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Supplementary appendix

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STAR supplementary appendix

Supplementary material for *Stereotactic radiotherapy for neovascular age-related macular degeneration (STAR): a pivotal, randomised, double-masked, sham-controlled device trial.*

Contents page

List of collaborators, committee members, national treatment centres and reading centre staff

STAR STUDY PROTOCOL

StereoTactic radiotherapy for wet Age-Related macular degeneration (STAR): A randomized, double-masked, sham-controlled, clinical trial comparing low-voltage X-ray irradiation with as needed ranibizumab, to as needed ranibizumab monotherapy.

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SYNOPSIS

MRC Medical Research Council
NHS National Institute for Health Research
Efficacy and Mechanism Evaluation Programme

Protocol Version (Date)	STAR Trial Protocol Version 1.9 (25 January 2019)
ClinicalTrials.gov Identifier	NCT02243878
ISRCTN	12884465
Full Title	StereoTactic radiotherapy for wet Age-Related macular degeneration (STAR): A randomized, double-masked, sham-controlled, clinical trial comparing low-voltage X-ray irradiation with as needed ranibizumab, to as needed ranibizumab monotherapy.
Short Title	STAR.
Sponsor	King's College London and King's College Hospital.
Funder	NIHR Efficacy and Mechanism Evaluation (EME) Programme
Objectives	To study the safety and efficacy of stereotactic radiotherapy for the treatment of pre-existing neovascular (wet) age-related macular degeneration (AMD).
Study Design	Randomized, double-masked, sham-controlled, multicenter, clinical trial.
Study Population	Patients receiving anti-VEGF treatment for neovascular AMD.
Number of Participants	411
Number of Groups/Arms	One treatment arm (16 Gy stereotactic radiotherapy - SRT), One control arm (sham treatment).
Gender/Age	Males and females aged at least 50 years old.
Number of Centers	Approximately 25 recruiting sites and 3 treatment centers.
Key Eligibility Criteria	Males and females with wet AMD requiring anti-VEGF treatment at the time of entry to the study.
Treatment Modality	0 (Sham) or 16 Gray SRT delivered in a single session at baseline, using the IRay® device (Carl Zeiss Meditec AG). Participants will receive a single intravitreal injection of 0.5 mg ranibizumab given on the same day, shortly after SRT. Thereafter they will be assessed every 28 days, and if predefined retreatment criteria are met they will receive an intravitreal injection of ranibizumab.
Study Duration	Participants will be treated at baseline and followed every 28 days for 24 months, with safety visits at month 36 and month 48.

Safety Measures	Incidence of adverse events (AEs) Incidence of serious adverse events (SAEs)
Primary Efficacy Measure	Primary efficacy measure: Mean number of ranibizumab injections over 24 months. Secondary efficacy measure: Mean change in ETDRS visual acuity at 24 months.

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2. INVESTIGATOR SIGNATURE PAGE

STAR protocol: StereoTactic radiotherapy for wet Age-Related macular degeneration (STAR): A randomized, sham-controlled, double-masked, clinical trial.

My signature confirms that I have carefully read, and that I understand this protocol. I agree to follow the study procedures as outlined in this protocol in compliance with Good Clinical Practice and all other regulatory requirements.

This protocol contains confidential information with respect to products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties for a period of three years from the date of this agreement, or until this information becomes a matter of public knowledge, or until a formal agreement for that purpose has been entered into by the parties.

_____
Print Name of Investigator Site

_____
Print Name of Principal Investigator

_____ _____
Principal Investigator's Signature Date

MRC Medical Research Council
NHS National Institute for Health Research
Efficacy and Mechanism Evaluation Programme

3. BACKGROUND

3.1. Age-Related Macular Degeneration

Age-related macular degeneration (AMD) accounts for more UK blind registrations than all other eye diseases combined.[1] There are two forms of AMD: the dry atrophic form and the wet neovascular form. Wet AMD is associated with the formation of choroidal neovascularization (CNV) in the macula. The incompetent new vessels leak blood and fluid into and under the macula, which in turn causes macular scarring and loss of central vision. The overall prevalence of wet AMD is estimated to be 1.2%, increasing to 2.5% in those aged 65 or older, and 6.3% in those aged 80 years or older.[2] There are thought to be 263,000 affected individuals in the UK, and 39,700 new cases each year.[2] As the population ages the prevalence is projected to increase by one-third over 8 years.[2]

Over the past decade, a number of therapies have been introduced to treat the neovascular form of AMD (nAMD), with generally increasing levels of efficacy. The Macular Photocoagulation Study found that focal laser photocoagulation to CNV lesions was beneficial to visual outcomes. [3, 4] However, a large proportion of CNV lesions are subfoveal, and direct laser ablation led to a permanent and immediate loss of central vision.

Photodynamic therapy (PDT) using verteporfin (Visudyne®, Novartis, Frimley, UK) for selective photochemical angio-occlusion of neovascular vessels showed better results in both the TAP and VIP trials. [5, 6] In these studies PDT treatment reduced moderate visual loss, but only a few patients demonstrated improved vision.

A variety of drugs have subsequently been introduced that target vascular endothelial growth factor (VEGF), delivered via intraocular injection. Pegaptanib (Macugen®, Pfizer, Sandwich, UK) was the first anti-VEGF agent approved by the Food and Drug Administration (FDA) for the treatment of nAMD, in December 2004. The VISION trial found that 70% of patients receiving a 0.3 mg intravitreal injection every 6 weeks lost <3 lines of vision versus 55% of control patients receiving sham injection, across all lesion types, at 12 months.[7]

Ranibizumab (Lucentis®, Novartis), a monoclonal fragment derived from the anti-VEGF antibody bevacizumab, was approved by the FDA in June 2006 for the treatment of wet AMD. Approximately 95% of ranibizumab treated patients maintained or improved vision compared with approximately 64% of patients treated with PDT. The MARINA study subsequently demonstrated that 95% of ranibizumab treated patients experienced visual improvement or stabilization compared with 62% of sham-treated patients after 12 months. Moreover, 34% of patients experienced 15 letter increases in vision. In both the MARINA and ANCHOR studies, patients received monthly ranibizumab injections. [8, 9]

Bevacizumab (Avastin®, Novartis) is a full-length, recombinant, humanized, monoclonal anti-VEGF antibody that is licensed for the treatment of colorectal cancer. Although it does not have marketing authorization for the treatment of nAMD, it has been widely adopted as an off-label nAMD treatment since its first use in 2005. [10, 11] There is no commercial incentive for the

manufacturer of bevacizumab to seek marketing authorization for nAMD, as the parent company produces ranibizumab.

The CATT trial, a large, US government-sponsored, randomized controlled study of nAMD, compared four intravitreal treatment arms: ranibizumab administered monthly; ranibizumab administered on a monthly 'as required' (*prn)* basis; bevacizumab administered monthly; and bevacizumab administered monthly *prn.*[12] The *prn* arms involved monthly review, and treatment was mandated at any of these visits if there was evidence of disease activity, such as reduced visual acuity (VA) or fluid leakage on retinal imaging. For both drugs, treatment administered monthly was found to be non-inferior to *prn* dosing. Also, bevacizumab was non-inferior to ranibizumab when given using the same dosing regimen. The mean number of *prn* treatments over 12 months was 6.9 for ranibizumab and 7.7 for bevacizumab. All treatments had favourable safety profiles. More serious adverse events occurred in the bevacizumab group, but the events did not fall into any particular category; specifically, they did not point to an increased risk of arteriothromboembolism, or the types of events that were associated with treatment using much higher systemic doses for cancer.

The results of the CATT study are important given that the effect of bevacizumab on vision was non-inferior to the results for ranibizumab, but the drug costs differed considerably. The per patient drug cost in the monthly ranibizumab arm was US$23,400 compared to US$595 for monthly bevacizumab (US$13,800 versus US$385 for the *prn* arms). The American Academy of Ophthalmologists issued a statement following publication of the CATT results, noting that: "The initial results of the CATT study affirm the position of the American Academy of Ophthalmology that both Lucentis and Avastin should be available for the treatment of AMD". A survey by the American Society of Retinal Specialists in 2012 indicated that bevacizumab was the most commonly used treatment for nAMD in the USA, accounting for more anti-VEGF injections than all other agents combined.[13]

IVAN is a large, UK, multicentre, National Institute of Health Research (NIHR)-backed, randomized controlled trial (RCT) making a head-to-head comparison of ranibizumab and bevacizumab given monthly and on a *prn* basis.[14] The comparison of ranibizumab and bevacizumab was statistically inconclusive, but a meta-analyis that included the IVAN and CATT data showed equivalence in terms of visual outcome.[14] IVAN found that continuous and discontinuous treatment were equivalent in terms of vision. There was no difference in the proportion of participants experiencing a serious systemic adverse event, but significantly fewer participants in the bevacizumab arm had arteriothrombotic events or heart failure. Bevacizumab treatment was significantly less expensive; continuous and discontinuous ranibizumab cost £9,656 and £6,398 per patient per year respectively, versus £1,654 and £1,509 for bevacizumab.[14] At the end of year two the median number of injections that patients required was similar comparing bevacizumab and ranibizumab groups, at 19 versus 18 injections (with the continuous and discontinuous arms combined, as per the trial's factorial design).[15]
Aflibercept (Eylea®, Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) is a soluble decoy receptor fusion protein targeting VEGF and is designed for intraocular injection. In a prespecified combined analysis of the VIEW 1 and VIEW 2 studies, aflibercept given monthly or two monthly (following induction with three, monthly injections) was found to be non-inferior

to monthly ranibizumab with respect to vision, with a similar safety profile and anatomic outcomes.[16]

In the UK there are two National Institute for Health and Care Excellence (NICE)-approved treatments for nAMD: ranibizumab and, more recently, aflibercept. NICE recommends that ranibizumab treatment commences with monthly injections for three months. Thereafter patients are reviewed monthly, and treated with ranibizumab on a *prn* basis if there is evidence of disease activity. NICE guidance on aflibercept states that it should be administered in accordance with its summary of product characteristics, namely monthly for three months then two-monthly, over the first year. Thereafter NICE advises that the treatment interval may be extended based on visual and anatomic outcomes, as determined by the treating doctor.

Despite the impressive results with anti-VEGF therapy and the possibility of reduced drug costs with bevacizumab, intravitreal monotherapy for nAMD still has significant drawbacks. In the SUSTAIN trial,[17] a large study investigating monthly *prn* dosing with ranibizumab, the mean visual gain of the group as a whole was 3.9 letters, but almost 50% of patients failed to maintain their initial vision gain by Month 12, or lost vision from the outset.

The total cost of nAMD treatment is likely to increase in the UK over time, as every year 40,000 new cases of nAMD emerge,[2] adding to those already on treatment. The incidence of nAMD is also expected to increase as the population ages. Most importantly, anti-VEGF monotherapy entails an enormous burden of care for patients, with regular hospital review for the remainder of their life, and regular intraocular injections. There is therefore a large unmet need for a more durable treatment that reduces the economic cost nAMD treatment, and the considerable burden faced by patients who require chronic anti-VEGF monotherapy.

The STAR trial investigates a new CE marked device that uses radiation to treat nAMD, so called stereotactic radiotherapy (SRT). The feasibility studies detailed below indicate that SRT has the potential to produce a more durable and cost-effective treatment than anti-VEGF monotherapy.

SRT is not designed to replace anti-VEGF therapy in all patients, but to reduce the frequency of anti-VEGF therapy. STAR will use ranibizumab as the anti-VEGF agent in both the treatment and control arms. Ranibizumab was chosen over bevacizumab as it is licensed for use in the eye, and at present bevacizumab is used in only a small minority of NHS hospitals, such that the results with bevacizumab may be less generalisable. Bevacizumab may slow recruitment if prospective participants are anxious about swapping to an off label treatment, and preliminary discussions with prospective sites indicated some investigators would prefer to use ranibizumab. Further, ranibizumab was used in the phase II INTREPID study (detailed below), which helps inform the STAR statistical analysis. Aflibercept's mandated dosing in year 1 means it is not possible to determine if radiation reduces the need for anti-VEGF treatment, the primary outcome measure.

3.2. Ionizing Radiation

X-rays produce high-energy photons that generate hydroxyl (OH^-) ions when they collide with water molecules. This is used clinically to target DNA. Although X-rays can directly affect DNA,

the main effect is mediated by the hydroxyl ions, which cause fragmentation of DNA. Ionizing radiation has been used extensively for both malignant and benign disease, although its use in cancer treatment is particularly well established. Radiation affects all cells in its path, but it preferentially damages proliferating cells that, unlikely non-dividing cells, are unable to repair cleaved DNA. Consequently they cannot continue the division cycle and undergo apoptosis.

Ionizing radiation can be categorized by the means through which it is generated, or by its mode of delivery. In brachytherapy, where the ionization energy is generated by short acting electrons, the ionizing radiation source is delivered directly to the lesion via surgery or other intervention. The source used in brachytherapy is traditionally an isotope, which produces ionizing radiation as it decays. Because the isotope is always decaying and emitting energy, storage is an issue, and dosing is difficult to control. Recently, an electronic brachytherapy source has been developed which can deliver X-rays on command, but the source needs to be proximate to the lesion. Electronic brachytherapy utilizes very low energy photons (<50 keV) with a very short range of action, emulating the electron-emitting brachytherapies.

Teletherapy is the term given to radiation formed into a beam (of photons typically), which can be projected at an internal body target from an external source. External beam radiotherapy (EBRT) is the more modern term given to this type of therapy. The generation of the beam can be accomplished with certain decaying isotopes such as Cobalt-60, but most modern EBRT equipment delivers ionizing radiation electronically.

Stereotactic radiosurgery or stereotactic radiotherapy (SRT) is the term given to teletherapy devices which direct beams from different angles to overlap at the target area, so as to minimize exposure to surrounding healthy tissues, and precisely localize energy delivery.

The energy level generated by EBRT X-ray devices is important. Most EBRT devices in clinical use today are linear accelerators which generate photons with X-ray energies over one million electron volts (MeV), enabling the X-Rays to penetrate skin and bone. Consequently, with such high energy emission, linear accelerators are highly regulated, and need to be placed in rooms with very thick walls. Linear accelerators require large power supplies and cooling measures. X-ray sources which generate thousands of electron volts (keV) are called orthovoltage (if >100keV) or low voltage (if <100keV), and do not require extensive shielding, power supplies, or cooling. For example, a portable chest X-ray machine can be placed in any room in a hospital.
The treatment system used in this study (IRay®, , Newark, NJ, USA) utilizes a low voltage X-ray source, and therefore can be placed in most clinical settings, including an ophthalmology outpatient clinic. Energy is absorbed as low voltage X-rays pass through tissue. Consequently, when a beam is targeted at the retina, the sclera receives a higher dose than the retina. To compensate for this phenomenon, the dose is divided into three separate beams in different locations along the sclera, but all three beams overlap on the retinal target.

The *gray* (Gy), a common measure of deposited ionizing energy, is equal to the absorption of one joule of energy by one kilogram of matter. The biological effects of radiation vary based upon the type of delivered energy and the tissues involved. A whole-body exposure of ≥10Gy of high-energy radiation, delivered at one time, can be fatal to humans.[18] Clinically, radiation is typically

measured in milligray (mGy). The radiation exposure from a typical chest X-ray is 0.4 mGy,[19] and that from an head computed tomography (CT) scan is 40 mGy.[20]

3.3. Rationale for Ionizing Radiation Therapy in AMD

Significant theoretical, experimental and clinical evidence suggests that low dose external beam radiation is a useful therapy in nAMD. Ionizing beam radiation is the standard of care in oncology, where radiation is used to destroy dividing cells, while leaving normal cells intact. The purpose of radiotherapy in AMD would be multifold. First, radiation is known to attenuate the inflammatory response, and is therefore likely to attenuate the acute and delayed inflammatory response that is thought to play a role in CNV reactivation. Second, radiation would inhibit the rapid formation of fibroblasts after treatment and thus lead to less scar formation, as it does in the treatment of dermal keloids.[21] Third, it would lead to the death of rapidly dividing endothelial cells - the main pathological component of the CNV.[22]

Theoretically, precise radiation delivery to the macula can selectively inhibit proliferating endothelial cells with limited destruction of retinal tissue and no systemic side effects. Takahasi and colleagues found that new capillaries or vessels are more radiosensitive than larger vessels or fibroblasts.[23] Vascular endothelial cells in particular are more susceptible to radiation than other mesenchymal cells types such as fibroblasts and smooth muscle cells.[24] Further work has demonstrated that macrophages and inflammatory cells are notably radiosensitive. This is a particularly useful finding, since inflammatory cells and macrophages are found in choroidal neovascular complexes.[25] Since macrophages are known to release proangiogenic cytokines and growth factors, shutting down these cell lines would theoretically lead to less CNV recurrence and reduced need for retreatment.

Miyamoto and colleagues demonstrated the beneficial effect of focal radiation in a rabbit model of CNV, where leakage from the CNV lesions was significantly reduced in the eyes irradiated with 20 Gy compared to controls.[26] Histologic and immunohistochemical studies following irradiation demonstrated decreased vascular formation and number of vascular endothelial cells in the subretinal membrane of the treated eyes.

3.4. Early Studies of Radiation for Neovascular AMD

Chakravarthy was the first to describe the use of radiotherapy as a treatment for nAMD, in 1993.[27] Patients received a total of 10 to 15 Gray that was delivered via an external beam directed from the temporal area and aimed at the macula. The total dose was divided into five fractions of 2 to 3 Gray each, given in different treatment sessions. Nineteen treated patients were compared to seven patients who declined treatment. Vision was stable or improved in 63% of the treated patients whereas 86% of the controls lost vision. The treated group had angiographic lesion regression in 77% of cases, but all lesions in the control group enlarged. Several RCTs followed but these generally failed to establish that radiation offered visual benefit over the natural history of wet AMD.[28-36]. The largest RCT, the RAD study, randomized 205 patients to 8 fractions of 2 Gy

external beam radiation or to sham radiation treatment. The mean VA reduced 3.5 lines in the treatment arm and 3.7 lines in the sham arm, a non-significant difference.

However, the devices used to deliver radiation produced a wide beam across ipsilateral and contralateral critical structures. Marcus *et al* reported that 63% of the dose was delivered to the contralateral brain, 1.5% to the ipsilateral optic nerve, and 1.2% to the ipsilateral lens.[35] As a result of this imprecision only a small amount of radiation could be applied to the macula at each setting, without risking collateral damage. Furthermore, the patients' eyes were neither tracked nor immobilized, so it was not possible to confirm that the dose of radiation was delivered to the macula.

Although the early studies did not collectively establish that external beam radiotherapy improved visual outcomes, many found less scarring compared to the natural history of nAMD. Hart *et al* reported 35 patients with bilateral disease who received radiotherapy for subfoveal CNV lesions up to 40 months previously, and noted improved vision and asymmetric scarring favoring the radiation treated eye.[37]

Support for larger doses in smaller fractions comes from studies using brachytherapy, which has the advantage of being able to deliver high energy to focused regions. In a prospective controlled study of 86 patients, Jaakkola *et al* reported the use of external Sr^{90} plaque with single doses of 15 Gy and 12.6 Gy.[38] The 15 Gy group demonstrated significantly better preserved VA compared to controls. The control eyes lost an average of 3.02, 3.95, and 4.90 lines at 6, 12, and 24 months, respectively, while the treated group lost 0.24, 0.82, and 2.41 lines. The 12.6 Gy group did not show a significant difference compared to the control, suggesting improved effectiveness for the higher dose.

3.5. Epimacular Brachytherapy

Subsequently, researchers reported the use of epimacular brachytherapy (EMB) as a means of delivering targeted radiation to the macula of patients with wet AMD. The EMB device (NeoVista Inc., Fremont, California, USA) delivers radiation to the fovea via an endoscopic probe containing a strontium-90 source. The patient first undergoes pars plana vitrectomy and then the probe is held over the macula for 3-4 minutes to deliver 24 Gray. Following positive results from initial uncontrolled studies[39-41] two pivotal trials were undertaken, the first (CABERNET) in treatment naïve patients, and the second (MERLOT) in previously treated patients. The CABERNET study (ClinicalTrials.gov identifier, NCT00454389) failed to show non-inferiority of visual acuity at the pre-specified 10% non-inferiority margin.[42] EMB did however demonstrate a favorable safety profile. The most significant adverse event, other than the expected post-vitrectomy cataract, was a 3% rate of non-proliferative radiation retinopathy. Interestingly, the 10 participants with suspected radiation retinopathy all met the primary endpoint (losing fewer than 10 ETDRS letters), and they gained, on average, 4.4 Early Treatment of Diabetic Retinopathy (ETDRS) letters over 2 years – better than the other EMB cases without radiation retinopathy. MERLOT (NCT01006538) recently reported its top line 12 month results (Jackson TL, Retina Day, Royal College of Ophthalmologists' Annual Congress, Liverpool, 20th May 2013) and, like CABERNET, failed to meet its co-primary endpoints. MERLOT safety outcomes have yet to be reported.

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3.6. Overview of IRay Stereotactic Radiotherapy (SRT) System

The IRay system is an outpatient-based radiotherapy platform that provides stereotactic application of low energy X-ray to the retina. The system uses three highly collimated beams of radiation that pass through the inferior sclera to overlap at the macula, administered in a single treatment session. Unlike EMB, SRT does not require vitrectomy. This may be advantageous as vitrectomy reduces the half-life of intravitreal drugs,[43] so that any remaining disease activity may be hard to control with anti-VEGF agents.[44] Further, with IRay, the entire 4mm treatment zone receives 90% of the intended dose, whereas with EMB the dose declines exponentially with increasing distance from the radioactive source,[45] so that larger lesions receive a reduced dose at their outer margin.

The IRay system is described in detail in the User Manual, but they key components of the device are summarized below:

1. Low energy X-ray tube, generator, and cooling unit. The system produces a highly collimated, narrow beam, designed to treat only the target lesion, and minimize scatter to surrounding healthy tissues.

2. Self-contained robotic tube positioning system.

3. Treatment planning model, which inputs standard eye parameters, such as axial length, to calculate the required beam positioning. The diameter of each beam on the sclera is 3.5 mm, diverging slightly to 4 mm at the retina.

4. I-Guide™ scleral interface, designed to stabilize the eye along its central axis in relation to the IRay system. The I-Guide incorporates a contact lens, based upon a standard Haag-Streit model, which holds the eye in the appropriate treatment location, and a reflector, which "communicates" with the X-ray tube positioning robot. The I-Guide is attached to the head restraint component of the device.

The SRT device will be used to delivery 16 Gray of radiation to the macula. The total body dose is low (< 0.5 mSv), equivalent to a dental X-ray or the radiation absorbed during normal life over a 3 month interval.

3.7. Stereotactic Radiotherapy Clinical Trials

The iRay system external beam radiation treatment was studied in a single center, open-label, non-randomized, Phase I clinical trial (CLH001MEX; ClinicalTrials.gov identifier: NCT01217762) designed to evaluate the safety and tolerability of SRT in participants with active subfoveal CNV secondary to AMD. Ranibizumab was injected at days 0 and 30. Patients were then assessed monthly and re-injected as needed, if one of the following findings were observed:

- An increase of >100 microns in central subfield on optical coherence tomography (OCT) compared to the recorded thickness from the previously scheduled study visit.
- Evidence of new macular haemorrhage on examination.
- New area of classic CNV.
- A ≥10-letter decrease in best corrected visual acuity (BCVA) compared to the recorded VA score from the previously scheduled study visit, associated with any OCT evidence of fluid in the macula.

Patients were required to have VAs in the range of 20/40 to 20/320 (69 to 24 ETDRS letters) and lesion sizes less than 11 disc areas, although some protocol violations were permitted, as the study was designed primarily to assess safety.

Sixty-two participants were enrolled and treated. Of these, two participants received treatment at 11 Gy, 28 received treatment at 16 Gy, administered between two injections of ranibizumab, 13 received 16 Gy without prior baseline ranibizumab treatment (the "Radiation First" cohort), and 19 received treatment at 24 Gy, administered between two injections of ranizumab. Enrolment in the radiation-first regimen was discontinued as a result of initial loss in vision seen in some of these participants, that was not typically observed in eyes treated with ranibizumab prior to radiation. One participant in the 16 Gy with ranibizumab group was subsequently found to have had a retinal vein occlusion, and was excluded from the efficacy evaluation.

Thirteen participants in the radiation-first 16 Gray arm completed 12 months follow up. All except one were treatment naïve at enrolment. Eleven eyes (85%) lost <15 ETDRS letters, seven (54%) gained ≥0 ETDRS letters and 0 gained ≥15 ETDRS letters. There were no radiation related safety events.[46]

Of the 47 participants who received SRT between two anti-VEGF injections, 28 received 16 Gy and 19 received 24 Gy. The mean VA improved by 8.4 letters in the 16 Gy group and by 7.8 letters in the 24 Gy group at month 12.[47] All participants lost <15 letters. Participants received a mean of only 1.0 additional injection over 12 months. The mean change in OCT central subfield thickness from baseline to month 12 was -107 and -87 μm for the 16 Gy and 24 Gy groups, respectively. There was no reported radiation retinopathy at 12 months, but it is important to note that experience with EMB suggests radiation retinopathy is more likely to occur in year 2 than year 1.[48]

Based on these positive phase I data the INTREPID (**I**Ray Plus A**n**ti-VEGF **Tre**atment For **P**atients W**i**th Wet AM**D**) study was initiated to further investigate SRT. INTREPID is a randomized, double-masked, sham controlled, dose-ranging, phase II commercial clinical trial (ClinicalTrials.gov identifier: NCT01016873). A total of 230 participants were randomized to 16 Gy, 24 Gy or sham SRT. Full eligibility criteria are as published,[49] but the key inclusion criteria were:

1. Participants must have neovascular AMD diagnosed within the previous 3 years, have received at least three injections with Lucentis or Avastin within the previous year, and

have the need for treatment with anti-VEGF therapy due to increased fluid or persistent cysts on OCT, or leakage on FA.

2. Total lesion size of <12 disc areas and a CNV lesion with a greatest linear dimension (GLD) of <6 mm, but not greater than 3 mm from the center of the fovea to the furthest point on the lesion perimeter.
3. Corrected visual acuity of 75 to 25 letters in the study eye.

All participants had a baseline ranibizumab injection alongside their SRT, and were retreated with ranibizumab on a monthly *prn* basis out to Month 12. Retreatment criteria were less aggressive than current treat-until-dry regimens[12] but reflected standard trial design at that time:

- A 100-micron increase in central subfield thickness from lowest previous OCT measurement.
- New or increased macular haemorrhage documented by fundus photographs.
- A >5 letter decrease in BCVA since the last visit or the baseline BCVA, with disease activity, for example, persistent or increased fluid on OCT or leakage on fluorescein angiography (FA).

The primary outcome was the number of *prn* ranibizumab injections over 12 month.

INTREPID met its primary endpoint. Both the 16 Gy and 24 Gy SRT arms received significantly fewer ranibizumab treatments compared with the sham arm. The mean of the 16 and 24 Gy arms were 2.64 (median, 2) and 2.43 (median, 2) respectively versus 3.74 (median, 3.5) in the control arm (P = 0.013 and P = 0.004, respectively, versus sham).[49]

In terms of vision, the sham arm lost 1.3 letters more than the 16 Gy arm, and 2.0 letters more than the 24 Gy arm (–1.57 versus –0.28 and +0.40 letters, respectively). The 16 Gy, 24 Gy, and sham arms lost <15 letters in 93%, 89%, and 91% of eyes, respectively.[49]
The structural changes appeared to favour the SRT arm. Total mean angiographic lesion area changed by –1.15 mm^2, +0.49 mm^2, and +0.75 mm^2, in the 16 Gy, 24 Gy and sham arms respectively. The mean CNV lesion area decreased by 0.16 mm^2, 0.18 mm^2, and 0.10 mm^2, respectively. OCT central subfield thickness decreased by 85.9 µm, 70.4 µm, and 33.5 µm, respectively.[49]

The safety profile was favorable at 12 months. The number of adverse events (AEs) and the serious AEs (SAEs) were similar across arms. No AEs were attributed to the delivery of radiation with no radiation retinopathy reported. No SAEs were observed in the study eye.[49] As noted previously though, radiation retinopathy may occur beyond a 1 year window.
A post-hoc subgroup analysis was undertaken to determine which baseline characteristics best predict the response to SRT (TL Jackson *et al*, In press, Retina). This found that the following features were associated with a positive response to SRT:

- Significant macular leakage, defined as a macular fluid volume greater than the median.
- Lesion size ≤ 4 mm in greatest linear dimension (GLD), corresponding to the 4mm treatment zone at the macula.

For eyes with a GLD ≤ 4 mm and significant macular leakage (26% of the trial population, the so-called, 'best-responders') there was a highly significant, 54% reduction in injection frequency versus comparable sham patients, and also better visual acuity (6.83 letters superior to sham; P=0 .0037). There was also a 71 micron greater reduction in OCT central subfield thickness (P=0.027). There was no apparent difference when considering 16 or 24 Gray.

Other features that helped predict a positive response to SRT included an absence of fibrosis, classic lesions, age > 75 years, and the presence of a pigment epithelial detachment (PED).

INTREPID was not designed to assess the effect of SRT on VA, nor the durability of treatment beyond 12 months. After month 12, participants reverted to standard care, but there were annual safety visits out to 3 years. Thus, the efficacy results beyond year 1 need to be interpreted with caution, however, at year 2 there was a continued significant reduction in injection frequency. In the best-responder group this reduction was 45% (p = 0.001), with VA 4.4 letters better than the control group (P 0.24). Year 3 INTREPID results are not yet published.

These encouraging results support the conduct of a prospective, multicenter, randomized, sham-controlled, double-masked study of SRT, with refined case selection, longer efficacy and safety review, and sufficient patient numbers to make reliable conclusions on the effect of SRT on VA in the 'best-responder' population.

4. STUDY DESIGN

4.1. Objective

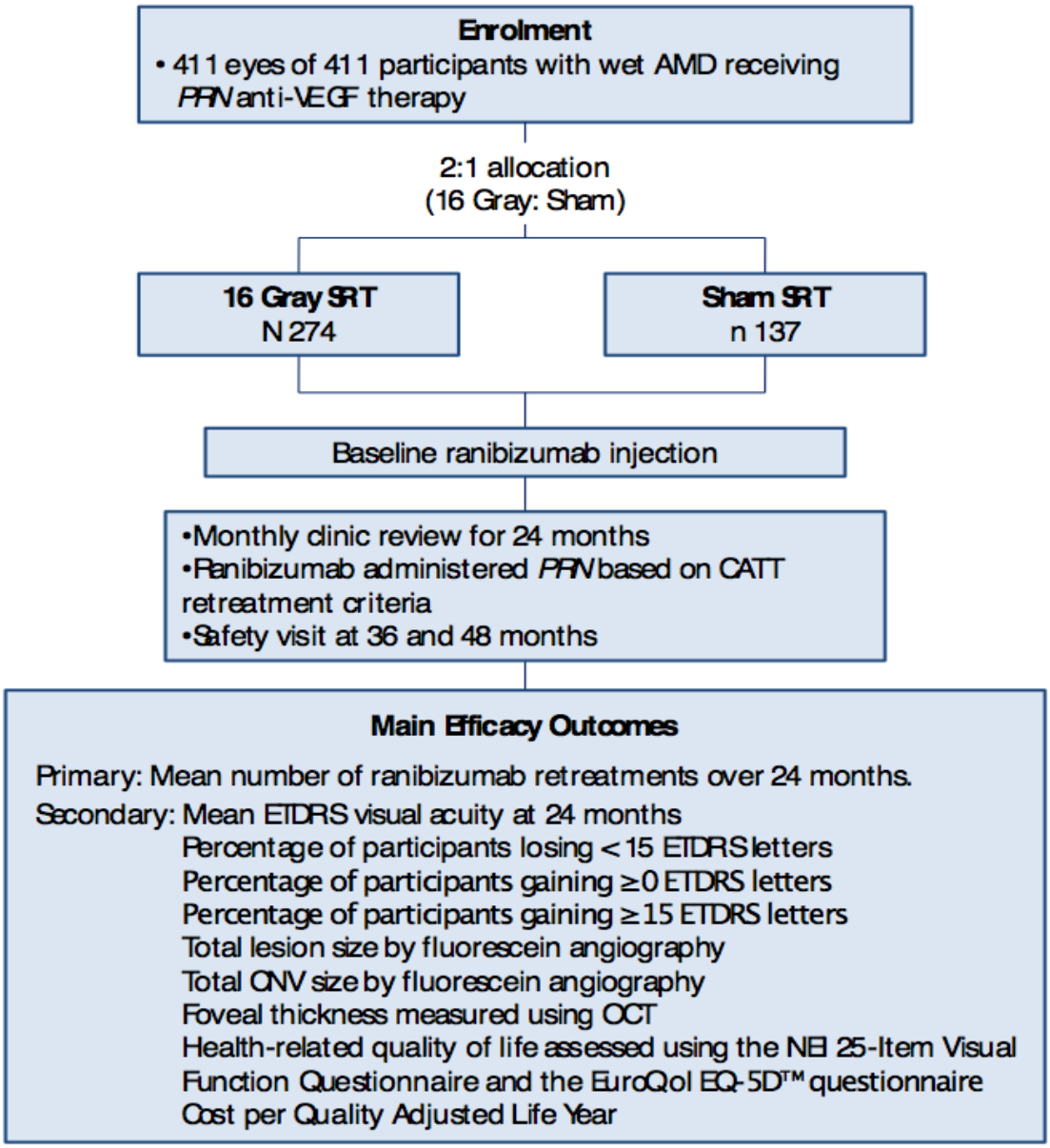
The key objective of the STAR study is to evaluate the safety and efficacy of low voltage external beam radiotherapy, in combination with anti-VEGF therapy, for the treatment of neovascular AMD. Specifically, this study will evaluate whether SRT reduces the need for ranibizumab injections, compared with ranibizumab monotherapy. STAR will also determine if SRT produces a non-inferior visual outcome compared with anti-VEGF monotherapy.

4.2. Description of the Study

This study aims to enroll 411 participants in a double-masked, multicentre, sham-controlled clinical trial.

Participants will receive a single treatment of SRT using the IRay system (sham or 16 gray) with a concomitant baseline intravitreal injection of 0.5 mg ranibizumab. Thereafter, participants will attend clinic for a review every month (28 days) for 24 months, and ranibizumab will be administered at the visit if defined retreatment criteria are met (termed ranibizumab monthly *prn*). Two safety visits occur subsequently, one at 36 months and the other at 48 months.

The trial is summarized in the following diagram:



Abbreviations: AMD, age-related macular degeneration; CATT, comparison of AMD treatments trial ; ETDRS, early treatment of diabetic retinopathy study; PRN , 'as required' dosing; SRT, stereotactic radiotherapy; VEGF, vascular endothelial growth factor; CNV, choroidal neovascularization; OCT, optical coherence tomography; NEI, National Eye Institute.

MRC Medical Research Council
NHS National Institute for Health Research
Efficacy and Mechanism Evaluation Programme

5. OUTCOME MEASURES

5.1. Efficacy

The following outcomes will be reported at Month 24.

5.1.1. Primary Measure

Number of as required (*prn*) ranibizumab injections during the first 24 months.

5.1.2. Secondary Measure

Mean ETDRS VA.

5.1.3. Other Secondary Measures (at 2 years)

- Percentage of participants losing < 15 ETDRS letters
- Percentage of participants gaining ≥ 0 ETDRS letters
- Percentage of participants gaining ≥ 15 ETDRS letters
- Total lesion size by fluorescein angiography
- Total CNV size by fluorescein angiography
- Foveal thickness measured using OCT
- Health-related quality of life assessed using the National Eye Institute 25-Item Visual Function Questionnaire and the EuroQol EQ-5D™ questionnaire
- Cost per Quality Adjusted Life Year (QALY)

5.2. Safety Outcome Measures

Safety will be evaluated by assessing adverse events (AEs) and serious adverse events (SAEs). The trial will specifically report the incidence of radiation retinopathy or radiation-related microvascular changes, and arteriothrombotic events.

6. SELECTION OF STUDY PARTICIPANTS AND STUDY EYE

The trial will randomize 411 patients with previously treated, wet AMD. After giving fully informed written consent, patients with wet AMD will be screened for participation in the study.

For patients with two eligible eyes, the patient may select which eye they wish to allocate as the study eye. Patients should fulfill the following criteria to be eligible for enrolment:

1. Inclusion Criteria

1. Participants must have neovascular AMD in the study eye, for which they have received at least 3 prior intravitreal injections of either bevacizumab (Avastin), aflibercept (Eylea), ranibizumab (Lucentis), or pegaptanib (Macugen).

2. Participants must have received an anti-VEGF injection in the study eye within 4 months prior to enrolment.

3. Participants must require treatment with anti-VEGF therapy at the time of enrolment, due to OCT evidence of subretinal fluid and/or cystoid macular oedema, **and** have a macular volume that is greater than **a pre-defined threshold** that varies for each different make of SD-OCT machine. The threshold for each approved machine is shown in Appendix 2.

4. Participants must be at least 50 years of age.

2. Exclusion Criteria

1. Disciform scarring that involves the fovea, in the study eye.

2. Visual acuity worse than 6/96 (24 ETDRS letters) in the study eye.

3. Lesion size greater than 4 mm in greatest linear dimension, or greater than 2 mm from the centre of the fovea to the furthest point on the lesion perimeter, to include active choroidal neovascular leakage, pigment epithelial detachment and haemorrhage, as determined by fluorescein angiography.†

4. An axial length of less than 20 mm, or greater than 26 mm, in the study eye.

5. Contraindication or sensitivity to contact lens application, including recurrent corneal erosions, in the study eye.

6. Type 1 or Type 2 diabetes mellitus.

7. Retinopathy in the study eye.

8. Prior, current or anticipated treatment in the study eye for age-related macular degeneration, other than anti-VEGF agents, including submacular surgery, subfoveal thermal laser photocoagulation, photodynamic therapy (PDT), or transpupillary thermotherapy (TTT).

9. Presence of an intravitreal device in the study eye.

10. Previous radiation therapy to the study eye, head, or neck with the exception of radio-iodine treatment for hyperthyroidism, epimacular brachytherapy to the non-study eye, or IRay SRT to the non-study eye.

11. Inadequate pupillary dilation or significant media opacities in the study eye, including cataract, which may interfere with visual acuity testing, the clinical evaluation of the posterior segment, or fundus imaging.

12. Study eyes with CNV due to causes other than AMD, including presumed ocular histoplasmosis syndrome (POH), angioid streaks, multifocal choroiditis, choroidal rupture, and pathological myopia (greater than 8 Dioptres spherical equivalent). Participants with retinal angiomatous proliferation (RAP) or idiopathic polypoidal choroidal vasculopathy (IPCV) are *not* excluded.

13. Known allergy to intravenous fluorescein, ICG or intravitreal ranibizumab.

14. Intraocular surgery or laser-assisted in situ keratomileusis (LASIK) in the study eye within 12 weeks prior to enrolment.

15. Prior pars plana vitrectomy in the study eye.

16. Current participation in another interventional clinical trial, or participation in such a clinical trial within the last six months.

17. Unwilling, unable, or unlikely to return for scheduled follow-up for the duration of the trial.

18. Women who are pregnant at the time of radiotherapy.

19. Participants with an implantable cardioverter defibrillator (ICD) or pacemaker implant (or any implanted device) where the device labelling specifically contraindicates patients undergoing X-ray.

20. Any other condition, which in the judgment of the investigator, would prevent the participant from granting informed consent or completing the study, such as dementia, and mental illness (including generalized anxiety disorder and claustrophobia).

† **See Appendix 9 for details.**

7. COMPLIANCE WITH LAWS AND REGULATIONS

The conduct of this study will conform to all applicable national, European, and international standards. Principal Investigators working at the national SRT treatment sites (those providing SRT) will liaise with a Consultant Clinical Radiation Expert and Senior Medical Physicist to

ensure that treatment is compliant with local and national regulations governing the use of radiation therapy.

All national SRT treatment sites participating in this study will attain the appropriate local licensing requirements permitting the utilization of X-ray systems with energy levels of 100 keV.

8. STUDY TREATMENTS

Participants meeting the inclusion and exclusion criteria will be randomized to 16 Gy SRT or Sham SRT in a 2:1 ratio. Treatment allocation will be double masked. Both groups will also be treated with a baseline intravitreal injection of 0.5 mg ranibizumab, and then ranibizumab administered using defined retreatment criteria.

8.1. Stereotactic Radiotherapy (SRT) and Randomization

SRT will be provided in two or more UK national treatment centres (NTCs). Participants will travel from their recruiting site to the NTC for SRT, and then return to their recruiting site for study follow-up. Recruiting centres will supply the NTCs with their patients' axial length (usually via biometry), which is needed to target the radiation beam correctly.

Zeiss will deliver the SRT system with an operating manual to the NTCs. During this study, Zeiss support personnel will be available as needed to support the NTC investigators administering SRT. In addition, NTC investigators will undergo training on the use of the IRay system prior to study initiation.

The NTCs will be responsible for randomizing patients when they attend for treatment.
Treatment assignment will be made via a secure password-protected website, which will provide a four letter/number alphanumeric code that, once entered into the IRay device, will dictate whether active or sham treatment is given. Patients and all study personnel, including the operator, will be masked to whether active or sham treatment is delivered.

The randomization service is available at the King's College London Clinical Trials Unit's online secure randomization service, available under Useful Links via 'Randomisation Service – Advanced' at the CTU website (www.ctu.co.uk) or directly at:

https://cturandomisation.iop.kcl.ac.uk/ProjectIndex/Default.aspx.
https://cturandomisation.iop.kcl.ac.uk/STAR/Login.aspx?ReturnUrl=%2fSTAR%2f

Participants will receive a 16 Gy dose of radiation (or sham treatment) delivered to the macula. The radiotherapy will be delivered in a single session with the IRay SRT device, utilizing three sequential beams, each depositing 5.3 Gy at the macula through calculated scleral entry points and crossing the pars plana region of the eye. If it is not possible to obtain clear access for all three beams then it may, on occasion, be necessary to deliver radiation through two beams. The dose of

radiation will therefore be 8 Gy per beam, identical to the dose delivered in each of the three beams used in the 24 Gy arm of the INTREPID study.[49]

The IRay User Manual, provided in Appendix 8, details the technique for using the device. An ophthalmologist will administer the treatment in accordance with the instructions given in the User Manual.

The IRay device provides a printout showing the details of the treatment delivered to a given participant. This includes information such as the time needed to deliver treatment and a topographic isodose colour map. Two copies should be printed. One should return with the patient to the recruiting site, to be filed in the source documents. The other should be filed in the NTC. Both copies should include the participant study ID and the randomization code entered into the IRay device.

8.2. Sham Treatment

Control participants will undergo a procedure that is identical to active treatment (as detailed above), but the device will not deliver radiation.

8.3. Ranibizumab Treatment

8.3.1. Initial ranibizumab treatment

All participants will receive a 0.5 mg baseline, intravitreal injection of ranibizumab (Lucentis) alongside SRT. The timing of the ranibizumab injection is important, as studies indicate that SRT is more effective if given alongside anti-VEGF therapy.[46, 47] To ensure that this occurs the baseline ranibizumab will be administered in the SRT national treatment centres, immediately after SRT. The injection is given after SRT rather than before, in order to avoid possible discomfort from the application of the I-Guide during SRT.

8.3.2. Ranibizumab retreatment criteria

After the initial ranibizumab treatment participants will be reviewed every 28 days in the recruiting site, and 0.5 mg intravitreal ranibizumab (Lucentis) will be administered at that visit if the CATT retreatment criteria apply, as provided below:

> CATT: "Treatment is warranted if there are signs of active CNV. It is anticipated that most retreatment decisions will be driven by the presence or absence of fluid (subretinal, intraretinal fluid, or sub-RPE) on the OCT. Eyes with fluid on OCT should be treated, with the exception of eyes in which there has been no decrease in fluid after three consecutive monthly injections. For such eyes, it is possible that continued treatment may be futile and the ophthalmologist and patient may choose to suspend treatment. Treatment may be reinstituted in these eyes at a later visit if there is increased fluid (relative to the visit when treatment was stopped) on OCT.

If there is no fluid on OCT, but there are other signs of active CNV, the eye should be treated. These signs include new subretinal or intraretinal haemorrhage, persistent subretinal or intraretinal haemorrhage, decreased visual acuity relative to the last visit without another explanation, increased lesion size on fluorescein angiography relative to the last angiogram, or leakage on fluorescein angiography.

Fluorescein angiography is required at specific visits and may be used in deciding whether treatment is warranted. Fluorescein angiography may be obtained at other visits to aid in the decision on whether treatment should be applied. Fluorescein angiography may also be obtained when there is no fluid on OCT and the decision to treat is based on new subretinal or intraretinal haemorrhage or decreased visual acuity relative to the last visit without another explanation.

Patients who present for a "non-scheduled" study examination may be retreated if they meet the above criteria for retreatment and at least four weeks have elapsed since the last study treatment. If the patient is retreated, no additional intravitreal study treatment may be administered for the next 23 days."

8.3.3. Injection technique

Ranibizumab must be administered by a qualified ophthalmologist or specialist nurse experienced in intravitreal injections. The drug should be inspected for particulate matter and discoloration prior to injection. The injection should be undertaken using aseptic conditions, including the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum, and with the availability of sterile paracentesis if needed.
The periocular skin, eyelid and ocular surface should be disinfected with povidone iodine 5%, following topical anaesthesia.

The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 ml should be delivered and then the needle should be held in position for at least 5 seconds to minimize reflux. A different scleral site should be used for subsequent injections.

8.3.4. Ranibizumab supply and storage

It is anticipated that all sites will already have a regular supply of ranibizumab (Lucentis), given that it is a commonly administered intravitreal injection. The MHRA have determined that STAR is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) and as such routine NHS ranibizumab stock may be used, without specific trial labeling. Ranibizumab must be stored in accordance with the manufacturer's instructions and also in accordance with local policy. The safety and supply of ranibizumab will be overseen by the site's non-trial pharmacy, but if any issues of concern arise, the Chief Investigator or Trial Manager should be informed.

8.4. Participant treatment at study end

Participants randomized to the sham treatment may be offered active treatment at the end of the study, if the study shows that the benefits of the SRT outweigh the risks, treatment is clinically indicated for a given patient in their study eye, the patient wishes to undergo treatment with SRT, and the treatment device remains serviceable and available to the Sponsor.. SRT will be provided free of charge at atleast one national treatment centre.

9. CONCOMITANT AND EXCLUDED THERAPIES

Concomitant medications are any prescription drugs used by a patient during the study, until conclusion of study participation (Month 48) or early termination. The paper source documents and electronic case report forms will record administration of these medications. Use of concomitant treatment with a clinical device should also be recorded.

No other experimental or investigational treatments are allowed during this study, including ocular experimental and investigational treatments in the study eye.

10.CATARACT SURGERY

If cataract surgery is required, it should be performed at least 90 days after radiation is delivered, and at least 30 days prior to the Month 12 or Month 24 visit. Cataracts that require surgery should be recorded as an SAE.

11. STUDY ASSESSMENTS

A table of the procedures by visit is given in Appendix 1, and summarized below. Written informed consent must be obtained prior to all screening events. Investigators must undertake the necessary tests and examinations at each visit and complete the paper source documents in full. These data must then be uploaded onto the central, web-based electronic case report form (eCRF).

11.1.ASSIGNMENT OF PATIENT IDENTIFICATION

A patient identification (ID) number, which will be assigned at screening, should be used on all study-related documents. To maintain confidentiality, the participant's name should not be recorded on any study document other than the informed consent form. The participant ID will have six digits. The first two digits will identify the site. The following four digits will be assigned

to patient undergoing screening, sequentially across all sites, regardless of whether screening was successful or not. The assignment of an ID number to screen failures will facilitate preparation of the CONSORT flow diagram when analyzing the data.

11.2. DAY -14 TO DAY 0: SCREENING

The following assessments will be performed at the screening visit. If necessary, the assessments may occur over a maximum of fourteen days, although it is preferred that they are completed over a much shorter time span, ideally one or two days. The patient is enrolled after screening is complete (Day 0). All treatment administered following successful enrolment will be recorded as part of the study.

All ocular assessments will be undertaken **on both eyes** at the screening visit:

- Demographic information
- Medical history
- Blood pressure
- Ophthalmic history, including medication use
- Best corrected visual acuity using ETDRS (VA) at 4 meters (performed prior to dilating eyes)
- Ophthalmic examination including slit lamp and indirect ophthalmoscopy (Ophthalmic Exam)
- Intraocular pressure (IOP)
- Cataract Assessment (AREDS 2008 criteria)
- Optical coherence tomography (OCT)**ᵅ**
- Fluorescein and indocyanine green angiography (FA and ICG)*
- Fundus photography (photos)*
- Biometry of the globe †
- Health-related quality of life and visual function questionnaires

ᵅ The OCT scan at screening is used to determine whether the macular volume is greater than the pre-defined threshold in order to satisfy the inclusion criteria. See Appendix 2 for details.

* The OCT, FA and fundus photographs are sent to the reading centre at baseline, month 12, 24, 36, and 48 but not at other visits unless retinopathy is identified at such other visits. ICG is only undertaken at baseline, and in centres that have the facility to undertake ICG.

† Biometry is undertaken as part of the screening process but the axial length is used by the SRT device to calculate the delivery of radiation to the macula. Therefore, the biometry results should accompany participants to the national SRT treatment centres. If biometry results are already available at the time of enrolment, these retrospective results can be used instead of repeating biometry.

Day 0 is defined as the day the patient successfully enrolls in the study. The measurements recorded during screening will constitute the baseline values for subsequent comparison.

All screen failures and the reasons for non-eligibility will be entered onto the source document and uploaded onto the eCRF. Randomization occurs at the national treatment centres.

Only successfully screened patients should proceed with the following tests.

11.3. Day 0 to Day 21: Stereotactic Radiotherapy

Once screening is complete and the patient is deemed eligible to enrol then SRT should be administered within 21 days (Day 0 to 21). SRT will be delivered using the IRay system at dedicated national treatment centers. The technique is described further in Section 8. The baseline ranibizumab will be injected on the same day, as detailed below.

11.4. Day 0 to Day 21: Ranibizumab Treatment

Studies suggest that SRT is more effectively when given alongside anti-VEGF therapy, and so the timing of the baseline ranibizumab is important.[46, 47, 50, 51] Therefore the first ranibizumab injection will be administered at the national treatment centres shortly after SRT, ensuring that ranibizumab and SRT are both given on the same day. The injection technique is described in Section 8.

11.5. Monthly Review

Participants will return every 28 days for measurement of ETDRS VA, slit lamp examination of the anterior segment and fundus, and OCT, in the study eye. Fluorescein angiography will be undertaken only if clinically indicated. The first monthly review should be 28 days after the initial ranibizumab.

Ranibizumab will be administered at any of the monthly visits if the CATT retreatment criteria apply,[i] as provided in Section 8.3.2. Best-corrected ETDRS VA and OCT examination will be undertaken by trial-certified staff, as detailed in the appendices and as advised by the reading centre. Full refraction will be undertaken at every third monthly visit over the first 24 months, and yearly thereafter, namely at baseline and months 3, 6, 9, 12, 15, 18, 21, 24, 36 and 48. The monthly OCTs are not sent to the reading centre except at Baseline, Month 12, 24, 36, and 48. The OCT central subfield thickness should be recorded in the source documents and eCRF for all OCTs (including those at Month 12, 24, 36, and 48). Examination of the non-study eye should be undertaken as clinically indicated.

Monthly assessment is mandated by the study protocol for the first 24 months. Following the Month 24 visit there are two mandated safety visits at Month 36 and Month 48. The Month 36 and 48 visits are designed to ensure that participants remain in a study setting, with the infrastructure to report any adverse effects occurring in that period, including radiation retinopathy, and to facilitate detection of delayed radiation retinopathy by clinical examination and angiography. The interval of follow-up and treatment regimen between Month 24 and Month 48 is as clinically indicated, and study data will not be routinely collected during this interval. However, please remember to record all their anti-VEGF injections, in the study eye and non-study eye, either as they occur or at the month 36 or month 48 visits.

Any adverse events should, however, be recorded and clinicians are encouraged to examine the retina on a regular basis, looking specifically for retinopathy.

11.6. Month 12, 24, 36 and 48

At the one year assessment, the following will be performed **on both eyes**:

- BCVA and full refraction
- Ophthalmic examination
- IOP
- Cataract Assessment (AREDS 2008 criteria)
- OCT
- Fluorescein angiogram and fundus photographs
- Health-related quality of life and visual function questionnaires

At the end of the trial participants in the SRT Arm will be provided with a card noting that they were treated with radiation, to pass to their treating retinal specialist. The card will detail the clinical features of radiation retinopathy, and a request that if there is any evidence of radiation retinopathy then the specialist should contact the Chief Investigator.

11.7. Withdrawal of Participants and Treatment Stopping Rules

Participants have the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care. Participants who withdraw from the study must be made aware that the detection of radiation damage may be less likely outside of the clinical trial, and they should be encouraged to seek regular retinal examination for at least four years after SRT.

Patients who wish to withdraw from the study will be asked to complete procedures outlined in the next annual visit (Month 12, 24, 36 or 48). The fluorescein angiogram that is undertaken at the annual visits is important in excluding radiation retinopathy. If a fluorescein angiogram was obtained in the 3 months prior to exiting the study it does not need to be repeated, but all other procedures in the annual visit should be completed.

Because SRT is administered as a single treatment at the start of the study, there are no defined treatment stopping rules for SRT. Treatment with ranibizumab may be discontinued if clinically indicated, as detailed in the CATT study[12] and as reproduced below:

"If in the best medical judgment of the treating ophthalmologist it is believed that there is no chance of any benefit to the patient from additional intravitreal injections in terms of preserving vision or retinal anatomy, intravitreal injections of the study drug may be suspended. Examples of this scenario would include patients with very large areas of central atrophy or subretinal fibrosis who have no evidence of residual macular function."

Suspension of ranibizumab therapy does not exclude participants from the trial, and follow up is clinically important to detect radiation retinopathy.

Treatment complications (for example, endophthalmitis, retinal detachment, and traumatic cataract) will not normally be considered absolute contraindications to continue with anti-VEGF treatment, or reasons to exit the trial.

12.CLINICAL PARAMETERS

Ophthalmic assessments will include ETDRS best corrected VA, fluorescein angiography, ICG angiography (in centres with ICG capability), optical coherence tomography and colour fundus photographs. The number of anti-VEGF injections will also be recorded. Whenever possible, the same person should perform the evaluations specified by the protocol at each study visit. Except where otherwise indicated, ocular assessments should be performed on the study eye only.

12.1 ETDRS Best-Corrected Visual Acuity

Manifest refraction and VA measurement must be performed according to the standard procedure originally developed for ETDRS and adapted for the Age Related Eye Disease Study (AREDS) protocol. The trial frame spectacle correction used to test VA should be updated every three months during the first 24 months, but the previous month's refraction can be used for intervening monthly visits. Full refraction is also required at baseline and all annual visits out to month 48. VA testing by the ETDRS protocol is detailed in Appendix 3. VA will be tested by trial certified examiners, in trial certified examination rooms, at each visit.

12.2 Fluorescein and Indocyanine Green Angiography

Fluorescein angiograms (FAs) will be undertaken at screening and then yearly thereafter. In addition, indocyanine green angiography (ICG) will be undertaken at baseline, in centres with ICG capability. All angiograms will be performed using digital photography equipment certified by the central reading center (CARF, Queen's University of Belfast). All photographers must be certified by the reading centre prior to undertaking any angiograms on trial participants. The reading center

will provide a protocol for image acquisition and transfer. This protocol must be strictly adhered to. Images must be transferred to the reading centre within 7 days of obtaining them. Additional FAs will be undertaken when required by clinical need or because retinopathy has been observed; these should be acquired using the same protocol, and using certified equipment and photographers.

12.3 Optical Coherence Tomography (OCT)

Spectral domain OCT will be utilised to assess subretinal fluid, intraretinal thickening, and neovascular lesions at each visit. At each of monthly visit the Investigator will review the participant's OCT. At set visits (Baseline and Month 12, 24, 36 and 48) the OCT will also be sent to the reading centre for masked assessment. The OCT machine and technician will be certified by the reading centre prior to study commencement. OCTs will be acquired and transferred in a timely manner, using the protocol specified by the reading centre. Extra OCTs may be taken when retinopathy has been observed or at unscheduled visits, using the same protocol, equipment and staff, as specified by the reading centre.

Monthly OCT images that are not sent for central reading should be captured using the same approved device, technician, and technique of image acquisition. The OCT scan should be centered on the fovea, in the same position each month. The OCT software will provide an objective thickness reading in the **central 1 mm subfield**. This reading is recorded each month as part of the study. It may also be used, alongside other criteria, to determine if retreatment is required. This automated reading should be checked for errors as it is possible that the OCT software fails to correctly identify the inner and outer neural retina limits correctly. To check for errors it is best to review a higher magnification radial line scan. If there are segmentation errors then a manual adjustment should be made, by repositioning all the central segmentation lines and re-reading the central 1mm subfield value. This corrected value should be recorded in the source documents and eCRF, and it should also be recorded that a manual adjustment was made.

OCTs that require central reading should be sent to the reading centre within 7 days of their acquisition, and in accordance with the protocol supplied by the reading centre.

12.4 AREDS Lens Grading Protocol

Radiation can cause cataract in phakic eyes. The IRay device is designed to minimize lens exposure, and the INTREPID study did not find an increased rate of cataract in treated eyes.[49] Nonetheless, in phakic eyes the AREDS Lens Grading Protocol will be used to assess any lens opacity (See Appendix 4).

12.5 Biometry of the Globe

The axial length of the globe may be determined via any commercially available A-Scan immersion ultrasonography system, or an IOLMaster®/equivalent machine. The axial length, must be recorded in the eCRF. The axial length is used in the computer algorithm that ensures that the

IRay device correctly targets radiation on the macula. The patient's axial length should be measured by the recruiting site and then provided to the SRT national treatment centres. Biometry is also used to exclude patients with an axial length of less than 20 mm, or greater than 26 mm, in the study eye. If suitable biometry is already available at the time of enrolment this can be used, instead of repeating biometry on-study. Retrospective biometry should be filed in the study documents and forwarded to the National Treatment Centre, as per on-study biometry.

13. HEALTH ECONOMIC AND QUALITY OF LIFE EVALUATION

The health economic component of STAR will estimate the relative cost-effectiveness of SRT compared to no SRT and help determine whether SRT provides value for money for the NHS. The main outcome measure will be quality of life which will be used to calculate a cost per quality-adjusted life year (QALY) gained for SRT plus ranibizumab versus ranibizumab alone.

Participants will complete the National Eye Institute 25 Item Visual Function Questionnaire (VFQ-25)[52] and the EuroQoL EQ-5D[53] at enrolment and then yearly until the study ends at month 48. The questionnaires, with instructions, are provided in the source documents. While there is overlap between the EQ-5D and VFQ-25 questionnaires, using both allows comparison of VFQ-25 results for this trial population to those reported for other eye trials. This provides some indication of the baseline quality of life (in terms of visual function) and a change in response to treatment of the population compared on a common scale with other trial populations. The EQ-5D, a generic c quality of life questionnaire will allow comparison of the study results against other (non-vision) health care interventions.

The base case analysis will take an NHS and personal and social services perspective in accordance with NICE guidance.[54, 55] Since there is no Health Research Group (HRG) code specific to intravitreal injection or AMD monitoring, we will use microcosting estimates of the cost of ranibizumab injections and associated monitoring that were collected previously within the IVAN trial.[14] This costing work will be replicated to estimate the cost of administering SRT alongside ranibizumab in routine clinical practice. The number of ranibizumab injections, monitoring consultations and ocular imaging procedures (angiography and OCT) will be collected on standard trial forms. At each study visit, participants will be asked to provide data on all hospital admissions and contacts with medical professionals or eye clinic liaison officers and the reasons for such admissions and contacts in addition to any residential care, low vision aids and personal care received.

The base case analysis will include all resource use accrued by trial participants, although a sensitivity analysis including only those costs associated with the study eye or expected adverse events will also be conducted. Data on all hospital admissions and outpatient consultations between randomization and the end of the efficacy study will also be collected from Hospital Episode Statistics to ensure that costs are not underestimated by participant's recall, missed appointments and/or withdrawal from the study. Analysis of costs and cost-effectiveness will follow standard NICE guidelines.[54] We anticipate using bootstrapping to estimate the uncertainty

around incremental costs and QALYs, which will be presented as cost-effectiveness acceptability curves.

14. ADVERSE EVENT REPORTING

This section describes the protocol requirements for recording and reporting adverse events. In this section, the term "study treatment" means both SRT using the IRay device (16 Gy or sham) and injection of ranibizumab.

14.1 Adverse Events (AE)

An adverse event (AE) includes any untoward sign, symptom, disease, or condition associated with the use of the study treatment (SRT or ranibizumab) regardless of the suspected cause. Conditions or diseases that are chronic but stable should not be recorded on AE pages of the eCRF.

14.2 Serious Adverse Events (SAE)

An AE should be classified as a serious adverse event (SAE) and reported as such, if it meets one or more of the following criteria:

- It results in death (i.e., the AE actually causes or leads to death)
- It is life threatening (i.e., the AE places the participant at immediate risk of death)
- It results in hospitalization or prolongation of hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the participant's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- The investigator considers it an important medical event because, based on medical judgment, it may jeopardize the participant or require medical or surgical intervention to prevent one of the outcomes listed above
- It is considered sight-threatening by the investigator.

Hospitalizations for the following reasons will not be recorded as SAEs:

- Hospitalization or prolongation of hospitalization for diagnostic, medical or surgical procedures for preexisting conditions;
- Hospitalization or prolongation of hospitalization required to allow outcome measurement for the study;
- Hospitalization or prolongation of hospitalization for treatment of the target disease of the study.

14.3 Sight-Threatening Events

An event is considered sight-threatening and should be reported as an SAE if it meets one or more of the following criteria:

- It is associated with a decrease in visual acuity of >30 ETDRS letters (compared with the assessment of visual acuity at the last visit)
- It is associated with a decrease in visual acuity to the level of Light Perception or worse
- It required surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of antibiotics, or laser or retinal cryopexy with gas) to prevent permanent loss of sight
- It is associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis)
- In the opinion of the investigator it may require medical or surgical intervention to prevent permanent loss of sight.

14.4 Adverse Event Assessment

All participants who have been exposed to the study treatment will be evaluated for AEs at each visit. All AEs, regardless of severity or seriousness and whether or not they are ascribed to the study treatment, will be recorded in the source documents and eCRF using standard medical terminology.

All AEs will be evaluated beginning with onset, and evaluation will continue until resolution is noted, or until the investigator determines that the participant's condition is stable. The investigator will take appropriate and necessary therapeutic measures required for resolution of the AE. Any medication or other intervention necessary for the treatment of an AE must be recorded on the concomitant medication section of the source documents and eCRF.

All AEs will be characterized by the following criteria:

- Event term
- Intensity or severity
- Expectedness
- Outcome
- Treatment or action taken.

14.5 Adverse Event Terms

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used. Only one medical concept, preferably a diagnosis instead of individual symptoms, should be recorded as the event.
If more than one distinct AE occurs, each event should be recorded separately.
However, if known at the time of reporting, a diagnosis (i.e., disease or syndrome) should be recorded on the eCRF rather than individual signs and symptoms (e.g., record congestive heart failure rather than dyspnoea, rales, and cyanosis). If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as a separate AE. If a diagnosis is subsequently established, this information should be reported on the source documents and eCRF as follow-up information.

Signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as a separate AE).

AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause; a "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE event term. For example:

Orthostatic hypotension ⇒fainting and fall to floor ⇒head trauma ⇒neck pain

The primary event is orthostatic hypotension and the sequelae are head trauma and neck pain.

If a participant is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be recorded as the event. For example, if a participant is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass.

14.6 Adverse Event Intensity/Severity

All AEs should be graded on a three-point scale (mild, moderate, severe) for intensity/severity. Unless otherwise defined in the protocol, these definitions are as follows:

Mild: Transient; no medical intervention/therapy required and does not interfere with daily activities.

Moderate: Low level of concern and only mild to moderate limitation in daily activities; some assistance may be needed; minimal or no medical intervention/therapy required.

Severe: Severe limitation in daily activities, significant assistance required; significant medical intervention/therapy required.

There is a distinction between the severity and the seriousness of an AE. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a serious adverse event

(SAE). For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for SAEs listed in the section Serious Adverse Events, above.

14.7 Treatment or Action Taken

The intervention taken to treat an AE is defined as:

- None
- Medical intervention
- Surgical intervention
- Other (specify).

14.8 Adverse Event Outcome

The clinical outcome of an AE will be characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Ongoing (i.e. continuing at time of study discontinuation)
- Death.

14.9 Adverse Event Follow up

All AEs and SAEs will be followed through to resolution or 30 days after the participant terminates from the study, whichever occurs first.

The Sponsor or its designee may follow-up with the site by telephone, fax, email, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

14.10 Reporting Adverse Events

Two kinds of events must be reported to the Chief Investigator/Trial Manager within 24 hours of learning of their occurrence.

a. Serious adverse events
b. Important Medical Event (IME)

Please complete the paper SAE Form and mark as an IME or SAE and submit.

IMEs which require reporting via the SAE form

- Retinopathy or signs of retinopathy
- Cataracts requiring surgery
- Microvascular abnormalities in the study eye
- Diabetes

Immediately after the trial personnel become aware of any of these two types of events, the Principal Investigator with responsibility at each research site must report them to the Chief Investigator or the organizing research team on the form specified. The Principal Investigator or his/her research team must also follow all through to outcome, and report to the Chief Investigator, or to the organizing research team on the form specified.

In addition, the Investigator should expeditiously notify the Chief Investigator of any of these two kinds of adverse events that occurs after a participant has completed or discontinued from study participation.

Contact details for submission to:
Chief Investigator (Tim Jackson) or Trial Manager (Riti Desai)

The initial report can be made by completing the SAE form, emailing or faxing to:

King's Clinical Trials Unit (KCTU)
Email: ctu@kcl.ac.uk
Fax: 0207 848 5229

A record of this notification (including the date of notification) must be clearly documented to provide an audit trail. In the case of incomplete information at the time of initial reporting, a follow up report should be provided as soon as the information becomes available.

14.11 Reporting Device Malfunctions

The IRay device that delivers SRT is CE marked. All device malfunctions must be reported to the device manufacturer, Carl Zeiss Meditec AG with a copy to the Chief Investigator. When a device malfunction is associated with an AE or SAE, the AE or SAE should be reported separately to the Sponsor, as noted in the section above.

The address for reporting a device malfunction is given below, but to expedite reporting the device manufacturer should be contacted by email or telephone, as detailed below:

14.12 Reports to Research Ethics Committees (RECs)

The Chief Investigator will report to the relevant Research Ethics Committee (REC).

Reporting timelines are as follows:

- SAEs which are fatal or life-threatening must be reported not later than 7 days after the Sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SAEs that are not fatal or life-threatening must be reported within 15 days of the Sponsor first becoming aware of the reaction.

The Chief Investigator will provide an annual report of all SAEs which will be distributed to the Data Monitoring and Ethics Committee (DMEC) or the REC, as appropriate.

14.13 Preferred Terminology

The following list details the preferred terminology for a range of potential ocular adverse events. The list also includes some non-ocular events that may be relevant to the trial population, and adverse reactions reported in clinical trials of ranibizumab. The list is not intended to be exhaustive but, where possible, these terms should be used to describe adverse events. If an event does not fit one of the following diagnoses it should nonetheless be recorded. The expected AEs are given in the next section. Where possible it is better to record a diagnosis rather than a symptom.

Age-related macular degeneration, dry; Age-related macular degeneration, neovascular (wet); Anaphylaxis; Anaemia; Angina; Anisocoria; Anterior chamber flare; Anterior uveitis; Anxiety; Aphakia; Arcus senilis; Arthralgia; Astigmatism; Atrial fibrillation.

Bacterial keratitis; Blepharitis; Blepharospasm; Blurred vision (specify diagnosis if possible); Branch retinal artery occlusion; Branch retinal vein occlusion (BRVO); Bronchitis.

Capillary dilation (see also retinal telangiectasia)*, Capillary closure (see also Retinal Ischaemia)*; Cardiac arrest; Cataract; Cellulitis; Central retinal artery occlusion; Central retinal

vein occlusion (CRVO) ; Central serous retinopathy (CSR); Chalazion; Chemosis; Choroidal effusion; Choroidal folds; Choroidal ischaemia; Choroidal naevus; Choroidal neovascularization (CNV); Chronic obstructive pulmonary disease; Conjunctival abrasion; Conjunctival bleb; Conjunctival haemorrhage (see also sub-conjunctival haemorrhage); Conjunctival hyperaemia; Conjunctivitis, allergic; Conjunctivitis, bacterial; Conjunctivitis, other; Conjunctivitis, viral; Contact lens intolerance; Corneal abrasion; Corneal infection (see also bacterial keratitis); Corneal oedema; Corneal opacity; Corneal staining; Cotton wool spots*; Cough (specify diagnosis if possible).

Deep vein thrombosis, Diabetic maculopathy; Diabetic retinopathy; Diabetes (specify type); Diplopia, monocular; Diplopia, binocular; Disciform scarring of macula; Drusen; Dry eye syndrome (please classify as described in Appendix 7); Dyspnoea.

Ectropion; Endophthalmitis, culture negative; Endophthalmitis, culture positive; Endophthalmitis, suspected (no culture obtained); Entropion; Epiphora; Epiretinal membrane (ERM); Episcleritis; Esophoria; Esotropia; Eye drop hypersensitivity; Eye irritation; Eye pain; Eye pruritus; Eyelid bruising; Eyelid cyst; Eyelid swelling; Eyelid pain; Exophoria; Exotropia

Facial pain; Flare (see anterior chamber flare); Foreign body sensation, of eye.

Gastroenteritis; Gastrointestinal haemorrhage (specify site); Gastrointestinal perforation (specify site); Geographic atrophy; Glaucoma, angle closure; Glaucoma, open angle; Glaucoma, other.

Haemorrhage of eye, unspecified (see also choroidal haemorrhage, conjunctival haemorrhage, subconjunctival haemorrhage, optic disc haemorrhage, retinal haemorrhage, subretinal haemorrhage, and retrobulbar haemorrhage); Headache; Hyperaemia of eye (specify diagnosis if possible); Hypercholestrolaemia; Hypermetropia; Hypertension; Hypertensive retinopathy; Hypotony (IOP <5mmHg).

Idiopathic polypoidal choroidal vasculopathy (IPCV); Increased intraocular pressure (>30 mmHg or >10 from screening); Influenza; Insomnia; Intraretinal microvascular abnormality (IRMA); Iris atrophy; Iris ischaemia; Iridocyclitis; Iritis (refer to anterior uveitis, posterior uveitis, uveitis, iridocyclitis, pars planitis, or vitritis).

Keratitis (see also punctuate keratitis); Keratopathy; Keratoconjunctivitis.

Lacrimation, increased; Lattice degeneration of the retina; Limb pain.

Macular atrophy; Macular depigmentation; Macular fibrosis (see also disciform scar of macula, and macular scarring); Macular hole, full thickness; Macular hole, partial thickness; Macular oedema, Macular pucker; Macular scarring (see also macular fibrosis and disciform scar of macula); Metamorphopsia; Microvascular abnormality of retina (see retinal microvascular abnormality); Myocardial infarction (MI); Myopia.

Nausea; nystagmus.

Ocular hypertension; Optic disc atrophy; Optic disc cupping; Optic disc haemorrhage; Optic disc neovascularization*; Optic disc palor; Optic disc swelling; Optic neuritis; Optic neuropathy, other; Optic neuropathy, radiation induced.

Pars planitis**;** perforation of globe; Perivascular sheathing*; Photopsia; Pigment epithelial detachment (PED); Posterior capsular opacification (PCO); Posterior uveitis; Posterior vitreous detachment (PVD); Ptosis; Pulmonary embolus; Punctate keratitis; Pupillary deformity. **R**adiation retinopathy*; Relative afferent papillary defect (RAPD); Retinal angiomatous proliferation (RAP); Retinal atrophic hole; Retinal degeneration; Retinal detachment, rhegmatogenous; Retinal detachment, serous; Retinal detachment, tractional; Retinal exudates; Retinal haemorrhage; Retinal ischaemia*; Retinal macroaneurysm; Retinal microaneurysm*; Retinal microvascular change*; Retinal neovascularization (not associated with neovascular age-related macular degeneration); Retinal oedema; Retinal tear; Retinal telangiectasia*; Retinal vascular tortuosity*; Retinopathy* (see also diabetic retinopathy, hypertensive retinopathy, radiation retinopathy, and sickle retinopathy); Retrobulbar haemorrhage; RPE atrophy; RPE depigmentation; RPE hyperpigmentation; RPE tear.

Scleritis; Scotoma; Sickle retinopathy; Sinusitis; Stroke; Subconjunctival haemorrhage (see also conjunctival haemorrhage); Subretinal (or submacular) haemorrhage; Subretinal (or submacular) fibrosis.

Telangiectasia (see retinal telangiectasia)*; Transient ischaemic attack (TIA).

Upper respiratory tract infection; Urinary tract infection; Uveitis (see also anterior uveitis, posterior uveitis, iridocyclitis, pars planitis, or vitritis).

Venous Thrombosis (specify site); Visual field defect; Vitreomacular traction (VMT); Vitreous haemorrhage; Vitreous opacity; Vitritis.

Wound healing complications (delayed or non healing wounds)

*these changes may be associated with radiation retinopathy – see section below.

14.14 Expectedness

All AEs will be evaluated as to whether they are expected or unexpected.

- **Expected (anticipated):** An AE is expected if it is identified in the list of expected adverse events below, or in the latest ranibizumab Summary of Product Characteristics, or the latest User Manual of the IRay SRT device, or the Patient Information Sheet.
- **Unexpected (unanticipated):** An adverse event is unexpected if it is not identified in the list of adverse events below or in the latest ranibizumab Summary of Product

Characteristics, or the latest User Manual of the IRay SRT device, or the Patient Information Sheet.

Expected (Anticipated) AE:

- **Dry Eye Syndrome (DES):** A worsening of 2 grades or a finding of Grade 4 (marked) or Grade 5 (severe) on the Oxford Grading Scheme (see Appendix 7) will be considered an AE.
- **Keratitis:** Inflammation of the cornea and/or conjunctiva due to infectious or other etiologies (e.g. autoimmune). A worsening of 2 grades or a finding of Grade 4 (marked) or Grade 5 (severe) on the Oxford Grading Scheme will be considered an adverse event).
- **Keratopathy:** (Also known as superficial punctate, or epithelial, keratopathy): Spots or lesions on the epithelium which may be caused by drying of the cornea or by trauma. A worsening of 2 grades or a finding of Grade 4 (marked) or Grade 5 (severe) on the Oxford Grading Scheme will be considered an AE.
- **Anterior uveitis:** Presence of inflammatory cells in the anterior chamber. The presence of aqueous flare alone is not considered to constitute iritis and should be documented as anterior chamber flare.
- **Iridocyclitis:** Presence of inflammatory cells in both the aqueous and vitreous.
- **Posterior Uveitis**: Inflammation in the uveal tract (iris, ciliary body, and choroid), either primary or secondary to keratitis or systemic diseases.
- **Vitritis:** Presence of active inflammation in the vitreous, as demonstrated by the presence of inflammatory cells (trace or greater). Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, haemorrhage, or other causes.
- **Endophthalmitis:** Diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause (trace benign, aqueous pigmented cells visible by slit lamp that are caused by dilation and are not red or white blood cells or the result of any ocular disorder should not be recorded as an AE). Endophthalmitis should be classified as culture positive, culture negative, or suspected (no culture obtained).
- **Cataract:** Lens changes consisting of an increase (worsening) >2 categories from baseline (using the AREDS Lens Grading Protocol) in nuclear opalescence, cortical cataract, or posterior subcapsular evaluation observed at two consecutive visits.
- **Vitreous Haze:** Vitreous haze that obscures or partially obscures the view of the fundus.
- **Vitreous Haemorrhage:** Haemorrhage within the vitreous cavity.
- **Increased IOP**: IOP ≥30 mmHg or an increase in IOP of ≥10 mm from baseline recorded on two separate occasions or an increase in IOP that requires intervention.

- **Significant Decrease in Visual Acuity:** >30 ETDRS letters (compared with the last assessment of visual acuity, or from baseline).
- **Rhegmatogenous retinal detachment:** Macular on or macular off detachment of the neurosensory retina.
- **Retinal haemorrhage:** Subhyaloid, intraretinal, or subretinal haemorrhage. See also the section of retinopathy below.
- **Cystoid macular oedema:** Cystoid, intraretinal fluid within the macular area visible by examination, angiography, or OCT.
- **Macular fibrosis:** Fibrosis of the macula, including disciform scarring and macular scarring.
- **Macular atrophy:** Atrophy of the macular neurosensory retina, macular retinal pigment epithelium, or both.
- **IGuide™ & Eyelid Retractor-associated Adverse Events:**
  - Sensitivity or allergic reaction to the coupling gel
  - Corneal abrasion
  - Conjunctival haemorrhage
  - Conjunctival abrasion
  - Eye irritation (including foreign body sensation)
  - Eyelid bruising
  - Eyelid pain.
- **Retinopathy (also called microvascular abnormalities, MVAs):** Occlusive microangiopathy secondary to endothelial cell loss and capillary closure. Any cases of retinopathy, regardless of the suspected cause, and regardless of seriousness, must be recorded as an AE and reported to the Chief Investigator. Investigators are not required to determine whether or not **radiation retinopathy** is present, but they must report any cases of retinopathy or signs of **retinopathy**, to the Chief Investigator and for review by an expert panel. The following clinical features of **retinopathy** may occur secondary to a range of disorders or to radiation. Each should be treated as a sign of retinopathy if it occurs in the study eye.
  - **Retinal microaneurysms**
  - **Telangiectasia**
  - **Retinal haemorrhage (except that attributed to the AMD lesion itself)**
  - **Cotton-wool spots (nerve fiber layer infarcts)**
  - **Capillary dilation**
  - **Capillary closure (non-perfusion)**
  - **Perivascular sheathing**
  - **Retinal neovascularization**

- **Optic disc neovascularization.**

If **retinopathy,** or a sign of **retinopathy**, is observed by a study Investigator, the Investigator should obtain fundus photographs and perform fluorescein angiography and OCT. The Investigator should inform the Chief Investigator and then send the photographs, FA, and OCT to the central Reading Centre(s) for evaluation.

14.15 Relatedness

Serious adverse events should be assessed in terms of the causality or relatedness to the following events:

- Ranibizumab drug
- Ranibizumab injection procedure
- Stereotactic radiotherapy

This relationship should be classified as follows:

- Not related
- Remote
- Possible
- Probable
- Definite

14.16 Retinopathy Evaluation

As noted in the preceding section, an Investigator who detects retinopathy or signs of retinopathy will forward fundus photographs, angiography, and OCT scans to the Reading Centre(s). If the Reading Centre confirms retinopathy, or detects a case of retinopathy during routine image review, it will forward the fundus photographs, angiography, and OCT for that case to a **Retinopathy Evaluation Committee**. The Retinopathy Evaluation Committee will consist of experts in reading FAs, and experts in the clinical characteristics of radiation retinopathy. The Chief Investigator will forward the Retinopathy Evaluation Committee the full CRF, including baseline and on-study medical history. The Retinopathy Evaluation Committee may request other information and, if it is available, it will be provided to them. The Retinopathy Evaluation Committee will decide by majority vote whether or not radiation retinopathy is present. The committee will be the final arbiter as to whether or not radiation retinopathy is present, but it may review its decision if new, relevant, clinical information emerges for a particular case.

14.17 Keratopathy, Keratitis and Dry Eye

Radiation may cause keratopathy, keratitis and dry eye, although the IRay system is designed to minimize this risk by using three separate beams. If any of these conditions occur the Oxford Grading System, as given in Appendix 7, should be used to grade the severity of disease. If keratopathy, keratitis or dry eye occur they should be recorded as an AEs in the eCRF.

15. STUDY DISCONTINUATION

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

1. The incidence or severity of adverse events in this or other studies indicates an unacceptable potential health hazard to participants.
2. Patient enrollment is unsatisfactory.
3. Data recording is inaccurate or incomplete.
4. The Trial Steering Committee recommends that the trial should be discontinued.

16. STATISTICAL PLAN

16.1 Efficacy Outcomes and Hypotheses

The study's primary hypothesis is that the mean number of ranibizumab injections during the first 24 months after randomization will be less in the SRT group than in the sham group. The secondary hypothesis is that participants who undergo SRT will have a non-inferior visual outcome compared with those in the sham group.

16.1.1 Primary Outcome

The primary outcome is the number of as required (*prn*) ranibizumab injections during the first 24 months after randomization. SRT will be considered superior to sham if the mean number of injections in the SRT group is statistically less than the mean in the sham group.

16.1.2 Secondary Outcome

SRT will be considered non-inferior to sham treatment if the lower bound of the 95% confidence interval for the difference in mean change in ETDRS VA at 24 months, between the SRT and sham groups, is no greater than 5 letters.

16.1.3 Other secondary outcomes (at 24 months)

- Percentage of participants losing < 15 ETDRS letters
- Percentage of participants gaining ≥ 0 ETDRS letters
- Percentage of participants gaining ≥ 15 ETDRS letters

- Total lesion size by fluorescein angiography
- Total CNV size by fluorescein angiography
- Foveal thickness measured using OCT
- Health-related quality of life assessed using the National Eye Institute 25-Item Visual Function Questionnaire and the EuroQol EQ-5D™ questionnaire
- Cost per Quality Adjusted Life Year (QALY)

16.2 Safety Measures

Safety will be evaluated by assessing adverse events (AEs) and serious adverse events (SAEs). The trial will specifically report the incidence of radiation retinopathy or radiation-related microvascular changes, and arteriothrombotic events.

16.3 Sample Size Justification

16.3.1 Summary

If SRT produces a 25% reduction, group sample sizes of 248 and 124 (ratio: 2:1) achieve 90% power to detect a difference of 2.5 injections between the null hypothesis that both group means are 10 injections and the alternative hypothesis that the mean of the active treatment group is 7.5 injections, with a standard deviation (SD) of 7 for both, and a significance level (alpha) of 0.05 (two-sided) using a two-sample t-test. A 2:1 ratio adds only 42 patients but boosts recruitment and safety data.

We expect VA in the SRT group to be non-inferior compared to the control group. The SD of the mean change in VA was estimated as 12 letters from INTREPID. Group sample sizes of 248 and 124 achieve 97% power to detect non-inferiority in the mean changes in VA using a one-sided, two-sample t-test assuming a SD of 12 for both groups. The margin of equivalence is 5 letters. The true difference between the means is assumed to be 0. The significance level (alpha) of the test is 0.025.

In the INTREPID study, 2.2% of the randomized population were lost to follow up by year 1. Year 2 data are not representative as INTREPID had minimal review in year 2. The CABERNET study had 93% of data available for analysis at the end of year 2. We anticipate a 10% loss to follow-up over two years for STAR, so we aim to recruit 274 participants in the active arm and 137 in the control arm (total 411). Sample size calculations were performed using PASS software.

16.3.2 Justification for parameters used in the sample size calculations.

The INTREPID study (ClinicalTrial.gov identifier: NCT01016873) compared patients treated with low-voltage x-ray, external-beam, SRT plus ranibizumab *prn* to patients treated with sham SRT plus ranibizumab *prn*. Since INTREPID studied anti-VEGF-experienced patients the results of that study are more relevant to the STAR population than the results of CATT, which studied

anti-VEGF-naïve participants. Participants in INTREPID were randomized to 16 Gy plus ranibizumab *prn*, 24 Gy plus ranibizumab *prn*, or sham radiotherapy (either 16 Gy or 24 Gy) plus ranibizumab *prn*. The mean changes in ETDRS VA at 12 months (±SD) were 0.28 ± 8.77, 0.40 ± 10.33, and 1.57 ± 11.90, respectively. The pooled SD across all groups is therefore 10.4, with approximate 95% confidence limits of 9.6 and 11.5. For power calculations for STAR, the assumed SD of the mean change in VA is 12 letters.

The treatment arm of the present study (STAR) will receive 16 Gy SRT, as used in the INTREPID study. Both arms will receive ranibizumab *prn*, as used in the CATT trial. The primary outcome is the ranibizumab re-injection rate over 2 years. CATT reported a mean (±SD) of 6.9 ± 3.0 ranibizumab retreatments to the end of year 1 and 12.6 ± 6.6 to the end of year 2. The year 2 retreatment rate is most relevant to the STAR control group, which recruits patients with previously treated disease (CATT participants were treatment-naive at enrolment). The year 2 CATT retreatment was calculated to be 5.7 injections (12.6 – 6.9), so we might expect our control group to receive twice this (11.4) over two years. As CATT was undertaken in the US, to allow more conservative assumptions in case the injection rate is lower in the UK, we assume the injection rate to be 10 injections over 2 years in our control group, with a SD of 7 (based on INTREPID data which showed the SD was 69% of the mean). A 25% reduction in the number of injections is thought to be clinically and economically meaningful. Notwithstanding the fact that the second year of INTREPID was primarily designed to assess safety and not efficacy, this figure also matches the 25% reduction in the injection rate in the 2 year results of INTREPID, comparing the combined radiotherapy arms to the sham arm (Jackson et al, 2015).

16.4 Randomization

Once baseline assessments are complete, participants will be randomized to SRT and sham in a 2:1 ratio. Randomization is at the patient level and is performed using an online randomization system set up by the King's Clinical Trials Unit (KCTU) at King's College London, available at:

https://cturandomisation.iop.kcl.ac.uk/ProjectIndex/Default.aspx.

Randomization is stratified by national treatment centre with variable block sizes to ensure that patients are allocated to the two arms within each treatment centre in a 2:1 ratio.

16.5 Analysis Population

The primary analysis population for efficacy will be the Intent-to-Treat population, consisting of all randomized patients. All efficacy analyses will be performed by randomized group assignment. The primary and secondary outcome will be at Month 24.

The analysis population for safety will consist of all participants treated. All safety analyses will be performed by actual treatment received.

16.6 Statistical Methodology

The primary analysis of this trial will occur after all data from the first 24 months are available. At this time, the data from the first 24 months will be locked and the Sponsor will be unmasked. This section briefly describes the methods to be used to analyze the data. A Statistical Analysis Plan (SAP), to be written prior to unmasking the data, will describe the statistical analysis of the primary and secondary outcomes in detail. Should the methods in the SAP differ from the description in this protocol, the methods in the SAP shall prevail.

16.6.1Efficacy

16.6.1.1Analysis of primary outcome

The principal analyses of primary outcome will be performed according to an "intent-to-treat" principle. All randomized patients in these analyses will be classified according to their assigned treatment at randomization, regardless of the patient's adherence. The primary analysis is to test the mean difference in number of ranibizumab retreatments up to and including Month 24 between the SRT and sham group (ranibizumab monotherapy). Previous research (CATT and INTREPID) has suggested that the number of injections is approximately normally distributed. In this case, a multiple linear regression analysis will be used to assess the treatment effect with adjustment for the baseline stratification factor – National Treatment Centre. The analysis will not include the initial mandated ranibizumab treatment as it is administered to all participants, and does not reflect the effect of SRT or sham treatment. The treatment effect is evaluated at the two-sided 0.05 significance level.

16.6.1.2Analysis of secondary outcomes

The change in visual acuity (VA) will be formally tested statistically for non-inferiority. The change in VA in the SRT arm compared to the change in VA in the control arm from baseline to Month 24 will be analysed by using a multiple linear regression model with adjustment for the baseline stratification factor (treatment centre) and the baseline VA score. Multiple linear regression will be used rather than repeated measure analysis because although there will be 24 monthly visits for patients in the trial, the focus of interest is the mean changes in VA from baseline to Month 24.

Data from the other secondary outcomes (listed in Section 15.1.3) will be summarized. Statistical analysis of these outcomes will be descriptive, with differences and 95% confidence intervals where possible. There will be no correction for multiple testing. Mean vision change and mean OCT thickness will be plotted against time (24 monthly visits over two years) as summary measures showing vision change over time and OCT thickness over time.

16.6.2Safety

Safety will be evaluated by assessing the incidence of adverse events (AEs), the incidence of serious adverse events (SAEs).

The trial will specifically report the incidence of radiation retinopathy/microvascular abnormalities, and arteriothrombotic events.

AEs, SAEs, and other findings will be summarized by presenting the percentages of participants with each event for each treatment group. When relevant, the time course of AEs will be presented.

16.7 Interim analysis

The usual rationale for an interim analysis is to consider stopping the treatment (or the trial) however as this treatment is given at baseline, it is not possible to subsequently stop treatment. As such we elected not to include an interim analysis. The DMC will examine the recruitment rate, data completeness and monitor safety, and will recommend whether the study should continue, stop, be suspended, or be modified, based on their findings.

17. RECORDKEEPING

The investigator must maintain the following accurate, current, and complete records relating to his/her participation in the study:

- All correspondence with another investigator, REC, Sponsor, monitor, including required reports
- Records of each participant's source documents and exposure to the device, including signed and dated consent forms and medical records, progress notes, hospital or clinical charts and nurses' notes
- All relevant observations, including records concerning adverse device or drug effects, information and data on the condition of the participant upon entering and during the course of the study, including information about relevant previous medical history and the results of all diagnostic tests
- The protocol, with documents showing the dates of and reasons for each deviation from the protocol
- Source documents
- Fundus fluorescein and ICG angiography and OCT images

All study records should be maintained in a locked, limited-access area.

The Investigator will act as custodian for the trial data at each site. The following guidelines will be strictly adhered to:

- Patient data will be anonymised
- All anonymised data will be stored on a password protected computer
- All trial data will be stored and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006.

The local Principal Investigator shall maintain all study records until notified by the Chief Investigator that retention is no longer required. If the Investigator moves from the site at which he/she conducted the study and/or maintained the study records, the Investigator shall notify the

Chief Investigator in writing whether the records will remain at the site at which the study was conducted or be moved to another location, and if another location, where and under whose custody. The Investigator shall notify the Sponsor as soon as possible in the event of destruction or loss of any study records

18. STUDY MONITORING REQUIREMENTS

The Sponsor, or its designees, will monitor the trial in a manner consistent with the regulatory requirements and Good Clinical Practice (GCP). Study monitoring involves the following elements:

- The Sponsor's personnel may meet with investigators prior to the initiation of the study in order to review the adequacy of the patient population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator with the study protocol.

- The Sponsor's personnel may meet with the investigators at the time enrollment is initiated in order to ensure that patients are being properly selected, that the methods described in the study protocol are thoroughly understood by the investigator, that study data are being correctly recorded, and that the protocol is being correctly implemented.

- The Sponsor's personnel, or designee, may visit the clinical site at any time during the course of the study to review source documents, study data, clinical data, and all other documents, and to interview study personnel.

- Telephone consultations between the Sponsor's personnel and site staff will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.

19. PROTOCOL DEVIATIONS AND AMENDMENTS

Investigators should make every attempt to not deviate from the protocol. Deviations can ultimately affect the scientific soundness of the protocol, as well as the rights, safety and welfare of the participants. An Investigator who feels that a deviation from the protocol is necessary must submit a request to the Chief Investigator or Trial Manager by email. A form will be supplied to document all protocol deviations and these will be summarized in the final study report. Prior approval of a protocol deviation is not required for clinically urgent actions that are undertaken to protect participants, if the delay needed for prior approval would increase the risk to the participant. A protocol deviation form must be sent to the Chief Investigator for all deviations that occur.

The Sponsor will make all changes to the protocol as an amendment to the protocol and approved by the REC prior to implementation.

20. PARTICIPANT IDENTIFICATION NUMBER

Once a participant has provided informed consent, including signing the informed consent form, a Participant Identification (ID) Number will be assigned. The first two digits of the ID number will be the site number followed by a three-digit number in sequential order (i.e. 01001, 01002, etc.). This ID number will be retained throughout the study.

The ID number and participant initials are to be recorded on all study documents and will link the study treatment and the study documents to the participant's name and medical record. To maintain confidentiality, the participant's name should not be recorded on any study document other than the informed consent form and the Participant ID log. Participants who withdraw from the study will not be replaced.

21. ETHICAL AND REGULATORY PRECEPTS

21.1 Principal Investigator's Responsibility

The Principal Investigators (PI) at each site must comply with the signed Sponsor-Site Agreement. The PI must have and maintain current good clinical practice (GCP) training, and ensure that all trial staff do likewise. He or she may delegate tasks to appropriately trained staff, but he or she maintains responsibility for their conduct. The PI shall ensure that there is a delegation log detailing all staff involved in the conduct of the trial at his or her site.

21.1.1Media and Public Relations

If the PI intends to advertise for participants, whether in a professional or consumer publication, radio, television or community notices, all advertising must receive prior approval of the Sponsor and the Chief Investigator. The PI must also involve his or her Communications team prior to issuing any press releases, or dealing with the media.

21.1.2 Authorization of Treatment Costs

The PI will ensure that local healthcare commissioning bodies, such as Clinical Commissioning Groups or equivalent, are informed of and agree to the trial treatment costs, or that the treatment costs are covered by existing commissioning arrangements. Note that there is no cost for SRT, which is provided free of charge, and most sites are anticipated to already have funding for ranibizumab treatment, consistent with NICE guidance. The PI will not pass on research costs to commissioning bodies, only agreed treatment costs.

21.2 Radiation Licensing/Certification

The following requirements apply only to sites that are acting as the national treatment centres providing SRT.

All SRT treatment centers will have attained the appropriate national and local licensing requirements to allow for the utilization of the IRay system at the participating institution. All SRT treatment sites will have obtained licenses to administer SRT, in accordance with the requirements of the Administration of Radioactive Substances Advisory Committee (ARSAC). Each SRT treatment site will provide proof of documentation of the licensure to the Sponsor prior to treating any participants in this study.

A Radiation Safety Officer (RSO) or Medical Physicist will be involved in the oversight of the radiation use at each SRT treatment site, and a named individual will be identified to the Sponsor.

A named clinical radiation expert, such as a Radiation Oncologist or Nuclear Medicine Consultant, will oversee the delivery of radiation treatment at each SRT treatment site. A named individual taking overall responsibility for the delivery of SRT will be identified to the Sponsor.

21.3 Regulatory Authority and Research Ethics Committee Approval

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

The Medicines and Healthcare products Regulatory Agency (MHRA) has reviewed the STAR protocol. They have determined that the trial is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) as defined by the EU Directive 2001/20/EC and that no submission to the Clinical Trials Unit at the MHRA is required.

The protocol and related documents will be submitted for review to a UK Research Ethics Committee (REC) prior to trial commencement. The details of the REC will be provided to participants and study sites by the Sponsor.

Annual progress and safety reports and a final report at the conclusion of the trial will be submitted to the REC within the timelines defined in the Regulations.

Prior to recruitment of any participants into the study at each participating site, Site Specific Approval (SSA) and NHS Research and Development approval must also be obtained.

Any changes to the protocol must be discussed and approved by Sponsor in writing unless the change is made to assure the safety of the participant.

Signed consent forms must remain in each participant's study file and must be available for verification by study monitors at any time.

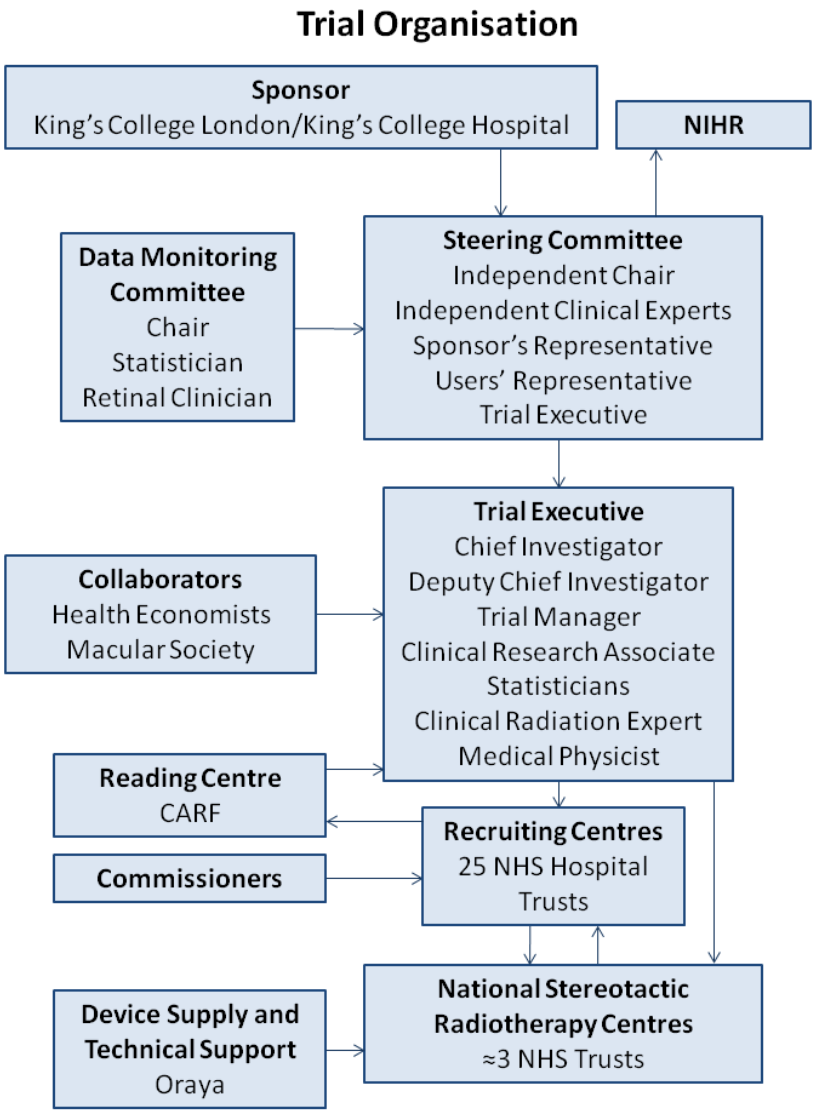
21.4 Indemnity and Insurance

Clinical Negligence Scheme for Trusts (CNST) provides indemnity that covers clinical negligence and harm caused.

22. MANAGEMENT AND ORGANIZATION

The chart on the next page shows the organizational structure of the STAR trial. In summary, a trial Executive will run the study, under the oversight of a Trial Steering Committee (TSC) that will meet approximately every six months. A Data Monitoring and Ethics Committee (DMEC) will have access to unmasked data, as needed, and will report to the TSC. King's College London (KCL) and King's College Hospital will co-sponsor the trial, and they will collectively take ultimate responsibility for the conduct of the trial.
The Sponsor will contract with recruiting sites to undertake the research through a Site-Sponsor agreement. Recruiting Centres will enrol participants and manage all their clinical care within the trial, with the exception a single treatment with SRT, which will be undertaken at national SRT treatment centres. The Sponsor will contract with the Central Angiographic Reading Centre (CARF) at Queen's University of Belfast to read the angiograms and OCTs, supplied to CARF by the Recruiting Centres. Recruiting Centres will have contracts with their usual healthcare commissioners, such as local Clinical Commissioning Groups (CCGs), to cover the treatment costs within the trial. The National Institute of Health Research funds the research costs through

its Efficacy and Mechanism Evaluation programme and representatives will be invited to attend TSC meetings.



22.1 Data Monitoring and Ethics Committee

The Data Monitoring and Ethics Committee (DMEC) will have access to unblinded data to monitor safety and will make recommendations to the Trial Steering Committee. The DMEC will adhere to the terms of the DMEC Charter shown in Appendix 5.

22.2 Trial Steering Committee

The Trial Steering Committee (TSC) will provide general oversight of the trial. The Terms of Reference are provided in Appendix 6.

23. INFORMED CONSENT

The Investigator is responsible for obtaining the legally effective informed consent of the participant. In carrying out this responsibility, the investigator (and other involved team members) should recognise that informed consent is not just a signature on an informed consent form, but a process during which the participant and those with whom the participant wishes to consult (such as family members, friends, and personal physicians) are provided with sufficient information about the study under circumstances that allow the participant to consider whether or not to participate and to minimize the possibility of undue influence or coercion.

Once the REC has approved the Patients Information Sheet and Informed Consent Form, the form should be used as the basis of the information presented to the participant during the informed consent process. The form should be provided to the participant early in the process, so that he/she has ample time to read it and discuss it with others if he or she wishes to do so.

Each of the following key elements must be discussed with the participant:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the participant's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the participant.
- A description of any benefits to the participant or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant.
- A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained and that notes the possibility that regulatory authorities and external monitors may inspect the records.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research participants' rights, and whom to contact in the event of a research-related injury to the participant.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

- A statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or foetus, if the participant is or may become pregnant) which are currently unforeseeable.
- Anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent.
- Any additional costs to the participant that may result from participation in the research.
- The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.

Once the informed consent process is complete and the participant has reached a decision as to whether to participate, the investigator should record the decision in the case history form. A participant who decides to participate should be asked to sign the Informed Consent Form. A copy of the signed form should be given to the participant, and the signed form should be included with the participant's study records.

If there is any new information which may affect a participant's willingness to continue participating in the trial, he or she will be re-consented with an amended or supplementary Patient Information Sheet and Consent Form.

24. DATA MANAGEMENT AND DATA PROTECTION

All study data will be initially entered onto paper source documents and then transferred into the online eCRF. All requested information must be entered on the eCRF. If an item is not available or not applicable this fact should be indicated. Data management must comply with the Data Protection Act 1998. The data management team and study monitors may raise queries using the electronic system, and the study site Investigator must provide a response in a timely manner.

To ensure the quality of clinical data across all participants and sites, data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol. To resolve any questions arising from the clinical data, data queries and/or site notifications will be created in the database for resolution.

The IRay device logs a number of parameters that are used to assess system performance, such as X-ray output, motion metrics, alignment assessments, high voltage power supply stability, and I-Guide motion. These data are stored in log-files ("runtime logs") that contain no patient-identifying information. As such, self-test logs and runtime logs can be extracted without revealing patient data. The device manufacturer will be given permission to extract these log-files to monitor and improve device functionality, subject to approval from the Caldicott guardian at the Sponsor's site.

25. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

The Investigator(s) shall permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (e.g., patients' case sheets, ocular images). Where necessary, inspection may also take place at a site's facilities.

26. PUBLICATION POLICY, INTELLECTUAL PROPERTY AND FINANCES

It is intended that the results from this study be published in high quality, peer-reviewed, medical journals. The main paper will report the safety and efficacy outcomes at the 24 month endpoint, with supplementary reports covering the month 36 and month 48 safety outcomes. The named authors will comprise researchers who have made a significant contribution to study design, clinical or statistical analysis, and manuscript preparation. These authors will present data on behalf of the STAR study group which will include, amongst others, Principal Investigators who have made a substantial contribution to the trial, such as high levels of recruitment. The format for acknowledging the STAR study group will depend on the target journal. Principal Investigators or other researchers may approach or be invited by the Chief Investigator to prepare and submit other manuscripts in their own right, or on behalf of the STAR study group. The authorship lists will be determined by the Chief Investigator. The Trial Steering Committee and Data Monitoring and Ethics Committee will be invited to review and approve the key outcome papers.

Researchers involved in this study will submit all data for pooled analysis by the Chief Investigator. Researchers will not present, publish or disseminate any study data, including case reports and case series, without the prior permission of the Chief Investigator.

This investigator-initiated trial is co-sponsored King's College London (KCL) and King's College Hospital, who own any intellectual property arising from the trial. The device manufacturer (Oraya Therapeutic, Inc, Newark, USA) provided material that was used in the INTREPID study protocol that was then adapted for use in the STAR protocol. Oraya also provided peer review of the protocol using a panel of external experts, but the STAR Chief Investigator retained final editorial control. The protocol was also modified in response to the peer review process that formed part of the application to the National Institute for Health Research (NIHR) for trial funding.

Zeiss will provide free SRT device use for the duration of the trial, and technical and training staff to support SRT at the National Treatment Centres. Zeiss will not have ownership of any of the clinical data obtained in this study, and will not be represented on the Trial Steering Committee. Zeiss will be invited to critique key publications prior to submission, but the Sponsor will retain exclusive editorial control. Zeiss will not have access to trial data during the trial.

Research costs will be covered by a grant from the NIHR via the Efficacy and Mechanism Evaluation (EME) programme. The Sponsor will make a site payment to Recruiting Centres for each participant that they recruit, to cover local research costs. Treatment costs will be funded by local healthcare commissioning groups. The Principal Investigators at each site must ensure that

their healthcare commissioners have agreed to fund participants' treatment costs for the 48 month trial duration, prior to site initiation. The STAR trial is part of the UK Clinical Research Network Study Portfolio and so Recruiting Centres will be eligible to apply for service support from their Comprehensive Local Research Network (CLRN).

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28. APPENDIX 1: SCHEDULE OF ASSESSMENTS

Assessment	Screening	SRT with baseline ranibizumab†	Monthly review* (Month 1-11)	Month 12	Monthly review* (Month 13-23)	Month 24	Month 36	Month 48
Visit Window: *Day 0 = Day of successful enrolment*	Day -14 to 0	Day 0 to 21	±7 days	±7 days	±7 days	±7 days	±14 days	±14 days
Informed Consent	X							
Demographics	X							
Ophthalmic History	X							
Med History/Con Meds	X							
Blood Pressure	X							
EDTRS Visual Acuity†	X		X	X	X	X	X	X
Intraocular Pressure	X			X		X	X	X
Cataract Assessment	X			X		X	X	X
Biometry§	X							
OCT (sent to reading centre)	X			X		X	X	X
OCT (*not* sent to reading centre)	X		X		X			
Fundus Photographs (sent to reading centre)	X			X		X	X	X
Fluorescein Angiography (sent to reading centre)	X			X		X	X	X
Indocyanine Green Angiography** (sent to reading centre)	X							
Stereotactic Radiotherapy with mandated baseline Ranibizumab‡		X						
Ranibizumab injection if required (*prn*)			X	X	X	X	X	X
Health Economics questionnaires			X	X	X	X	X	X
EQ-5D and VFQ-25 patient questionnaires	X			X		X	X	X
AEs/ConMed changes			X	X	X	X	X	X

* Monthly review entails review every 28 days rather than by calendar month. The first monthly review should be scheduled 28 ± 7 days after stereotactic radiotherapy/baseline ranibizumab. It is preferable to allow at least 23 days between visits as this is the minimum time between ranibizumab injections.
** Indocyanine green may be omitted in centres that do not have ICG capability, if pre-agreed by Sponsor.

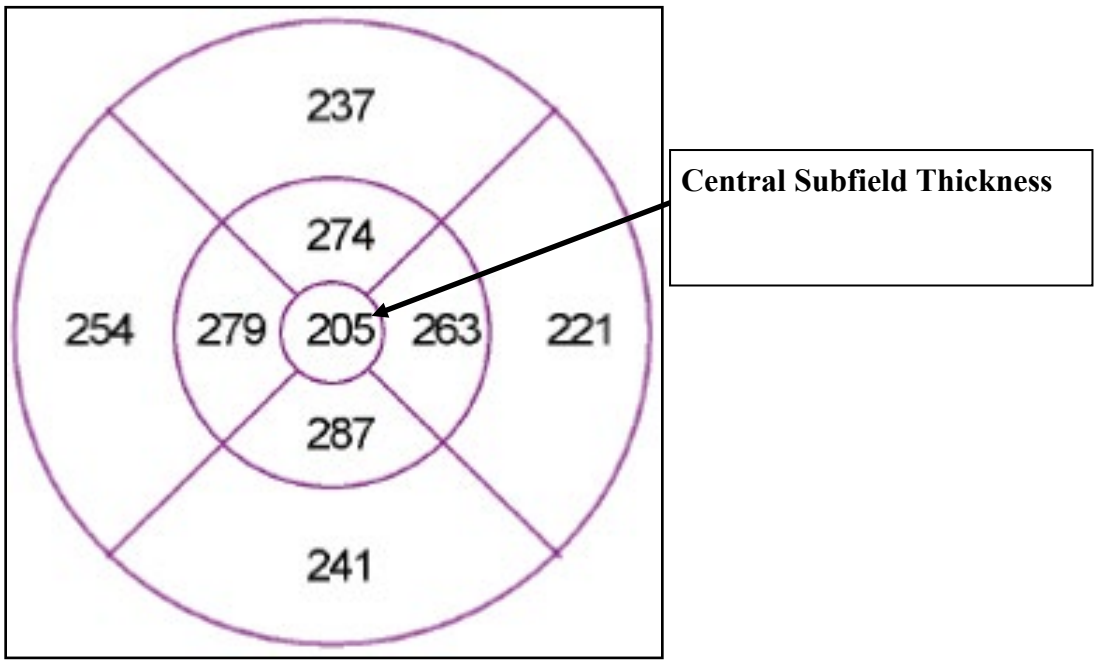
MRC Medical Research Council
NHS National Institute for Health Research
Efficacy and Mechanism Evaluation Programme

† Trial certified best-corrected visual acuity is required at each visit. Full refraction is undertaken at screening and then updated at months 3, 6, 9, 12, 15, 18, 21, 24, 36 and 48.
‡The baseline mandated ranibizumab injection should be given at the National Treatment Centres following stereotactic radiotherapy
§ Retrospective biometry can be used, if available.

29. APPENDIX 2: ASSESSMENT OF CENTRAL SUBFIELD THICKNESS AND MACULAR VOLUME

1. Central Subfield Thickness

On the OCT result page, the following ETDRS grid is displayed for all machines. The central subfield thickness measurement is the value at the centre of the circle (arrow). Before recording the central subfield thickness please make sure that the grid is centred at the fovea and the segmentations errors are corrected as described for each of the OCT machines (see below).



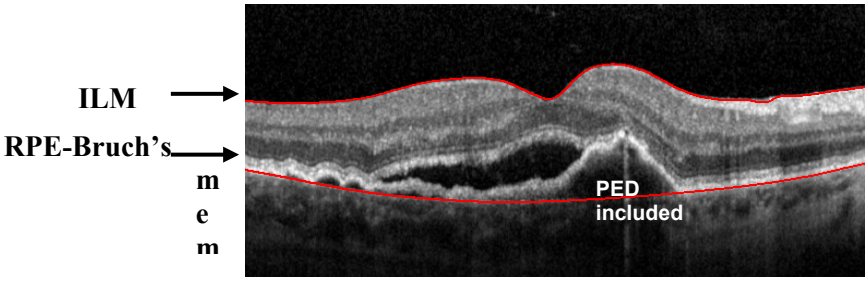
2. Macular Volume

In order to be eligible for inclusion on the STAR study, the macular volume for the study eye needs to be calculated during screening. This measurement, generated by the SD-OCT machines, must then be compared with the pre-defined threshold for each of the OCT machines. It is important to note that variation occurs between different machines, and therefore this check must be performed against the correct SD-OCT machine values (see below). Before recording the

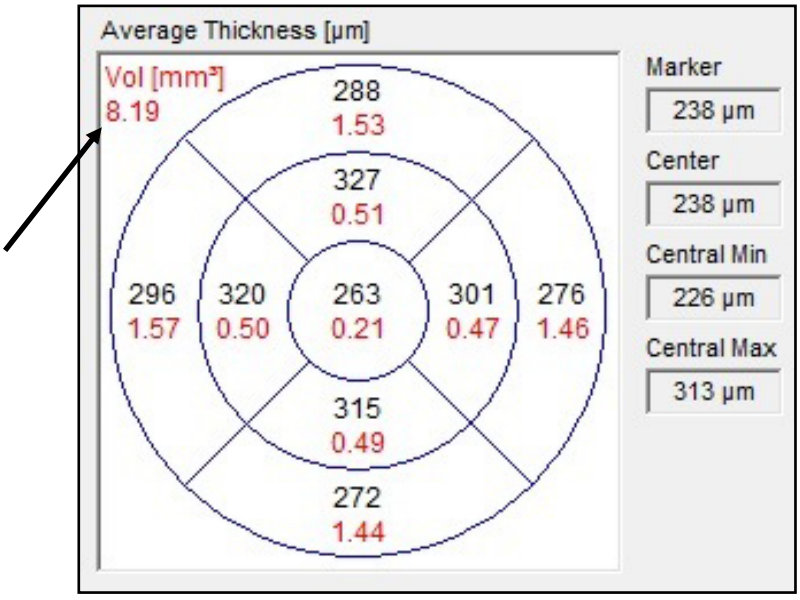
macular volume please make sure that the grid is centered at the fovea and the segmentations errors are corrected as described for each of the OCT machines.

Spectralis

A 30˚ x 25˚ macular cube with 31 line scans should be used (see imaging protocol). Once the scan has been completed, either the machine operator or clinician should check and manually adjust (if needed) each line scan to ensure no segmentation errors have occurred. The segmentation lines should be positioned on the internal limiting membrane (ILM) anteriorly, and the RPE-Bruch's membrane complex posteriorly, **to include pigment epithelial detachments (PEDs)** (see figure below and details in the imaging protocol).



Once the scan has been centered at the fovea and any segmentation errors have been corrected, the thickness map tab can be clicked, which will load the following diagram;

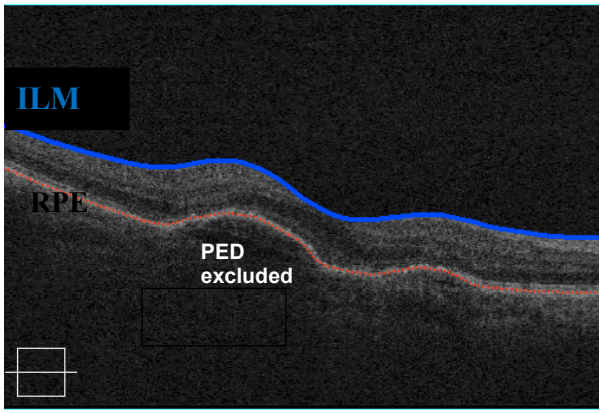


The macular volume is displayed in red at the top left corner (arrowed).

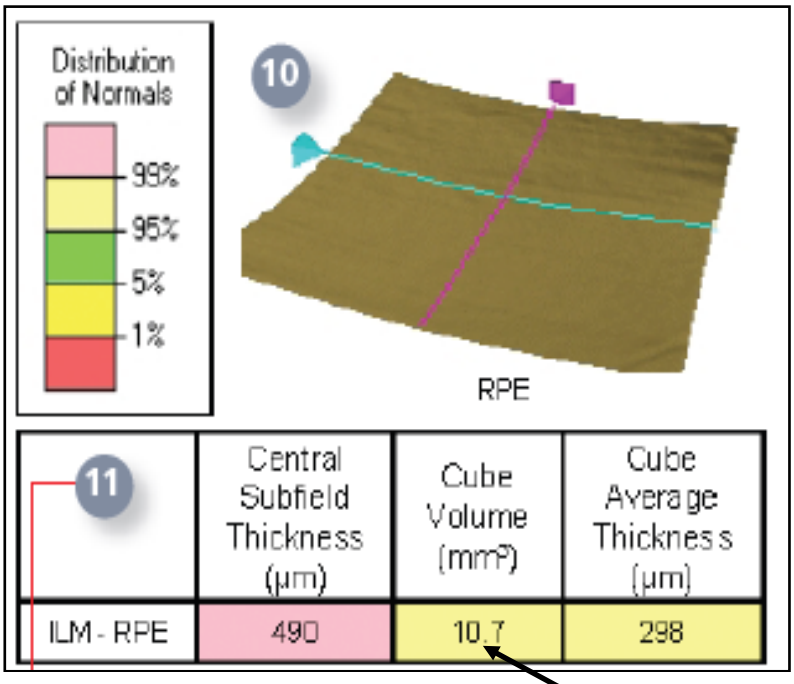
To meet the inclusion criteria, the macular volume must exceed **8.15 mm^3**.

Cirrus

A Macular Cube 512 x 128 should be used (see imaging protocol). Once the scan has been completed, either the machine operator or clinician should check and manually adjust (if needed) each line scan to ensure no segmentation errors have occurred. Segmentation lines should be placed on the ILM anteriorly, and the RPE posteriorly, **to exclude pigment epithelial detachments (PEDs) (see figure below).**



Once the scan has been centred at the fovea and any segmentation errors have been corrected, the data analysis information can be displayed, which will load the following information:



To meet the inclusion criteria, the macular volume must exceed **9.57 mm^3**.

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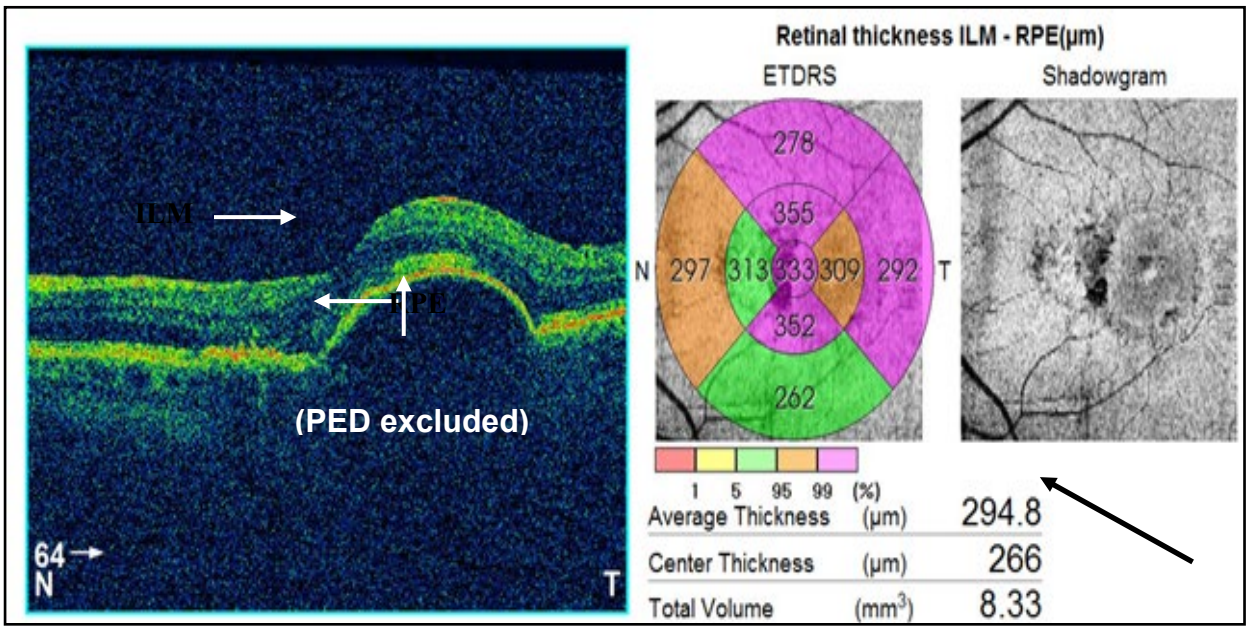
Topcon

A 3D Scan, 6x6mm, 512x128 should be used (see imaging protocol). Once the scan has been completed, either the machine operator or clinician should check and manually adjust (if needed) each line scan to ensure no segmentation errors have occurred. Segmentation lines should be placed on the ILM anteriorly, and the RPE posteriorly**, to exclude pigment epithelial detachments (PEDs) (see figure below - left).**

Once the scan has been centered at the fovea and any segmentation errors have been corrected, the "Report" button should be clicked, and the option "show volume" clicked. This will display the ETDRS grid with volumes for each individual segment:



To meet the inclusion criteria, the macular volume must exceed **6.94 mm^3**.

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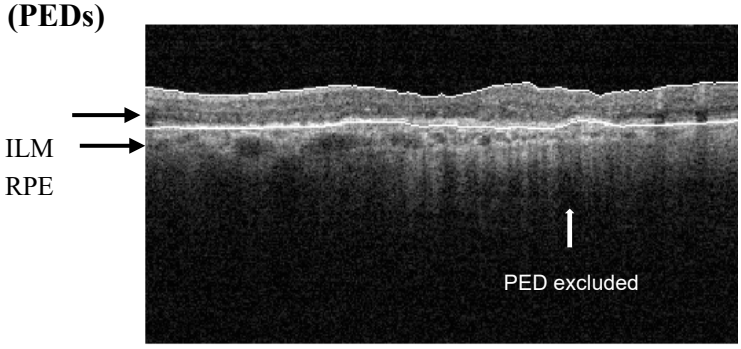
Optovue

A Retina Map scan should be used. Once the scan has been completed, either the machine operator or clinician should check and manually adjust (if needed) each line scan to ensure no segmentation errors have occurred. Segmentation lines should be placed on the ILM anteriorly, and the RPE posteriorly, **to exclude pigment epithelial detachments (PEDs) (see figure below).**



After saving the segmentation adjustments, the macular volume will be recalculated.
In the Retina Map Report the total macular volume is displayed at the bottom of the thickness and volume parameter table (arrow).

Section	Thick (µm)	Vol(mm³)
Fovea	270	0.212
ParaFovea	324	2.038
S. Hemisphere	328	1.031
I. Hemisphere	321	1.008
Tempo	315	0.495
Superior	332	0.521
Nasal	330	0.519
Inferior	320	0.503
Perifovea	296	3.718
S. Hemisphere	303	1.906
I. Hemisphere	288	1.813
Tempo	281	0.884
Superior	307	0.963
Nasal	313	0.983
Inferior	283	0.888
Vol within: 0.212(1mm) 2.250(3mm) 5.968(5mm)		

To meet the inclusion criteria, the macular volume must exceed **5.47 mm³**.

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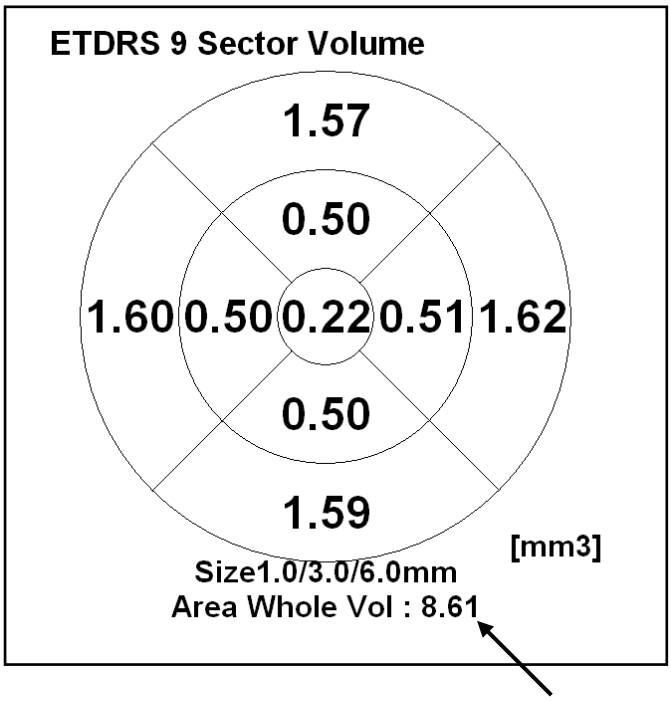
Nidek

A Macula Map scan should be used (see imaging protocol). Once the scan has been completed, either the machine operator or clinician should check and manually adjust (if needed) each line scan to ensure no segmentation errors have occurred. The segmentation lines should be positioned on the internal limiting membrane (ILM) anteriorly, and the RPE-Bruch's membrane complex posteriorly **to include pigment epithelial detachments (PEDs),** as illustrated in the Spectralis section above (details in the imaging protocol).

Once the scan has been centred at the fovea and any segmentation errors have been corrected, the Analysis Chart should be used to record the macular volume.

The macular volume is displayed on the bottom right of the ETDRS sector grid (arrowed).



To meet the inclusion criteria, the macular volume must exceed **8.20 mm^3**.

30. APPENDIX 3: ASSESSMENT OF VISUAL ACUITY

Visual acuity (VA) is measured at **baseline and monthly** for 24 months, and then at the **annual** visits thereafter (months 36 and 48). Full refraction will be undertaken at every third of the monthly visits over the first 24 months, and at the annual visits thereafter, namely at baseline (screening) and months 3, 6, 9, 12, 15, 18, 21, 24, 36 and 48.

For the intervening visits up to month 24, where full refraction is not mandated, the trial certified VA examiner should use the previous full refraction.

Refraction and VA measurements will be performed for all patients by trained vision examiners only. The **name** of the vision examiner should be documented in the patient's **source document** at each visit. VA examiners are "masked" to trial assignment and previous VA testing results. Therefore VA examiners should not have access to the patient's chart or previous VA testing results. Only the previous refraction should be made available. Refraction should be conducted prior to VA testing to obtain best-corrected vision as described below. Visual acuity is measured at all trial visits using standard charts, lighting, and procedures, including the visits that do not mandate a full refraction.

Equipment

Refraction equipment required includes:

1. Retroilluminated Light box and ETDRS 4 meter distance acuity chart set
2. Trial lens frames
3. Trial lens set with plus or minus cylinder lenses
4. Jackson cross-cylinders of 0.25, 0.50, and 1.00 diopters
5. Pinhole occluder
6. Tissues or eye pads and tape
7. A 1 meter rigid measuring stick

Visual Acuity Charts

Chart 1 is used for testing the VA of the RIGHT eye; Chart 2 for testing the LEFT eye; and Chart R (or 3) for refraction only. Patients should not be allowed to see any of the charts before the examination.

Visual Acuity Lane and Visual Acuity Box

A distance of **4 meters** is required between the patient's eyes and the VA chart. With the box light off, not more than **15 foot-candles of light** (161.4 Lux) should fall on the center of the chart. To measure the amount of light, the room is set up for VA testing, but with the box light off. The light meter is placed at the fourth line from the top of the chart, with its back against the chart and the reading is taken. If more than one lane is available for testing VA, the VA of an individual patient

should be measured in the same lane at each visit, if possible. If different lanes are used to test VA, they must each meet the same standards.

Retro illuminated ETDRS charts are used in this trial. The illuminator box will be either wall-mounted or mounted on a stand. . The light box should be mounted at a height such that top of third row letter is 49 ± 2 inches from floor.
The VA light box is equipped with two General Electric 20-watt fluorescent tubes (or equivalent lightbox housing 24 Watt Fluorescent tubes) and ballast. Each tube is partly covered by a 12 or14-inch fenestrated sleeve, which is centered on the tube and open in the back. This serves as a "baffle" to produce even illumination over the testing chart. Because the illumination of fluorescent tubes diminishes by 5 percent during the first 100 hours and by another 5 percent during the next 2000 hours, new tubes should be kept on for a total time period of 4 days (96 hours) before use in the study, and should be replaced once a year. Luminance will be confirmed with a use of a light meter (Sekonik L-398A) at the outset of the trial to confirm a minimum luminance of 85 cd/m2 (80-160 cd/m2).

A **sticker** should be placed on the back of the light box, indicating the date on which the present tubes were installed. A spare set of burned in bulbs should be available on site.

Beginning Approximate Refraction

At the Baseline visit, the patient's beginning refraction is determined by one of the following ways:

If the patient's VA is 6/30 (20/100) or better and the patient does not require glasses for distance vision, then the beginning approximate refraction should be no lens correction or plano.

If the patient's VA is 6/30 (20/100) or better and the patient requires glasses for distance viewing, the glasses should be measured using a focimeter, and these measurements are used for the beginning refraction.

If the patient's VA is less than 6/30 (20/100) with or without correction, then retinoscopy or autorefraction should be performed to determine the beginning approximate refraction.

If the patient wears contact lenses for refraction, a notation should be made that the refraction was over contact lenses. It is suggested that the patient wear the contact lenses for future examinations. If the patient is not a regular contact lens wearer and wore the lenses by mistake, they should be removed and you should wait at least 30 minutes before beginning the refraction. The patient should be reminded not to wear contact lenses at subsequent visits.

Refractions are performed with either plus or minus cylinder power. Whichever cylinder type is used at baseline (minus or plus) must be used for all subsequent visits.Best correction results should be recorded on the sponsor provided worksheet which will be included in the source documents. At each **follow-up visit**, **the results of the protocol refraction from the previous**

visit are used as the beginning approximate refraction. If the previous refraction is not available for some reason, the procedure described immediately above should be used. Whilst previous refraction results are made available at subsequent visits, **previous VA results should not be visible to the examiners at subsequent testing, so that assessment of VA is masked to prior visual function.**

The charts used for measuring distance VA must NOT be used for refraction. Refraction for each eye should be performed at **4 meters** unless the patient's VA measured at 4 meters on the refraction chart (Chart R or Chart 3) is **worse than 6/48 (20/160).If VA is worse than 6/48 (20/160) the eye is refracted at 1.0 meter**. If during the refraction process at one meter, the patient is reading letters on the eighth line or lower line of the chart, the refraction should continue at 4 meters. Whenever a patient cannot read any letters on the top line of Chart R or Chart 3 at 1.0 meter the vision should be checked with a pinhole to see whether reduced vision is due, at least in part, to a larger refractive error. If there is no improvement with the pinhole, then the eye is exempt from refraction.

Patient Refraction

Patient refraction allows one to determine the best correction for a patient to perform the VA tests. The **"push plus"** approach is used. Add minus diopter spherical corrections **only when the patient is able to read at least one more letter** on a line or a letter on a smaller line.

Procedure

1. Measure and record the distance vision of the eye being tested using Chart R while occluding the fellow eye. The fellow eye should be lightly patched with an eye pad or tissue and tape. Patients should be reminded to blink and encouraged to use eccentric fixation, or their side vision, when necessary.
2. All refraction and vision testing must be done at 4 meters or 1 meter. Distance for 4 meters is 13 feet and 1.5 inches or 157.5 inches. The one meter distance is 39 and 3/8 inches.
3. All patients should be seated for testing. A **rigid measuring device** should be used to measure the distance from the patient to the chart if testing is done at **1 meter**. The distance is measured from the outer canthus to the center of the second letter (left eye) or fourth letter (right eye) of the third line of the chart. For **4 meter** testing, **clear and permanent floor markings** should be used to mark the distance for consistency.
4. Place and adjust the trial frame on the patient's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupils. Adjust the lens cells for the proper distance from the cornea. Be sure the trial frame is comfortable on the patient's face.
5. Occlude the left eye by lightly patching with an eye pad or tissue and tape.
   Place the spherical lens correction in the compartment closest to the eye.
   The cylindrical lens correction, if present, is placed in the compartment in front of the spherical correction. Adjust the axis.

6. **Spherical Correction:** To determine the highest plus or least minus sphere, refract the right eye. The following refraction steps are recommended for VAs of 6/3 (20/10) to 6/24 (20/80) with the beginning approximate refraction. For VAs less than 6/24 (20/80), refer to the

refraction table for the appropriate sphere and cylinder powers and testing distance (See summary below) and follow a similar procedure. *Note: Whenever VA is improved to a higher range, refraction should be performed with the smaller sphere and cylinder powers given for the better VA level (See table at end of appendix).*

a) Hold a **+0.50 sphere** in front of the patient's right eye. The patient should be looking at the smallest legible line on the VA chart. In these exact words, ask the patient, **"Is this better, worse, or no change?"**

b) If the patient responds that the vision is **worse or blurred**, remove the +0.50 sphere from in front of the trial frame and **go to Step 6d**.

c) If the patient responds **better or no change**, remove the +0.50 sphere from in front of the trial frame and replace the spherical lens in the trial frame with a spherical lens that is one-half diopter more positive .Continue this procedure by returning to Step 6a and repeating this process **until a +0.50 makes the vision worse** or blurred and then go to Step 6d.

d) Hold a **-0.50 sphere** in front of the patient's right eye. In these exact words, ask the patient, "Is this better, worse or no change?" If the patient replies "worse" or "no change", go to Step 6f.If they reply "better" go to step 6e.

e) Hold the -0.50 sphere in front of the eye. If the patient responds that the vision is better, ask the patient to read the VA chart. **Only when the VA is improved, by at least one letter**, **may you increase the minus** by 0.50 (or decrease the plus) and repeat Step 6d.Whenever VA is not improved, go to Step 6f.

f) Remove the -0.50 sphere from in front of the eye and hold a +0.50 sphere in front of the right eye. In these exact words, ask the patient, "Is this better, worse, or no change?"If the patient responds that vision is better or unchanged, then return to Step 6c.Otherwise, go to Step 7. **Spherical testing should always end with a plus lens.**

7. **Cylinder Axis:** To determine and refine the cylinder axis for **PLUS** cylinder, proceed as follows; *(If **minus** cylinders are used, the appropriate technique using minus cylinders must be employed and minus cylinder must be used throughout the trial.)*

a) Have the patient look at a line which is either **one or two lines larger** than the smallest line the patient is able to read. Ask the patient to focus on a rounded letter such as "C", "D", or "O". The patient should focus on this same letter throughout this procedure.

b) If a cylinder is present in the beginning approximate refraction, then go to Step 7c. Otherwise, follow the option listed below to determine if cylinder may be needed.

Testing for cylinder when there is none in the beginning approximate refraction:

Place a **+0.50 diopter** cylinder with the positive axis first at 90°, then compare this to no cylinder; repeat this procedure for 180°, then 45°, and 135° always comparing to no cylinder after each axis position. If the patient says that vision is improved at any one of the four axis positions, place a +0.50 cylindrical lens in the trial frame at the preferred axis and go to step 7c.If the patient prefers no cylinder at all four axis positions, then go to Step 9.

c) Place the +0.25 diopter hand held cross-cylinder (for VA 6/3 – 6/24; 20/10-20/80) first with the positive axis 45° to the right of the preferred cylinder axis (as determined above), and second with the positive axis 45° to the left of the preferred cylinder axis. Ask the patient, "Which do you like better, position one or position two?" Also, tell the patient that

both positions may blur their vision. The patient must choose the least blurred position, either one or two. "Neither" is allowed only if both positions are equally blurred or equally good.

d) If "neither" position is better and this was the first test of axis position, move the axis of the cylinder in the trial frame 15° to the right or left and return to Step 7c.Otherwise, proceed to Step 7e.

e) When one position is preferred over another, move the cylinder to the preferred positive axis position in the step sizes noted below and return to Step 7c.If no single position is better than another than go to Step 8.

Cylinder Refinement *suggested* axis step sizes

Cylinder Power	Axis Step Sizes
<1.00D	15º
1.00 to <2.00D	10 º
2.00 to <3.00D	5 º
3.00 to<5.00D	3 º
5.00 to<8.00D	2 º

1. **Cylinder Power**: Cylinder power is refined by following the steps:
   a) Ask the patient to look at the **smallest line** that can be read on the VA chart.
   b) Test the cylinder power by placing the 0.25 diopter cross-cylinder (for vision of 6/3 - 6/24; 20/10-20/80) first with the positive axis and second with the negative axis coincident with the cylinder axis. Ask the patient, "Which is better, position one or position two?" Do not give the patient the choice of neither.
   c) If the patient prefers the minus axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. Repeat the process until the patient cannot choose one of the cross cylinder positions over the other. If the patient indicates a change that would introduce negative cylinder power, remove all cylinder power and continue testing for positive cylinder power at an axis 90°away from the previous axis. Otherwise go to Step 8d.
   d) If the patient prefers the plus axis coincident with the cylinder axis, increase the power of the cylinder by 0.25 diopters and return to Step 8b.Otherwise proceed to Step 8e.

e) When the patient feels that both positions are equally bad or good, and the cylinder power in the trial frame has changed by more than 0.50 diopter, return to Step 7c and re-check the axis if necessary. Otherwise, proceed to Step 9.
Note:If the cylinder is changed by more than 0.50 diopter, the ***spherical equivalent*** *should be maintained.(For each 0.50* ***plus*** *CX increase, add –0.25 to the sphere, for each 0.50* ***minus*** *CX increase, add +0.25 to the sphere).*

9. **Spherical Correction** ***Refinement****:* Recheck, or ***"refine"*** the power of the sphere by adding+**0.25 and -0.25** spheres and changing the spherical power by 0.25 diopter increments of the appropriate sign until the patient cannot detect any improvement in vision. As a reminder, **minus sphere should only be added if the patient can read additional letters** and spherical testing should always begin and end with a plus lens.
10. Record the lens corrections obtained by patient refraction for the right eye on the examination form in the section for VA measurements as the corrections obtained by protocol refraction for the right eye.
11. Repeat the entire process (Steps 1-10) for the left eye and record the refraction result on the VAE worksheet.

Best Corrected Visual Acuity Measures

As a reminder, Charts 1, 2, and R (or 3) are used for testing the right eye, left eye, and refraction, respectively. Patients should not see the charts until the test begins. The lens correction from the patient refraction should be in the trial frame worn by the patient. All eyes must be tested at 4 meters first, even if the refraction was performed at 1 meter.

The patient should be seated comfortably directly in front of the chart so that the eyes remain at the 4 meter distance. Testing always begins with the right eye. The fellow should be occluded with a folded tissue or eye pad lightly taped over the eye behind the trial frame serves as an effective occluder that allows eccentric fixation without inadvertent use of the covered eye. After testing the right eye, occlusion of the right eye should be done BEFORE Chart 2 is put up for testing the left eye.

The patient is asked to read the letters slowly, approximately one letter per second. The patient should be told that only one chance is given to read each letter, but they may change their mind before moving to the next letter. If the patient is unsure about the identity of the letter, then the patient should be encouraged to guess.

The patient should begin by reading the top line of the chart and continue reading every letter on each smaller line, from left to right on each line. ***The patient should be encouraged to continue reading even if making mistakes. Each letter read is counted.*** **The examiner circles every correct letter read and totals each line and the whole column (0 if no letters are correct) on the data collection form. An X is put through letters read incorrectly. Letters, for which no guess was attempted, are not marked. When a patient reaches a level where he/she cannot guess, the examiner may stop the test provided that the patient has made errors on previous guesses, which is a clear indication that the best VA has been obtained.**

When a patient cannot read at least 20 letters on the chart at 4.0 meters, the patient is tested at 1.0 meter. The distance from the patient to the chart should be measured again using the rigid one meter stick. The distance is measured from the outer canthus to the center of the fourth letter (right eye) or the second letter (left eye) of the third line of the chart. The spherical correction in the trial frame should be changed by adding +0.75 to correct for the closer test distance. The patient may fixate eccentrically or turn or shake his/her head to improve VA. Particular care should be taken to make sure the patient does not move forward when testing at 1 meter. The patient should be reminded to blink.

The examiner should not tell the patient if a letter was identified correctly. The patient may be encouraged by neutral comments, such as "good", "next", and "OK". The examiner should not stand close to the chart during testing. Attention should be focused on the patient and the data collection form. If the patient has difficulty locating the next line to read, the examiner may go up to the chart and point briefly to the next line to be read, but then must move away from the chart.

When 20 or more letters are read at 4 meters the VA score for that eye is recorded as the number of letters correct plus 30 (refer to the VA worksheet) The patient gets credit for the 30 1M letters even though they did not have to read them. Otherwise, the VA score is the number of letters read correctly at 1.0 meter plus the number, if any, read at 4M.If no letters are read correctly at either 4.0 meters or 1 meter, then the VA score is recorded as 0.

Testing for Count Fingers Vision, Hand Motion Vision and Light Perception/No Light Perception (NLP) Vision

If the patient's VA is so poor that he/she cannot read any chart letters when tested at one meter then the patient's ability to count fingers, detect hand motion, or have light perception should be evaluated.

Testing for Count Fingers Vision

In testing for count fingers vision, the examiner's hand holding 1, 2, or 5 fingers is held steady at a distance of two feet directly in front of the eye being examined. The fellow eye is completely occluded with a patch on the face. A light should be shown directly on the hand from behind the patient. The examiner's fingers should be presented in random order and repeated 5 times. Eccentric fixation, if present, should be encouraged. If the patient correctly identifies three of the five presentations, then count fingers vision is noted. If not, then the patient must be tested for hand motion vision.

Testing for Hand Motion Vision

The examiner's hand with all fingers spread out should be extended two feet directly in front of the eye being examined. The fellow eye should be occluded with a patch on the patient's face. A light should be shone directly on the examiner's hand from behind the patient. The examiner's hand should be moved in an up-and-down direction (vertically) or in a side-to-side direction (horizontally) at a constant speed of approximately one back and forth presentation per second. The patient is instructed that the examiner's hand will be presented and they will have to respond

to the question: “What am I doing with my hand?” This should be repeated five times. Three out of five correct responses indicate that hand motion vision is present. If the patient does not correctly identify three of five presentations, then you must test for light perception.

Testing for Light Perception/No Light Perception Vision

Light perception should be tested with an indirect ophthalmoscope in a darkened room. The fellow eye should be completely patched and also covered by the patient’s hand. The indirect ophthalmoscope light should be in focus at 1 meter with the rheostat set at maximum voltage. From that distance the beam should be directed in and out of the patient’s eye at least four times, and the patient should be asked to respond when he or she sees the light. If the examiner is convinced that the patient perceives the light, vision should be recorded as “light perception”, if not, vision should be recorded as “no light perception”.

4M Refraction Protocol Summary							
Refraction Distance	Check Sphere First		Check Cylinder Axis then Power			Sphere "Refinement"	
If VA on "R" chart is between:	Power (a)	Increment	Axis (b)	Power (c)	Increment	Power (d)	Increment
6/3 -6/24 20/10 - 20/80 (4 meters)	+.50 -.50	+.50 -.50	.25 JCC	.25 JCC	+.25 -.25	+.25 -.25	+.25 -.25
6/30 – 6/48 20/100 - 20/160 (4 meters)	+1.00 -1.00	+1.00 -1.00	.50JC C	.50 JCC	+.50 -.50	+.50 -.50	+.50 -.50
6/60 -6/120 20/200 - 20/400 (1 meter)	+2.00 -2.00	+2.00 -2.00	1.00 JCC	1.00 JCC	+1.00 -1.00	+1.00 -1.00	+1.00 -1.00
<6/120 <20/400 (1.0 meters) sequence refraction a-d	+2.00 -2.00	+2.00 -2.00	No cylinder test required			No refinement required	

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31. APPENDIX 4: AREDS CLINICAL LENS OPACITY GRADING PROCEDURES

Despite the fact that the IRay device is designed to minimise lens exposure to radiation and the INTREPID study did not find that stereotactic radiotherapy caused cataract, it is possible that radiotherapy will produce lens opacity and clinically significant cataract, For this reason, the trial mandates regular assessment of lens opacity using a validated clinical system and standardized photographs. This study uses the ARED lens opacity grading procedure (2008). The standard photograph is provided on the next page. To grade the lens opacity, proceed as follows:

- Dilate pupils to at least 5 mm diameter
- Use slit lamp with ~10X magnification
- Use brightest beam intensity
- Nuclear opacity

  Orient beam at 45° to viewing axis

  Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width

  Compare opalescence of nucleus with that in standard photos
- Cortical and PSC opacities

  Select wide slit beam setting optimum for retro-illumination of lens

  Visualize lens opacities against red fundus reflex background

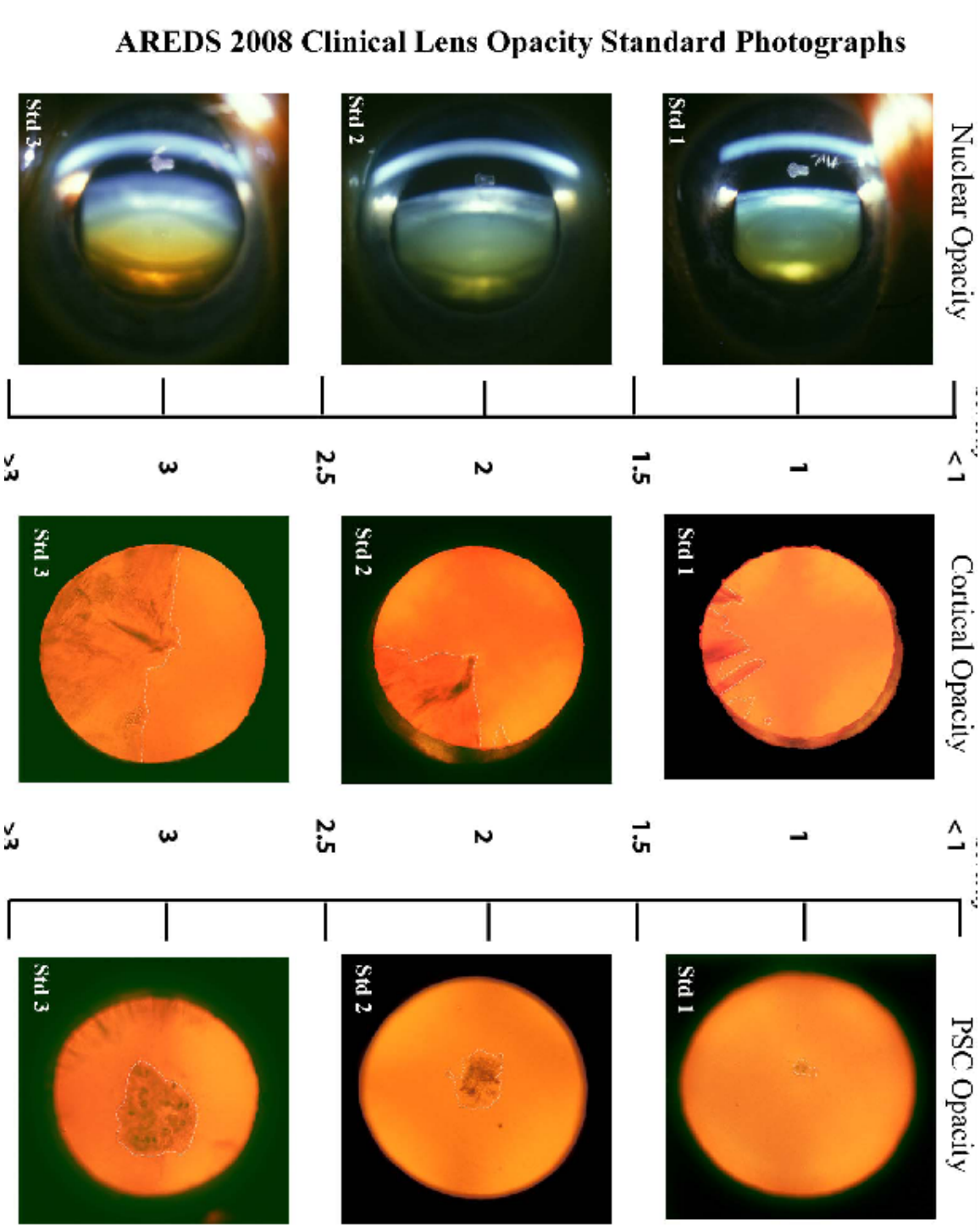
  Count only opacities definitely visible against red reflex

  Mentally combine all cortical opacities into one contiguous area

  Compare total opacity area with that in standard photos
- Classify each opacity with scale defined by 3 standard photos
- Select nearest half-step which is

  Similar to standard or between two standards

  Obviously less than mildest standard or greater than most severe



32. APPENDIX 5: DATA MONITORING AND ETHICS COMMITTEE CHARTER

1. INTRODUCTION

This charter was developed for the Data Monitoring and Ethics Committee (DMEC) for the clinical study, StereoTactic radiotherapy for wet Age-Related macular degeneration (STAR). The STAR trial is co-sponsored by King's College London and King's College Hospital (the Sponsor). This charter describes the roles and responsibilities of the DMEC. By accepting a position on the DMEC, members are indicating that they agree to the following terms of reference.

2. ROLES AND RESPONSIBILITIES OF THE DMEC

The primary role of the DMEC will be to ensure the safety of participants in the STAR trial. The STAR trial recruits patients with neovasular (wet) age-related macular degeneration (AMD). It investigates the safety and efficacy of stereotactic radiotherapy (SRT) delivered using a device developed by Carl Zeiss Meditec AG. Participants in the trial will also receive 'as required' (prn) anti-VEGF treatment with ranibizumab. Details of the trial are provided in the Protocol. All members of the DMEC agree to carefully read and consider the protocol in its entirety.

The DMEC will periodically evaluate safety data, and make consequent recommendations to the Trial Steering Committee (TSC). The TSC may accept, reject, or modify DMEC recommendations.

The Sponsor will ensure that all Adverse Events (AEs) and Serious Adverse Events (SAEs) and are reported to the DMEC. The primary emphasis of the DMEC member's review of these events will be on safety, so as to inform the TSC of any specific safety concerns in a timely manner.

The recommendations of the DMEC to the TSC may include:

- Discontinuation of the study if it is concluded by majority vote that the study participants are exposed to an unacceptable risk.
- Permanently or temporarily halt enrollment into the study.
- Modification of the study protocol.
- Continue the study according to the protocol and any related amendments.

3. DMEC MEMBERSHIP

1. Members

The names and contact information for the DMEC members is provided by the Sponsor on the study website. A copy of each DMEC member's curriculum vitae will be collected at the outset

of their involvement, and retained by the Sponsor. This may be provided to any regulatory agency that requires a copy. A DMEC member may not participate in the STAR trial as a principal or co-investigator, or as a personal physician to any study participant.

2. Confidentiality

All members will treat as confidential the reports, meetings, discussions, emails and minutes pertaining to the STAR trial.

3. Conflict of Interest Guidelines

A declaration of interests form will be provided by the Sponsor. Each DMEC member must disclose any financial interests which create a potential conflict with respect to their role on the DMEC. Members of the DMEC will not buy, sell, or hold stock or stock options in Carl Zeiss Meditec AG, or competing companies, until the trial is concluded and the final outcomes have been reported in the scientific literature. Each member agrees not to serve as a paid consultant to Carl Zeiss Meditec AG, or a competing company, for the duration of the study. This guideline also applies to the member's spouse and dependents. Members of the DMEC will be responsible for advising the DMEC Chair, the TSC, and Sponsor of any changes in relation to their financial interests, or any other matter that creates a potential conflict of interest. The Sponsor will collect and retain the declarations of interest and if any potential conflict of interest arises, the Sponsor will inform the TSC. The TSC will be responsible for deciding whether a financial or other interest impacts on a member's objectivity, and may require a member to resign from the DMEC. Members of the DMEC will not be paid for their role, but reasonable expenses will be reimbursed by the Sponsor.

4. Duration of DMEC Membership

The Chief Investigator, on behalf of the Sponsor, will propose members for the DMEC to the National Institute of Health Research (NIHR), who will approve or amend as appropriate. The DMEC membership will serve for the duration of the STAR trial, including long-term follow-up of participants. If a member cannot continue to serve on the DMEC, the reason must be indicated in writing to the DMEC Chair. If a member, including the Chair, leaves the DMEC, a replacement will be sought. If the TSC has concerns that a member of the DMEC is not fulfilling his or her role, they may, by majority vote, require that the member resigns.

4. DMEC MEETINGS

1. Initial Organizational Meeting

The initial meeting of the DMEC will be organizational in nature. The meeting will formally establish and thoroughly acquaint the DMEC members with the STAR trial protocol and other pertinent information. The meeting will allow DMEC members to provide input on future interactions between the DMEC, the Sponsor, and the TSC. Invited attendees will include the DMEC members, the Chief Investigator, Trial Statistician, and the Sponsor's representatives.

The format of data reports will be agreed between the DMEC and the Trial Statistician.

2. Interim Analysis

The STAR trial administers SRT at baseline. Although the INTREPID study reported favourable safety data,49 the main risk of SRT is likely to be radiation retinopathy, and that may not emerge in patients until the second or possibly subsequent years. For this reason the trial has extended follow up out to 4 years. Because radiation retinopathy has delayed onset the trial may be fully recruited by the time most cases emerge. Therefore, stopping the trial due to radiation retinopathy may only serve to reduce the chance of its detection. For this reason an interim safety analysis may not be as useful as it might be for trials with ongoing treatment. Nonetheless, the DMEC will be at liberty to request an interim analysis and if requested they will work with the Trial Statistician to determine the nature of the analysis.

3. Scheduled Meetings

Meetings may occur in-person or by teleconference. Meetings will occur approximately every six months in the first year, and then every six to 12 months thereafter. The frequency of scheduled meetings may change depending on participant enrollment and safety event rates. The Sponsor, TSC and the DMEC may each request an unscheduled DMEC teleconference or in-person meeting.

4. Quorum and Voting

A quorum of three DMEC members, including the Chair, is required to hold any meeting that requires voting, such as a recommendation to halt, suspend, and substantially alter the trial. A majority vote of members in attendance at the meeting passes a recommendation to the TSC or Sponsor. Non-quorate meetings may proceed if required, but minutes should be made as per quorate meetings and substantial recommendations may not be voted on.

5. Meeting Format

The meeting will begin with an open session to review the enrollment data and the status of the STAR trial. The Trial Statistician and the Chief Investigator (or their deputies), will be available to present the information and answer any questions from the DMEC.

A closed session will immediately follow the open session to discuss trial safety. In the event that efficacy data need to be reviewed in order to put risk/benefit in perspective, efficacy data may also be considered. This session will be attended by the DMEC members and the Trial Statistician who is unmasked to study treatment groups. The Trial Statistician and his or her team will be non-voting attendees of the closed DMEC sessions. Once the Trial Statistician has presented the data reports, the DMEC will usually request that he or she leaves the meeting prior to a private discussion and, if required, voting by DMEC members. Upon completion of the DMEC meeting, the Chair will convey the committee's recommendations to the Sponsor, Chief Investigator and TSC within 14 days.

5. COMMUNICATION

1. Data Reports and Trial Statistician

The Trial Statistician will be appointed by the Sponsor. The Trial Statistician will prepare reports for the DMEC meetings, at least seven days prior to each meeting. The format and content of these reports will be as requested by the DMEC, and will be agreed at the initial organizational meeting. The DMEC and Trial Statistician must ensure that masked data are not disclosed to the Sponsor, Investigators, Trial Manager and other members of the research team, prior to data lock. The Trial Statistician may however unmask a Data Manager and junior statistician, if they are required to assist with data handling. These members of the data management team must also ensure that they do not unmask data to other trial staff. Whilst the Trial Statistician may be required to present unmasked data to the DMEC, he or she will not have access to the closed reports prepared by the DMEC.

2. Protocol Amendments

The Sponsor will be responsible for informing the DMEC of all substantial amendments to the protocol. The DMEC are not required to approve amendments, but the DMEC may submit recommendations to the Sponsor and TSC.

3. Data Access

If the DMEC requests additional information concerning the study data, the DMEC Chair will contact the Trial Statistician who will provide the data. Only the DMEC will have access to the closed DMEC reports, until the study dataset is locked.

If the DMEC recommends stopping or suspending the trial, the TSC may request some or all of the data from the DMEC reports, and may seek independent statistical or other analysis prior to making a decision to stop or suspend the trial.

4. DMEC Minutes

The Chair of the DMEC will prepare, with administrative assistance from someone unaffiliated with the Sponsor, two sets of minutes following each meeting. The first set of minutes will cover the open session, and the second set of minutes will cover the closed session. The DMEC Chair will distribute the open minutes to all who attended the meeting, but the closed minutes will only be sent to DMEC members. The minutes will be circulated within 1 month of the meeting. The open and closed minutes will be approved at the subsequent meeting, in their respective sessions. The DMEC will forward the closed minutes to the Chief Investigator and Sponsor at the conclusion of the trial.

5. DMEC Recommendations

At each DMEC meeting, the DMEC will recommend whether the study should continue, stop, or be modified based on their findings. The DMEC will provide written recommendations about the trial to the TSC Chair, Chief Investigator and Sponsor within 14 days of the meeting. A shorter timeline may be required if there are urgent findings.

Upon receipt of the DMEC recommendations, the TSC will consider the DMEC recommendations, review the status of the trials, and determine a timely course of action. The TSC may identify expert individuals to review the DMEC Reports. These individuals will have the clinical, statistical, regulatory or other expertise needed to assist the TSC. The TSC may seek input from regulatory agencies and then make a decision to accept or disregard the recommendation of the DMEC. The Sponsor, Chief Investigator, TSC and DMEC will assure that confidentiality of the data, and DMEC recommendations, are maintained.

If the DMEC recommends stopping the trial and the TSC agrees by majority vote, then the Sponsor will inform all regulatory agencies of the decision and notify all investigational centers.

33. APPENDIX 6: TRIAL STEERING COMMITTEE TERMS OF REFERENCE

The following are the terms of reference for the Trial Steering Committee (TSC) of the STAR trial. By accepting a position on the TSC, members are indicating that they agree to the following terms of reference, and that they have read and considered the entire contents of the STAR protocol.

The role of the TSC is to provide general oversight of the trial.

1. Membership of TSC

TSC membership will include members of the trial team, and independent TSC members. Independent TSC members may not participate in the STAR trial other than as members of the TSC. Independent members should comprise a voting majority.

1.1. Confidentiality

TSC members will treat as confidential the reports, meetings, discussions, emails and minutes pertaining to the STAR trial.

1.2. Appointment to the TSC

The Chief Investigator, on behalf of the Sponsor, will propose members for the TSC to the National Institute of Health Research (NIHR), who will approve or amend as appropriate.

1.3. Conflict of Interest

Each TSC member must disclose any financial interests on a Declaration of Interests form provided by the Sponsor. This must record any potential conflict with respect to their role on the TSC. Members of the TSC will be responsible for advising the TSC Chair, and Sponsor, of any relevant changes in their financial interests, or any other matter that creates a potential conflict of interest, such as a family relationship with members of the trial executive. The TSC, Sponsor and NIHR will be jointly responsible for deciding whether a financial or other interest impacts on a member's objectivity, and may require a member to resign from the TSC. Members of the TSC will not be paid for their role, but reasonable expenses will be reimbursed by the Sponsor.

1.4. Duration of TSC Membership

The TSC membership will serve for the duration of the STAR trial, including long-term follow-up of participants. If a member leaves the TSC the NIHR, in discussion with the Sponsor, may appoint a replacement. If the TSC has concerns that a member of the committee is not fulfilling his or her role, they may, by majority vote, require that the member resigns.

2. TSC Meetings

Meetings may occur in-person or by teleconference. Meetings will occur at the start of the trial and then approximately every six to 12 months. The frequency of scheduled meetings may change depending on participant enrolment and safety event rates. The Sponsor, NIHR, TSC or Data Monitoring and Ethics Committee (DMEC) may each request an unscheduled TSC teleconference or in-person meeting.

2.1 Quorum and Voting

A quorum consists of five TSC members, including the Chair. The TSC may hold non-quorate meetings, but a quorum is required for any meeting at which a vote will be taken. Once a quorum is established, a majority of those present is needed for a vote to pass.

For a meeting at which early termination or suspension of the study is under consideration, a quorum consists of at least eight members (more than half of whom are independent members) and the Chair and Chief Investigator (or their deputies) must be present Once this quorum is established, a majority of those present is needed for a vote to pass to terminate or suspend the study.

2.2 Protocol Amendments

The Sponsor retains the right to make amendments as it sees fit, but protocol amendments, other than administrative amendments, will be presented to the TSC for its approval at the next scheduled TSC meeting. If a proposed amendment affects the safety of trial participants, or the overall integrity of the trial, then the Chief Investigator will seek approval of the TSC Chair before implementing change, unless urgent amendments are needed to safeguard patient safety. The Chair may request a special meeting of the TSC to review proposed amendment.

2.3 Data Access

The Chief Investigator or Trial Manager will provide the TSC with key study data during the course of the trial, such as recruitment figures, adverse events, and serious adverse events. The TSC will however remain masked with respect to treatment assignments and treatment outcomes, until the trial is formally unmasked.

2.4 Minutes

An independent scribe, provided by the Sponsor, will minute each meeting of the TSC. The minutes will be circulated by the Trial Manager or Chief Investigator within 6 weeks of the meeting. The minutes will be amended as necessary and approved at the next TSC meeting. The Sponsor will maintain a record of all minutes. If required, the TSC will provide any reports requested by the Research Ethics Committee and, if applicable, the MHRA

3 Data Monitoring Committee Recommendations

At each DMEC meeting, the DMEC will recommend whether the study should continue, stop, be suspended, or be modified, based on their findings. The DMEC will provide written

recommendations about the trial to the TSC Chair, Chief Investigator and Sponsor within six weeks of the meeting. A shorter timeline is required if there are urgent findings, including a DMEC recommendation to stop or suspend the trial.

The recommendations of the DMEC to the TSC may include:

- Discontinuation of the study.
- Permanently or temporarily halt enrollment into the study.
- Modification of the study protocol.
- Continue the study according to the protocol and any related amendments.

Upon receipt of the DMEC recommendations, the TSC will consider the DMEC recommendations, review the status of the trials, and determine a course of action. The TSC may accept, reject, or modify DMEC recommendations. If the DMEC recommends discontinuation of the study or halting enrolment, the TSC Chair will convene an urgent meeting of the TSC.

The TSC may identify expert individuals to review the DMEC reports. These individuals will not have the clinical, statistical, regulatory or other expertise needed to assist the TSC. The Sponsor, Chief Investigator, TSC and DMEC will assure that confidentiality of the data, and DMEC recommendations, are maintained.

34. APPENDIX 7: DRY EYE GRADING

APPENDIX 6

DEWS	**DRY EYE: DIAGNOSTIC TEST TEMPLATE**	
RAPPORTEUR	A.J.Bron	21st Oct 04
TEST	**GRADING STAINING: Oxford Schema**	
TO DIAGNOSE	The scheme is used to estimate surface damage in dry eye.	REFERENCES
VERSION of TEST	[V 1]	
DESCRIPTION	Surface damage to the exposed eye, assessed by staining, is graded against standard charts.	
CONDUCT of TEST	**Grading Schema:** Staining is represented by punctate dots on a series of panels (A-E). Staining ranges from 0-5 for each panel and 0-15 for the total exposed inter-palpebral conjunctiva and cornea. The dots are ordered on a log scale	Bron Evans Smith 2003

PANEL	Grade	Criteria
A 	0	Equal to or less than panel A
B 	I	Equal to or less than panel B, greater than A
C 	II	Equal to or less than panel C, greater than B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or less than panel E, greater than D
>E	V	Greater than panel E

Conduct of Test:

- Dye is instilled.
- Slit-lamp is set (eg, 16 magnification with x10 oculars with Haag-Streit).
- Cornea: The upper eyelid is lifted slightly to grade the whole corneal surface,
- Conjunctiva: To grade the temporal zone, the subject looks nasally; to grade the nasal zone the subject looks temporally.
- (The upper and lower conjunctiva can also be graded).

Selection of dyes:

A list dyes and filters can be found in the original paper.
With fluorescein, staining must be graded as quickly as possible after instillation, since the dye then diffuses rapidly into the tissue and its high luminosity blurring the stain margin. Staining after rose bengal or lissamine green, persists at high contrast and may therefore be observed for a considerable period. This is convenient for both grading and photography.

Fluorescein sodium

1. Quantified drop instillation

eg 2 µl of 2% sterile fluorescein instilled into each conjunctival sac with a micro-pipette (using a sterile tip). In very dry eye, larger volumes risk the possibility of inadequate dilution into the fluorescent range.

2. Unquantified instillation — impregnated paper strips

This is a convenient approach in the clinic using the following method of application:

- A single drop of unit dose saline is instilled onto a fluorescein-impregnated strip.
- When the drop has saturated the impregnated tip, the excess is shaken into a waste bin with a sharp flick.
- The right lower lid is then pulled down and the strip is tapped onto the lower tarsal conjunctiva. A similar procedure is carried out on the left.

If too large a volume is delivered then the concentration in the tear film will be too high, and the tear film and staining pattern will be non-fluorescent.

continued

APPENDIX 6 *continued*

3.Timing
The fluorescein break-up time (FBUT) is usually performed prior to grading staining. Since fluorescein diffuses rapidly into tissues, punctate staining blurs after a short period. It is therefore essential to assess staining rapidly, in sequence, in the right and then the left eye, so that the staining patterns observed are equally crisp.
If it is intended to photograph the staining pattern for grading, then photography should follow immediately after each instillation.

Exciter and Barrier Filters
The absorption peak of fluorescein sodium occurs between 465 - 490 nm and the emission peak between 520 - 530 nm. A suggested filter pair for detection of fluorescein staining is a yellow, Kodak Wratten 12 barrier filter (transmitting above 495 nm) or an orange Wratten 15 filter (transmitting above 510 nm) in combination with a blue Wratten 47 or 47A exciter filter. The 47A shows greater transmittance than the Wratten 47 over the absorption range. The 'cobalt' filter of many slit-lamps is suitable to use with a Wratten 12 or 15 barrier.

Where more light is required for photographic purposes, narrow band-pass, interference filters can be used.

The use of both exciter and barrier filters allows both the cornea and conjunctiva to be assessed using a single stain. This is a major advantage in clinical trials where it is otherwise customary to employ fluorescein to grade corneal staining and rose bengal or lissamine green to grade conjunctival staining.

Disadvantages of Fluorescein Staining
Blurred pattern if reading is delayed. Delay in photographing fluorescein staining results in blurred images of the staining pattern.

Rose Bengal
The intensity of rose bengal staining is dose dependent. If drop size or concentration is reduced to minimize stinging, the amount of staining is also reduced. Use of impregnated strips will give weaker staining than use of a full drop of 1% solution. Best results are achieved with, eg, 25 µl 1%, instilled into the conjunctival sac. Because rose bengal stings, instillation is best preceded by a topical anesthetic.

Instillation Technique
1) eg, a drop of Proxymetacaine is instilled into the conjunctival sac followed, after recovery, by;
2) A drop of rose bengal 1.0%. This is instilled onto the upper bulbar conjunctiva with the upper lid retracted and the patient looking down.
3) Since both anaesthetic and drop may stimulate reflex tearing, the test should follow measurement of the FBUT and of the Schirmer test. (Conjunctival staining due to insertion of the Schirmer paper can usually be distinguished from that due to dry eye disease).

Both eyes may be stained prior to grading, since there is no risk of the staining pattern in the first eye being obscured by the time the second eye is graded.
The cited paper gives advice about avoidance of overspill.

Visibility
Rose bengal staining on the conjunctiva shows up well against the sclera and may be enhanced using a red-free (green) light source. Corneal staining may show up well against a blue iris, but is difficult to see against a dark brown iris.

Phototoxicity
Photo-activation of rose bengal by sunlight increases post-instillation symptoms, especially in severe dry eye with heavy staining. This post-instillation pain can be minimized by liberal irrigation with normal saline at the end of the test.

Lissamine green stains the eye in a similar manner to rose bengal but is as well tolerated as fluorescein. Visibility and dose-dependency are the same as rose bengal and staining is persistant so that photography need not be performed immediately after instillation.
Lissamine green is available as impregnated strips or may be ordered as a pre-prepared solution. A 25 µl 1% drop will give more intense staining. Because the drop is well tolerated, no anaesthetic is required.

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35. APPENDIX 8: IRAY USER MANUAL

CARL ZEISS MEDITEC, INC.

IRAY® RADIOTHERAPY SYSTEM, MODEL 5000
USER MANUAL

Foreign patents pending.

The IRay System is an investigational device and is not available for sale in the U.S.A.

0400-0102 Rev A 2016-06

36. APPENDIX 9: ASSESSMENT OF GREATEST LINEAR DIMENSION AND LESION DISTANCE FROM THE FOVEA

One of the key exclusion criteria is the lesion size and distance from the centre of the fovea to the furthest point on the lesion perimeter. This assessment is done for the study eye on the fluorescein angiogram, at screening.

The measurement relates to the area of active leakage on fluorescein angiography. The measurement should be taken on an early phase of angiography. The measurement includes active CNV leakage, pigment epithelial detachment and haemorrhage that is contiguous with the active leakage. Atrophy, inactive fibrosis, RPE tears and haemorrhages that are not related to the area of active leakage are not included in the measurement.

Two separate measurement must be performed:

- greatest linear dimension (GLD) - the maximum diameter of the area of active leakage defined as above; in order for the patient to be eligible for the study, this must not exceed 4 mm; the GLD must be recorded in the source documents.
- distance from the centre of the fovea to the furthest point on lesion perimeter (same lesion as above) - in order for the patient to be eligible for the study this must be less than 2 mm.

If the area of the lesion is uncertain on fluorescein angiography, OCT can be used to help determine the active leakage, but the final measurement must be taken on fluorescein angiography.

The greatest linear dimension is also measured and recorded in the source documents at month 12 and month 24 visits.

Signed: _____ **Tim Jackson (Chief Investigator) 25 January 2019**

STAR study statistical analysis plan

STAR Trial

StereoTactic radiotherapy for wet Age-Related macular degeneration (STAR): A randomised, double-masked, sham-controlled, clinical trial comparing low-voltage X-ray irradiation with as needed ranibizumab, to as needed ranibizumab monotherapy.

Statistical Analysis Plan Version 1·4

Version 1·4 started: 14/04/2022

ISRCTN: 12884465

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Signature:

Date: 29 April 2022

CONTENTS

This document contains up to date statistical analysis plans (with version numbers and dates).

A) Quantitative Analysis Plan
B) Economic Analysis Plan
C) Schedule of Assessments and Measures

A) QUANTITATIVE ANALYSIS PLAN

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1. Description of the trial

The key objective of the STAR study is to evaluate the safety and efficacy of low voltage external beam radiotherapy, in combination with anti-VEGF therapy, for the treatment of neovascular (wet) AMD. Specifically, this study will evaluate whether Stereotactic RadioTherapy (SRT) reduces the need for ranibizumab injections, compared with ranibizumab monotherapy. STAR will also determine if SRT produces a non-inferior visual outcome compared with anti-VEGF monotherapy.

This study aims to enrol 411 participants in a double-masked, multicentre, sham-controlled clinical trial.

Participants will receive a single treatment of SRT using the iRay system (Gray) with a concomitant baseline intravitreal injection of 0.5 mg ranibizumab. Thereafter, participants will attend clinic for a review every month (28 days) for 96 weeks (*prn*). Two safety visits occur subsequently, one at 36 months (144 weeks) and the other at 48 months (192 weeks).

1.1 Principal research objectives to be addressed

Hypothesis: For patients with neovascular (wet) age-related macular degeneration (AMD), 16 Gray SRT, together with as needed, intravitreal, anti- vascular endothelial growth factor (VEGF) therapy, results in fewer intravitreal anti-VEGF injections and a non-inferior visual acuity outcome, compared with anti-VEGF monotherapy.

Aim: To determine the safety and efficacy of 16 Gray SRT.

Primary objectives

To investigate:

- If 16 Gray SRT, in conjunction with anti-VEGF therapy, reduces anti-VEGF injection frequency.

Secondary objectives

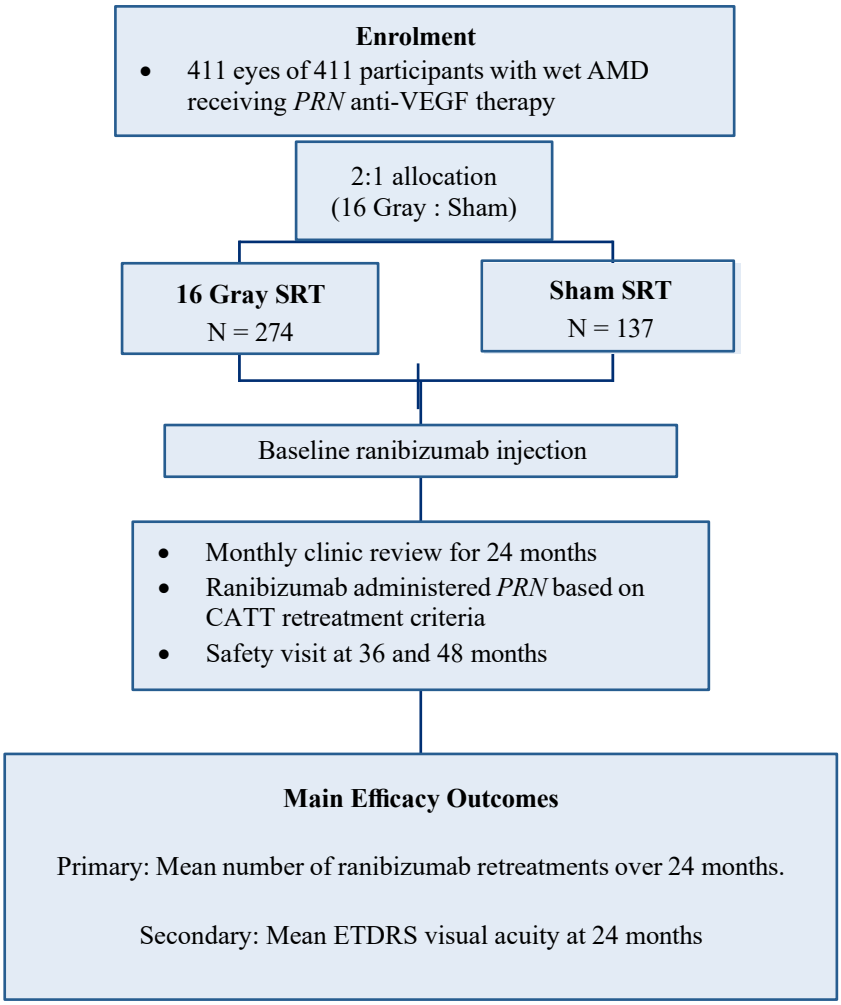
To investigate:

- If 16 Gray SRT, in conjunction with anti-VEGF therapy, achieves a visual acuity outcome that is not inferior to anti-VEGF monotherapy.
- If 16 Gray SRT is safe.
- If 16 Gray SRT is cost-effective.
- If there are baseline structural features associated with a poor response to anti-VEGF therapy and a positive response to SRT.
- If retinal microvascular changes occur in response to SRT, and if so, how do these evolve over time?

1.2 Trial design and flowchart

Randomised, double-masked, sham-controlled, multicenter, clinical trial.

Figure 1. Trial design flow diagram



Abbreviations: AMD, age-related macular degeneration; CATT, comparison of AMD treatments trial; ETDRS, early treatment of diabetic retinopathy study; *PRN*, *pro re nata* 'as required' dosing; SRT, stereotactic radiotherapy; VEGF, vascular endothelial growth factor.

1.3 Method of allocation of groups

Once baseline assessments are complete, participants will be randomized to SRT and sham in a 2:1 ratio. Randomisation is at the patient level and is performed using an online randomisation system set up by the King's Clinical Trials Unit (KCTU) at King's College London. Randomisation is stratified by national treatment centre with variable block sizes to ensure that patients are allocated to the two arms within each treatment centre in a 2:1 ratio. The procedure is as follows: The patient travels from their local recruiting site having been determined as eligible. Staff at the national treatment centre then use the online randomisation system to get an alphanumeric code. This is entered into the iRay system, and that will administer sham treatment or active treatment. The person delivering radiation/sham does not know which has been selected, as the machine fires up and prepares a dose map in the same way for each treatment.

1.4 Study duration and frequency of follow up

Participants will be treated at baseline and followed every 28 days for 24 months, with safety visits at month 36 and month 48.

1.5 Data collection

The trial will randomize 411 patients with previously treated, wet AMD. After giving fully informed written consent, patients with wet AMD will be screened for participation in the study. For patients with two eligible eyes, the patient may select which eye they wish to allocate as the study eye. Patients should fulfil the following criteria to be eligible for enrolment:

1.5.1 Eligibility screening

Key Eligibility Criteria

- Males and females with wet AMD requiring anti-VEGF treatment at the time of entry to the study.

In details:

Inclusion Criteria

- Participants must have neovascular AMD in the study eye, for which they have received at least 3 prior intravitreal injections of either bevacizumab (Avastin), aflibercept (Eylea), ranibizumab (Lucentis), or pegaptanib (Macugen).
- Participants must have received an anti-VEGF injection in the study eye within 4 months prior to enrolment.
- Participants must require treatment with anti-VEGF therapy at the time of enrolment, due to optical coherence tomography (OCT) evidence of subretinal fluid and/or cystoid macular oedema, and have a macular volume that is greater than a pre-defined threshold that varies for each different make of SD-OCT machine. The threshold for each approved machine is shown in Appendix 2 (protocol).
- Participants must be at least 50 years of age.

Exclusion Criteria

- Disciform scarring that involves the fovea, in the study eye.

- Visual acuity worse than 6/96 (24 ETDRS letters) in the study eye.
- Lesion size greater than 4 mm in greatest linear dimension, or greater than 2 mm from the centre of the fovea to the furthest point on the lesion perimeter, to include active choroidal neovascular leakage, pigment epithelial detachment and haemorrhage, as determined by fluorescein angiography.
- An axial length of less than 20 mm, or greater than 26 mm, in the study eye.
- Contraindication or sensitivity to contact lens application, including recurrent corneal erosions, in the study eye.
- Type 1 or Type 2 diabetes mellitus.
- Retinopathy in the study eye.
- Prior, current or anticipated treatment in the study eye for age-related macular degeneration, other than anti-VEGF agents, including submacular surgery, subfoveal thermal laser photocoagulation, photodynamic therapy (PDT), or transpupillary thermotherapy (TTT).
- Presence of an intravitreal device in the study eye.
- Previous radiation therapy to the study eye, head, or neck with the exception of radio-iodine treatment for hyperthyroidism, epimacular brachytherapy to the non-study eye, or IRay SRT to the non-study eye.
- Inadequate pupillary dilation or significant media opacities in the study eye, including cataract, which may interfere with visual acuity testing, the clinical evaluation of the posterior segment, or fundus imaging.
- Study eyes with CNV due to causes other than AMD, including presumed ocular histoplasmosis syndrome (POH), angioid streaks, multifocal choroiditis, choroidal rupture, and pathological myopia (greater than 8 Dioptres spherical equivalent). Participants with retinal angiomatous proliferation (RAP) or idiopathic polypoidal choroidal vasculopathy (IPCV) are *not* excluded.
- Known allergy to intravenous fluorescein, indocyanine green (ICG) or intravitreal ranibizumab.
- Intraocular surgery or laser-assisted in situ keratomileusis (LASIK) in the study eye within 12 weeks prior to enrolment.
- Prior pars plana vitrectomy in the study eye.
- Current participation in another interventional clinical trial or participation in such a clinical trial within the last six months.
- Unwilling, unable, or unlikely to return for scheduled follow-up for the duration of the trial.
- Women who are pregnant at the time of radiotherapy.
- Participants with an implantable cardioverter defibrillator (ICD) or pacemaker implant (or any implanted device) where the device labelling specifically contraindicates patients undergoing X-ray.
- Any other condition, which in the judgment of the investigator, would prevent the participant from granting informed consent or completing the study, such as dementia, and mental illness (including generalized anxiety disorder and claustrophobia).

1.5.2 Efficacy Measures

The following outcomes will be reported at Month 24

Primary Measure

- Number of as required (*prn*) ranibizumab injections during the first 24 months.

Secondary Measure

- Mean ETDRS VA.
- Percentage of participants losing < 15 ETDRS letters
- Percentage of participants gaining ≥ 0 ETDRS letters
- Percentage of participants gaining ≥ 15 ETDRS letters
- Total lesion size by fluorescein angiography
- Total CNV size by fluorescein angiography
- Foveal thickness measured using OCT
- Health-related quality of life assessed using the National Eye Institute 25- Item Visual Function Questionnaire and the EuroQol EQ-5D™ questionnaire
- Cost per Quality Adjusted Life Year (QALY)

1.5.3 Safety Outcome Measures

Safety will be evaluated by assessing adverse events (AEs) and serious adverse events (SAEs). The trial will specifically report the incidence of radiation retinopathy or radiation-related microvascular changes, and arteriothrombotic events.

1.6 Sample size estimation (including clinical significance)

Summary

If SRT produces a 25% reduction, group sample sizes of 248 and 124 (ratio: 2:1) achieve 90% power to detect a difference of 2.5 injections between the null hypothesis that both group means are 10 injections and the alternative hypothesis that the mean of the active treatment group is 7.5 injections, with a standard deviation (SD) of 7 for both, and a significance level (alpha) of 0.05 (two-sided) using a two-sample t-test. A 2:1 ratio adds only 42 patients but boosts recruitment and safety data.

We expect VA in the SRT group to be non-inferior compared to the control group. The SD of the mean change in VA was estimated as 12 letters from the INTREPID study. Group sample sizes of 248 and 124 achieve 97% power to detect non-inferiority in the mean changes in VA using a one-sided, two-sample t- test assuming a SD of 12 for both groups. The margin of equivalence is 5 letters. The true difference between the means is assumed to be 0. The significance level (alpha) of the test is 0.025.

In the INTREPID study, 2.2% of the randomized population were lost to follow up by year 1. Year 2 data are not representative as INTREPID had minimal review in year 2. The CABERNET study had 93% of data available for analysis at the end of year 2. We anticipate a 10% loss to follow-up over two years for STAR, so we aim to recruit 274 participants in the active arm and 137 in the control arm (total 411). Sample size calculations were performed using PASS software.

Justification for parameters used in the sample size calculations.

The INTREPID study (ClinicalTrial.gov identifier: NCT01016873) compared patients treated with low-voltage x-ray, external-beam, SRT plus ranibizumab *prn* to patients treated with sham SRT plus ranibizumab *prn*. Since INTREPID studied anti-VEGF-experienced patients the results of that study are more relevant to the STAR population than the results of CATT, which studied anti-VEGF-naïve participants. Participants in INTREPID were randomized to 16 Gray plus ranibizumab *prn*, 24 Gray plus ranibizumab *prn*, or sham radiotherapy (either 16 Gray or 24 Gray) plus ranibizumab *prn*. The mean changes in ETDRS VA at 12 months (±SD) were -0.28 ± 8.77, 0.40 ± 10.33, and -1.57 ± 11.90,

respectively. The pooled SD across all groups is therefore 10.4, with approximate 95% confidence limits of 9.6 and 11.5. For power calculations for STAR, the assumed SD of the mean change in VA is 12 letters.

The treatment arm of the present study (STAR) will receive 16 Gray SRT, as used in the INTREPID study. Both arms will receive ranibizumab *prn*, as used in the CATT trial. The primary outcome is the ranibizumab re-injection rate over 2 years. CATT reported a mean (±SD) of 6.9 ± 3.0 ranibizumab retreatments to the end of year 1 and 12.6 ± 6.6 to the end of year 2. The year 2 retreatment rate is most relevant to the STAR control group, which recruits patients with previously treated disease (CATT participants were treatment-naive at enrolment). The year 2 CATT retreatment was calculated to be 5.7 injections (12.6 – 6.9), so we might expect our control group to receive twice this (11.4) over two years. As CATT was undertaken in the US, to allow more conservative assumptions in case the injection rate is lower in the UK, we assume the injection rate to be 10 injections over 2 years in our control group, with a SD of 7 (based on INTREPID data which showed the SD was 69% of the mean). A 25% reduction in the number of injections is thought to be clinically and economically meaningful. Notwithstanding the fact that the second year of INTREPID was primarily designed to assess safety and not efficacy, this figure also matches the 25% reduction in the injection rate in the 2-year results of INTREPID, comparing the combined radiotherapy arms to the sham arm (Jackson et al, 2015).

1.7 Brief description of proposed analyses

Analyses will be carried out by the trial statistician. In the first instance data will be analysed under intention-to-treat assumptions (i.e. analyse all those with data in groups as randomised irrespective of treatment received).

2. Data analysis plan – Data description

2.1 Recruitment and representativeness of recruited patients

Recruitment, randomisation and follow-up for STAR will be summarised by arm in a CONSORT flow-diagram. This will include the main reasons for there being missing data (withdrawal, lost to follow up) by stages of the trial, and will also include the numbers for whom this occurs per arm. Also included will be the number randomised, who comprise the intention to treat trial population, and the numbers followed-up to be in the analyses of the primary outcome.

2.2 Baseline comparability of randomised groups

Baseline characteristics of each group will be summarised as mean and standard deviation for continuous variables with median and interquartile range for highly skewed data, and count and percentage for categorical variables. No significance testing on baseline variables will be performed.

The baseline characteristics will include patient demographics, randomisation stratifiers, ophthalmic history, medical history, EDTRS visual acuity, and other baseline (screening) clinical measures. This will allow an assessment of whether there is clinically important imbalance in any variables.

2.3 Loss to follow-up on outcome data

The proportions of participants with any missing data will be summarised by variable in each arm and at each time point. The baseline characteristics of those with missing primary outcome data will be compared statistically to those with complete follow up using appropriate univariate statistical tests. The reasons for withdrawal from the trial will be summarised in the CONSORT flow diagram.

Patients entering the trial have already become accustomed to one or two monthly hospital review and retention rates are expected to be high. In INTREPID loss to follow up at one year was 2.2%. CABERNET had 93% of data available for analysis at 2 years follow up. Our study size and power calculations allow for a 10% loss to follow up at the 2 year primary endpoint. To address any missingness that occurs, we will conduct a sensitivity analysis of the primary outcome that adjusted for any factors shown to be different between those present and those with full primary outcome data.

2.4 Adverse event reporting

AEs, adverse reactions (AR), SAEs, and serious adverse reactions (SAR) will be summarised as counts and percentages with 95% confidence intervals by trial arm. Where patients have not received the allocated treatment, this will be noted in reporting AEs so that the denominator for AEs is the number who actually received each treatment.

2.5 Descriptive statistics for outcome measures

The following outcomes will be reported at Month 24.

Primary Measure

- Number of as required (*prn*) ranibizumab injections during the first 24 months. This will be analysed as a continuous variable since while it is discrete, it is expected to have a wide range (1 to 20, as shown in the INTREPID study).

Secondary Measure

- Mean ETDRS VA.
- Percentage of participants losing < 15 ETDRS letters
- Percentage of participants gaining ≥ 0 ETDRS letters
- Percentage of participants gaining ≥ 15 ETDRS letters
- Total lesion size by fluorescein angiography
- Total CNV size by fluorescein angiography
- Foveal thickness measured using OCT
- Health-related quality of life assessed using the National Eye Institute 25- Item Visual Function Questionnaire and the EuroQol EQ-5D™ questionnaire
- Cost per Quality Adjusted Life Year (QALY)

Continuous outcome measures (per treatment arm) will be summarised as mean and standard deviation, with median and interquartile range where there is extreme skewness; categorical outcome measures as count and percentage. Also, mean vision change and mean OCT thickness will be plotted against time (24 monthly visits over two years) as summary measures showing vision change over time and OCT thickness over time to demonstrate the biological response to radiation.

3. Data analysis plan – Inferential analysis

3.1 Main analysis of treatment differences

The main statistical analyses will estimate the difference in mean outcome between patients randomised to SRT and sham by intention to treat at 24 months. Group difference estimates and associated 95% confidence intervals will be reported.

3.1.1 Analysis of primary outcomes

The principal analyses of primary outcome will be performed according to "intent-to-treat" principle. All randomized patients in these analyses will be classified according to their assigned treatment at randomization, regardless of patient's adherence. The primary analysis is to test the mean difference in number of ranibizumab retreatments up to and including Month 24 between the SRT and sham group (ranibizumab monotherapy). Previous research (CATT and INTREPID) has suggested that the number of injections is approximately normally distributed. In this case, a multiple linear regression analysis will be used to assess the treatment effect with adjustment for the baseline stratification factor – treatment centre. The analysis will not include the initial mandated ranibizumab treatment as it is administered to all participants, and

does not reflect the effect of SRT or sham treatment. The treatment effect is evaluated at the two-sided 0.05 significance level.

In the event that the number of injections is not normally distributed, a data transformation will be used to give normally distributed residuals. In the unlikely event that no transformation is possible, analysis will be based on a non- parametric approach, a stratified Wilcoxon-Mann-Whitney (WMW) test (the van Elteren test), adjusted for the baseline stratification factors and the median difference with 95% confidence interval calculated by the (stratified) Hodges-Lehmann estimation.

3.1.2 Analysis of secondary outcomes

The change in visual acuity (VA) will be formally tested statistically for non- inferiority. The change in VA in the SRT arm compared to the change in VA in the control arm from baseline to Month 24 will be analysed by using a multiple linear regression model with adjustment for the baseline stratification factor (treatment centre) and the baseline VA score. Multiple linear regression will be used rather than repeated measure analysis because although there will be 24 monthly visits for patients in the trial, the focus of interest is the mean changes in VA from baseline to Month 24.

Data from the other efficacy outcomes (listed in Section 1.5.2) will be summarized. Statistical analysis of these outcomes will be descriptive, with differences and 95% confidence intervals where possible. There will be no correction for multiple testing. Mean vision change and mean OCT thickness will be plotted against time (24 monthly visits over two years) as summary measures showing vision change over time and OCT thickness over time.

3.1.3 Planned subgroup analyses

Subgroup analyses of number of injections, mean VA and OCT thickness (as a forest plot) will be conducted for pre-specified subgroups defined by the following key variables. All subgroup effects will be tested by fitting an interaction factor in the model so that differences between subgroups will only be confirmed if the test for interaction is statistically significant. All tests will be at a statistically significance level of 5%.

1. Total angiographic lesion size, as per reading centre evaluation (above and below the median)
2. Greatest distance of the lesion from the foveal centre, as per the reading centre evaluation
3. Angiographic lesion type per reading centre:
    1. Type 1 (occult)
    2. Type 2 (classic)
    3. Type 3 (retinal angiomatous proliferation (RAP))
    4. Mixed (minimally classic)
    5. Idiopathic polypoidal choroidal vasculopathy (IPCV)
4. OCT macular volume per reading centre (above and below median)
5. Baseline vision in ETDRS letters (above and below median)
6. Duration of disease (above and below median)

7. Number of prior anti-VEGF injections excluding that given at baseline (above and below median)
8. Presence of absence of vitreomacular adhesion on OCT, as per reading centre.
9. Lens status (phakic or pseudophakic)

3.1.4 Statistical considerations

Missing outcome data
To address any missingness that occurs, we will conduct a sensitivity analysis of the primary outcome that adjusted for any factors shown to be different between those present and those with full primary outcome data.

Method for handling non-compliance

The number of patients who have not completed their full treatment protocol is expected to be few but will be noted. In addition to the primary intention-to-treat analysis the effect of actually receiving treatment as defined in the protocol will also be estimated by comparing the two arms in just those who have received the full protocol.

Method for handling non-conformity in randomisation
In the case that randomised treatment code is incorrectly applied by unforeseen reason, we will identify the patients potentially affected and establish which, if any, of those patients received the opposite treatment allocation to that randomised. Analyses will be based on intention-to-treat (ITT). A sensitivity analysis will be carried out using the 'actually received' treatment.

COVID-19 sensitivity analysis
The COVID-19 pandemic has affected research globally. For the UK-based STAR trial, national lockdown measures instituted in March 2020 have the potential to impact the primary outcome (number of ranibizumab injections up to year 2) if participants elected not to attend for review, or if hospitals changed their management pathway to mitigate the risks of patients contracting COVID.

To assess the impact of COVID-19, a sensitivity analysis of the primary outcome has been predefined, prior to data lock. This sensitivity analysis will be used to help interpret the main primary endpoint analysis, which remains intent-to-treat. The sensitivity analysis aims to assess how the pandemic might have altered the trial's primary outcomes.

The sensitivity analysis involves an evaluation of the primary outcome in four predefined sub-populations:

i. Participants whose year 2 primary endpoint was completed before the onset of the national lockdown on 23rd March 2020. These participants will have been largely or fully unaffected by the pandemic.

ii. Participants whose year 2 primary endpoint was completed after the onset of the national lockdown on 23rd March 2020. These participants will have been affected by the pandemic to varying degrees depending on when they enrolled and hoe many of their monthly visits occurred during the pandemic.

iii. Participants whose compliance up to their year 2 primary endpoint was sufficient.

iv. Participants whose compliance up to their year 2 primary endpoint may be compromised.

The distinction between group 3 and 4 is based on the application of predefined rules, which categorise visits as green (compliant), amber (some deviation but not one that is unlikely to materially affect the primary outcome), and red (deviations that may have affected the primary outcome). Participants will be considered to be sufficiently compliant with the protocol (group 3) if they had no more than 4 red visits or 8 amber visits up to their year 2 primary endpoint. The rules to categorise each visit are shown in appendix A.

Compliance will be shown graphically for the entire population, using a novel 'compliance' schematic. This will show the visit timeline for each participant up to the year 2 primary endpoint. Sequential visits will be shown in green, amber or red, as a horizontal row. The colour coded visit timeline for each participant will be stacked one above the other, from first to last participant recruited. Withdrawals will be shown in white, and deaths in black. Additionally, the onset of COVID restrictions will be marked on each participant's timeline (if it applies), so that the overall compliance, death rate, and withdrawals in the trial can be compared graphically before and after lockdown.

3.2 Exploratory analyses

Any examination of subgroups, not specifically identified in the protocol, will be considered exploratory in nature and will be clearly identified.

3.3 Interim analysis

The usual rationale for an interim analysis is to consider stopping the treatment (or the trial) however as this treatment is given at baseline, it is not possible to subsequently stop treatment. As such we elected not to include an interim analysis. The DMC will examine the recruitment rate, data completeness and monitor safety, and will recommend whether the study should continue, stop, be suspended, or be modified, based on their findings.

4. Software

Data management: An online data collection system for clinical trials (MACRO; InferMed Ltd) will be used. This is hosted on a dedicated server at King's College London and managed by King's CTU (KCTU). The KCTU Data Manager will extract data periodically as needed and provide these in comma separated (.csv) format.

Statistical analysis: Statistical software package R will be used for data description and the main inferential analysis.

B) SCHEDULE OF ASSESSMENTS AND MEASURES

Assessment	Screening	SRT with baseline ranibizumab †	Monthly review* (Month 1-11)	Month 12	Monthly review* (Month 13-23)	Month 24	Month 36	Month 48
Visit Window: *Day 0 = Day of successful enrolment*	Day -14 to 0	Day 0 to 21	±7 days	±7 days	±7 days	±7 days	±14 days	±14 days
Informed Consent	x							
Demographics	x							
Ophthalmic History	x							
Med History/Con Meds	x							
Blood Pressure	x							
EDTRS Visual Acuity	x		x	x	x	x	x	x
Intraocular Pressure	x			x		x	x	x
Cataract Assessment	x			x		x	x	x
Biometry	x							
OCT (sent to reading centre)	x			x		x	x	x
OCT (*not* sent to reading centre)	x		x		x			
Fundus Photographs (sent to reading centre)	x			x		x	x	x
Fluorescein Angiography (sent to reading centre)	x			x		x	x	x
Indocyanine Green Angiography (sent to reading centre)	x		x (?)					
Stereotactic Radiotherapy with mandated baseline Ranibizumab†		x						
Ranibizumab injection if required (*prn*)			x	x	x	x	x	x
EQ-5D and VFQ-25 patient questionnaires‡	x			x		x	x	x
AEs/ConMed changes			x	x	x	x	x	x

Appendix A: Compliance rules

Assessment Categorisation Red, Amber, Green.	**Visits (by month)**					
	1-11	**12**	**13-23**	**24**	**36**	**48**
Visit attendance† 'Missed consultation' As indicated by the status form (SF – not done [888/8888]) 'Visit out of window' For the purpose of this analysis, visits up to month 24 are in window if they are either within 14 days of the study visit planner target visit date, or from 21 to 42 days after the last visit. The greater tolerance for longer than shorter visits is because a shorter visit might reduce the likelihood of needing an injection, whereas a slightly longer visit will probably not, as macular fluid persists. For the two safety visits at month 36 and 48, the visit is in window if it occurs with 21 days of target, per the study scheduler, or from 49 to 57 weeks of the last visit. 'Visit within window' The visit is in window if it meets one of the criterions listed immediately above.						
ETDRS VA Not performed at visit – Visual acuity (Monthly or Annuals) = Q1 Visual acuity study eye = 888 - Visual acuity not performed but injection required at same visit regardless, due to other disease activity– i.e. Ranibizumab retreatment form states one of the following: ○ Q2 Evidence of subretinal, intraretinal, or sub-RPE fluid on OCT? = 1 Yes ○ Q3 New or persistent subretinal or intraretinal haemorrhage? = 1 Yes ○ Q5 Increased lesion size on fluorescein angiography relative to last angiogram? = 1 Yes ○ Q6 Leakage on fluorescein angiography? = 1 Yes Performed per protocol	x	x*	x	x*	x*	x*

Fundus examination (posterior segment abnormality): Not performed at visit – Fundal examination (Monthly) = 888 Not performed but any of the following performed (as they allow doctor to see fundus): o OCT undertaken = Q2 Right central subfield thickness (µm) *or* Q7 Left central subfield thickness (µm) contains value – ie value that is not 7777 or 8888 or 9999. o Fundus Photography = Q1 Performed on both eyes = 1 Yes o Fluorescein Angiography (Annual) = Q1 Performed = 1Yes Not performed but any of the following mandated treatment anyway (Ranibizumab retreatment form states one of the following): o Q2 Evidence of subretinal, intraretinal, or sub-RPE fluid on OCT? = 1 Yes o Q3 New or persistent subretinal or intraretinal haemorrhage? = 1 Yes o Q5 Increased lesion size on fluorescein angiography relative to last angiogram? = 1 Yes Q6 Leakage on fluorescein angiography? = 1 Yes Performed per protocol	x	x	x	x	x	x
OCT Not performed at visit – OCT = 8888 - OCT not performed but injection required anyway– i.e. Ranibizumab retreatment form states one of the following: o Q3 New or persistent subretinal or intraretinal haemorrhage? = 1 Yes o Q5 Increased lesion size on fluorescein angiography relative to last angiogram? = 1 Yes o Q6 Leakage on fluorescein angiography? = 1 Yes - OCT wrongly recorded as not performed (OCT 888) but actually was: o Q2 Evidence of subretinal, intraretinal, or sub-RPE fluid on OCT? = 1 Yes Performed per protocol	x		x			

Ranibizumab injection (prn) Ranibizumab injection not given when indicated – i.e. Ranibizumab retreatment form indicates both of: ○ Q1 Does the patient require ranibizumab retreatment (regardless of whether injection actually given)? = 1 Yes ○ Q8 Ranibizumab 0.5µg administered? = 0 No Given when indicated, but out of window by >14 days Given when indicated, within 14-day window	x	x	x	x	x	x

†If a visit was missed but determined to be amber because no injection was needed at the next visit, ignore the fact that VA, OCT and fundus examination were 'missing' during the non-attended visit, even if their absence would otherwise define a red visit.

Typical codes on MACRO:
888/8888 = not done 999/9999 = data unknown
777/7777 = not available or not applicable
1 = Yes
0 = No

Amendments to version 1.0

Version 1.1 (29 July 2015) includes following amendments:

3.1.4 Statistical considerations

Method for handling non-conformity in randomisation

In the case that randomised treatment code is incorrectly inputted by human error, we will identify the patients potentially affected and establish which, if any, of those patients received the opposite treatment allocation to that randomised. Analyses will be based on treatment actually received and any deviation from the randomisation will be documented. A sensitivity analysis will be carried out excluding those affected patients.

Amendments to version 1.1

Version 1.2 (19 August 2015) includes the following change of wording in the method for handling non-conformity in randomisation (under 3.1.4 Statistical considerations): 'human error' is changed to 'unforeseen reason'.

Amendments to version 1.2

Version 1.3 (06 November 2015) includes following amendments in the planned subgroup analyses (section 3.1.3) regarding names of angiographic lesion subtypes:

Angiographic lesion type per reading centre:

1. Type 1 (occult)
2. Type 2 (classic)
3. Type 3 (retina angiomatous proliferation (RAP))
4. Mixed (minimally classic)
5. Idiopathic polypoidal choroidal vasculopathy (IPCV)

Amendments to version 1.3

Version 1.4 (14 April 2022) includes the following amendments:

- Addition of "COVID-19 sensitivity analysis" section under "3.1.4 Statistical considerations".
- Addition of appendix A defining visit compliance rules for the planned COVID-19 sensitivity analysis.
- Removal of section B "Economic Analysis Plan" (a separate document detailing the plan for health economic analysis will be provided).

Reference List

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Health economic analysis: *Methodology and assumptions*

1. Statistical analysis approach for costing data

Base case analysis took a National Health Service (NHS) and personal social services perspective, following National Institute of Health and Care Excellence (NICE) reference case.[1] A two-year time horizon was chosen, matching the primary endpoint. This included resource use from randomisation to patients' 24-month visit (inclusive).

We conducted intention-to-treat analysis, including all participants randomised who had complete data on the primary endpoint, irrespective of whether they received the allocated treatment. Participants were analysed in the groups to which they were randomised, irrespective of treatment received. Costs were assigned to all participants who received active SRT (regardless of treatment allocation) and no cost was applied to participants who did not attend consultations for injection/monitoring or for SRT.

The costing analysis focussed on main cost drivers, namely: SRT, ranibizumab and consultations for intravitreal injection and/or monitoring the need for retreatment. Costs more than 48 weeks after randomisation were discounted at 3·5% per annum.[1] The reference year for costs was 2021-2. No cost was applied to visits that were scheduled but not attended (regardless of the reason for non-attendance). No cost was therefore applied to visits that were missed due to the COVID pandemic or lockdowns: this approach avoids imposing unnecessary assumptions on the analysis and allows for the fact that participants whose vision has deteriorated may be more likely to attend the clinic during a lockdown than participants whose vision remained stable. Ranibizumab was costed as Lucentis (not a biosimilar) in the base case analysis. Since there is no publicly available data on the price paid by the NHS, we used the list price in the economic evaluation. In line with the primary outcome, complete-case analysis was conducted, excluding participants who withdrew or died before the 24-month primary outcome visit. There were no other missing data on the resource use items used in this analysis, so no imputation was conducted. Value-added tax (VAT) was excluded, as per the NICE manual.[1] Patient transport costs to the National Treatment Centres were excluded from the base case analysis on the basis that they would be not normally be funded by the NHS. No cost was applied to sham stereotactic radiotherapy (SRT). Since radiotherapy would be expected to affect only the study eye, data were not collected on treatments or consultations related to the fellow eye and all monitoring visits and ranibizumab injections were costed on the basis that only one eye was being treated.

Analysis of costs in months 1-24 used linear regression to adjust for age, gender, baseline EQ-5D-5L utility, baseline EDTRS visual acuity and the number of months from the start of COVID restrictions (23rd March 2020) to the second anniversary of each participant's randomisation. This was done to minimise the risk of bias from chance imbalance between randomised groups. Adjusting for age and gender primarily adjusts for any chance difference in mortality that may result from imbalance in age/gender, while adjusting for baseline EQ-5D utility is an established method to avoid bias in quality adjusted life year (QALY) calculations.[2] We adjusted for the timing of COVID restrictions to overcome any chance imbalance in the number of follow-up appointments and injections that may have been cancelled due to COVID that could otherwise have led to bias. Analyses on the cost of SRT and ranibizumab at baseline were not adjusted for covariates since the only between-participant variability arose from participants who did not attend the appointment or received the opposite treatment from their randomised allocation. Baseline EQ-5D-5L was valued using the Hernandez Alva crosswalk tariff[3] that forms part of the NICE reference case.[1] Costing analyses were conducted in Stata version 17·0 (StataCorp, College Station TX).

Bootstrapping was used to quantify uncertainty; linear regression models were estimated on each bootstrap replicate. All p-values for the costing analysis are two-sided bootstrap p-values. Unit costs, including the cost of SRT, were assumed to be fixed with no uncertainty.

A separate paper will report EQ-5D results, cost-utility analysis and a full costing analysis, including all consultations and procedures related to the study eye extensive sensitivity analyses will be reported separately alongside the full economic evaluation, including analyses varying the cost of SRT and ranibizumab and methods to allow for missing data.

2. Assumptions underpinning estimation of the unit cost of stereotactic radiotherapy (SRT)

- We assumed there would be one SRT device in each of the nine regions in England, and one in each devolved nation (Wales, Scotland and Northern Ireland). Patients' SRT appointments were assumed to be grouped together to reduce costs, so that on average 12 patients would be treated on each day. For example, if there were 240 patients needing treatment in any given year, we assumed that the SRT device would be run on 20 days with 12 patients each.
- Average number of patients per SRT device per day: 12, based on a 7·5 hour working day, with 30 minutes set up at start of day and 30-minute appointments.
- Prevalent patients with neovascular age-related macular degeneration (nAMD) who currently receive anti-vascular endothelial growth factor (VEGF) injections, but have not yet had SRT, were assumed to undergo SRT over the next 5 years (one fifth of patients in each year)
- The number of prevalent patients with nAMD having anti-vascular endothelial growth (VEGF) factor treatment in England was assumed to be 232,375, based on the number of prevalent patients in England eligible for anti-VEGF treatment.[4]
- The number of incident patients with nAMD having anti-VEGF per year in England was assumed to be 36,793, based on the number of incident patients in England eligible for anti-VEGF treatment.[4]
- The proportion of patients who would have SRT was assumed to be 22%. In the original INTREPID study, 272 patients were screened, of whom 230 were eligible. The STAR study was then based on the best-responder subset, which comprised 26% of the INTREPID population.[5] We therefore assumed that 22% of patients are eligible ((0·26 x 230)/272).
- Patients' travel costs were excluded.

3. Table S1: Unit costs used in costing analysis

Resource	Cost	Source
Monitoring consultation	159·05	Outpatient procedure code for retinal tomography (Ophthalmology) 19 years and over BZ88A in National Schedule of NHS Costs Year 2021-22 Outpatient procedures.[6]
Injection consultation	157·39	Weighted average of two procedure codes (weighting by number of examinations in England): BZ86B Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1 (Ophthalmology) and BZ87A Minor Vitreous Retinal Procedures, 19 years and over (Ophthalmology). National Schedule of NHS Costs Year 2021-22 Outpatient procedures.[6]
Ranibizumab (Lucentis)	£551·00	British National Formulary 2022. Cost per vial or pre-filled disposable injection containing ranibizumab (Lucentis) 10 mg/mL solution for injection.[7]
SRT	£1,342·91	Estimated in Table S2, appendix p 115; and Table S3, appendix pp 116

Table S1: Abbreviations: anti-VEGF, anti-Vascular Endothelial Growth Factor; nAMD, neovascular age-related macular degeneration; SRT, stereotactic radiotherapy.

4. Table S2: Cost and healthcare resources for providing stereotactic radiotherapy*

Variable cost per treatment	Minutes per SRT	Cost/hour, including overheads and on-costs[8]	Cost/SRT	Source
Licence fee payable to Zeiss for each NHS treatment	N/A	N/A	£1,250	Oraya/Zeiss, personal communication. Figure excludes VAT.
Junior medical physicist (band 7) undertaking each radiotherapy treatment	30	£53·00	£26·50	
Junior physicist (band 7) - daily QC and warm-up test and power down	3	£53·00	£2·65	Assumes 0.6 hours' staff time per day of running and that an average of 12 patients are treated on each day the SRT machine is run.
Junior doctor (registrar [likely to be ST3 specialist band]) undertaking stereotactic radiotherapy and an intravitreal anti-VEGF injection	45	£73·00	£54·75	This includes 15 minutes to administer an intravitreal injection and 30 minutes to administer SRT.
Band 3 admin clerk to book/schedule appointments	12·5	£19·12	£3·98	
Yearly oversight by Medical Physics expert (band 8A). Compliance with IR(ME)R17 including: Engineer's report after servicing; IR(ME)R training for staff; Incidents; Meetings (45 hours/year regardless of patient numbers)	2·4	£73·00	£2·96	Minutes per SRT estimated in Table S3, appendix p 116.
Yearly oversight by Radiation Protection Adviser (band 8C). Compliance with IR(ME)R17 including: radiation safety training; local rules; risk assessment; radiation safety policy; environmental monitoring (22·5 hours/year regardless of patient numbers)	1·2	£102·00	£2·07	
TOTAL cost per SRT			**£1,342·91**	

Table S2: Time estimates and staff seniority were provided by clinicians and physicists involved in Stereotactic radiotherapy (SRT) clinics at King's College Hospital, London, the centre undertaking the largest volume of on-trial SRT treatments. Abbreviations: IR(ME)R17, Ionising Radiation (Medical Exposures) Regulations 2017; NHS, National Health Service; QC, quality control; ST3, specialist trainee year 3; SRT, stereotactic radiotherapy.

5. Table S3: Cost of Medical Physics expert and Radiation Protection Adviser

Region	All ages population Mid-2019[9]	% of English population*	Number of SRT patients based on prevalence and incidence used in NICE costing template[4]		Total patients/year if prevalent cases are spread over 5 years		Number of days/year the SRT machine is used		Minutes per SRT band 8a physicist/SRT (45 hours/year)		Cost per SRT of band 8a physicist (£73/hour[8])		Minutes per SRT band 8c physicist (22·5 hours/year)		Cost per SRT of band 8c physicist (£102/hour[8])	
			Prevalent cases	Incident cases/year	Years 1-5	Years 6-10	Years 1-5	Years 6-10	Years 1-5	Years 6-10	Years 1-5	Years 6-10	Years 1-5	Years 6-10	Years 1-5	Years 6-10
NORTH EAST	2,669,941	5%	2,425	384	869	384	72	32	3·1	7·0	£3·78	£8·56	1·6	3·5	£2·64	£5·98
NORTH WEST	7,341,196	13%	6,668	1,056	2,389	1,056	199	88	1·1	2·6	£1·37	£3·11	0·6	1·3	£0·96	£2·17
YORKSHIRE AND THE HUMBER	5,502,967	10%	4,998	791	1,791	791	149	66	1·5	3·4	£1·83	£4·15	0·8	1·7	£1·28	£2·90
EAST MIDLANDS	4,835,928	9%	4,392	695	1,574	695	131	58	1·7	3·9	£2·09	£4·72	0·9	1·9	£1·46	£3·30
WEST MIDLANDS	5,934,037	11%	5,390	853	1,931	853	161	71	1·4	3·2	£1·70	£3·85	0·7	1·6	£1·19	£2·69
EAST	6,236,072	11%	5,664	897	2,030	897	169	75	1·3	3·0	£1·62	£3·66	0·7	1·5	£1·13	£2·56
LONDON	8,961,989	16%	8,140	1,289	2,917	1,289	243	107	0·9	2·1	£1·13	£2·55	0·5	1·0	£0·79	£1·78
SOUTH EAST	9,180,135	16%	8,338	1,320	2,988	1,320	249	110	0·9	2·0	£1·10	£2·49	0·5	1·0	£0·77	£1·74
SOUTH WEST	5,624,696	10%	5,109	809	1,831	809	153	67	1·5	3·3	£1·79	£4·06	0·7	1·7	£1·25	£2·84
WALES	3,152,879	6%	2,864	453	1,026	453	86	38	2·6	6·0	£3·20	£7·25	1·3	3·0	£2·24	£5·06
SCOTLAND	5,463,300	10%	4,962	786	1,778	786	148	65	1·5	3·4	£1·85	£4·18	0·8	1·7	£1·29	£2·92
NORTHERN IRELAND	1,893,667	3%	1,720	272	616	272	51	23	4·4	9·9	£5·33	£1·06	2·2	5·0	£3·72	£8·43
Weighted average across regions									**1·5**	**3·4**	**£1·81**	**£4·10**	**0·7**	**1·7**	**£1·27**	**£2·87**
Mean across all years									**2·4**		**£2·96**		**1·2**		**£2·07**	

Table S3: Assumes an average of 12 patients per machine per day. Estimated from the values in the second column. Values sum to >1 as Scotland, Wales and Northern Ireland are not in English prevalence/incidence figures. These values are used to estimate the number of prevalent and incident patients. Abbreviations: NICE, National Institute of Health and Care Excellence; SRT, stereotactic radiotherapy.

Health economic analysis: *Costing analysis tables*

6. Table S4: Costing analysis results: Mean cost of stereotactic radiotherapy, ranibizumab, administration of intravitreal injections and 4-weekly monitoring consultations.

Cost	SRT + ranibizumab (n=241)	Sham SRT + ranibizumab (n=118)	Difference
SRT and first ranibizumab dose†	£1,894	£728	£1,165
Ranibizumab and monitoring up to month 24‡	£11,315 (£10,592, £12,031)	£13,045 (£12,234, £13,862)	-£1,730 (-£2,647, -£835)*
Total cost of SRT, ranibizumab and monitoring‡	£13,209 (£12,486, £13,925)	£13,774 (£12,960, £14,594)	-£565 (-£1,483, £332)

Table S4: Data are mean cost (95% confidence interval). Results were analysed on a complete-case intention-to-treat basis on participants for whom the primary endpoint data were complete, excluding patients who died or withdrew. The reference year for costs was 2021-2. Confidence intervals are based on bootstrapping. Abbreviation: SRT, stereotactic radiotherapy.

** p=0·0002 for between-group difference based on two-sided bootstrap p-values.*

† Confidence intervals not shown, since the only variation between patients resulted from four patients in the sham SRT group who did not receive SRT due to non-attendance, or received the opposite treatment.

‡ Discounted 3·5% following UK's National Institute for Health and Care Excellence (NICE) reference case.[1] *Cost estimates from months 1-24 are adjusted for age, gender, baseline EQ-5D-5L utility, baseline best-corrected visual acuity and the number of months from the start of the first UK COVID lockdown to the second anniversary of randomisation (when the primary outcome was assessed). Mean values are presented for women aged 78 years, who were randomised > 24 months before COVID restrictions (and hence were unaffected by the COVID pandemic) with visual acuity of 69 letters and EQ-5D-5L utility of 0·84.*

7. Table S5: Estimate of the number of anti-VEGF injections avoided and potential budget impact from SRT for high-income countries globally

Item	Proportion of patients	Number of patients in high income countries	Reference
People aged 50 years and over 2023	N/A	489,941,685	World Bank: population of high-income countries aged ≥50 in 2023 https://databank.worldbank.org/source/population-estimates-and-projections
Number of anti-VEGF injections avoided per patient treated SRT vs. sham	2·9 (1·6, 4·2)	N/A	Table 2
Saving per patient treated SRT vs. sham	£565 (£332, £1,483)	N/A	Table S4 STAR study costing analysis, including cost of SRT, ranibizumab injections and monitoring consultations - over 2 years (2021/2 prices)
Budget impact for prevalent cohort			
Prevalence of late-stage wet age-related macular degeneration	1·20%	5,879,300	Prevalence in England: NICE resource impact template for faricimab for wet age-related macular degeneration https://www.nice.org.uk/guidance/ta800/resources
Proportion of people who are eligible for anti-VEGF	85·00%	4,997,405	NICE resource impact template for faricimab for wet age-related macular degeneration https://www.nice.org.uk/guidance/ta800/resources
Number of prevalent people likely to have SRT	22%	1,099,429	In the original INTREPID study, 272 patients were screened, of whom 230 were eligible. The STAR study was then based on the best responder subset, which comprised 26% of the INTREPID population. We therefore assumed that 22% of patients are eligible.
Injections avoided over first 2 years - prevalent patients	N/A	3,188,345	Reduction in injections (2.9) multiplied by number of potential patients
Cost saving over first 2 years - prevalent patients	N/A	£620,966,594	Cost saving per patient (£565) multiplied by number of potential patients
Budget impact for incident cohort			
Incidence of late-stage wet age-related macular degeneration	0.19%	930,889	Incidence in England: NICE resource impact template for faricimab for wet age-related macular degeneration https://www.nice.org.uk/guidance/ta800/resources
Proportion of people who are eligible for treatment	85·00%	791,256	NICE resource impact template for faricimab for wet age-related macular degeneration https://www.nice.org.uk/guidance/ta800/resources
Number of incident people likely to have SRT each year	22%	174,076	In the original INTREPID study, 272 patients were screened, of whom 230 were eligible. The STAR study was then based on the best responder subset, which comprised 26% of the INTREPID population. We therefore assumed that 22% of patients are eligible.
Number of injections avoided over first 2 years after SRT - incident patients	N/A	504,821	Reduction in injections (2·9) multiplied by number of potential patients
Cost saving over first 2 years after SRT - incident patients	N/A	£98,319,711	Cost saving per patient (£565) multiplied by number of potential patients
Annual figures: Incident and prevalent cohorts combined			
Number of injections avoided per year	N/A	1,846,583	Number for prevalent cohort plus number for incident cohort, all divided by two
Cost saving per year	N/A	£359,643,152	Number for prevalent cohort plus number for incident cohort, all divided by two

8. Health economic analysis: *References*

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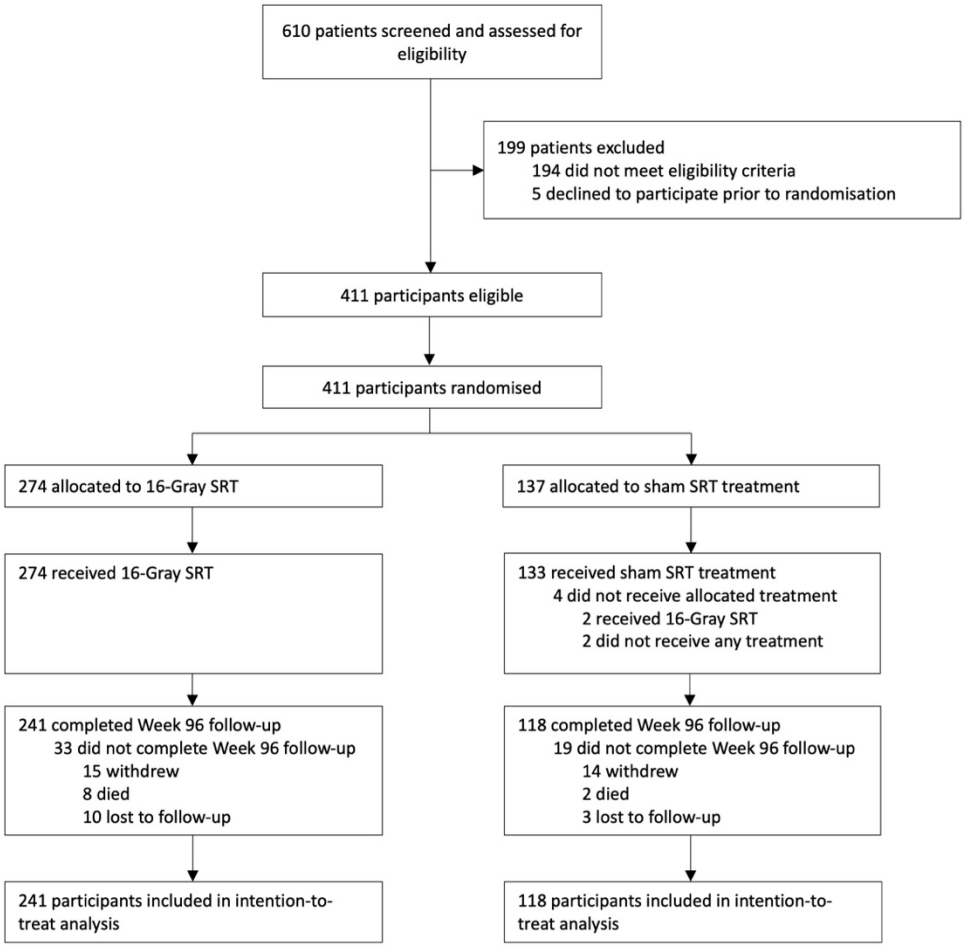
9. CONSORT flow diagram



Compliance, missingness and deviations: *Compliance*

10. Table S6: Classification of visit compliance

Assessment Categorisation Red (poor compliance), Amber (reduced compliance), Green (per protocol)
Visit attendance Red = 'Missed consultation' Amber = 'Visit out of window' For the purpose of this analysis, visits up to week 96 are in window if they are either within 14 days of the study visit planner target visit date, or from 21 to 42 days after the last visit. The greater tolerance for longer than shorter visits is because a shorter visit might reduce the likelihood of needing an injection, whereas a slightly longer visit will probably not, as macular fluid persists. Green = 'Visit within window'
Best-correct visual acuity Red = Not performed at visit and does not meet criteria for amber Amber = Visual acuity not performed but injection required at same visit regardless, due to other disease activity (for example, fluid on OCT such that visual acuity would not alter decision to inject) Green = Performed as per protocol
Fundus examination Red = Not performed at visit and does not meet criteria for amber Amber = Not performed but any of the following performed (as they allow doctor to see fundus): o OCT o Fundus Photography o Fluorescein Angiography Not performed but any of the following mandated treatment anyway: o Evidence of subretinal, intraretinal, or sub-RPE fluid on OCT o New or persistent subretinal or intraretinal haemorrhage o Increased lesion size on fluorescein angiography relative to last angiogram o Leakage on fluorescein angiography Green = Performed as per protocol
Optical coherence tomography Red = Not performed at visit and does not meet criteria for amber Amber = OCT not performed but injection required anyway: o New or persistent subretinal or intraretinal haemorrhage o Increased lesion size on fluorescein angiography relative to last angiogram o Leakage on fluorescein angiography OCT wrongly recorded as not performed but actually was, as investigator records evidence of subretinal, intraretinal, or sub-RPE fluid on OCT Green = Performed as per protocol
Ranibizumab injection Red = Ranibizumab injection not given when indicated Amber = Given when indicated, but out of window by >14 days Green = Given when indicated, within 14-day window

Compliance, missingness and deviations: *Missingness*

11. Table S7: Missingness in baseline and outcome variables.

	SRT (N=274)	Sham SRT (N=137)	Overall (N=411)
Demographic characteristics			
Age	-	-	-
Female	-	-	-
Ethnicity	-	-	-
Smoking status	-	-	-
Ophthalmic variables at baseline			
AMD duration	5 (2%)	6 (5%)	11 (3%)
Number of previous anti-VEGF injections	1 (<1%)	7 (5%)	8 (2%)
Lens status	-	-	-
ETDRS visual acuity	-	-	-
Total lesion size	15 (6%)	7 (5%)	22 (5%)
Total active lesion size	23 (8%)	8 (6%)	31 (8%)
Central subfield thickness	1 (<1%)	-	1 (<1%)
Total macular volume	5 (2%)	4 (3%)	9 (2%)
Patient-reported quality of life at baseline			
NEI VFQ-25 composite score	7 (3%)	-	7 (2%)
EQ-5D-5L (VAS)	5 (2%)	-	5 (1%)
Outcomes at Week 96			
Number of *p.r.n.* anti-VEGF injections	33 (12%)	19 (14%)	52 (13%)
ETDRS visual acuity	35 (13%)	17 (12%)	52 (13%)
Total lesion size	72 (26%)	35 (26%)	107 (26%)
Total active lesion size	140 (51%)	54 (39%)	194 (47%)
Central subfield thickness	27 (10%)	19 (14%)	46 (11%)
NEI VFQ-25 composite score	33 (12%)	18 (13%)	51 (12%)
EQ-5D-5L (VAS)	33 (12%)	18 (13%)	51 (12%)

Table S7: Data are count (%). Abbreviations: anti-VEGF = anti-Vascular Endothelial Growth Factor; EQ-5D-5L (VAS), Euroquol questionnaire with visual analogue scale; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; NEI VFQ-25, National Eye Institute 25-item visual function questionnaire; p.r.n. = pro-re-nata dosing regimen; SRT = stereotactic radiotherapy.

Compliance, missingness and deviations: *Deviations*

12. Table S8: Participant protocol deviations by randomised allocations

Participants (n, %)	SRT (n = 274)	Sham-SRT (n = 137)	Overall (n = 411)
Any protocol deviation, at any visit up to week 96	240 (88%)	127 (93%)	367 (89%)
Deviation affecting primary outcome (week 96)	54 (20%)	21 (15%)	75 (18%)
Out of window assessments	165 (60%)	93 (68%)	258 (63%)
Non-certified Assessor	80 (29%)	44 (32%)	124 (30%)
Missed Visit*	**111 (41%)**	**58 (42%)**	**169 (41%)**
Participant cancelled	38 (14%)	16 (12%)	54 (13%)
Participant unwell	20 (7%)	15 (11%)	35 (9%)
To bring back into window	17 (6%)	13 (9%)	30 (7%)
All other reasons	61 (22%)	37 (27%)	98 (24%)
Missed Assessment*	**85 (31%)**	**35 (26%)**	**120 (29%)**
Staff unavailable	24 (9%)	9 (7%)	33 (8%)
Site error	53 (19%)	16 (12%)	69 (17%)
Equipment failure	14 (5%)	5 (4%)	19 (5%)
Participant health concerns	7 (3%)	5 (4%)	12 (3%)
Participant refusal	2 (1%)	1 (1%)	3 (1%)
Other^	61 (22%)	30 (22%)	91 (22%)

Table S8: Data are presented as participants (n) and proportion with specific deviation in allocated group (%). Abbreviations: SRT, stereotactic radiotherapy.
**Categories and sub-categories of deviations may not add up to total as participants may have deviated for more than one reason on separate occasions.*
^Other deviations were broad and heterogenous, with the most common being clinicians choosing to defer treatment, despite being indicated, for clinical and safety reasons. Other reasons included administrative and data capture entry errors, drug shortages, and non-certified vision rooms being used among others.

13. Table S9: All protocol deviations by randomised allocation

All visits with deviations up to week 96 (n, %)	SRT (n = 1113)	Sham-SRT (n = 616)	Overall (n = 1729)
Deviations potentially affecting primary outcome	87 (8%)	43 (7%)	130 (8%)
Out of window visits	492 (44%)	296 (48%)	788 (46%)
Non-certified assessor	132 (12%)	80 (13%)	212 (12%)
Missed Visit	**209 (19%)**	**143 (23%)**	**352 (20%)**
Participant cancelled	52 (5%)	25 (4%)	77 (4%)
Participant unwell	32 (3%)	23 (4%)	55 (3%)
To bring back into window	24 (2%)	18 (3%)	42 (2%)
All other reasons	101 (9%)	77 (13%)	178 (10%)
Missed Assessment	**153 (14%)**	**47 (8%)**	**200 (12%)**
Staff unavailable	29 (3%)	14 (2%)	43 (3%)
Site error	97 (9%)	22 (4%)	119 (7%)
Equipment failure	14 (1%)	5 (1%)	19 (1%)
Participant health concerns	10 (1%)	5 (1%)	15 (1%)
Participant refusal	3 (<1%)	1 (<1%)	4 (<1%)
Other^	127 (11%)	50 (8%)	177 (10%)

Table S9: Data are presented as deviations (n) and proportion of specific deviation out of all recorded deviations in each group (%). Abbreviations: SRT, stereotactic radiotherapy.
^Other deviations were broad and heterogenous, with the most common being clinicians choosing to defer treatment, despite being indicated, for clinical and safety reasons. Other reasons included administrative and data capture entry errors, drug shortages, and non-certified vision rooms being used among others.

Sensitivity Outcomes

14. Table S10: Sensitivity analyses of missing data and COVID pandemic impact: primary outcome

		Mean number of injections		Difference (95% confidence interval)	P-Value
		SRT	Sham SRT		
Base Intention-To-Treat (ITT) model		(N=241) 10·3	(N=118) 13·3	-2·9 (-4·2 to -1·6)	<0·0001*
(i)	All assessments up to primary outcome completed before COVID lockdown [a]	(N=152) 10·7	(N=73) 13·7	-3.0 (-4·6 to -1·4)	0·0004*
(ii)	At least one assessment up to primary outcome after COVID lockdown [b]	(N=89) 9·4	(N=45) 12·5	-3·1 (-5·3 to -0·8)	0·0077*
(iii)	Fully compliant population model [c]	(N=225) 10·4	(N=100) 13·5	-3·1 (-4·5 to -1·7)	<0·0001*
(iv)	Reduced compliance population model [d]	(N=16) 10·1	(N=18) 11·8	-1·7 (-4·3 to 0·9)	0·20
Base ITT model with additional adjustments [e]		(N=241) 10·3	(N=118) 13·3	-3·0 (-4·3 to -1·7)	<0·0001*
Per-Protocol model [f]		(N=243) 10·3	(N=116) 13·2	-2·9 (-4·2 to -1·6)	<0·0001*
Base ITT model with multiple imputation [g]		(N=274) 10·5	(N=137) 13·3	-2·8 (-4·1 to -1·4)	<0·0001*

*Table S10: All models are adjusted for baseline stratification factor – National Treatment Centre. The mean in stereotactic radiotherapy (SRT) group is calculated by adding the obtained coefficients to the mean number of injections in the sham SRT group (i.e., adjusted means). *Denotes significant test (p < 0·05).*

a. *Main ITT model restricted to participants who completed all 24 visits (primary outcome) before the COVID lockdown 23 March 2020 (population (i) in primary outcome manuscript).*
b. *ITT model restricted to participants who had at least one visit due after lockdown (population (ii) in primary outcome manuscript).*
c. *ITT model restricted to the more compliant population defined as participants who had no more than four non-compliant (red) visits or eight less compliant (amber) visits, and who did not die or withdraw (population (iii) in the primary outcome manuscript). Definitions of red and amber visits are given in Statistical analysis plan Appendix A, appendix pp 108-110; and Table S6, appendix p 121.*
d. *ITT model restricted to the less compliant population (population (iv) in primary outcome manuscript).*
e. *Main intention-to-treat (ITT) model with additional adjustment for variables showing significant difference (p < 0·05) between participants with complete primary outcome and those without (as detailed in Table S7, appendix p 122).*
f. *Groups categorized according to the received treatment (i.e., per-protocol analysis) irrespective of compliance.*
g. *ITT model on multiply imputed dataset. Multiple imputation with chained equations was applied to generate 20 datasets. Baseline demography, ophthalmic history, and recruitment site were used to impute the 52 incomplete values in the primary outcome. Parameter estimates were finally combined using Rubin's principles.*

Base ITT model was undertaken as per statistical analysis plan for primary outcome. Models (i) – (iv) are pre-specified and labelled in the protocol and statistical analysis plan. All other models are are post-hoc.
Abbreviations: anti-VEGF, anti-Vascular Endothelial Growth Factor; ITT, intention-to-treat model; SRT, stereotactic radiotherapy.

Clinical efficacy outcomes: *Primary and secondary outcomes by sex*

15. Table S11: Primary and secondary efficacy outcomes at Week 96 by sex

	Male			Female		
	SRT (N=103)	Sham (N=43)	Adjusted regression coefficient (95% CI)	SRT (N=138)	Sham (N=75)	Adjusted regression coefficient (95% CI)
Primary outcome						
Number of *prn* anti-VEGF injections, mean (SD)	11 (6·6)	14 (6·0)	-3·5 (-5·7 to -1·4)	11 (6·1)	13 (5·7)	-2·8 (-4·5 to -1·2)
Secondary outcomes						
Change in visual acuity score, mean (SD)	-1·5 (11)	-3·8 (10)	1·1 (-3·0 to 5·1)	-4·0 (11)	-0·2 (12)	-3·8 (-7·2 to -0·5)
ETDRS visual acuity, mean (SD)	66 (14)	68 (15)	-	65 (16)	69 (16)	-
Losing < 15 ETDRS letters	92 (89%)	41 (93%)	-	117 (86%)	71 (93%)	-
Gaining ≥ 0 ETDRS letters	54 (52%)	18 (41%)	-	53 (39%)	40 (53%)	-
Gaining ≥ 15 ETDRS letters	4 (4%)	2 (5%)	-	3 (2%)	1 (1%)	-
Total lesion size (mm^2), median (IQR)	8·0 (4·4-12)	7·5 (3·7-11)	-	8·5 (5·2-12)	7·2 (4·3-12)	-
Total active lesion size (mm^2), median (IQR)	6·5 (3·7-12)	6·2 (2·8-9·6)	-	7·9 (5·1-12)	6·5 (4·0-12)	-
Central subfield thickness (µm), mean (SD)	309 (127)	316 (108)	-	302 (134)	302 (96)	-
NEI VFQ-25 composite score, median (IQR)	89 (76-95)	90 (83-96)	-	87 (72-94)	81 (60-92)	-
EQ-5D (VAS), median (IQR)	85 (75-95)	85 (79-95)	-	85 (70-95)	80 (70-90)	-

Table S11: Data are n (%), median (interquartile range), or mean (standard deviation). The figures are unadjusted, except for the regression coefficients, which are adjusted for the treatment centre in the case of the primary outcome, and for both the treatment centre and baseline visual acuity in the case of the change in visual acuity score. Structural outcomes (lesion size, active lesion size and central subfield thickness) are those from the independent reading centre. Sex was self-reported. This table was prepared at the request of Lancet, during peer review. Abbreviations: EQ-5D-5L (VAS), Euroquol questionnaire with visual analogue scale; ETDRS, Early Treatment Diabetic Retinopathy Study; IQR, interquartile range; NEI VFQ-25, National Eye Institute 25-item visual function questionnaire; prn, pro-re-nata; SD, standard deviation; SRT, stereotactic radiotherapy; VEGF, vascular endothelial growth factor; mm2, millimeter squared; µm, micrometer; 95% CI, 95% confidence interval.

Clinical efficacy outcomes: *Number of injections*

16. Table S12: Mean and cumulative number of ranibizumab injections per 4-weekly visit

Visit week	Number participants		Mean injections		Cumulative mean injections	
	SRT	Sham	SRT	Sham	SRT	Sham
4	273	132	0·73	0·72	0·73	0·72
8	268	126	0·74	0·74	1·48	1·48
12	265	131	0·69	0·71	2·07	2·14
16	252	120	0·67	0·69	2·68	2·76
20	243	118	0·64	0·69	3·21	3·44
24	254	127	0·61	0·65	3·67	3·91
28	259	123	0·59	0·65	4·1	4·57
32	258	121	0·57	0·64	4·54	5·11
36	254	120	0·56	0·64	5	5·73
40	249	114	0·55	0·62	5·45	6·25
44	257	124	0·53	0·61	5·78	6·66
48	259	127	0·51	0·6	6·14	7·17
52	256	117	0·5	0·6	6·55	7·81
56	252	116	0·5	0·6	6·97	8·39
60	250	115	0·49	0·59	7·36	8·9
64	256	120	0·48	0·58	7·64	9·36
68	254	119	0·47	0·58	8·04	9·87
72	250	117	0·47	0·58	8·44	10·41
76	248	113	0·47	0·57	8·85	10·89
80	243	110	0·46	0·57	9·28	11·35
84	247	118	0·46	0·56	9·6	11·84
88	244	116	0·45	0·56	9·98	12·29
92	242	114	0·45	0·55	10·39	12·74
96	241	118	0·45	0·56	10·71	13·33

Table S12: Mean, number and cumulative mean number of ranibizumab injections from week 4 to week 96, excluding the baseline injection as that reflected pre-existing disease activity and was mandated in all participants. Abbreviations: SRT, stereotactic radiotherapy.

17. Figure S1: Mean number of ranibizumab injection each 4-weekly visit

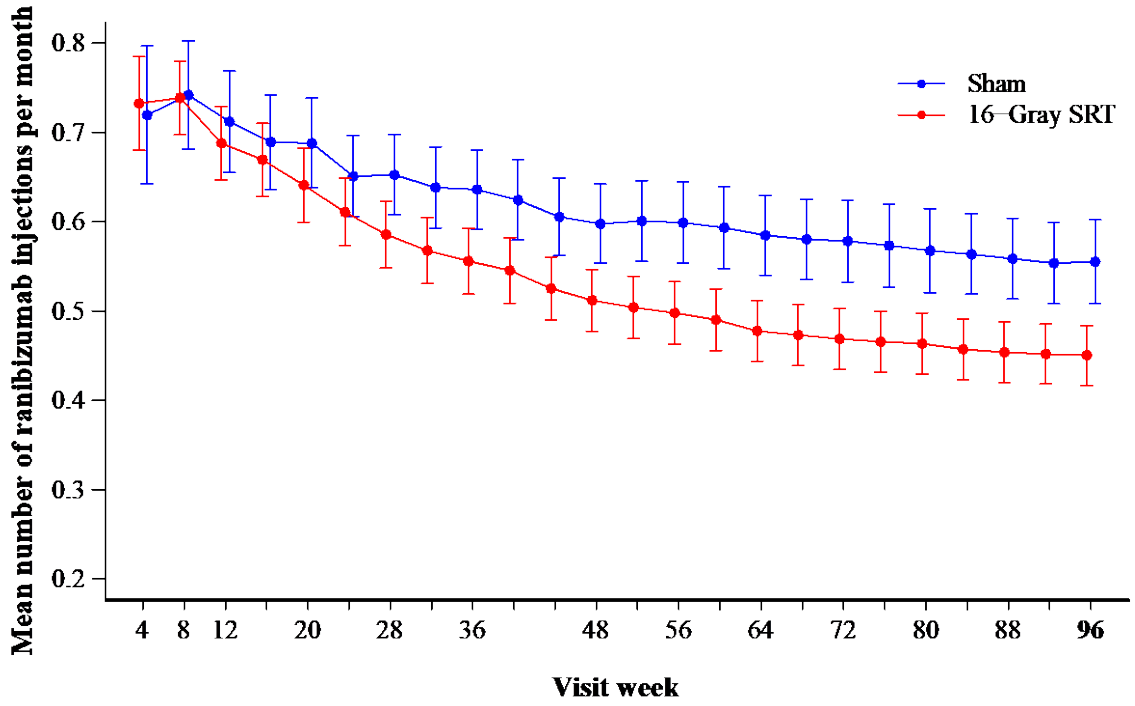


Figure S1: Mean number of ranibizumab injection from week 4 to week 96, in the stereotactic radiotherapy (SRT) and sham SRT groups. Error bars show the 95% confidence interval. Abbreviations: SRT, stereotactic radiotherapy.

18. Figure S2: Number of injections by participants

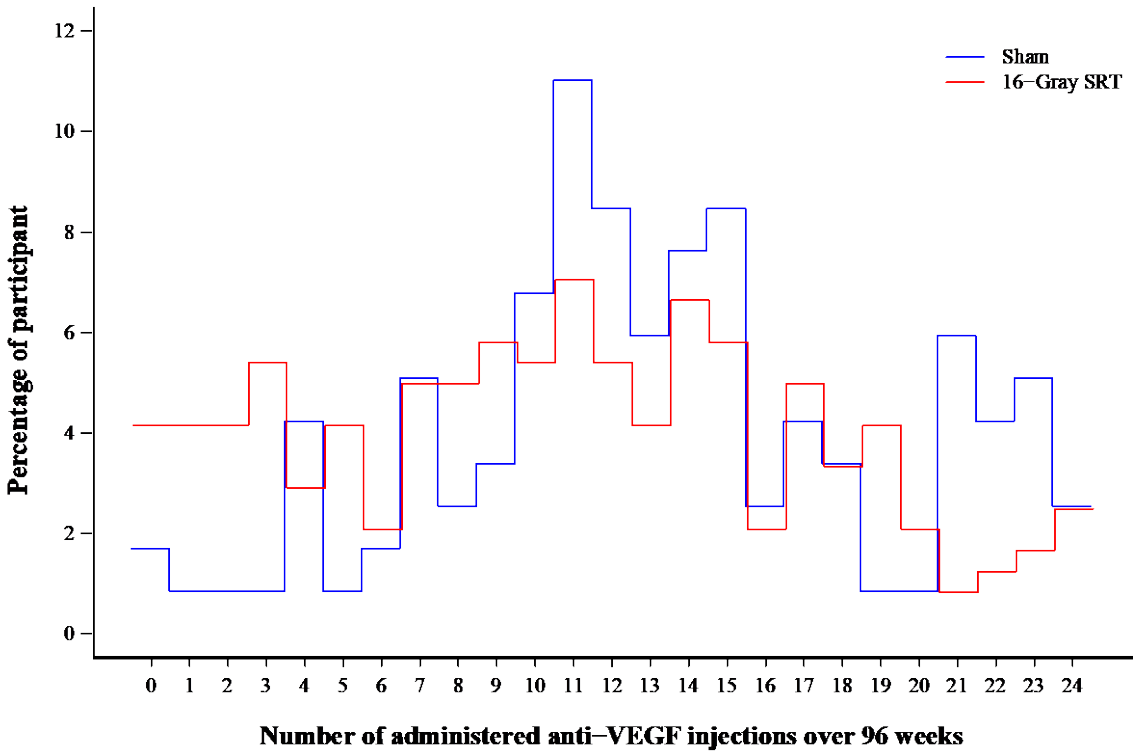


Figure S2: Number of injections participants received over 96 weeks, comparing the stereotactic radiotherapy (SRT) and sham SRT groups. Abbreviations: SRT, stereotactic radiotherapy; VEGF, vascular endothelial growth factor.

Clinical efficacy outcomes : *Visual acuity*

19. Figure S3: Mean visual acuity over time

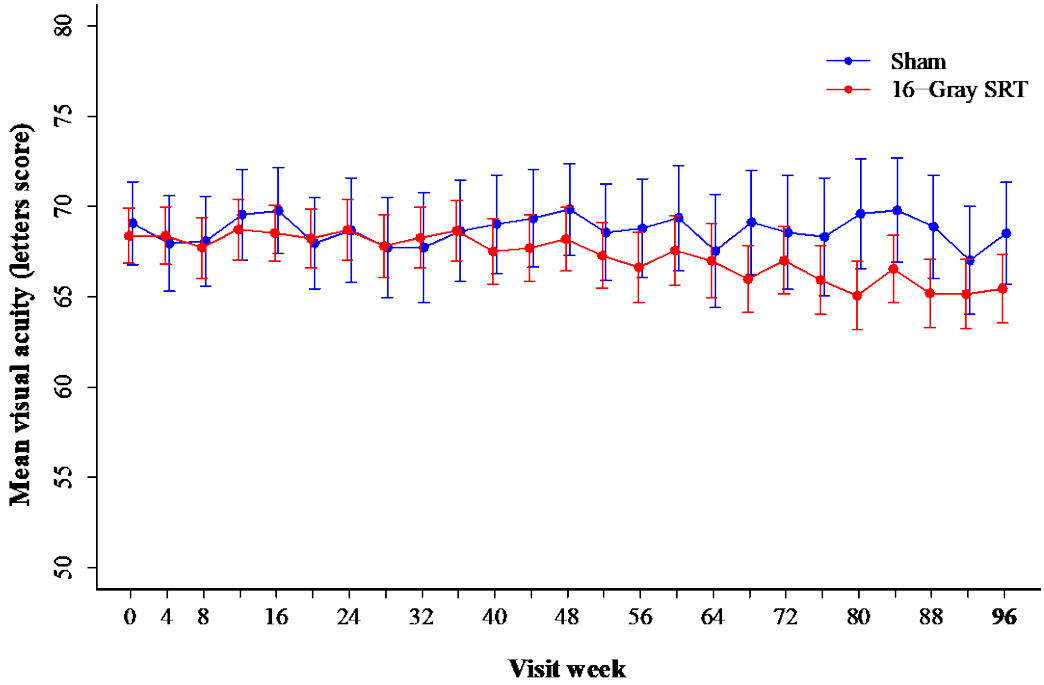


Figure S3: Mean Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at each 4-weekly visit to week 96, comparing the stereotactic radiotherapy (SRT) and sham SRT groups. Error bars show the 95% confidence interval. Abbreviations: SRT, stereotactic radiotherapy.

Clinical efficacy outcomes : *Central subfield thickness*

20. Figure S4: Optical coherence tomography central subfield thickness over time

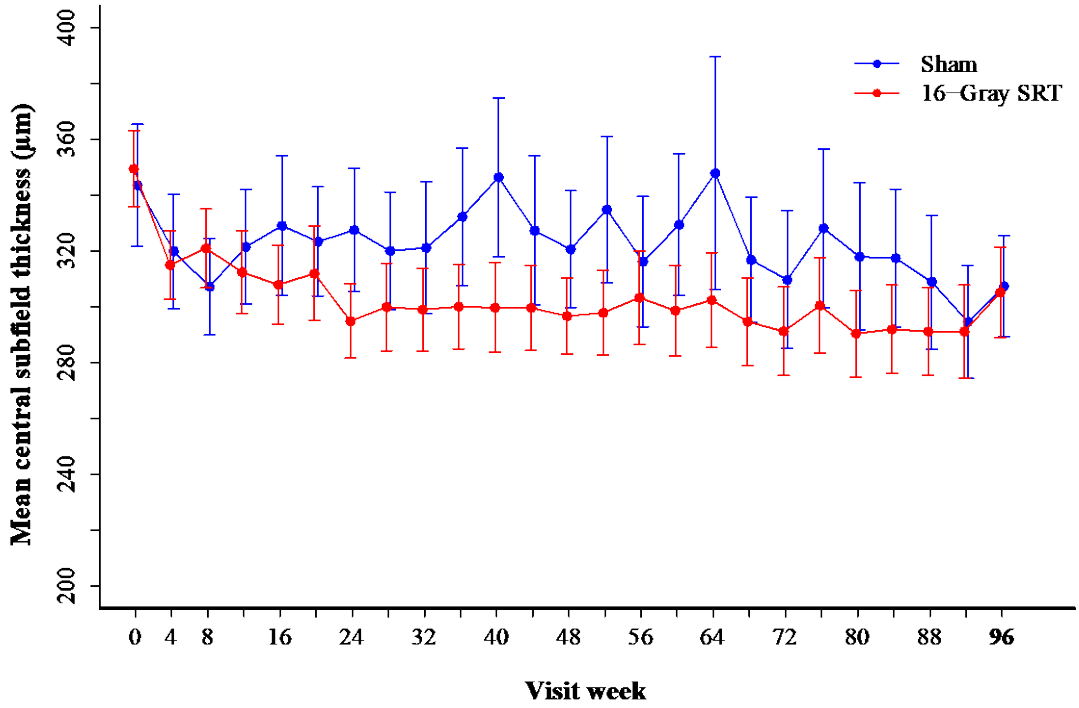


Figure S4: Optical coherence tomography (OCT) central 1mm subfield thickness in the central 1 mm subfield, at each 4-weekly visit to week 96, comparing the stereotactic radiotherapy (SRT) and sham SRT groups. Values were determined automatically by each site's OCT device, but masked site clinicians were required to manually correct any segmentation errors. Separate analyses, used for the predefined OCT secondary outcome, were undertaken by the reading centre at baseline and yearly thereafter. Error bars show the 95% confidence interval of the mean. Abbreviations: OCT, optical coherence tomography; SRT, stereotactic radiotherapy; µm, micrometer.

Clinical efficacy outcomes : *Reading-centre imaging outcomes*

21. Table S13: Reading centre-determined optical coherence tomography analysis

	SRT	Sham SRT	Difference in means (SRT – Sham)
Baseline	N = 274	N = 137	
Total centrepoint thickness, µm	373 (356 to 389)	369 (342 to 395)	4 (-27 to 35)
Neurosensory retinal thickness, µm	258 (246 to 270)	270 (248 to 292)	-12 (-36 to 13)
Subretinal fluid height, µm	92 (80 to 103)	118 (96 to 141)	-26 (-52 to -1·1)
PED height, µm	122 (107 to 138)	101 (80 to 122)	21 (-4·5 to 47)
At week 48	N = 259	N = 127	
Total centrepoint thickness, µm	279 (260 to 298)	288 (261 to 315)	-9.4 (-42 to 23)
Neurosensory retinal thickness, µm	196 (182 to 209)	199 (180 to 218)	-3·1 (-27 to 20)
Subretinal fluid height, µm	83 (67 to 100)	89 (71 to 108)	-5·9 (-30 to 18)
PED height, µm	102 (89 to 116)	106 (86 to 126)	-3·9 (-28 to 20)
At week 96	N = 241	N = 118	
Total centrepoint thickness, µm	237 (219 to 256)	272 (241 to 303)	-35 (-70 to 0·9)
Neurosensory retinal thickness, µm	174 (160 to 188)	177 (158 to 196)	-3·3 (-27 to 20)
Subretinal fluid height, µm	84 (63 to 104)	94 (70 to 117)	-9·9 (-40 to 21)
PED height, µm	88 (76 to 99)	122 (99 to 145)	-34 (-60 to -8·5)

Table S13: Optical coherence tomography thicknesses measured at the centre of the fovea by the independent reading centre at the respective timepoints. Total centrepoint thickness was measured from the inner limiting membrane to the basement membrane, inclusive of all fovea-involving subretinal fluid and pigment epithelial detachment. Neurosensory retinal thickness was measured from the inner limiting membrane to the outer ellipsoid zone only. Data are mean (95% confidence interval). Abbreviations: PED, pigment epithelial detachment; SRT, stereotactic radiotherapy; µm, micrometer.

22. Table S14: Reading centre-determined proportion of eyes with subretinal fluid and pigment epithelial detachment

		SRT	Sham SRT
		N = 273	N = 134
Presence of subretinal fluid	Screening	128 (46%)	74 (56%)
		N = 258	N = 124
	Week 48	54 (20%)	43 (32%)
		N = 234	N = 116
	Week 96	48 (17%)	37 (28%)
		N = 273	N = 134
Presence of pigment epithelial detachment	Screening	220 (80%)	109 (82%)
		N = 258	N = 124
	Week 48	205 (74%)	101 (76%)
		N = 234	N = 116
	Week 96	180 (65%)	97 (73%)

Table S14: Reading centre-determined presence or absence of subretinal fluid and pigment epithelial detachment. Data are n (%). Abbreviations: SRT, stereotactic radiotherapy

Clinical efficacy outcomes : *Subgroup analyses*

23. Figure S5: Difference in number of injections by pre-specified subgroup

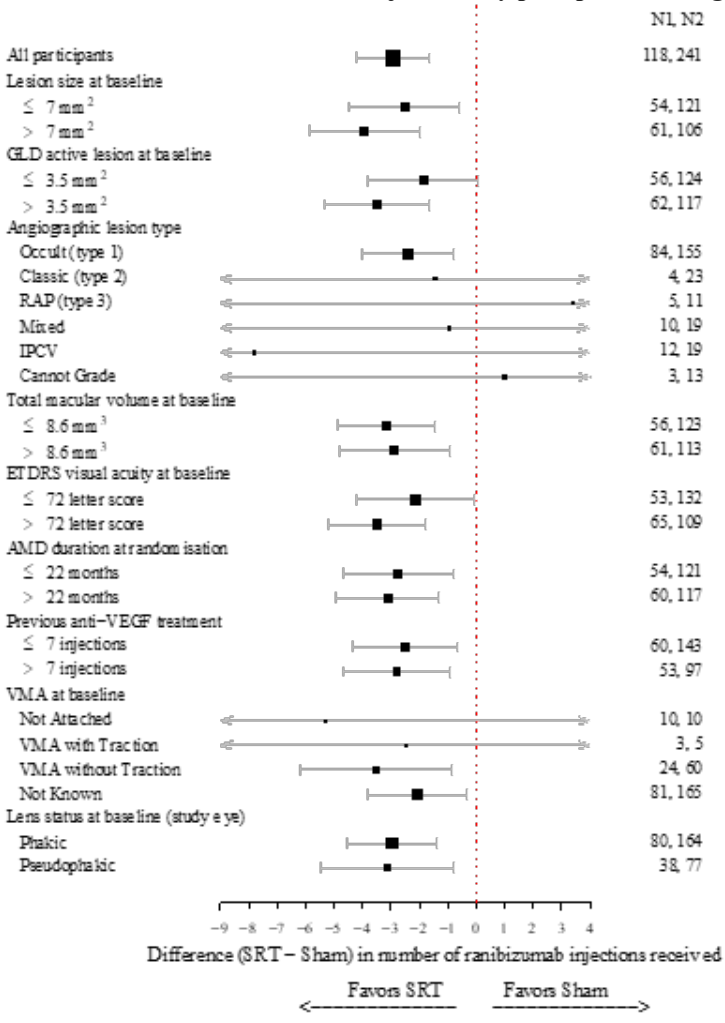


Figure S5: Difference in number of injections by pre-specified subgroups. N1 = Sham-SRT eyes, N2 = SRT eyes. Abbreviations: AMD, age-related macular degeneration; ETDRS, early treatment of diabetic retinopathy study; GLD, greatest linear dimension; IPCV, idiopathic polypoidal choroidal vasculopathy; RAP, retinal angiomatous proliferation; SRT, stereotactic radiotherapy; VEGF, vascular endothelial growth factor; VMA, vitreomacular adhesion; mm^3, millimeters cubed; mm^2, millimetres squared..

24. Figure S6: Difference in final visual acuity by pre-specified subgroup

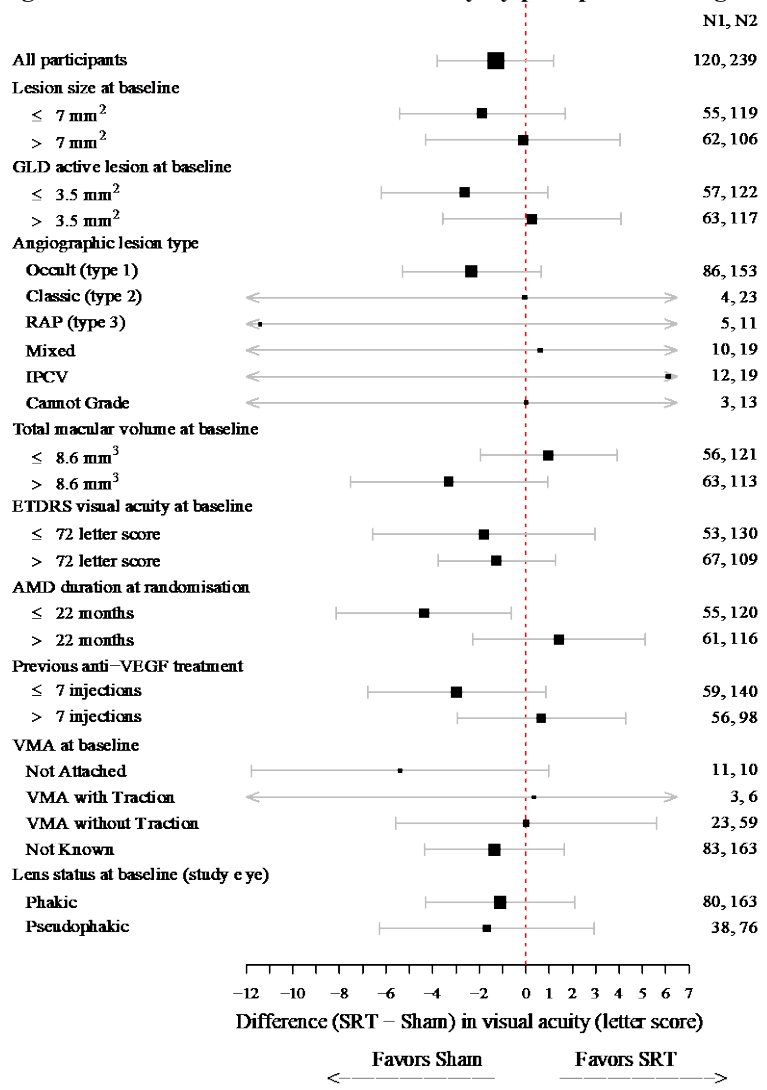


Figure S6: Difference in final visual acuity by pre-specified subgroups. N1 = Sham-SRT eyes, N2 = SRT eyes. Abbreviations: AMD, age-related macular degeneration; ETDRS, early treatment of diabetic retinopathy study; GLD, greatest linear dimension; IPCV, idiopathic polypoidal choroidal vasculopathy; RAP, retinal angiomatous proliferation; SRT, stereotactic radiotherapy; VEGF, vascular endothelial growth factor; VMA, vitreomacular adhesion; mm^3, millimeters cubed; mm^2, millimetres squared.

25. Figure S7: Difference in final optical coherence tomography central subfield thickness by pre-specified subgroup

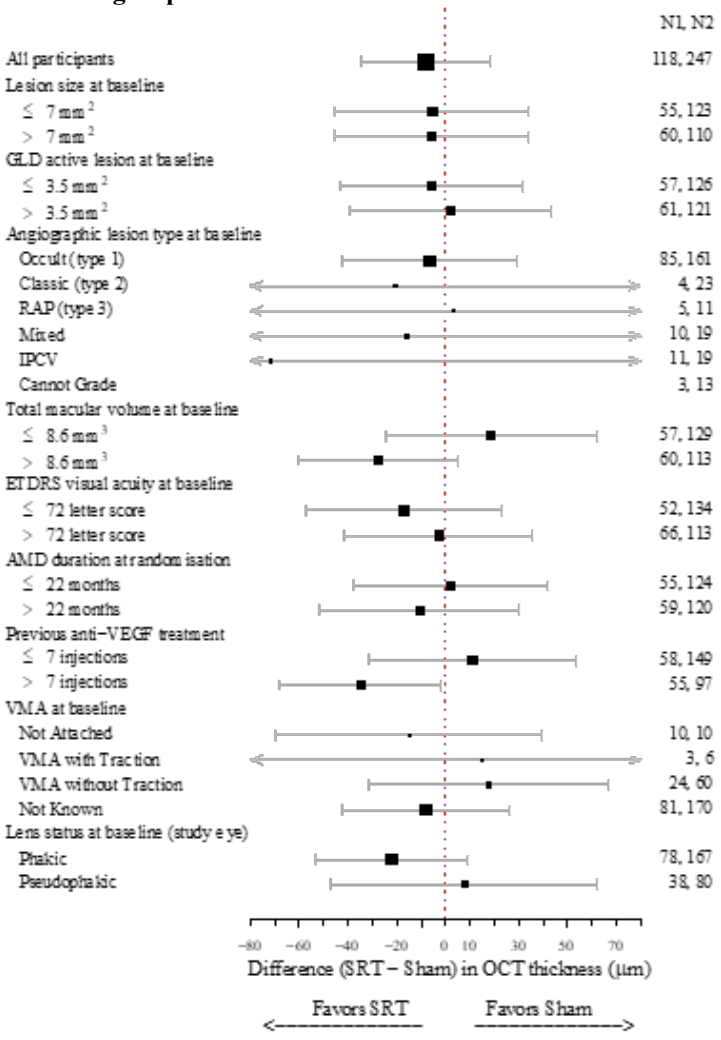


Figure S7: Difference in final central subfield OCT thickness by pre-specified subgroups. N1 = Sham-SRT eyes, N2 = SRT eyes. Abbreviations: AMD, age-related macular degeneration; ETDRS, early treatment of diabetic retinopathy study; GLD, greatest linear dimension; IPCV, idiopathic polypoidal choroidal vasculopathy; OCT, optical coherence tomography; RAP, retinal angiomatous proliferation; SRT, stereotactic radiotherapy; VEGF, vascular endothelial growth factor; VMA, vitreomacular adhesion; mm^3, millimeters cubed; mm^2, millimetres squared.

Safety: *Adverse events*

26. Table S15: Adverse events and serious adverse events in the study eye by received treatment

	Adverse events		Serious adverse events	
	SRT	**Sham SRT**	**SRT**	**Sham SRT**
	(N=276)	(N=133)	(N=276)	(N=133)
Total number of events (n)	148	62	70	17
Participants with event/s	95 (34%)	44 (33%)	45 (16%)	13 (10%)
1 event	60 (22%)	32 (24%)	30 (11%)	10 (8%)
2 events	24 (9%)	8 (6%)	10 (4%)	2 (2%)
3 events	6 (2%)	2 (2%)	3 (1%)	1 (1%)
≥ 4 events	5 (2%)	2 (2%)	2 (1%)	-
Days to first event	181 [56-334]	174 [84-300]	335 [220-514]	228 [141-314]
Ocular events				
Cataract/cataract surgery	-	-	28 (10%)	12 (9%)
Macular haemorrhage	1 (<1%)	-	2 (1%)	-
Conjunctival/subconjuctival haemorrhage	14 (5%)	6 (45%)	2 (1%)	-
Endophthalmitis	-	-	1 (<1%)	1 (<1%)
YAG capsulotomy	8 (3%)	-	2 (1%)	-
Ocular Events of Special Interest: Retina microvascular changes (mandated reporting as an SAE)*	-	-	10 (4%)	-
Telangiectasia	-	-	1 (<1%)	-
Cotton wool spot	-	-	4 (1%)	-
Exudates	-	-	2 (1%)	-
Retinal haemorrhage	-	-	6 (2%)	-
Retinal microaneurysm	-	-	1 (<1%)	-
Retinal neovascularisation	-	-	-	-
Optic disc neovascularisation	-	-	-	-
Capillary dilation	-	-	-	-
Perivascular sheathing	-	-	-	-
Other retinopathy suspected related to radiotherapy	-	-	5 (2%)	-

*Table S15: Data are n (%), median [interquartile range]. Multiple events in the same category were counted only once. *To ensure prompt and vigilant reporting of any radiation-related retinal damage, the protocol instructed site investigators to report any retinal microvascular change as a serious adverse event (SAE), even if it would not otherwise meet the definition of an SAE. Abbreviations: SAE, serious adverse event; SD, standard deviation; SRT, stereotactic radiotherapy; YAG, Yttrium-Aluminium-Garnet*

373 **27. Table S16: All adverse events and serious adverse events by received treatment**
374

	Adverse Events		Serious Adverse Events		Combined Adverse and Serious Adverse Events	
	SRT (N=276)	**Sham SRT** (N=133)	**SRT** (N=276)	**Sham SRT** (N=133)	**SRT** (N=276)	**Shan SRT** (N=133)
Total number of events (n)	817	392	214	73	1031	465
Participants with event/s	213 (77%)	100 (75%)	113 (41%)	47 (35%)	231 (84%)	108 (81%)
1 event	45 (16%)	33 (25%)	61 (22%)	28 (21%)	40 (14%)	30 (23%)
2 events	44 (16%)	18 (14%)	30 (11%)	15 (11%)	47 (17%)	23 (17%)
3 events	32 (12%)	12 (9%)	10 (4%)	1 (0·8%)	31 (11%)	13 (10%)
≥ 4 events	92 (33%)	37 (28%)	12 (4%)	3 (2%)	113 (41%)	42 (32%)
Days to first event, median [IQR]	127 [44-266]	151 [68-310]	295 [169-506]	274 [135-472]	129 [42-272]	142 [54-270]
Deaths	-	-	6 (2%)	1 (0·8%)	6 (2%)	1 (0·8%)
Arterial thromboembolic event	4 (1%)	2 (1·5%)	5 (2%)	3 (2%)	9 (3%)	5 (4%)
Cerebrovascular Event	1 (1%)	1 (2·9%)	1 (0·6%)	1 (1%)	2 (4%)	2 (7%)
Myocardial Infarction	1 (1%)	-	1 (0·6%)	1 (1%)	2 (4%)	1 (4%)
Acute Myocardial Infarction	1 (1%)	-	2 (1%)	-	3 (6%)	0 (0%)
AE body system code						
Blood and lymphatic system disorders	8 (3%)	2 (1·5%)	-	1 (0·8%)	8 (3%)	3 (2%)
Cardiac disorders	30 (11%)	7 (5·3%)	12 (4%)	5 (4%)	39 (14%)	10 (8%)
Congenital, familial and genetic disorders	-	-	1 (0·4%)	-		
Ear and labyrinth disorders	18 (7%)	8 (6%)	2 (0·7%)	-	20 (7%)	8 (6%)
Endocrine disorders	4 (1%)	1 (0·8%)	4 (1%)	-	8 (3%)	1 (0·8%)
Eye disorders	108 (39%)	50 (38%)	47 (17%)	16 (12%)	131 (48%)	60 (45%)
Gastrointestinal disorders	43 (16%)	18 (14%)	6 (2%)	-	47 (17%)	18 (14%)
General disorders and administration site conditions	14 (5%)	7 (5%)	-	-	14 (5%)	7 (5%)
Hepatobiliary disorders	3 (1%)	2 (2%)	6 (2%)	2 (2%)	8 (3%)	3 (2%)
Immune system disorders	3 (1%)	2 (2%)	-	-	3 (1%)	2 (2%)
Infections and infestations	98 (36%)	54 (41%)	7 (3%)	4 (3%)	103 (37%)	54 (41%)
Injury, poisoning and procedural complications	32 (12%)	14 (10%)	7 (3%)	1 (0·8%)	36 (13%)	15 (11%)
Investigations	12 (4%)	3 (2%)	-	-	12 (4%)	3 (2%)
Metabolism and nutrition disorders	7 (3%)	2 (2%)	2 (0·7%)	1 (0·8%)	9 (3%)	2 (2%)
Musculoskeletal and connective tissue disorders	60 (22%)	27 (20%)	4 (1%)	4 (3%)	63 (23%)	29 (22%)
Neoplasms benign, malignant and unspecified	6 (2%)	7 (5%)	7 (3%)	5 (4%)	13 (5%)	9 (7%)
Nervous system disorders	23 (8%)	11 (8%)	1 (0·4%)	1 (0·8%)	24 (9%)	12 (9%)

Psychiatric disorders	2 (0·7%)	2 (2%)	-	1 (0·8%)	2 (0·7%)	3 (2%)
Renal and urinary disorders	12 (4%)	6 (5%)	6 (2%)	2 (2%)	17 (6%)	7 (5%)
Reproductive system and breast disorders	2 (1%)	3 (2%)	-	-	2 (1%)	3 (2%)
Respiratory, thoracic and mediastinal disorders	28 (10%)	14 (10%)	10 (4%)	5 (4%)	37 (13%)	17 (13%)
Skin and subcutaneous tissue disorders	29 (10%)	9 (7%)	-	-	29 (10%)	9 (7%)
Social circumstances	2 (1%)	2 (2%)	-	-	2 (1%)	2 (2%)
Surgical and medical procedures	30 (11%)	17 (13%)	41 (15%)	11 (8%)	67 (24%)	28 (21%)
Vascular disorders	15 (5%)	3 (2%)	3 (1%)	2 (2%)	17 (6%)	5 (4%)

*Table S16: Data are n (%) or median [interquartile range]. *Multiple events in the same category were counted only once. Abbreviations: AE, adverse event; IQR, interquartile range; SRT, stereotactic radiotherapy*

28. Table S17: Intensity and relatedness of adverse events in the study eye

	Adverse Events in the study eye		Serious Adverse Events in the study eye	
	SRT (N=148)	**Sham SRT** (N=62)	**SRT** (N=70)	**Sham SRT** (N=17)
Intensity				
Mild	110 (74%)	43 (69%)	38 (54%)	6 (35%)
Moderate	29 (20%)	15 (24%)	25 (36%)	7 (41%)
Severe	9 (6%)	4 (7%)	7 (10%)	4 (24%)
Relatedness to any intervention				
Definite	18 (12%)	7 (11%)	-	-
Probable	17 (12%)	11 (18%)	8 (11%)	1 (6%)
Possible	22 (15%)	7 (11%)	27 (39%)	4 (24%)
Remote	12 (8%)	7 (11%)	24 (34%)	7 (41%)
None	79 (53%)	30 (48%)	11 (16%)	5 (29%)
Relatedness to SRT				
Definite	-	-	-	-
Probable	2 (1%)	1 (1%)	5 (7%)	-
Possible	13 (9%)	2 (3%)	20 (29%)	2 (12%)
Remote	11 (7%)	7 (11%)	29 (41%)	9 (53%)
None	122 (82%)	52 (84%)	16 (23%)	6 (35%)
Relatedness to anti-VEGF treatment				
Definite	-	-	-	-
Probable	2 (1%)	1 (1%)	-	-
Possible	12 (8%)	2 (3%)	6 (9%)	2 (12%)
Remote	10 (7%)	7 (11%)	11 (16%)	5 (29%)
None	124 (84%)	52 (84%)	53 (76%)	10 (59%)
Relatedness to intravitreal injection				
Definite	18 (12%)	7 (11%)	-	-
Probable	15 (10%)	11 (18%)	3 (4%)	1 (6%)
Possible	18 (12%)	6 (10%)	8 (11%)	3 (18%)
Remote	9 (6%)	5 (8%)	10 (14%)	1 (6%)
None	88 (60%)	33 (53%)	49 (70%)	12 (71%)
Outcomes				
Ongoing	48 (32%)	20 (33%)	21 (30%)	1 (6%)
Resolved with sequelae	10 (7%)	6 (10%)	13 (19%)	9 (53%)
Resolved without sequelae	89 (60%)	34 (57%)	36 (51%)	7 (41%)

Table S17: Data are count (%, to number of events in corresponding group). Populations defined according to the received treatment. Abbreviations: anti-VEGF, anti-Vascular Endothelial Growth Factor; SRT, stereotactic radiotherapy.

29. Table S18: Intensity and relatedness of adverse events

	Adverse Events		Serious Adverse Events	
	SRT (N=817)	**Sham SRT** (N=392)	**SRT** (N=214)	**Sham SRT** (N=73)
Intensity				
Mild	501 (61%)	235 (60%)	56 (26%)	13 (18%)
Moderate	266 (33%)	138 (35%)	70 (33%)	28 (38%)
Severe	50 (6%)	19 (5%)	88 (41%)	32 (44%)
Relatedness to any intervention				
Definite	20 (2%)	9 (2%)	-	-
Probable	19 (2%)	12 (3%)	10 (5%)	2 (3%)
Possible	28 (3%)	10 (3%)	29 (14%)	4 (6%)
Remote	28 (3%)	14 (4%)	37 (17%)	14 (19%)
None	722 (88%)	347 (88%)	138 (64%)	53 (73%)
Relatedness to SRT				
Definite	1 (0·1%)	1 (0·3%)	-	-
Probable	2 (0·2%)	2 (0·5%)	6 (3%)	-
Possible	13 (2%)	2 (0·5%)	20 (9%)	2 (3%)
Remote	19 (2%)	10 (3%)	36 (17%)	12 (16%)
None	782 (96%)	377 (96%)	152 (71%)	59 (81%)
Relatedness to anti-VEGF treatment				
Definite	-	-	-	-
Probable	3 (0·4%)	1 (0·3%)	1 (0·5%)	1 (1%)
Possible	17 (2%)	3 (0·8%)	7 (3%)	2 (3%)
Remote	18 (2%)	11 (3%)	20 (9%)	9 (12%)
None	779 (95%)	377 (96%)	186 (87%)	61 (84%)
Relatedness to intravitreal injection				
Definite	19 (2%)	8 (2%)	-	-
Probable	16 (2%)	11 (3%)	3 (1%)	1 (1%)
Possible	20 (2%)	9 (2%)	9 (4%)	3 (4%)
Remote	16 (2%)	5 (1%)	12 (6%)	2 (3%)
None	746 (91%)	359 (92%)	190 (89%)	67 (92%)
Outcomes				
Ongoing	234 (29%)	125 (32%)	55 (26%)	18 (25%)
Resolved with sequelae	77 (9%)	32 (8%)	41 (19%)	24 (33%)
Resolved without sequelae	497 (61%)	232 (60%)	107 (50%)	29 (40%)
AE related to study eye	148 (18%)	62 (16%)	70 (33%)	17 (23%)

Table S18: Data are count (%, to number of events in corresponding group). Populations defined according to the received treatment. Abbreviations: AE, adverse event; anti-VEGF, anti-Vascular Endothelial Growth Factor; SRT, stereotactic radiotherapy.

Safety: *Microvascular abnormalities and impact on acuity*

30. Table S19: Reading centre-determined microvascular abnormalities by received treatment at Week 48 and Week 96

		Microvascular abnormalities		
		SRT (N=274)	**Sham SRT (N=137)**	**Overall (N=411)**
Baseline	Detected with photographs	2	1	3
	Detected with angiography	8	5	13
	Detected with either modality	8	5	13
	Fovea-involving	0	0	0
		SRT (N=247)	**Sham SRT (N=115)**	**Overall (N=362)**
Week 48	Detected with photographs	20	4	24
	Detected with angiography	39	8	47
	Detected with either modality	41	9	50
	Fovea-involving	9	0	9
		SRT (N=223)	**Sham SRT (N=109)**	**Overall (N=332)**
Week 96	Detected with photographs	50	6	56
	Detected with angiography	74	12	86
	Detected with either modality	77	13	90
	Fovea-involving	22	3	25

Table S19: The microvascular abnormalities were those detected by the independent reading centre, rather than those reported by site investigators. Data are count. N represent the number of participants with available, gradable imaging at respective timepoints. Abbreviations: SRT, stereotactic radiotherapy.

31. Table S20: Mean change in best-corrected visual acuity between baseline and week 96 by microvascular abnormality status and fovea involvement

	Change in ETDRS BCVA	
	SRT	**Sham SRT**
	(N=77)	(N=13)
MVA positive	-0·7 (9·8)	4·9 (14)
	(N=146)	(N=96)
MVA negative	-3·4 (11)	-1·4 (8·8)
	(N=22)	(N=3)
Fovea-involving MVA	-4·2 (11)	7·3 (8)
	(N=52)	(N=10)
Non-fovea-involving MVA	0·6 (9·3)	4·2 (15)

*Table S20: Data are mean (standard deviation) and detail the findings of the independent reading centre. *Discrepancy between total MVA positive eyes (N=90) and total of Fovea-involving MVA and Non-fovea-involving MVA eyes (N=87) is due to masking from blood or cotton wool spots such that grading of fovea involvement was not possible. Abbreviations: BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; MVA, microvascular abnormality; SRT, stereotactic radiotherapy.*

32. STAR study Investigators

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- Mandeep Bindra: Stoke Mandeville Hospital, Aylesbury
- Ben Burton: James Paget University Hospital, Great Yarmouth
- Indra Dias: Calderdale Royal Hospital, Halifax
- Christiana Dinah: Central Middlesex Hospital, London
- Ravikiran Gandhewar: Royal Derby Hospital, Derby
- Marianne Shiew and Athanasios Georgas: Hinchingbrooke Hospital, Hinchingbrooke
- Srinivas Goverdhan: Dorset County Hospital, Dorchester
- Edward Hughes: Sussex Eye Hospital, Brighton
- Timothy Jackson (Chief Invstigator): King's College Hospital, London
- Afsar Jafree: William Harvey Hospital, Ashford
- Sobha Joseph: Heart of England, Birmingham
- Tarek Kashab: Mid Cheshire Hospital, Crewe
- Luke Membrey: Maidstone Hospital, Maidstone
- Geeta Menon: Frimley Park Hospital, Frimley
- Aseema Misra: Norfolk & Norwich University Hospital, Norwich
- Niro Narendran: New Cross Hospital, Wolverhampton
- Douglas Newman: Cambridge University Hospitals, Cambridge
- Jignesh Patel: Essex County Hospital, Colchester
- Sudeshna Patra: Whipps Cross Hospital, London
- Robert Petrarca and Izadi Shahrnaz: Epsom & St Helier's Hospital, Carshalton
- Prakash Priya: Princess Alexandra Hospital, Harlow
- Arora Rashi: Salisbury District Hospital, Odstock
- Richard Haynes: Bristol Eye Hospital, Bristol
- Paritosh Shah: Yeovil Hospital, Yeovil
- George Sheen: Hillingdon Hospital, London
- Paul Tesha: United Lincolnshire Hospital Trust, Lincoln
- Eleni Vrizidou, Ramiro Salom and Ansari Gulrez: Queens Hospital, Romford

33. STAR study National Treatment Centres

a. Lead clinicians

- Chris Brand: Royal Hallamshire Hospital, Sheffield
- Timothy Jackson: King's College Hospital, London
- Ramesh Sivaraj: Solihull Hospital, Birmingham
- Aseema Misra: Norfolk & Norwich University Hospital, Norwich
- Romi Chhabra: Manchester Royal Eye Hospital, Manchester

b. Lead medical physicist or Radiation Protection Officers

- Giles D. Morrison: Royal Hallamshire Hospital, Sheffield
- Cornelius Lewis and Patricia Clinch: King's College Hospital, London
- Jane Waller: Solihull Hospital, Birmingham
- Nattapon Boonarpha: Manchester Royal Eye Hospital, Manchester
- Amanda Webster: Norfolk & Norwich University Hospital, Norwich

34. Trial Steering Committee Members

- Richard Wormald, Cochrane Eyes and Vision Group, International Centre for Eye Health, London School of Hygiene and Tropical Medicine (independent voting clinical chair)
- Winfried Amoaku, Associate Professor and Reader in Ophthalmology and Visual Sciences, University of Nottingham (independent voting clinician)
- Clare Bailey, Consultant Ophthalmic Surgeon, Bristol Eye Hospital (independent voting clinician)
- Professor Timothy Jackson, Professor of Retinal Research and Consultant Ophthalmic Surgeon, King's

College London and King's College Hospital (voting clinical chief investigator)
- Luke Membrey, Consultant Ophthalmic Surgeon, Maidstone Hospital (non-voting principal investigators' representative)
- Professor Barnaby Reeves, Professor of Health Services Research, University of Bristol (non-voting trialist)
- Professor Mandeep Sagoo, Professor of Ophthalmology and Ocular Oncology and Consultant Ocular Oncologist, University College London and Moorfields and St Bartholomew's Hospital (independent voting clinician)
- Professor Yanzhong Wang, Professor of Medical Statistics, King's College London (voting trial statistician)
- Professor Robert West, Professor of Biostatistics, Leeds Institute of Health Sciences (independent voting statistician)
- Cathy Yelf, Head of External Relations, Macular Society (non-voting lay representative)

35. Data Monitoring and Ethics Committee Members

- Professor Craig Ramsay, Professor of Statistics, Health Services Research Unit, University of Aberdeen
- Professor Paulo Stanga, Professor of Ophthalmology and Retinal Regeneration and Consultant Ophthalmologist and Vitreoretinal Surgeon, University of Manchester and Manchester Royal Eye Hospital
- Professor Heinrich Heimann, Professor of Ophthalmology and Consultant Ocular Oncologist, University of Liverpool and Royal Liverpool University Hospital

36. NetwORC UK Reading Centres

- Belfast Ophthalmic Reading Centre: Tunde Peto, Usha Chakravarthy, Alan Sproule, Alyson Muldrew, Barbra Hamill, Catherine Jamison, Graham Young, Malcolm Brown, Michael Quinn, Peter Blows
- Liverpool Ophthalmic Reading Centre: Savita Madhusudhan, Pauline Lenfestey, Alia Ali, David Parry, Handan Akil, Sophie Leach
- Moorfields Ophthalmic Reading Centre: Daniela Florea, Irene Leung
- Central Administrative Research Facility (CARF): Vittorio Silvestri, Michelle McGaughey, Clare Newell, Karleigh Kelso, Sara Shields