample evidence in the literature indicating that small incision phaco-assisted cataract surgery with a Posterior Chamber (PC) implant results in less than 5% cell loss at the one year post op period, and that cell loss occurring after 1 year occurs at a rate not significantly greater than that occurring in otherwise normal ageing eyes. Whereas initial results relating to endothelial cell loss following the implantation of telescopic implants were concerning, figures for these devices have improved significantly as devices have evolved becoming more compact and easier to insert. Current estimates of post-surgical endothelial cell loss following telescopic implantation are in the region of 20%.

We have chosen to establish arbitrary safety, age adjusted, lower limits below which we would not wish the endothelial cell counts to fall once full post-surgical recovery has occurred (12 months). In the youngest cohort of patients, those aged 50 to 59 years, we have selected a figure of three times the minimal sustainable value referred to above (500 c/ mm^2), namely a minimal safe pre-operative endothelial cell count of 1500 cells/ mm^2 . For older patients we have modified this figure in line with age matched normative data as despite having a predicted lower pre surgical cell count they will require less reserve than younger patients as they will have a shorter lifespan. We believe the safety margin is large enough to cover both those with < 30% guttata as well as those who are free of corneal guttata. Eyes noted to have a view of the more than 30% of the central corneal endothelial cell layer obscured by guttata will be deemed ineligible for inclusion in the study.

The values outlined in the table below 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 (Normal Range) (cells/ mm^2)	2100-2900	2000-2800	1800-2600	1500-2300
EC Density (Mean) (cells/ mm^2)	2500	2400	2200	1900
Minimal acceptable ECD in eyes with <30% guttata (cells/ mm^2)	1500	1440	1320	1140

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.