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

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*Listed in the appendix pp 141–42

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Summary

Background Neovascular age-related macular degeneration (nAMD) is a leading cause of blindness. The first-line therapy is anti-vascular endothelial growth factor (anti-VEGF) agents delivered by intravitreal injection. Ionising radiation mitigates key pathogenic processes underlying nAMD, and therefore has therapeutic potential. STAR aimed to assess whether stereotactic radiotherapy (SRT) reduces the number of anti-VEGF injections required, without sacrificing visual acuity.

Methods This pivotal, randomised, double-masked, sham-controlled trial enrolled participants with pretreated chronic active nAMD from 30 UK hospitals. Participants were randomly allocated in a 2:1 ratio to 16-Gray (Gy) SRT delivered using a robotically controlled device or sham SRT, stratified by treatment centre. Eligible participants were aged 50 years or older and had chronic active nAMD, with at least three previous anti-VEGF injections, including at least one in the last 4 months. Participants and all trial and image reading centre staff were masked to treatment allocation, except one unmasked statistician. The primary outcome was the number of intravitreal ranibizumab injections required over 2 years, tested for superiority (fewer injections). The main secondary outcome was Early Treatment Diabetic Retinopathy Study visual acuity at two years, tested for non-inferiority (five-letter margin). The primary analysis used the intention-to-treat principle, and safety was analysed per-protocol on participants with available data. The study is registered with ClinicalTrials.gov (NCT02243878) and is closed for recruitment.

Findings 411 participants enrolled between Jan 1, 2015, and Dec 27, 2019, and 274 were randomly allocated to the 16-Gy SRT group and 137 to the sham SRT group. 240 (58%) of all participants were female, and 171 (42%) of all participants were male. 241 participants in the 16-Gy SRT group and 118 participants in the sham group were included in the final analysis, and 409 patients were treated and formed the safety population, of whom two patients allocated to sham treatment erroneously received 16-Gy SRT. The SRT group received a mean of 10·7 injections (SD 6·3) over 2 years versus 13·3 injections (5·8) with sham, a reduction of 2·9 injections after adjusting for treatment centre (95% CI −4·2 to −1·6, p<0·0001). The SRT group best-corrected visual acuity change was non-inferior to sham (adjusted mean letter loss difference between groups, −1·7 letters [95% CI −4·2 to 0·8]). Adverse event rates were similar across groups, but reading centre-detected microvascular abnormalities occurred in 77 SRT-treated eyes (35%) and 13 (12%) sham-treated eyes. Overall, eyes with microvascular abnormalities tended to have better best-corrected visual acuity than those without. Fewer ranibizumab injections offset the cost of SRT, saving a mean of £565 per participant (95% CI −332 to 1483).

Interpretation SRT can reduce ranibizumab treatment burden without compromising vision.

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Introduction

Age-related macular degeneration (AMD) is a common disease, affecting 8% of adults globally.[1] It is a leading cause of blind registration in many high-income and upper-middle income countries.[2,3] Although thought to be part of the same disease process, there are two commonly described phenotypes: a slowly progressive, atrophic, dry AMD, and a more acute wet, or neovascular, AMD (nAMD). nAMD is treated with long-term intravitreal injections of drugs that inhibit vascular endothelial growth factor (VEGF), a key driver of vascular leakage and proliferation. Anti-VEGF injections are the most commonly performed eye procedure in many countries, and impose a considerable burden on patients. Each injection carries only a small risk of severe sight loss from infectious endophthalmitis, but risks

Research in context

Evidence before this study

Neovascular age-related macular degeneration (nAMD) is a common disease and a leading cause of blindness. It is treated with repeated intraocular injections of anti-vascular endothelial growth factor (anti-VEGF) drugs, which cost about US$10 billion globally each year. Radiation mitigates many of the pathogenic processes that cause nAMD, and therefore has clinical potential, but the mode of delivery alters efficacy. A Cochrane systematic review undertaken in May, 2020 evaluating radiotherapy for AMD found only one randomised controlled trial (the INTREPID study) evaluating stereotactic radiotherapy (SRT). We undertook an updated on MEDLIINE, Embase, and CENTRAL search using search terms adapted from the Cochrane review, focused on stereotactic radiotherapy AND (neovascular OR wet OR exudative) adj2 (age-related macular degeneration OR macular degeneration OR AMD) AND (random* OR meta*); from Jan 1, 2004, when anti-VEGF therapy emerged, to Nov 8, 2023, without language restrictions, and found no additional trials. The phase 2, 230 participant, dose-ranging, double-masked, sham-controlled INTREPID trial showed a statistically significant 29% reduction in intraocular ranibizumab therapy in a 16-Gray (Gy) SRT group at the one-year primary endpoint. Given the importance of nAMD, a larger study was required to establish efficacy and safety beyond one year.

Added value of this study

This double-masked, sham-controlled trial randomised 411 participants and is the largest study of SRT for nAMD. It used a robotically controlled device delivering a one-off dose of 16-Gy SRT. The primary outcome was ranibizumab intraocular injection frequency over two years, which SRT reduced by 22% (p<0·0001). The difference in visual acuity between groups was non-inferior at the prespecified five-letter margin. Adverse event rates were similar between groups, but 77 (35%) participants in the SRT group developed microvascular abnormalities versus 13 (12%) in the sham SRT group, but these did not adversely impact mean visual acuity. Savings from reducing ranibizumab retreatment more than offset the cost of providing SRT, with a mean saving of £565 per participant.

Implications of all the available evidence

If widely implemented, SRT could reduce the burden of nAMD treatment for patients, and the global cost of delivering nAMD treatment. SRT could potentially avoid 1·8 million anti-VEGF injections per year globally across all high-income countries.

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See Online for appendix

accumulate with repeated treatment, reaching almost 1% with time.[4] In the USA alone, nAMD anti-VEGF treatment and monitoring costs US$10·7 billion yearly,[5] with annual societal costs of nAMD blindness estimated at $16 billion.[6] Patient priority-setting exercises identified the need for a non-invasive treatment that avoids, or at least reduces, intravitreal injections.[7]

Radiation has therapeutic potential, as it mitigates many of the factors that cause nAMD, including cell proliferation, fibrosis and inflammation.[8,9] Radiation was first trialled as a nAMD treatment in 1993,[10] using a repurposed external beam radiotherapy device. The results suggested a biological effect, but not one that would be considered sufficient since anti-VEGF agents emerged.

In the 2010s an automated robotically controlled device was developed specifically to treat nAMD (IRay, Carl Zeiss, Jena, Germany),[11] delivering a one-off outpatient treatment that takes 10–20 min. It was assessed in the IRay in Conjunction with Anti-VEGF Treatment for Patients with Wet AMD (INTREPID) study, a phase 2, 230-participant, double-masked, multicentre, dose-ranging, randomised controlled trial (RCT) of 16-Gray (Gy), 24-Gy, or sham stereotactic radiotherapy (SRT).[12] The primary outcome was the number of ranibizumab anti-VEGF injections required in the year after SRT. INTREPID showed a statistically significant, 29% reduction in ranibizumab injections with SRT versus sham SRT. Over 2 years, 18 (13%) of 140 SRT-treated participants had retinal microvascular abnormalities (MVAs) attributed to treatment (a type of radiation retinopathy), but these were subtle and only seen in ocular imaging reviewed by a specialist independent reading centre. The MVAs were not sight-threatening, except for two instances (1%) involving the fovea which might therefore have affected vision.[13]

Given the global importance of nAMD a larger and longer trial than INTREPID is needed, alongside a cost-effectiveness evaluation. The current study aimed to test the safety and efficacy of 16-Gy SRT for the treatment of nAMD, with key outcomes evaluated at 96 weeks. We hypothesised that SRT would reduce the frequency of anti-VEGF therapy, without sacrificing best-corrected visual acuity (BCVA).

Methods

Study design and participants

STAR was an investigator-initiated, pivotal, double-masked, sham-controlled device RCT which took place in 30 UK National Health Service (NHS) hospitals. SRT was administered at one of three NHS National Treatment Centres, then participants returned to their recruiting site for follow-up. All participants provided written informed consent. The study was undertaken in accordance with the Declaration of Helsinki and CONSORT guidelines, and received a favourable opinion from a national research ethics service (London–City and East, Oct 23, 2013; 13/LO/1207), with oversight from an independent data monitoring and ethics committee. The published study protocol is available in the appendix (pp 4–92).[14]

Eligible participants were aged 50 years or older and had chronic active nAMD, with at least three previous

anti-VEGF injections, including at least one in the last 4 months; if two eyes were eligible, the participant chose one as the study eye. Study eyes had to require an injection at the time of enrolment, with a macular volume 8·15 mm³ or greater (varying by machine), measured using spectral-domain optical coherence tomography (SD-OCT). People with diabetes were excluded, alongside patients in whom the study eye had previous nAMD treatment other than anti-VEGF therapy; those with foveal scarring; an Early Treatment Diabetic Retinopathy Study[15] (ETDRS) BCVA letter score worse than 24 (6/96); a lesion diameter greater than 4 mm, or extending more than 2 mm from the foveal centre. Full exclusion criteria are shown in the appendix (pp 22–23). Baseline ocular imaging was sent to an independent reading centre but, for pragmatic reasons and to enhance generalisability, eligibility was determined by the attending ophthalmologist (appendix pp 22–23).

Randomisation and masking

Participants were individually randomly allocated using the Clinical Trials Unit's online randomisation system, stratified by national treatment centre with variable block sizes to ensure a 2:1 allocation ratio at each centre. The randomisation system generated an alphanumeric code that was entered into the SRT device, corresponding to 16-Gy or sham dosing programmed into the machine. The device alignment checks, treatment cues, and tracking and gating algorithm were identical irrespective of allocation. Participants and all trial and image reading centre staff were masked to treatment allocation, except the device technician assigning the alphanumeric codes at trial start, and one unmasked statistician (HAW) , who linked these codes to the randomised allocations at the trial start, and to facilitate data and ethics committee unmasking if requested. The statistical analysis plan (appendix pp 93–112) was completed before the data lock, with a masked statistician (YW) undertaking the analysis before allocation unmasking.

For the **Medical Dictionary for Regulatory Activities** see https://www.meddra.org/

Procedures

At baseline, trial certified staff, using trial certified equipment, recorded manifest refraction, BCVA starting at 4 m using the ETDRS protocol,[15] slit-lamp ocular examination, lens grading,[16] SD-OCT, digital fundus photography, fluorescein angiography, indocyanine green angiography (in sites with this capability), five-level EuroQol health-related quality-of-life (EQ-5D-5L) questionnaire, and the National Eye Institute 25-item visual function questionnaire (VFQ-25).

We selected 16-Gy SRT as it showed similar efficacy to 24-Gy in INTREPID, but could theoretically offer greater safety. Treatment was as described previously.[12] Briefly, an eye stabilisation device used a suction-coupled contact lens secured to the cornea and connected to a positioning gimble with infrared reflectors. The reflectors were tracked by the SRT device, which paused treatment if the eye moved out of position. The robotically controlled device generated three sequential 5·33 Gy highly collimated beams of x-ray irradiation, applied through separate points via the inferior pars plana to avoid lens irradiation, and overlapping at the macula. Participants received intravitreal 0·5 mg ranibizumab (Lucentis, Novartis, Frimley, UK) immediately after SRT. For the comparator group, treatment was identical, except it used a 0 Gy dose.

Participants then returned to their recruiting site for review every 4 weeks, with 0·5 mg ranibizumab administered if the Comparison of Age-related Macular Degeneration Treatments Trial (CATT) retreatment criteria were met.[17] The appendix details visit activities (pp 62–63) and retreatment criteria (pp 25–26).

After the 96-week primary endpoint all participants reverted to standard NHS care, but with full trial assessments at years 3 and 4 to determine long-term safety and real-world efficacy (to be reported subsequently).

Outcomes

The primary outcome was the mean number of pro re nata (PRN) ranibizumab injections in the 96 weeks after random allocation, excluding the injection given with SRT which reflected disease activity at randomisation and was mandated in both groups, but including any injection required at week 96 and unscheduled visits. Superiority (fewer injections) of SRT compared to sham was tested by comparing the mean numbers of injections in the two groups. The main secondary outcome was the change in ETDRS BCVA from baseline to week 96, tested for non-inferiority at a five-letter margin.[18] Other secondary clinical outcomes were the percentage of participants losing fewer than 15 ETDRS letters, gaining 0 or more letters, gaining 15 or more letters, angiographic total lesion and choroidal neovascularisation size (in mm²), foveal thickness (µm), EQ-5D-5L utility score, and VFQ-25 composite score.

The main safety outcomes were adverse events and serious adverse events (SAEs), labelled by preferred term and grouped by system organ class using the Medical Dictionary for Regulatory Activities (version 17.1, September 2014). Adverse events of special interest were arteriothrombotic events and retinal MVAs. To facilitate the speed and visibility of reporting, the protocol mandated that investigators report any retinal MVAs as SAEs. Thereafter, the chief investigator could downgrade them to important medical events if the reporting form or site principal investigator indicated that the MVA did not meet the other protocol criteria for SAE (causing sight loss, disability, permanent damage, death, or hospitalisation). The reading centre also looked specifically for MVAs, using multimodal imaging.

A costing analysis compared nAMD treatment costs for SRT plus ranibizumab PRN against ranibizumab PRN monotherapy from an NHS perspective. This included the cost of SRT, monitoring consultations every 4 weeks, and ranibizumab injections. A full health

economic evaluation analysis including EQ-5D-5L utilities, other resource use, and sensitivity analyses will be reported separately. The cost of SRT was micro-costed based on the manufacturer's licence fee charged for each use, and staff costs (appendix pp 115–116).

When the UK COVID-19 lockdown commenced on March 23, 2020, the UK's Royal College of Ophthalmologists advised that patients with nAMD should nevertheless attend for regular review, but local pathways varied, as did individual participants' willingness to attend. Non-attendance had the potential to affect the primary outcome, the number of ranibizumab injections. To assess the pandemic's effect on the trial, a primary outcome sensitivity analysis was defined before the data lock, analysing four overlapping populations. First, participants completing the week 96 primary endpoint before lockdown; second, participants completing week 96 after lockdown started; third, participants whose compliance up to week 96 was deemed sufficient (compliant group); and fourth, participants whose compliance up to week 96 might have been compromised for any reason, not just the pandemic (reduced compliance group).

The distinction between the compliant and reduced compliance groups relied on predefined rules (appendix p 121), categorising visits as green (fully compliant or per-protocol), amber (visit deviation, but not one probable to materially affect the primary outcome), and red (deviations that might affect the primary outcome). Compliant group participants had up to four red visits, or eight amber visits, out of their 25 planned visits to week 96; but if they had more than four red or eight amber visits they were considered part of the reduced compliance group. The categorisation and compliance rules were agreed by a majority independent-trial steering committee and the resulting sensitivity analyses were added by protocol amendment before data lock. Compliance is shown using a novel compliance cube schematic.

Statistical analysis

Sample size estimation was informed by CATT and INTREPID.[12,17] With a 2:1 allocation, 411 individuals (274 for SRT and 137 for sham) were needed to detect a clinically meaningful reduction in ranibizumab treatments (2·5 injections over 96 weeks), from a mean (SD) of 10 (7), with 90% power, a two-sided significance level of 5%, and up to 10% loss to follow-up. This sample size also allowed 97% power with a one-sided significance level of 2·5% to demonstrate non-inferiority in mean BCVA change (the main secondary outcome), assuming an SD of 12 letters and a five-letter margin.[18]

Multiple linear regression was used to estimate the effect of treatment on injection frequency including the national treatment centre as a covariate. We used similar regression methods to analyse BCVA change. Other secondary outcomes were summarised descriptively as mean (SD), median (IQR), or count (%). The primary analysis used the intention-to-treat (ITT) principle with safety analysed per-protocol on participants with available data. The primary analysis was supplemented with sensitivity analyses to verify the robustness of the results to missing data and non-compliance, comprising base ITT model with additional adjustments, multiple imputation, per-protocol and the pandemic compliance analyses detailed above (see appendix p 125). Statistical analyses were performed using R software version 4.2.2. The study was registered with ClinicalTrials.gov (NCT02243878), and is closed for recruitment.

Role of the funding source

The UK's Medical Research Council (MRC) and National Institute of Health and Care Research (NIHR) Efficacy and Mechanism Evaluation Programme funded the trial. The funder had no role in data collection, analysis, interpretation, writing of the manuscript, or the decision to submit for publication. nAMD treatment was funded through usual NHS commissioning. The NIHR Comprehensive Research Network provided local support. The lead sponsor (King's College London) and clinical co-sponsor (King's College Hospital) designed and executed

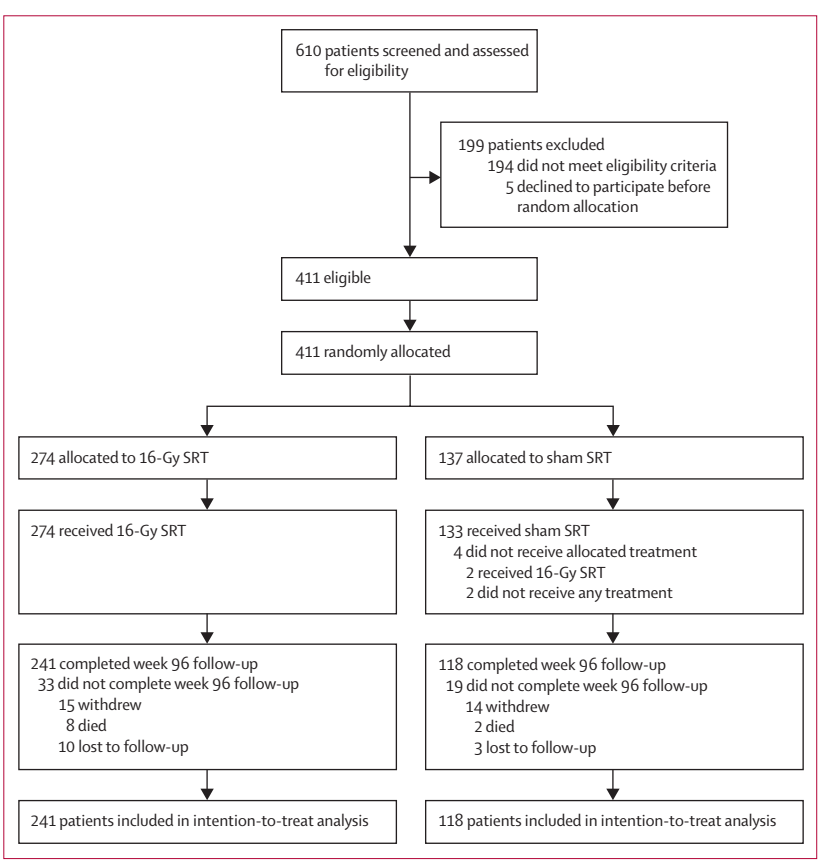

Figure 1: **Trial profile**
16-Gy=16-Gray. SRT=stereotactic radiotherapy.

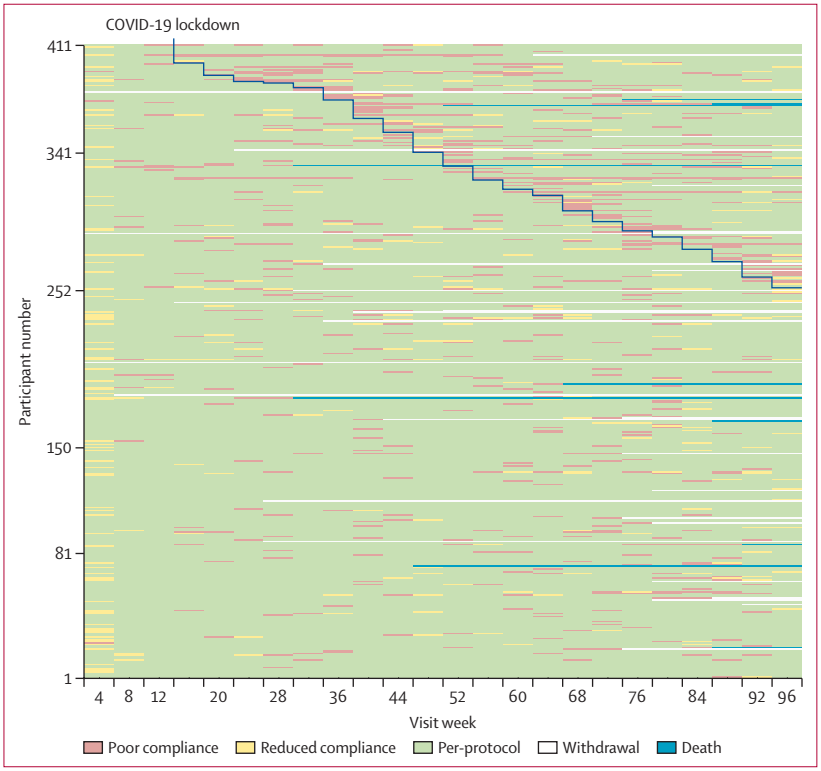

Figure 2: **Compliance diagram**
An individual's sequential visits are shown along a horizontal row as green (per-protocol), amber (a deviation, but not one probable to affect the primary outcome) or red (a deviation that could affect the primary outcome, as defined in the appendix [p 121]). Withdrawals are shown in white, and deaths in light blue. Individuals' timelines are then stacked one above the other, from the first to last participant recruited. Hence each participant's compliance over time can be viewed from left to right, and overall compliance of the trial itself can be viewed from bottom to top. The onset of the UK's lockdown (March 23, 2020) is marked in dark blue on each participant's timeline, so that the overall compliance, death rate, and withdrawals can be compared graphically, before and after lockdown, with the COVID-19 period occupying the top right corner.

the trial, and collected, analysed and interpreted the data. Oraya/Carl Zeiss provided free SRT devices for use in the trial, and was invited to offer technical corrections to the manuscript, but no changes were requested.

Results

Between Jan 1, 2015, and Dec 27, 2019, 610 patients were screened. After 199 patients were excluded for not meeting the eligibility criteria or declining to participate, 411 patients were recruited (ITT population) and randomly allocated to either 16-Gy SRT (274 participants) or sham SRT treatment (137 participants). 409 patients were treated and formed the safety population, of whom two patients allocated to sham treatment erroneously received 16-Gy SRT. 359 (87%) of 411 patients completed their week 96 follow-up (figure 1).

Figure 2 shows the novel compliance cube diagram. Compliance was worse in the month after participants enrolled, with more amber visits (deviations unlikely to affect the primary outcome), but compliance usually improved by month 2. Withdrawals and deaths varied little over the life of the trial. The dark blue line shows lockdown onset, when 252 participants (61%) of 411 had already reached the primary endpoint. For many participants, compliance reduced immediately after lockdown, with more red visits (deviations that could affect the primary outcome), but this effect was generally short-lived.

Table 1 shows the baseline characteristics. 240 (58%) of all participants were female, and 171 (42%) of all participants were male; with sex self-reported by participants. The majority of patients (397 [97%] of 411) were of white ethnicity, and both the SRT and sham SRT groups had a mean of seven previous anti-VEGF injections.

At the week 96 primary endpoint, the SRT group received a cumulative mean of 10·7 (SD 6·3) ranibizumab injections, compared with 13·3 injections (5·8) in the sham SRT group (table 2). After adjusting for national treatment centre there was a highly significant 22% decrease in the cumulative number of ranibizumab injections comparing SRT with sham, by an average of 2·9 injections (95% CI –4·2 to –1·6, p<0·0001). The difference between groups was greater in year 2 than year 1 (figure 3), although the number of injections was lower with 16-Gy SRT than sham SRT at all visits except at week 4 (appendix p 128). The cumulative injections by month is shown in the appendix (p 127), with a categorical breakdown of injection frequency presented graphically (p 128).

The sensitivity analyses were supportive of the primary analysis, suggesting the pandemic did not materially affect the primary outcome (appendix p 125). For example, participants who received 16-Gy SRT who reached the week 96 primary outcome before lockdown received 3·0 fewer injections than those in the sham group (95% CI –4·6 to –1·4, p=0·0004), and the protocol-compliant group received 3·1 fewer injections (–4·5 to –1·7, p<0·0001), both similar to the main analysis. The per-protocol analysis, based on treatment received, found 16-Gy SRT resulted in 2·9 fewer injections than the sham treatment (–4·2 to –1·6, p<0·0001).

Both groups showed reasonably stable BCVA at the week 96 endpoint. At baseline, the mean letter score was 68·4 (SD 12·9) in the SRT group and 69·1 (13·7) in the sham group. At week 96, BCVA worsened by 3·0 and 0·6 letters respectively, to 65·4 (15·0) and 68·5 (15·6). After adjustment for baseline BCVA and national treatment centre, the SRT group had a greater BCVA worsening than the sham group, but this difference was small (1·7 letters, 95% CI –4·2 to 0·8), not statistically significant (p=0·17), and within the five-letter non-inferiority margin. Figure 4 shows mean change in acuity over time and the appendix (p 129) shows mean acuity.

Table 2 shows other secondary outcomes, disaggregated by sex in the appendix (p 126). In general, categorical BCVA changes at week 96 were similar across groups, although a post-hoc analysis found that male participants

	SRT (N=274)	Sham SRT (N=137)
Demographic characteristics		
Age, years	78 (7·0)	78 (7·4)
Sex		
Female	158 (58%)	82 (60%)
Male	116 (42%)	55 (40%)
Ethnicity		
White	268 (98%)	129 (94%)
Black or Black British	1 (<1%)	0
Asian or Asian British	3 (1%)	7 (5%)
Other	2 (1%)	1 (1%)
Smoking status		
Current smoker	27 (10%)	15 (11%)
Ex-smoker	114 (42%)	61 (45%)
Non-smoker	133 (49%)	61 (45%)
Ophthalmic characteristics		
Angiographic lesion subtype		
Classic	24 (9%)	4 (3%)
Minimally classic	20 (7%)	10 (7%)
Occult	181 (66%)	96 (70%)
RAP	13 (5%)	6 (4%)
IPCV	21 (8%)	14 (10%)
Ungradable	15 (5%)	7 (5%)
nAMD duration, months*	22 (11–45)	22 (12–42)
Number of previous anti-VEGF injections*	7 (5–9)	7 (5–10)
ETDRS visual acuity, letter score	68·4 (12·9)	69·1 (13·7)
Lens status		
Aphakic	1 (<1%)	2 (1%)
Pseudophakic	92 (34%)	45 (33%)
Phakic	181 (66%)	90 (66%)
Central subfield thickness, µm	349 (115)	343 (130)
Total lesion size, mm²*	6·9 (3·8–11)	7·1 (4·1–11)
Total active lesion size, mm²*	6·5 (3·7–10)	6 (4–10)
Total macular volume, mm³	8·8 (1·2)	8·9 (1·3)
Patient-reported quality of life		
NEI VFQ-25 composite score*	87 (77–94)	87 (70–93)
EQ-5D-5L (VAS)*	90 (80–95)	85 (75–95)

Data are n (%) or mean (SD) unless marked with an asterisk. All ophthalmic history variables relate to the study eye. Missing data are detailed in the appendix (p 122). Anti-VEGF=anti-vascular endothelial growth factor. EQ-5D-5L (VAS)=EuroQol-5D questionnaire with visual analogue scale. ETDRS=Early Treatment Diabetic Retinopathy Study. IPCV=idiopathic polypoidal choroidal vasculopathy. nAMD=neovascular age-related macular degeneration. NEI-VFQ-25=National Eye Institute (USA) 25-item visual function questionnaire. RAP=retinal angiomatous proliferation. SRT=stereotactic radiotherapy. *Median (IQR).

Table 1: **Baseline characteristics**

	SRT (N=241)	Sham SRT (N=118)	Adjusted regression coefficient (95% CI), p-value†
Primary outcome			
Number of PRN anti-VEGF injections	10·7 (6·3)	13·3 (5·8)	−2·9 (−4·2 to −1·6), p<0·0001
Secondary outcomes			
Change in visual acuity score	−2·9 (11)	−1·5 (11)	−1·7 (−4·2 to 0·8), 0·17
ETDRS visual acuity	65·4 (15·0)	68·5 (15·6)	..
Losing < 15 ETDRS letters	209 (87%)	112 (93%)	..
Gaining ≥ 0 ETDRS letters	107 (45%)	58 (48%)	..
Gaining ≥ 15 ETDRS letters	7·0 (3%)	3·0 (3%)	..
Total lesion size*	8·3 (4·7 to 12·0)	7·3 (4·1 to 11·0)	..
Total active lesion size*	7·3 (4·5 to 12·0)	6·4 (3·6 to 11·0)	..
Central subfield thickness, µm	305 (130)	307 (101)	..
NEI VFQ-25 composite score*	88 (73 to 94)	86 (66 to 94)	..
EQ-5D (VAS)*	85 (75 to 95)	80 (70 to 90)	..

Data are n (%) or mean (SD) unless marked with an asterisk. 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 for the change in visual acuity score. Detailed missing data are provided in the appendix (p 122). Structural outcomes (lesion size, active lesion size, and central subfield thickness) are from the independent reading centre. Anti-VEGF=anti-vascular endothelial growth factor. EQ-5D-5L (VAS)=Euroquol questionnaire with visual analogue scale. ETDRS=Early Treatment Diabetic Retinopathy Study. NEI VFQ-25=National Eye Institute 25-item visual function questionnaire. PRN=pro re nata. SRT=stereotactic radiotherapy. *Median (IQR). †Of the secondary outcomes, statistical testing was only prespecified for the change in acuity score, tested for non-inferiority at a five-letter margin. As they were not pre-specified, statistical comparisons are not presented for other secondary outcomes.

Table 2: **Primary and secondary efficacy outcomes at week 96**

treated with SRT had a BCVA change that was 1·1 letters better than males treated with sham, whereas female patients treated with SRT had a BCVA change that was −3·8 letters worse than females treated with sham. At week 96 the reading centre-determined median total angiographic lesion sizes were similar, at 8·3 mm² (IQR 4·7–12·0) with SRT and 7·3 mm² (4·1–11·0) with sham, with total active lesion size measuring 7·3 mm² (4·5–12·0) and 6·4 mm² (3·6–11·0) respectively.

The mean week 96 reading centre-determined foveal centrepoint thickness was 237 microns (95% CI 219–256) with 16-Gy SRT and 272 microns (241–303) with sham, the benefit driven by less subretinal fluid and reduced pigment epithelial detachment height with SRT (appendix p 131). From week 24, SRT produced greater and more consistent improvement (reduced thickening) in central subfield thickness, as determined by investigators (figure 5 and appendix p 130).

The week 96 VFQ-25 and EQ-5D-5L scores were similar between the two groups. The SRT group had a median VFQ-25 composite score of 88 (IQR 73–94) and EQ-5D-5L score of 85 (75–95) *vs* 86 (66–94) and 80 (70–90) with sham, respectively.

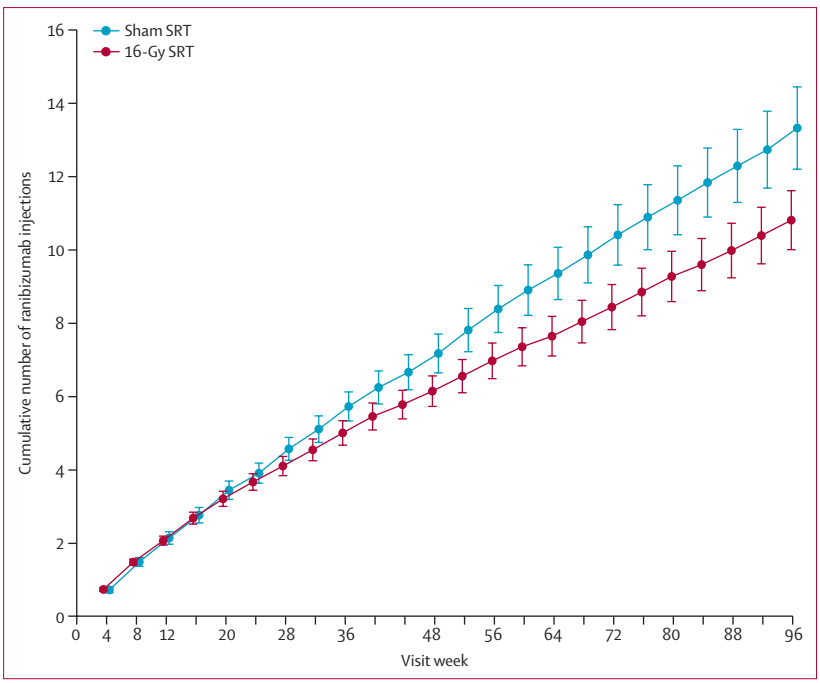

Figure 3: **Primary outcome—number of ranibizumab injections**
Mean cumulative number of ranibizumab injections in the SRT and sham SRT groups from the first 4-weekly visit to week 96 primary outcome, with error bars showing the 95% CI. 16-Gy=16-Gray. SRT=stereotactic radiotherapy.

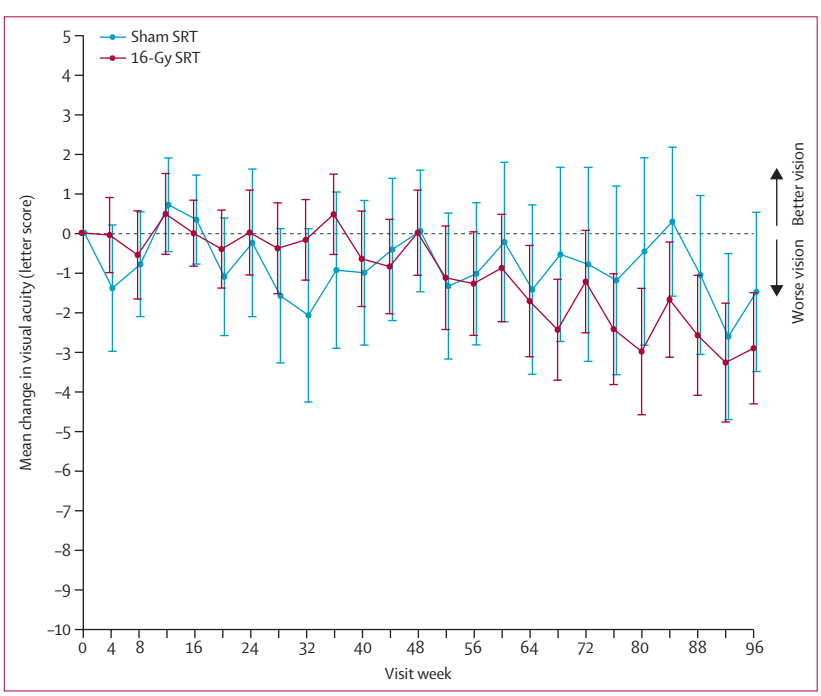

Figure 4: **Change in best-corrected visual acuity**
Errors bars show the 95% confidence intervals. 16-Gy=16-Gray. SRT=stereotactic radiotherapy.

Prespecified subgroup analyses are presented in the appendix (pp 132–134). The primary outcome analysis favoured SRT over sham in all subgroups, with the exception of 16 participants with retinal angiomatous proliferation.

Systemic safety was similar across groups (appendix pp 136–137), but with more cardiac adverse events following SRT (39 [14%] of 276 *vs* 10 [8%] of 133). The intensity and relatedness of adverse events and SAEs are shown in the appendix (pp 138–139). Of the adverse events of special interest, systemic arteriothrombotic adverse events occurred in 9 (3%) of 276 in the SRT group and 5 (4%) of 133 in the sham group. Investigators reported study eye MVAs or related features (retinopathy, cotton wool spots, telangiectasia, or exudates) in 10 (4%) of 276 eyes in the SRT group, and no eyes in the sham group, labelling severity as mild in nine eyes, moderate in one, with none considered severe.

Study eye adverse events were generally similar across groups (appendix p 135); more laser capsulotomies occurred in the SRT group, although this was still a low percentage of participants (8 [3%] of 276). All study eye SAEs occurred in under 1% of participants, except for cataract and cataract surgery in 28 (10%) of 276 in the SRT group and 12 (9%) of 133 in the sham group, and MVAs as noted above. Although more participants in the SRT group had study eye-related SAEs (45 [16%] of 276 *vs* 13 [10%] of 133), this was mostly due to the difference in MVAs and related features. The most vision-threatening SAE was endophthalmitis, occurring in one (0·4%) of 276 in the SRT group and one (0·8%) of 133 in the sham group. In the SRT group, 80 (37%) of 218 study eye adverse events and SAEs (combined) were thought to be SRT-related, compared with 21 (27%) of 79 with sham (appendix p 138). In addition to requiring site investgators to look specifically for MVA and report these as SAEs, the reading centre looked for MVAs using multimodal imaging. At baseline, it found study eye MVAs in eight (3%) of 274 in the SRT group and five (4%) of 137 in the sham group, increasing to 41 (17%) of 247 and nine (8%) of 115 at week 48, and 77 (35%) of 223 and 13 (12%) of 109 at week 96 (appendix p 140). At week 96, MVAs that involved at least part of the fovea and thus had the potential to affect vision were present in 22 (10%) of 223 in the SRT group and three (3%) of 109 in the sham group. We therefore undertook a post-hoc analysis investigating the effect of reading centre-detected MVAs on week 96 BCVA. Eyes with MVAs tended to have better vision than those without, except for SRT-treated eyes with foveal involvement, which had BCVA very slightly worse (0·8 letters) than MVA-negative eyes (appendix p 140).

From our costing analysis, SRT was estimated to cost £1343 per participant (appendix pp 115–116). Allowing for missed SRT and participants not receiving their allocated treatment, the initial cost of SRT and the first ranibizumab dose (£551 per dose list price)[19] was £1165 per participant higher in the SRT group (appendix p 117). However, subsequently SRT reduced the frequency of ranibizumab injections during weeks 4 to 96, saving £1730 per participant (95% CI 835 to 2647, p=0·0002). Combining

the cost of SRT, monitoring, and less ranibizumab gave a net saving over 96 weeks; the mean cost difference was –£565 (95% CI –1483 to 332, p=0·21) per participant from SRT. Across all high-income countries, around 174 000 incident patients and 1·1 million prevalent patients may be eligible for SRT, potentially avoiding 1·8 million anti-VEGF injections, with a net saving of £360 million per year (appendix p 118).

Discussion

This study showed a statistically significant 22% reduction (2·9 injections, p<0·0001) in ranibizumab retreatment for nAMD in the 2 years following 16-Gy SRT. The between-group difference in the number of injections increased over time. This benefit occurred without sacrificing BCVA, which was relatively stable following SRT, and non-inferior to anti-VEGF monotherapy. The rates of adverse events were generally similar between groups, and although more MVAs were reported in the 16-Gy group, these were mostly mild and did not adversely affect mean BCVA. The added cost of SRT was more than offset by the reduction in ranibizumab therapy. Assuming non-inferior vision and acceptable safety, it seems probable that many patients would prefer a treatment that reduces intravitreal injections.[20]

Our results are similar to INTREPID, but both differ from two RCTs of an epimacular brachytherapy surgical device, which observed no reduction in anti-VEGF injections.[21,22] Surgery removed the vitreous gel and this might partially explain the disappointing results, as vitrectomy is known to increase intravitreal anti-VEGF drug clearance.[23] Identifying the most active part of the nAMD lesion and holding the probe the correct distance from the retinal surface is highly user-dependent, and dose declines exponentially with increasing distance from the strontium source.[21,22]

We selected ranibizumab PRN as the anti-VEGF treatment. Unlike aflibercept's treat-and-extend marketing authorisation, ranibizumab's authorisation facilitated PRN dosing, providing the best chance of detecting a difference in injection frequency between groups. As we show in the appendix (p 128), 43 (18%) of 241 in the SRT group required three or fewer injections over 2 years, compared with just five (4%) of 118 in the sham SRT group; with a treat-and-extend aflibercept regimen participants would have received at least seven injections over 2 years, even if there was no disease activity after SRT.

It is not known if similar benefits would occur with other anti-VEGF agents, but this might be predicted on biological grounds, given that most agents rely primarily on anti-VEGF-A inhibition, and RCTs show no significant difference in efficacy between ranibizumab, bevacizumab, and aflibercept.[17,24,25] It is not known if newer intravitreal drugs, such as faricimab,[26] or higher doses of existing anti-VEGF drugs,[27] which have longer dosing intervals, might erode the benefit of SRT. Conversely, combining a sustained decrease in disease activity from SRT and longer-acting drugs might together produce the fewest injections and greatest benefit.

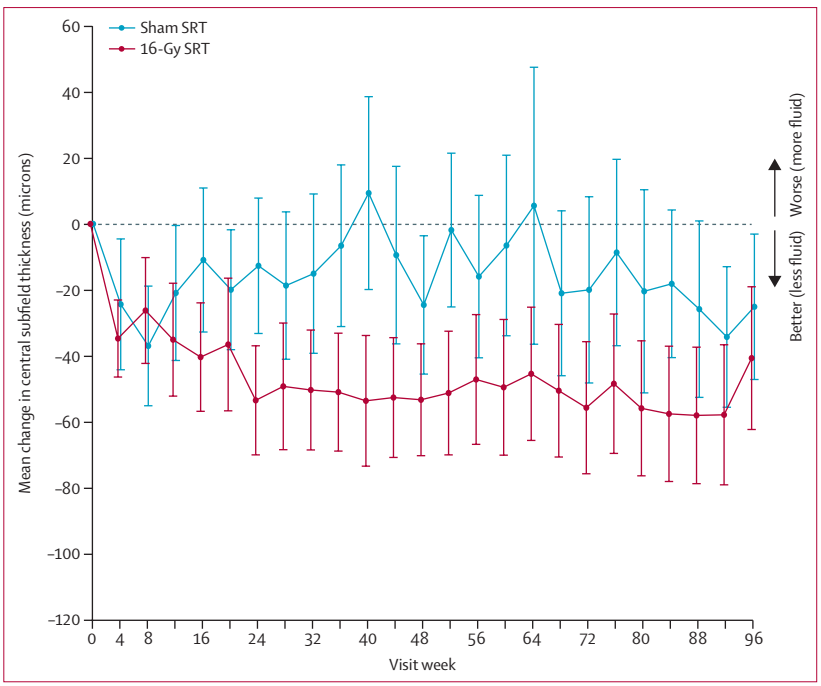

Figure 5: **Change in macular central subfield thickness**
Site investigators recorded the automated central subfield measurement from their spectral domain optical coherence tomography device, after manually correcting any segmentation errors, if present. Error bars show the 95% CIs. 16-Gy=16-Gray. SRT=stereotactic radiotherapy.

Real-world studies suggest that the vision gains seen in the anti-VEGF registration trials are not always replicated in routine clinical practice. The reasons may be multifactorial, but it is generally accepted that real-world undertreatment is commonplace, which is in turn associated with worse outcomes.[28] One-off SRT may have real-world advantages[29] if it offers more stable disease that is less influenced by patient adherence, capacity constraints, and peaks and troughs in intravitreal drug levels. For example, the OCT measurements shown in the Results suggest that there was more consistent reduction in macular leakage with SRT, and less variability month by month.

Our results extend to year 2. Whilst this is longer than the primary outcome of many nAMD trials, it is not yet known if the safety and benefit of SRT will extend for longer;[30] however our data suggest increasing benefit with respect to injection frequency over time. It is also unknown if BCVA will diverge with longer follow-up if complications of SRT emerge, but over our follow-up period BCVA was relatively stable and similar in both groups. An improvement in BCVA was not expected, as participants were already receiving anti-VEGF treatment, unlike the treatment naive participants in the anti-VEGF registration trials, who benefited from commencing intravitreal injections.

At week 96, the SRT group had a greater reduction in centrepoint thickness than sham SRT (95% CI of difference in mean –70 to 0·9 microns), driven by reduced subretinal fluid and pigment epithelial detachment height (appendix p 131). These differences might have predicted a BCVA benefit over sham treatment, but subretinal fluid and pigment epithelial detachments have less of a functional effect than other manifestations of exudation such as subretinal hyper-reflective material and intraretinal fluid,[31] especially if trial-standard refraction optically adjusts for neuroretinal elevation.

Safety review showed relatively similar adverse event rates across groups. The main difference was greater occurrence of MVAs in the SRT group. Investigators were required to look specifically for MVAs, and associated changes such as cotton wool spots or telangiectasia, both on examination and with annual angiography; they reported MVAs in 4% of the SRT group over 2 years, with none in the sham group. One incidence was of moderate severity and all others were considered mild, with none thought to have affected vision. The fact that MVAs were predominantly mild may explain the much lower MVA detection rate compared to the reading centre (35% in the SRT group *vs* 12% in the sham group at week 96). Paradoxically, reading centre-detected MVAs seemed protective of final vision, in both groups. In the SRT group, this may be due to the effect of SRT being relatively greater in eyes which manifested MVAs, thereby leading to better nAMD disease control; whereas in the sham group, this could be due to random chance as there were few affected eyes. SRT-treated participants with fovea-involving MVAs lost more vision than those with extrafoveal MVAs, but they were still only very slightly worse than those without MVAs (0·8 letters), suggesting relatively little deleterious effect overall.

Strengths of this study include its randomised, double-masked, sham-controlled design, reading centre image review, and incorporation of a health economic analysis. Recruiting previously treated patients enhances generalisability to the largest pool of people with nAMD, but results might differ if SRT was used as a primary therapy. Selection of patients by the clinical investigator, without reading centre involvement, might introduce selection variability, but it enhances generalisability as a reading centre would not be used outside of a trial. Baseline characteristics were similar to real-world studies,[32] and the primary outcome favoured SRT across multiple subgroups, further supporting generalisability. STAR has longer efficacy follow-up than INTREPID, but even longer is desirable, with real-world follow-up extended to 4 years planned.

This trial is smaller than some AMD drug trials, but is sufficiently powered to detect a clinically meaningful difference in the number of treatments delivered, and our results support the assumptions underlying the sample size calculation. We observed a reduction of 2·9 injections versus 2·5 predicted, an observed injection SD of 6·3 for 16-Gy SRT and 5·8 for sham SRT versus 7·0 predicted, and an observed change in BCVA SD of 11 in both groups versus the predicted 12. It is one of the largest nAMD device RCTs. Disaggregation of BCVA results by sex suggested that men had a better vision response to SRT than women, but it is uncertain whether this reflects a biological difference in clinical response, the influence of confounding variables, or perhaps a chance finding, but as a post-hoc analysis this small difference needs to be interpreted with caution.

The costing analysis focused on the cost of SRT, anti-VEGF injections, and monitoring visits. A full economic evaluation, including all NHS costs related to the study eye and analysis of EQ-5D-5L utilities, will be reported separately. Future studies might investigate reports that increased choroidal thickness predicts a better BCVA response to SRT.[30]

The COVID-19 pandemic had the potential to influence the primary endpoint. Compliance shortly after the pandemic was compromised, but this effect was mostly short-lived. The most common deviation was missed or delayed visits, which could result in fewer ranibizumab retreatments. However, 61% of participants had reached the 96-week primary endpoint before lockdown and their results mirrored the primary analysis, with the SRT group receiving 3·0 fewer injections than sham. Benefits in the compliant population model were also similar (3·1 fewer injections). These secondary analyses were specified before the data lock, and suggest the pandemic did not change the trial's main finding (appendix p 125).

In summary, SRT can reduce the frequency of ranibizumab retreatment for people with chronic, active nAMD, with non-inferior vision versus ranibizumab monotherapy, and acceptable safety. The cost of SRT is more than offset by fewer ranibizumab injections.

Contributors

TLJ was the chief investigator, led the bid for funding, wrote the protocol, conceived the compliance diagram, and prepared the first draft of the manuscript. RD was the trial manager throughout, and LR is the current associate trial manager and trial monitor. YW and JP were co-applicants on the bid for funding, and designed the statistical analysis plan, which was executed by HAW under their supervision. UC was a clinical co-applicant on the bid for funding and directed the reading centre. TP led the reading centre image analysis. HD and SW designed and conducted the costing analysis. CL was the medical physics lead and co-applicant on the bid for funding; PC was the subsequent lead medical physicist. JEN was the trial's clinical research fellow and led the source document design and preparation, followed by CNL as clinical research fellow, who coordinated and made the manuscript revisions. JMO was the clinical radiation expert and co-applicant on the bid for funding. BCR was the deputy chief investigator, trial methodologist, and co-applicant on the bid for funding. All authors reviewed and critiqued the manuscript, and were responsible for the decision to submit the manuscript for publication. HAW and YW had access to and verified the data, following data cleaning by LR, RD, and CNL. HD had access to the data and undertook the costing and health economic analysis.

Declaration of interests

Oraya/Zeiss provided free use of the SRT device at the STAR National Treatment Centres. BCR, TP, YW, HAW, JMO, and JP declare no

competing interests. TLJ is a consultant or adviser to 2CTech, Alcon, Dutch Ophthalmic Research Centre, iLumen, Opthea, Outlook Therapeutics, Oxurion, and Regeneron. He has received conference support from Roche, and an advisory board payment from Oraya in 2013. TP has participated in advisory boards for Apellis and received investigator initiated research funds paid to her institution from Boehringen Ingelheim; as well as receiving speakers fees from Heidelberg, Zeiss, and Optos. UC serves on a data monitoring committee for Adverum and is a consultant to Apellis, Boehringer Ingelheim, Isarna, Iveric, and Hoffman La Roche. JEN is an adviser to Solvemed, has received lecture fees from Novartis, and has received conference support from Dutch Ophthalmic Research Centre. HD and SW are financially supported in part by the National Institute for Health and Care Research (NIHR) Oxford Biomedical Research Centre. CNL has undertaken contracting work for Opthea. TLJ, LR, RD, CNL, CL, PC and JEN's NHS employer receives site fees for patients enrolled on commercial retinal trials of AMD and other conditions.

Data sharing

The data are held by King's College London, London, UK. Applications to share the deidentified and anonymised trial data with other investigators for use in future research will be considered, subject to review of the aims and scientific methods of the application, and any contractual obligations required by organisations involved in the study. Requests for data sharing or collaboration should be made to the corresponding author.

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