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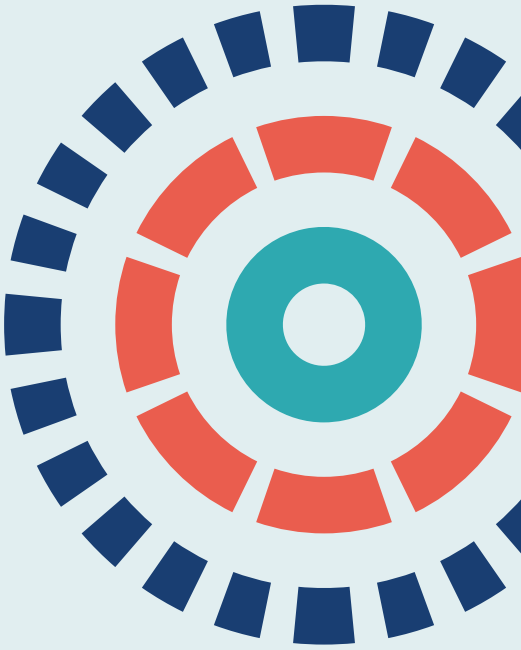

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Intravitreal ranibizumab versus aflibercept versus bevacizumab for macular oedema due to central retinal vein occlusion: the LEAVO non-inferiority three-arm RCT

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This report

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Abstract

Intravitreal ranibizumab versus aflibercept versus bevacizumab for macular oedema due to central retinal vein occlusion: the LEAVO non-inferiority three-arm RCT

Philip Hykin,[1,2*] A Toby Prevost,[3] Sobha Sivaprasad,[1,2] Joana C Vasconcelos,[3] Caroline Murphy,[4] Joanna Kelly,[4] Jayashree Ramu,[1] Abualbishr Alshreef,[5] Laura Flight,[5] Rebekah Pennington,[5] Barry Hounsome,[†] Ellen Lever,[4] Andrew Metry,[5] Edith Poku,[5] Yit Yang,[6] Simon P Harding,[7] Andrew Lotery,[8] Usha Chakravarthy[9] and John Brazier[5]

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Background: Licensed ranibizumab (0.5 mg/0.05 ml Lucentis®; Novartis International AG, Basel, Switzerland) and aflibercept (2 mg/0.05 ml Eylea®; Bayer AG, Leverkusen, Germany) and unlicensed bevacizumab (1.25 mg/0.05 ml Avastin®; F. Hoffmann-La Roche AG, Basel, Switzerland) are used to treat macula oedema due to central retinal vein occlusion, but their relative clinical effectiveness, cost-effectiveness and impact on the UK NHS and Personal Social Services have never been directly compared over the typical disease treatment period.

Objective: The objective was to compare the clinical effectiveness and cost-effectiveness of three intravitreal antivascular endothelial growth factor agents for the management of macula oedema due to central retinal vein occlusion.

Design: This was a three-arm, double-masked, randomised controlled non-inferiority trial.

Setting: The trial was set in 44 UK NHS ophthalmology departments, between 2014 and 2018.

Participants: A total of 463 patients with visual impairment due to macula oedema secondary to central retinal vein occlusion were included in the trial.

Interventions: The participants were treated with repeated intravitreal injections of ranibizumab ($n = 155$), aflibercept ($n = 154$) or bevacizumab ($n = 154$).

Main outcome measures: The primary outcome was an increase in the best corrected visual acuity letter score from baseline to 100 weeks in the trial eye. The null hypothesis that aflibercept and bevacizumab are each inferior to ranibizumab was tested with a non-inferiority margin of −5 visual acuity letters over 100 weeks. Secondary outcomes included additional visual acuity, and imaging outcomes, Visual Function Questionnaire-25, EuroQol-5 Dimensions with and without a vision bolt-on, and drug side effects. Cost-effectiveness was estimated using treatment costs and Visual Function Questionnaire-Utility Index to measure quality-adjusted life-years.

Results: The adjusted mean changes at 100 weeks in the best corrected visual acuity letter scores were as follows – ranibizumab, 12.5 letters (standard deviation 21.1 letters); aflibercept, 15.1 letters (standard deviation 18.7 letters); and bevacizumab, 9.8 letters (standard deviation 21.4 letters). Aflibercept was non-inferior to ranibizumab in the intention-to-treat population (adjusted mean best corrected visual acuity difference 2.23 letters, 95% confidence interval −2.17 to 6.63 letters; $p = 0.0006$), but not superior. The study was unable to demonstrate that bevacizumab was non-inferior to ranibizumab in the intention-to-treat population (adjusted mean best corrected visual acuity difference −1.73 letters, 95% confidence interval −6.12 to 2.67 letters; $p = 0.071$). A post hoc analysis was unable to demonstrate that bevacizumab was non-inferior to aflibercept in the intention-to-treat population (adjusted mean best corrected visual acuity difference was −3.96 letters, 95% confidence interval −8.34 to 0.42 letters; $p = 0.32$). All per-protocol population results were the same. Fewer injections were required with aflibercept (10.0) than with ranibizumab (11.8) (difference in means −1.8, 95% confidence interval −2.9 to −0.8). A post hoc analysis showed that more bevacizumab than aflibercept injections were required (difference in means 1.6, 95% confidence interval 0.5 to 2.7). There were no new safety concerns. The model- and trial-based cost-effectiveness analyses estimated that bevacizumab was the most cost-effective treatment at a threshold of £20,000–30,000 per quality-adjusted life-year.

Limitations: The comparison of aflibercept and bevacizumab was a post hoc analysis.

Conclusion: The study showed aflibercept to be non-inferior to ranibizumab. However, the possibility that bevacizumab is worse than ranibizumab and aflibercept by 5 visual acuity letters cannot be ruled out. Bevacizumab is an economically attractive treatment alternative and would lead to substantial cost savings to the NHS and other health-care systems. However, uncertainty about its relative effectiveness should be discussed comprehensively with patients, their representatives and funders before treatment is considered.

Future work: To obtain extensive patient feedback and discuss with all stakeholders future bevacizumab NHS use.

Trial registration: Current Controlled Trials ISRCTN13623634.

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List of abbreviations

A&E	accident and emergency
AE	adverse event
AIC	Akaike information criterion
ALDVMM	adjusted limited dependent variable mixture model
AMD	age-related macular degeneration
APTC	Antiplatelet Trialists' Collaboration
BCVA	best corrected visual acuity
BIC	Bayesian information criterion
BRAVO	RanibizumaB for the treatment of macular edema following BRAnch Retinal Vein Occlusion
BRVO	branch retinal vein occlusion
BSE	better-seeing eye
CASP	Critical Appraisal Skills Programme
CATT	Comparison of Age-related macular degeneration Treatments Trials
CEAC	cost-effectiveness acceptability curve
CFP	colour fundus photography
CFT	central foveal thickness
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CLRN	Comprehensive Local Research Network
COST	cone outer segment tip
CRF	case report form
CRT	central retinal thickness
CRUISE	Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety
CRVO	central retinal vein occlusion
CST	central subfield thickness
CUA	cost–utility analysis
CVI	Certificate of Vision Impairment
CVOS	Central Vein Occlusion Study
DD	disc diameter
DMEC	Data Monitoring and Ethics Committee
DMO	diabetic macula oedema
DRIL	disorganisation of the retinal inner layers
DS	dioptre sphere
eCRF	electronic case report form
ELM	external limiting membrane
EMA	European Medicines Agency
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
EQ-5D-V	EuroQol-5 Dimensions with vision bolt-on
ETDRS	Early Treatment Diabetic Retinopathy Study
EZ	ellipsoid zone
FDA	Food and Drug Administration
FFA	fundus fluorescein angiography
GP	general practitioner
HCHS	Hospital and Community Health Service
HORIZON	An Open-Label, Multicentre Extension Study to Evaluate the Safety and Tolerability of Ranibizumab in Subjects with Choroidal Neovascularization Secondary to Age-Related Macular Degeneration or Macular Oedema Secondary to Retinal Vein Occlusion Who Have Completed a Genentech-Sponsored Ranibizumab
HRF	hyper-reflective foci

HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
INMB	incremental net monetary benefit
IQR	interquartile range
ITT	intention to treat
IVAN	Inhibit VEGF in Age-related choroidal Neovascularisation
KCTU	King's Clinical Trials Unit
LEAVO	a multicentre, Phase III, double-masked, randomised controlled non-inferiority trial comparing the clinical effectiveness and cost-effectiveness of intravitreal therapy with ranibizumab (Lucentis) versus aflibercept (Eylea) versus bevacizumab (Avastin) for macular oedema due to central retinal Vein Occlusion
LME	linear mixed effects
M	macular ring
MAE	mean absolute error
MHRA	Medicines and Healthcare products Regulatory Agency
MO	macular oedema
NetwORC	Network of Ophthalmic Reading Centres
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMB	net monetary benefit
nvAMD	neovascular age-related macular degeneration
NVD	neovascularisation disc
NVE	neovascularisation elsewhere
NVG	neovascular glaucoma
NVI	neovascularisation of the iris
OCT	optical coherence tomography
PAS	Patient Access Scheme
PIN	patient identification number
QALY	quality-adjusted life-year
QMUL	Queen Mary University of London
R	ring
RAPD	relative afferent pupillary defect
RCT	randomised controlled trial
RETAIN	extended follow-up of patients with macular edema due to bRanch rETinal vein occlusion or centrAl retinal veIn occlusioN previously treated with intravitreal ranibizumab
RMSE	root-mean-square error
RVO	retinal vein occlusion
SA	substantial amendment
SAE	serious adverse event
SCORE2	Study of Comparative Treatments for Retinal Vein Occlusion 2
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SE	standard error
SUR	seemingly unrelated regression
SUSAR	suspected unexpected serious adverse reaction
TA	technology appraisal
TMG	Trial Management Group
TSC	Trial Steering Committee
VEGF	vascular endothelial growth factor
VFQ-25	Visual Function Questionnaire-25 items
VFQ-UI	Visual Function Questionnaire-Utility Index
WSE	worse-seeing eye

Plain English summary

The eye functions like a camera. The retina, at the back of the eye, is the camera film, and the centre, the macula, allows us to see fine details. Approximately 6500 people each year in England and Wales are affected by fluid leaking out of congested tiny blood vessels, causing macular swelling or oedema. The cause is blockage of the main vein that normally drains blood from the retina.

Three drugs, injected into the eye in tiny amounts every 4–8 weeks, have been shown to improve the vision of people with this condition. Two drugs, ranibizumab (0.5 mg/0.05 ml Lucentis®; Novartis International AG, Basel, Switzerland) and aflibercept (2 mg/0.05 ml Eylea®; Bayer AG, Leverkusen, Germany), are licensed for UK use, but the third, bevacizumab (1.25 mg/0.05 ml Avastin®; F. Hoffmann-La Roche AG, Basel, Switzerland), is not, even though it is much cheaper and used extensively worldwide. To our knowledge, no trials have compared the three drugs over the typical 2-year treatment period.

This multicentre, Phase III, double-masked, randomised controlled non-inferiority trial comparing the clinical effectiveness and cost-effectiveness of intravitreal therapy with ranibizumab (Lucentis) versus aflibercept (Eylea) versus bevacizumab (Avastin) for macular oedema due to central retinal Vein Occlusion (LEAVO) was designed to compare ranibizumab, aflibercept and bevacizumab in this type of macular oedema. The trial showed that all three drugs improved vision a lot, but bevacizumab improved vision to a slightly lesser degree than the other two drugs. All patients should be aware of these findings before considering their treatment options.

A comparison of the costs and benefits of ranibizumab, aflibercept and bevacizumab, using data from the trial and other sources, found that all three led to similar improvements in quality of life. Because aflibercept and ranibizumab are so much more expensive, they may be poor value for money. If patients, their representatives and funders all agree, it may be possible to treat this type of macular oedema with bevacizumab, which is cheaper, keeping the other agents available if needed.

Scientific summary

Background

Approximately 5200 cases of visual impairment due to central retinal vein occlusion-related macular oedema occur yearly in England and Wales and require treatment with repeated intraocular injections of antivascular endothelial growth factor agents. Treatment typically lasts for 2 years. Two agents, ranibizumab (0.5 mg/0.05 ml Lucentis®; Novartis International AG, Basel, Switzerland) and aflibercept (2 mg/0.05 ml Eylea®; Bayer AG, Leverkusen, Germany), are licensed and recommended by the National Institute for Health and Care Excellence.

An alternative low-cost option, unlicensed bevacizumab (1.25 mg/0.05 ml Avastin®; F. Hoffmann-La Roche AG, Basel, Switzerland), is utilised globally. All three antivascular endothelial growth factor agents are also used in the treatment of other retinal disorders. Despite clinical evidence that bevacizumab is non-inferior to ranibizumab and is cost-effective in neovascular age-related macular degeneration and diabetic macular oedema, it is not used in the NHS. The reasons for this include a lack of clinical evidence in certain indications, concerns over whether or not high-quality bevacizumab could be manufactured on the scale required for NHS use and the fact that it is not licensed or recommended by the National Institute for Health and Care Excellence. Therefore, in 2012, the National Institute for Health and Care Excellence Decision Support Unit recommended further comparative studies of these agents in retinal diseases, resulting, in 2014, in the development of this multicentre, Phase III, double-masked, randomised controlled non-inferiority trial comparing the clinical effectiveness and cost-effectiveness of intravitreal therapy with ranibizumab (Lucentis) versus aflibercept (Eylea) versus bevacizumab (Avastin) for macular oedema due to central retinal Vein Occlusion (LEAVO). No new antivascular endothelial growth factor agents or other treatments have superseded antivascular endothelial growth factor agents in vein occlusion-related macula oedema. Since LEAVO was initiated, the US Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) trial (Scott IU, VanVeldhuisen PC, Ip MS, Blodi BA, Oden NL, Awh CC, *et al.* Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. *JAMA* 2017;**317**:2072–87) reported the non-inferiority of bevacizumab to aflibercept with respect to visual acuity at 6 months in 362 patients with macula oedema due to central retinal vein occlusion or hemiretinal vein occlusion. A systematic review of antivascular endothelial growth factor therapy confirmed that there were no randomised controlled trials comparing all three antivascular endothelial growth factor agents in vein occlusion. LEAVO is, therefore, the first randomised controlled trial, to our knowledge, that has evaluated the comparative clinical effectiveness and cost-effectiveness of these three antivascular endothelial growth factor agents in central retinal vein occlusion-related macula oedema over the typical duration of the disease.

Objectives

The following research questions were addressed in this trial:

- Is bevacizumab non-inferior to ranibizumab in eyes with macula oedema due to central retinal vein occlusion in terms of best corrected visual acuity at 100 weeks?
- Is aflibercept non-inferior to ranibizumab in eyes with macula oedema due to central retinal vein occlusion in terms of the best corrected visual acuity at 100 weeks?
- What is the short-term and long-term cost-effectiveness of aflibercept and bevacizumab versus ranibizumab in the treatment of macula oedema due to central retinal vein occlusion?

Methods

Design

This was a multicentre, prospective, three-arm, double-masked, randomised controlled non-inferiority trial to evaluate the clinical effectiveness, cost-effectiveness and side-effect profile of three antivascular endothelial growth factor agents in the management of central retinal vein occlusion-related macula oedema over 100 weeks.

Setting

The trial was set in the ophthalmology departments of 44 UK NHS trust hospitals.

Participants

Participants were adults with visual impairment due to central retinal vein occlusion-related macula oedema of < 12 months' duration, with a visual acuity letter score in the study eye of between 19 (≈ 3/60 Snellen) and 78 (≈ 6/9 Snellen) and spectral-domain optical coherence tomography central subfield thickness of ≥ 320 µm.

Interventions

Using a web-based randomisation service, eligible patients were allocated (1 : 1 : 1) to repeated intravitreal injections of ranibizumab, aflibercept or bevacizumab by the method of minimisation, with the following factors: visual acuity (19–38, 39–58 or 59–78 Early Treatment Diabetic Retinopathy Study letters), disease duration (< 3 months, 3–6 months or > 6 months) and treatment naive (yes or no). Participants in all trial arms had a mandated injection at baseline and at 4, 8 and 12 weeks. From weeks 16 to 96, treatment was given if one or more of the predefined re-treatment criteria were met; the criteria were a decrease in visual acuity of > 5 letters between the previous and the current visit, attributed to an increase in optical coherence tomography central subfield thickness; an increase in visual acuity of > 5 letters between the previous and the current visit; an optical coherence tomography central subfield thickness of ≥ 320 µm due to intraretinal or subretinal fluid; and an optical coherence tomography central subfield thickness increase of > 50 µm from the lowest previous measurement. From week 24, the visit interval could be increased from 4 to 8 weeks if re-treatment criteria were not met at three consecutive visits. Re-treatment was withheld if visual acuity was > 83 letters; it could be suspended if there was minimal response to three consecutive injections and could be restarted if clinical deterioration occurred.

Follow-up

Participants were followed up for 100 weeks.

Clinical outcomes

The primary outcome was the change in refracted visual acuity letter score from baseline to 100 weeks in the study eye. Secondary outcomes in the study eye included a gain of ≥ 10 and ≥ 15 visual acuity letters, losses of < 15 or ≥ 30 visual acuity letters at 52 and 100 weeks, change in optical coherence tomography central subfield thickness from baseline to 52 and 100 weeks, optical coherence tomography central subfield thickness of < 320 µm at 52 and 100 weeks, and the number of injections by 100 weeks. Adverse events were recorded over the weeks.

Statistical analysis

Part of this section has been reproduced from Hykin P, Prevost AT, Vasconcelos JC, Murphy C, Kelly J, Ramu J, *et al.* Clinical effectiveness of intravitreal therapy with ranibizumab vs aflibercept vs bevacizumab for macular edema secondary to central retinal vein occlusion: a randomized clinical trial. *JAMA Ophthalmol* 2019;**137**:1256–64. This is an open access article distributed under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium. The text includes minor additions and formatting changes to the original.

The standard deviation was anticipated to be 14.3 letters, based on the available data, and the sample size was set at 459 patients for at least 80% power to detect non-inferiority against a margin of −5 Early Treatment Diabetic Retinopathy Study letters for each intervention compared with ranibizumab using a two-sided 95% confidence interval from an analysis-of-covariance test with adjustment for baseline visual acuity. The primary outcome of refracted visual acuity was compared between the aflibercept and ranibizumab groups and between the bevacizumab and ranibizumab groups, primarily at the 100-week point, adjusting for baseline using a linear mixed-effects model and allowing for within-patient correlation of repeated measures over time using an unstructured covariance matrix. All participants with at least one milestone visit were included in the model; therefore, those without follow-up data did not contribute to the analysis. Fixed effects included the main effects and interactions with 'time' (defined as milestone visits at 12, 24, 52, 76 and 100 weeks) of treatment group, disease duration (< 3 or ≥ 3 months), the baseline of the outcome and its missing indicator required for the missing indicator method. The test for non-inferiority was one-sided at the 2.5% significance level, and presented as an estimated effect with two-sided 95% confidence intervals compared with the non-inferiority margin of −5 letters. The per-protocol population was defined as a subset of the intention-to-treat population who were eligible and received minimal sufficient treatment exposure, defined as four treatments correctly assessed and received during the first six visits. For the analysis of the primary outcome, the mixed-effects model was re-fitted in the per-protocol population. Non-inferiority was declared if the estimated 95% confidence interval for the difference in means lay wholly above the margin of −5 letters in both the intention-to-treat and the per-protocol analysis models, primarily at 100 weeks and secondarily at 52 weeks (and implicitly one-sided $p < 0.025$ for both). Analyses were completed according to the intention-to-treat strategy under a missing-at-random assumption, together with a principled sensitivity analysis in the full intention-to-treat and per-protocol populations. This assessed sensitivity to the handling of missing 100-week data using three recommended scenarios affecting either any or all groups. Secondary continuous outcomes were analysed only on the intention-to-treat basis, for superiority, and with the same model specification as for the primary outcome, except with baseline visual acuity represented by its minimisation categories, and reported as adjusted differences in means. Safety and Antiplatelet Trialists' Collaboration events were reported as proportions and compared between groups, with Wilson's 95% confidence intervals for rare events. All superiority tests were two-sided at the 5% significance level and effect sizes were interpreted cautiously with 95% confidence intervals.

Health economic analysis

The primary health economic analysis was a model-based cost–utility analysis adopting a lifetime horizon and an NHS payer perspective, using discrete event simulation modelling. The model utilised data from LEAVO, which were supplemented with evidence from external sources. Cost-effectiveness was expressed in terms of the incremental cost per quality-adjusted life-year, estimated using the Visual Function Questionnaire-Utility Index, the EuroQol-5 Dimensions and the EuroQol-5 Dimensions with vision bolt-on. A within-trial analysis was conducted as a secondary analysis. Scenario analyses considered the impact of price discounts for aflibercept and ranibizumab.

Results

Between December 2014 and 2016, eligibility was determined for 586 patients; 463 patients were randomly assigned to receive ranibizumab ($n = 155$), aflibercept ($n = 154$) or bevacizumab ($n = 154$). Participants' baseline characteristics were similar between the treatment groups. A total of 454 and 443 participants were included in the prespecified intention-to-treat and per-protocol linear mixed-effects models, and the 100-week visit was completed by 135 (87.1%) participants in the ranibizumab group, 133 (86.4%) participants in the aflibercept group and 139 (90.3%) participants in the bevacizumab group.

Clinical results

The mean gain in visual acuity letter score was ranibizumab +12.5 (standard deviation 21.1), aflibercept +15.1 (standard deviation 18.7) and bevacizumab +9.8 (standard deviation 21.4) at 100 weeks. At 100 weeks, the trial was unable to demonstrate that bevacizumab was non-inferior to ranibizumab in either the intention-to-treat (adjusted mean best corrected visual acuity difference−1.73 letters, 95% confidence interval −6.12 to 2.67 letters; $p = 0.071$) or the per-protocol population (adjusted mean best corrected visual acuity difference−1.67 letters, 95% confidence interval −6.02 to 2.68 letters; $p = 0.066$). Aflibercept was non-inferior to ranibizumab in both the intention-to-treat (adjusted mean best corrected visual acuity difference 2.23 letters, 95% confidence interval −2.17 to 6.63 letters, $p = 0.0006$) and the per-protocol populations (adjusted mean best corrected visual acuity difference was 3.49 letters, 95% confidence interval −0.91 to 7.88 letters; $p < 0.0001$), but it was not superior. At 52 weeks, aflibercept and bevacizumab were non-inferior to ranibizumab. The proportions of participants in the three groups who had a best corrected visual acuity letter gain of ≥ 15 were similar: 47% in the ranibizumab group, 52% in the aflibercept group and 45% in the bevacizumab group. There were no differences across the groups in the proportion of patients who had ≥ 10 best corrected visual acuity letter gain or < 15 best corrected visual acuity letter loss.

The adjusted difference in optical coherence tomography central subfield thickness at 100 weeks for aflibercept versus ranibizumab was −29.3 (95% confidence interval −60.9 to 2.3), whereas for bevacizumab versus ranibizumab, it was 21.9 (95% confidence interval −9.7 to 53.4). However, a significantly greater proportion of participants had an optical coherence tomography central subfield thickness of < 320 µm at 52 weeks in the aflibercept group (76%) than in the ranibizumab group (63%), a mean difference of 12.4% (95% confidence interval 1.7% to 23.1%). This was also the case at 100 weeks for aflibercept (81%) compared with ranibizumab (66%), a mean difference of 15.3% (95% confidence interval 4.9% to 25.7%), but for bevacizumab compared with ranibizumab a difference was found only at week 24 (mean difference −18.7%, 95% confidence interval −30.1% to −7.4%). The corresponding proportions at 52 weeks and 100 weeks for bevacizumab were −10.7% (95% confidence interval −22.3% to 0.9%) and −7.4% (95% confidence interval −18.9% to 4.1%).

By 100 weeks, participants in the ranibizumab group had received a mean of 11.8 injections, compared with 10.0 injections received by participants in the aflibercept group and 11.5 injections received by those in the bevacizumab group. The difference between the aflibercept and ranibizumab groups was significant at week 24 (mean difference −0.4, 95% confidence interval −0.6 to −0.2), week 52 (mean difference −1.1, 95% confidence interval −1.6 to −0.5) and week 100 (mean difference −1.9, 95% confidence interval −2.9 to −0.8). There was one case of infectious endophthalmitis in the bevacizumab group. The frequency of all ocular adverse and Antiplatelet Trialists' Collaboration-defined events occurred with an expected, and similar, frequency in the three groups.

Aflibercept became a standard of care after LEAVO was initiated, so the comparative effectiveness of aflibercept and bevacizumab became highly relevant and a post hoc analysis was conducted. This analysis showed that bevacizumab was not non-inferior to aflibercept in both the intention-to-treat (adjusted mean best corrected visual acuity difference−3.96 letters, 95% confidence interval −8.34 to 0.42 letters; $p = 0.32$) and the per-protocol populations (adjusted mean best corrected visual acuity difference −5.15 letters, 95% confidence interval −9.52 to −0.79 letters; $p = 0.47$).

Economic results

The main findings of the model-based and within-trial cost–utility analyses suggest that bevacizumab is an economically attractive alternative to the licensed products ranibizumab and aflibercept.

The model-based economic analysis found that all three antivascular endothelial growth factor agents generated similar quality-adjusted life-years. Aflibercept generated the highest costs, followed by ranibizumab and then bevacizumab. Using the Visual Function Questionnaire-Utility Index, bevacizumab generated more quality-adjusted life-years than ranibizumab and aflibercept. The mean difference in

quality-adjusted life-years between ranibizumab and bevacizumab was −0.044 (95% confidence interval −0.074 to 0.013), and the mean difference in costs was £11,873 (95% confidence interval £11,458 to £12,288), so bevacizumab was said to dominate ranibizumab, and the 95% confidence interval for the incremental net monetary benefit at £30,000 per quality-adjusted life-year was −£14,316 to −£12,067. The mean difference in quality-adjusted life-years between aflibercept and bevacizumab was −0.109 (95% confidence interval −0.161 to −0.057), and the mean difference in costs was £4800 (95% confidence interval £4445 to £5154), so bevacizumab was said to dominate aflibercept, and the 95% confidence interval for the incremental net monetary benefit at £30,000 per quality-adjusted life-year was −£21,864 to −£18,040. The mean difference in quality-adjusted life-years between aflibercept and ranibizumab was −0.065 (95% confidence interval −0.097 to −0.033), and the mean difference in costs was £4800 (95% confidence interval £4445 to £5154), so ranibizumab was said to dominate aflibercept, and the 95% confidence interval for the incremental net monetary benefit at £30,000 per quality-adjusted life-year was −£7917 to −£5603. The finding that bevacizumab was the most cost-effective intervention was robust to scenario analyses. The costs of aflibercept and ranibizumab would need to be discounted by at least 95% to be comparable to the cost of bevacizumab (at £28 per injection over a patient's lifetime).

In the within-trial base-case analysis, the difference in mean total costs was £1245 between aflibercept and ranibizumab (95% confidence interval £421 to £2070), −£6760 between bevacizumab and ranibizumab (95% confidence interval −£7546 to −£5973) and £7984 between aflibercept and bevacizumab (95% confidence interval £7209 to £8759). Bevacizumab was dominant (less costly and with no difference in benefit) compared with ranibizumab, with a probability of cost-effectiveness of 1.00 at the £20,000 per quality-adjusted life-year threshold. Aflibercept was more costly than ranibizumab, with a mean quality-adjusted life-year difference of 0.004 (95% confidence interval −0.0430 to 0.0518), an incremental cost-effectiveness ratio of £283,595 per quality-adjusted life-year gained and a probability of cost-effectiveness of 0.04 at the £20,000 per quality-adjusted life-year threshold. Aflibercept was dominated by bevacizumab (more costly, with a mean quality-adjusted life-year difference of −0.015, 95% confidence interval −0.0618 to 0.0322) with a probability of cost-effectiveness of 0.00 at both the £20,000 and the £30,000 per quality-adjusted life-year thresholds.

Conclusions

All three antivascular endothelial growth factor agents are effective therapies for macula oedema secondary to central retinal vein occlusion, with no differences from a safety perspective. Although aflibercept was demonstrated to be non-inferior to ranibizumab, the trial was unable to demonstrate that bevacizumab was non-inferior to either, meaning that we cannot rule out the possibility that bevacizumab may be worse by 5 visual acuity letters. However, patients' health-related quality-of-life assessments were similar across treatment groups, and bevacizumab was found to be the most cost-effective option. The trial results are, therefore, divergent. We believe that bevacizumab could be introduced into the NHS as a first-line agent for this condition only after a review of these results and in agreement with patients, their representatives and funders. If patients are fully informed and understand the clinical results of the trial, as our small post-trial patient questionnaire suggests, a majority may consent to bevacizumab treatment with the proviso that licensed medications be available to them as an option if their response to bevacizumab is less than expected. If adopted, bevacizumab would result in substantial savings to the NHS, and potentially to health-care systems around the world.

Trial registration

This trial is registered as ISRCTN13623634.

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Chapter 1 Introduction

Background

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder,[1,2] after diabetic retinopathy, and comprises branch RVO, hemiretinal vein occlusion and central retinal vein occlusion (CRVO). CRVO has a prevalence of 0.08–0.41%[3–5] and a 15-year cumulative incidence rate of 0.5%.[6,7] Approximately 6860 people develop CRVO every year in England and Wales, of these, 5150 develop visual impairment due to macula oedema (MO), which is unlikely to improve spontaneously[8–11] and is therefore potentially eligible for treatment, according to the National Institute for Health and Care Excellence (NICE).[12,13]

Central retinal vein occlusion is characterised by retinal haemorrhages, venous dilatation and tortuosity in all four quadrants of the retina.[1,7] An increase in hydrostatic pressure at the venous end of the retinal capillary network reduces retinal perfusion, upregulating the production of vascular endothelial growth factor (VEGF), which, in turn, increases retinal capillary permeability and is probably the major cause of MO,[14] although the raised hydrostatic pressure per se probably plays a part.[7] VEGF promotes iris and retinal neovascularisation in severe cases. The characteristic presentation of CRVO is sudden painless unilateral decrease in vision due to MO.[8] In severe cases, vision is affected by macular ischaemia or the development of iris neovascularisation and, subsequently, neovascular glaucoma with elevated intraocular pressure, pain, redness and visual loss if the condition is left untreated. CRVO may be bilateral in 5% of cases, and the risk of developing RVO in the contralateral eye within 12 months is approximately 5%.[7,8]

Central retinal vein occlusion has two distinct clinical subtypes.[7,8] Non-ischaemic CRVO is characterised by a visual acuity of $\geq$ 6/30, no relative afferent pupillary defect (RAPD), mild to moderate retinal venous dilatation and tortuosity, and intraretinal haemorrhage and MO. Ischaemic CRVO is characterised by a visual acuity of $\leq$ 6/36, the presence of a RAPD, and intraretinal haemorrhage with venous dilatation and tortuosity greater than the Central Vein Occlusion Study (CVOS) standard photograph,[15] with complications that include MO, macular ischaemia, retinal ischaemia, iris and retinal neovascularisation and neovascular glaucoma.[16] Optical coherence tomography (OCT) confirms and characterises the MO, and fundus fluorescein angiography (FFA) confirms and characterises the extent of macular and retinal ischaemia and the presence of retinal neovascularisation; both investigations guide management.[7,8] Novel morphological OCT biomarkers for CRVO have been identified that may provide important diagnostic and prognostic information, although, to our knowledge, none has been utilised in a large prospective clinical trial to date.[17–19] Conventional seven-field FFA is semiquantitative and, if the total area of angiographic non-perfusion is at least 10 disc areas in size, the prognosis is less good than for the non-ischaemic subtype.[20,21] More recently, wide-angled FFA has allowed a greater proportion of the peripheral retina to be imaged, although the exact amount and distribution of non-perfusion that characterises the subtypes of CRVO have not been well defined.[22,23] Eyes with larger areas of retinal ischaemia on conventional FFA are more prone to neovascular complications.[20] Approximately 15–20% of cases present with ischaemic CRVO, and in 25–34% of cases non-ischaemic CRVO converts to the ischaemic subtype within 3 years.[20,24] Neovascular complications such as iris neovascularisation are typically managed using a combination of retinal laser therapy and anti-VEGF therapy.[7,8]

In non-inferiority ophthalmology clinical trials, the primary outcome has typically been a visual acuity difference of –5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. This is thought to represent a meaningful difference between two treatments, based on the following:

- Most patients in a busy clinic setting can reliably distinguish an 8-letter (1.5-line) difference on an ETDRS visual acuity chart, but they may perform better than this in a clinical trial setting.[25]
- A 5-letter (1-line) improvement in mean visual acuity in retinal studies typically results in a 50% increase in the number of patients gaining 15-letter (3-line) improvement in visual acuity, suggesting that this is a meaningful difference.[26]
- The choice of a 5-letter margin was 32% higher than the available estimated 12-month placebo-controlled effect of 6.6 letters for ranibizumab (0.5 mg/0.05 ml Lucentis®; Novartis International AG, Basel, Switzerland), the standard (comparator) treatment in this multicentre, double-masked, randomised controlled non-inferiority trial comparing the clinical effectiveness and cost-effectiveness of intravitreal therapy with ranibizumab (Lucentis) versus aflibercept (Eylea) versus bevacizumab (Avastin) for macular oedema due to central retinal Vein Occlusion (LEAVO). This margin choice was, therefore, consistent with maintaining assay sensitivity sufficiently to be able to declare non-inferiority [see www.journalslibrary.nihr.ac.uk/programmes/hta/119203/#/documentation (accessed 14 July 2020)].
- This margin was accepted by the funder.

Although a 4-letter change has been used as a non-inferiority margin, this was not common practice at the time LEAVO was designed, and we wanted to ensure that LEAVO would be as similar as possible to alternative comparable studies of anti-VEGF therapy in CRVO [e.g. Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2)[27]].

Central retinal vein occlusion-related macular oedema and antivascular endothelial growth factor therapy

Visual impairment in CRVO is primarily due to MO; it is typically significant, resolution is likely to occur in only the mildest non-ischaemic cases[24] and the anatomical improvement of MO may not result in a corresponding improvement in visual acuity.[8] Presenting visual acuity is typically a good predictor of final visual outcome: patients who present with an initial visual acuity of $\geq$ 6/12 will probably retain good vision, whereas 80% of those who present with a visual acuity of $\leq$ 6/60 do not improve to > 6/60.[20] The natural history arm of the CVOS showed no change in mean baseline visual acuity over 3 years;[20] this finding is supported by the sham arms in the Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety (CRUISE),[9] GALILEO[28–30] and COPERNICUS[10,28,30,31] licensing trials for ranibizumab and aflibercept (2 mg/0.05 ml Eylea®; Bayer AG, Leverkusen, Germany), in which patients who were initiated on treatment 6 months after randomisation to sham did not achieve as large visual gains as participants randomised to prompt therapy. Therefore, prompt treatment is typically recommended to maximise visual outcomes.

First-line therapy for MO is repeated intravitreal injections of anti-VEGF agents to block the action of VEGF, thereby reducing capillary permeability.[9,32–38] Early studies excluded patients with ischaemic CRVO[33,39] as it was questionable whether or not a significant improvement in vision would result from anti-VEGF therapy. More recent (2017) studies[40] did not exclude such patients, and this is the approach we adopted in LEAVO to ensure that our study population fully reflected a general UK population likely to present for treatment.

To date, three anti-VEGF agents have been used in the treatment of MO due to CRVO:

1. Ranibizumab is a humanised, affinity-matured VEGF antibody fragment that binds to and neutralises all isoforms of VEGF-A. Ranibizumab was the first anti-VEGF therapy to demonstrate improved visual outcomes in patients with neovascular age-related macular degeneration (nvAMD),[41,42] and in 2012 it was licensed by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for MO due to CRVO. This was based on the CRUISE data[9] that showed that monthly intraocular ranibizumab therapy improved the mean best corrected visual acuity (BCVA) by +15 ETDRS letters at 6 months and a pro re nata regimen with monthly monitoring improved the mean BCVA by +14 ETDRS letters by 12 months.[9] In an open-label extension [An Open-Label, Multicentre Extension Study to Evaluate the Safety and Tolerability of Ranibizumab in Subjects with Choroidal Neovascularization Secondary to Age-Related Macular Degeneration or Macular Oedema Secondary to Retinal Vein Occlusion Who Have Completed a Genentech-Sponsored Ranibizumab study (HORIZON)] from months 12 to 24, the mean visual acuity in CRVO only patients reduced by 4.1 letters with an average of 3.5 injections in 12 months. Ranibizumab was well tolerated: 6.5% of patients had some degree of cataract after 2 years and < 1% had a rise in intraocular pressure.[38]
2. Aflibercept is a fusion protein of the key domains of VEGF receptors 1 and 2 and human IgG Fc that blocks all VEGF-A isoforms and placental growth factor. In 2014, it was licensed by the FDA and the EMA for CRVO based on the GALILEO and COPERNICUS studies, which showed a mean gain of +16.2 letters in BVCA at 12 months and a mean gain of +13.0 letters in BCVA at 24 months, with 60% gaining ≥ 15 letters at 12 months and 49.1% gaining ≥ 15 letters at 24 months.[29–31] Despite these results, and the fact that it was non-inferior to ranibizumab when given every 8 weeks after a loading phase in nvAMD, suggesting improved cost-effectiveness,[43] no clinical trial had been undertaken to directly compare aflibercept with ranibizumab or bevacizumab (1.25 mg/0.05 ml Avastin®; F. Hoffmann-La Roche AG, Basel, Switzerland), even though NICE recommended aflibercept for MO due to CRVO [NICE technology appraisal (TA) guidance 305[12]]. Cumulative safety data have not, to date, shown an increased risk of any ocular or systemic adverse events (AEs) with aflibercept compared with other drugs used for these indications.
3. Bevacizumab is a monoclonal antibody that also inhibits VEGF; it is licensed by the EMA for the treatment of cancer but is used off-label for treatment in the eye. However, it was crucial to fully assess bevacizumab's suitability for intraocular use because (1) it is substantially cheaper than ranibizumb and aflibercept when divided by a compounding pharmacy into multiple doses from a single 4-ml vial; (2) it was found by the Decision Support Unit[44] to be used in NHS trusts across the UK for nvAMD, diabetic macula oedema (DMO), RVO and other less common indications, such as choroidal neovascularisation due to myopia and retinal dystrophies; (3) it is widely used in UK private practice; and (4) there have been concerns about possible systemic side effects following intraocular injection of bevacizumab.[45] Bevacizumab was found to be non-inferior to ranibizumab in terms of macular dysfunction and final visual acuity over 2 years in two large clinical trials: the Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN)[45] trial and the Comparison of Age-related macular degeneration Treatments Trials (CATT).[46] These trials also found no increased risk of local or systemic side effects with bevacizumab compared with ranibizumab; although more patients receiving bevacizumab were hospitalised due to serious adverse events (SAEs), the investigators thought that these SAEs were unrelated to bevacizumab.[47]

Two independent reviews[48,49] had previously suggested an increase in bevacizumab-related side effects, increasing the need to compare the safety of bevacizumab directly with that of ranibizumab. NICE Technology appraisal (TA) 283[13] (on ranibizumab) and NICE TA305[12] (on aflibercept) for MO secondary to CRVO recommended that additional head-to-head trials including bevacizumab were needed for RVO to carefully examine clinical effectiveness and cost-effectiveness. Therefore, it was proposed that LEAVO be conducted in MO due to CRVO to (1) compare the clinical effectiveness of ranibizumab, aflibercept and bevacizumab in a pragmatic trial over 24 months that followed up patients over the natural history of the disease, (2) compare the cost-effectiveness of the agents in a trial that closely resembled clinical practice and (3) describe the safety profile of each agent in terms of ocular and systemic AEs over 24 months.

Evidence update post LEAVO initiation

Ranibizumab, aflibercept and bevacizumab continue to be used in many countries for multiple retinal diseases, with bevacizumab the most frequently given anti-VEGF agent worldwide, as the licensed alternatives remain too costly. Despite convincing case series and early trials employing bevacizumab, full-scale randomised controlled trials (RCTs) were commissioned and completed by the UK National Institute for Health Research (NIHR) and the US National Institutes of Health to compare bevacizumab with ranibizumab in nvAMD[45,46] prior to the licensing of aflibercept. To our knowledge, no RCTs have compared all three agents for nvAMD. Nevertheless, after a review of all the available evidence, the NICE Guideline Committee reported that all three agents were of equivalent efficacy and had similar side effects,[50] and systematic reviews found no differences in the risk of vision-threatening complications or systemic AEs.[51,52]

Despite this, bevacizumab has not achieved widespread use in the UK. The reasons for this include no clear position on the issue from NHS England or the Medicines and Healthcare products Regulatory Agency (MHRA); likely conflicts of interest among key stakeholders, including physicians; and the belief in some quarters that bevacizumab is an unlicensed medication, rather than a licensed medication being used in an off-label indication. Most recently, a UK judicial review (the Whipple judgement, September 2018), brought by the manufacturers of aflibercept and ranibizumab against north of England Clinical Commissioning Groups that had adopted a policy that off-label bevacizumab should be the preferred option for the treatment of nvAMD, ruled that this was lawful.[53] However, this outcome is now subject to appeal by the manufacturers and the uncertainty continues, which is frustrating as the economic case for bevacizumab is overwhelming. The only retinal condition for which the three anti-VEGF agents have been compared is DMO. The visual gains at 2 years in eyes with moderate and severe visual loss (visual acuity of $\leq$ 20/50) occurred earlier and were greater in eyes receiving aflibercept therapy. However, among patients with mild initial visual impairment, visual gains were similar across treatment arms, suggesting that bevacizumab could be used for these patients.[54]

Robust data remain lacking on long-term comparisons of outcomes with anti-VEGF agents for MO due to CRVO. After the initiation of LEAVO, the secondary outcomes of the randomised, double-masked, Phase III licensing trials of aflibercept for CRVO, the COPERNICUS and GALILEO studies, became available. These showed that the visual and anatomic improvements after fixed monthly dosing through to week 24 and continued pro re nata dosing with monthly monitoring from week 24 to week 52 were largely maintained up to 100 weeks if monitored every 8 weeks, and diminished if monitored quarterly from week 52 to week 100.[29–31] The 12-month single-arm study of an individualised dosing regimen of ranibizumab driven by stabilisation criteria in 357 patients with CRVO also resulted in significant gain in visual acuity (CRYSTAL).[55] The mean number of injections by 12 months was 8.8, with better outcomes in eyes with CRVO of < 3 months' duration and lower baseline visual acuity. The visual outcomes were similar in eyes with and eyes without baseline macular ischaemia. The study also showed that visual acuity could be stabilised with visual acuity-guided re-treatment criteria up to 100 weeks.[56]

Although these trials compared each anti-VEGF agent with sham treatment for MO due to CRVO, RCTs comparing these agents over a longer term have been limited. A RCT comparing aflibercept and ranibizumab on a treat-and-extend regimen over 18 months showed that the frequency of injections was significantly lower in the aflibercept arm than in the ranibizumab arm.[57] The SCORE2 study group randomised 362 patients with MO due to CRVO or hemiretinal vein occlusion 1 : 1 to receive monthly aflibercept or bevacizumab for 6 months, and reported that intravitreal bevacizumab was non-inferior to aflibercept with respect to visual acuity.[27] The participants who responded well to monthly aflibercept and those who responded well to bevacizumab for 6 months in SCORE2 were further randomised to receive either monthly injections or treat-and-extend regimens of aflibercept (for those who responded

well to aflibercept) and bevacizumab (for those who responded well to bevacizumab). The 12-month outcome showed that the treat-and-extend arm of each anti-VEGF agent required up to two fewer injections from 6 to 12 months than the monthly mandated treatment arms, although the difference in visual outcomes showed significant variability.[58] A RCT comparing aflibercept and bevacizumab on a one plus pro re nata basis found that those in the aflibercept arm required fewer injections at 12 months.[59]

The COMRADE-C trial was a Phase IIIb, multicentre, double-masked, randomised clinical trial that compared a ranibizumab loading phase followed by pro re nata dosing with 0.7 mg of dexamethasone, given only at baseline, for MO due to CRVO, and showed a favourable outcome with ranibizumab.[60] A 2019 systematic review[61] evaluating the effectiveness and adverse effects of ranibizumab, aflibercept and bevacizumab in three common retinal conditions, including RVO, reported that none of the 17 included studies showed a clinically important difference (i.e. $\geq$ 5 letters) in visual acuity gains between agents. There was insufficient evidence to compare bevacizumab and ranibizumab in RVO. Overall, the authors reported that no agent had a clear advantage over another in effectiveness or safety, but in two trials[61] both aflibercept and ranibizumab were significantly less cost-effective than repackaged bevacizumab.[61]

Another systematic review and network analysis of 11 RCTs of the three anti-VEGF agents for RVO found no statistically significant differences in the proportion of patients who gained at least 15 letters in BCVA, in the mean change from baseline in BCVA, or in the mean change from baseline in central macular thickness at 6 months.[62] However, to date, no RCTs have compared all three anti-VEGF agents for treating this condition over the at least 2-year duration of the disease.

To our knowledge, the LEAVO trial is the first RCT evaluating the comparative clinical effectiveness, cost-effectiveness and relative safety of these three anti-VEGF agents for CRVO-related MO over 100 weeks. In summary, if bevacizumab was shown in LEAVO to be non-inferior to ranibizumab, and aflibercept was non-inferior to ranibizumab, with no new safety concerns, it could be considered for NHS use in MO due to CRVO. In addition, this would provide evidence of its equivalence to the licensed medications in multiple indications and lend substantial support to the case for using bevacizumab in the treatment of nvAMD and other retinal diseases.

Clinical trial objective

The objective of the trial was to compare the relative clinical effectiveness and cost-effectiveness of the anti-VEGF agents bevacizumab (investigational treatment), aflibercept (investigational treatment) and ranibizumab (standard care) in MO due to CRVO over 100 weeks. The trial was intended to determine if bevacizumab or aflibercept was as effective as ranibizumab in reducing visual loss from MO due to CRVO, whether or not they had an equivalent side-effect profile and whether or not either could be considered or recommended for NHS treatment based on non-inferior clinical effectiveness and superior cost-effectiveness.

Primary objectives

- To determine whether or not bevacizumab is non-inferior to ranibizumab in treating visual loss due to MO secondary to CRVO.
- To determine whether or not aflibercept is non-inferior to ranibizumab in treating visual loss due to MO secondary to CRVO.

Secondary objectives

- To determine the difference between arms in terms of mean change in BCVA at 52 weeks.
- To determine the difference between arms in the proportion of participants with ≥ 15 ETDRS letter improvement (appreciable visual gain), ≥ 10-letter improvement, < 15-letter loss and ≥ 30-letter loss (severe visual loss) at 52 and 100 weeks.
- To determine the difference between arms in the proportion of participants with ≥ 73 ETDRS letters or > 6/12 Snellen equivalent (i.e. approximate driving visual acuity), ≤ 58 ETDRS letters (≤ 6/24) and ≤ 19 letters (≤ 3/60) [Certificate of Vision Impairment (CVI) partial and severe visual impairment] at 52 and 100 weeks.
- To determine the difference between arms in the mean change in OCT central subfield thickness (CST) and macular volume at 52 and 100 weeks.
- To determine the difference between arms in the proportion of participants with an OCT CST of < 320 µm [as measured with the Spectralis® (Heidelberg Engineering, Inc., Franklin, MA, USA) or equivalent] at 52 and 100 weeks (key guide to subsequent NHS clinical practice).
- To determine the differences between arms in the mean number of intravitreal injections given to each participant at 100 weeks.
- To determine any differences in the relative effectiveness of the investigational treatments and comparator on quality of life and resource use, reported as incremental cost-effectiveness ratios (ICERs), at 52 and 100 weeks.
- To detect any differences in the prevalence of local and systemic side effects at 100 weeks.
- To determine the differences between arms at 100 weeks in the proportion of (1) persistent non-responders who develop a change in retinal non-perfusion, compared with screening, and (2) participants who develop anterior and posterior segment neovascularisation.
- To determine the differences between arms in terms of mean change in BCVA at 100 weeks.
- To determine the differences between arms in changes in area of non-perfusion at 100 weeks and OCT anatomical features from baseline to 100 weeks.

Chapter 2 Methods

Trial design

LEAVO was a Phase III, randomised, controlled, double-masked, non-inferiority clinical trial conducted to evaluate the relative clinical effectiveness and cost-effectiveness of intravitreal bevacizumab and aflibercept, compared with ranibizumab, for MO due to CRVO. The intention was to randomise 459 participants with MO due to CRVO in at least one eye in a ratio of 1 : 1 : 1 to ranibizumab (0.5 mg/0.05 ml), aflibercept (2.0 mg/0.05 ml) and bevacizumab (1.25 mg/0.05 ml), all of which would be administered by repeated intravitreal injection, and to follow up these participants for 100 weeks. The study was conducted in the UK NHS across 44 ophthalmology centres that had staff with expertise in retinal disorders and a proven track record of effectiveness research.[2]

Participants

The trial population, from which the trial sample was drawn, was adults aged ≥ 18 years with MO secondary to CRVO of < 12 months' duration who attended one of the 44 NHS ophthalmology centres. The complete inclusion and exclusion criteria are listed in the following sections.

Selection of participants

Inclusion criteria

- Subjects of either sex aged ≥ 18 years.
- Clinical diagnosis of centre-involving MO due to CRVO.
- Central retinal vein occlusion of ≤ 12 months' duration.
- Best corrected visual acuity ETDRS letter score in the trial eye of between 78 (approximate Snellen equivalent: 20/32) and 19 (approximate Snellen equivalent: 20/400).
- Optical coherence tomography CST of > 320 µm (as measured with the Spectralis) (or equivalent with an alternative OCT device) predominantly due to MO secondary to CRVO in the trial eye.
- Media clarity, pupillary dilatation and subject co-operation sufficient for adequate fundus imaging of the trial eye.
- Best corrected visual acuity ETDRS letter score in the non-trial eye of ≥ 14 (approximate Snellen equivalent: 20/600).

Exclusion criteria

The following applied to the trial eye only, unless specifically stated otherwise:

- Macular oedema considered to be caused by a condition other than CRVO (e.g. DMO, Irvine–Gass syndrome).
- An ocular condition present that, in the opinion of the investigator, might have affected MO or altered visual acuity during the trial (e.g. vitreomacular traction).
- Any diabetic retinopathy or DMO on baseline clinical examination of the trial eye.
- Moderate or severe non-proliferative diabetic retinopathy or quiescent, treated or active proliferative diabetic retinopathy or MO in the non-trial eye. Note that mild non-proliferative diabetic retinopathy only was permissible in the non-trial eye.
- History of treatment for MO due to CRVO in the previous 90 days with intravitreal or peribulbar corticosteroids or in the previous 60 days with anti-VEGF drugs or more than six prior anti-VEGF treatments in the previous 12 months.

- Active iris or angle neovascularisation, neovascular glaucoma, untreated neovascularisation disc (NVD), neovascularisation elsewhere (NVE) and vitreous haemorrhage or treatment for these conditions in the previous month.
- Uncontrolled glaucoma (i.e. eye pressure of > 30 mmHg) either untreated or being treated with antiglaucoma medication at screening.
- Any active periocular or intraocular infection or inflammation (e.g. conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis).

Systemic exclusion criteria

- Uncontrolled blood pressure, defined as a systolic value of > 170 mmHg and a diastolic value of > 110 mmHg.
- Myocardial infarction, stroke, transient ischaemic attack, acute congestive cardiac failure or any acute coronary event < 3 months before randomisation.
- Women of childbearing potential, unless they were using an effective method of contraception during the trial and for 6 months after their last injection for the trial. Effective contraception was defined as one of the following:[63]
    - Barrier method – condoms or occlusive cap with spermicides.
    - True abstinence – when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal were not acceptable methods of contraception.
    - Tubal ligation or bilateral oophorectomy (with or without hysterectomy).
    - Male partner sterilisation. The vasectomised male partner should be the only partner of the female participant.
    - Use of established oral, injected or implanted hormonal methods of contraception and intrauterine device.
- Pregnant or lactating women.
- Men who did not agree to an effective form of contraception for the duration of the trial and for 6 months after their last injection for the trial.
- Hypersensitivity to the active ingredients of aflibercept, bevacizumab or ranibizumab, or to any of the excipients of these drugs.
- Hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanised antibodies.
- A condition that, in the opinion of the investigator, would preclude participation in the trial.
- Participation in an investigational trial involving an investigational medicinal product within 90 days of randomisation.

Rescreening of patients[2]

Patients could be rescreened in the following circumstances:

- Patients who did not meet the BCVA or OCT CST inclusion criteria could be rescreened a minimum of 4 weeks after their last screening visit if they were thought to meet the eligibility criteria.
- Individuals who did not meet other modifiable inclusion criteria, for example blood pressure, could be rescreened a minimum of 2 weeks after the last screening visit.

All assessments performed at the initial screening visit were repeated during the rescreening visit, except FFA if the rescreening visit was within 10 weeks of the original screening visit. If a patient was found to be eligible on rescreening and was randomised, their initial entry on the electronic case report form (eCRF) system was updated, rather a 'new' patient being created on the system. This avoided such patients being incorrectly counted twice in the Consolidated Standards of Reporting Trials (CONSORT) diagram.

Recruitment

The trial recruited participants from 44 UK ophthalmology centres over 24 months. Recruitment was competitive; however, each site was allocated a minimum target number of participants to recruit and was encouraged to exceed this if possible. Sites were set up strategically: larger sites with greater capacity were initiated first to maximise early recruitment and to ensure that the recruitment period was fully utilised. Eligible patients were invited to participate via their local clinics, or in an invitation letter. At each site, participants were identified from subspecialty retinal, general and eye casualty clinics. Once identified, potential participants underwent a clinical examination, followed by discussion of the trial with an experienced trial clinician, and were provided with the patient information sheet.[2]

Trial procedures

Informed consent procedure

The principal investigator or designated subinvestigator was responsible for ensuring that a patient was fully consented after being provided with an adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial. Patients were advised that any data collected would be held and used in accordance with the Data Protection Act 1998.[64] Patients were given at least 24 hours after receiving the patient information sheet to consider taking part. The principal investigator or designee recorded in the medical notes the date when the patient information sheet was given to the patient and the facts that patients were under no obligation to enter the trial and that they could withdraw at any time without giving a reason. No clinical trial procedures were conducted before consent was taken from a participant; consent denoted enrolment in the trial. A copy of the signed informed consent form was given to the participant. The original signed form was retained at the trial site and a copy was placed in the medical notes. If new safety information resulted in significant changes in the risk/benefit assessment, or if there were significant changes to the protocol or patient information sheet, participants were consented again as appropriate.

Randomisation

Only one eye of each participant was randomised to the trial. In 95% of cases, one eye was affected by CRVO and so was the 'worse-seeing eye' and was randomised. On rare occasions, participants had bilateral CRVO that met the eligibility criteria. In these cases, the worse-seeing eye was randomised unless the participant opted for randomisation of the 'better-seeing eye'. The plan was to recruit 459 adult participants with MO due to CRVO and to randomise them 1 : 1 : 1 at the level of the individual using the method of minimisation incorporating a random element. The three stratifying factors were (1) visual acuity, stratified by screening BCVA letter score [of ≤ 38 (approximate Snellen equivalent: $\leq$ 6/60), 39–58 (approximate Snellen equivalent: 6/48 to 6/24) or ≥ 59 (approximate Snellen equivalent: $\geq$ 6/18)]; (2) duration of disease, from date of CRVO diagnosis to commencement of therapy (< 3, 3–6 or > 6 months); and (3) treatment naive versus previous treatment. Each participant was randomised to one of three arms: bevacizumab, aflibercept or ranibizumab.[2]

A patient identification number (PIN) was generated by registering a patient on the MACRO eCRF system (InferMed Macro; Elsevier Ltd, Amsterdam, the Netherlands), after consent had been obtained. Randomisation was carried out in a bespoke web-based randomisation system hosted at the King's Clinical Trials Unit (KCTU). A unique PIN was generated in the MACRO program; this was recorded on all source data worksheets and was used to identify a participant throughout the trial.[2,63] The trial manager allocated all authorised site staff a username and password for the randomisation system. All authorised staff members, who were typically the principal investigator or designee, logged in to the randomisation system and entered a participant's details, including the unique PIN. Once a participant had been randomised, the system automatically generated e-mails to key staff in the trial. Unmasked e-mails sent to site pharmacies alerted them to a participant's treatment arm: ranibizumab, aflibercept or bevacizumab. The pharmacy department used the e-mail to cross-check the trial prescription to ensure that the correct medication was dispensed for the correct participant.

Additional masked e-mails were generated from the randomisation system and sent to key trial site staff,[63] and unmasked e-mails were sent to the emergency unmasking service (ESMS Global Ltd, London, UK) and unmasked trial management staff.[2]

Masking of treatment allocation

In randomisation process, only the pharmacy at a local trial site was informed by e-mail of a subject's treatment allocation; a copy of the e-mail was sent to the emergency unmasking service (ESMS Global Ltd) and to unmasked trial management staff. The trial drug that a participant received was transferred to the dedicated injection room in an opaque masking bag designed to securely and safely transport medication. A unique seal was attached to the bag before it left the pharmacy. The bag had a safe zipped compartment containing a printed form detailing a participant's unique PIN, their date of birth, the date the drug was dispensed and the injection batch number. Before a participant entered the injection room, the unmasked injector broke the seal and took the drug out of the masking bag. Bevacizumab was provided in a prefilled syringe, but ranibizumab and aflibercept were provided in a vial and drawn into a syringe by the unmasked injector. The syringe was placed on the injection trolley out of view of the participant, who was then invited into the room and asked to lie on the bed, and then received the injection. During the trial the manufacturer of ranibizumab began to provide the drug, in a unique prefilled syringe and vials ceased to be available. In this situation, the unmasked injector took care not to allow the participant to see the syringe either before or after the injection had been given. This was achieved by administering the injection while the participant was lying down and the injection was given via the pars plana in any quadrant of the eye, with the syringe brought to and taken away from the injection site via a participant's inferotemporal field of vision so that it did not pass across their line of sight. The unmasked injector signed the source notes to the effect that the treatment in the masked bag had been administered to the participant, without specifying the treatment, and also signed the printed form that was in the masking bag. The empty syringe with needle and vial were disposed of in the injection room. The masking bag and completed printed form were returned to the pharmacy. The outer packaging of the drug was disposed of in the injection room.[2]

The clinical assessment team, including the site principal investigator, optometrist (i.e. assessor of the primary outcome), site trial co-ordinator, clinical investigator, clinical assessment trial nurse and ophthalmic technician, remained masked throughout the trial, as there was no record of a participant's treatment arm in the source notes or the case report form (CRF). Similarly, co-ordinators or administrators completing questionnaires with participants in person (or, in extreme circumstances, only over the telephone at specific time points) had details of a participant's PIN only. If, at any time, information regarding treatment allocation was shared with the outcome assessors, this was recorded in the trial master file, and the person(s) involved met with the site principal investigator to ensure that no repetition occurred and undertook not to convey this information either to the participant or to others involved in the project. Certain secondary outcomes (e.g. interpretation of FFA) occurred at the remote Network of Ophthalmic Reading Centres (NetwORC) UK (Belfast, UK), where the assessors were masked to the treatment allocation. These masking procedures avoided both performance and detection bias. We have described the completeness of outcome data for each outcome, including any unmasking in error, reasons for attrition and exclusions from the analysis.[2] The trial statisticians had access to the accumulating outcome data that were required for reporting to the Data Monitoring and Ethics Committee (DMEC). Both trial statisticians attended both the open and the closed DMEC meetings.

Screening and baseline assessment

A patient had to receive the patient information sheet not later than 24 hours before the screening assessment. The screening and baseline visits could be undertaken on the same day, provided that all test results were available. A patient could return within 10 days of screening for the baseline assessment, at which point the screening procedures were still valid and were not repeated at baseline (see *Appendix 3*, *Table 29*).

Milestone and non-milestone visits

Trial milestone assessments, when key research data were collected, occurred at baseline and at weeks 12, 24, 52, 76 and 100. These visits, as well as treatment visits at weeks 4 and 8, were calculated and agreed with a participant prior to randomisation (with flexibility of 0 to 14 days for weeks 4, 8 and 12, and of −14 to 14 days for weeks 24, 52, 76 and 100, from the date of randomisation). It was mandatory for all participants to attend all milestone visits, even if a milestone visit fell < 4 weeks after a treatment visit or if a participant was being followed up every 8 weeks and the next milestone visit fell during the 8-week interval. The intervening trial treatment visits were deliberately flexible to allow normal clinical practice treatment follow-up to be accommodated. All data from the trial milestone visits were entered into the eCRF. For regular treatment visits, only the following information was entered into the eCRF: BCVA; OCT CST; whether or not an injection was given; and, if no injection was given, the reason why. At milestone visits, refracted visual acuity was tested and health economic questionnaires were completed; colour photography was undertaken at baseline and at weeks 52 and 100; and FFA was undertaken at baseline and at week 100, in addition to the clinical examination and OCT tests performed at all other trial visits (see *Appendix 3*, *Table 29*).

Trial assessments and methods

Participant demographics, medical and ophthalmic history

This information was retrieved from the participant, from hospital medical records or from a general practitioner. Data included age, sex and ethnic background. Data were also collected on clinically relevant medical history and management in the preceding 24 months, and on any ocular history and treatment.[2]

Visual acuity tests

Visual acuity tests were performed by a certified optometrist in a certified visual acuity testing lane using validated ETDRS vision charts and standard operating procedures.[65,66] Refracted visual acuity was carried out in both eyes at screening,[63] at weeks 12, 24, 52, 76 and 100, and at the point of withdrawal. For all other visits, the visual acuity was tested with the previous most recent protocol refraction. Visual acuity examiners were masked to the treatment. The visual acuity scores were recorded in the eCRF[2] (see *Appendix 4*).

Standard ophthalmic examination

A standard ophthalmic examination using slit-lamp biomicroscopy included an undilated examination for neovascularisation of the iris (NVI), RAPD and tonometry in both eyes at all visits. Dilated fundus examination was performed in both eyes at all milestone visits (i.e. at screening, at baseline, at weeks 12, 24, 52, 76 and 100, and at the point of withdrawal). At all other visits, dilated fundus examination was performed in the trial eye and, at the discretion of the investigator, in the non-trial eye. Gonioscopy, if indicated, was carried out prior to dilatation at any visit.[2]

Spectral-domain optical coherence tomography

The CST and total macular volume in both eyes were recorded in the eCRF from the spectral-domain optical coherence tomography (SD-OCT) thickness map at every visit, and, if applicable, at the point of withdrawal.[63] Any SD-OCT machine could be used for the trial, but the same model of SD-OCT machine had to be used for each individual throughout the period of the trial. SD-OCT images at screening and at weeks 52 and 100 only were transferred to and read by masked graders at the independent NetwORC UK. NetwORC UK provided each site with a trial imaging protocol on how to acquire SD-OCT images, colour fundus photographs and fundus fluorescein angiographs and how to transfer these to NetwORC UK to them. Initial grading of all OCT images at baseline and at weeks 52 and 100 was performed by NetwORC UK. The grading took into account intraretinal oedema, classified as diffuse, cystic or mixed; determined subretinal fluid as being present or absent; and determined vitreoretinal interface abnormalities as being present (as either an epiretinal membrane

or vitreomacular traction) or absent. Following the contract variation, additional grading parameters were assessed at NetwORC UK in collaboration with specialised retinal graders at Moorfields Eye Hospital, utilising additional definitions and analyses that had been developed while the trial was in progress.[1,67,68] Only images captured using a Spectralis OCT machine had sufficient detail to support the enhanced grading definitions. Retinal morphology was assessed using the Spectralis® Heidelberg Macular Raster OCT device (Heidelberg Engineering, Inc.) of 31 line scans, 30 × 25 mm in size, at an interscan distance of 240 µm or the equivalent for alternative devices. MO was graded using the entire line-scan series and the central 1500 µm, that is seven scans were employed for vitreomacular interface abnormality and subretinal detachment or equivalent. The remaining parameters were graded using the central 1000 µm only, that is central five-line scans only. A magnification of 300% was used to assess the ellipsoid zone (EZ), disorganisation of the retinal inner layers (DRIL)[67,68] and hyperreflective foci (HRF),[69,70] with 100% magnification for the remaining parameters. HRF, external limiting membrane (ELM), EZ and cone outer segment tips (COSTs) were graded as positive only if the foveal line showed involvement of the foveal depression such that it was distorted, lessened or absent.[2] For the grading of normal and abnormal individual morphological features, see *Appendix 5*, *Specific grading of individual morphological optical coherence tomography features*, and *Figures 22* and *23*.

Colour fundus photography

Non-stereo, seven-field conventional or wide-angle colour fundus photography (CFP) was performed at screening and at weeks 52 and 100 in the trial eye. CFP confirmed the diagnosis of CRVO and assisted interpretation of features identified by FFA, for example to differentiate between non-perfusion and masking due to haemorrhage. If applicable, CFP was also performed at the point of withdrawal, and at any other trial visit, as per investigator discretion. Colour fundus photographs were transferred to and read by masked graders at the independent NetwORC UK. Either a colour camera capable of taking seven-field colour fundus photographs or a wide-angle system was used, but the same model of camera was used for each individual throughout the trial. The colour photographs were graded by the NetwORC UK.[2]

Fundus fluorescein angiography

Non-stereo, seven-field conventional or wide-angle FFA was performed at screening and at week 100 in the trial eye. Any FFA system capable of taking seven-field FFA pictures or a wide-angle system was allowed, but the same system had to be used in the same individual throughout the trial.[2] FFA was used to quantify the degree of retinal ischaemia and for identification of retinal neovascularisation (see *Appendix 5*, *Fundus fluorescein angiography grading*). Pseudo-anonymised FFA images were transferred to NetwORC UK, where the standard NetwORC UK 13-sector grid (see *Appendix 5*, *Figure 24*) was applied over the wide-angle or montaged seven-field angiography pictures at baseline and at 100 weeks. The first 100 gradings were double-graded. Discrepancies were adjudicated. Subsequently, one in every eight gradings was double-graded. Kappa values for key fields (e.g. detection of new vessels on the disc and new vessels elsewhere) were required to be > 0.8. Any graders who did not achieve this were required to undergo additional training. Each sector in the grid was semiquantified in terms of percentage of non-perfusion (nil, 1–25%, 26–50%, 51–75% and 76–100%), and all available sets of images were analysed to identify how many participants in each arm had experienced a two-step increase (e.g. zero to 26–50%, or 26–50% to 76–100%) in one to five or more sectors (see *Appendix 5*, *Figure 24*). This technique was used in preference to the ischaemic index, which estimates the ratio of ischaemic to total retinal area but is very susceptible to image quality and is applicable to wide-angled images only.[22] Therefore, during the trial we used the concentric rings method, which displays superimposed concentric circles, centred on the fovea.[23,71,72] The innermost circle was 1 disc diameter (DD) in size, and is not graded as it represents the foveal avascular zone. The second circle, representing the macular ring (ring M), has a radius of 2.5 DD. Each of the subsequent rings (rings 1, 2, 3 and 4) is placed at increments of 2.5 DD in radius from the foveal centre. Each of these rings is subdivided into 12 equal segments.[23] To calculate the size of the concentric rings required, we assumed that the mean axial length was 24 mm, and excluded 2 mm from this to account for the cornea and part of the anterior

chamber. In the model eye, the radius was 11 mm (diameter 22 mm); therefore, the full circumference would have been 69.1 mm ($\pi = 3.142$). The wide-angled imaging system (Optos®; Optos, Inc., Marlborough, MA, USA) was able to image 200 degrees of the retina; we used this to calculate the average diameter of retina obtained in a single central image. This was calculated to be 38.4 mm. Using the DD of 1.8 mm, this meant that the diameter of the image was 21.3 DD. A diameter of 21.3 DD resulted in the need for a macular ring plus three/four further rings.[23] Based on our validation study, we identified that ring 4 was gradable, but the superior and inferior segments of rings 3 and 4 were ungradable because the ultra-wide field image had better clarity in the horizontal meridian. For details of this method, see *Appendix 5*, *Figure 25*.

Health economic questionnaires

The following quality-of-life and resource use questionnaires were administered at baseline, at 12, 24, 52, 76 and 100 weeks, and at the point of withdrawal: the National Eye Institute Visual Function Questionnaire-25 items (VFQ-25), EuroQol-5 Dimensions (EQ-5D), EuroQol-5 Dimensions with vision bolt-on (EQ-5D-V), and a bespoke resource use questionnaire [see www.journalslibrary.nihr.ac.uk/programmes/hta/119203/#/documentation (accessed 14 July 2020)].

Treatment allocation guess form

Participants and masked optometrists were asked to complete a treatment allocation guess form at week 100, or at the point of withdrawal, to assess how well participant and assessor masking worked in the trial.[2]

Definition of the end of the trial

Participants were enrolled in the trial for approximately 100 weeks from the point of randomisation. The end of the trial was defined as the last participant's last trial visit.

Treatment procedures

Treatment schedule

After mandated administration in all three trial arms at baseline and at 4, 8 and 12 weeks, further pro re nata intervention was administered at weeks 16 and 20 if re-treatment criteria were met and if visual acuity was ≤ 83 letters.

Regardless of whether a treatment was given, the participant was reviewed in 4 weeks. From weeks 24 to 96, the interval was initially 4 weeks (with a visit window of −14 to 14 days), with the potential for the interval to increase to 8 weeks (with a visit window of −14 to 14 days) if criteria for 'stability' were achieved. 'Stability' was defined as three successive visits from week 16 onwards at which treatment criteria were not met, and so the first time at which treatment could be deferred for 8 weeks was week 24.

Similarly, 'success' was defined as an ETDRS letter score of > 83 letters, and if this was present at any re-treatment visit from week 16 onwards, treatment was not given at that visit and the participant was reviewed subsequently. The review occurred 4 weeks later if the initial visit was at 16 weeks, 20 weeks or any other visit if treatment had been given at this or the preceding visit. If no treatment had been given at these two visits, the participant was reviewed 8 weeks later. If, at any subsequent visit, re-treatment criteria were met and BCVA was ≤ 83 ETDRS letters, then re-treatment was commenced (*Figure 1*). At each visit between weeks 24 and 96 inclusive, 'non-responder treatment suspension' criteria could be met. If so, the principal investigator, or their designee, at their discretion, could suspend treatment to prevent therapy in a participant who had not responded to at least their last three injections. If the criteria for restarting therapy after 'non-responder treatment suspension' were met, then the participant had to resume therapy. If re-treatment criteria were met at one of the visits that took place every 8 weeks or at an unscheduled visit, then visits every 4 weeks were resumed. Treatment could be 'deferred' in certain circumstances, but the participant was asked to still attend the milestone visits.

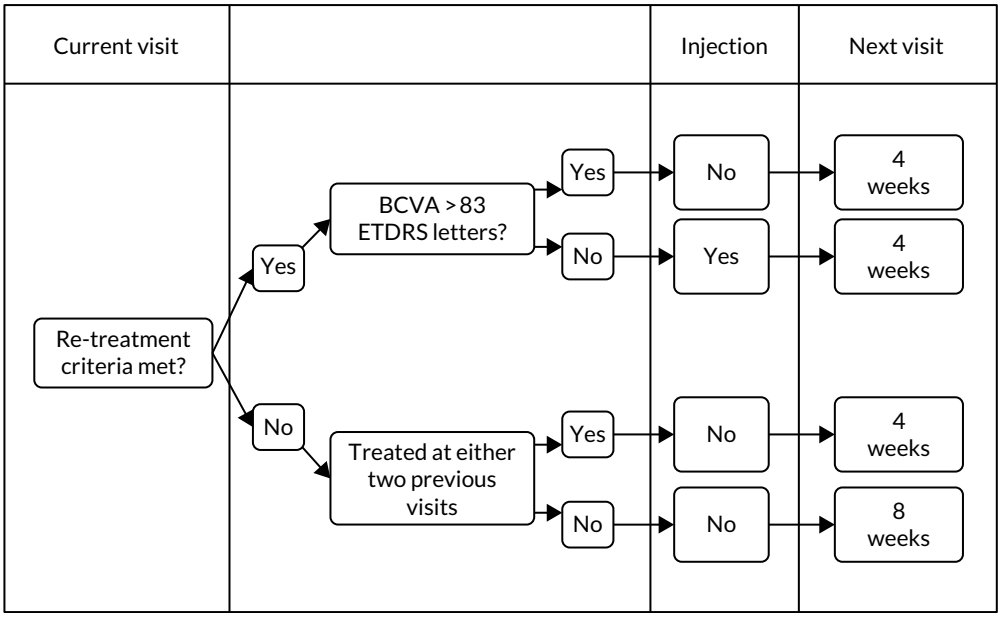

FIGURE 1 Re-treatment algorithm for weeks 24–96 of the trial.

Re-treatment criteria

Criteria were met if one or more of the following was present:

- a decrease in visual acuity of ≥ 6 letters between the current and most recent visit, attributed to an increase in OCT CST
- an increase in visual acuity of ≥ 6 letters between the current and most recent visit
- OCT CST of > 320 µm (on Spectralis, or of > 300 µm on other machines) because of intraretinal or subretinal fluid
- an OCT CST increase of > 50 µm from the lowest previous measurement.

Investigational medicinal products

Comparator: ranibizumab (0.5 mg/0.05 ml)

Ranibizumab is a humanised recombinant monoclonal antibody fragment that binds to VEGF A, preventing receptor interaction and blocking downstream action of VEGF, that is increased vascular permeability, leading to MO in CRVO. It is licensed by the EMA, and NICE has recommended it for use in the treatment of nvAMD, DMO and RVO. NICE TA283[13] for MO due to RVO was issued in May 2013. Ranibizumab has been the mainstay of routine clinical care for this condition since the third quarter of 2013 and was the comparator in this trial. It was supplied to each site hospital pharmacy directly from the manufacturer as a part of routine hospital stock.[2]

Intervention: aflibercept (2.0 mg/0.05 ml)

Aflibercept is a fusion protein that includes the key binding domains of human VEGF receptors 1 and 2 with human IgG Fc and acts as a dummy receptor for all VEGF isoforms and placental growth factor, preventing increased permeability and MO in CRVO. At initiation of this trial, it was licensed by the EMA, and NICE has recommended it for nvAMD. NICE TA305[12] was published in February 2014; NICE recommends this drug as first-line use for CRVO-related MO. Aflibercept was supplied in a glass vial to each site hospital pharmacy directly from the manufacturer as part of routine hospital stock.[2]

Intervention: bevacizumab (1.25 mg/0.05 ml)

Bevacizumab is a full-length humanised monoclonal antibody that binds to VEGF A, forming a protein complex incapable of binding to the VEGF receptor, thus blocking downstream VEGF action. In this trial, bevacizumab was supplied in a prefilled plastic syringe in a sealed package to each trial site pharmacy from the Liverpool and Broadgreen Pharmacy Aseptic Unit, Royal Liverpool University Hospital, Liverpool, UK.[2]

Site pharmacy storage, ordering and handling procedures of investigational medicinal products

A trial medication dispensing and return log was maintained by the trial site pharmacies. Administration records from these sites were retained by the pharmacy and monitored by the trial manager to ensure that accurate CRF data were recorded. The randomisation system was linked to the investigational medicinal product (IMP) supply. Each site pharmacy was also responsible for appropriate storage, dispensing, disposal, and recall and destruction logs, in accordance with good manufacturing practice[73] and good clinical practice,[74] and the site hospital pharmacy's approved policies for IMP accountability and management. Furthermore, each site pharmacy maintained a record of trial drug administration, based on the pre-printed form signed by the unmasked investigator that was returned to the pharmacy at each centre.[2]

Investigational medicinal product accountability

Used and unused trial study medication and study medication accountability

Each masking bag contained a pre-printed form that listed the details of the participant's unique PIN, date of birth, date the drug was dispensed and injection batch number. After performing the intravitreal injection, the unmasked injector signed this form to confirm that the drug had been given to the allocated patient, and they then returned it in the masking bag to the pharmacy. All used drug vials and syringes were disposed of in the injection room and not returned to the pharmacy. Pharmacies in each site maintained a trial medication dispensing log, including date dispensed, batch number, expiry date and return log. The return log was compiled from the form signed by the unmasked injector. In addition, the trial-specific prescriptions were maintained in the pharmacy file for audit purposes. Any administration errors were reported to the chief investigator and trial statistician. In the event that an injection was not given as scheduled, the reason was documented in the participant's notes and the CRF. The trial monitor checked the pharmacy records against the eCRF. All records were reconciled with the investigator site file at the end of the trial.[2]

Description and justification of route of administration and dosage of investigational medicinal product

The approved route of administration (i.e. by intravitreal injection through the pars plana of the eye) was used in all cases under sterile conditions in a designated treatment area in accordance with the guidelines[75] for intravitreal injection of the Royal College of Ophthalmologists and any approved procedures at the individual site hospital. The injection could be performed by the unmasked injector(s) only, who was (were) on the hospital site LEAVO delegation log and was (were) experienced in intravitreal injection procedures. The dosages of ranibizumab (0.5 mg/0.05 ml) and aflibercept (2.0 mg/0.05 ml) used in this trial were approved by the EMA, and NICE recommends these doses of these agents for intraocular use.[12,13] The dosage of bevacizumab (1.25 mg/0.05 ml) was the dosage used in the IVAN clinical trial and the CATT of treating wet age-related macular degeneration (AMD), and the standard dose used in clinical practice. Post-injection checks were conducted in accordance with local hospital policy and included a visual acuity, intraocular pressure or optic nerve head perfusion check, or a combination of these. The interval between two doses of all three drugs was not recommended to be less than 4 weeks.[2]

Management of complications

Complications, such as the development of ischaemic CRVO, neovascularisation of the angle, NVI, neovascular glaucoma (NVG), NVE and NVD, in the trial eye were recorded as AEs. The diagnosis and management of these complications of CRVO in the trial were at investigator discretion and based on local practice. Laser therapy formed the mainstay of therapy and was recorded as a concomitant procedure.[7,8]

Recording and reporting of adverse events and reactions

Routine reporting

The MHRA definitions of AEs and SAEs were adopted for this trial. AEs were reported by the site in the AEs log in the eCRF. All SAEs, serious adverse reactions and suspected unexpected serious adverse reactions (SUSARs) were recorded and reported on the SAE form to the chief investigator/delegate within 24 hours of learning of their occurrence. A record of this notification (including date of notification) was clearly documented to provide an audit trail. In the case of incomplete information at the time of initial reporting, a follow-up report was provided as soon as the information became available. The sites responded promptly to any queries raised by the chief investigator/delegate. The principal investigator/delegate, who had to be a clinician at the site, assessed the relationship of the SAE to any of the trial interventions. The chief investigator was responsible for assessing the expected or unexpected nature of all serious adverse reactions. The chief investigator/delegate, with the support of the KCTU, ensured that Moorfields Eye Hospital, as sponsor, was made aware of any SUSARs and serious adverse reactions that occurred. The chief investigator/delegate, in conjunction with the sponsor, was responsible for reporting all SUSARs to the MHRA and relevant ethics committee within the appropriate time frame.

All principal investigators were informed of all SAEs that were assessed as fulfilling the criteria for a SUSAR (i.e. possibly, probably or definitely related to any trial intervention, and unexpected as per the summary of product characteristics or the protocol).[2]

Planned 'hospitalisations', non-emergency procedures and adverse event reporting

Some AEs met the definition of serious but did not need to be reported on a SAE report form. Common ophthalmology- and non-ophthalmology-related events that resulted in planned, non-emergency hospital admissions for the investigation or treatment of those events and that were not possibly, probably or definitely related to the IMPs did not need to be reported on a SAE report form. These events were recorded on the AE form and the investigation and treatment of ophthalmology-related events were recorded on the ophthalmology-related concomitant procedure forms. All concomitant medications were recorded on the concomitant medication form. These forms were updated following each trial visit to ensure that the independent DMEC received accurate reports of the occurrence and treatment of AEs.[2]

Pregnancy

In the event that a female participant became pregnant, this was reported to the KCTU on a pregnancy form sent by fax or e-mail as soon as the investigator became aware of it. The pregnancy was monitored to determine outcome. Any information related to the pregnancy following the initial report was reported on a follow-up pregnancy form.[2]

Data management

Confidentiality

Data were handled, computerised and stored in accordance with the Data Protection Act 1998.[64] Participants were identified via a unique PIN, their date of birth and their initials. Identifiable information was stored in the eCRF and did not leave the site. Any participant contact information was stored in the site on password-protected computers or in secured locations with restricted access.

Data collection tools and source document identification

Written informed consent was obtained before screening and other trial-specific procedures were performed. SAE data were collected on paper SAE report forms and e-mailed or faxed to the KCTU. Summary details of SAEs were transcribed to the AE section of the eCRF. For all other data collected, source data worksheets were used for each patient and data were entered onto the eCRF database. Source data worksheets were reconciled at the end of the trial with a patient's NHS medical notes in the recruiting site. During the trial, critical clinical information was written in the medical notes to ensure that informed medical decisions could be made in the absence of the trial team. Trial-related clinical letters were copied to the medical notes during the trial. It was the responsibility of the principal investigator and his/her team to ensure that the accuracy of all data entered in the worksheets and the eCRF was in accordance with good clinical practice. The delegation log identified all those personnel with responsibilities for data collection and handling, including those who had access to the trial database. The principal investigator was responsible for ensuring that source data worksheets were filed in a suitably secure location so that source data verification could be undertaken throughout the trial.[2]

Data handling and analysis

All trial data and site files were kept on site in a secure location with restricted access.

The trial used an eCRF created using the InferMed MACRO database system. Data were managed using this system. The eCRF was created in collaboration with the trial statistician and the chief investigator and maintained by the KCTU. It was hosted on a dedicated secure server in King's College London. This system is regulatory compliant; has a full audit trail, data discrepancy functionality and database lock functionality; and supports real-time data cleaning and reporting. The trial manager was responsible for providing usernames and passwords to permitted local trial personnel. Only those authorised by the trial manager were able to use the system.[2,63]

Quality assurance

The trial incorporated a range of data management quality assurance functions. The eCRF system contained a range of validations defined by the trial team that alerted sites to inconsistencies in the data being entered, which were monitored by the trial manager. The trial manager provided trial training and ongoing trial support, and conducted regular monitoring visits at each site, checking source data for transcription errors. Any necessary alterations to entered data were date- and time-stamped in the eCRF. A detailed monitoring plan and data management plan was developed and updated as the trial progressed, detailing the quality control and quality assurance checks to be undertaken.[2]

Database lock and record-keeping

Prior to database lock, the trial manager reviewed any outstanding warnings on the eCRF and resolved or closed these, as appropriate. Local trial personnel resolved any queries that arose. Once all queries were resolved, no further changes were made to the database unless specifically requested by the trial office in response to the statistician's data checks. The trial principal investigator reviewed all of the

data for each participant and provided e-mail sign-off to verify that all data were complete and correct. At this point, all data were formally locked for analysis. At the end of the trial, each site was supplied with a CD-ROM containing the eCRF data for their site. This was filed locally for any future regulatory inspection or internal audit. The chief investigator is the custodian for the data generated from the trial and is responsible for archiving the original data. All data will be archived for at least 5 years from the end of the trial and will be archived in accordance with sponsor's and regulatory requirements. Principal investigators were responsible for securely archiving local data generated, essential documents and source data in accordance with local requirements, but for at least 5 years from the end of the trial.[2]

Statistical considerations

Sample size calculation

Bevacizumab and aflibercept were hypothesised to be substantially inferior to ranibizumab if, in each case, the mean of the primary outcome (i.e. change in BCVA ETDRS letter score) was worse by a margin of 5 letters, a previously used non-inferiority margin,[26,76] representing the minimum visual acuity change that a patient may distinguish. A similar CRVO population[9] reported a standard deviation (SD) of 14.3 letters in the ranibizumab (0.5 mg) arm; the 12-month rate of those lost to follow-up was 8.4% in the ranibizumab arms (0.5 mg and 0.3 mg). In the absence of 24-month data, we assumed a comparable SD of 14.3 letters at 100 weeks, and allowed for 15% dropout. The two null hypotheses, that bevacizumab was substantially inferior to ranibizumab, and that aflibercept was substantially inferior to ranibizumab, were each planned to be rejected if the estimated 95% confidence interval (CI) for the difference in treatment means was wholly above the 5-letter margin in each case. Assuming equal efficacy, there was 80% power to reject each null hypothesis and to declare non-inferiority, with 130 followed-up patients analysed per arm. Allowing for 15% missing data at 100 weeks, 459 patients were planned to be randomised to the three arms (equal allocation ratio of 153 participants per arm). Sample size calculations were performed using nQuery Advisor version 4.0 (Statistical Solutions, Saugus, MA, USA). The primary method of analysis was a linear mixed-effects (LME) model with adjustment for baseline, which was expected, other things being equal, to increase the power to detect non-inferiority. The primary method of analysis included all available refracted data of the primary outcome up to and including 100 weeks, including data from the 15% of participants who we anticipated could miss the 100-week primary outcome end point.[2]

Statistical considerations

The trial statisticians were responsible for all statistical aspects of the trial, from design through to analysis and dissemination.[2] A detailed statistical analysis plan was completed before the start of the trial; it was commented on by the DMEC and approved by the Trial Steering Committee (TSC). The plan was accompanied by a health economics analysis plan, and was updated and re-approved by the TSC when the protocol was amended.

Target population

The target population, to which inferences from the end of this trial were intended to generalise, was adult patients with MO due to CRVO.

Trial population

The trial population, from which the trial sample was drawn, was further defined to be adults aged $\geq$ 18 years, with visual impairment due to CRVO-related MO of $<$ 12 months' duration, who attended one of the 44 ophthalmology centres in the UK that had staff with expertise in retinal disorders and a proven track record of effective research. Only one eye per participant was included in the trial.

Hypotheses

The hypotheses refer to the populations of relevant patients, rather than to trial subjects:

- The working hypothesis – the so-called 'working hypothesis' was the hypothesis that motivated the trial, which the trial results may or may not support. It was that the change in BCVA is non-inferior in patients treated with either aflibercept or bevacizumab, compared with patients treated with ranibizumab.
- The statistical null hypothesis 1 – bevacizumab is inferior to ranibizumab in eyes with MO due to CRVO at 100 weeks.
- The statistical null hypothesis 2 – aflibercept is inferior to ranibizumab in eyes with MO due to CRVO at 100 weeks.
- Statistical alternative hypothesis 1 – bevacizumab is non-inferior to ranibizumab in eyes with MO due to CRVO at 100 weeks.
- Statistical alternative hypothesis 2 – aflibercept is non-inferior to ranibizumab in eyes with MO due to CRVO at 100 weeks.

Treatment arms

The trial was randomised with equal allocation of participants in a 1 : 1 : 1 ratio to the three arms (see *Chapter 2*, *Randomisation*).

Trial samples

Intention to treat

The achieved trial sample comprised those patients who consented to participate and were actually randomised to the trial.[63] These patients were the trial subjects. This randomised trial sample was also the trial intention-to-treat (ITT) population. The ITT principle states that every subject will be analysed according to the treatment group to which they are randomised. In this trial, subjects' data were analysed according to the ITT strategy,[77] under which at least one analysis is recommended to be based on the ITT population. The trial ITT population comprised all randomised participants, regardless of whether there was an error in their eligibility (inclusion/exclusion), whether they had withdrawn post randomisation and whether the correct trial treatments or other interventions were received.[63]

Per protocol

A per-protocol set of subjects was also included. These were defined as the subset found to be eligible at entry and who had minimal sufficient exposure to the treatment regimen, defined as four treatments correctly assessed and received during the first six visits up to week 20. For each of the first four visits, a correct treatment was defined as receiving the injection. For the fifth and sixth visits, a correctly assessed and received treatment was defined to be the receipt of an injection if this was indicated to be required by the re-treatment criteria, or the non-receipt of an injection if this was indicated by the re-treatment criteria.

The main reason for having a per-protocol set was that this was a non-inferiority trial, and so the use of the full analysis set would not generally be conservative [see the International Conference on Harmonisation (ICH) guidance, E9, section 5.2.3[78]]. As Lesaffre[79] states, 'dropouts and a poor conduct of the study might direct the results of the two arms towards each other'. Although this can be interpreted as an indication that the per-protocol analysis is the conservative choice for non-inferiority studies, Garrett[80] states that 'The perceived conservative nature of the PP [per protocol] population appears to be much more a reflection of reduced patient numbers than the presence of bias, while bias can be in either direction depending on the pattern of violations'. Moreover, with two active treatments, it may be more likely that any bias affecting both treatments is reduced, in comparison with a placebo-controlled trial.[63]

Prominence

Non-inferiority was declared only if both the ITT and the per-protocol analyses supported a non-inferiority conclusion. The Committee on Proprietary Medical Products Points-to-Consider and several other papers support this.[63] The requirement to declare non-inferiority in both the ITT and the per-protocol analyses emphasised the adherence to treatment protocol and the minimisation of exclusions, maintaining power.

Outcomes

Primary outcome

The primary outcome was BCVA in the trial eye, measured in ETDRS letter score at 4 m at 100 weeks. Measurements of BCVA at milestone visits were included in the analysis of the primary outcome. Any BCVA measurement was excluded from the analysis if it is was > 3 SDs below the mean at that time point (including all measurements) and taken within 3 months of the occurrence of a vitreous haemorrhage, or was from another cause unrelated to maculopathy secondary to CRVO (e.g. NVG).

Secondary outcomes

The secondary efficacy outcome measures are listed in the following sections according to their type of variable. They were formally analysed at 52 and 100 weeks, but also measured at other time points.

Continuous outcome variables

- Visual acuity and clinical outcomes:
  - change from baseline in ETDRS letter score measured at 4 m at 52 weeks
  - change from baseline in mean OCT CST at 52 and 100 weeks
  - change from baseline in macular volume at 52 and 100 weeks
  - number of injections performed in the trial eye by 100 weeks
  - change in retinal non-perfusion as assessed by mean disc area of non-perfusion at 100 weeks.
- Patient-reported outcomes:
  - National Eye Institute VFQ-25 composite score, distance and near subscales at 52 and 100 weeks.
  - quality of life (measured using the EQ-5D and the EQ-5D-V) at 52 and 100 weeks.
- Economic reported outcomes (detailed in the health economics analysis plan):
  - quality-of-life scales (measured using the VFQ-25, the EQ-5D and the EQ-5D-V) at 0, 12, 24, 52, 76 and 100 weeks.
  - resource use at 0, 12, 24, 52, 76 and 100 weeks.

Categorical outcome variables

- Visual acuity and clinical outcomes:
  - participants with ≥ 15 ETDRS letter improvement (appreciable visual gain), ≥ 10-letter improvement, < 15-letter loss and ≥ 30-letter loss (severe visual loss) at 52 and 100 weeks
  - participants with ≥ 73 ETDRS letters, or > 6/12 Snellen equivalent (i.e. approximate driving visual acuity), ≤ 58 letters (≤ 6/24 Snellen equivalent) and ≤ 19 letters (≤ 3/60 Snellen equivalent) (CVI partial and severe visual impairment) at 52 and 100 weeks

- participants with OCT CST of < 320 µm (on the Spectralis, or of < 300 µm on other machines) at 52 and 100 weeks (key guide to subsequent NHS clinical practice)
- participants with the anatomical OCT features of diffuse intraretinal oedema, intraretinal cystic change, subretinal fluid or vitreomacular interface abnormality (either vitreomacular traction or epiretinal membrane) over time and at 100 weeks
- participants with a change in retinal non-perfusion at 100 weeks.

- Safety and tolerability:

  - prevalence of local and systemic side effects at 100 weeks
  - participants who were persistent non-responders and who developed anterior and posterior segment neovascularisation at 100 weeks.

Subgroup variables

Three subgroup variables were considered: (1) baseline visual acuity (low, moderate and high: ≤ 38 letters, 39–58 letters and 59–78 letters, respectively), (2) disease duration (< 3 months or ≥ 3 months) and (3) ischaemic compared with non-ischaemic. These variables were based on the fact that the visual gain in the worse-vision group may be higher than that achieved by the better-vision group, and this effect may differ between arms. The shorter the duration of disease, the better the visual acuity outcomes, and this may have varied between treatment arms.

Outcomes requiring derivation

The VFQ-25 is a validated tool for assessing vision-related quality of life. It consists of a base set of 25 vision-targeted questions, representing 11 vision-related subscales, plus an additional single-item question rating general health. The overall composite score is computed as the simple average of the vision-targeted subscale scores, excluding the general health rating question. The overall score can range from 0 (worst possible score) to 100 (best possible score).

The EQ-5D and the EQ-5D-V

The EQ-5D is a generic instrument for describing and valuing health. It is based on a descriptive system that defines health in terms of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension [in the EuroQol-5 Dimensions, five-level version (EQ-5D-5L)] has five response categories corresponding to 'no problems', 'slight problems', 'moderate problems', 'severe problems' and 'unable to/extreme problems'. A preference-based score ranges from states worse than dead (< 0) to 1 (full health), anchoring dead at 0. In addition, the EQ-5D includes a visual analogue scale, which records a respondent's self-rated health on a vertical scale where the end points are labelled 'best imaginable health state' (marked as 100) and 'worst imaginable health state' (marked as 0). The EQ-5D-V is similar to the EQ-5D-5L, but with another dimension (vision) added to overcome perceived inadequacies in a particular population.

More information is given in *Chapter 4*, *Health-related quality-of-life measures*.

Defining outliers

Outliers are observations that have extreme values relative to other observations under the same conditions. An outlier was defined as a data point at least 4 SDs from the mean of its distribution of values observed across other participants. A 'bivariate outlier' for checking was defined as a pair of successive serial data points of the same measure for a participant whose difference was at least 4 SDs from the mean of all participants' such differences. Simple plots of successive pairs of serial measures were used throughout the 24-month period to help identify outliers for data-checking.[63]

Handling outliers

Outliers were identified for further investigation by looking at the distributions of the data using histograms, scatterplots or box plots. Univariate tests for the compatibility of the distribution with a normal distribution were not undertaken because they can be too sensitive to departures that are often not relevant to the comparison of means (central limit theorem).

Once an outlier was found, a masked member of the team with sufficient clinical experience was involved in the decision about whether a data value was impossible or implausible or plausible. If an outlier was impossible, then it was set to missing. If an outlier was clinically plausible, then the outlier remained. If an outlier was clinically implausible (but possible), then it was not ignored or deleted, but was retained for the ITT analysis. If outliers remained in the distribution of a variable, then data transformations or non-parametric methods of analysis were considered. A sensitivity analysis was undertaken to check whether or not the outlier was influential by obtaining results with and then without the inclusion of the outlier. If the conclusions changed, then this was noted.[63]

Baseline comparability of randomised groups

Baseline descriptions of participants by treatment and overall were summarised. No significance testing was carried out as any differences found might have been chance-generated and not for hypothesised reasons. Continuous variables, such as OCT CST values and VFQ-25 scores, were summarised using means and SDs and/or medians and interquartile ranges (IQRs) for variables presenting a skewed distribution. Categorical variables, such as the proportion of participants gaining $\geq$ 15 BCVA letters or participants with OCT CST of $<$ 320 µm, were described using numbers and percentages.

Comparison of rates of adherence and follow-up

High compliance and low attrition rates were anticipated for this trial based on previous clinical trial experience. In CRUISE (a study on CRVO), 91.6% of participants completed the active treatment arms at 12 months, and withdrawals were mainly due to physician and patient decisions.[8] A cumulative dropout of approximately 15% by year 2 was predicted for LEAVO and this was reflected in the sample size calculations. Nevertheless, compliance rates and attrition rates were compared and reported by arm using Fisher's exact test.

Analysis covariates

The ICH E9 guideline[78] recommends that consideration be given to accounting for randomisation stratifiers by adjusting for them as covariates in the linear model. This tends to improve the precision of estimated treatment effects. Therefore, for continuous outcomes, the analysis included adjustment for the randomisation stratifiers of screening BCVA letter score (three levels) and disease duration (two levels). This excluded the third stratifier of previous treatment (eye treatment naive vs. had received previous treatment), because the numbers of participants who had received previous treatment was very small; this was approved in the statistical analysis plan [see www.journalslibrary.nihr.ac.uk/programmes/hta/119203/#/documentation (accessed 14 July 2020)] by the TSC.

Baseline

The corresponding baseline measure for a continuous outcome is also often predictive of the outcome at follow-up. Therefore 'baseline' (if a baseline measure was collected) was included as an additional covariate when modelling continuous outcomes.[63] This was the case for visual acuity and CST.

Statistical model

The following description of the statistical analysis was applied to obtain results for each of the two investigational treatments, bevacizumab and aflibercept, compared with the standard treatment, ranibizumab.

Primary outcome analysis

The primary efficacy measure was the change from baseline in refracted BCVA in the trial eye, using the ETDRS letter score, at 100 weeks. The continuous primary outcome was a participant's longitudinal change in BCVA from baseline to 100 weeks. As more fully described later, this baseline is adjusted for as a continuous covariate. This analysis approach gives results equivalent to those of an approach in which the primary outcome is instead defined to be the cross-sectional 100-week measurement in the same participants. Of these two equivalent approaches, we chose to analyse BCVA and other continuous outcomes at the cross-sectional measurement point. This is convenient, because it means that, if a baseline measurement is missing in a participant with a 100-week outcome, the end point is not considered to be missing. The primary outcome may, therefore, be referred to later as the 100-week visual acuity, rather than as the change in BCVA from baseline to 100 weeks.

The primary outcome was analysed using a LME model incorporating the five post-baseline measurements of the refracted BCVA outcome (at 12, 24, 52, 76 and 100 weeks). This mixed model was, by definition, a mix of random- and fixed-effect terms. The random effect in the model was the participant, represented as a random intercept at each follow-up time point, with allowance for within-participant correlation in the adjusted post-baseline outcomes. The fixed effects in the model were the main effect terms for arm; the two stratifiers, visual acuity and disease duration; 'time'; and the baseline of the outcome and its missing indicator required for the missing indicator method. The other fixed effects in the model were the interactions between 'time' and each of the other fixed effects in the model. This model allowed the treatment effect to be formally tested at 52 weeks and at the primary time point of 100 weeks, and estimated at 24 and 76 weeks.[63]

Intention-to-treat strategy

Outcome data were valid and included if the BCVA measure was refracted. All randomised subjects who provided at least one post-baseline valid measurement were included.[63]

Per-protocol analysis

For the analysis of the primary outcome, the mixed-effects model was refitted in a reduced per-protocol population, as described in *Chapter 2*, *Per protocol*.[63] Only valid (refracted) measurements were included, and so the per-protocol analysis was a subset of the outcome measurements in the 52- and 100-week ITT analysis LME model.

Concluding non-inferiority

Non-inferiority was concluded only if this had been declared by both the ITT analysis and the per-protocol analysis at 100 weeks. Non-inferiority was also assessed secondarily in the ITT and per-protocol populations at 52 weeks from the same models. Non-inferiority was declared if the estimated 95% CI for the difference in means lay wholly above the margin of –5 letters in both the ITT and per-protocol analysis models, primarily at 100 weeks and secondarily at 52 weeks.

Superiority

If non-inferiority was concluded, superiority was assessed from the ITT LME model by reporting the *p*-value from the two-sided test of the hypothesis of a zero difference in population means using a 5% significance level without the need for correction for multiple testing.[63] In addition, it was planned that, if both investigative treatments were considered non-inferior to the standard treatment at 100 weeks, the investigative treatments would be assessed for superiority relative to each other.

Subgroup analysis

The two subgroup variables were assessed by extending the primary outcome model to include an interaction between arm and each categorical subgroup variable.[63] Subgroup variables with more than two categories that were ordinal were entered as linear in the interaction. The treatment effects were presented in each subgroup category with a 95% CI.

Sensitivity to missing data

An expert missing-data group concluded that, rather than statisticians reacting to missing data at the end of a trial, there should be comprehensive, proactive planning for handling missing data at the stage of designing trials. The group recommended that there should be consideration of missing-data mechanisms (e.g. missing at random), and, if the missing data may be informative, that appropriate sensitivity analyses be undertaken to investigate the robustness of the inferences to the different assumptions made by the main analysis. It has also been recommended that analyses allowing for non-response and low intervention uptake (or compliance) are best specified in advance and included in the analysis plan. As it is expected that compliance will be high from the fear of loss of sight, and as non-inferiority is concluded only when declared in both a compliant per-protocol population and a less compliant ITT population, the focus was the handling of missing data.[63]

A sensitivity analysis was undertaken to assess the possibility of alternative plausible values of treatment effect arising from potential mishandling of missing data in the primary analysis model.

The LME model for the primary outcome analysis described above was the first of a two-part approach called the ITT strategy, in which a second analysis examined the sensitivity of the results to missing data in the full randomised, ITT population. This met the ideal of ITT. The approach to missing data taken in the trial followed the published implementation paper[81] of the ITT strategy. This was then also applied again to the per-protocol population so that the non-inferiority conclusion could be reassessed under the sensitivity analysis.[63]

For the sensitivity analysis, we prespecified a range for best visual acuity from −20 letters to 20 letters, over which the mean of the unobserved outcome data might depart (or be different) from the mean of the observed outcome data.[82] In other words, this range could be thought of as the extent to which a typical subject for whom data are missing may, on average, have had a different estimated treatment effect compared with the corresponding subject for whom outcome data were observed (given the same baseline covariates and follow-up data in the LME model). The range (−20 to 20 letters) was chosen to represent both negative and positive departures that could potentially arise as the 'net effect' of alternative reasons that may be unknown, such as dropout as a result of no anticipated further improvement, or dropout as a result of no improvement so far, together with no anticipated achievable improvement.[63]

This range of 40 letters (from −20 to 20) was generously wide for exploring the sensitivity of the main results to departures from the missing-at-random assumption, because 20 letters (as the maximum departure in either direction) is larger than the detectable between-arm treatment effect of 3 lines (15 letters) seen in superiority trials (difference in means), which is a sizeable shift in the mean of the distribution for dropouts, compared with completers.

At the end of the trial, the fractions of individuals for whom data were missing for visual acuity at 100 weeks were available in each arm: f_i (for intervention) and f_c (for control). The parameter representing excess visual acuity in those missing, compared with those observed, δ, will take values by passing across the range −20 to 20. Three scenarios were undertaken in the sensitivity analysis.[77,81,82] These reflected whether or not departures from the missing-at-random assumption applied in the intervention arms only (aflibercept and bevacizumab), in the control arm only (ranibizumab), or in both arms equally and

in the same direction (thereby potentially cancelling out across the sensitivity range, if the dropout rate were to be the same in both arms):[63]

- Scenario 1 – the treatment effect from the LME model will be increased by $f_i\delta$.
- Scenario 2 – the treatment effect from the LME model will be increased by $-f_c\delta$.
- Scenario 3 – the treatment effect from the LME model will be increased by $(f_i - f_c)\delta$.

Sensitivity analysis to use of concomitant treatments

The use of concomitant treatments was monitored by the DMEC.[63] It was planned that, if necessary, a sensitivity analysis would be undertaken to examine the robustness of the 100-week per-protocol analysis to the use of concomitant treatments.

Secondary outcome analysis

Secondary outcome analyses (see *Appendix 3*, *Table 28*) were on an ITT basis only. All tests were two-sided at the 5% significance level and were interpreted cautiously, with a focus on interpreting effect sizes with 95% CIs. Safety outcomes were reported as unadjusted patient proportions and as rates within and between arms, with 95% CIs, using exact methods when appropriate. Significance tests were used sparingly and were restricted, when possible, to addressing stated hypotheses.

Analysis of continuous outcomes

As for the primary outcome, the analyses of continuous secondary outcomes were compared between arms at 100 weeks using the LME model. The baseline was adjusted for as a covariate, for outcomes for which this was collected at baseline. The missing indicator method was used when there were missing data at baseline. The remaining stratifiers were adjusted for in their categorical form. Time was represented as categorical contrasts in main effect form and in interaction with all other fixed effects. For skewed outcomes, 95% CIs were obtained using the non-parametric bootstrap percentile method.[63]

Analysis of binary outcomes

For the binary outcomes, such as the proportion of participants with a $\geq$ 15 ETDRS letter improvement, differences between two proportions with 95% CIs have been used. Safety outcomes have been reported as unadjusted patient proportions and as rates within and between arms, with 95% CIs, using exact methods when appropriate.[63]

Safety meta-analysis

It was not possible to perform a safety meta-analysis because of the lack of comparative outcome data for anti-VEGF therapy in CRVO. Two other comparative studies were completed during LEAVO: the multicentre SCORE2[27] clinical trial, which compared aflibercept and bevacizumab, given by mandated monthly injection over 6 months, and a small comparative study[59] of aflibercept versus bevacizumab in 50 patients with MO due to CRVO who were followed up for 12 months. The latter trial did not publish any tabulated AE data and was discounted. A direct comparison was made with the SCORE2 safety data by comparing them with the first 6 months of LEAVO safety data; this information is presented in the results (see *Chapter 3*, *Comparison with SCORE2 safety data*).

Patient and public involvement

As a result of consulting the user involvement officer from the Research Design Service London prior to trial start-up, we (1) consulted the Diabetes Research Network online lay member panel, (2) met with the Central and East London Comprehensive Local Research Network (CLRN) lay member group and (3) formed a service user advisory group of RVO patients. They were asked to comment on the non-expert summary, asked to comment on a brief Microsoft PowerPoint® (Microsoft Corporation,

Redmond, WA, USA) overview of the project, asked specific questions and asked to give comments. Overall, they were very supportive; felt that the trial was of benefit to patients; and said that they would definitely participate, although they felt that the dexamethasone intravitreal implant (Ozurdex®; Allergan plc, Dublin, Ireland), originally intended to be a trial arm, should be excluded because of its limited efficacy and side-effect profile. In addition, they thought that aflibercept should be included as it may reduce the frequency of visits and invasive procedures (e.g. dilating and checking the non-trial eye at each visit, which should be avoided when possible), and that they would wish to help in the development of the patient information sheet. This feedback led to us removing Ozurdex from the project; including aflibercept as a third trial arm; minimising trial research visits to six in 2 years; and not dilating the non-trial eye at each visit, to help participants work and commute after their trial visit and to enhance our participant retention activities. The UK RVO service user group helped in the development of the patient information sheet and consent form, reviewing and refining these to make them more accessible and easily understood by all potential participants. One member of the patient group became a member of the TSC, attending every meeting and actively contributing to each.

Once the LEAVO clinical and health economic outcomes were available, the members of the CRVO service user group at Moorfields, additional RVO patients, members of the renamed Barts Health/Queen Mary University of London (QMUL) lay panel and patients with a history of eye disease from the Barts Health/QMUL extended users group were sent a cover letter and questionnaire regarding the trial, which had been reviewed and agreed with the Barts Health/QMUL lay panel chairperson and Moorfields Eye Hospital Biomedical Research Centre patient and public involvement lead. See *Chapter 3*, *Patient and public involvement*, for the results. A member of the Royal National Institute of Blind People served as a member of the TSC.

Trial committees

Trial Steering Committee

The TSC was the committee responsible for monitoring the overall integrity, conduct and safety of the trial. It monitored trial progress, investigated any SAEs, and took account of regular reports from the DMEC and communication from the Trial Management Group (TMG). Ultimate responsibility for any decision required on the trial's continuation lay with the TSC. The TSC comprised an independent chairperson, a professor of statistics, an independent ophthalmologist and general physician, a consultant in public health, a senior Department of Health and Social Care policy-maker and two patient representatives. TSC meetings were held at least annually and arranged by the chief investigator and the trial manager in conjunction with the chairperson. For a list of committee members, see *Appendix 2*. A representative of Moorfields Eye Hospital (the sponsor) was invited to each meeting.[2]

Data Monitoring and Ethics Committee

An independent DMEC of three individuals, one professor of statistics and two retina specialists, met regularly to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial (see *Appendix 2*). Its terms of reference were to receive and review the progress and accruing data of the trial and to provide the TSC with advice and recommendations on trial conduct. The trial would have been discontinued on the basis of new safety information, or for other reasons given by the DMEC and/or TSC, sponsor, regulatory authority or Research Ethics Committee concerned. All data reviewed by the DMEC determined safety issues. All serious adverse reactions were reported to the KCTU within 24 hours of learning of their occurrence.[2]

Trial Management Group and site monitoring

The TMG was responsible for monitoring the delivery of the trial on a day-to-day basis, and was supported and managed via the KCTU. The TMG membership consisted of the chief investigator, the co-lead, the trial manager, the data manager, the lead and trial statisticians and senior members of

the KCTU. Other members of the wider research team were also invited on a meeting-by-meeting basis, depending on the scope covered. Trial conduct and data collected were monitored by a combination of central review and site monitoring visits to ensure that these were in accordance with good clinical practice. Trial site monitoring was undertaken by the trial manager, the assistant trial manager and an experienced KCTU trial monitor. The main areas of focus were consent, SAEs and essential documents in trial site files.

Site monitoring included:

- reviewing all consent forms in the site file and medical notes
- source data verifying SAEs against medical records
- source data verifying a proportion of the primary outcome measure against medical records
- checking essential documents in the investigator site file and trial files.

Central reviews included:

- ensuring accuracy and completeness of all applications for trial authorisations and submissions of progress/safety reports, prior to submission
- ensuring that all documentation essential for trial initiation was in place prior to site authorisation
- reporting and following up all monitoring findings with the appropriate persons in a timely manner.

The investigators and institutions also permitted trial-related monitoring, audits, Research Ethics Committee review and regulatory inspections, providing direct access to source data/documents. Trial participants were informed of this during the informed consent discussion. Participants consented to provide access to their medical notes.

Approvals, reporting and compliance

The trial was approved by the National Research Ethics Committee Service London South East (reference number 14/LO/1043); Clinical Trials Authorisation was given by the MHRA (number 11412/0220/001-0005), and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) number was 2013-003272-12. The trial was run using the standard operating procedures of the sponsor, Moorfields Eye Hospital NHS Foundation Trust. The sponsor provided the oversight of the trial, and the KCTU collaborated with the sponsor to ensure efficient trial delivery. The trial was reported in accordance with the Consolidated Standards of Reporting Trials statement.

Summary of changes made to protocol

After initial substantial amendments [substantial amendment (SA) 1 to SA3] at commencement of the trial clarified the handling of several key issues (e.g. pregnancy, contraception and nurse injectors), subsequent substantial amendments mainly dealt with the addition of sites or a change in principal investigator (see *Appendix 3*, *Table 30*). SA6, approved by the Research Ethics Committee on 11 February 2016, included changes to the protocol, in particular the eligibility criteria, to increase recruitment to the trial. The key change requested by the trial team was to increase the upper limit of permissible visual acuity at screening from 73 (Snellen equivalent 6/12) to 78 (Snellen equivalent 6/9) letters. This was to increase recruitment across all trial sites because, as the protocol stood, patients in clinical practice with a visual acuity of 6/9 may have been excluded from the trial, as their visual acuity was too good, and go on to receive treatment in the NHS, and be lost to the trial. This change to the upper limit would potentially allow patients with a visual acuity of 6/9 to enrol in the trial. However, the DMEC and TSC statisticians were concerned that this could introduce a ceiling effect if an abnormally large number of patients with good visual acuity and limited potential to improve were randomised, and could even lead to the trial

erroneously declaring non-inferiority. Thus, the statisticians stated that they could not agree to this change unless additional data from other studies was obtained by the chief investigator to determine whether or not a significant ceiling effect was likely to occur. After consultation with the relevant trial sponsors and/or chief investigators, the LEAVO chief investigator and co-lead were able to provide the DMEC and TSC with unpublished results from recent clinical trials (the CRYSTAL[55] study of RVO and the US DRCR.net Protocol T sudy[54] of DMO) that showed no significant ceiling effect and that a large proportion of such cases gained significant visual acuity. Based on this new information, the TSC and DMEC allowed the protocol change. Additional changes to the eligibility criteria were approved, including an increase (from three to six) in the number of anti-VEGF injections a participant could have received prior to randomisation. The rescreening interval was reduced from 4 to 2 weeks because a number of participants who failed initial screening sought treatment elsewhere before rescreening was possible.

Chapter 3 Clinical results

Participant flow

The original contract commenced on 1 May 2014, with recruitment to start on 1 November 2014. An early contract variation was requested by the LEAVO team, and approved by NIHR, for the contract to commence on 1 June 2014 and for recruitment to start on 1 December 2014. Recruitment was predicted to take 18 months and, therefore, was to finish on 31 May 2016, with last participant, last visit to take place by 31 May 2018, and the trial to close on 31 October 2018. The first participant was randomised on 12 December 2014, but the last was randomised on 16 December 2016, almost exactly 24 months later. As a result, a contract variation was sought to extend the trial by 6 months so that the last participant, last visit would occur by 30 November 2018, and the trial would close on 30 April 2019. The last participant, last visit was actually on 21 November 2018.

Therefore, between December 2014 and December 2016, 586 patients were assessed across 44 UK NHS hospitals (see *Appendix 1*, *Table 27*) for eligibility. Of these patients, 123 were excluded: 117 were ineligible, one withdrew consent and five did not proceed for other reasons. Therefore, 463 were managed on protocol (see *Appendix 3*, *Table 29*), randomly assigned to receive ranibizumab ($n = 155$), intravitreal aflibercept ($n = 154$) or bevacizumab ($n = 154$), and constituted the ITT population Randomisation was balanced across treatment groups, across hospital sites and within baseline visual acuity strata. The per-protocol population consisted of 145 participants in the ranibizumab arm, 146 in the aflibercept arm and 152 in the bevacizumab arm. Among the ITT population, the 100-week visit was completed by 135 participants in the ranibizumab arm, 133 in the aflibercept arm and 139 in the bevacizumab arm; among the per-protocol population, the same visit was completed by 133 participants in the ranibizumab arm, 128 in the aflibercept arm and 139 in the bevacizumab arm (*Figure 2*).

Recruitment

Overview

NIHR acknowledges the need for experienced trial management and recommends the involvement of a specialised clinical trials unit to conduct trials. We were fortunate to have the multidisciplinary team from the KCTU participate in the trial. As a LEAVO collaborator, the team provided a trial manager, deputy trial manager and experienced monitors, in addition to a senior and a junior statistician, and the expertise of their core team, including the Clinical Trials Unit operations manager, senior data manager and trial methodologist. All these members attended TMG, TSC and DMEC meetings, when appropriate. In addition, the KCTU team members were all available for advice and guidance on a daily basis; working in conjunction with the trial manager, the KCTU was, ultimately, the cornerstone of the trial.[63] It recognised the need to open as many sites as quickly as possible and its senior team spent many hours with the trial manager, ensuring that she was fully familiar with the trial and was able to begin site initiations before recruitment commenced on 1 December 2014. The largest and most experienced sites (e.g. Moorfields and Leeds) were initiated first. Unfortunately, a few weeks before the initiation of the first site, the original trial manager was absent on sick leave and she announced her resignation at the beginning of December 2014. Not unexpectedly, this had a significant impact on site initiation and could have led to very prolonged trial delays. Fortunately, an experienced assistant trial manager had just been appointed and agreed to step up to the trial manager position within a few days of starting. Quite understandably, he took time to familiarise himself with the trial protocol and procedures; therefore, the trial fell significantly behind with site initiations and recruitment. The low point was 39 participants recruited by the end of May 2015, against a predicted target of 76 (51%). However, the new trial manager began to recover the situation in the second quarter

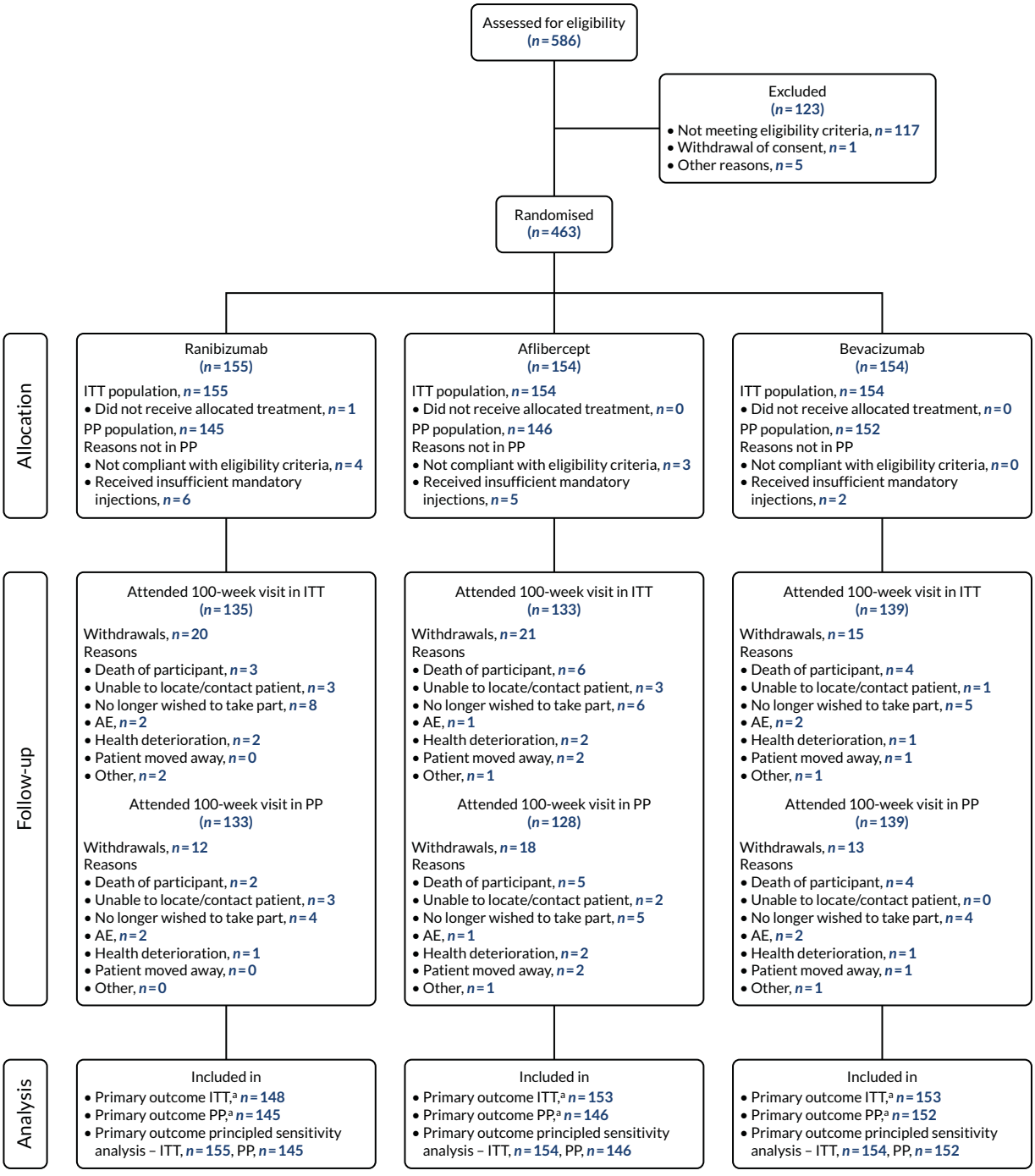

FIGURE 2 The LEAVO CONSORT diagram. a, Models include all participants who have had at least one follow-up visit. PP, per protocol. Reproduced from Hykin *et al.*[2] This is an open access article distributed under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium. This includes minor additions and formatting changes to the original.

of 2015, and the number of site initiations increased: we initiated only eight sites in the first 4 months of recruitment, compared with 13 sites in the succeeding 2 months. As a result, actual recruitment kept pace with predicted recruitment in October, November and December 2015. By November 2015, that is after 12 months of recruitment, we had opened 38 sites, against a target of 40, and recruited 176 participants, against a target of 268 (66%). An additional eight sites were subsequently initiated, to give 46 greenlighted sites open in the first quarter of 2016. By 31 May 2016, when recruitment should have been completed, we had recruited 320 participants, against a target of 459 (70%); by December 2018, we had completed recruitment almost exactly 6 months behind schedule (*Figure 3*).

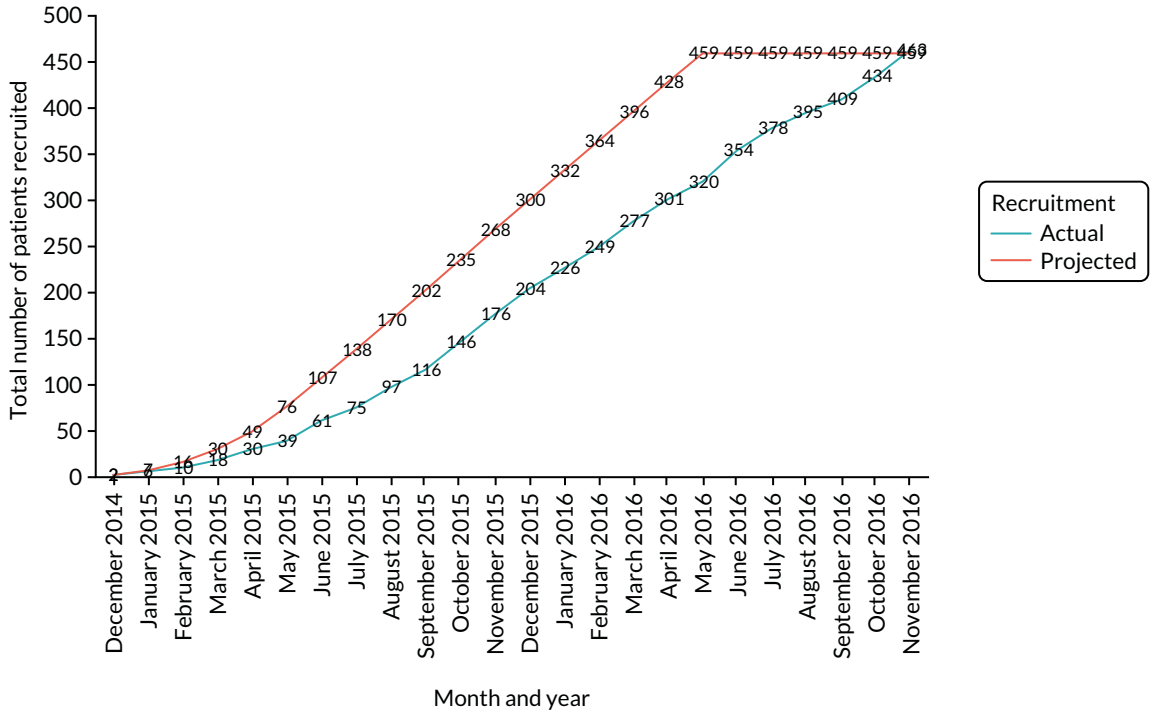

FIGURE 3 Actual vs. projected recruitment per month.

Table 1 shows the number of participants recruited each month by site, and *Table 2* shows the number of participants whom each site recruited per trial arm.

Barriers to recruitment and corrective strategies

The following barriers to recruitment were identified:

- Availability of trial staff, for example masked injectors and trial co-ordinators. Despite fulfilling our initial trial site requirements, several sites were unable to provide sufficient clinician unmasked injector cover (e.g. Rugby) as a result of limited staff availability, or sufficient research co-ordinator time for the trial (e.g. Addenbrooke's and Hillingdon), the latter in some cases because NHS support costs attributable to LEAVO were not available to the local trial team. We largely resolved the former issue in a substantial amendment that allowed nurses and optometrists who were certified intravitreal injectors in standard NHS clinics to provide unmasked injector cover for LEAVO.
  We also approached a number of local ophthalmology CLRNs to provide additional co-ordinator time for the trial based on CLRN support costs, and received very helpful support from Rupert Bourne, CLRN National Lead for Ophthalmology, in this regard.
- Difficulties with the protocol. The following changes were made to the protocol (see *Appendix 3*, *Table 30*) –
  - The upper limit of the visual acuity eligibility at baseline was increased from 73 (Snellen equivalent: ≈ 6/12) to 78 letters (Snellen equivalent: ≈ 6/9). Patients in clinical practice with a visual acuity of 6/9 had previously been excluded from the trial as their visual acuity was too good, and they were receiving NHS treatment instead. The change allowed patients with a visual acuity of 6/9 to enrol in the trial.
  - The inclusion criterion for diabetic retinopathy in the trial eye was changed from 'any previously documented diabetic retinopathy or diabetic macular oedema in the study eye' to 'any diabetic retinopathy or diabetic macular oedema at baseline clinical examination of the study eye'.[2]
    This was to prevent patients being excluded from the trial who presented with a documented history of diabetic retinopathy, which may not have been reliable, rather than clinical evidence based on the trial screening examination.

TABLE 1 The number of participants recruited by each site, by calendar month

	Participants (*n*)																									
	2014	2015												2016												
Site	December	January	February	March	April	May	June	July	August	September	October	November	December	January	February	March	April	May	June	July	August	September	October	November	December	Total
Moorfields Eye Hospital	2	3	1	5	3	5	4	2	4	6	3	4	4	3	2	2	3	0	4	4	3	2	5	3		77
King's College Hospital									1						1		2				1				1	6
Wolverhampton Eye Infirmary, New Cross Hospital															4	2	2		4	3	2	2	1	1		21
St Paul's Eye Unit, Royal Liverpool University Hospital												2	2				2	1	2				2	2		13
University Hospital Southampton					2		4					3				2		1	1					1		14
Royal Victoria Hospital, Belfast								1	3			4		1	1	1			1	1				1		14
Royal Blackburn Hospital											1	1							1			1				4
Bradford Royal Infirmary					1			3		2	3	1		1	1	1	1		1	1	2					18
Sussex Eye Hospital					1		4		1		1					2	1					1				11
Bristol Eye Hospital			2	2			1	1		1		1	1					2			1		1			13
West Suffolk Hospital						1	1	1				2	2	1	1		1		1							11
Torbay Hospital											1	1	2			2						1				7
Essex County Hospital						1	1		1		1				2	1	1						1	1	1	11
Hospital of St Cross, Rugby							1											2		1				1		5
Birmingham and Midlands Eye Centre							2	1	4	3	1	1	4													16
Kent and Canterbury Hospital								1										1	1					1		4

Site	Participants (*n*)																									
	2014	2015												2016												
	December	January	February	March	April	May	June	July	August	September	October	November	December	January	February	March	April	May	June	July	August	September	October	November	December	Total
Frimley Park Hospital					2			1	1		1	1	2	3	1		1		1	1						15
Whipps Cross University Hospital														1												1
James Paget University Hospital									1	1						2			1				1	1		7
Royal Surrey County Hospital											3	1														4
Harrogate District Hospital					1	1																				2
York Teaching Hospital					1		1				1	1		1												5
Darlington Memorial Hospital										1	1	1			1											4
St James's University Hospital, Leeds		1	2	1			2	1			1	1	1	1		1				1				1		14
Hillingdon Hospital							1				1						2		2						1	7
Eye, Ear and Mouth Unit, Maidstone Hospital											2		1	2	1		1		2	2	1	1	1			14
Manchester Royal Eye Infirmary								1	1					1		1	2				2	1				9
Royal Victoria Infirmary, Newcastle upon Tyne									2	2		3	1			2	1	1								12
Luton and Dunstable University Hospital												1	1	1						1	1					5
Cardiff Eye Unit, University Hospital of Wales													1	1		1							2			5
Sunderland Eye Infirmary						1		1	2	1	3		3		1			3				2	2	2		21

continued

TABLE 1 The number of participants recruited by each site, by calendar month (*continued*)

	Participants (*n*)																											
	2014	2015													2016													
Site	December	January	February	March	April	May	June	July	August	September	October	November	December	January	February	March	April	May	June	July	August	September	October	November	December	Total		
Royal Glamorgan Hospital											1	2	1	1	1	1		2	3				1	1		14		
Royal Hallamshire Hospital									1		2		1	1	3	1		2		1			1			13		
Addenbrooke's Hospital											1		1						2	2		1	1	3		11		
Gartnavel General Hospital																	1		1		1	1			1	5		
Royal Bolton Hospital														1	1	1			2				1			6		
Calderdale Royal Hospital										1	1		1	1										2		6		
Leicester Royal Infirmary															1	1		1	1	1						5		
Norfolk and Norwich Hospital																	2			1				1		4		
Cheltenham General Hospital											1				1				1	1	1				1	6		
Hull Royal Infirmary																		3		1		1	1			6		
Western Eye Hospital																3	1		1	1	2		2			10		
James Cook University Hospital																			1					2		3		
Princess Alexandra Hospital, Harlow																1				1			2			4		
Total per month	2	4	5	8	11	9	22	14	22	19	30	30	29	21	23	28	24	19	34	24	17	14	25	24	5	463		
Cumulative total	2	6	11	19	30	39	61	75	97	116	146	176	205	226	249	277	301	320	354	378	395	409	434	458	463	463		

TABLE 2 The number of participants recruited to each trial arm, by site

Site	Participants (*n*)			
	Ranibizumab	Aflibercept	Bevacizumab	Total
Moorfields Eye Hospital	25	24	28	77
King's College Hospital	3	2	1	6
Wolverhampton Eye Infirmary, New Cross Hospital	8	6	7	21
St Paul's Eye Unit, Royal Liverpool University Hospital	5	6	2	13
University Hospital Southampton	3	6	5	14
Royal Victoria Hospital, Belfast	6	3	5	14
Royal Blackburn Hospital	0	1	3	4
Bradford Royal Infirmary	3	7	8	18
Sussex Eye Hospital	6	1	4	11
Bristol Eye Hospital	5	2	6	13
West Suffolk Hospital	6	4	1	11
Torbay Hospital	3	3	1	7
Essex County Hospital	3	2	6	11
Hospital of St. Cross, Rugby	1	1	3	5
Birmingham and Midlands Eye Centre	5	5	6	16
Kent and Canterbury Hospital	2	2	0	4
Frimley Park Hospital	5	5	5	15
Whipps Cross University Hospital	0	1	0	1
James Paget University Hospital	4	3	0	7
Royal Surrey County Hospital	0	1	3	4
Harrogate District Hospital	0	1	1	2
York Teaching Hospital	0	4	1	5
Darlington Memorial Hospital	4	0	0	4
St James's University Hospital, Leeds	6	4	4	14
Hillingdon Hospital	2	2	3	7
Eye, Ear and Mouth Unit, Maidstone Hospital	5	5	4	14
Manchester Royal Eye Infirmary	2	4	3	9
Royal Victoria Infirmary, Newcastle upon Tyne	5	3	4	12
Luton and Dunstable University Hospital	1	2	2	5
Cardiff Eye Unit, University Hospital of Wales	3	1	1	5
Sunderland Eye Infirmary	8	7	6	21
Royal Glamorgan Hospital	5	6	3	14
Royal Hallamshire Hospital	3	4	6	13
Addenbrooke's Hospital	2	5	4	11
Gartnavel General Hospital	0	3	2	5
Royal Bolton Hospital	3	2	1	6
Calderdale Royal Hospital	2	3	1	6
Leicester Royal Infirmary	2	1	2	5

continued

TABLE 2 The number of participants recruited to each trial arm, by site (*continued*)

Site	Participants (*n*)			
	Ranibizumab	Aflibercept	Bevacizumab	Total
Norfolk and Norwich Hospital	1	2	1	4
Hull Royal Infirmary	0	2	4	6
Cheltenham General Hospital	4	2	0	6
Western Eye Hospital	1	4	5	10
James Cook University Hospital	2	1	0	3
Princess Alexandra Hospital, Harlow	1	1	2	4
Total	155	154	154	463

  - The allowed number of previous anti-VEGF injections was increased from three to six in order to allow patients who had had longer-term treatment for MO due to CRVO (i.e. six injections) to be considered for the trial.
  - Patients who had had recent pan-retinal photocoagulation for NVE, NVD or NVI were considered eligible for the trial within 1 month of treatment rather than within 3 months, as treatment within 1 month would not have had an adverse outcome on anti-VEGF therapy 1 month later.
  - The protocol was altered to change the rescreening interval to 2 weeks, except for visual acuity eligibility, which remained at 4 weeks. Several patients had not enrolled in LEAVO because, for example, they had forgotten to take blood pressure medication, leading to high blood pressure and a screen fail. If they needed to wait 4 weeks before rescreening, as the protocol originally stated, then they typically opted for NHS treatment in the interim; being able to rescreen after 2 weeks prevented them being lost to NHS care.

- Number of sites. Although we planned for 40 sites initially, four withdrew before being initiated, and so we took an early decision to add additional sites. Initially, we planned for a further 12 sites, which would have taken the total to 48 active sites. However, two of these withdrew, and 10 were greenlighted, although one failed to recruit any participants. Nevertheless, these additional sites made a very significant contribution to the last 6 months of recruitment.
- Site equipment. Several sites had issues with equipment, in particular with wide-angled fluorescein angiography imaging devices and information technology support that allowed communication with the KCTU randomisation software and MACRO trial database, and also allowed data export to the reading centre. We worked with the sites and providers of equipment (e.g. Optos wide-angled imaging) to overcome these issues as quickly as possible.
- Although we had held an investigator meeting prior to the trial start, a number of optometrists had not been able to attend this and required certification before a site could be greenlighted to recruit patients. To minimise certification delays, we arranged for prompt visits by either lead trial optometrist to any site to undertake optometry certification.
- Other measures that were used to try to maximise recruitment included the following –

  - A monthly newsletter to every site detailing progress[63] and acknowledging each site that had recruited one or more participants in the previous month.
  - An e-mail from the chief investigator to each site team every 2 months encouraging further recruitment.
  - A thank-you e-mail to each site from the chief investigator after each participant was recruited.
  - Reward vouchers each month to the site recruiting the most participants and ‘best site of the month’.
  - Very prompt replies to any site that had queries on any aspect of the trial. We think that this point was critical in keeping sites focused on recruitment and willing to recruit over and above their target, which was something we specifically asked large sites to do.

Withdrawals

Appendix 3, *Table 31*, shows the number of participants who did not complete the week 100 visit in the three arms, and the week of their last visit. *Appendix 3*, *Table 32*, shows the number of weeks all withdrawal participants participated in the trial and the reasons for withdrawal. Withdrawals were balanced across treatment arms; overall, more participants completed their week 100 visit [87.9% (407/463)] than had been predicted in the sample size calculation (85%).

Baseline data

Baseline characteristics were well balanced between groups for age, sex and eye involved (*Table 3*). In the ranibizumab, aflibercept and bevacizumab arms, the mean baseline BCVA was 53.6 (SD 15.1), 54.1 (SD 15.3) and 54.4 (SD 14.2) ETDRS letters, respectively. The numbers recruited to the three stratifier subgroups for visual acuity were equal across arms. The median duration of CRVO in each treatment group was < 1 month; the numbers of participants in the duration of CRVO subgroups of 3–6 months and > 6 months were small and so these groups were combined for analysis purposes, a change that was approved in the final version of the statistical analysis plan. Similarly, the number of participants receiving prior treatment was so small that this stratifier was not analysed. OCT CST was 731.3 µm (SD 227.6 µm), 673.2 µm (SD 189.4 µm) and 676.1 µm (SD 207.0 µm) for the ranibizumab, aflibercept and bevacizumab arms, respectively, with the apparent difference between ranibizumab and the other two groups being approximately 0.5 of a SD, and likely to be attributable to chance.

TABLE 3 Baseline ocular and systemic characteristics in each group

Characteristic	Total (*N* = 463)	Ranibizumab (*N* = 155)	Aflibercept (*N* = 154)	Bevacizumab (*N* = 154)
Age (years), mean (SD)	69.1 (13.0)	69.2 (13.0)	68.7 (13.2)	69.3 (12.8)
Female, *n* (%)	198 (42.8)	70 (45.2)	60 (39.0)	68 (44.2)
Right eye was trial eye, *n* (%)	226 (48.8)	81 (52.3)	67 (43.5)	78 (50.6)
Mean (SD) BCVA letter score in the trial eye[a,b]	54.1 (14.8)	53.6 (15.1)	54.1 (15.3)	54.4 (14.2)
BCVA letter score in trial eye*, n *(%)				
19–38	85 (18.4)	31 (20.0)	27 (17.5)	27 (17.5)
39–58	166 (35.9)	56 (36.1)	55 (35.7)	55 (35.7)
59–78	212 (45.8)	68 (43.9)	72 (46.8)	72 (46.8)
Median (IQR) duration of CRVO (months)[a]	0.9 (0.4–1.7)	0.9 (0.5–1.8)	0.9 (0.4–1.7)	0.9 (0.4–1.7)
Duration of trial eye CRVO*, n *(%)				
< 3 months	401 (86.6)	134 (86.5)	129 (83.8)	138 (89.6)
3–6 months	38 (8.2)	11 (7.1)	19 (12.3)	8 (5.2)
> 6 months	24 (5.2)	10 (6.5)	6 (3.9)	8 (5.2)
***Previous treatment in trial eye*, n *(%)*[a]**				
Nil	446 (96.5)	148 (96.1)	149 (96.8)	149 (96.8)
Anti-VEGF therapy	16 (3.5)	6 (3.9)	5 (3.2)	5 (3.2)
***CRVO ischaemic status at baseline (trial eye)*, n *(%)*[a]**				
Non-ischaemic	406 (87.9)	137 (89.0)	135 (87.7)	134 (87.0)
Ischaemic	56 (12.1)	17 (11.0)	19 (12.3)	20 (13.0)

continued

TABLE 3 Baseline ocular and systemic characteristics in each group (*continued*)

Characteristic	Total (*N* = 463)	Ranibizumab (*N* = 155)	Aflibercept (*N* = 154)	Bevacizumab (*N* = 154)
OCT (trial eye),[a,c] mean (SD)				
CST (μm)	693.6 (209.8)	731.3 (227.6)	673.2 (189.4)	676.1 (207.0)
Total volume (mm^3)	12.7 (2.8)	13 (2.9)	12.3 (2.6)	12.8 (2.9)
Lens status (trial eye),* n *(%)				
Cataract	131 (28.4)	41 (26.6)	44 (28.6)	46 (29.9)
Pseudophakia	68 (14.7)	29 (18.8)	20 (13)	19 (12.3)
Blood pressure (mmHg),[a] mean (SD)				
Systolic	143.0 (16.8)	143.1 (17.6)	142.6 (17.0)	143.1 (15.7)
Diastolic	79.7 (10.4)	80.1 (10.2)	79.1 (10.6)	79.9 (10.6)

a Not recorded for one ranibizumab participant, who was randomised in error.
b For one participant in each arm, the baseline best refracted visual acuity test was incomplete or not performed.
c For total volume, data were further missing for two ranibizumab participants and one bevacizumab participant.

Derivation of the intention-to-treat model and per-protocol populations

Participants included in the prespecified ITT LME model were derived as follows:

1. The BCVA data were available for 407 of 463 randomly assigned participants (ranibizumab, $n = 135$; aflibercept, $n = 133$; and bevacizumab, $n = 139$) at 100 weeks. *Table 4* shows the available BCVA data at 12, 24, 52, 76 and 100 weeks by arm. The model included all participants who had at least one of these follow-up visits; therefore, those without follow-up data did not contribute to the analysis.
2. Only the 76-week measurement in one bevacizumab participant was excluded because of the presence of retinal detachment within 3 months of BCVA recordings, and BCVA was > 3 SDs below the mean at that time point (including all measurements).
3. Therefore, no participants were removed on this basis from the LME model analysis and the ITT and per-protocol populations were not modified by this.
4. A total of 20 participants did not meet the per-protocol definition, so 443 participants constituted the per-protocol population (see *Figure 2*).[63]

TABLE 4 Unadjusted refracted BCVA available at each milestone visit

	Mean (SD) BCVA letter score; *n* participants			
Visit	Total (*N* = 463)	Ranibizumab (*N* = 155)	Aflibercept (*N* = 154)	Bevacizumab (*N* = 154)
Screening	54.1 (14.8); 459	53.6 (15.1); 153	54.1 (15.3); 153	54.4 (14.2); 153
12 weeks	68.4 (15.8); 443	67.5 (16.5); 146	70.4 (15.1); 148	67.3 (15.8); 149
24 weeks	65.8 (17.9); 432	65 (19.1); 145	67.3 (16.9); 146	64.9 (17.7); 141
52 weeks	66.3 (18.4); 413	65.4 (19.4); 139	67.2 (17.6); 139	66.4 (18.3); 135
76 weeks	65.9 (19.0); 397	65.7 (19.4); 136	66.2 (18.1); 128	65.9 (19.6); 133
100 weeks	66.2 (19.6); 407	65.6 (19.9); 135	68.4 (17.9); 133	64.6 (20.8); 139

Outcomes and estimations

Primary outcome

The mean gain in BCVA letter score was 12.5 with ranibizumab (SD 21.1), 15.1 with aflibercept (SD 18.7) and 9.8 with bevacizumab (SD 21.4) at 100 weeks (*Figure 4*). First, the primary outcome at 100 weeks was unable to show that bevacizumab was non-inferior in terms of BCVA in both the ITT and per-protocol populations (*Table 5*). The 95% CI for the adjusted difference between arms at 100 weeks lay below the prespecified acceptable margin of −5 letters (*Figure 5*). Second, aflibercept was non-inferior, but not superior, to ranibizumab in terms of BCVA in both the ITT and the per-protocol populations (see *Table 5* and *Figure 5*). The 95% CI for the adjusted difference between arms at 100 weeks lay above the prespecified acceptable margin of −5 letters (see *Figure 5*). The mean BCVA letter score at 24 weeks had decreased by approximately 3 letters across groups following pro re nata injections at weeks 16 and 20, when fewer injections were given (ranibizumab injections, $n = 123$; aflibercept, $n = 76$; and bevacizumab, $n = 121$), but increased gradually thereafter across groups to week 100, during which period participants were seen at least every 8 weeks and received injections promptly if re-treatment criteria were met (see *Figure 4*). Such peak-and-trough changes in visual acuity were closely mirrored by OCT trough and peak CST results over the 2-year period.

The principled sensitivity analysis for missing data supported the primary outcome results (*Figures 6* and *7*). The sensitivity analysis for outliers was not conducted, as there were no outliers in the ITT and per-protocol populations [see www.journalslibrary.nihr.ac.uk/programmes/hta/119203/#/documentation (accessed 14 July 2020)]. The sensitivity analysis for concomitant treatments taken by one participant in the trial supported the primary outcome results.

The sensitivity analysis assessed the potential impact on the treatment effect from including participants with unobserved BCVA 24-month primary outcome data in the adjusted primary outcome model. In this analysis, participants with unobserved data were, on average, specified to be able to have score ranging from −20 to 20 BCVA letters away from the scores of their counterparts who did have outcome data observed. This was applied to participants in three scenarios. Scenario 1 involved applying this to participants in the investigative treatment arm (aflibercept) only. Scenario 2 involved applying this to those in the comparator arm (ranibizumab) only. Scenario 3 involved applying this to participants in both

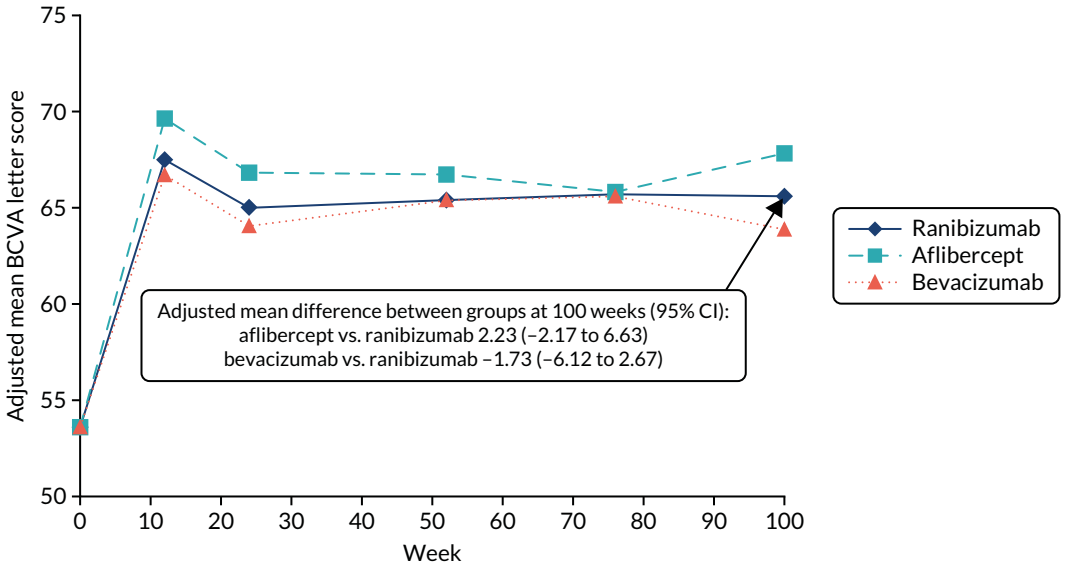

FIGURE 4 Adjusted mean BCVA letter score across groups to 100 weeks. Reproduced from Hykin *et al.*[2] This is an open access article distributed under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium. This includes minor additions and formatting changes to the original.

TABLE 5 Primary outcome at 100 weeks

Mean (SE) BCVA at screening		Mean (SE) BCVA at 100 weeks; *n* participants		Adjusted difference between groups (95% CI) at 100 weeks	*p*-value for non-inferiority ($p < 0.025$ is significant)	*p*-value for superiority ($p < 0.05$ is significant)
Aflibercept	***Ranibizumab***	***Aflibercept***	***Ranibizumab***			
Aflibercept vs. ranibizumab ITT						
54.1 (1.2)	53.6 (1.2)	68.4 (1.6); 133	65.6 (1.7); 135	2.23 (−2.17 to 6.63)[a,b]	0.0006	0.32
Aflibercept vs. ranibizumab per protocol						
55.0 (1.2)	53.6 (1.3)	69.5 (1.5); 128	65.7 (1.7); 133	3.49 (−0.91 to 7.88)[a,c]	< 0.0001	0.12
Bevacizumab	***Ranibizumab***	***Bevacizumab***	***Ranibizumab***			
Bevacizumab vs. ranibizumab ITT						
54.4 (1.1)[a]	53.6 (1.2)	64.6 (1.8); 139	65.6 (1.7); 135	−1.73 (−6.12 to 2.67)[b]	0.071	0.44
Bevacizumab vs. ranibizumab per protocol						
54.4 (1.2)	53.6 (1.3)	64.6 (1.8); 139	65.7 (1.7); 133	−1.67 (−6.02 to 2.68)[c]	0.066	0.45

SE, standard error.
a Non-inferior relative to ranibizumab.
b The LME model incorporates 454 participants (ranibizumab, $n = 148$; aflibercept, $n = 153$; and bevacizumab, $n = 153$) with BCVA at 100 weeks.
c The LME model incorporates 443 participants (ranibizumab, $n = 145$; aflibercept, $n = 146$; and bevacizumab, $n = 152$) with BCVA at 100 weeks.

Note
The 95% CI for the adjusted difference between arms at 100 weeks lay above the prespecified acceptable margin of −5 letters.

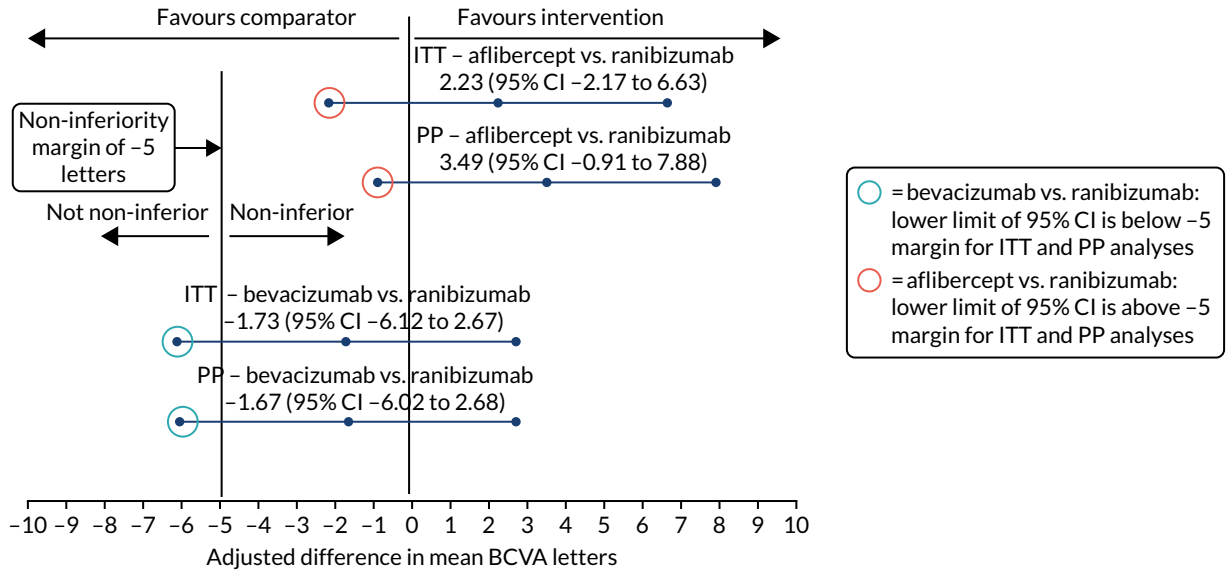

FIGURE 5 Forest plot of the primary outcome at 100 weeks. PP, per protocol. Reproduced from Hykin *et al.*[2] This is an open access article distributed under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium. This includes minor additions and formatting changes to the original.

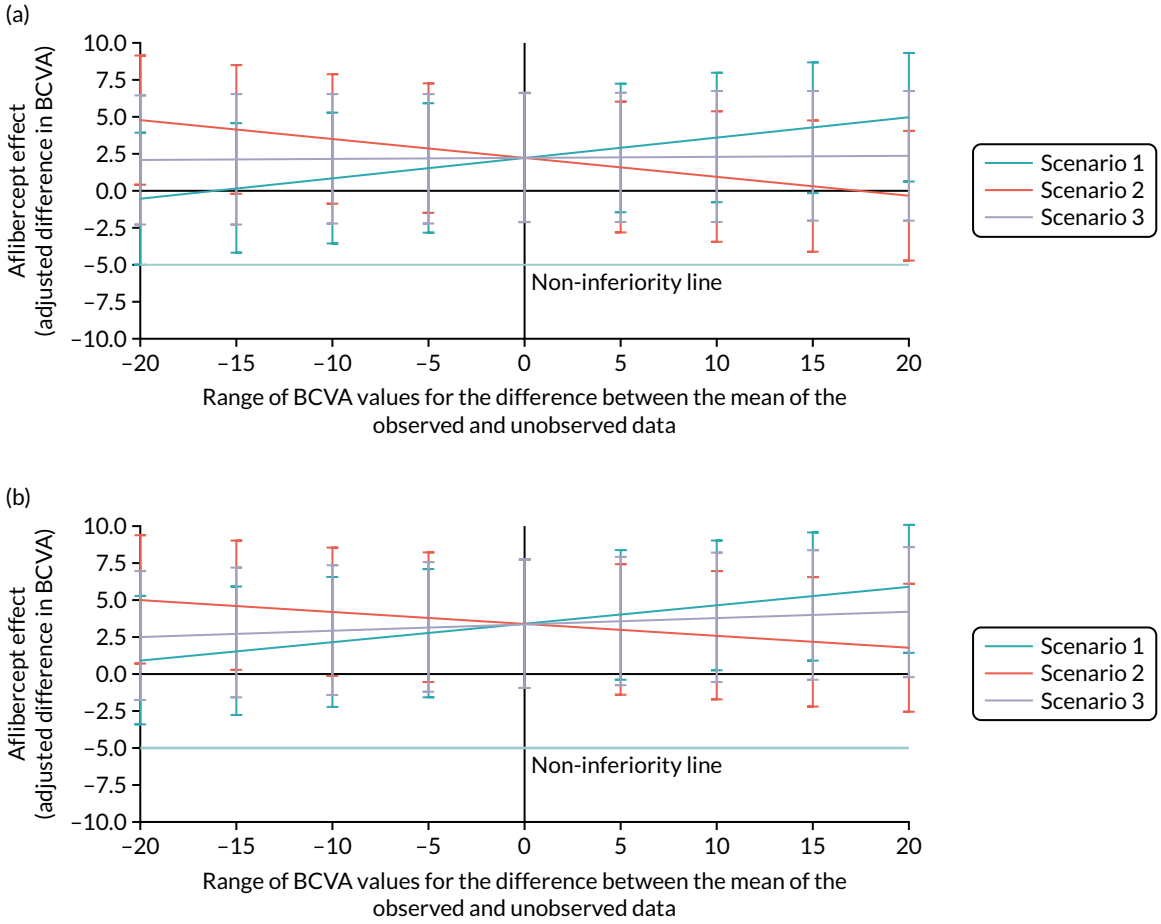

FIGURE 6 Sensitivity analysis for the missing-at-random assumption in the primary outcome analysis assessing non-inferiority of aflibercept. (a) ITT; and (b) per protocol. Reproduced from Hykin *et al.*[2] This is an open access article distributed under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium. This includes minor additions and formatting changes to the original.

arms equally. The *x*-axis in *Figures 6* and *7* represents the range of −20 to 20 BCVA letter scores that those participants with unobserved data were, on average, specified to be able to have relative to the scores of their counterparts who did have data outcome observed. This analysis follows previously described methods.[81] The treatment effect in the main analysis is shown at zero. Vertical bars are 95% CIs for the treatment effect. The 95% CI bars all lie above the non-inferiority margin of −5 letters, supporting the non-inferiority of aflibercept in both the ITT (see *Figure 6a*) and the per-protocol (see *Figure 6b*) populations.

For scenario 3, and within most of the ranges of scenarios 1 and 2, the lower CI limit lay below the non-inferiority margin of −5 letters, supporting the main analysis conclusion that bevacizumab lacked non-inferiority. The difference in the mean between those with unobserved BCVA data and those with observed BCVA data would need to be assumed to be 12 letters higher for bevacizumab than for ranibizumab in scenario 1 (or 12.4 letters higher in scenario 2) in order to change the main analysis conclusion of a lack of non-inferiority in both the ITT (see *Figure 7a*) and the per-protocol (see *Figure 7b*) populations.

Secondary visual acuity outcomes

Both aflibercept and bevacizumab were non-inferior to ranibizumab at 52 weeks (*Table 6*). The 95% CI for the adjusted difference in BCVA between arms lay above the prespecified acceptable non-inferiority margin of −5 letters at 52 weeks for both aflibercept and bevacizumab.

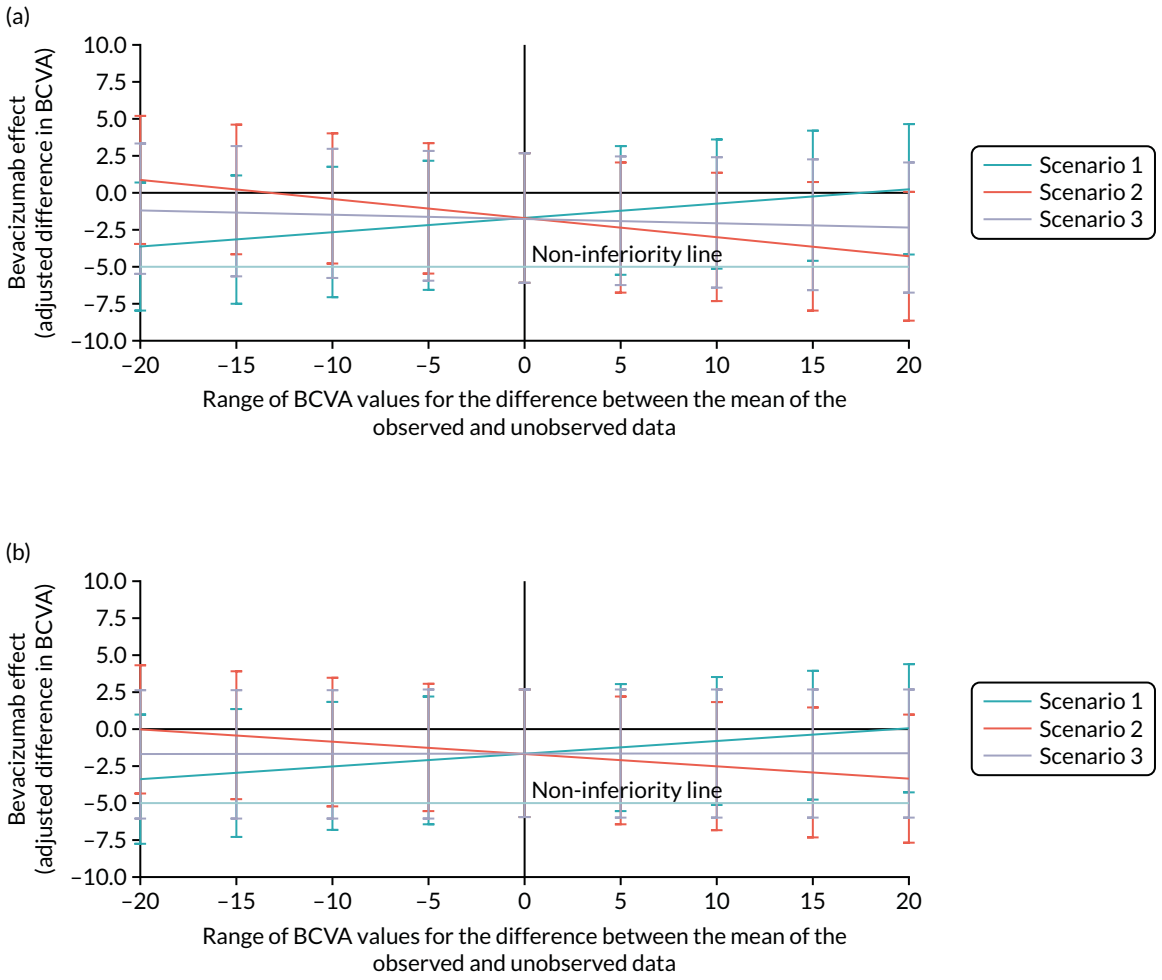

FIGURE 7 Sensitivity analysis for the missing-at-random assumption in the primary outcome analysis assessing non-inferiority of bevacizumab. (a) ITT; and (b) per protocol. Reproduced from Hykin *et al.*[2] This is an open access article distributed under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium. This includes minor additions and formatting changes to the original.

The proportions of participants with a ≥ 15-letter gain were 47%, 52% and 45% (*Figure 8*) in the ranibizumab, aflibercept and bevacizumab arms, respectively, with 63%, 68% and 63%, respectively, gaining ≥ 10 letters at 100 weeks (*Figure 9*).

The proportions of participants with a < 15-letter loss were 90%, 93% and 90% in the ranibizumab, aflibercept and bevacizumab arms, respectively (*Figure 10*), and the proportion of participants with a ≥ 30-letter loss in BCVA was < 6% in each group (*Figure 11*).

There were no meaningful differences in the proportion of participants in each group who had prespecified categorical outcomes, for example a final visual acuity of < 19 letters (i.e. eligible for blind registration) (*Table 7*). Furthermore, there were no subgroup differences in the final visual acuity outcome by baseline stratifiers (*Tables 8–10*).

The were no differences between subgroups in the treatment effects on final visual acuity for any of the three baseline stratifiers.

TABLE 6 Adjusted BCVA at 52 weeks

Mean (SE) BCVA at screening		Mean (SE) BCVA at 52 weeks		Adjusted difference between groups (95% CI) at 52 weeks	*p*-value for non-inferiority ($p < 0.025$ is significant)	*p*-value for superiority ($p < 0.05$ is significant)
Aflibercept	***Ranibizumab***	***Aflibercept***	***Ranibizumab***			
Aflibercept vs. ranibizumab ITT						
54.1 (1.2)	53.6 (1.2)	67.2 (1.5) ($n = 139$)	65.4 (1.6) ($n = 139$)	1.33 (−2.62 to 5.28)[a,b]	0.0008	0.51
Aflibercept vs. ranibizumab per protocol						
55.0 (1.2)	53.6 (1.3)	68.4 (1.4) ($n = 133$)	65.5 (1.7) ($n = 137$)	2.15 (−1.81 to 6.1)[a,c]	0.0002	0.29
Bevacizumab	***Ranibizumab***	***Bevacizumab***	***Ranibizumab***			
Bevacizumab vs. ranibizumab ITT						
54.4 (1.1)	53.6 (1.2)	66.4 (1.6) ($n = 135$)	65.4 (1.6) ($n = 139$)	−0.02 (−3.97 to 3.94)[a,b]	0.0067	0.99
Bevacizumab vs. ranibizumab per protocol						
54.4 (1.2)	53.6 (1.3)	66.4 (1.6) ($n = 135$)	65.5 (1.7) ($n = 137$)	0.05 (−3.88 to 3.98)[a,c]	0.0058	0.98

SE, standard error.
a Non-inferior relative to ranibizumab.
b The LME model incorporates 454 participants (ranibizumab, $n = 148$; aflibercept, $n = 153$; and bevacizumab, $n = 153$) with BCVA at 52 weeks.
c The LME model incorporates 443 participants (ranibizumab, $n = 145$; aflibercept, $n = 146$; and bevacizumab, $n = 152$) with BCVA at 52 weeks.

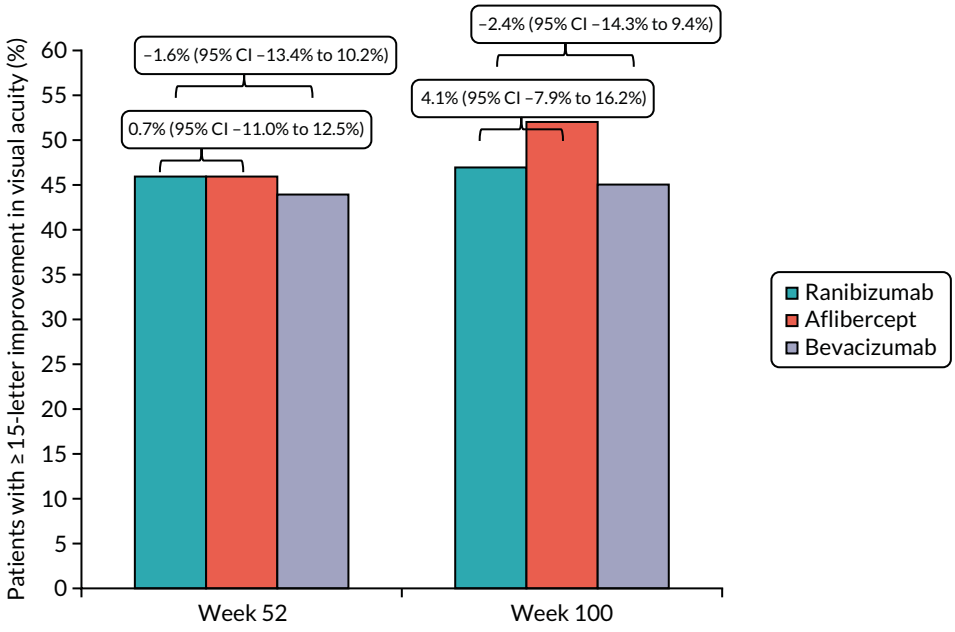

FIGURE 8 Percentage of participants in each group with BCVA improvement of ≥ 15 ETDRS letters at 52 and 100 weeks. Reproduced from Hykin *et al.*[2] This is an open access article distributed under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium. This includes minor additions and formatting changes to the original.

Optical coherence tomography outcomes

The mean reductions in OCT CST from baseline to 100 weeks were −405 µm for ranibizumab (95% CI −450 µm to 360 µm), −378 µm for aflibercept (95% CI −412 µm to −343 µm), and −334 µm for bevacizumab (95% CI −374 µm to −293 µm). There were no clinically relevant differences across treatment groups for the adjusted difference in CST at 100 weeks: aflibercept versus ranibizumab was

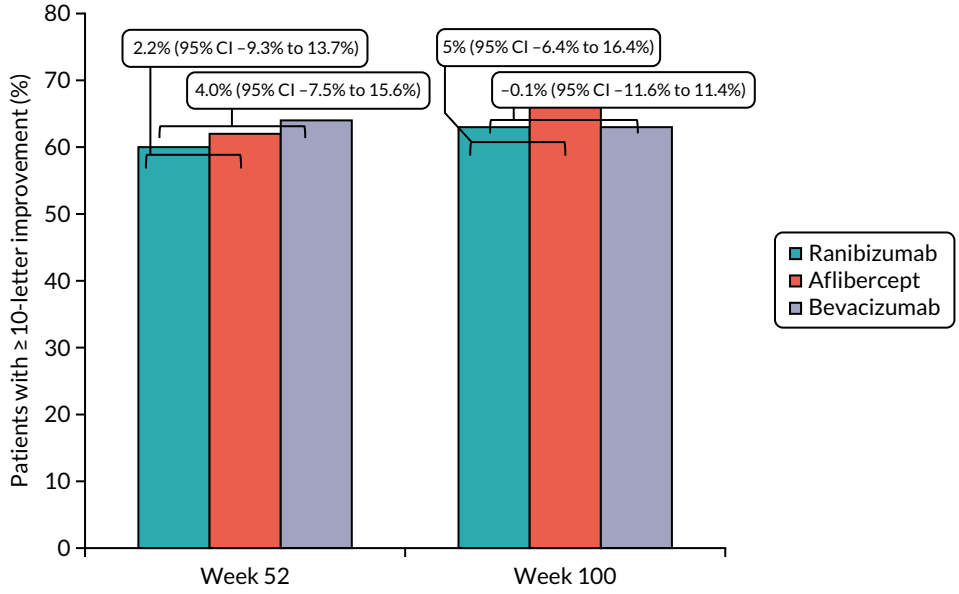

FIGURE 9 Percentage of participants in each group with improvement of ≥ 10 ETDRS letters at 52 and 100 weeks.

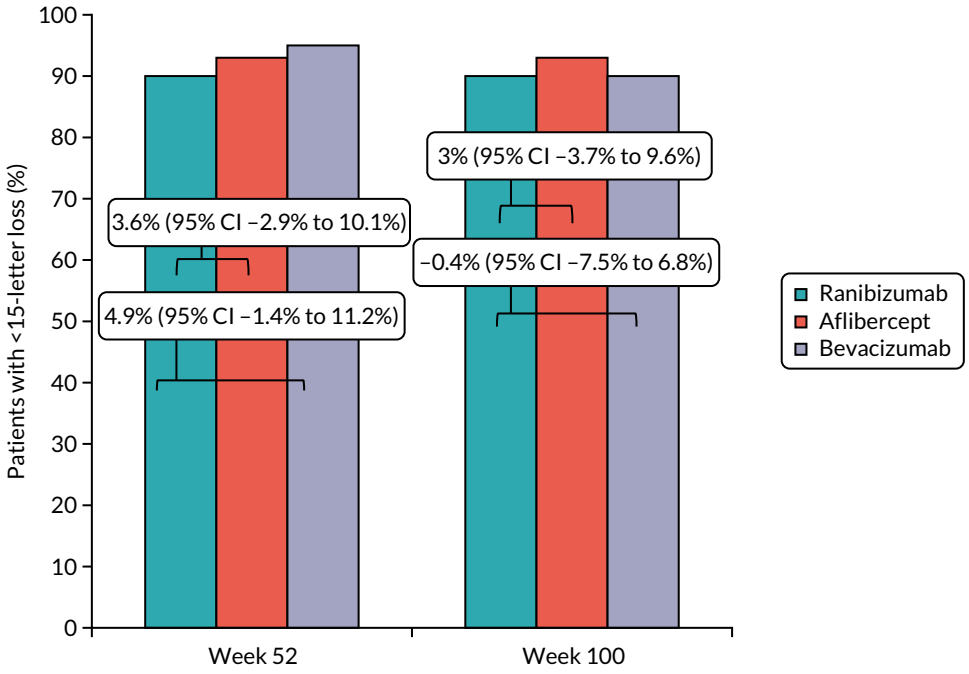

FIGURE 10 Percentage of participants in each group with loss of < 15 ETDRS letters at 52 and 100 weeks.

−29.3 µm (95% CI −60.9 µm to 2.3 µm); and bevacizumab versus ranibizumab was 21.9 µm (95% CI −9.7 µm to 53.4 µm). The adjusted mean OCT CST across groups increased by approximately 50 µm following pro re nata visits at weeks 16 and 20, closely mirroring the visual acuity data, and decreased gradually thereafter to week 100 (*Figure 12*). There was no difference in mean macular volume in each trial group at 100 weeks (see *Appendix 3*, *Table 33*).

The proportion of participants with an OCT CT of < 320 µm at 52 weeks was significantly higher in the aflibercept group (76%) than in the ranibizumab group (63%), a difference of 12.4% (95% CI 1.7% to 23.1%). A similar difference was found at 100 weeks [aflibercept group (81%) and ranibizumab group (66%), a 15.3% difference (95% CI 4.9% to 25.7%)], but a difference between the bevacizumab and ranibizumab groups was found only at week 24 (−18.7%, 95% CI −30.1% to −7.4%) (*Figure 13*).

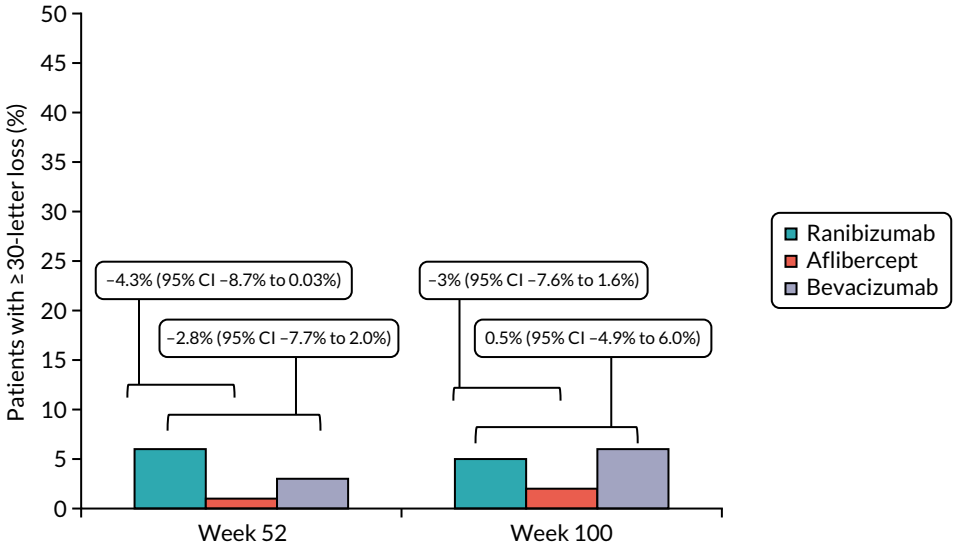

FIGURE 11 Percentage of participants per group with loss of ≥ 30 ETDRS letters at 52 and 100 weeks.

TABLE 7 Categorical visual acuity outcomes by treatment group

Outcome	Trial group, % (*n*/*N*)			Difference in proportions (95% CI)	
	Ranibizumab	Aflibercept	Bevacizumab	Aflibercept vs. ranibizumab	Bevacizumab vs. ranibizumab
Participants with ≥ 73 ETDRS letters (> 6/12 Snellen equivalent) at 100 weeks	47 (63/135)	44 (59/133)	41 (57/139)	−2.3 (−14.2 to 9.6)	−5.7 (−17.4 to 6.1)
Participants with ≤ 58 ETDRS letters (≤ 6/24 Snellen equivalent) at 100 weeks	29 (39/135)	20 (26/133)	30 (42/139)	−9.3 (−19.5 to 0.9)	1.3 (−9.5 to 12.1)
Participants with < 19 ETDRS letters (< 3/60 Snellen equivalent) at 100 weeks	3 (4/135)	2 (2/133)	4 (6/139)	−1.5 (−5.0 to 2.1)	1.4 (−3.1 to 5.8)
Participants with ≥ 73 ETDRS letters (> 6/12 Snellen equivalent) at 52 weeks	42 (59/139)	42 (59/139)	39 (53/135)	0 (−11.6 to 11.6)	−3.2 (−14.8 to 8.4)
Participants with ≤ 58 ETDRS letters (≤ 6/24 Snellen equivalent) at 52 weeks	28 (39/139)	25 (35/139)	24 (32/135)	−2.9 (−13.3 to 7.5)	−4.4 (−14.7 to 6.0)
Participants with < 19 ETDRS letters (< 3/60 Snellen equivalent) at 52 weeks	4 (5/139)	1 (2/139)	4 (5/135)	−2.2 (−5.8 to 1.5)	0.1 (−4.3 to 4.5)

TABLE 8 Visual acuity outcomes stratified by baseline visual acuity

Visual acuity	Mean (SE) at screening		Mean (SE) at 100 weeks		Adjusted difference between groups (95% CI)
	Aflibercept	*Ranibizumab*	*Aflibercept*	*Ranibizumab*	
Aflibercept vs. ranibizumab ITT[a]					p = *0.91*[b]
BCVA≤ 38 letters	27.3 (1.2)	27.9 (1.1)	59.4 (4.2) (*n* = 25)	55.1 (3.9) (*n* = 30)	3.3 (−6.8 to 13.4)
BCVA 39–58 letters	51.2 (0.8)	51.3 (0.7)	65.8 (2.6) (*n* = 48)	65.2 (2.8) (*n* = 45)	−0.5 (−8.0 to 7.0)
BCVA 59–78 letters	66.4 (0.6)	66.5 (0.5)	74.2 (1.8) (*n* = 60)	71.2 (2.3) (*n* = 60)	4.2 (−2.4 to 10.7)
Aflibercept vs. ranibizumab per protocol[c]					p = *0.97*[b]
BCVA ≤ 38 letters	28.7 (1.0)	27.9 (1.1)	61.7 (4.3) (*n* = 22)	54.9 (4.1) (*n* = 29)	5.3 (−5.1 to 15.7)
BCVA 39–58 letters	51.1 (0.8)	51.5 (0.7)	67.2 (2.6) (*n* = 46)	65.2 (2.8) (*n* = 45)	2.0 (−5.4 to 9.5)
BCVA 59–78 letters	66.4 (0.6)	66.6 (0.6)	74.2 (1.8) (*n* = 60)	71.5 (2.4) (*n* = 59)	4.0 (−2.5 to 10.4)
	Bevacizumab	*Ranibizumab*	*Bevacizumab*	*Ranibizumab*	
Bevacizumab vs. ranibizumab ITT[a]					p = *0.81*[b]
BCVA ≤ 38 letters	28.8 (1.1)	27.9 (1.1)	53.8 (4.7) (*n* = 23)	55.1 (3.9) (*n* = 30)	−2.8 (−12.9 to 7.3)
BCVA 39–58 letters	52.5 (0.7)	51.3 (0.7)	64.9 (2.3) (*n* = 50)	65.2 (2.8) (*n* = 45)	−2.3 (−9.7 to 5.2)
BCVA 59–78 letters	65.5 (0.6)	66.5 (0.5)	68.2 (2.7) (*n* = 66)	71.2 (2.3) (*n* = 60)	−1.0 (−7.5 to 5.5)
Bevacizumab vs. ranibizumab per protocol[c]					p = *0.82*[b]
BCVA ≤ 38 letters	28.8 (1.1)	27.9 (1.1)	53.8 (4.7) (*n* = 23)	54.9 (4.1) (*n* = 29)	−2.6 (−12.6, 7.3)
BCVA 39–58 letters	52.5 (0.7)	51.5 (0.7)	64.9 (2.3) (*n* = 50)	65.2 (2.8) (*n* = 45)	−2.2 (−9.6, 5.2)
BCVA 59–78 letters	65.6 (0.6)	66.6 (0.6)	68.2 (2.7) (*n* = 66)	71.5 (2.4) (*n* = 59)	−1.1 (−7.5, 5.4)

SE, standard error.
a The LME model incorporates 454 participants (ranibizumab, *n* = 148; aflibercept, *n* = 153; and bevacizumab, *n* = 153).
b *p*-value from interaction test for differential effect between subgroup categories.
c The LME model incorporates 443 participants (ranibizumab, *n* = 145; aflibercept, *n* = 146; and bevacizumab, *n* = 152).

Injection number

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By 100 weeks, ranibizumab group participants had received a mean of 11.8 injections, compared with 10.0 injections for the aflibercept group and 11.5 injections for the bevacizumab group. The difference between the aflibercept and ranibizumab groups was meaningful as early as week 24 [mean difference: −0.4 at week 24 (95% CI −0.6 to −0.2); −1.1 at week 52 (95% CI −1.6 to −0.5); and −1.9 at week 100 (95% CI −2.9 to −0.8)] (*Figure 14*).

Post hoc bevacizumab versus aflibercept analysis

After being approved by the DMEC, a post hoc analysis was unable to demonstrate that bevacizumab was non-inferior to aflibercept in the ITT analysis at 52 weeks (adjusted mean difference −1.35 letters, 95% CI −5.29 to 2.59 letters) or at 100 weeks (adjusted mean BCVA difference was −3.96 letters, 95% CI −8.34 to 0.42 letters; $p = 0.32$). The results of the per-protocol analysis were similar. At 100 weeks, there was a significant difference of 1.6 (95% CI 0.5 to 2.7) between the mean number of injections received by participants randomised to bevacizumab and the mean number received by those randomised to aflibercept.

TABLE 9 Visual acuity outcomes stratified by disease duration at baseline

Disease duration	Mean (SE) at screening		Mean (SE) at 100 weeks		Adjusted difference between groups (95% CI)
	Aflibercept	***Ranibizumab***	***Aflibercept***	***Ranibizumab***	
Aflibercept vs. ranibizumab ITT[a]					p = *0.14*[b]
CRVO < 3 months	54.4 (1.4)	53.9 (1.3)	68.2 (1.7) (*n* = 113)	66.5 (1.9) (*n* = 116)	0.8 (−3.9 to 5.6)
CRVO ≥ 3 months	52.6 (2.5)	51.5 (3.3)	69.3 (3.2) (*n* = 20)	60.6 (3.9) (*n* = 19)	10 (−1.3 to 21.4)
Aflibercept vs. ranibizumab per protocol[c]					p = *0.21*[b]
CRVO < 3 months	55.5 (1.3)	54.0 (1.4)	69.5 (1.7) (*n* = 108)	66.6 (1.9) (*n* = 114)	2.2 (−2.5 to 7.0)
CRVO ≥ 3 months	52.6 (2.5)	51.5 (3.3)	69.3 (3.2) (*n* = 20)	60.6 (3.9) (*n* = 19)	10.0 (−1.1 to 21.2)
	Bevacizumab	***Ranibizumab***	***Bevacizumab***	***Ranibizumab***	
Bevacizumab vs. ranibizumab ITT[a]					p = *0.33*[b]
CRVO < 3 months	55.0 (1.2)	53.9 (1.3)	65.5 (1.8) (*n* = 127)	66.5 (1.9) (*n* = 116)	−1.2 (−5.8 to 3.5)
CRVO ≥ 3 months	49.5 (4)	51.5 (3.3)	54.9 (5.2) (*n* = 12)	60.6 (3.9) (*n* = 19)	−7.9 (−20.8 to 5)
Bevacizumab vs. ranibizumab per protocol[c]					p = *0.32*[b]
CRVO < 3 months	55.0 (1.2)	54 (1.4)	65.5 (1.8) (*n* = 127)	66.6 (1.9) (*n* = 114)	−1.1 (−5.7 to 3.6)
CRVO ≥ 3 months	49.5 (4.2)	51.5 (3.3)	54.9 (5.2) (*n* = 12)	60.6 (3.9) (*n* = 19)	−7.9 (−20.7 to 4.8)

SE, standard error.
a The LME model incorporates 454 participants (ranibizumab, *n* = 148; aflibercept, *n* = 153; and bevacizumab, *n* = 153).
b *p*-value from interaction test for differential effect between subgroup categories.
c The LME model incorporates 443 participants (ranibizumab, *n* = 145; aflibercept, *n* = 146; and bevacizumab, *n* = 152).

TABLE 10 Visual acuity outcomes stratified by ischaemic or non-ischaemic CRVO at baseline

Ischaemic or non-ischaemic CRVO	Mean (SE) at screening		Mean (SE) at 100 weeks		Adjusted difference between groups (95% CI)
	Aflibercept	***Ranibizumab***	***Aflibercept***	***Ranibizumab***	
Aflibercept vs. ranibizumab ITT[a]					p = *0.15*[b]
Non-ischaemic CRVO	55.9 (1.2)	55.1 (1.2)	68.5 (1.7) (*n* = 115)	66.3 (1.8) (*n* = 122)	1.1 (−3.6 to 5.9)
Ischaemic CRVO	41.3 (3.8)	41.6 (4.1)	67.3 (3.6) (*n* = 18)	59.3 (6.5) (*n* = 13)	11.2 (−1.9 to 24.3)
Aflibercept vs. ranibizumab per protocol[c]					p = *0.25*[b]
Non-ischaemic CRVO	56.8 (1.2)	55.2 (1.3)	69.8 (1.6) (*n* = 111)	66.4 (1.8) (*n* = 120)	2.7 (−2.0 to 7.4)
Ischaemic CRVO	42.7 (3.7)	40.8 (4.3)	67.4 (3.8) (*n* = 17)	59.3 (6.5) (*n* = 13)	10.8 (−2.2 to 23.8)
	Bevacizumab	***Ranibizumab***	***Bevacizumab***	***Ranibizumab***	
Bevacizumab vs. ranibizumab ITT[a]					p = *0.85*[b]
Non-ischaemic CRVO	55.5 (1.2)	55.1 (1.2)	65.3 (1.8) (*n* = 121)	66.3 (1.8) (*n* = 122)	−1.7 (−6.4 to 3.0)
Ischaemic CRVO	47.2 (3.7)	41.6 (4.1)	60.2 (5.9) (*n* = 18)	59.3 (6.5) (*n* = 13)	−0.4 (−13.4 to 12.7)
Bevacizumab vs. ranibizumab per protocol[c]					p = *0.73*[b]
Non-ischaemic CRVO	55.6 (1.2)	55.2 (1.3)	65.3 (1.8) (*n* = 121)	66.4 (1.8) (*n* = 120)	−1.8 (−6.4 to 2.9)
Ischaemic CRVO	46.5 (3.8)	40.8 (4.3)	60.2 (5.9) (*n* = 18)	59.3 (6.5) (*n* = 13)	0.6 (−12.3 to 13.6)

SE, standard error.
a The LME model incorporates 454 participants (ranibizumab, *n* = 148; aflibercept, *n* = 153; and bevacizumab, *n* = 153).
b *p*-value from interaction test for differential effect between subgroup categories.
c The LME model incorporates 443 participants (ranibizumab, *n* = 145; aflibercept, *n* = 146; and bevacizumab, *n* = 152).

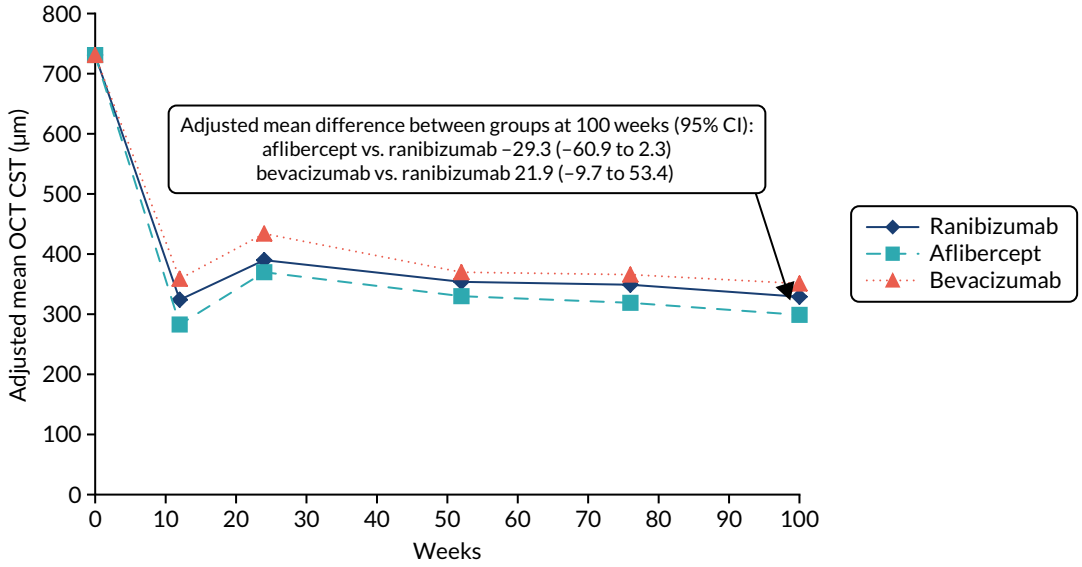

FIGURE 12 Adjusted mean OCT CST across groups to 100 weeks. Reproduced from Hykin *et al.*[2] This is an open access article distributed under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium. This includes minor additions and formatting changes to the original.

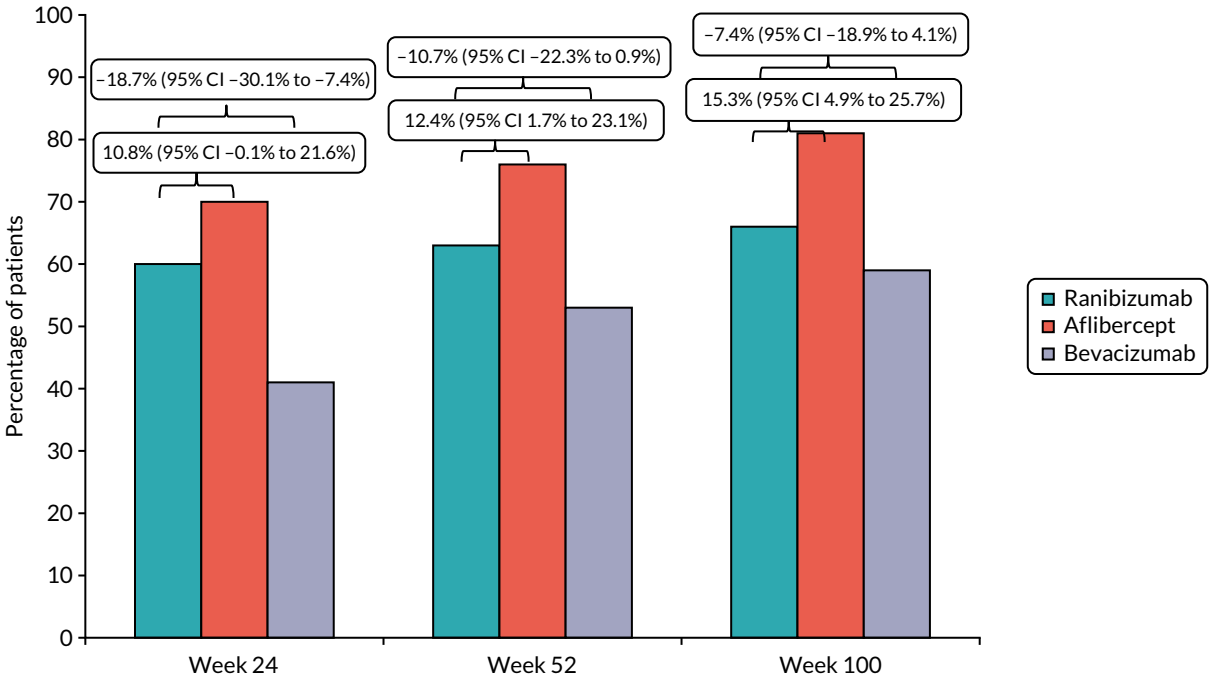

FIGURE 13 Percentage of participants with OCT CST of < 320 µm at 24, 52 and 100 weeks. Reproduced from Hykin *et al.*[2] This is an open access article distributed under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium. This includes minor additions and formatting changes to the original.

Retinal imaging

Optical coherence tomography imaging

The OCT morphological grading for MO, subretinal detachment and vitreomacular interface abnormality was available for 456 (98.4%) and 396 (85.5%) participants at baseline and week 100, respectively, and showed no difference for any parameter across treatment arms in prevalence or change with time. Across all subgroups, the percentage of participants with any MO and subretinal detachment at baseline had decreased significantly by week 52, and by 75% at week 100 (*Table 11*).

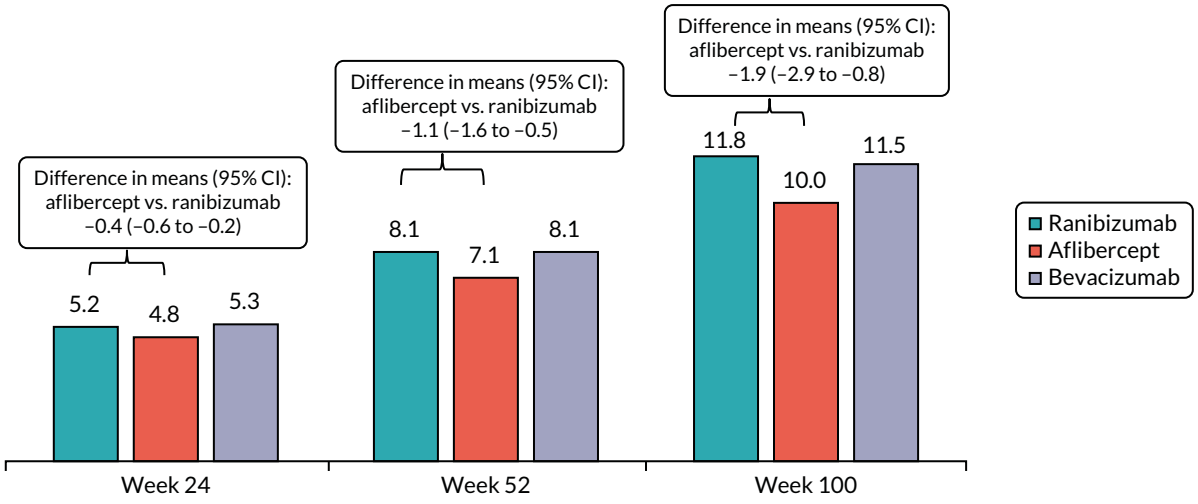

FIGURE 14 Mean number of injections across treatment groups by weeks 24, 52 and 100. Reproduced from Hykin *et al.*[2] This is an open access article distributed under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium. This includes minor additions and formatting changes to the original.

TABLE 11 The OCT anatomical outcomes for MO, subretinal fluid and vitreomacular traction abnormality, by treatment group

Outcome	All	Ranibizumab	Aflibercept	Bevacizumab
MO				
Baseline				
Null (*n*)	7	3	1	3
No evidence, *n* (%)	5 (1)	2 (1)	2 (1)	1 (1)
Diffuse, *n* (%)	19 (4)	8 (5)	8 (5)	3 (2)
Cystic, *n* (%)	90 (20)	25 (16)	33 (22)	32 (21)
Mixed, *n* (%)	342 (75)	117 (77)	110 (72)	115 (76)
Week 52				
Null (*n*)	53	21	13	19
No evidence, *n* (%)	147 (36)	56 (42)	62 (44)	29 (21)
Diffuse, *n* (%)	64 (16)	18 (13)	24 (17)	22 (16)
Cystic, *n* (%)	103 (25)	27 (20)	35 (25)	41 (30)
Mixed, *n* (%)	96 (23)	33 (25)	20 (14)	43 (32)
Week 100				
Null (*n*)	67	22	24	21
No evidence, *n* (%)	150 (38)	55 (41)	59 (45)	36 (27)
Diffuse, *n* (%)	55 (14)	17 (13)	19 (15)	19 (14)
Cystic, *n* (%)	87 (22)	26 (20)	29 (22)	32 (24)
Mixed, *n* (%)	104 (26)	35 (26)	23 (18)	46 (35)

continued

TABLE 11 The OCT anatomical outcomes for MO, subretinal fluid and vitreomacular traction abnormality, by treatment group (*continued*)

Outcome	All	Ranibizumab	Aflibercept	Bevacizumab
Subretinal detachment				
Baseline				
Null (*n*)	26	9	8	9
No evidence, *n* (%)	126 (29)	39 (27)	45 (31)	42 (29)
Questionable, *n* (%)	9 (2)	6 (4)	1 (1)	2 (1)
Definite, *n* (%)	196 (43)	62 (41)	63 (41)	71 (48)
Week 52				
Null (*n*)	55	22	13	20
No evidence, *n* (%)	352 (86)	113 (85)	124 (88)	115 (86)
Questionable, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)
Definite, *n* (%)	56 (14)	20 (15)	17 (12)	19 (14)
Week 100				
Null (*n*)	67	22	24	21
No evidence, *n* (%)	342 (86)	118 (89)	111 (85)	113 (85)
Questionable, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)
Definite, *n* (%)	54 (14)	15 (11)	19 (15)	20 (15)
Vitreomacular interface abnormality				
Baseline				
Null (*n*)	9	3	1	5
No evidence, *n* (%)	250 (55)	87 (57)	88 (58)	75 (50)
Questionable, *n* (%)	8 (2)	3 (2)	2 (1)	3 (2)
Definite, *n* (%)	196 (43)	62 (41)	63 (41)	71 (48)
Week 52				
Null (*n*)	53	21	13	19
No evidence, *n* (%)	221 (54)	73 (54)	76 (54)	72 (53)
Questionable, *n* (%)	4 (1)	0 (0)	3 (2)	1 (1)
Definite, *n* (%)	185 (45)	61 (46)	62 (44)	62 (46)
Week 100				
Null (*n*)	67	22	24	21
No evidence, *n* (%)	219 (55)	74 (56)	77 (59)	68 (51)
Questionable, *n* (%)	9 (2)	4 (3)	4 (3)	1 (1)
Definite, *n* (%)	168 (42)	55 (41)	49 (38)	64 (48)

Notes
Null = not available because participant withdrew or image was not taken or not saved. Ungradable = grader was unable to grade because of poor image quality or feature(s) obscured (e.g. by overlying MO).

Spectral-domain OCT (Spectralis) image grading was undertaken for additional parameters, including DRIL, COST visibility loss, EZ disruption, loss of ELM integrity and presence of intraretinal HRF. Of 463 participants, 337 were enrolled at sites where Spectralis OCT was available; of these participants, 267 had gradable images at baseline and at weeks 52 and 100 (*Table 12*). There was no difference in the prevalence of any parameter across treatment groups at any time point. In all treatment groups, DRIL was observed to decrease, and the ELM, EZ and COST retinal layers became better defined with time. This may have

TABLE 12 Morphological grading of novel OCT parameters

		Trial group, *n* (%)		
	All (*N* = 267), *n* (%)	**Ranibizumab (*N* = 92)**	**Aflibercept (*N* = 89)**	**Bevacizumab (*N* = 86)**
DRIL				
Baseline				
Absent	86 (32)	30 (33)	31 (35)	25 (29)
Present	149 (56)	51 (55)	48 (54)	50 (58)
Ungradable	32 (12)	11 (12)	10 (11)	11 (13)
Week 52				
Absent	189 (71)	71 (76)	60 (67)	58 (68)
Present	61 (23)	18 (19)	21 (24)	22 (26)
Ungradable	17 (6)	4 (4)	8 (9)	5 (6)
Week 100				
Absent	178 (67)	60 (65)	61 (69)	57 (66)
Present	68 (25)	23 (25)	24 (27)	21 (24)
Ungradable	21 (8)	9 (10)	4 (4)	8 (9)
HRF				
Baseline				
Absent	62 (23)	24 (26)	20 (22)	18 (21)
Present	204 (76)	68 (74)	68 (76)	68 (79)
Ungradable	1 (0)	0 (0)	1 (1)	0 (0)
Week 52				
Absent	132 (49)	49 (53)	42 (47)	41 (48)
Present	135 (51)	44 (47)	47 (53)	44 (52)
Ungradable	0 (0)	0 (0)	0 (0)	0 (0)
Week 100				
Absent	96 (36)	30 (33)	39 (44)	27 (31)
Present	168 (63)	62 (67)	48 (54)	58 (67)
Ungradable	3 (1)	0 (0)	2 (2)	1 (1)
ELM				
Baseline				
Intact	66 (25)	20 (22)	24 (27)	22 (26)
Not intact	44 (16)	17 (18)	18 (20)	9 (10)
Ungradable	157 (59)	55 (60)	47 (53)	55 (64)

continued

TABLE 12 Morphological grading of novel OCT parameters (*continued*)

	All (*N* = 267), *n* (%)	Trial group, *n* (%)		
		Ranibizumab (*N* = 92)	Aflibercept (*N* = 89)	Bevacizumab (*N* = 86)
Week 52				
Intact	198 (74)	71 (76)	62 (70)	65 (76)
Not intact	50 (19)	18 (19)	20 (22)	12 (14)
Ungradable	19 (7)	4 (4)	7 (8)	8 (9)
Week 100				
Intact	200 (75)	69 (75)	67 (75)	64 (74)
Not intact	49 (18)	19 (21)	16 (18)	14 (16)
Ungradable	18 (7)	4 (4)	6 (7)	8 (9)
EZ *Baseline*				
Intact	46 (17)	15 (16)	18 (20)	13 (15)
Not intact	61 (23)	21 (23)	21 (24)	19 (22)
Ungradable	160 (60)	56 (61)	50 (56)	54 (63)
Week 52				
Intact	174 (65)	64 (69)	54 (61)	56 (66)
Not intact	75 (28)	25 (27)	29 (33)	21 (25)
Ungradable	18 (7)	4 (4)	6 (7)	8 (9)
Week 100				
Intact	172 (64)	57 (62)	61 (69)	54 (63)
Not intact	75 (28)	30 (33)	22 (25)	23 (27)
Ungradable	20 (7)	5 (5)	6 (7)	9 (10)
COSTs *Baseline*				
Intact	16 (6)	8 (9)	5 (6)	3 (3)
Not intact	78 (29)	23 (25)	31 (35)	24 (28)
Ungradable	173 (65)	61 (66)	53 (60)	59 (69)
Week 52				
Intact	54 (20)	13 (14)	25 (28)	16 (19)
Not intact	170 (64)	64 (69)	53 (60)	53 (62)
Ungradable	43 (16)	16 (17)	11 (12)	16 (19)
Week 100				
Intact	65 (24)	17 (18)	25 (28)	23 (27)
Not intact	169 (63)	66 (72)	53 (60)	50 (58)
Ungradable	33 (12)	9 (10)	11 (12)	13 (15)

represented better visualisation with time, as MO decreased, rather than a specific reconstitution of the parameter. Further investigation and correlation of these findings with visual outcomes will be the subject of a further publication.

Fundus fluorescein angiography image analysis

Of 463 participants at baseline, 461 underwent FFA. At 100 weeks, 407 completed the ITT analysis; 377 underwent FFA, and 30 did not because they declined or had experienced an adverse reaction to the dye at baseline or there were intravenous cannulation/technical difficulties. Of the 377 participants who underwent FFA, 53 could not be graded for other reasons (e.g. the participant had received panretinal photocoagulation before or during the trial), and for 14 participants all images were ungradable, leaving 310 participants with gradable images (*Table 13*). The percentages of participants in each arm with two-step, or more, worsening in one or more quadrants appeared more frequent in the aflibercept group than in the bevacizumab group, but, as the number of affected quadrants increased, the result across groups tended to converge. Overall, the data showed no meaningful difference between treatment groups in terms of the number of participants with at least two-step worsening of non-perfusion in one or more quadrants.

The novel concentric ring method for analysing non-perfusion in disc areas, developed by the LEAVO team during the trial, was applicable to 235 of 463 participants randomised who underwent wide-angled Optos FFA. Of these, 184 had images successfully performed at both entry and exit; among these, 31 eyes were poor-quality images either at baseline or at exit. This left 153 gradable images that were converted into disc areas of non-perfusion and form the basis of the comparison between trial groups (*Tables 14* and *15*).

The median value of baseline non-perfusion for all participants was 28.6 disc areas (IQR 10.4–47.4 disc areas), mostly in the peripheral retina. There was more non-perfusion in the periphery and, notably, in the posterior pole in the ranibizumab (19%) and aflibercept (19%) groups than in the bevacizumab (2%) group. This baseline imbalance between groups was seen at week 100, particularly in the percentage of participants showing an increase in posterior non-perfusion, which may simply reflect higher baseline non-perfusion and, therefore, greater likelihood of progressing. A detailed appraisal of these data is currently being undertaken and will form the basis of a further report.[83]

Treatment allocation guess form

The optometrists assessing primary outcomes provided a response on the treatment allocation guess form for 409 of their 463 participants: for 356, they said they did not know; for 53, they made a guess, and were correct in 18 instances, which is consistent with chance. Of the 409 participants, 406 provided a response: 386 did not know and 20 made a guess, of whom eight [i.e. 2% (8/406)] guessed correctly, which is consistent with chance.

TABLE 13 Change in capillary non-perfusion based on FFA image characteristics available at baseline and week 100

	Trial group, *n* (%)		
Sectors with two-step, or more, capillary non-perfusion worsening (*n*)	**Ranibizumab (*N* = 105)**	**Aflibercept (*N* = 96)**	**Bevacizumab (*N* = 109)**
0	73 (70)	62 (65)	86 (79)
1	11 (10)	18 (19)	9 (8)
2	8 (8)	6 (6)	4 (4)
3	5 (5)	4 (4)	3 (3)
4	4 (4)	1 (1)	1 (3)
5	1 (1)	1 (1)	0 (0)
≥ 6	3 (3)	4 (4)	6 (6)

TABLE 14 Amount of retinal non-perfusion per arm

	Amount of retinal non-perfusion, median (IQR)							
	All (*N* = 153)		Ranibizumab (*N* = 57)		Aflibercept[a] (*N* = 48)		Bevacizumab (*N* = 48)	
Retinal area	Cells	Disc areas	Cells	Disc areas	Cells	Disc areas	Cells	Disc areas
Baseline								
Total area	3 (1 to 5)	28.6 (10.4 to 47.4)	2.5 (1 to 5.3)	24.6 (8.0 to 49.6)	3.3 (1.6 to 5)	30.2 (16.4 to 48.7)	3 (0.9 to 4.5)	28.9 (8.6 to 44.4)
Posterior (M + R1)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
% (*n*) subjects with posterior > 0	14 (21)	14 (21)	19 (11)	19 (11)	19 (9)	19 (9)	2 (1)	2 (1)
Peripheral (R2–R4)	3 (1 to 5)	28.4 (10.4 to 47.4)	2.5 (0.8 to 5)	24.6 (7.3 to 49.1)	3 (1.6 to 5)	30.2 (16.2 to 48.7)	3 (0.9 to 4.5)	28.9 (8.6 to 44.4)
Week 100								
Total area	3 (1.5 to 6)	30.2 (15.5 to 55.1)	2.5 (1.3 to 7)	25.0 (13.0 to 61.4)	3.8 (2 to 9.4)	37.0 (20.7 to 72.9)	3 (1 to 4.5)	30.2 (10.4 to 44.4)
Posterior (M + R1)	0 (0 to 0)	0 (0 to 0)	0 (0 to 1)	0 (0 to 4.4)	0 (0 to 1.9)	0 (0 to 5.5)	0 (0 to 0)	0 (0 to 0)
% (*n*) subjects with posterior > 0	22 (33)	22 (33)	26 (15)	26 (15)	29 (14)	29 (14)	8 (4)	8 (4)
Peripheral (R2–R4)	3 (1.5 to 5.5)	30.2 (15.1 to 51.1)	2.5 (1.3 to 6.3)	25.0 (11.9 to 59.1)	3.5 (2 to 7.5)	35.2 (20.7 to 69.6)	3 (1 to 4.5)	30.2 (10.4 to 44.4)
Change in total area	0.0 (–1.0 to 2.0)	0.0 (–5.4 to 16.0)	0.0 (–1.0 to 002.0)	0.0 (–9.1 to 15.6)	1.0 (–1.0 to 3.0)	4.7 (–2.0 to 24.3)	0.0 (–1.0 to 2.0)	0.0 (–9.3 to 15.9)
Change in posterior	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.8)	0.0 (0.0 to 1.5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
% (*n*) subjects with an increase in posterior	17 (26)	18 (27)	19 (11)	19 (11)	25 (12)	27 (13)	6 (3)	6 (3)
Change in peripheral	0.0 (–1.0 to 2.0)	0.0 (–7.1 to 15.8)	0.0 (–1.0 to 2.0)	0.0 (–9.9 to 15.8)	1.0 (1.0 to 2.0)	4.7 (0.0 to 18.0)	0.0 (–1.0 to 2.0)	0.0 (–9.3 to 15.9)

a Data were missing for one participant in the aflibercept arm at 100 weeks.

TABLE 15 Comparison of the changes from baseline in the amount of retinal non-perfusion between arms

	Difference in medians (95% CI)			
	Aflibercept – ranibizumab		Bevacizumab – ranibizumab	
Change from baseline	Cells	Disc areas	Cells	Disc areas
Change in total area	1.0 (0 to 2.0)	5.6 (0 to 14.1)	0.0 (–1.0 to 1.0)	0.0 (–7.8 to 6.0)
Participants with an increase in posterior (%)	6.0 (–9.7 to 22.0)	8.0 (–8.0 to 24.1)	–13.0 (–25.6 to 0.3)	–13.0 (–25.6 to 0.3)
Change in peripheral	1.0 (0 to 2.0)	5.6 (0 to 13.4)	0.0 (–1.0 to 1.0)	0.0 (–7.8 to 6.5)

Safety outcomes

There was one case of infectious endophthalmitis in a trial eye, which followed trabeculectomy bleb infection rather than intravitreal injection. The frequencies of all ocular AEs and Antiplatelet Trialists' Collaboration (APTC)-defined events were similar between trial arms (*Table 16*). At 52 weeks, the proportions of participants who were persistent non-responders (defined as not more than a 5-letter gain in visual acuity and an OCT CST decrease of < 50 µm after 24 weeks) were 1/139 for ranibizumab, 5/133 for aflibercept and 5/135 for bevacizumab; at 100 weeks, only one participant, in the bevacizumab group, was a non-responder. During the trial, 25 (5.4%) eyes developed an ischaemic CRVO, 13 (2.8%) developed anterior segment neovascularisation and 6 (1.3%) developed retinal neovascularisation, with no difference across arms (see *Table 16*).

TABLE 16 Ocular AEs and APTC events

		Trial arm, *n* (%)			Difference (95% CI) (%)	
AE	Total (*N* = 463), *n* (%)	Ranibizumab (*N* = 155)	Aflibercept (*N* = 154)	Bevacizumab (*N* = 154)	Aflibercept vs. ranibizumab	Bevacizumab vs. ranibizumab
Ocular AEs						
Infectious endophthalmitis	1 (0.2)	0 (0)	0 (0)	1 (0.6)	0.0 (–2.4 to 2.4)	–0.6 (–3.6 to 1.8)
Traumatic cataract	0 (0)	0 (0)	0 (0)	0 (0)	0.0 (–2.4 to 2.4)	0.0 (–2.4 to 2.4)
Retinal tear	1 (0.2)	1 (0.6)	0 (0)	0 (0)	–0.6 (–3.6 to 1.9)	–0.6 (–3.6 to 1.9)
Retinal detachment	3 (0.6)	0 (0)	1 (0.6)	2 (1.3)	0.6 (–1.8 to 3.6)	1.3 (–1.3 to 4.6)
Conversion to ischaemic CRVO	25 (5.4)	8 (5.2)	10 (6.5)	7 (4.5)	1.3 (–4.2 to 7.0)	–0.6 (–5.9 to 4.6)
Anterior segment neovascularisation	13 (2.8)	5 (3.2)	5 (3.2)	3 (1.9)	0.0 (–4.5 to 4.5)	–1.3 (–5.6 to 2.8)
Retinal neovascularisation	6 (1.3)	1 (0.6)	4 (2.6)	1 (0.6)	2.0 (–1.4 to 5.9)	0.0 (–3.0 to 3.0)
Vitreous haemorrhage	6 (1.3)	0 (0)	2 (1.3)	4 (2.6)	1.3 (–1.3 to 4.6)	2.6 (–0.2 to 6.5)
IOP elevation	27 (5.8)	13 (8.4)	9 (5.8)	5 (3.2)	–2.5 (–8.6 to 3.4)	–5.1 (–10.9 to 0.2)

continued

TABLE 16 Ocular AEs and APTC events (*continued*)

AE	Total (*N* = 463), *n* (%)	Trial arm, *n* (%)			Difference (95% CI) (%)	
		Ranibizumab (*N* = 155)	Aflibercept (*N* = 154)	Bevacizumab (*N* = 154)	Aflibercept vs. ranibizumab	Bevacizumab vs. ranibizumab
Systemic APTC events						
Cardiovascular – vascular deaths	5 (1.1)	2 (1.3)	2 (1.3)	1 (0.6)	0.0 (−3.4 to 3.4)	−0.6 (−4.0 to 2.4)
Cardiovascular – non-fatal MI	2 (0.4)	0 (0)	0 (0)	2 (1.3)	0.0 (−2.4 to 2.4)	1.3 (−1.3 to 4.6)
Cardiovascular – non-fatal stroke	6 (1.3)	2 (1.3)	4 (2.6)	0 (0)	1.3 (−2.4 to 5.3)	−1.3 (−4.6 to 1.3)

IOP, intraocular pressure; MI, myocardial infarction.

Eight ranibizumab, seven aflibercept and eight bevacizumab arm participants required panretinal photocoagulation. Two pregnancies were reported during the trial: one in a participant and one in the spouse of a participant. Both of these were followed to term with the delivery of normal neonates.

Systemic serious AEs occurred with an expected and similar frequency between groups (see *Table 16*), and there were no meaningful differences between groups in the frequency of AEs in the same body system (*Table 17*).

TABLE 17 Comparison between groups of serious AEs by body system

Body system	Total (*N* = 463), *n* (%)	Trial arm, *n* (%)		
		Ranibizumab (*N* = 155)	Aflibercept (*N* = 154)	Bevacizumab (*N* = 154)
Cardiovascular – other	31 (6.7)	8 (5.2)	14 (9.1)	9 (5.8)
Respiratory	20 (4.3)	4 (2.6)	6 (3.9)	10 (6.5)
Hepatic	1 (0.2)	1 (0.6)	0 (0)	0 (0)
Gastrointestinal	19 (4.1)	8 (5.2)	8 (5.2)	3 (1.9)
Genitourinary	13 (2.8)	2 (1.3)	7 (4.5)	4 (2.6)
Endocrinal	1 (0.2)	0 (0)	0 (0)	1 (0.6)
Haematological	1 (0.2)	0 (0)	1 (0.6)	0 (0)
Musculoskeletal	10 (2.2)	1 (0.6)	4 (2.6)	5 (3.2)
Neoplastic	4 (0.9)	0 (0)	1 (0.6)	3 (1.9)
Neurological	6 (1.3)	1 (0.6)	3 (1.9)	2 (1.3)
Psychiatric	2 (0.4)	1 (0.6)	0 (0)	1 (0.6)
Immunological	0 (0)	0 (0)	0 (0)	0 (0)
Dermatological	2 (0.4)	0 (0)	2 (1.3)	0 (0)
Allergies	1 (0.2)	0 (0)	1 (0.6)	0 (0)
Ophthalmological	9 (1.9)	3 (1.9)	3 (1.9)	3 (1.9)
Ear, nose and throat	1 (0.2)	0 (0)	0 (0)	1 (0.6)
Other	9 (1.9)	3 (1.9)	3 (1.9)	3 (1.9)

Comparison with Study of Comparative Treatments for Retinal Vein Occlusion 2 safety data

Although it was not possible to perform a safety meta-analysis because of the lack of comparative outcome data in CRVO, as described in *Chapter 2*, the data from SCORE2 during the initial comparative 6 months were compared with the safety data from the first 6 months of LEAVO (*Table 18*). A larger number of conversions to ischaemic CRVO were recorded in LEAVO than in SCORE2. This may have been because in LEAVO conversion to ischaemic CRVO was recorded as a direct question in each trial visit sheet; because of early enrolment in LEAVO compared with SCORE 2; and because of the treatment-naive status of most LEAVO participants at randomisation. There were more vitreous haemorrhages recorded in LEAVO than in SCORE2, and more vascular deaths recorded in SCORE2 than in LEAVO. The prevalence of these events was low and it was not thought that there were any meaningful differences between the two studies in the number or type of AEs.

TABLE 18 Comparison of LEAVO and SCORE2 AEs at 6 months

	LEAVO (*n*)			SCORE2 (*n*)	
Event	**Ranibizumab**	**Aflibercept**	**Bevacizumab**	**Aflibercept**	**Bevacizumab**
Trial eye					
Infectious endophthalmitis	0	0	1	–	–
Non-infectious endophthalmitis	0	0	0	0	1
Neovascular glaucoma	1	1	0	1	0
Conversion to ischaemic CRVO	8	6	6	1	0
Retinal detachment	0	1	1	0	1
Vitreous haemorrhage	0	2	4	0	1
APTC events					
Non-fatal MI	0	0	0	1	2
Non-fatal stroke	0	1	0	1	0
Vascular death	0	0	0	3	2
Excluding vascular death					
Death from any other cause	1	1	0	1	1
Ocular and systemic AEs, not limited to trial eye					
Participants with any AE	108	99	115	82	98
Total number of all AEs	301	337	323	184	263
Participants with any SAE	19	7	14	14	14
Total number of all SAEs	20	10	14	18	25

MI, myocardial infarction.

Patient and public involvement

The lay panel members co-developed the contents and wording of the questions in the following questionnaire.

1. Cost of the medication: if the cheaper medication Avastin was as good as Eylea and Lucentis in improving your vision, and as safe, would you be happy to be given Avastin for your affected eye?
2. Licensed medications: if the cheaper medication Avastin was as good as Eylea and Lucentis in improving your vision, and bearing in mind Avastin is as safe as the other two (see above), would you be concerned about taking Avastin because it had not been licensed by the UK MHRA (i.e. the UK regulatory body that approves new drugs for use in the UK)?
3. Effect of the medications: if the cheaper unlicensed medication Avastin was slightly better at improving vision in your affected eye than the licensed medications Eylea and Lucentis (e.g. an improvement of 2 letters on a visual acuity chart. There are 5 letters on each line, so the difference would be just less than half a line), under this circumstance, would you be happy to be given Avastin? If no, what would be the reason?
4. Effect of the medications: if the cheaper unlicensed medication Avastin was slightly less good at improving vision in your affected eye than the licensed medications Eylea and Lucentis (e.g. a loss of 2 letters on a visual acuity chart. There are 5 letters on each line, so the difference would be just less than half a line), would you be happy to be given Avastin?
5. Effect of the medications: if the cheaper unlicensed medication Avastin was slightly less good (i.e. if you closed your good eye you noticed a slight central blur in the affected eye when reading, but not when looking in the distance and not when using both eyes together), but you were still able to do all regular activities, such as drive, read books and magazines, work machinery, use power tools, would you be happy to be given Avastin?
6. Effect of the medications: if you were asked to commence treatment with Avastin, would you be more likely to agree to this if a licensed alternative (e.g. Eylea) was available that you could change over to if your response to the Avastin was less than expected?

The feedback regarding the final questionnaire content was positive (i.e. it was an important trial to have done, the text was easy to follow and the questions were clear). The results of the trial were under embargo pending publication at the time the questionnaire was sent to patients [$n = 22$: seven with a history of RVO (but not LEAVO participants), 15 with a history of diabetic eye disease and three regular lay panel members]. The results of the patient and public involvement LEAVO questionnaire are given in *Table 19*.

TABLE 19 Trial results: post-trial patient questionnaire feedback

	Question, *n* (%) responses					
Answer	**1**	**2**[a]	**3**	**4**	**5**	**6**
Yes	22 (100)	6 (27)	20 (91)	11 (50)	15 (68)	22 (100)
Maybe	0 (0)	2 (9)	2 (9)	3 (14)	1 (5)	0 (0)
No	0 (0)	13 (59)	0 (0)	8 (36)	6 (27)	0 (0)

a One nil response.

Chapter 4 Health economic evaluation

Introduction

Economic evaluation forms an important part of health technology assessments by evaluating the cost-effectiveness of interventions to determine whether or not they represent value for money. In England, NICE evaluates interventions through its technology appraisal and guidelines programmes. Each programme has a methods guide, which describes a reference case that should be used in cost-effectiveness analyses.[84,85] Our analyses use NICE's preferred methods in conjunction with other good practice guidelines[86,87] to evaluate the cost-effectiveness of intravitreal ranibizumab, aflibercept and bevacizumab for MO due to CRVO.

NICE's preferred method for cost-effectiveness analysis of interventions delivered in an NHS setting is cost–utility analysis (CUA).[84,85] CUA allows comparisons to be made between disease areas by using a common measure of outcome: cost per quality-adjusted life-year (QALY). QALYs combine morbidity and mortality by using a 'utility' to measure health-related quality of life (HRQoL). Utilities are anchored between 0 and 1, where 1 represents perfect health and 0 represents death (utilities of < 0 are permitted, reflecting health states considered to be worse than death).

A CUA is used to compare two or more interventions, using incremental analysis. The outcome of a CUA is an ICER, calculated by dividing the incremental (additional) costs by the incremental QALYs associated with the intervention. The incremental costs are calculated as the difference between the total costs for the intervention and the total costs for the comparator. The incremental QALYs are calculated as the difference between the total QALYs for the intervention and the total QALYs for the comparator.

The results of a CUA can be used in decision-making to determine whether or not interventions represent good value for money. The simplest decisions concern dominance. An intervention is said to 'dominate' the comparator (and the comparator is 'dominated') when the intervention leads to lower costs and more QALYs than the comparator. In this case, the decision to use the intervention instead of the comparator is clear, as it reduces costs and improves outcomes. In the situation in which an intervention is more costly and leads to more QALYs than the comparator, a decision rule is required to determine whether or not the gain in QALYs is worth the additional cost. In this case, the ICER can be compared with a threshold representing the maximum the funder is willing to pay for each additional QALY.

NICE does not have a specific threshold, but considers a range of maximum acceptable ICERs when deciding if an intervention is cost-effective. Interventions with ICERs of $<$ £20,000 per QALY are generally considered to be cost-effective, whereas decisions regarding interventions with ICERs of between £20,000 and £30,000 per QALY will need to consider additional factors such as uncertainty, innovation, whether or not the HRQoL benefits have been adequately captured, whether or not the treatment meets specific criteria for life-extending treatments at the end of life, and the non-health objectives of the NHS. At $>$ £30,000 per QALY, a stronger case is required for NICE to consider an intervention to be cost-effective.[84]

Overview of health economic evaluation methods

Interventions

A full health economic evaluation was conducted, comparing three interventions for MO due to CRVO using data collected as part of LEAVO. The interventions were as follows:

- Interventions (investigational treatments) –
  - Arm A, treatment: an intravitreal injection of aflibercept (2.0 mg/0.05 ml) administered at baseline and at 4, 8 and 12 weeks as a mandated injection. From week 16 to week 96, treatment was given if one or more re-treatment criteria were met, as specified in the trial protocol.[88] Beyond the 100-week trial period, injections were given based on treatment continuation rules.
  - Arm B, treatment: an intravitreal injection of bevacizumab (1.25 mg/0.05 ml) administered at baseline and at 4, 8 and 12 weeks as a mandated injection. From week 16 to week 96, treatment was given if one or more re-treatment criteria were met. Beyond the 100-week trial period, injections were given based on treatment continuation rules.
- Comparator (standard care) –
  - Arm C, control: an intravitreal injection of ranibizumab (0.5 mg/0.05 ml) administered at baseline and at 4, 8 and 12 weeks as a mandated injection. From week 16 to week 96, treatment was given if one or more re-treatment criteria were met. Beyond the 100-week trial period, injections were given based on treatment continuation rules.

Method of economic evaluation

The economic evaluation comprises two parts: a model-based analysis (the primary analysis) and a within-trial analysis (the secondary analysis). The model-based analysis evaluates the three interventions over participants' lifetimes, extrapolating clinical outcomes beyond the trial period and relating these to costs and QALYs. The within-trial analysis evaluates the three interventions during the trial period using the individual patient-level cost and HRQoL data collected during the trial. The economic evaluation uses CUA. The methods for the economic evaluation were prespecified in health economic and decision-modelling analysis plan (and associated addendum) documents, prior to database lock.[89]

The within-trial analysis provides the short-term cost-effectiveness evidence using individual patient-level data on quality of life and costs; therefore, it avoids extrapolation uncertainty. The model-based analysis provides the long-term cost-effectiveness evidence (extrapolating outcomes and costs beyond the trial period); this is the preferred approach for resource allocation decision-making (in line with NICE's *Guide to Methods of Technology Appraisal 2013*[84]). To support the development of the economic model, a systematic literature review was undertaken to identify evidence to inform inputs and assumptions.

Settings

Perspective

The economic evaluation uses the NHS and Personal Social Services perspective, consistent with the NICE methods guides.[84,85] Included costs are those incurred by the NHS and Personal Social Services, and so include costs for health-care resource use and interventions. Societal costs, lost productivity and a patient's personal expenditure (e.g. travel costs) are excluded.

Discounting

Future costs and health outcomes are discounted to reflect time preference. The discount rate for both costs and QALYs is 3.5% per year, consistent with the NICE methods guides.[84,85]

Time horizon

The model-based analysis uses a lifetime horizon, calculating costs and QALYs until all modelled patients have died. The within-trial analysis uses the 100-week trial time horizon. NICE states that the time horizon should be 'long enough to reflect all important differences in costs or outcomes between the technologies being compared'[84] (© NICE 2013 *Guide to Methods of Technology Appraisal 2013*. Available from www.nice.org.uk/process/pmg9/. All rights reserved. Subject to Notice of rights). Using a lifetime horizon reflects the long-term differences between the interventions in terms of effectiveness, time on treatment/discontinuation, and safety outcomes.

Presentation of results

Incremental and pairwise analyses

The economic evaluation reports fully incremental analyses, consistent with the NICE methods guides,[84,85] and pairwise analyses, to allow the comparison of each pair of interventions. For the model-based analysis, the fully incremental analysis is presented in *Results: model-based analysis*, and the pairwise comparisons are presented in *Appendix 6*, *Tables 59–61*. For the within-trial analysis, pairwise comparisons are presented in *Results: within-trial analysis*, and the fully incremental analysis is presented in *Appendix 6*, *Table 66*.

Characterisation of uncertainty

The model-based and within-trial analyses each present a base-case analysis and scenario analyses using alternative settings. The base-case and scenario analyses from the model-based analysis use probabilistic sensitivity analysis to incorporate parameter uncertainty (see *Methods: within-trial analysis*). For deterministic results, see *Appendix 6*, *Table 58*.

The base-case and scenario analyses from the within-trial analysis use seemingly unrelated regression to consider the correlation between total costs and QALYs (see *Methods: within-trial analysis*), and the probabilistic sensitivity analysis is presented as an additional scenario using base-case settings (see *Results: within-trial analysis*).

Quality assurance

The model was developed by two economic modellers. When one economic modeller added coding or inputs to the model, the other modeller checked these to identify and resolve any errors. The model was debugged by following simulated patients throughout the model, and verifying that the model was picking up the correct inputs and that calculations were being performed as intended. Simulated patient histories for a sample of patients were reviewed to ensure face validity. Results were compared with those from previous models and the within-trial analysis to ensure external validity. The within-trial analysis was checked for face validity, and coding was checked for errors by a second health economist.

Overview of systematic literature review

Objectives

A systematic literature review was undertaken in line with current recommendations.[90,91] The aim of this review was to identify evidence to inform inputs and assumptions for the long-term (> 2 years) economic model of LEAVO. Data requirements for patients with MO secondary to CRVO who were treated with intravitreal injections of ranibizumab (0.5 mg/0.05 ml), aflibercept (2.0 mg/0.05 ml) and bevacizumab (1.25 mg/0.05 ml) comprised:

- relative clinical effectiveness and safety (including withdrawals and mortality)
- HRQoL estimates
- resource use and costs related to treatment, clinic visits, staffing and equipment

- presence of ischaemic CRVO at baseline
- prior treatment for CRVO at baseline
- trial eye OCT CST
- trial eye BCVA
- non-trial eye OCT CST
- non-trial eye BCVA
- new-onset MO
- injection frequency.

Methods

Literature searching

Eight electronic databases were searched: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, The Cochrane Library, the Health Technology Assessment (HTA) database, NHS Economic Evaluation Database (NHS EED), EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Web of Science. Searches were conducted on 28 June 2018, and the databases were searched from the date of inception to 28 June 2018. Additional searches included checking reference lists of relevant studies, grey literature searching and contacting authors.

Free-text terms and subject headings relating to the condition and interventions of interest were used to develop a search strategy (see *Appendix 6*, *Systematic literature review to support the long-term health economic model*). To identify systematic reviews, randomised trials, observational studies and economic studies (including quality-of-life studies), appropriate search filters were applied in selected databases.

Study selection, data extraction, critical appraisal and synthesis

Study selection was completed using a two-stage process based on prespecified eligibility criteria (see *Appendix 6*, *Table 35*). The titles and abstracts of retrieved records were screened. Potentially relevant full-text articles were then retrieved for detailed examination. Studies were considered for inclusion if they reported on patients with MO secondary to CRVO treated with selected anti-VEGFs [ranibizumab (Lucentis) (0.5 mg/0.05 ml), aflibercept (Eylea) (2.0 mg/0.05 ml) or bevacizumab (Avastin) (1.25 mg/0.05 ml) as a monotherapy, vs. a control, i.e. another active treatment or sham injection]. Prospective uncontrolled before-and-after studies were also reviewed for inclusion. Studies reporting the natural history of CRVO were also sought for inclusion.

Data relating to study characteristics, population characteristics, interventions administered and reported outcomes of interest were extracted into summary tables. After applying the rating of hierarchies of evidence of data sources for economic models[92] in study selection (see *Appendix 6*, *Table 55*), the most appropriate methodological quality checklist endorsed by the Critical Appraisal Skills Programme (CASP)[93] was used for quality assessment of the included studies. The methodological quality of individual studies was considered in study selection. Study selection, data extraction and critical appraisal were undertaken by one reviewer and checked by a second reviewer. Disagreements were resolved by discussion.

Tabular and narrative syntheses were completed because the clinical and methodological heterogeneity of included studies precluded meta-analysis of available evidence.

Results

A total of 1338 unique records were retrieved through literature searches and supplementary searching. Of these, three articles[24,34,94] provided evidence of limited relevance for informing or validating the LEAVO economic model (see *Appendix 6*, *Figure 26*). A summary of included studies is presented in *Table 20*. For a list of excluded studies with reasons, see *Appendix 6*, *Table 56*.[95]

TABLE 20 Summary of included studies in systematic review

Characteristic	Campochiaro *et al.*[34]	Novartis[94]	McIntosh *et al.*[24]
Study characteristics			
Sample size (CRVO): patients/eyes	32 patients	1048 patients • TN: 327 • TnN(R): 577 • TnN(other): 164	3271 eyes
Intervention(s)	IVR	IVR	N/A
Treatment schedule	TER	Not reported	N/A
Study name	RETAIN	LUMINOUS (NCT01318941)	N/A
Study design; setting	Non-RCT (open-label extension of CRUISE); USA	Non-RCT (observational, non-interventional, multicentre, open-label, single-arm study); 43 countries, 494 centres	Systematic review of various study types
Funding	Genentech, Inc., San Francisco, CA, USA	Novartis International AG	Allergan plc
Duration of follow-up (years)	4	5	3
Baseline characteristics			
Mean age (years)	66.9 (SD not reported)	69.7 (SD 12.32)	N/A
% female	Not reported	41.5%	N/A
Duration of CRVO at baseline (months)	4.6	12.6 (SD 20.2)	N/A
BCVA (letters)	50	44.7 (SD 23.88)	N/A
SD-OCT (μm), mean (SD)	639	463.5 (212.5)[a]	N/A
% of patients with ischaemic CRVO	Not reported	Not reported	N/A
VFQ-25 composite score	Not reported	73.0 (SD 20.62)	N/A
Previous ocular history	Not reported	• RVO (16.5%) • Glaucoma (10.4%) • Cataract operation (9.1%) • Cataract (6.0%)	N/A

continued

TABLE 20 Summary of included studies in systematic review (*continued*)

Characteristic	Campochiaro *et al.*[34]	Novartis[94]	McIntosh *et al.*[24]
Medical history	Not reported	Cardiovascular risk factor,[b] 4–61.3%	N/A
Outcomes			
Primary study outcomes	• Mean change in BCVA • Percentage of patients with resolution of MO	• Mean change in BCVA • Mean change in CRT • Ocular and systemic AEs	• Baseline visual acuity • Percentage of patients with MO at baseline • Development of neovascularisation, NVG and vitreous haemorrhage • Conversion of non-ischaemic CRVO to ischaemic CRVO • Rate of fellow eye involvement
Secondary outcomes	• Percentage of patients gaining or losing ≥ 15 letters from baseline • Percentage of patients with BCVA of ≥ 20/40 • Percentage of patients with BCVA of ≤ 20/200 • Mean change from baseline in CFT, measured by the ZEISS Stratus OCT Model 3000 (Insight Eye Equipment, St Louis, MO, USA) • Percentage of patients with CFT of ≤ 250 µm at each study visit • Ocular and systemic AEs	• Change in VFQ-25 scores from baseline • Number of injections • Number of visits and re-treatments • Time interval between injections • Reasons for re-treatment or treatment termination	Not reported
Quality assessment of included studies			
Evidence rating (Coyle and Lee[92])	4[c]	4;[c] 2 to 3;[d] 1[e]	3[d]
Methodological quality (CASP)	Unclear quality	Unclear quality	Good quality

Characteristic	Campochiaro *et al.*[34]	Novartis[94]			McIntosh *et al.*[24]
Results					
Visual acuity					
Mean BCVA from baseline	***Mean follow-up: 51.4 months***	***Month 24***	***Month 36***	***Month 48***	
% of participants with BVCA of ≥ 20/40	43.8	Not reported	Not reported	Not reported	Not reported
% of participants who gained ≥ 15 letters	53.1	28.1	Not reported	Not reported	
MO					
Mean retinal thickness	***Month 48 (CFT)***	***Month 24 (CRT)***	***Month 36 (CRT)***	***Month 48 (CRT)***	
	• All participants: 220.6 ($n = 28$) • Participants with resolved MO: 171.3 ($n = 13$) • Participants with unresolved MO: 263.4 ($n = 15$) • $p = 0.01$	• TN: 372.9 ($n = 32$) • TnN(R): 304.9 ($n = 45$) • TnN(other): 321.5 ($n = 19$)	• TN: 290.3 ($n = 7$) • TnN(R): 411.2 ($n = 11$) • TnN(other): 375.0 ($n = 2$)	• TN: not reported • TnN(R): not reported • TnN(other): not reported	Not reported
% of participants with CFT of ≤ 250 µm	All participants: 43.8% (14/32)	Not reported			Not reported
Resource use					
Mean number of injections per participant (ranibizumab), by time point					
Month 24	4.5	• TN: 5.5 • TnN(R): 5.5 • TnN(other): 6.2			Not reported
Month 36	3.6	• TN: 5.8 • TnN(R): 5.8 • TnN(other): 6.6			
Month 48	3.3	• TN: 5.8 • TnN(R): 5.8 • TnN(other): 6.7			

continued

TABLE 20 Summary of included studies in systematic review (*continued*)

Characteristic	Campochiaro *et al.*[34]	Novartis[94]	McIntosh *et al.*[24]
Total number of injections (ranibizumab)			
All participants	19.2 ($n = 32$ participants)	6224 ($n = 1048$ participants); approximately 3% were treated in both eyes	
Participants with resolved MO	28.5	Not reported	
Participants with unresolved MO	8.7		
Mean duration between consecutive injections (weeks)	Not reported	• All participants: 10.57 • TN: 9.28 • TnN(R): 11.12 • TnN(other): 11.61	
Number of visits	Not reported	11.6 visits by month 48	
Concomitant treatments	Scatter photocoagulation ($n = 2$)	37.1% (CRVO primary treated eye set) received ocular concomitant medications and significant non-drug therapies (not specified) 70.8% (CRVO safety set) received concurrent systemic medications and significant non-drug therapies (not specified)	

Characteristic	Campochiaro *et al.*[34]	Novartis[94]	McIntosh *et al.*[24]
AEs			
Ocular events	Four severe ocular AEs were reported (BRVO and CRVO patients)	All ocular AEs: 10.4% (109/1048) Ocular SAEs: 0.95% (10/1048) Ocular severe AEs: 1.05% (11/1050) Infectious endophthalmitis: not reported Retinal detachment: not reported Retinal (pigment epithelium) tear: not reported Anterior chamber reaction:[f] not reported Conjunctival haemorrhage: 0.57% (6/1048) Vitreous haemorrhage: 0.38% (4/1048) Cataract: 1.91% (20/1048) Glaucoma: 0.95% (10/1048) Ocular hypertension (raised intraocular pressure of > 21 mmHg): 0.57% (6/1048) Increased intraocular pressure: 0.86% (9/1048) Visual loss: 0.57% (6/1048) Retinal ischaemia: 0.19% (2/1048) Retinal neovascularisation: 0.19% (2/1048) MO: 0.57% (6/1048)	Not reported

continued

TABLE 20 Summary of included studies in systematic review (*continued*)

Characteristic	Campochiaro *et al.*[34]	Novartis[94]	McIntosh *et al.*[24]
Systemic AEs	13 severe systemic AEs were reported, including two deaths. Lack of clarity about the incidence of remaining systemic events in patients with CRVO	All systemic AEs: 10.69% (112/1048) Serious systemic AEs: 6.01% (63/1048) Severe systemic AEs: 3.82% (40/1048) Death: 1.53% (16/1048) Hospitalisation: not reported Non-ocular haemorrhage (gastrointestinal, pulmonary, other non-ocular bleeds): not reported Arterial thromboembolism: not reported Hypertension: 0.76% (8/1048) Myocardial infarction: not reported Cerebrovascular accident (stroke): 0.29% (3/1048) Transient ischaemic attack: 0.29% (3/1048) Systemic AEs, possibly related to ranibizumab and/or ocular injection: 0.29% (3/1048)	Not reported
HRQoL			
Change in HRQoL (VFQ-25 composite score) from baseline	Not reported	• Month 24: mean −8.3 (SD 15.47) • Month 36: median −49.3 (IQR −49 to −49)[g]	Not reported

Characteristic	Campochiaro *et al.*[34]	Novartis[94]	McIntosh *et al.*[24]
Natural history			
Baseline visual acuity	50.0 ETDRS letters	44.7 ETDRS letters	Initial visual acuity generally poor < (20/40) in all patients. Patients with ischaemic CRVO tend to have lower mean initial visual acuity (20/200) Generally, initial visual acuity decreases over time. Ischaemic CRVO is associated with lower subsequent visual acuity over time
Development and resolution of MO	Not reported	Not reported	MO resolution occurs in approximately 30–31% of non-ischaemic CRVO eyes by 15 months post occlusion MO resolves in up to 73% of ischaemic CRVO eyes by 15 months post occlusion
Development of NV	Not reported	Not reported	33% of non-ischaemic CRVO eyes develop NV by 12–15 months post occlusion Up to 20% of ischaemic CRVO eyes develop NV by 8 or 9 months post occlusion
Development of NVG	Not reported	Not reported	NVG develops in 23–60% of ischaemic CRVO eyes by 12–15 months post occlusion

continued

TABLE 20 Summary of included studies in systematic review (*continued*)

Characteristic	Campochiaro *et al.*[34]	Novartis[94]	McIntosh *et al.*[24]
Development of VH	Not reported	Not reported	VH develops in 10% of CRVO eyes by 9 months post occlusion
Conversion from non-ischaemic CRVO to ischaemic CRVO	Not reported	Not reported	Up to 27% of non-ischaemic CRVO eyes convert to ischaemic CRVO within 10 weeks–13 months post occlusion
Fellow eye involvement	Not reported	Not reported	Bilateral RVO is present in 0.4–43% of CRVO cases at presentation Within 3 years, 1.4% of patients with CRVO develop a CRVO in the fellow eye Within 30 months, 5% of patients with CRVO develop a BRVO in the fellow eye Within 1 year 5% of patients with CRVO develop any RVO in the fellow eye

BRVO, branch retinal vein occlusion; CFT, central foveal thickness; CRT, central retinal thickness; IVR, intravitreal ranibizumab; N/A, not applicable; NV, neovascularisation; RETAIN, extended follow-up of patients with macular edema due to bRanch rETinal vein occlusion or centrAl retinal veIn occlusioN previously treated with intravitreal ranibizumab; TER, treat-and-extend regimen; TN, treatment-naive eyes; TnN(R), treatment non-naive (ranibizumab) eye; TnN(other), treatment non-naive (other ocular treatments) eyes; VH, vitreous haemorrhage.

a Reported for primary treated eye.
b Includes hypertension (58.7–63.9%), hypercholesterolemia/hyperlipidaemia (23.9–37.0%), diabetes (18.8–24.8%) and obesity (7.6–15.3%).
c Relates to clinical effect sizes and AEs.
d Relates to baseline clinical data.
e Relates to resource use.
f Includes acute intraocular inflammation, uveitis (inflammation of the anterior chamber) and hypopyon.
g The analysis included one patient.

Included studies

None of the studies provided a head-to-head comparison of the clinical effectiveness outcomes of interest. Two non-randomised studies, the extended follow-up of patients with macular edema due to bRanch rETinal vein occlusion or centrAl retinal veIn occlusioN previously treated with intravitreal ranibizumab (RETAIN) study ($n = 32$ participants)[34] and the LUMINOUS study ($n = 1048$ participants),[94] provided long-term clinical effectiveness data for ranibizumab only. Participants in the RETAIN study had previously completed two pivotal multicentre US-based Phase III RCTs [CRUISE, for patients with CRVO, and RanibizumaB for the treatment of macular edema following bRAnch Retinal Vein Occlusion (BRAVO), for patients with BRVO][9,33,96] and a subsequent follow-up trial.[38] The mean follow-up period of the RETAIN study was 49.7 months (with a maximum follow-up of 60 months).[34] The LUMINOUS study was a 5-year international multicentre post-authorisation study ($n = 43$ countries, 494 centres) that evaluated the long-term effectiveness and safety of ranibizumab for all its indications in the real-world setting. Participants with CRVO made up 3.5% ($n = 1048$) of the entire study population of LUMINOUS ($n = 30,153$ patients). Evidence relating to the natural history for CRVO was obtained from a systematic review ($n = 31$ studies, 3271 eyes).[24]

Summary of findings

No clinical effectiveness evidence was identified relating to the long-term (i.e. > 2 years' follow-up) head-to-head comparison of intravitreal injections of ranibizumab (0.5 mg/0.05 ml), aflibercept (2.0 mg/0.05 ml) and bevacizumab (1.25 mg/0.05 ml) in patients with MO secondary to CRVO. There was extensive variation in the reporting and assessment of outcomes of interest.

Long-term visual outcomes were influenced by treatment schedules, CRVO subtype and MO resolution.[34,94] Monthly injections with ranibizumab provided an initial improvement in BCVA and MO resolution. However, this effect was reduced when treatment schedules were on an 'as-needed' basis or when follow-up intervals were less frequent.[34] Improved long-term outcomes were observed in patients with early MO resolution [resolved MO vs. unresolved MO at year 4: mean BCVA 73.2 ETDRS letters (20/32) vs. 56.1 ETDRS letters (20/80); mean central foveal thickness (CFT), 171.30 µm vs. 263.40 µm, respectively].[34] Less than 5% (30/1048) of patients provided relevant data for visual acuity outcomes beyond 2 years of follow-up in the LUMINOUS study. Therefore, the observed general trends in improved vision (gain of 10 or 15 letters in visual acuity, $n = 2$–8 patients; gain of > 10 letters or a final BCVA of ≥ 73 letters, $n = 1$ patient, at 48 months) and MO resolution [mean change from baseline −257.1 µm (SD 179.91 µm), $n = 7$ patients, at 36 months] need to be interpreted with caution.[34] No data were available for mean change from baseline visual acuity according to ETDRS letter categories (LUMINOUS) beyond month 24 for the entire population with CRVO.

Evidence relating to the risk of systemic and ocular AEs following long-term ranibizumab use was mixed because of inadequate sample sizes and inconsistent definitions and reporting. The review also found that most patients with CRVO present with MO.[24] Of the 32 patients enrolled in the RETAIN study, 14 experienced MO resolution (43.8%).[34] A statistically significant difference in change in CFT was noted between patients with resolved MO and those with unresolved MO (263.4 µm vs. 220.6 µm; $p = 0.01$). The authors reported that 'more than half still required an average of 6 injections during year 4 to control oedema, and only 25% of those patients had BCVA of 20/40 or better'.[34]

The mean number of injections of 0.5 mg of ranibizumab administered in RETAIN was 19.2 over 54 months of follow-up ($n = 28$ patients).[34] The mean number of injections per patient administered in years 2, 3 and 4 of the study was 4.5, 3.6 and 3.3, respectively. By contrast, the mean number of injections per patient was 5.9 in LUMINOUS, by month 48.[94] A total of 6224 ranibizumab injections were received by patients with CRVO.[94] Although the majority of patients received treatment in only one eye, an estimated 3% were treated in both eyes.[94] Differences in prior intravitreal treatment status did not influence the number of injections received between subgroups.

Available evidence suggests that, after 3 years of treatment, patients receiving ranibizumab tend to experience improved quality of life [VFQ-25 composite score change from baseline of 3.6 (SD 10.70)].

The LUMINOUS study[94] reflected real-world management to a greater degree than the RETAIN study.[34] This could explain the higher rate of withdrawals observed. For detailed results of the systematic review, see *Appendix 6*, *Tables 36–54* and *Figure 27*.

Conclusion

Overall, there was limited evidence to adequately compare the long-term clinical effectiveness and cost-effectiveness of anti-VEGFs used in the management of MO secondary to CRVO. Comparative long-term studies of available vascular therapies for patients with MO secondary to CVRO are needed to inform treatment choices. For a detailed report of this systematic review, see *Appendix 6, Systematic literature review to support the long-term health economic model*.

Methods: model-based analysis

Model design

A discrete event simulation is used for the health economic model. Discrete event simulations are structured around a set of mutually exclusive events and model the pathway of individual patients through those events according to the time at which each event happens. Each individual patient has specific characteristics that may influence which events happen and when. A patient's history through the model is recorded and can influence if and when future events happen. Events can occur at any time. Discrete event simulations are so named because they model a discrete sequence of events, but they operate in continuous time (rather than in discrete time intervals).

A discrete event simulation model has five key advantages in this application:

1. Health states are not required – each individual patient's visual acuity can be tracked over time on a continuous scale.
2. The trial eye and non-trial eye can be modelled separately using data on the change in visual acuity over time.
3. Each patient's history (previous visits and visual acuity) can be tracked, so the treatment continuation rule (see *Chapter 2*, *Treatment schedule*) from LEAVO can be used.
4. The follow-up visit times can be modelled by fixing the time to milestone visits and using the treatment continuation rule from LEAVO to determine other visit times.
5. Individual patients can have different baseline characteristics, to incorporate heterogeneity.

The model diagram is shown in *Figure 15*. The model was built and all analyses were run in Simul8 Professional Edition (SIMUL8 Corporation, Boston, MA, USA). Once a patient is simulated and has baseline characteristics and an intervention assigned, their times to events are set; these times may be fixed or sampled from a distribution. For times to each event, see *Model inputs*. The event with the shortest time is the next event that the patient experiences, at which point their characteristics, QALYs and costs are updated. The patient then waits until the next event. The model ends when either the patient has died or the model time horizon is reached. The process is repeated for a large number of patients, and the total costs and QALYs are calculated. The same patients are then simulated through the model again, but with a different intervention. The total costs and QALYs are compared for each intervention to calculate cost-effectiveness results.

At each model event, costs, utilities, total costs and QALYs are updated. Each model event (i.e. visit to ophthalmologist, ocular AE, withdrawal, new-onset MO in the non-trial eye, annual change in visual acuity, death, model end) is explained in more detail in the following subsections.

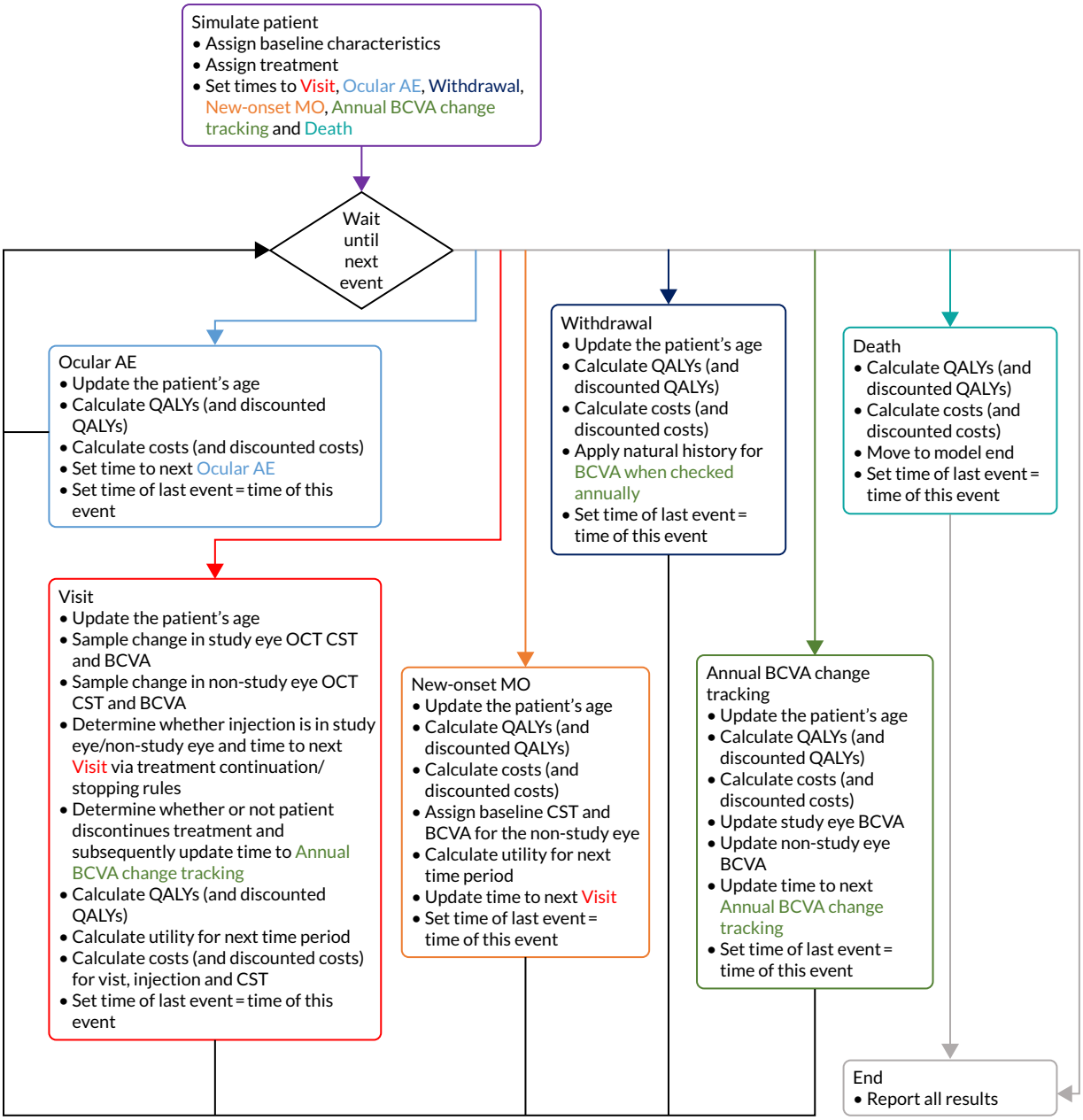

FIGURE 15 Health economic model structure. Reproduced with permission from Pennington *et al.*[95] This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Model events

Visit to ophthalmologist

When a modelled patient visits the ophthalmologist, their visual acuity (measured using BCVA letter score) and CST are updated in both eyes, and decision rules are used to determine whether or not the patient receives an anti-VEGF injection, and the time to their next visit.

Within the 100-week trial period, the model uses the same treatment continuation rules as specified in the LEAVO protocol:[88]

- All patients (except those who have withdrawn) attend visits and have a mandated injection at baseline and at 4, 8 and 12 weeks.
- All patients attend visits at weeks 16 and 20, but have an anti-VEGF injection only if their BCVA is > 83 letters and they meet one of the following the re-treatment criteria:
    - decrease in visual acuity of ≥ 6 letters between the previous and the current visit, attributed to an increase in OCT CST
    - increase in visual acuity of ≥ 6 letters between the previous and the current visit
    - an OCT CST of > 320 µm
    - an OCT CST increase of > 50 µm from the lowest previous visit.
- From weeks 24 to 96, the same re-treatment criteria as at weeks 16–20 are applied. If the patient does not meet the re-treatment criteria and was not treated at either of the two previous visits, the time to their next visit is increased from 4 weeks to 8 weeks.

Beyond the trial period, the treatment continuation rules are informed by advice from five clinicians involved in LEAVO (PH, SS, AL, YY and Michael Williams) and by guidance from the Royal College of Ophthalmologists.[8] The following rules are applied:

- If the patient has not had an injection since year 1, they do not receive an injection and do not visit the ophthalmologist again.
- Within the first 5 years, the same re-treatment criteria as used in LEAVO are applied to determine whether or not a patient has an injection, but the time to the next visit is increased to 12 weeks. If the patient does not meet the re-treatment criteria and was not treated at either of the two previous visits, they do not receive an injection and do not visit the ophthalmologist again.
- After 5 years, patients no longer receive injections. They have three further follow-up visits with the ophthalmologist, 12 weeks apart.

For patients who will not visit the ophthalmologist again, the time to visit is set to infinity, and the time to annual change in BCVA score is set at 1 year.

Ocular adverse event

Patients who have an ocular AE are assumed to incur a cost for treating the AE, and remain on treatment. As patients may have more than one AE, the time to AE is resampled from the same distribution.

Withdrawal

Patients who withdraw are assumed to immediately discontinue their assigned intervention and receive no treatment. They no longer visit their ophthalmologist to be assessed for or to receive treatment. As patients cannot withdraw more than once, the time to withdrawal is set at infinity.

New-onset macular oedema in the non-trial eye

Patients may develop MO in the non-trial eye. When this occurs, to reflect the associated change in visual acuity and CST associated with MO, the patient is assigned a new BCVA and CST measurement for the non-trial eye. This is sampled from the baseline characteristics of the trial eye for patients of the same sex and similar age.

Patients who develop MO in the non-trial eye are assumed to receive the same intervention in their non-trial eye as was assigned to their trial eye. Patients who are still on their assigned treatment (and who have not discontinued because of treatment continuation rules or withdrawal) will receive treatment in both eyes, whereas patients who have discontinued or withdrawn from treatment in their trial eye will receive treatment in the non-trial eye only. If a patient is still receiving treatment in their trial eye, their initial visit for the non-trial eye will occur at the same time as the next visit for the trial eye.

After this point, the same treatment continuation rule is applied to each eye to determine when the next visit for each eye occurs. If a patient is not still receiving treatment in their trial eye, the patient immediately has a visit for the non-trial eye and follows treatment continuation rules for that eye only.

As patients cannot redevelop MO in the non-trial eye, the time to new-onset MO is then set at infinity.

Annual change in visual acuity

Visual acuity is used to predict utility and resource use. While patients are still visiting the ophthalmologist, their visual acuity is updated at each visit. Once the patient no longer receives injections or no longer has follow-up visits, their visual acuity is tracked using an annual change event. After each annual change, the time to the next annual change is set at 1 year.

Death

When a modelled patient dies, they move immediately to the model end event.

Model end

Once a modelled patient reaches the model end, their costs and QALYs are reported.

Model inputs

Baseline characteristics

The model uses the baseline characteristics of LEAVO participants to preserve the relationship between characteristics. Each modelled patient has the baseline age, sex, trial and non-trial eye BCVA and CST of one of 452 LEAVO participants for whom all of these variables were available at baseline. This approach is consistent with other simulation models in ophthalmology.[97]

Central subfield thickness and visual acuity

The re-treatment algorithm assesses both OCT CST and BCVA, so both must be modelled for treated eyes. BCVA in both eyes is important for predicting HRQoL, so BCVA is modelled for both eyes.

Treated eyes

Growth models (longitudinal analyses to estimate growth trajectories over a period of time) are fitted to CST and BCVA from the LEAVO data. In these models, CST (or BCVA) at weeks 12, 24, 52, 76 and 100 are estimated as a function of time, baseline CST (or BCVA), age at baseline, intervention, number of injections and time since last injection. Sex is found not be a significant predictor of CST or BCVA, so it is excluded. Intervention is not a significant predictor of CST or BCVA, but it is included to reflect numerical differences between the interventions.

The equation for y_{it}, the BCVA score for patient i at time t, is as follows:

$$y_{it} = \eta_{1i} + \eta_{2i} \times t + \gamma_{1t} \times \textit{number of injections} + \gamma_{2t} \times \textit{days since injection} + \varepsilon_{it}, \quad (1)$$

where

$$\eta_{1i} = \eta_1 + \alpha_1 \times \frac{\text{age at baseline}}{10} + \alpha_2 \times \frac{\text{BCVA at baseline}}{10} + \alpha_3 \times tn2 + \alpha_4 \times tn3 + \xi_i^1 \quad (2)$$

and

$$\eta_{2i} = \eta_2 + \beta_1 \times \frac{\text{age at baseline}}{10} + \beta_2 \times \frac{\text{BCVA at baseline}}{10} + \beta_3 \times tn2 + \beta_4 \times tn3 + \xi_i^2, \quad (3)$$

where $tn2 = 1$ for aflibercept and 0 otherwise, and $tn3 = 1$ for bevacizumab and 0 otherwise, and ξ is an error term.

(The equation for CST follows the same structure, but uses CST at baseline/100 instead of BCVA at baseline/10.)

Whereas η, α and β (age at baseline, CST or BCVA at baseline and intervention) are time-invariant covariates, γ_1 and γ_2 (number of injections and time since last injection) are time-variant covariates, with values available at 12, 24, 52 and 76 weeks only. To estimate CST and BCVA in the economic model, these covariates are used at the week 12, 24, 52, 76 and 100 visits. For other visits, the following approaches are used:

- Weeks 4 and 8 – CST and BCVA are calculated at week 12, and linear interpolation is used to estimate CST and BCVA at the week 4 and week 8 visits.
- Visits from week 16 to week 100, excluding weeks 24 and 52 – CST and BCVA are calculated for the closest milestone visits before and after the non-milestone visits, and interpolation is used to estimate BCVA at the non-milestone visits.
- Visits beyond week 76 – the time-varying covariates appear similar towards the end of LEAVO, and so models that restricted these covariates to be the same at weeks 76 and 100 were compared with unrestricted models. Log-likelihood tests indicated that the null hypothesis that the restricted models were true should not be rejected. The restricted models suggest that the effect of the number of injections and time since last injection flatten towards the end of LEAVO and can, therefore, be used to extrapolate beyond 100 weeks.

Untreated eyes

Untreated eyes are considered to be eyes that never received treatment or eyes whose treatment has ended or been withdrawn. The same assumption is used for treated eyes whose most recent injection was at least 1 year ago.

Central subfield thickness is not modelled for the non-trial eye unless the patient develops MO in the non-trial eye, in which case CST and BCVA for the non-trial eye are modelled using the same approach as for the trial eye.

Best corrected visual acuity is modelled for untreated eyes using natural history data. The Beaver Dam Eye Study[98] was a large population-based study that recorded BCVA in patients over 5 years. This study[98] reported the letters gained or lost in the left and right eyes for people aged < 55, 55–64, 65–74 and ≥ 75 years, and has been used in previous CRVO economic models.[51] Combining the right and left eye data, the annual average decrease in BCVA is –0.02 letters [standard error (SE) 0.04 letters] for those aged 55–64 years, 0.26 letters (SE 0.04 letters) for those aged 65–74 years and 0.76 letters (SE 0.06 letters) for those aged ≥ 75 years. There is no change for people aged < 55 years. These data appear consistent with a study of the natural history in CRVO,[99] which reports that increasing age was positively associated with visual acuity deterioration, and over 2–5 years in eyes with non-ischaemic CRVO MO, 14% improved, 47% stayed the same and 39% worsened.

Ocular adverse events

The model considers the same ocular AEs as reported in the safety analysis in LEAVO: infectious endophthalmitis, traumatic cataract, retinal tear, retinal detachment, conversion to ischaemic CRVO, anterior segment neovascularisation, retinal neovascularisation, and vitreous haemorrhage and intraocular pressure elevation. As relatively few patients experienced these AEs in LEAVO (e.g. only one patient had infectious endophthalmitis), modelling the time to specific events would be highly uncertain and, in some cases, impossible. Therefore, the model considers the time to any ocular AE, using the data for all ocular AEs (and applying a cost per average AE; see *Adverse event costs*). When the date of the AE was missing, multiple imputation was used to impute the date based on the trial arm and whether or not an AE occurred.

Survival analysis was used to fit parametric models to extrapolate time to event beyond the trial period. The log-rank test found no statistically significant difference between the time to first AE and time to subsequent AEs ($p = 0.128$), and the number of subsequent AEs was small, so the time to first AE is used as the time to first or subsequent AEs in the model.

Although the time to AE is not statistically significantly different between the interventions ($p = 0.683$), they are modelled separately to reflect numerical differences in the deterministic analysis. The probabilistic analysis considers the uncertainty around point estimates, reflecting that the interventions are not significantly different. According to the Akaike information criterion (AIC) and Bayesian information criterion (BIC), the Weibull was the best-fitting parametric model. As no data are available on the ocular AE rates for any of the three interventions beyond the trial period (see *Overview of systematic literature review*), external validation is not possible. The Weibull is therefore used to model the time to AEs. All three interventions have the same shape parameter of 0.745, demonstrating that the probability of having an ocular AE decreases over time.

Withdrawal

Survival analysis was used to fit parametric models to extrapolate time to withdrawal beyond the trial period. The three interventions are modelled separately to reflect numerical differences, despite non-statistically significant differences in the data ($p = 0.572$). The AIC and BIC are similar between parametric models, and no external validation was possible because of a lack of data. The Weibull distribution is used to model time to withdrawal event, with shape parameter of 1.385, demonstrating that the probability of withdrawing increases over time.

New-onset macular oedema

Eight of 463 patients in LEAVO either had new-onset MO recorded as an AE or received an anti-VEGF injection in the non-trial eye. This is a small number of observations to fit parametric models to using survival analysis; instead, it is assumed that the occurrence of new-onset MO follows an exponential distribution. The rate of new-onset MO is calculated as 0.009 per year.[100]

Mortality

As only 13 LEAVO participants died, the data are not sufficiently mature to be analysed and included in the model. Instead, the model applies an age- and sex-standardised mortality ratio to the probability of death[101] for the general UK population[102] in order to represent the increased mortality associated with CRVO.

Number of simulated patients

A drawback of individual-level simulation approach is introducing first-order uncertainty (also known as stochastic uncertainty), whereby the mean cost and benefit outcomes may vary between different model runs even if the same input parameters for a given individual (patient) are used.[103] To reduce this type of uncertainty, 7000 patients are simulated for each model run. This ensured that a sufficient number of combinations of different patient characteristics are achieved, and that first-order uncertainty is accounted for by allowing a uniform coverage of a random number seed. *Appendix 6*, *Figure 28*, shows that total costs and QALYs are stable when $\geq$ 7000 patients are sampled.

Health-related quality of life

The model considers patients' BCVA over their lifetimes. To include patients' utilities over time, the model predicts utility from BCVA and other demographic variables. This prediction is termed a 'mapping' or 'crosswalk' and may be used in economic evaluation to convert clinical measures to health utilities when either utility data are not directly available or there is a need to relate clinical outcomes to health utilities in the long term. Developing a mapping requires a data set that contains both the clinical measure and the utility measure. LEAVO provided this data set for BCVA and three measures of utility.

Health-related quality-of-life measures

Three HRQoL questionnaires were used to collect health utility data in the trial:

1. the VFQ-25[104]
2. the EQ-5D[105]
3. the EQ-5D-V.[106]

As specified in the health economic analysis plan and the trial protocol, the VFQ-25 was chosen as the primary measure, with the EQ-5D and EQ-5D-V used in secondary analyses.[9,12] The EQ-5D has been shown to perform poorly in eye disorders, including AMD.[107] Although the VFQ-25 may not meet the NICE reference case,[84] non-EQ-5D utility values have been used in economic evaluations in many cases, including eye conditions.[108]

Each HRQoL questionnaire was collected at the six milestone visits of LEAVO: baseline and weeks 12, 24, 52, 76 and 100. Utility scores from the VFQ-25 were calculated using the Visual Function Questionnaire-Utility Index (VFQ-UI) for each patient.[109] This tariff uses six items (questions 6, 11, 14, 18, 20 and 25), representing six of the VFQ-25 subscales.[110] Using the crosswalk, the EQ-5D health states were converted to the three-level scale, as this is preferred by NICE.[111,112] Utility scores for the EQ-5D-V were calculated by first taking the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), score and then subtracting the EQ-5D-V score as a utility decrement applied to the individual patient-level data.[106]

Mapping from best corrected visual acuity to utility

Data from all milestone visits were combined to maximise the number of observations using a complete-case analysis. At each observation, variables were generated for the visual acuity in the better-seeing eye (BSE) and the worse-seeing eye (WSE), according to whether BCVA was greater in the trial eye or the non-trial eye.

Standard statistical models are often a poor fit to the distribution of utility data[113] (particularly EQ-5D data), so adjusted limited dependent variable mixture models (ALDVMMs) are used. Mixture models can be used to represent latent classes (discrete variables that are inferred rather than directly observed) within an overall population, or to provide a very flexible semiparametric framework for modelling distributions with unusual shapes. Limited dependent variables are those whose range of possible values are restricted. ALDVMMs, therefore, represent a flexible framework for developing models to reflect the distribution of utility data.

The ALDVMMs were estimated with one to four components (classes).[114] Models were fitted for the three utility measures. The independent variables used to predict utility in the components were age, sex, BSE BCVA and WSE BCVA. The interaction between the BSE and the WSE was considered as a variable, but its inclusion worsened model fit; therefore, it was excluded from the model specification. BSE BCVA and WSE BCVA are used to determine the probability of a patient belonging to the different components. Intervention is not included as an independent variable, as its impact on utility is expected to be through changing BCVA and not through a treatment-specific effect.

To determine the number of components that should be used for each utility measure, model fit was compared using the mean error, mean absolute error (MAE), root-mean-square error (RMSE), AIC, BIC and visual inspection. In each utility measure, the mean error, MAE and RMSE were generally similar for models with two, three and four components for which component membership was predicted by the BCVA score of the BSE and the WSE. The AIC and BIC, which penalise models with more parameters to reduce overfitting, indicated that the best-fitting model for VFQ-UI has three components, whereas the best-fitting models for the EQ-5D and the EQ-5D-V have two components. *Appendix 3*, *Table 34*, shows the model parameters.

The utility in each component is calculated as follows:

1. A temporary variable u is calculated by multiplying the within-component coefficients by the individual patient's characteristics (as per a regression equation).
2. Parameter a is calculated as –

$$a = \frac{u_u - u}{\sigma}. \tag{4}$$

3. Parameter b is calculated as –

$$b = \frac{u_l - u}{\sigma}. \tag{5}$$

4. Parameter c is calculated as –

$$c = \varphi(a) - \varphi(b). \tag{6}$$

5. Parameter d is calculated as –

$$d = \Phi(a) - \Phi(b). \tag{7}$$

6. If parameter c is between –0.00000001 and 0.00000001 parameters, c is set to 0 and d is set to 1.
7. The expected utility within the component is calculated as –

$$\left(1 - \Phi(a) + \left(\Phi(a) - \Phi(b)\right)\right) \times \left(u + \left(\sigma \times \frac{c}{d}\right)\right) + \left(u_l \times \Phi(b)\right), \tag{8}$$

where u_u is the highest feasible utility next to 1, l is the lowest feasible utility, σ is the variance of the component, φ is the probability density function for the normal distribution with mean 0 (SD 1), and Φ is the cumulative distribution function for the normal distribution with mean 0 (SD 1).

The probability of belonging to each component is calculated by the exponentiation of the product of the between-components by an individual patient's characteristics. For the last component, this will equal 1. The probabilities are then normalised by dividing by the sum of all probabilities.

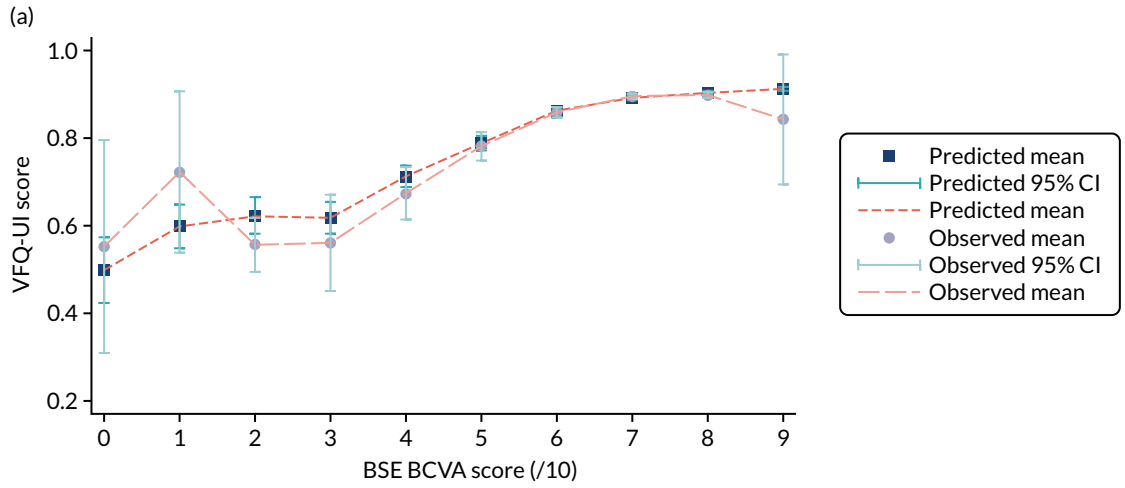

FIGURE 16 The VFQ-UI mapping comparison of observed and predicted scores: (a) VFQ-UI score vs. BSE BCVA score; (b) VFQ-UI score vs. WSE BCVA score; (c) VFQ-UI score vs. BSE ETDRS score; and (d) VFQ-UI score vs. WSE ETDRS score. (*continued*)

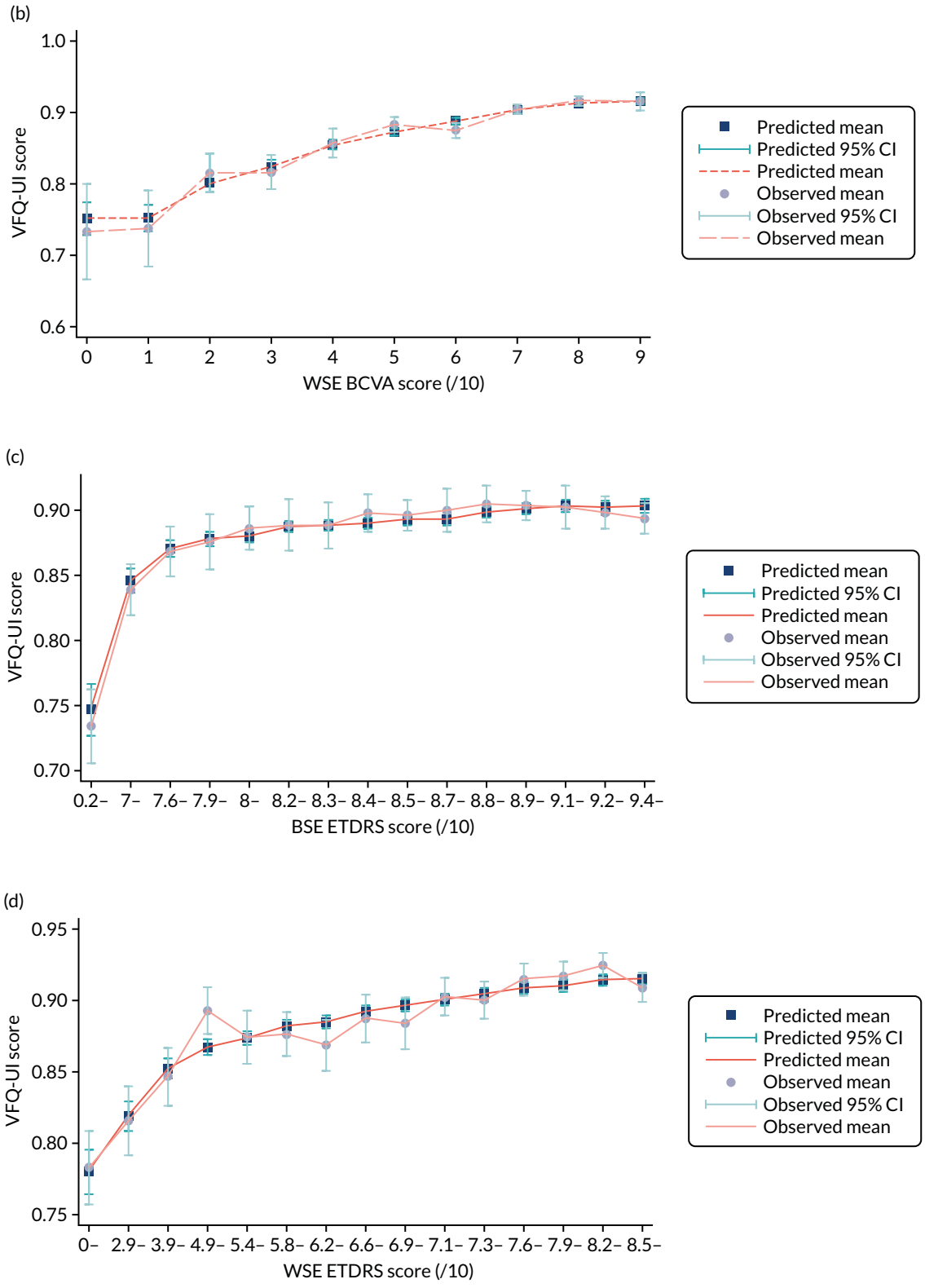

FIGURE 16 The VFQ-UI mapping comparison of observed and predicted scores: (a) VFQ-UI score vs. BSE BCVA score; (b) VFQ-UI score vs. WSE BCVA score; (c) VFQ-UI score vs. BSE ETDRS score; and (d) VFQ-UI score vs. WSE ETDRS score.

The expected utility within each component is multiplied by the probability of belonging to each component. The sum of these gives a patient's utility. The relationship between visual acuity and utility for the BSE and the WSE is provided in *Figure 16*. A Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) tool that calculates a patient's utility score (VFQ-UI, EQ-5D, EQ-5D-V) based on our mappings is provided.[115]

Resource use and costs

Costs were calculated using Great British pounds for 2017/18; when costs were not available for this year, they were inflated using the Hospital and Community Health Service (HCHS) index.[116]

Intervention costs

The list price is £551.00 for the ranibizumab injection and £816.00 for the aflibercept injection.[117] These prices are used in the base-case analysis. A discount is applied to these costs in scenario analyses to explore the impact of confidential Patient Access Schemes (PASs). The list price of bevacizumab is £243.00; however, this is the cost of a large infusion vial of the drug.[117] As discussed in *Chapter 2*, *Intervention: bevacizumab (1.25 mg/0.05 ml)*, during LEAVO, the injections of bevacizumab were separated from the larger bottle into pre-filled syringes by the Liverpool and Broadgreen Pharmacy Aseptic Unit.[88] This compounding of the drug was deemed to be legal in a judicial review in 2018, which cited the price per injection as £28.[55] It is assumed that this price includes any costs associated with compounding the drug, such as staff time and storage costs. This price is used in the base-case analysis. Patients incur an injection cost for each eye that is treated.

Visit costs

When a simulated patient visits the ophthalmologist to be assessed against re-treatment criteria, and possibly treated with an anti-VEGF injection, costs are incurred for the visit itself, the OCT examination (if performed) and the drug cost of the injection.

The cost of the initial visit is £140.04: a first multiprofessional consultant-led outpatient ophthalmology visit. Subsequent visits cost £105.19: a follow-up multiprofessional consultant-led outpatient ophthalmology visit.[118] Patients who are receiving treatment in both eyes incur 1.5 times the visit costs, representing clinician advice that approximately half of all patients would have both eyes treated in a single visit, and the other half would require two separate visits.

The cost of the OCT examination is £108.21: a minor vitreous retinal outpatient ophthalmology procedure.[118] This is incurred for each eye for which re-treatment criteria are assessed.

Disease management costs

A bespoke resource use questionnaire was developed to capture resource use relating to a participant's eye condition during the 100-week trial. Participants were asked to complete the questionnaire at baseline and at weeks 12, 24, 52, 76 and 100. Although resource use questionnaires can be vulnerable to recall bias, the questionnaire captured 9 of the 10 questions recommended as core items in standardised resource measures,[119] collecting information relating to hospital admissions, health-care contacts and continuous care and support of patients.

The model includes resource use for the following:

- visits to the eye consultant, general practitioner (GP), general practice nurse, accident and emergency (A&E), eye A&E and optometrist
- low-vision appointments
- telephone calls to the eye hospital helpline, ophthalmologist and GP.

Resource use data were analysed from the resource use questionnaire in LEAVO, with completed measures combined for all patients across the trial period to maximise the number of observations.

Resources with < 10 observations were excluded. Participants who developed new-onset MO or who had an AE were excluded from the analysis to prevent double-counting of the resource use associated with these events.

Ordinary least squares regression was performed to estimate the relationship between WSE BCVA and resource use per 3-month period (a higher BCVA score predicted less resource use). When WSE BCVA was not a statistically significant predictor of resource use, the model used the mean resource use for all patients.

The resource use questionnaire asked patients to indicate the number of events, such as the number of visits to eye casualty, number of telephone calls with health-care professionals or number of hours of care received, over the previous 3 or 6 months. However, the duration of each visit was not recorded; therefore, average estimates were used based on the NHS *Reference Costs 2017/18*[118] or the *Unit Costs of Health and Social Care 2018*,[116] when relevant.

When a patient reported a hospital admission, if an associated procedure was named as the reason for the admission, average resource costs associated with the procedure were used based on the NHS reference costs. The number of bed-days reported by a participant was then used to adjust the cost by adding or subtracting the difference between the number of bed-days reported by the participant and the number expected for the procedure, multiplied by the cost of an excess bed-day. If the same concomitant procedure was also reported for this participant, costs were only counted once using the information provided by the participant relating to length of stay. If no reason was recorded for the admission, then the cost of a non-elective excess bed-day was used.[118]

The costs and parameters for the resource use regressions are shown in *Appendix 3*, *Table 34*.

Adverse event costs

As the model considers any ocular AE, modelled patients who experience ocular AEs incur the average cost for an ocular AE, based on the proportion of participants in LEAVO experiencing each ocular AE. This is calculated by multiplying the number of each type of ocular AE by the cost for treating that ocular AE, and dividing the total by the number of participants in LEAVO who experienced ocular AEs. The cost per ocular AE is the same for the three interventions at £317.96. Costs for each ocular AE are from NHS *Reference Costs 2017/18*[118] or the *British National Formulary*,[117] and are shown in *Appendix 3*, *Table 34*.

Blindness costs

Modelled patients may become blind when the BCVA score of both eyes is at ≤ 35 letters, consistent with the definition of severely sight-impaired from the Royal National Institute of Blind People[120] and previous models in MO.[51,112] Blindness was tracked at visit and annual BCVA change, both of which are events at which BCVA scores can change. BCVA scores can fluctuate throughout a patient's lifetime, meaning that a patient can experience more than one blindness episode in their life.

Two sets of costs associated with blindness are defined from literature: one-off costs and recurrent costs.[112,121] When a patient becomes blind for the first time, one-off costs associated with blindness are incurred, including blind registration, low-vision aids and low-vision rehabilitation. As long as a patient remains blind, they incur recurrent costs, including community care, residential care, treatment for depression and hip replacement.

The costs of blindness registration, daily community care and weekly residential care are £60.50, £27.64 and £115.40, respectively.[116] Low-vision rehabilitation and hip replacement unit costs are estimated at £153 and £4170, respectively.[118] The costs of low-vision aids and the annual costs of depression are estimated from Meads and Hyde[122] and TA460,[123] respectively, both of which are inflated to 2018 values using the HCHS indices.[116]

The proportion of blind patients receiving each service is taken from Colquitt *et al.*[121]

The costs and proportion of patients incurring these costs are shown in *Appendix 3*, *Table 34*.

Addressing uncertainty

The base-case analysis uses the VFQ-UI, and scenario analyses consider the EQ-5D and EQ-5D-V. Scenario analyses consider shorter time horizons and a cost of £243 for bevacizumab.

Patient Access Schemes are in place for ranibizumab and aflibercept, offering a discount on the list price.[13,51] However, the level of discount is confidential and so is unknown. Therefore, we consider threshold analyses to determine the level of discount that would be needed to change the decision about the most cost-effective intervention.

Results are presented for the base-case, EQ-5D, EQ-5D-V and 100-week scenarios using probabilistic sensitivity analysis to incorporate parameter uncertainty. Whereas deterministic analysis (see *Appendix 6*, *Model-based analysis results: additional data*) uses point estimate (mean) inputs, probabilistic sensitivity analysis simultaneously samples all uncertain inputs from their associated distributions. Microsoft Excel was used to sample uncertain parameters from their distributions and to maintain relationships between related parameters. Mean total costs and QALYs are calculated for the modelled patient cohort for each simulation. 95% CIs around the mean and total costs and QALYs are presented using the SE to reflect the uncertainty around the mean. The mean of the mean total costs and QALYs for each intervention are calculated from all of the simulations and used to calculate mean probabilistic ICERs. The uncertainty around the mean probabilistic ICER is calculated using the incremental net monetary benefit (INMB) approach to avoid the mathematical limitations of interpreting uncertainty around a ratio.[124]

Running probabilistic sensitivity analysis on a discrete event simulation model is computationally expensive, but it is vital that a sufficient number of simulations are performed so that the model results converge. The number of simulations required for the results to converge can be calculated by comparing the upper and lower bounds of the INMB with zero for a defined cost-per-QALY threshold.[124] Using the tutorial provided by Hatswell *et al.*[124] and a threshold of £30,000 per QALY, very few probabilistic simulations are required for the analyses. This is because the ICERs are so far away from the threshold of £30,000 per QALY that there is very little uncertainty associated with the decision about which intervention is most cost-effective (the INMB CIs exclude zero). Probabilistic sensitivity analysis is presented using 500 simulations for all scenarios. This is sufficient to ensure that the INMBs have converged for each comparison of two interventions.

Methods: within-trial analysis

Method of economic evaluation

The methods for the within-trial analysis were prespecified in a health economic analysis plan prior to database lock.[89] The primary outcome of the within-trial health economic analysis was to establish the short-term cost-effectiveness of:

- aflibercept compared with ranibizumab
- bevacizumab compared with ranibizumab
- aflibercept compared with bevacizumab.

A fully incremental analysis (ranking the alternative treatment options by total costs and ruling out dominated and extendedly dominated options from the comparison) was also performed. The economic analysis used individual patient-level data collected as part of LEAVO. The total costs and QALYs over the 100-week follow-up period of the trial were used to calculate the incremental cost per QALY gained.

An ITT population was used, including all of the participants randomised to each treatment group. Analyses were conducted using Stata® version 15 (StataCorp LP, College Station, TX, USA) and R (The R Foundation for Statistical Computing, Vienna, Austria).

Health-related quality of life

The individual patient-level QALYs were calculated from the utility scores for each HRQoL questionnaire at baseline and at subsequent follow-up time points using linear interpolation.

Resource use

The costing approach included identification of resource use, measurement and valuation.[125] The resource use associated with delivery of the intervention, hospital admissions, health-care contacts, continuous care and support and concomitant medications and procedures, and the costs associated with blindness, were measured.

Identification of resource use

The within-trial analysis included costs related to a participant's eye condition as collected using the resource use questionnaire (see *Disease management costs*); the delivery of the intervention; and concomitant medications.

Information relating to concomitant medications was collected by health-care professionals. Resource use relating to the delivery of the intervention was captured at each visit, and included drug costs, outpatient appointment costs and the costs of any tests commonly conducted at these appointments.

Ocular AEs were captured using the resource use questionnaire and from data relating to concomitant procedures and medications. To capture the relevant costs associated with blindness, the costs of blind registration and low-vision aids were applied to participants who became partially or severely sighted during the trial. A participant was deemed to be partially sighted or severely sight-impaired if their BCVA score was $\leq$ 58 letters in both eyes.[120] These costs were applied once during the course of the trial, namely at the first time a participant met this criterion, as low-vision aids are thought to be incurred biannually.[50] It is assumed that the same proportion of participants who can register as severely sighted also register as partially sighted and the same costs are incurred for low-vision aids to give a conservative estimate of the cost of blindness. This analysis differs from the model-based analysis to include cost associated with blindness for partially sighted patients.

Measurement of resources

The costs of medications were costed according to standard NHS sources, when available.[117]

Valuation of resources

Unit costs, summarised in *Appendix 6*, *Table 57*, were applied to each resource use event at the individual patient level to calculate their total cost of resource use over the 100-week trial. Intervention costs used in the within-trial analysis are similar to those used in the model-based analysis (see *Intervention costs*).

Analytical methods

The base-case CUA was based on multiple imputation using chained equations to account for missing data. The VFQ-UI was used to calculate QALYs. The ICER was estimated comparing bevacizumab and aflibercept with ranibizumab, and aflibercept with bevacizumab. If applicable, the ICER was then compared with the NICE cost-effectiveness threshold range of £20,000–30,000 per QALY gained.

Missing data

Missing data can give misleading estimates in a within-trial cost-effectiveness analysis. A complete-case analysis uses only patients with no missing data on the key cost and benefit outcomes. This is undesirable because it reduces the sample size and affects the power of the study.[126] The following assumptions were made:

- When a patient died, their utility scores at all subsequent milestone visits were set at zero. Their costs at the next milestone visit were then assumed to be half the costs recorded at the previous visit, unless their next visit was at 52 weeks, in which case the costs were assumed to be the same as the week 24 costs.
- When a participant withdrew from the trial, if a withdrawal appointment was carried out, cost and utility data were assigned to the nearest milestone visit and all subsequent costs were set at zero and utilities were recorded as missing.

Once the assumptions had been applied to the data, patterns of missing data were assessed using the following descriptive analyses:

- proportion of missing data by treatment arm, at each follow-up period, to assess whether or not missing data differed by arm
- missing data patterns to determine whether or not data were missing for all items or individual items of utility scores and resource use items over the trial follow-up.

The multiple imputation chained equation method with predictive mean matching was used to impute missing values of costs, QALYs and baseline covariates. The year 1 QALY imputation model included the following covariates: age, sex, ethnicity, previous treatment, baseline utility, time since diagnosis, baseline BCVA in the trial eye and baseline BCVA in the non-trial eye. The year 2 QALY imputation model also included the imputed year 1 QALY data, as per recommendations by Faria *et al.*[126] The year 1 cost imputation model included the same covariates as the year 1 QALY model, as well as baseline resource use and site. The year 2 cost imputation model also included the imputed year 1 costs. The number of imputations was based on the highest percentage of missing data for the variables of interest (baseline utility, QALYs and total cost). The imputation was performed per randomisation arm for all imputed variables except baseline covariates for which data were missing, for which imputation was performed across all observations.

Seemingly unrelated regression

A seemingly unrelated regression (SUR) model was used to estimate the difference in mean total costs and QALYs between treatment arms, taking into account the correlation between total costs and QALYs.[127] The SUR model estimated the full variance–covariance matrix, which was further used to address uncertainty.[128] The regression equation for total costs included the randomisation arm. The regression equation for QALY included the randomisation arm and baseline utility in order to control for imbalances in baseline utility between treatment arms.[127,129] The model assumed a normal distribution for both costs and QALYs.[128] Marginal effects in each treatment arm were calculated using the SUR, without adjusting for baseline utility.

Addressing uncertainty

A parametric approach was used to address the uncertainty around the CUA estimates using the following key parameters estimated from the SUR output:

- difference in mean QALYs
- SE of mean differential QALYs
- difference in mean total costs
- SE of mean differential total costs
- covariance between total costs and QALYs.

To illustrate uncertainty, cost-effectiveness confidence ellipses and net monetary benefit (NMB) lines with CIs were produced for each pairwise comparison of treatments. In addition, a cost-effectiveness acceptability curve (CEAC) was constructed, illustrating the probability that each treatment was the most cost-effective compared with all alternative treatments at a range of threshold values that varied from £0 to £400,000. To calculate the probability that a treatment was the most cost-effective option, costs and QALYs for each treatment were sampled using a bivariate normal distribution.

Scenario analyses were calculated using SUR output as in the base-case analyses. The scenario analyses were as follows:

1. QALYs estimated using the EQ-5D, using imputed data
2. QALYs estimated using the EQ-5D-V, using imputed data
3. drug price discounts – the CUA carried out using imputed data and applying a 30% and 50% discount to the drug prices of ranibizumab and aflibercept, reflecting possible confidential PASs offered by pharmaceutical companies to the NHS
4. list price for bevacizumab – the CUA carried out using the list price for bevacizumab taken from the *British National Formulary* (£243)
5. complete-case analysis – the CUA carried out using complete-case data from LEAVO only
6. 52-week analysis – the CUA carried out using imputed data from LEAVO up to the week 52 milestone visit.

Results: model-based analysis

Base-case analysis

The results are presented in *Table 21*. In the base-case analysis, bevacizumab generates the most QALYs, followed by ranibizumab and aflibercept. Aflibercept generates the highest costs, followed by ranibizumab and bevacizumab. The CIs for the incremental costs and QALYS do not contain zero, demonstrating that there is a difference in both costs and effects for the three interventions (however, for QALYs this is numerically small). Bevacizumab dominates (i.e. it is more effective and less costly than) both ranibizumab and aflibercept. The 95% CIs for the NMB at £30,000 per QALY do not contain zero. At a threshold of £20,000–30,000 per QALY, bevacizumab is the most cost-effective intervention (ranibizumab dominates aflibercept).

The cost-effectiveness scatterplots (*Figure 17*) display the variation in the incremental costs and QALYs in the probabilistic samples. These are akin to presenting the SD; although they display the dispersion of the set of values, they do not present the uncertainty around the mean. The 95% CIs using the SE present the uncertainty around the mean, and show a difference in incremental QALYs for the three comparisons.

The CEAC (*Figure 18*) shows that, at £20,000 and at £30,000 per QALY, bevacizumab has the highest probability of being cost-effective (99.6% and 98.4%, respectively). Even at a threshold of £100,000 per QALY, bevacizumab has the highest probability of being cost-effective (92.8%). The probabilistic results demonstrate that bevacizumab is the most cost-effective intervention.

The difference in QALYs is due to the difference in the effectiveness of the three interventions (see *Table 5*) and the relationship between visual acuity and utility. The difference in costs is due to the difference in the cost of the intravitreal anti-VEGF injections (intervention costs), as demonstrated by the cost breakdown in *Table 22*. The trial eye CST and visit costs are higher for bevacizumab than for aflibercept and ranibizumab because patients require more injections of bevacizumab. However, the drug costs are lower for bevacizumab because the cost of the injection is much lower.

TABLE 21 Model-based analysis: base-case and scenario analysis results

Analysis	Total (95% CI)		Incremental (95% CI)		ICER (£) (95% CI)
	Costs (£)	QALYs	Costs (£)	QALYs	
Base-case analysis					
Bevacizumab	18,353 (17,782 to 18,925)	9.678 (9.572 to 9.785)			
Ranibizumab	30,226 (29,386 to 31,066)	9.635 (9.512 to 9.757)	11,873 (11,458 to 12,288)	−0.044 (−0.074 to −0.013)	Dominated (INMB:[a] −14,316 to −12,067)
Aflibercept	35,026 (33,990 to 36,062)	9.569 (9.429 to 9.710)	16,673 (16,036 to 17,310)	−0.109 (−0.161 to −0.057)	Dominated (INMB:[a] −21,864 to −18,040)
Scenario analysis: EQ-5D for utilities					
Bevacizumab	18,353 (17,782 to 18,925)	8.782 (8.740 to 8.823)			
Ranibizumab	30,226 (29,386 to 31,066)	8.795 (8.754 to 8.836)	11,873 (11,458 to 12,288)	0.013 (0.008 to 0.018)	908,532 (659,881 to 1,476,254)
Aflibercept	35,026 (33,990 to 36,062)	8.832 (8.790 to 8.874)	4800 (4445 to 5154)	0.037 (0.032 to 0.043)	128,513 (110,116 to 152,663)
Scenario analysis: EQ-5D-V for utilities					
Bevacizumab	18,353 (17,782 to 18,925)	8.346 (8.282 to 8.410)			
Ranibizumab	30,226 (29,386 to 31,066)	8.351 (8.283 to 8.419)	12,791 (12,148 to 13,434)	0.005 (−0.007 to 0.017)	2,491,676 (INMB:[a] −12,327 to −11,155)
Aflibercept	35,026 (33,990 to 36,062)	8.369 (8.289 to 8.449)	4800 (4445 to 5154)	0.018 (0.000 to 0.035)	268,963 (INMB:[a] −4930 to −3602)
Scenario analysis: 100-week time horizon					
Bevacizumab	6349 (6293 to 6405)	1.641 (1.631 to 1.651)			
Ranibizumab	15,254 (14,962 to 15,545)	1.641 (1.631 to 1.651)	8905 (8650 to 9161)	0.000 (0.000 to 0.001)	34,067,841 (217,070 to 10,420,696)
Aflibercept	18,844 (18,438 to 19,249)	1.646 (1.636 to 1.655)	3590 (3400 to 3780)	0.005 (0.004 to 0.005)	793,348 (688,418 to 926,352)
Scenario analysis: bevacizumab list price from the BNF[117] (£243)					
Bevacizumab	23,530 (22,884 to 24,176)	9.678 (9.572 to 9.785)			
Ranibizumab	30,226 (29,386 to 31,066)	9.635 (9.512 to 9.757)	6696 (6400 to 6992)	−0.044 (−0.074 to −0.013)	Dominated (INMB:[a] −9084 to −6937)
Aflibercept	35,026 (33,990 to 36,062)	9.569 (9.429 to 9.710)	11,496 (10,961 to 12,030)	−0.109 (−0.161 to −0.057)	Dominated (INMB:[a] −16,636 to −12,905)

BNF, *British National Formulary*.
a INMB at £30,000 per QALY.

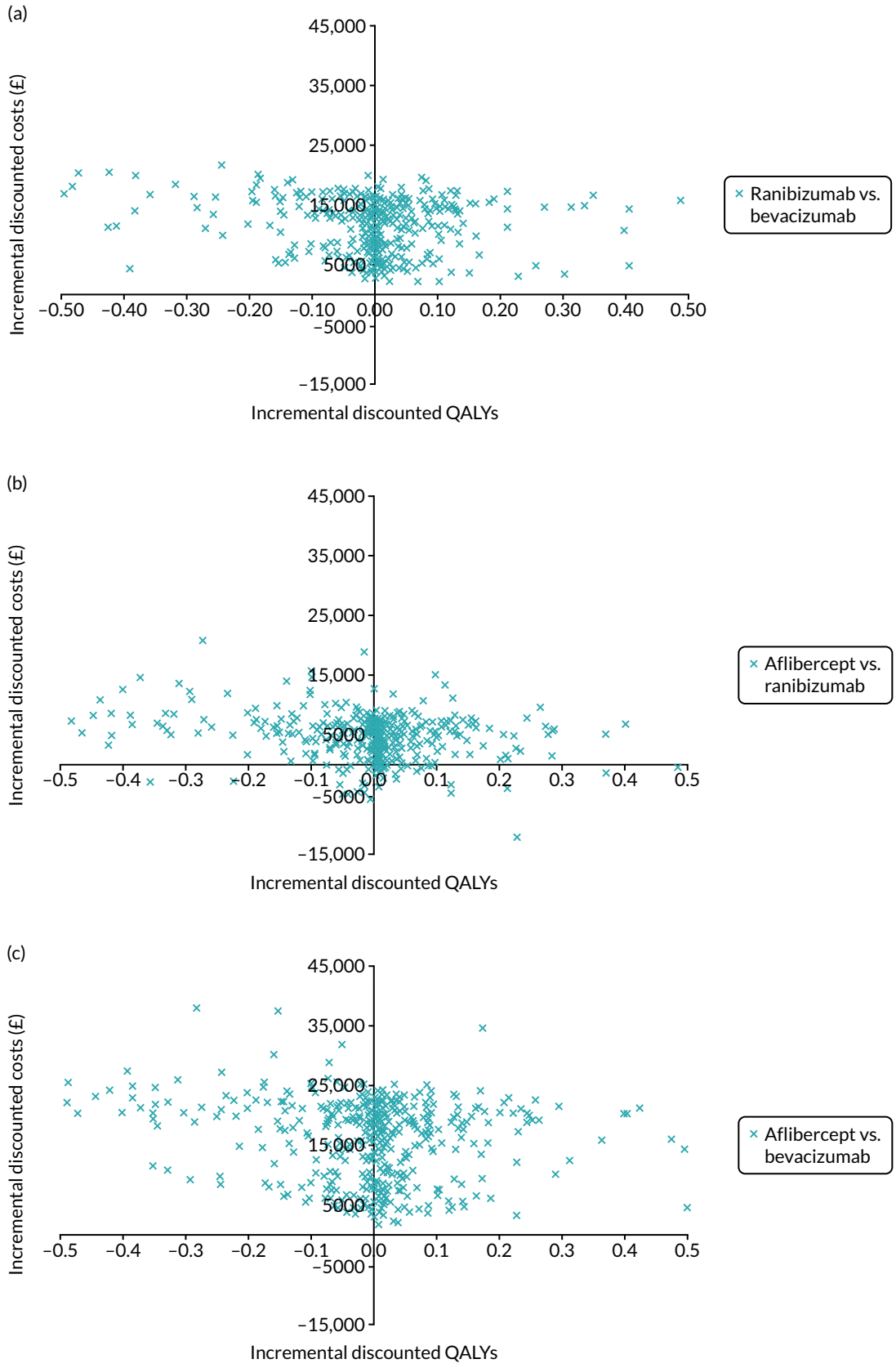

FIGURE 17 Model-based analysis: cost-effectiveness scatterplots. (a) Ranibizumab vs. bevacizumab; (b) aflibercept vs. ranibizumab; and (c) aflibercept vs bevacizumab.

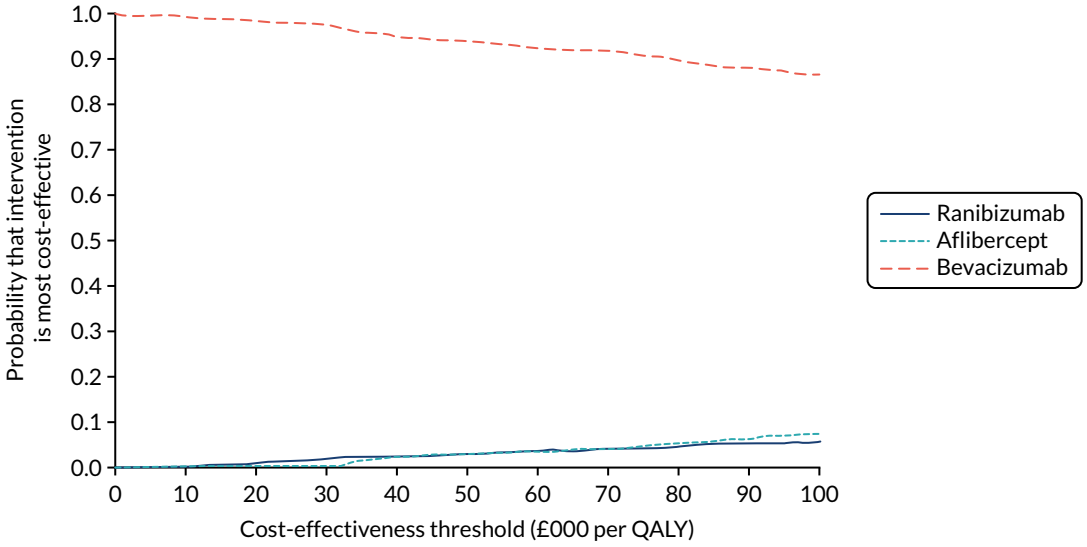

FIGURE 18 Model-based analysis: CEAC.

TABLE 22 Model-based analysis: base-case disaggregated costs

	Costs (£) (95% CI)		
Type of cost	**Ranibizumab**	**Aflibercept**	**Bevacizumab**
Treatment costs			
Trial eye intervention costs	11,785 (11,387 to 12,184)	17,156 (16,582 to 17,730)	634 (614 to 654)
Trial eye CST and visit costs	5427 (5351 to 5503)	5372 (5299 to 5444)	5622 (5542 to 5701)
Non-trial eye drug costs	771 (750 to 792)	1051 (1021 to 1081)	40 (39 to 41)
Non-trial eye CST and visit costs	268 (262 to 274)	249 (242 to 255)	276 (270 to 282)
Disease management costs	9588 (9049 to 10,127)	10,058 (9435 to 10,681)	9283 (8807 to 9759)
Ocular AEs costs	1322 (1238 to 1405)	109 (101 to 117)	1392 (1301 to 1483)
Blindness costs	1065 (918 to 1212)	1031 (886 to 1176)	1107 (957 to 1257)
Total costs	30,226 (29,386 to 31,066)	35,026 (33,990 to 36,062)	18,353 (17,782 to 18,925)

Scenario analyses

For the results of scenario analysis, see *Table 21*. In the scenarios using the EQ-5D and EQ-5D-V, the costs are unchanged from the base case using VFQ-UI, and the total QALYs for the three interventions are similar. Using the EQ-5D, aflibercept generates the most QALYs, followed by ranibizumab. This is different from the findings for the VFQ-UI base case because the relationship between visual acuity and utility differs for the three utility measures. In these scenarios, although ranibizumab and aflibercept are slightly more effective than bevacizumab, they are not cost-effective because they are much more expensive. The ICER for ranibizumab versus bevacizumab is £908,532 (95% CI £659,881 to £1,476,254) and for aflibercept versus ranibizumab is £128,513 (95% CI £110,116 to £152,663). Using the EQ-5D-V, the results indicate the same trends, but the CI for the incremental effectiveness of ranibizumab compared with bevacizumab contains zero, indicating that the difference is not statistically significant. The CI around the INMB is presented for this comparison, as the ICER may contain dominated results when ranibizumab is less effective than bevacizumab. Aflibercept is more effective than bevacizumab and ranibizumab, but it is not cost-effective.

Using a 100-week time horizon, as in LEAVO, bevacizumab is slightly less effective than ranibizumab and aflibercept, but the ICERs for ranibizumab versus bevacizumab and for aflibercept versus bevacizumab are £34,067,841 and £2,610,554 per QALY, respectively (see *Appendix 6*, *Table 62*). However, in this analysis, the 95% CIs for the incremental QALYs for ranibizumab versus bevacizumab contain zero, demonstrating that ranibizumab is not statistically significantly better. Bevacizumab remains the most cost-effective intervention in this scenario.

In the scenario using the list price of £243 per vial of bevacizumab, the costs for ranibizumab and aflibercept and the QALYS for the three interventions are unchanged from the base-case analysis, but the cost of bevacizumab has increased (see *Appendix 6*, *Table 63*). However, bevacizumab remains significantly cheaper than ranibizumab and aflibercept, demonstrated by the fact that the CIs for the incremental costs do not contain zero. Bevacizumab continues to dominate ranibizumab and aflibercept.

In deterministic analysis using a 5- and 10-year time horizon, bevacizumab remains the most cost-effective intervention at £20,000–30,000 per QALY (see *Appendix 6*, *Table 58*).

In deterministic analysis, to have comparable costs to bevacizumab, at £28 per injection, the PAS discounts for aflibercept and ranibizumab would need to be at least 95%.

Results: within-trial analysis

A total of 462 patients were included in the health economic analysis, with one patient excluded because they had been randomised in error. Thirteen people died and 42 participants withdrew or were lost to follow-up during the trial, and their subsequent costs and QALYs were adjusted, as described in *Method of economic evaluation*.

Data completeness

Over the 100-week data collection period, data were missing for some participants for baseline utility, QALY parameters for the three quality-of-life measures and total costs. For the extent of these missing data, see *Appendix 6*, *Table 64*. The highest proportion of missing data (56%) was recorded for total costs. There were only small differences in the proportion of missing data between the treatment arms. *Appendix 6*, *Figures 29–32*, explores the patterns of missing data for cost and HRQoL outcomes. The plots suggest that costs and utilities can be combined at each time period without any major loss of information. The plots suggested that the data were non-monotonic and missing at random; therefore, it was appropriate to use multiple imputation.[126]

Utilities

Figure 19 summarises the mean VFQ-UI utility score at each milestone visit, with 95% CIs. There is overlap between the intervals at each of the time points, suggesting no statistical differences between the three arms at all follow-up time points. The mean utility scores from the EQ-5D and the EQ-5D-V are provided (see *Appendix 6*, *Figures 34* and *35*, and *Table 65*).

Costs

Table 23 gives a breakdown of the total costs for each of the three treatment arms. Complete-case data were used for estimating the mean costs for each item, and the mean total costs were calculated from imputed data. The mean total costs in each arm are driven by the intervention costs, accounting for 84%, 87% and 76% of the total costs for ranibizumab, aflibercept and bevacizumab, respectively.

Appendix 6, *Figure 33*, shows histograms of the distribution of total costs by treatment arm. In each arm, few patients incurred extreme high costs, resulting in little skewedness in the cost data.

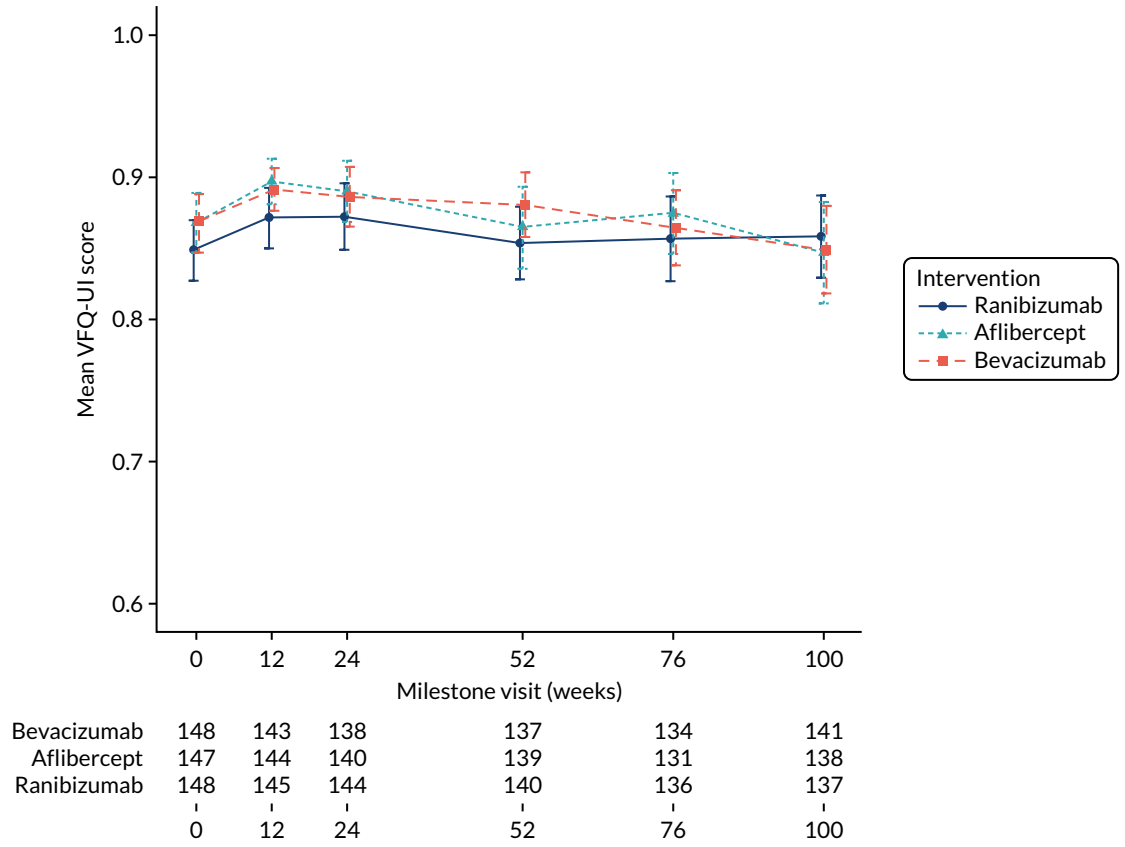

FIGURE 19 Within-trial analysis: mean utility scores calculated using the VFQ-UI over 100 weeks. Table shows number of observations at each time point. Reproduced with permission from Pennington *et al.*[95] This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Base-case analysis

In the base-case analysis (*Table 24*), the difference in mean total costs between aflibercept and ranibizumab was £1245 (95% CI £421 to £2070); between bevacizumab and ranibizumab arms, the difference was –£6760 (95% CI –£7546 to –£5973); and between aflibercept and bevacizumab, it was £7984 (95% CI £7209 to £8759). Bevacizumab dominated (less costly and with no difference in benefit) ranibizumab, with a probability of cost-effectiveness of 1.00 at the threshold of £20,000 per QALY.

Aflibercept was more costly, with a mean QALY difference of 0.004 (95% CI –0.0430 to 0.0518), than ranibizumab, with an ICER of £283,595 per QALY gained and a probability of cost-effectiveness of 0.04 at the threshold of £20,000 per QALY. Aflibercept was dominated by bevacizumab [more costly, with a mean QALY difference of –0.015 (95% CI –0.0618 to 0.0322)], with a probability of cost-effectiveness of 0.00 at the thresholds of £20,000 and £30,000 per QALY.

Uncertainty analysis

The CEAC generated from the parametric analysis, in the base-case analysis, is presented in *Figure 20*. The CEAC illustrates the probability that each treatment is the most cost-effective, compared with alternative treatments, at a range of threshold values. Bevacizumab has the highest probability of being the most cost-effective of the three treatments at all thresholds considered.

TABLE 23 Within-trial analysis: disaggregated costs for complete cases and total costs based on multiple imputation at 100 weeks

	Cost per patient (£)					
	Mean (SD); *n*			Mean (95% CI)		
Cost	Ranibizumab	Aflibercept	Bevacizumab	Aflibercept vs. ranibizumab	Bevacizumab vs. ranibizumab	Aflibercept vs. bevacizumab
Blindness	1.94 (15.28); 125	4.70 (23.51); 129	2.96 (18.79); 123	2.76 (−2.05 to 7.57)	1.02 (−3.85 to 5.88)	−1.74 (−6.57 to 3.08)
Concomitant medications	69.03 (342.27); 154	22.86 (26.40); 154	124.37 (907.96); 154	−46.17 (−171.35 to 79.01)	55.34 (−69.84 to 180.52)	101.51 (−23.67 to 226.69)
Concomitant procedures	173.23 (567.30); 154	222.60 (749.14); 154	217.57 (880.10); 154	49.37 (−116.66 to 215.4)	44.34 (−121.69 to 210.37)	−5.03 (−171.06 to 161)
Continuous care and support	7.11 (54.99); 99	38.76 (172.27); 88	10.43 (82.93); 90	31.66 (−0.75 to 64.07)	3.32 (−28.89 to 35.54)	−28.33 (−61.5 to 4.83)
Health-care contacts	729.36 (815.88); 91	710.46 (920.25); 92	740.14 (1065.62); 81	−18.89 (−289.62 to 251.84)	10.78 (−268.94 to 290.51)	29.68 (−249.33 to 308.68)
Hospital admissions	54.17 (479.35); 149	34.08 (239.58); 149	89.32 (689.04); 148	−20.10 (−134.43 to 94.23)	35.15 (−79.37 to 149.67)	−55.24 (−169.76 to 59.28)
Intervention	10,991.74 (3973.57); 154	12,445.31 (4231.59); 154	4784.99 (1247.34); 154	1453.57 (687.9 to 2219.23)	−6206.74 (−6972.41 to −5441.08)	7660.31 (6894.65 to 8425.98)
Total costs	13,014 (3605); 154	14,328 (3773); 154	6292 (3371); 154	1245 (421 to 2070)	−6760 (−7546 to −5973)	7984 (7209 to 8759)

TABLE 24 Within-trial analysis: base-case results using imputed 100-week data based on the VFQ-UI, adjusted for baseline utility score

Outcome	Intervention, mean (SD); *n*	Comparator, mean (SD); *n*	Difference,[a] mean (95% CI)	Probability of being cost-effective at £20,000 per QALY (at £30,000 per QALY)
Aflibercept vs. ranibizumab				
Cost (£)	14,328 (3773); 154	13,014 (3605); 154	1245 (421 to 2070)	–
QALY	1.651 (0.2374); 154	1.627 (0.2471); 154	0.004 (–0.0430 to 0.0518)	–
ICER			£283,595	0.04 (0.10)
Bevacizumab vs. ranibizumab				
Cost (£)	6292 (3371); 154	13,014 (3605); 154	–6760 (–7546 to –5973)	–
QALY	1.666 (0.2426); 154	1.627 (0.2471); 154	0.018 (–0.0282 to 0.0648)	–
ICER			Bevacizumab is dominant	1.00 (1.00)
Aflibercept vs. bevacizumab				
Cost (£)	14,328 (3773); 154	6292 (3371); 154	7984 (7209 to 8759)	–
QALY	1.651 (0.2374); 154	1.666 (0.2426); 154	–0.015 (–0.0618 to 0.0322)	–
ICER			Aflibercept is dominated	0.00 (0.00)

a Adjusted for baseline utility score.

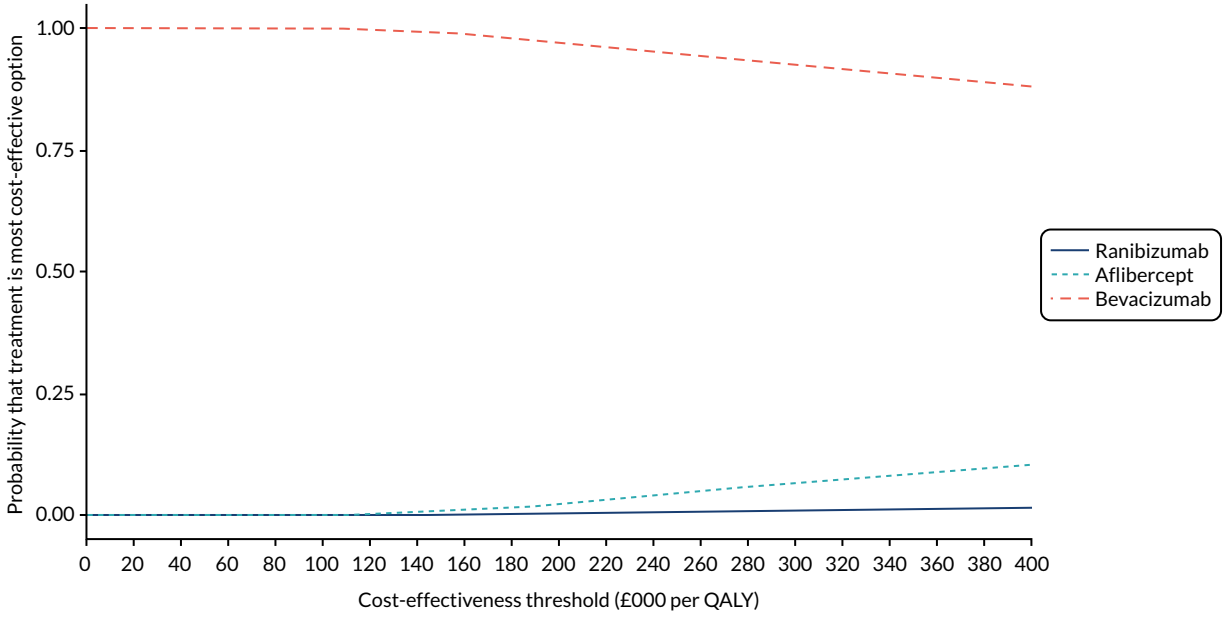

FIGURE 20 Within-trial analysis: CEAC.

The confidence ellipses graphs (see *Appendix 3*, *Figure 21a–c*) represent the point estimate of the ICER in the cost-effectiveness plane, with 50%, 75% and 95% CIs around the point estimate. The ICER for bevacizumab compared with ranibizumab falls in the south-east quadrant of the cost-effectiveness plane, with the 95% confidence ellipse wholly under the horizontal axis but spanning the vertical axis, suggesting certainty around the difference in costs but uncertainty around the difference in QALYs between the two interventions. The ICER for aflibercept compared with ranibizumab falls in the north-east quadrant, again with the 95% confidence ellipse wholly above the horizontal axis but spanning the vertical axis, suggesting certainty in the difference in costs but uncertainty in the difference in QALYs. Uncertainty is also illustrated (see *Appendix 6*, *Figure 36*) using the INMB.

Scenario analysis

The results from secondary analyses using the EQ-5D and the EQ-5D-V to estimate QALYs are summarised in *Table 25*. Although the three HRQoL measures (VFQ, EQ-5D and EQ-5D-V) generated slightly different results, the differences between the three interventions in terms of QALYs were small and uncertain in each analysis. The overall conclusion regarding the most cost-effective treatment is unchanged. Bevacizumab consistently dominates ranibizumab, and, although aflibercept might be slightly more clinically effective than bevacizumab and ranibizumab, it is more costly, resulting in a low probability of cost-effectiveness for both treatments at the £20,000 per QALY threshold.

The results from the fully incremental analysis show that bevacizumab dominates all alternative treatment options (i.e. it is less costly and more effective); therefore, ranibizumab and aflibercept are ruled out by dominance (see *Appendix 6*, *Table 66*).

The results from scenario analyses when discount rates of 30% and 50% are applied to the drug costs of ranibizumab and aflibercept are shown in *Table 26*. These findings suggest that the within-trial cost–utility base-case analysis results are not sensitive to these discount rates. Although the probability of aflibercept being cost-effective, compared with ranibizumab, increased to 11% and 24% at the £20,000 per QALY threshold for the 30% and 50% discounts, respectively, this was still a low probability. Bevacizumab was still cheaper and more effective than ranibizumab, and aflibercept was more costly and less effective than bevacizumab.

Results from scenario analyses using the list price of £243 for bevacizumab, complete-case data and a 52-week time horizon are summarised in *Appendix 6*, *Tables 67–69*. The same conclusions can be drawn from these analyses as from the base-case analysis, with bevacizumab remaining the most cost-effective treatment option.

Summary of findings from the economic evaluation

Main findings from the model-based analysis

The model-based analysis found that bevacizumab is consistently the most cost-effective intervention at a threshold of £20,000–30,000 per QALY. Bevacizumab, aflibercept and ranibizumab generate very similar QALYs, but bevacizumab leads to substantial cost savings, even when it is assumed that bevacizumab vials cannot be split, which would incur a higher cost per injection. The cost savings associated with bevacizumab are due to the much lower drug cost. For aflibercept and ranibizumab to have comparable costs to bevacizumab, and therefore have a chance of being cost-effective, the PAS discounts on the two licensed products would need to be at least 95%.

The findings were robust to sensitivity analyses, but the use of different utility measures led to differences in the absolute QALYs and ordering of each intervention. This indicates that the estimates of the differences in HRQoL are uncertain, but were consistently small across instruments.

TABLE 25 Within-trial analysis: results from secondary analyses using the EQ-5D and EQ-5D-V to estimate QALYs, adjusted for baseline utility score

Outcome	Mean (SD); *n*		Difference,[a] mean (95% CI)	Probability of being cost-effective at £20,000 per QALY (at £30,000 per QALY)
	Intervention	Comparator		
EQ-5D				
Aflibercept vs. ranibizumab				
Cost (£)	14,271 (3857); 154	13,068 (3636); 154	1196 (406 to 1986)	–
QALY	1.560 (0.3801); 154	1.513 (0.3744); 154	0.0184 (–0.0412 to 0.0779)	–
ICER			£65,023	0.13 (0.26)
Bevacizumab vs. ranibizumab				
Cost (£)	6273 (3384); 154	13,068 (3636); 154	–6783 (–7575 to –5990)	–
QALY	1.535 (0.3759); 154	1.513 (0.3744); 154	0.0098 (–0.0493 to 0.0690)	–
ICER (£)			Bevacizumab is dominant	1.00 (1.00)
Aflibercept vs. bevacizumab				
Cost (£)	14,271 (3857); 154	6273 (3384); 154	8035 (7246 to 8824)	
QALY	1.560 (0.3801); 154	1.535 (0.3759); 154	0.008 (–0.0529 to 0.0683)	
ICER			£1,041,476	0.00 (0.00)
EQ-5D-V				
Aflibercept vs. ranibizumab				
Cost (£)	14,273 (3720); 154	13,000 (3661); 154	1325 (499 to 2151)	
QALY	1.516 (0.3856); 154	1.472 (0.3666); 154	0.0433 (–0.0404 to 0.1269)	
ICER			£30,624	0.32 (0.49)
Bevacizumab vs. ranibizumab				
Cost (£)	6268 (3368); 154	13,000 (3661); 154	–6713 (–7499 to –5926)	–
QALY	1.500 (0.3757); 154	1.472 (0.3666); 154	0.0340 (–0.0471 to 0.1151)	–
ICER			Bevacizumab is dominant	1.00 (1.00)
Aflibercept vs. bevacizumab				
Cost (£)	14,273 (3720); 154	6268 (3368); 154	8012 (7232 to 8793)	–
QALY	1.516 (0.3856); 154	1.500 (0.3757); 154	0.0032 (–0.0837 to 0.0902)	–
ICER			£2,483,943	0.00 (0.00)

a Adjusted for baseline utility score.

TABLE 26 Within-trial analysis: results from scenario analyses using discount rates of 30% and 50% applied to aflibercept and ranibizumab, reflecting PASs available in the UK, adjusted for baseline utility score

Outcome	Mean (SD); *n*		Difference,[a] mean (95% CI)	Probability of being cost-effective at £20,000 per QALY (at £30,000 per QALY)
	Intervention	Comparator		
Discount of 30% applied to aflibercept and ranibizumab drug costs				
Aflibercept vs. ranibizumab				
Cost (£)	11,727 (2900); 154	10,893 (2848); 154	833 (203 to 1464)	–
QALY	1.651 (0.2426); 154	1.627 (0.2471); 154	0.004 (–0.0430 to 0.0518)	–
ICER			£189,133	0.11 (0.19)
Bevacizumab vs. ranibizumab				
Cost (£)	6227 (2700); 154	10,893 (2848); 154	–4656 (–5280 to –4033)	–
QALY	1.666 (0.2374); 154	1.627 (0.2471); 154	0.018 (–0.0282 to 0.0649)	–
ICER			Bevacizumab is dominant	1.00 (1.00)
Aflibercept vs. bevacizumab				
Cost (£)	11,727 (2900); 154	6227 (2700); 154	5476 (4837 to 6116)	
QALY	1.651 (0.2426); 154	1.627 (0.2471); 154	–0.015 (–0.0618 to 0.0322)	
ICER			Aflibercept is dominated	0.00 (0.00)
Discount of 50% applied to aflibercept and ranibizumab drug costs				
Aflibercept vs. ranibizumab				
Cost (£)	10,042 (2553); 154	9499 (2538); 154	497 (–71 to 1053)	–
QALY	1.651 (0.2426); 154	1.627 (0.2471); 154	0.004 (–0.0430 to 0.0518)	–
ICER			£111,622	0.24 (0.32)
Bevacizumab vs. ranibizumab				
Cost (£)	6201 (2419); 154	9499 (2538); 154	–3288 (–3842 to –2734)	–
QALY	1.666 (0.2374); 154	1.627 (0.2471); 154	0.018 (–0.0282 to 0.0649)	–
ICER			Bevacizumab is dominant	1.00 (1.00)
Aflibercept vs. bevacizumab				
Cost (£)	10,042 (2553); 154	6201 (2419); 154	3809 (3252 to 4365)	–
QALY	1.651 (0.2426); 154	1.666 (0.2374); 154	–0.015 (–0.0618 to 0.0322)	–
ICER			Aflibercept is dominated	0.00 (0.00)

a Adjusted for baseline utility score.

Main findings from the within-trial analysis

The within-trial health economic analysis found strong evidence that bevacizumab is considerably cheaper than ranibizumab and aflibercept, even when potential discount rates are applied to the two licensed products. There was no evidence to suggest a difference in HRQoL between the three treatments regardless of the HRQoL questionnaire used to measure utility; however, the estimates of QALY difference are uncertain. Bevacizumab is more cost-effective option than ranibizumab and aflibercept. Aflibercept is highly unlikely to be cost-effective in the short term (100 weeks), compared with ranibizumab or bevacizumab, using the commonly used cost-effectiveness threshold of £20,000–30,000 per QALY. The cost-effectiveness results are driven by the higher intervention cost for aflibercept, with no additional benefit in terms of QALYs.

Comparison of model-based and within-trial findings

The model-based and within-trial analyses both concluded that bevacizumab is the most cost-effective intervention for treating MO due to CRVO. Both analyses found small differences in QALYs between the three treatments, and substantial cost savings for bevacizumab. Despite the different approaches used for estimating utilities in the model- and trial-based analyses, the cost-effectiveness conclusion remained the same, indicating the robustness of the economic evaluation results.

The total QALYs for each intervention were similar for bevacizumab (model, 1.641; trial, 1.666), aflibercept (model, 1.646; trial, 1.651) and ranibizumab (model, 1.641; trial, 1.627). The total costs for each intervention were also similar for bevacizumab (model, £6349; trial, £6292), aflibercept (model, £18,844; trial, £14,328) and ranibizumab (model, £15,254; trial, £13,014). The similarities between the model- and trial-based costs and QALYs can be viewed as validation of the model-based analysis.

However, there are some differences between the model- and trial-based results. The model-based analysis leads to higher costs for each intervention, despite the exclusion of concomitant medications and procedures (although these make up < £250 per intervention in the trial-based analysis). The differences in costs may be explained by higher intervention drug and administration costs in the model. The within-trial analysis uses information recorded in LEAVO on whether or not a participant had an injection at each visit, whereas the model uses data from LEAVO in combination with the LEAVO re-treatment criteria to allow extrapolation beyond the trial period. The difference between the analyses indicates that some modelled patients receive the intervention when they did not in LEAVO.

The model results follow the same trend as the trial, in that the number of injections was smaller for aflibercept than for bevacizumab or ranibizumab, but the absolute number of injections in each arm is larger. The re-treatment criteria in the model dictate that patients will be re-treated if their CST is > 320 μm, and the CST data used in the model suggest that, on average, bevacizumab and aflibercept patients have a CST above this threshold throughout the trial. Variation between individual patients may have meant that a greater proportion of patients in the trial than in the model had a CST below the threshold. Alternatively, the difference may have arisen because the re-treatment criteria in the trial stipulated that patients should have a CST of > 320 μm due to intraretinal or subretinal fluid, and the model does not consider the reason for CST values. There may have been patients in the trial who had a CST of > 320 μm for other reasons who were not treated, but who would be assumed to be treated in the model. In addition, participants in LEAVO might have missed appointments, which would lead to reduced injection frequency.

There are also differences between the QALYs in the model-based and within-trial analyses. The model- and trial-based analyses both find no significant difference between bevacizumab and ranibizumab, but the model finds that aflibercept generates significantly more QALYs than the other two interventions. This is because the model-based analysis uses BCVA in both eyes (as well as age and sex) to predict utility (and utility is higher for patients with better visual acuity), but the within-trial analysis uses utility data directly. The trial utility data will capture other factors relating to patients' utility that may not relate to their BCVA, thus adding noise to the data. The relationship between visual acuity and utility is complex, non-linear and, in the observed LEAVO data for WSE, non-monotonic at times (see *Figure 16*). The mapping used ALDVMMs to try to capture the complex relationship and the distribution of utility data, but found some unusual features: typically ALDVMMs for EQ-5D contain at least three components, with one component representing patients with utility at or below zero. However, in this case, BCVA in the BSE or the WSE did not correlate with EQ-5D scores below zero, and so the model does not contain these separate components, as the covariates cannot predict membership of it.

Some of the QALY differences may also be due to differences in mortality. The within-trial analysis uses mortality data directly, and so includes the deaths of three participants in the ranibizumab group, six in the aflibercept group and four in the bevacizumab group. The model instead links mortality to

baseline age, sex and the presence of CRVO; because these are the same for the modelled patients on each treatment, there is no mortality difference between the treatments.

The model-based analysis does not include blind registration and low-vision aid costs for patients who are partially sighted, consistent with previous analyses.[13,51] The within-trial analysis captures these costs and includes blind registration and low-vision aid costs using the same estimates as for patients with severe sight impairment. As cost of blindness was a small proportion of the total costs in both the within-trial and model-based analyses, this difference does not influence the results.

Chapter 5 Discussion

Summary and interpretation of findings

Clinical effectiveness and side-effect profile

The results of this prospective multicentre Phase III RCT demonstrate that repeated intravitreal injections of the three anti-VEGF agents markedly improves BCVA in patients with MO secondary to CRVO over 100 weeks. Aflibercept was non-inferior to ranibizumab in the management of CRVO-related MO at 100 weeks, but it was not superior. The trial was unable to demonstrate that bevacizumab was non-inferior to ranibizumab, as the lower 95% CI extended beyond the non-inferiority margin of −5 letters. The results were consistent in that both the ITT and the per-protocol analyses gave similar results for both comparisons. Furthermore, subsequent sensitivity analyses supported the reliability of the two non-inferiority comparisons. Although post hoc analyses should be interpreted with caution, a comparison of bevacizumab with aflibercept could not demonstrate that bevacizumab was non-inferior to aflibercept.

In clinical terms, the result confirms aflibercept, as well as ranibizumab, use for MO due to CRVO, which was important to demonstrate as both are used widely in UK clinical practice but previously had not been compared directly for this condition. Bevacizumab, on the other hand, could be worse than ranibizumab and aflibercept, or it could be no worse. Practically, this means that, if a patient was being advised on treatments for MO due to CRVO with anti-VEGF therapy, the three agents could not be presented to the patient as being completely equivalent. Clinicians would have a low level of confidence in recommending that a patient who was receiving ranibizumab or aflibercept switch to bevacizumab therapy.

Other visual outcome results across the three groups were similar, with no meaningful differences between ranibizumab, aflibercept and bevacizumab in the number of participants in each group achieving key secondary end points, such as a gain of $\geq$ 15 BCVA letters or remaining stable (i.e. a $<$ 15-letter loss of visual acuity). The former means that, for patients commencing therapy, there is a 45–50% chance of achieving a three-line improvement in visual acuity. Patients can easily comprehend this by reference to a visual acuity chart when discussing the likely benefits of therapy with their clinician. All patients can be advised that, with regular attendance and adherence to treatment recommendations, there is at least a 90% chance that visual acuity will not deteriorate further. It is reassuring, from a patient perspective, to note that $<$ 4% of participants in the bevacizumab arm experienced a significant loss of vision of $\geq$ 30 letters, in keeping with data pertaining to ranibizumab and aflibercept in this and in previous studies.[29–31,33]

As anticipated, visual acuity improved rapidly during the initial monthly mandated injection phase, but a small mean decrease in visual acuity occurred across all three arms of the trial between weeks 16 and 24, which coincided with the pro re nata injection phase at week 16. Previous studies employed a protocol of six mandated monthly injections from week 0 to week 24.[9,21,27,29,31] During the trial design, we reviewed the available data and concluded that four mandated injections would be sufficient because in CRUISE the increase in visual acuity had reached a plateau by 4 months.[9] This may have been because the study enrolled a carefully selected population of people with non-ischaemic CRVO, who were likely to respond well to therapy. However, we now recognise that subsequent studies[27,29,31,58] that introduced broader and more generalisable eligibility criteria indicate that the initial gain in visual acuity takes longer to maximise. Thus, our findings suggest that the loading phase should be extended to 6 months. Had we employed the longer loading phase, it is possible that the gain in visual acuity achieved by the LEAVO participants at week 24 could have been some $\geq$ 3 letters higher, and more in keeping with gains at 6 months in other studies.[27,29,31]

It is also worth noting that SCORE2[27] and other studies, for example COPERNICUS,[29,31] did not maintain such early gains through 1 and 2 years, most likely because follow-up in year 2 was too infrequent to identify and treat those patients who needed regular medication. Notably, the final gain in visual acuity at week 100, compared with baseline, is higher in LEAVO than in any other previously reported study on this condition, and could possibly have been even higher.

We believe that this reflects the importance of timely monitoring in the second year of the study, which should initially be every 4 or 8 weeks, in keeping with the LEAVO protocol. Longer intervals of follow-up in other studies probably led to loss of initial visual gains.[31,34,38] It is possible that follow-ups every 4 or 8 weeks could be extended for selected patients, but this approach was not tested in LEAVO. The adjusted mean visual acuity gains at each time point after baseline had a consistent hierarchy throughout the trial, in that aflibercept group values were higher than ranibizumab group values, which, in turn, were higher than bevacizumab gains. Even at week 76, when the differences between the groups were small, this hierarchy was maintained.

As expected, the three anti-VEGF agents caused a significant and immediate reduction in adjusted OCT CST during mandated injection phase of baseline to 12 weeks. However, the CST increased by approximately 50 µm over the next three visits, as the number of injections administered reduced markedly. This was because intense treatment during the mandated phase meant that re-treatment criteria were frequently not met at the visits at 16 and 20 weeks, leading to a rebound increase in CST by week 24, which closely mirrored the decrease in visual acuity. However, as participants entered the remaining 18 months of the trial, their visits were regularly scheduled every 4 or 8 weeks, resulting in patients who met criteria for re-treatment being treated promptly. This meant that OCT values gradually decreased through to week 100, mirrored by a gradual increase in visual acuity during the same time period, in contrast to other studies in which OCT data did not closely reflect visual acuity changes.[27] A previously unreported finding was that a significantly greater percentage of participants in the aflibercept arm than in the ranibizumab arm had an OCT CST of < 320 µm at weeks 52 and 100. This suggests that aflibercept is more effective than ranibizumab at resolving MO in the longer term, a finding previously reported in exudative AMD and DMO.[43,54] Interestingly, bevacizumab was no less effective than ranibizumab in this regard, unlike in other retinal disorders.[54]

Fewer injections were required for aflibercept than for ranibizumab over 100 weeks, a difference that has been reported previously only in a treat-and-extend protocol.[57] The difference was significant as early as 24 weeks, and gradually increased by approximately 0.5 of an injection every 6 months. The post hoc analysis also found that fewer aflibercept than bevacizumab injections were required. This probably reflects the higher binding affinity of aflibercept to the VEGF molecule and a prolonged duration of action. This, coupled with a greater visual acuity gain and more patients achieving a normal thickness OCT CST at 2 years, would be a potential advantage of aflibercept over ranibizumab for MO due to CRVO.

No meaningful differences were seen between groups in OCT morphological grading at baseline or at 100 weeks.

Fundus fluorescein angiography did not detect differences across groups at baseline or exit, but, when the whole cohort is considered, there was overall change in distribution of non-perfusion at week 100, which we are further investigating.

No new safety concerns were identified in LEAVO to suggest any discrepancies in the overall safety profile of the three anti-VEGF agents, which is in keeping with previous reports. The chance of severe visual loss while undergoing anti-VEGF therapy remains low (i.e. in the order of 5% over 2 years) and has been noted in all previous studies.[9,27,29–31,57] This is typically due to development of an ischaemic CRVO, that is an increase in severity of the original occlusion to a point at which retinal blood inflow leads to compromised macular perfusion and possible neovascular complications. Patients were

promptly treated with panretinal photocoagulation in such cases, and anti-VEGF therapy for MO may have coincidentally limited the risk of neovascularisation.

When this trial was conceived, it was thought that small amounts of anti-VEGF agents were absorbed into the systemic circulation from an intraocular injection, resulting in a reduction in circulating VEGF concentrations and, possibly, in an increased risk of APTC events, although this cause–effect relationship has not been established. Hence, we planned, in the grant application, to perform a meta-analysis of all comparative anti-VEGF safety data from CRVO studies that we anticipated would be carried out simultaneously with LEAVO. In practice, only the comparative US SCORE2 study[27] and a small aflibercept versus bevacizumab trial have been conducted.[59] In addition, the SCORE2 investigators re-randomised their patients at 6 months, depending on whether or not the patients met predefined criteria of being good or poor responders.[58] Thus, a comparison was not possible beyond 6 months, and the comparative prevalence of AEs of anti-VEGF agents used in the two studies up to 6 months showed no difference. No study to date in multiple conditions, including nvAMD, DMO,[61] branch and central retinal condition and less common conditions such as pathological myopia, has shown an increased risk of APTC events with bevacizumab, and we do not believe that this issue would be a barrier to the use of this drug in the NHS. The recent judicial review by Mrs Justice Whipple[53] emphasised this point and she commented that ensuring that enough compounding pharmacies were available to ensure the large-scale safe production of significant amounts of the drug remained a key issue.

After the trial results were made available, we formulated a questionnaire to gather patient feedback, and received responses from members of the LEAVO CRVO users group that was formed prior to trial initiation, additional patients with RVO, the Barts Health/QMUL lay panel and Barts Heath diabetic patients who had a history of eye disease. We found that two-thirds of patients would consider bevacizumab treatment if the outcome could be worse than licensed alternatives but with such a small difference that it would be very unlikely to prevent them from carrying out their regular daily activities. All said that they would be more likely to agree to this if a licensed alternative was available should they not respond as expected to bevacizumab; provision would probably need to be made for this.

Limitations

The interpretation of the results should be considered in the context of patient eligibility and the trial treatment protocol. It is possible that the trial enrolled people whose eyes had limited potential for visual improvement because of a severe CRVO and compromised retinal perfusion and eyes with good visual acuity that had limited potential to improve because of a ceiling effect. Findings from secondary analyses were supportive but should be interpreted with caution as there was no adjustment for multiple testing. Aflibercept was considered an investigative agent because it was unlicensed when the trial commenced; therefore, all comparisons with bevacizumab were post hoc.

Generalisability (external validity)

The trial was undertaken in a wide range of UK ophthalmic centres. The trial eligibility criteria were purposely as broad as possible to ensure that a population would be recruited who represented patients presenting for NHS standard care. Unlike previous studies, patients with visual acuity of < 6/60 or with a relative afferent pupillary defect were not excluded. The protocol was amended to extend the upper limit of visual acuity from 74 (6/12) to 78 (6/9) letters to allow patients with MO but relatively good vision to enrol in the trial and not opt for NHS standard care. Patients with predisposing conditions (e.g. hypertension and glaucoma) were included and there was no restriction on concomitant medications or procedures during the trial; for example, a participant could undergo cataract surgery if his/her clinician deemed this necessary. The 4- to 8-week follow-up regimen in the second year ensured that the first-year visual acuity gains were maintained; we feel that this was an important part of the trial protocol for NHS centres to replicate. The centres involved in the trial ranged from small NHS departments through secondary referral centres to specialised ophthalmic-only

tertiary referral units. All centres and ophthalmologists were able to deliver the trial, and no special expertise or equipment beyond subspecialty retinal expertise was necessary. We believe that the trial is potentially applicable to all UK and overseas ophthalmic centres. We do not believe that there are any related outcomes that the trial did not assess that may affect applicability, and we believe that the 2-year primary outcome and follow-up intervals were appropriate. The concentrations of anti-VEGF therapy in the plasma after 4 weeks are immeasurably low and, because patients did not receive injections after week 96, we would not anticipate any harms occurring beyond week 100 relevant to the trial. The only exception to this might be pregnancy, but both the participant and the spouse of a participant in the trial who were pregnant carried to term with the delivery of normal neonates. Clearly, not all patients in clinical care will respond in the same manner as those in the trial cohort, but we would expect discrepancies only in magnitude rather than in direction, and mostly related to non-adherence to a robust treatment protocol. Overall, the patient feedback from the trial was very positive and we have no reason to believe that any subgroup of patients would decline to receive anti-VEGF therapy in a similar way to the trial protocol.

Overall evidence

Comparative clinical data

The only previous well-powered comparison of anti-VEGF drugs for MO secondary to CRVO prior to LEAVO was SCORE2,[27] which randomised 361 patients to aflibercept or bevacizumab, and treated them monthly from baseline to month 5 (six injections). The primary outcome was at 6 months. This differed from LEAVO, in which participants received monthly injections from baseline to month 3 (four injections) followed by pro re nata treatment at mandated visits at weeks 16 and 20, with milestone visual acuity assessments at 6 months. Greater mean BCVA letter gains were achieved in the first 6 months of SCORE2 than in LEAVO [aflibercept: SCORE2, mean 18.9 letters; LEAVO, mean 13.4 letters (SD 16.4 letters)]. This may be explained by the longer initial period of mandated monthly injections in SCORE2[27] or by differences in eligibility criteria. The baseline BCVA and case mix were dissimilar in these trials, with SCORE2 including patients with hemiretinal vein occlusion and LEAVO including patients with a baseline upper BCVA letter score of 78 (6/9), compared with 74 (6/12) in SCORE2. It is unknown whether or not the initial BCVA gains in SCORE2 could have been maintained through 2 years as the initial patient cohort was re-randomised at 6 months, depending on good and poor response to initial therapy.[58] The CRYSTAL study was a prospective single-arm study of ranibizumab therapy in CRVO with MO that followed up patients for 2 years, with a review at least every 8 weeks in year 2. Although this was a non-comparative study, the follow-up regimen was effective in maintaining first-year visual acuity gains in the second year, even though the number of injections in year 2 averaged only 3.3. This suggests that regular follow-up, with the targeting of patients in need of treatment, is of key importance.[56] Therefore, LEAVO is, to our knowledge, the only large clinical trial of MO due to CRVO to report comparative three-drug outcome data beyond 6 months with sustained visual acuity gains through 100 weeks across treatment arms.

Health economics analysis

The cost-effectiveness analysis found that bevacizumab was the most cost-effective intervention when compared with licensed agents (ranibizumab and aflibercept). In the treatment of MO due to CRVO, the model-based and within-trial analyses found small differences between the QALYs generated by aflibercept, ranibizumab and bevacizumab, but found that bevacizumab led to substantially lower costs. The finding that bevacizumab was the most cost-effective intervention was robust to scenario analyses that varied assumptions and data inputs. If bevacizumab was the standard of care and aflibercept or ranibizumab were new interventions being appraised by NICE, it is highly unlikely that they would be recommended as a cost-effective use of NHS resources.

Treatment with bevacizumab saves £5560 per year when compared with aflibercept, or £4546 per year when compared with ranibizumab (see *Appendix 6*, *Table 69*). If the estimated 5700 people

diagnosed with MO due to CRVO each year in England and Wales[8] were treated with bevacizumab instead of aflibercept, the NHS would save approximately £32M in 1 year (approximately £26M if the patients treated with bevacizumab instead of ranibizumab). Because the cost savings are due to a difference in intervention costs, this result would hold across other health-care systems, as long as the cost per injection for bevacizumab is lower than for aflibercept and ranibizumab.

This trial provides evidence of the cost-effectiveness of anti-VEGF treatment in MO due to CRVO, for which evidence is currently limited. A recent systematic review of the three interventions across retinal conditions did not identify any cost-effectiveness evidence in RVO.[58] This review identified two large US trials that provided evidence that ranibizumab and aflibercept are not cost-effective compared with bevacizumab in other retinal conditions (nvAMD and DMO). The cost-effectiveness findings for MO in the LEAVO trial are consistent with these findings.

The analyses adhered to good practice guidelines,[84,86,87,125,126] and had the strengths of being based on data from a well-conducted multicentre randomised trial and having good retention rates over a 100-week follow-up. A key strength of the economic evaluation is the use of three different HRQoL outcome measures, including both disease-specific (VFQ-UI and EQ-5D-V) and generic (EQ-5D) measures. A range of scenario analyses have also been performed providing evidence based on a range of discounted prices for the alternative medications. In the health economics literature, there is always a debate over the relative merits of condition-specific versus generic preference-based measures (in this case VFQ-UI vs. EQ-5D). The argument is that generic measures are not sensitive to particular disease-specific improvements; therefore, the VFQ-UI was seen as a better alternative for the LEAVO population. In addition, bolt-ons to generic measures, such as the EQ-5D-V, were proposed as an alternative approach to retain comparability across different disease areas while improving sensitivity. In this trial, we used the three alternative approaches; we found that the VFQ-UI generated more QALYs for each of the three interventions. However, the incremental QALYs were similar across the three quality-of-life measures.

The strengths of the model-based analysis lie in the model design and the data inputs. A discrete event simulation facilitates the use of a continuous BCVA scale, and avoids arbitrarily grouping patients. This enables the detection of small differences in visual acuity, which are linked to utility and costs, to ensure that the differences between the three treatments are reflected. The model structure further enables consideration of both eyes, and their relationship to utility. The utility mappings follow best practice guidelines[113] and up-to-date statistical methods to capture the distributions of utility. The inclusion of age and sex as variables in the utility mappings improved the model fit. In this trial population, quality of life is more likely to be affected by BCVA in both eyes (WSE and BSE). Therefore, our mappings were used to predict utility for each modelled patient using three quality-of-life measures (VFQ-UI, EQ-5D and EQ-5D-V) as a function of age, sex and BCVA in both eyes. Analysing resource use data from LEAVO allowed this to be linked to visual acuity to reflect the changing resource use associated with improvements or deterioration, which has not previously been captured in economic models for MO.[12,13] The use of growth models fitted to longitudinal BCVA and CST data allowed the extrapolation of these inputs over time, and avoided the need to make assumptions regarding effectiveness and injection frequency beyond the trial, as in previous models.[12,13]

There are large numbers of missing data in the health economic analysis, but the multiple imputation model for the trial-based analysis suggests that the results are robust. Resource use questionnaires are vulnerable to recall bias. However, in LEAVO, the resource use questionnaire was designed especially for the trial. Resource use is also a small proportion of the overall total cost in each arm, so any changes are unlikely to change the health economic conclusions. Furthermore, results from the complete-case analysis provided similar conclusions, and bevacizumab remained the most cost-effective option.

The primary outcome in LEAVO concerned visual acuity in the trial eye. The model-based analysis considered both the trial and the non-trial eyes and their relationship to utility. However, consideration

should be given to the relationship between these outcomes and the reality for patients; although clinical measures assess visual acuity in each eye separately, patients' overall sight is determined by their visual acuity in both eyes together. Patients' day-to-day functioning and quality of life may therefore not relate closely to the assessment of visual acuity in the trial eye, and this may explain why the differences in the utilities and QALYs between arms were not significant in the economic evaluation. The mapping from BCVA to utility used a robust estimator of the variance used in the statistical model. A limitation of this was the inclusion of repeated observations of the same patients to increase the number of observations available. A cluster-robust estimator of the SEs could have been used that is robust in the presence of correlation between observations for each individual. This does not change the estimated coefficients from the ALDVMM; it affects only the SEs used in the probabilistic sensitivity analyses.

Chapter 6 Conclusions

Implications for health care

LEAVO was unable to demonstrate that bevacizumab is non-inferior, that is it may be worse or may not be worse than ranibizumab and aflibercept in the management of MO due to CRVO. Clinicians would have a low level of confidence in recommending that bevacizumab is equivalent in clinical effectiveness to the licensed medications for the management of this condition. No differences were detected in the side-effect profile of the treatments in this trial, in keeping with previous trials in this indication. Patients' quality of life was not significantly different between treatment arms. This suggests that the clinical differences between the treatments were not sufficiently great to affect participants' regular daily activities, as appraised in this trial. However, it is possible that, in certain situations, patients may undertake or would wish to undertake a visual task in which a difference in visual acuity in one eye may be noticeable to them. It is also important to note that CRVO is typically a unilateral condition, and the vision-related quality of life is dependent on the BSE. Therefore, this finding is not applicable to other retinal conditions such as nvAMD and DMO, as a result of which a larger proportion of patients have bilateral visual impairment.

Compared with aflibercept and ranibizumab, bevacizumab was the most cost-effective treatment for MO due to CRVO. If aflibercept and ranibizumab were to be appraised by NICE in a multitechnology appraisal with bevacizumab, it is highly unlikely that they would be considered cost-effective. Treating patients with bevacizumab would certainly lead to cost savings to the NHS and other health-care systems. However, because the trial could not demonstrate that bevacizumab was non-inferior to the licensed medication, the trial results would need to be discussed in detail with patients, their representatives and funders before the treatment proceeded. The post-trial patient questionnaire responses suggest that approximately two-thirds of patients may be amenable to this approach, assuming that the licensed medications were available in reserve.

Recommendations for research

Additional patient involvement in this area would be required to help quantify more exact numbers of patients willing to consider bevacizumab therapy for MO due to CRVO, and the key factors that would dissuade other patients and whether or not these could be mitigated. This would probably require the full involvement of patients, patient advocate groups and funders to determine if bevacizumab could be introduced in this way. Further larger-scale clinical trials may also be justified for this condition.

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Publications

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Hykin P, Sivaprasad S, Prevost AT, Vasconcelos JC, Murphy C, Kelly J, *et al. Protocol 14PRT/06545: A Multicentre Phase 3 Double-masked Randomised Controlled Non-Inferiority Trial Comparing the Clinical and Cost Effectiveness of Intravitreal Therapy with Ranibizumab (Lucentis) vs. Aflibercept (Eylea) vs. Bevacizumab (Avastin) for Macular Oedema due to Central Retinal Vein Occlusion (LEAVO trial).* URL: www.thelancet.com/protocol-reviews/14PRT-06545 (25 May 2020).

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Data-sharing statement

Consent was not obtained for data-sharing with a third party. The presented data are anonymised and risk of identification is low. All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review. Three years after this report has been published, the data will be deposited with the research and development department in Moorfields Eye Hospital.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 The LEAVO study group

LEAVO study group

The LEAVO study group thanks all the patients who participated in the study, and all of the site investigators and research teams.

TABLE 27 The LEAVO Study Group

Site	Principal investigator
Moorfields Eye Hospital NHS Foundation Trust, London	Sobha Sivaprasad
King's College Hospital, London	Haralabos Eleftheriadis
New Cross Hospital, Wolverhampton & Midland Counties Eye Infirmary, Wolverhampton	Yit Yang
Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool	Michael Briggs
University Hospital Southampton NHS Foundation Trust, Southampton	Andrew Lotery
Royal Victoria Hospital, Belfast, and Queen's University Belfast	Michael Williams
Department of Ophthalmology, Royal Blackburn Hospital, Blackburn	Salwa Abugreen
Bradford Ophthalmology Research Network, Bradford Teaching Hospitals NHS Foundation Trust, Bradford	Faruque Ghanchi
Sussex Eye Hospital, Brighton	Edward Hughes
Bristol Eye Hospital, Bristol	Adam Ross
Department of Ophthalmology, West Suffolk NHS Foundation Trust, Suffolk	Nitin Gupta
Ophthalmology Department, Torbay Hospital, Devon	Stephen Turner Yinka Osoba
Essex County Hospital, Colchester	Jignesh Patel
Macular Unit, Hospital of St. Cross, Rugby	Sergio Pagliarini
Birmingham and Midlands Eye Centre, Birmingham	Peck-Lin Lip
Kent and Canterbury Hospital, Canterbury	Nishal Patel Afsar Jafree
Ophthalmology Department, Frimley Park Hospital NHS Foundation Trust, Surrey	Geeta Menon
Whipps Cross University Hospital, Barts Health NHS Trust, London	Sudeshna Patra
James Paget University Hospital, Norfolk	Ben Burton
Department of Ophthalmology, Royal Surrey County Hospital, Guildford, Surrey	Simon Taylor
Harrogate and District NHS Foundation Trust, Harrogate, North Yorkshire	Sarah Mackenzie
York Teaching Hospital NHS Foundation Trust, York	Richard Gale
Darlington Memorial Hospital, County Durham and Darlington NHS Foundation Trust	Komala Vadivelu
St James's University Hospital, Leeds	Martin McKibbin
Ophthalmology Department, Hillingdon Hospitals NHS Foundation Trust, London	Sheena George
Maidstone and Tunbridge Wells NHS Trust, Kent	Goncalo Almeida
Central Manchester Hospital, Manchester University NHS Foundation Trust, Manchester	Yvonne D'Souza

continued

TABLE 27 The LEAVO Study Group (*continued*)

Site	Principal investigator
Royal Victoria Infirmary, Newcastle upon Tyne	James Talks
Luton and Dunstable NHS University Hospital, Hertfordshire	Venki Sundaram
University Hospital of Wales, Cardiff	Sanjiv Banerjee
Sunderland Eye Infirmary, Sunderland	Maged Habib
Royal Glamorgan Hospital, North Glamorgan NHS Trust	Raghu Ram
Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield	Christopher Brand
Addenbrooke's Hospital, Cambridge	Doug Newman
Department of Ophthalmology, Gartnavel General Hospital, Glasgow	David Gilmour
Ophthalmology Department, Bolton NHS Foundation Trust, Bolton	Simon Kelly
Calderdale Royal Hospital, Halifax	Rehna Khan
University Hospitals of Leicester NHS Trust, Leicester	Theo Empeslidis
Department of Ophthalmology, Norfolk and Norwich Hospital, Norwich	Colin Jones
Cheltenham General Hospital, Gloucestershire	Emily Fletcher
Department of Ophthalmology, Hull and East Yorkshire Hospitals NHS Trust, Hull	Louise Downey
Western Eye Hospital, London	Saad Younis
James Cook University Hospital, South Tees NHS Foundation Trust, South Tees	Philip Severn
Princess Alexandra Hospital, Harlow, Essex	Priya Prakash

Appendix 2 The LEAVO study committees

We would like to thank the following for their valuable contribution to this study:

Trial Steering Committee members – Susan Downes (chairperson, Oxford Eye Hospital, UK), Irene Stratton (Gloucestershire Hospitals NHS Foundation Trust, UK), Hiten Dodhia (Lambeth and Southwark Councils, Public Health, London, UK), Greg Fell (Sheffield Council, Public Health, Sheffield, UK), Riaz Asaria (Royal Free London NHS Foundation Trust, London, UK), Jonathan Byrne (King's College NHS Foundation Trust, London, UK), Vanessa Burgess (NHS Lambeth Clinical Commissioning Group, London, UK), Alison Powling (Community Diabetes, Barts Health NHS Trust, London, UK) and Mrs Melba Ryde (lay representative).

Data Monitoring Committee members – Sarah Walker (chairperson, Oxford University, Oxford, UK), Consuela Moorman (Stoke Mandeville Hospital, Buckinghamshire Healthcare NHS Trust) and Baljean Dhillon (Centre for Clinical Brain Sciences, University of Edinburgh).

Appendix 3 Additional data: tables and figures

TABLE 28 Analyses used for secondary outcomes

Type of variable	Outcome	Method
Continuous	BCVA at 52 weeks	LME model
	Mean OCT CST at 52 and 100 weeks	LME model
	Macular volume at 52 and 100 weeks	LME model
	VFQ-25 composite score, distance and near subscales at 52 and 100 weeks	LME model
	Number of injections by 100 weeks	Difference in means with 95% CI
	Change in retinal non-perfusion at week 100 as assessed by disc areas of non-perfusion (in approximately 27 sites)	Difference in medians with 95% CI
Categorical	Participants with a $\geq$ 15 and $\geq$ 10 ETDRS letter improvement, $<$ 15 ETDRS letter loss and $\geq$ 30 ETDRS letter loss (severe visual loss) at 52 and 100 weeks	Differences in proportions with 95% CI
	Participants scoring $\geq$ 73 ETDRS letters, $\leq$ 58 ETDRS letters and $\leq$ 19 letters at 52 and 100 weeks	Differences in proportions with 95% CI consistent with a chi-squared test
	Participants with OCT CST of $<$ 320 µm at 52 and 100 weeks	Differences in proportions with 95% CI consistent with a chi-squared test
	Persistent non-responder participants at 52 and 100 weeks	Differences in proportions with 95% CI
	Participants developing ocular neovascularisation by 52 and 100 weeks	Differences in proportions with 95% CI
	Participants with OCT anatomical features (e.g. diffuse intraretinal oedema, subretinal fluid, vitreomacular interface abnormality, EZ disruption, DRIL) at 52 and 100 weeks	Differences in proportions with 95% CI
	Participants with change in area of retinal non-perfusion	Differences in proportions with 95% CI
	Prevalence of local and systemic side effects	Differences in proportions with 95% CI

TABLE 29 Complete trial assessment schedule from baseline to week 100

Assessment	Screening	Baseline	Week 4	8	12	16	20	24	28–48	52	56–72	76	80–96	100	Withdrawal visit
Variable treatment visits									4–8 weeks		4–8 weeks		4–8 weeks		13–97 weeks
Informed consent	✗														
Inclusion/exclusion criteria (✗1 if on different day[a])	✗	✗1													
Randomisation		✗													
Urine pregnancy test for women of child-bearing age	✗														
Patient demographics and medical and ophthalmic history	✗														
AEs	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Concomitant medication review	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Blood pressure	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
BCVA (ETDRS) in both eyes (✗2 if with refraction)	✗2	✗	✗	✗	✗2	✗	✗	✗2	✗	✗2	✗	✗2	✗	✗2	✗2
Standard ophthalmic examination of both eyes	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
OCT on both eyes	✗		✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Wide-angle or seven-field colour fundus photography	✗									✗				✗	✗
Wide-angle or seven-field FFA	✗													✗	✗
VFQ-25, EQ-5D and EQ-5D-V		✗			✗			✗		✗		✗		✗	✗
Resource use questionnaire		✗			✗			✗		✗		✗		✗	✗
Treatment allocation guess form														✗	✗
Administer IMP (✗3 if pro re nata treatment)		✗	✗	✗	✗	✗3	✗3	✗3	✗3	✗3	✗3	✗3	✗3		

a Most patients were screened and underwent the baseline examination on the same day, although it was possible to do this on a different day, in which case inclusion/exclusion criteria were reviewed at the baseline visit rather than at the screening visit.

TABLE 30 Summary of substantial amendments to the LEAVO protocol

Amendment number	Purpose	Sponsor classification	MHRA date approved	REC date approved	HRA date approved	Changes to documents
SA#1	• To cover MHRA grounds for non-acceptance • Changes to protocol and patient information sheet	Substantial	24 July 2014	4 September 2014	N/A	• Protocol and patient information sheet: changes to ensure that patients use contraception for 6 months after their last intravitreal injection of anti-VEGF therapy • Protocol: changes to exclusion criteria
SA#2	• Changes to protocol, patient information sheet, ICF • Also includes minor amendments to the protocol	Substantial	27 February 2015	10 November 2014	N/A	• Protocol: changes to inclusion and exclusion criteria; treatment allocation guess form; re-treatment criteria; criteria for restarting therapy; management of ischaemic CRVO, NVG, angle or iris neovascularisation; expectedness; secondary outcome • Patient information sheet: to reflect that visual acuity will form part of the routine eye exam; guidance on contraception • ICF: to reflect new patient information sheet
SA#3	New principal investigator at existing site, removal of site, addition of new site	Substantial	16 March 2015	17 February 2015	N/A	• Patient information sheet: amended following review of new SPCs; allows sites to use nurse injectors • ICF: to reflect new patient information sheet
SA#4	Adding sites: Calderdale Royal Hospital, Leicester Royal Infirmary, Norfolk and Norwich Hospital, Cheltenham General Hospital	Substantial	N/A	2 June 2015	N/A	None

continued

TABLE 30 Summary of substantial amendments to the LEAVO protocol (*continued*)

Amendment number	Purpose	Sponsor classification	MHRA date approved	REC date approved	HRA date approved	Changes to documents
SA#5	Adding sites: Hull Royal Infirmary, Gartnavel General Hospital, Western Eye Hospital, James Cook University Hospital, Princess Alexandra Hospital, Aberdeen Royal Infirmary; new principal investigator at existing site: Cheltenham General Hospital	Substantial	N/A	4 August 2015	N/A	None
SA#6	Changes to protocol, patient information sheet, ICF	Substantial	14 March 2016	11 February 2016	16 May 2016	• Protocol: changes to inclusion and exclusion criteria, rescreening, injectors, statistical changes, miscellaneous • Patient information sheet: changes to clarify who performs the injections and who prescribes antibiotic drops ICF: to reflect new patient information sheet
SA#7	New principal investigator at existing site: Darlington Memorial Hospital	Substantial	N/A	11 August 2016	N/A	None
SA#8	New principal investigator at existing site: Canterbury Hospital	Substantial	N/A	19 June 2017	20 June 2017	None
SA#9	Change of SPC regarding reference safety information	Substantial	2 August 2017	25 July 2017	22 August 2017	None
SA#10	New principal investigator at existing site: Darlington Memorial Hospital	Substantial	N/A	16 July 2018	16 July 2018	None
SA#11	New principal investigator at existing site: Torbay Hospital	Substantial	N/A	4 September 2018	4 September 2018	None

HRA, Health Research Authority; ICF, informed consent form; N/A, not applicable; REC, Research Ethics Committee; SA, substantial amendment; SPC, summary of product characteristics.

TABLE 31 Last visit week of withdrawal patients

Time point	Trial arm (*n*)			Total (*n*)
	Ranibizumab	Aflibercept	Bevacizumab	
Baseline	3	0	0	3
4 weeks	1	0	2	3
8 weeks	2	1	0	3
12 weeks	0	2	0	2
16 weeks	0	1	0	1
20 weeks	0	0	2	2
24 weeks	1	1	0	2
28 weeks	3	0	1	4
32 weeks	1	2	0	3
36 weeks	0	0	0	0
40 weeks	2	1	2	5
44 weeks	0	0	0	0
48 weeks	0	0	1	1
52 weeks	0	2	2	4
56 weeks	2	1	0	3
60 weeks	0	0	0	0
64 weeks	0	2	2	4
68 weeks	0	3	1	4
72 weeks	1	3	0	4
76 weeks	1	1	1	3
80 weeks	0	1	0	1
84 weeks	0	0	0	0
88 weeks	1	0	0	1
92 weeks	1	0	1	2
96 weeks	1	0	0	1
Total	20	21	15	56

TABLE 32 Reasons for and time to withdrawal

Date withdrawn	Date randomised	Weeks in trial (*n*)	Reason for withdrawal	Trial arm
30 June 2015	9 April 2015	12	Health deterioration	Ranibizumab
14 September 2015	24 June 2015	12	Participant no longer wish to take part	Aflibercept
6 November 2015	10 September 2015	8	Unable to locate/contact participant	Bevacizumab
6 November 2015	25 September 2015	6	Participant no longer wish to take part	Ranibizumab
8 December 2015	8 December 2015	0	Other	Ranibizumab

continued

TABLE 32 Reasons for and time to withdrawal (*continued*)

Date withdrawn	Date randomised	Weeks in trial (*n*)	Reason for withdrawal	Trial arm
8 January 2016	31 March 2015	40	Other	Bevacizumab
12 April 2016	19 May 2015	47	Participant no longer wishes to take part	Bevacizumab
26 May 2016	1 September 2015	38	Participant no longer wishes to take part	Aflibercept
1 June 2016	23 December 2015	23	Participant no longer wishes to take part	Bevacizumab
7 June 2016	13 October 2015	34	AE	Ranibizumab
21 June 2016	23 September 2015	39	Patient moving away from area	Aflibercept
22 July 2016	16 June 2015	57	Participant no longer wishes to take part	Ranibizumab
29 July 2016	18 April 2016	15	Other	Ranibizumab
19 August 2016	9 June 2016	10	Death of participant	Ranibizumab
30 August 2016	29 January 2016	31	Unable to locate/contact participant	Aflibercept
26 September 2016	3 November 2015	47	Health deterioration	Ranibizumab
12 October 2016	17 June 2015	69	Patient moving away from area	Bevacizumab
17 October 2016	28 August 2015	59	Participant no longer wishes to take part	Ranibizumab
19 October 2016	11 December 2015	45	Participant no longer wishes to take part	Ranibizumab
29 October 2016	18 February 2016	36	Death of participant	Aflibercept
31 October 2016	14 April 2016	29	Death of participant	Bevacizumab
8 November 2016	25 April 2016	28	Participant no longer wishes to take part	Aflibercept
9 November 2016	8 April 2015	83	Unable to locate/contact participant	Aflibercept
26 November 2016	26 January 2016	44	Participant no longer wishes to take part	Bevacizumab
18 December 2016	13 June 2016	27	Death of participant	Aflibercept
3 January 2017	26 August 2016	19	Death of participant	Aflibercept
3 January 2017	26 August 2015	71	Health deterioration	Aflibercept
12 January 2017	17 September 2015	69	Unable to locate/contact participant	Aflibercept
1 February 2017	13 April 2016	42	Participant no longer wishes to take part	Ranibizumab
9 February 2017	6 November 2015	66	Participant no longer wishes to take part	Bevacizumab
20 February 2017	23 October 2015	69	Other	Aflibercept
2 March 2017	28 April 2016	44	Participant no longer wishes to take part	Ranibizumab
9 March 2017	22 October 2015	72	Death of participant	Ranibizumab
10 March 2017	23 October 2015	72	Participant no longer wishes to take part	Bevacizumab
21 March 2017	27 October 2015	73	AE	Aflibercept
15 May 2017	3 March 2016	63	Death of participant	Ranibizumab
25 May 2017	31 December 2015	73	Participant no longer wishes to take part	Aflibercept
19 June 2017	16 October 2015	87	Death of participant	Aflibercept
1 August 2017	12 October 2015	94	Death of participant	Bevacizumab
5 September 2017	22 March 2016	76	Health deterioration	Bevacizumab
14 September 2017	25 February 2016	81	AE	Bevacizumab
10 November 2017	14 November 2016	52	Participant no longer wishes to take part	Aflibercept

TABLE 32 Reasons for and time to withdrawal (*continued*)

Date withdrawn	Date randomised	Weeks in trial (*n*)	Reason for withdrawal	Trial arm
13 November 2017	2 June 2016	76	Unable to locate/contact participant	Ranibizumab
17 November 2017	21 October 2015	108	Unable to locate/contact participant	Ranibizumab
27 November 2017	14 June 2016	76	Death of participant	Aflibercept
4 December 2017	28 October 2016	57	Death of participant	Bevacizumab
17 January 2018	28 October 2016	64	Death of participant	Bevacizumab
1 March 2018	17 June 2016	89	Participant no longer wishes to take part	Ranibizumab
29 March 2018	23 June 2016	92	Participant no longer wishes to take part	Aflibercept
5 May 2018	18 October 2016	81	Death of participant	Aflibercept
4 June 2018	10 October 2016	86	Patient moving away from area	Aflibercept
13 August 2018	24 November 2016	90	AE	Bevacizumab
13 September 2018	11 October 2016	100	Participant no longer wishes to take part	Ranibizumab
5 October 2018	29 November 2016	96	Health deterioration	Aflibercept
13 November 2018	30 November 2016	102	AE	Ranibizumab
27 November 2018	4 November 2016	108	Unable to locate/contact participant	Ranibizumab

TABLE 33 Comparison of OCT macular volume at 52 and 100 weeks

Time point	Treatment A	Treatment B	Adjusted difference between groups[a] (95% CI)
Aflibercept vs. ranibizumab			
	Aflibercept	*Ranibizumab*	
Mean (SE)			
At screening	12.3 (0.2)	13.0 (0.2)	
At 52 weeks	9.1 (0.2); $n = 140$	9.2 (0.2); $n = 138$	
At 100 weeks	8.6 (0.1); $n = 133$	8.9 (0.1); $n = 135$	
Adjusted difference			
At 52 weeks			−0.1 (−0.6 to 0.4)
At 100 weeks			−0.2 (−0.6 to 0.3)
Bevacizumab vs. ranibizumab			
	Bevacizumab	*Ranibizumab*	
Mean (SE)			
At screening	12.8 (0.2)	13.0 (0.2)	
At 52 weeks	9.4 (0.2); $n = 135$	9.2 (0.2); $n = 138$	
At 100 weeks	9.1 (0.2); $n = 135$	8.9 (0.1); $n = 135$	
Adjusted difference			
At 52 weeks			0.2 (−0.3 to 0.7)
At 100 weeks			0.3 (−0.2 to 0.7)

a The LME model incorporates 455 participants (ranibizumab, $n = 149$; aflibercept, $n = 153$; and bevacizumab, $n = 153$) with both CST and macular volume at either 52 weeks or 100 weeks.

TABLE 34 The input parameters for the health economic models

Parameter	Distribution	Mean (SE)	Source of mean	Source for SE
Intervention and related costs				
Ranibizumab injection	N/A	£551.00	BNF[117]	N/A
Aflibercept injection	N/A	£816.00	BNF[117]	N/A
Bevacizumab injection	N/A	£28.00	Judicial review[53]	N/A
CST cost	Gamma	£108.21	• Department of Health and Social Care[118] • NHS codes BZ87A	• Quartile data of the NHS codes • Department of Health and Social Care[130]
First visit cost	Gamma	£140.04	• Department of Health and Social Care[118] • NHS codes WF02B	
Follow-up visit cost	Gamma	£105.19	• Department of Health and Social Care[118] • NHS codes WF02A	
Costs associated with resource use				
A&E visit cost	Gamma	£160.23 (£9.34)	• Department of Health and Social Care[118] • Weighted average for NHS codes VB01Z to VB11Z	• Quartile data of the NHS codes (weighted) • Department of Health and Social Care[130]
Visit cost of ocular A&E	Gamma	£118.02 (£2.67)	• Department of Health and Social Care[118] • NHS codes WF01B	• Quartile data of the NHS codes • Department of Health and Social Care[130]
Visit cost of eye consultant	Gamma	£95.13 (£1.85)	• Department of Health and Social Care[118] • NHS codes WF01A	
Call cost to ophthalmologist	Gamma	£28.20 (£4)	• Department of Health and Social Care[118] • NHS codes WF01D	
Visit cost of optometrist/ optician	Gamma	£76.50 (£10.50)	• Department of Health and Social Care[118] • NHS codes WF01B	
Visit cost for low-vision appointment	N/A	£153.00	Estimated to be double the visit cost of optometrist/ optician	
Visit cost of GP	Gamma	£37.40 (£3.74)	Curtis and Burns[116]	10% assumption around the mean
Visit cost of practice nurse	Gamma	£17.79 (£1.78)		
Call cost to GP	Gamma	£28.00 (£2.80)		
Resource use parameters (every 3 months)				
A&E visit: WSE	Multinormal	−0.001	Analysis of LEAVO data	
A&E visit: constant		0.103		
Eye A&E visit: WSE	Multinormal	−0.002		
Eye A&E visit: constant		0.183		
GP visit: WSE	Multinormal	−0.004		

TABLE 34 The input parameters for the health economic models (*continued*)

Parameter	Distribution	Mean (SE)	Source of mean	Source for SE
GP visit: constant		0.441		
GP call: WSE	Multinormal	−0.001		
GP call: constant		0.082		
Eye consultant visit: WSE	Multinormal	−0.004		
Eye consultant visit: constant		1.163		
Low-vision appointment: WSE	Multinormal	−0.002		
Low-vision appointment: constant		0.137		
Nurse appointment: WSE	Multinormal	−0.001		
Nurse appointment: constant		0.083		
Optometrist appointment: WSE	Multinormal	0.000		
Optometrist: constant		0.054		
Ophthalmologist call: mean	Normal	0.013 (0.007)		
Helpline call: mean	Normal	0.025 (0.009)		
Blindness costs				
Percentage requiring community care	Beta	6% (0.6%)	Colquitt *et al.*[121]	10% assumption around mean
Percentage requiring hip replacement	Beta	5% (0.5%)	Colquitt *et al.*[121]	10% assumption around mean
Percentage requiring low-vision aids	Beta	33% (0.05%)	Colquitt *et al.*[121]	Margrain[131]
Percentage requiring low-vision rehabilitation	Beta	11% (1.1%)	Colquitt *et al.*[121]	10% assumption around mean
Percentage requiring residential care	Beta	30% (3%)	Colquitt *et al.*[121]	10% assumption around mean
Percentage requiring treatment for depression	Beta	39% (5.8%)	Colquitt *et al.*[121]	Galaria *et al.*[132]
Percentage requiring blindness registration	Beta	95% (0.05%)	Colquitt *et al.*[121]	Owen *et al.*[133]
Cost of community care (annual)	Gamma	£10,060.95 (£1006.10)	Curtis and Burns[116]	10% assumption around mean
Cost of hip replacement (annual)	Gamma	£4170.00 (£417.00)	• Department of Health and Social Care[118] • Code HT14C	10% assumption around mean
Cost of low-vision aids (one-off)	Gamma	£194.41 (£19.44)	Meads,[122] Curtis[116]	10% assumption around mean

continued

TABLE 34 The input parameters for the health economic models (*continued*)

Parameter	Distribution	Mean (SE)	Source of mean	Source for SE
Cost of low-vision rehabilitation (one-off)	Gamma	£153	Estimated to be double the visit cost of optometrist/optician	
Cost of residential care (annual)	Gamma	£6000.80 (£600.08)	Curtis and Burns[116]	10% assumption around mean
Cost of treatment for depression (annual)	Gamma	£2430.58 (£243.06)	NICE[123]	10% assumption around mean
Cost of blindness registration (one-off)	Gamma	£60.50 (£6.05)	Curtis and Burns[116]	10% assumption around mean
AEs				
Cost of AE	Gamma	£317.96 (£2.58)	Department of Health and Social Care[118]	Weighted variance from NHS reference costs[118]
Weibull distribution: shape parameter	Multinormal	0.745	Analysis of LEAVO data	
Weibull distribution: scale parameter – constant		−2.271		
Weibull distribution: scale parameter – aflibercept		−0.271		
Weibull distribution: scale parameter – bevacizumab		−0.049		
Withdrawal				
Weibull distribution: shape parameter	Multinormal	0.326	Analysis of LEAVO data	
Weibull distribution: scale parameter – constant		−2.966		
Weibull distribution: scale parameter – aflibercept		0.126		
Weibull distribution: scale parameter – bevacizumab		−0.227		
Mortality: hazard ratios for CRVO				
Female: aged 0–49 years	Log-normal	0.83 (2.89)	Bertelsen *et al.*[101]	Calculated from CIs
Female: aged 50–59 years	Log-normal	1.49 (1.86)	Bertelsen *et al.*[101]	Calculated from CIs
Female: aged 60–69 years	Log-normal	1.94 (1.27)	Bertelsen *et al.*[101]	Calculated from CIs
Female: aged 70–79 years	Log-normal	0.94 (1.25)	Bertelsen *et al.*[101]	Calculated from CIs
Female: aged ≥ 80 years	Log-normal	1.04 (1.23)	Bertelsen *et al.*[101]	Calculated from CIs
Male: aged 0–49 years	Log-normal	1.49 (1.88)	Bertelsen *et al.*[101]	Calculated from CIs
Male: aged 50–59 years	Log-normal	1.71 (1.54)	Bertelsen *et al.*[101]	Calculated from CIs
Male: aged 60–69 years	Log-normal	1.17 (1.3)	Bertelsen *et al.*[101]	Calculated from CIs
Male: aged 70–79 years	Log-normal	1.24 (1.14)	Bertelsen *et al.*[101]	Calculated from CIs
Male: aged ≥ 80 years	Log-normal	1.26 (1.22)	Bertelsen *et al.*[101]	Calculated from CIs

TABLE 34 The input parameters for the health economic models (*continued*)

Parameter	Distribution	Mean (SE)	Source of mean	Source for SE
BCVA and CST modelling				
BCVA: baseline age/10 on intercept	Normal	−0.19728 (0.049)	Analysis of LEAVO data	
BCVA: baseline BCVA/10 on intercept	Normal	0.56235 (0.041)		
BCVA: aflibercept on intercept	Normal	0.18927 (0.155)		
BCVA: bevacizumab on intercept	Normal	0.03001 (0.154)		
BCVA: baseline age/10 on slope	Normal	−0.25323 (0.06)		
BCVA: baseline BCVA/10 on slope	Normal	−0.15787 (0.047)		
BCVA: aflibercept on slope	Normal	−0.04577 (0.186)		
BCVA: bevacizumab on slope	Normal	−0.06674 (0.18)		
BCVA: days since injection at 12 weeks	Normal	−0.00083 (0.005)		
BCVA: days since injection at 24 weeks	Normal	−0.00536 (0.001)		
BCVA: days since injection at 52 weeks	Normal	0.00069 (0.001)		
BCVA: days since injection at ≥ 76 weeks	Normal	−0.00026 (0.0001)		
BCVA: number of injection at 12 weeks	Normal	0.10891 (0.072)		
BCVA: number of injection at 24 weeks	Normal	0.06345 (0.035)		
BCVA: number of injection at 52 weeks	Normal	−0.00871 (0.021)		
BCVA: number of injection at ≥ 76 weeks	Normal	−0.01121 (0.019)		
BCVA: intercept	Multinormal	4.811		
BCVA: slope	Multinormal	2.878		
CST: baseline age/10 on intercept	Normal	−0.1953 (0.048)		
CST: baseline CST/10 on intercept	Normal	0.13111 (0.029)		
CST: aflibercept on intercept	Normal	−0.46501 (0.151)		
CST: bevacizumab on intercept	Normal	0.22923 (0.149)		

continued

TABLE 34 The input parameters for the health economic models (*continued*)

Parameter	Distribution	Mean (SE)	Source of mean	Source for SE
CST: baseline age/10 on slope	Normal	0.29301 (0.067)		
CST: baseline CST/10 on slope	Normal	−0.04915 (0.039)		
CST: aflibercept on slope	Normal	0.36749 (0.205)		
CST: bevacizumab on slope	Normal	−0.02506 (0.197)		
CST: days since injection at 12 weeks	Normal	0.00231 (0.007)		
CST: days since injection at 24 weeks	Normal	0.02045 (0.003)		
CST: days since injection at 52 weeks	Normal	0.00239 (0.001)		
CST: days since injection at ≥ 76 weeks	Normal	0.00144 (0.001)		
CST: number of injection at 12 weeks	Normal	−0.00612 (0.103)		
CST: number of injection at 24 weeks	Normal	−0.0594 (0.056)		
CST: number of injection at 52 weeks	Normal	0.06798 (0.027)		
CST: number of injection at ≥ 76 weeks	Normal	0.06327 (0.022)		
CST: intercept	Multinormal	3.76348		
CST: slope	Multinormal	−2.75221		
Annual BCVA change				
Age 55–64 years: mean	Normal	0.0200 (0.002)	Klein *et al.*[98]	10% assumption around mean
Age 55–64 years: SD	Normal	0.0400 (0.004)	Klein *et al.*[98]	10% assumption around mean
Age 65–74 years: mean	Normal	−0.2600 (0.026)	Klein *et al.*[98]	10% assumption around mean
Age 65–74 years: SD	Normal	0.0400 (0.004)	Klein *et al.*[98]	10% assumption around mean
Age 65–74 years: mean	Normal	−0.7600 (0.076)	Klein *et al.*[98]	10% assumption around mean
Age 65–74 years: SD	Normal	0.0602 (0.060)	Klein *et al.*[98]	10% assumption around mean
Utility parameters: VFQ-UI				
Component 1: BSE/10	Multinormal	−0.00025	Analysis of LEAVO data	
Component 1: WSE/10		−0.00033		
Component 1: age/10		0.00922		
Component 1: male		0.00110		

TABLE 34 The input parameters for the health economic models (*continued*)

Parameter	Distribution	Mean (SE)	Source of mean	Source for SE
Component 1: constant		0.88490		
Component 2: BSE/10		0.02353		
Component 2: WSE/10		0.01637		
Component 2: age/10		0.03448		
Component 2: male		0.00751		
Component 2: constant		0.18926		
Component 3: BSE/10		0.00372		
Component 3: WSE/10		−0.00187		
Component 3: age/10		0.00638		
Component 3: male		−0.00413		
Component 3: constant		0.83403		
Probability of component 1 membership: BSE/10		0.25197		
Probability of component 1 membership: WSE/10		0.23102		
Probability of component 1 membership: constant		−2.31366		
Probability of component 2 membership: BSE/10		−0.41024		
Probability of component 2 membership: WSE/10		−0.04126		
Probability of component 2 membership: constant		4.00996		
Component 1: log-sigma		−4.78402		
Component 2: log-sigma		−2.24672		
Component 3: log-sigma		−3.49052		
Utility parameters: EQ-5D				
Component 1: BSE/10	Multinormal	0.01626	Analysis of LEAVO data	
Component 1: WSE/10		0.01022		
Component 1: age/10		−0.02851		
Component 1: male		0.02663		
Component 1: constant		0.86003		
Component 2: BSE/10		0.01693		
Component 2: WSE/10		−0.02069		
Component 2: age/10		0.04236		
Component 2: male		0.20485		
Component 2: constant		0.01774		

continued

TABLE 34 The input parameters for the health economic models (*continued*)

Parameter	Distribution	Mean (SE)	Source of mean	Source for SE
Probability of component 1 membership: BSE/10		0.39593		
Probability of component 1 membership: WSE/10		0.24805		
Probability of component 1 membership: constant		−2.76469		
Component 1: log-sigma		−1.99075		
Component 2: log-sigma		−1.32132		
Utility parameters: EQ-5D-V				
Component 1: BSE/10	Multinormal	0.00378	Analysis of LEAVO	
Component 1: WSE/10		−0.00730		
Component 1: age/10		0.04348		
Component 1: male		0.20676		
Component 1: constant		0.03574		
Component 2: BSE/10		0.02012		
Component 2: WSE/10		0.01255		
Component 2: age/10		−0.01937		
Component 2: male		0.01592		
Component 2: constant		0.73587		
Probability of component 1 membership: BSE/10		−0.53561		
Probability of component 1 membership: WSE/10		−0.20177		
Probability of component 1 membership: constant		3.77924		
Component 1: log-sigma		−1.25309		
Component 2: log-sigma		−1.93060		

BNF, *British National Formulary*; N/A, not applicable.

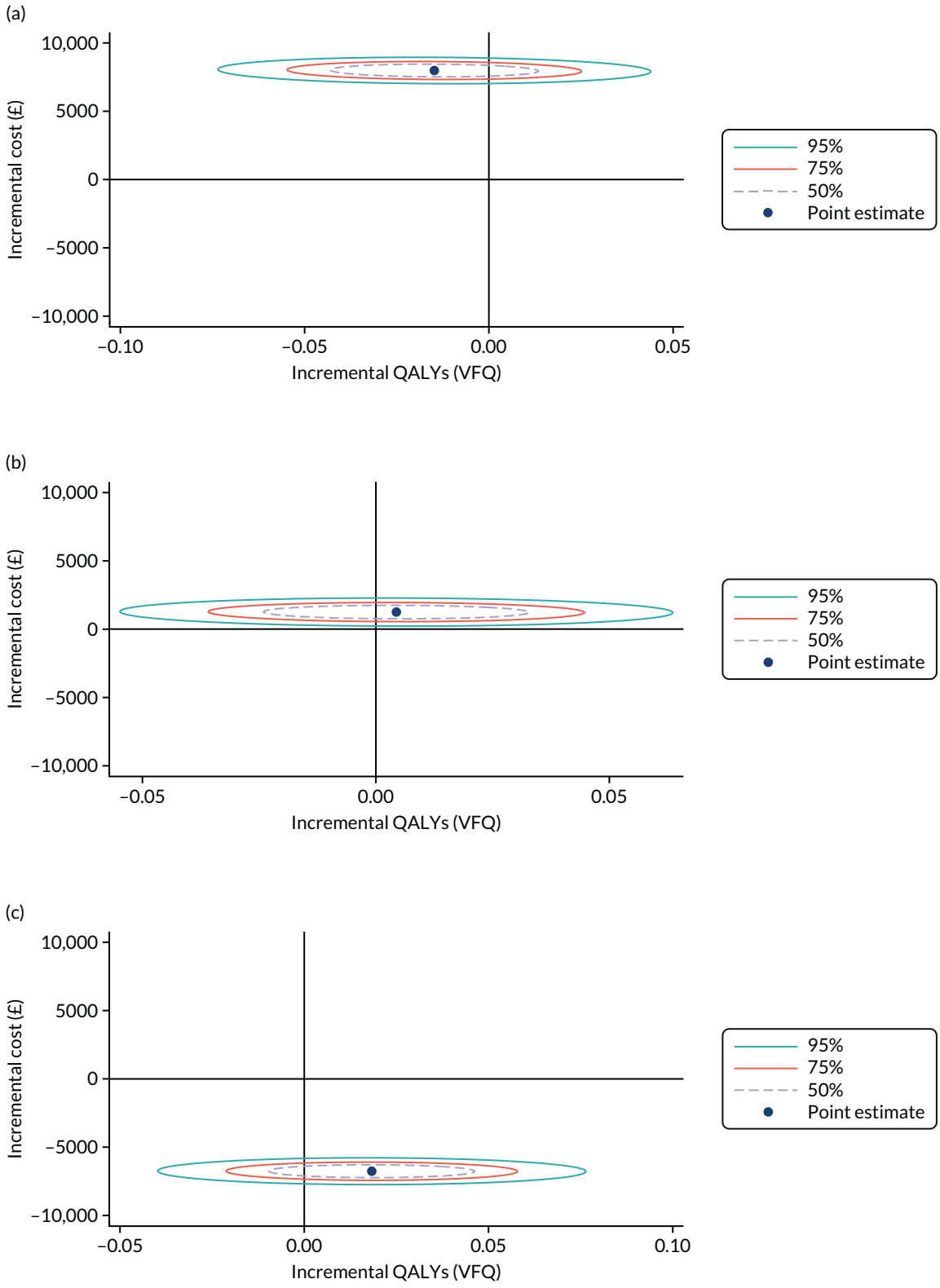

FIGURE 21 Within-trial analysis: confidence ellipses VFQ; VFQ-UI measure. (a) Aflibercept vs. bevacizumab; (b) aflibercept vs. ranibizumab; and (c) bevacizumab vs. ranibizumab.

Appendix 4 Procedure for assessing the primary outcome

Refracted visual acuity was performed by a certified optometrist who had signed and dated the site delegation log before study participation and was masked to patient treatment allocation. All procedures were performed in a certified visual acuity lane. The visual acuity examiners received the participants into the visual acuity lanes with a visual acuity worksheet form, trial number and detail of trial eye and non-trial eye to be refracted, but with no previous subject records or worksheet forms. BCVA was measured following refraction at screening and at 12, 24, 52, 76 and 100 weeks (and unscheduled visits if they were to be considered as milestone visits, including a withdrawal visit) in all participants in both eyes. At all other visits, visual acuity was recorded by masked personnel using the refraction results from the previous refraction visit.

Equipment and room set-up

The ETDRS chart R was used for refraction. The lightbox was illuminated with two cool daylight 20-W fluorescent tubes. New tubes were kept on for 96 hours before use. Room lights were turned off, and the chart lights were turned on. Any windows were covered. The illumination of the room was such that, with the room set up for testing, but with the chart light switched off, not more than 161.4 lux fell on the centre of the chart. The height of the chart needed to be such that the top of the third row of letters was 124.5 cm ($\pm$ 5 cm) from the floor. Full aperture trial lenses were used with a trial frame.

Refraction

The right eye was refracted first, with the participant seated 4 m from the chart. The fellow eye was occluded with a pad and tape. At the baseline visit, the initial acuity was measured with the participant's own spectacles or unaided if the participant did not have distance spectacles. The spectacles were analysed with a focimeter. Retinoscopy was performed to provide a starting point for subjective refraction. At follow-up visits, the previous refraction was used as the starting point. If the initial acuity was $\geq$ 6/60 (four letters read correctly), refraction was performed at 4 m. If the acuity was $<$ 6/60, refraction was performed at 1 m. Subjective refraction was performed using the format below. Plus/minus was offered in intervals appropriate to the level of acuity.

The sphere was checked as follows. Plus was added if it improved or made no difference to the visual acuity. This was continued until the offered plus blurred the visual acuity. Minus was added only if the subject read at least one more letter and the plus was rechecked. The cylinder axis was rechecked using a round letter on a row one or two lines above the lowest row the participant could read. The cylinder power was rechecked using a round letter on the lowest row the subject could read. The sphere was refined as before, offering plus, minus, then plus. The refraction recorded was the 4-m result. If the participant was tested at 1 m, 0.75 dioptre sphere (DS) was taken from the result to adjust for the 4-m distance. The procedure was repeated for the left eye.

Protocol for measuring ETDRS acuities

Best corrected visual acuity was measured using ETDRS chart 1 for the right eye and chart 2 for the left eye. Participants were not shown the charts until the test began. Each eye was tested at 4 m initially, even if the refraction had been performed at 1 m. The right eye was tested first, followed by the left.

The participant was seated 4 m from the chart. The distance was marked with clear and permanent floor markings. The left eye was occluded with a pad and tape and the lens correction from the subjective refraction was placed in the trial frame. What was required of the participant was then explained: there were 5 letters on each row, the letters were to be read slowly, there were no numbers on the chart, even if they were unsure of a letter they should guess, they could not go back and change their mind once they had attempted the next letter, and they could move their head or eye to give the best possible visual acuity as long as they did not lean forward.

The participant began by reading the top row of the chart and continued by reading every letter on each smaller line. The examiner recorded the results, circling each letter read correctly, putting a cross through each letter read incorrectly and leaving unmarked any letter for which no attempt was made. Participants were permitted to change their mind about a letter provided that the subsequent letter had not already been read. If a participant gave a choice of two letters, the examiner asked them to select one response only. The examiner did not read any letters out loud during the test, nor did they tell the participant if a letter had been identified correctly. If the participant lost their place, the examiner pointed to the next line to be read, but then moved away from the chart. The participant was asked and encouraged to move on to the next line as long as they correctly identified at least one letter on the previous line. The test was stopped when the participant could no longer guess, provided that mistakes had been made on previous guesses. Ideally, the aim was for four letters to be missed in a row.

If a participant could not read $\geq$ 20 letters at 4 m, the test was repeated at 1 m. In this case, only the first six rows needed to be attempted, and 0.75 DS was added to the prescription in the trial frame to correct for the shorter test distance. A rigid measuring device was used to ensure that the distance was correct, and care was taken to ensure that the participant did not move forward during testing. The visual acuity score was the number of letters read correctly at 4 m, plus the number of letters read correctly at 1 m. If a participant did not need to be tested at 1 m, that is they could read $\geq$ 20 letters at 4 m, then the score was the number of letters read correctly at 4 m, plus 30. The participant was given the credit for the 30 letters at 1 m, even though they did not have to read them. The approximate Snellen equivalent was also recorded (in metres). This was taken as the lowest row with one or no errors. If a participant could not read any letters on the ETDRS chart at 1 m, then their ability to detect hand movements or light perception was measured.

Testing for hand movement vision

The examiner held their hand steady approximately 0.5 m in front of the participant with all of their fingers outstretched. A light was shone directly on the hand from behind the participant. The fellow eye was completely occluded with a pad and tape. The examiner moved their hand from side to side or up and down at a constant speed of one back and forth presentation per second. The participant was asked 'In which direction am I moving my hand?'. This was to be repeated five times. Four out of five correct responses indicated hand movement vision. If this was not achieved, light perception was to be tested for.

Testing for light perception/no light perception

Light perception should be measured with an indirect ophthalmoscope in a darkened room. The indirect ophthalmoscope is focused at 1 m, with the rheostat on maximum voltage. The beam was directed in and out of the eye at least four times, and the participant was asked to respond when they see the light. Light perception was recorded if the examiner was convinced that the participant saw the light. If not, the acuity was 'no light perception'.

Appendix 5 Optical coherence tomography and fundus fluorescein angiography image grading

Specific grading of individual morphological optical coherence tomography features

Normal macula cross-sectional architecture with a Spectralis OCT device is shown in *Figure 22*, and key abnormal macula morphological features are shown in *Figure 23*.

- Vitreomacular interface abnormality:
  - Epiretinal membrane was defined as present if one or more of the following conditions were met – a macular pseudohole, a difference in optical reflectivity between membrane and retina, or a visible membrane tuft or edge.
  - Vitreomacular traction was present if a highly reflective band was observed on the surface of the retina at specific sites and elevated off the surface elsewhere, whether continuous or not with the posterior vitreous surface.

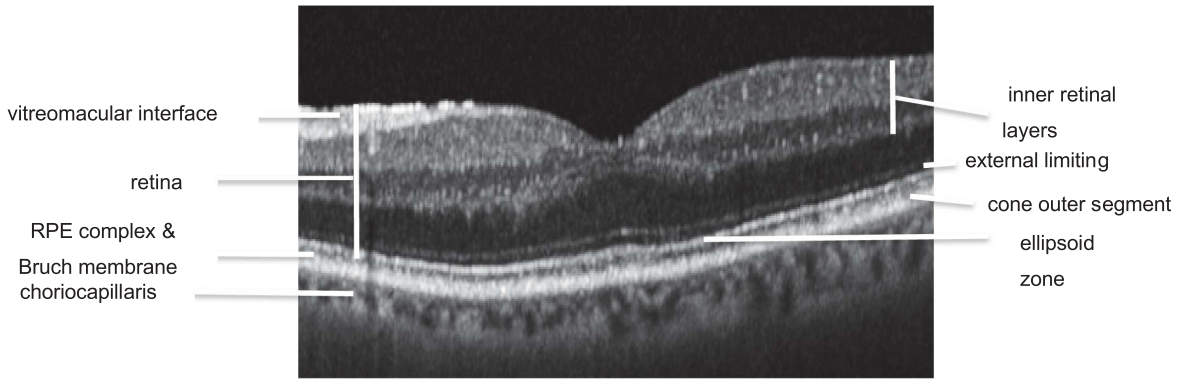

FIGURE 22 Normal macula architecture with a Spectralis OCT device.

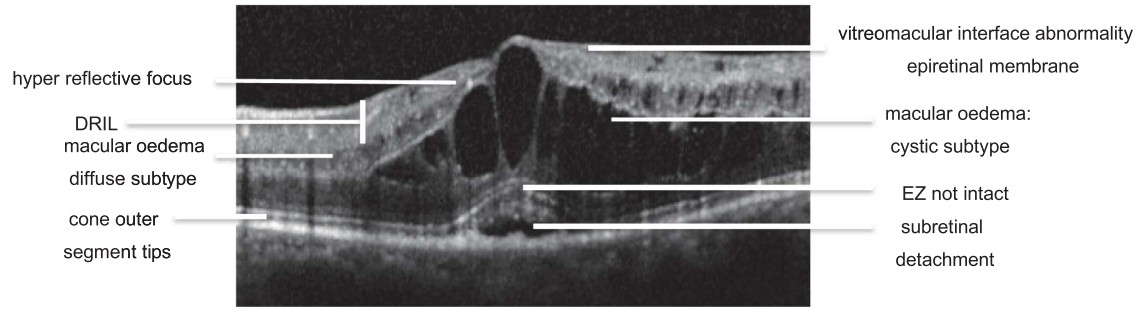

FIGURE 23 Abnormal macula morphological features on a Spectralis OCT device.

- Disorganisation of the retinal inner layers was defined as an area of the inner retina where the boundary between the ganglion cell layer, inner plexiform layer complex, inner nuclear layer and outer plexiform layer could not be separately identified in the central five line scans. The total amount of DRIL in each line scan was added and the average extent per line scan was calculated. If the total exceeded 50%, DRIL was graded positive. Lesser amounts and no DRIL were graded absent, and if shadowing prevented assessment, it was deemed ungradable. The averaged horizontal extent of DRIL per line scan was recorded.
- Macular oedema was classified as:
    - Diffuse retinal thickening, defined as sponge-like retinal swelling with reduced intraretinal reflectivity and the absence of hyporeflective spaces.
    - Cystoid macula oedema, defined as intraretinal cystoid spaces of low reflectivity with highly reflective septa separating cystoid-like cavities. Intraretinal cysts were further defined based on the greatest horizontal diameter of the largest cyst (small cysts, < 250 mm; medium cysts, ≥ 250 mm to < 500 mm; and large cysts, ≥ 500 mm).
    - The mixed pattern was graded present if diffuse retinal thickening and cystoid macula oedema were present together.
- Hyper-reflective foci: intraretinal abnormally bright dots distributed throughout all retinal layers, without a characteristic intraretinal location and optimally visualised under 'black-on-white' options. Any number of HRF was graded as 'present'; if none was visible, the grading was 'absent'.[69,70]
- External limiting membrane: the faint narrow line superior to the EZ was graded as intact if visible throughout the entire foveal line scan, not intact if disrupted or completely absent under high-contrast settings, and ungradable if there was shadowing of the oedematous retina.
- Ellipsoid zone: the EZ is synonymous with the third hyper-reflective band and is a distinct band just above the high-reflectance layer of the retinal pigment epithelium–choriocapillaris complex and COST line (see below), best detected in greyscale mode, and was graded as intact if visible throughout the foveal centre line scan, not intact if disrupted or completely absent based on continuity under high-contrast settings, or ungradable if there was shadowing of the oedematous retina.
- Cone outer segment tips: the COST line was defined as the hyper-reflective band between the retinal pigment epithelium and EZ bands and was graded as intact if visible throughout the entire foveal line scan, not intact if disrupted or absent in part or all of the central line scan and ungradable if image quality precluded grading.
- Subretinal detachment: this was characterised as present by a shallow elevation of the retina, with an optically clear space between the retina and the retinal pigment epithelium.

Fundus fluorescein angiography grading

Standard fundus fluorescein angiography grading

For the standard 13-sector ETDRS retinal grading grid, see *Figure 24*. The size and extent of the macula and zones are given in the figure, and the contained table summarises a two-step change in capillary non-perfusion.

Novel concentric ring template for calculating retinal non-perfusion

For the novel concentric ring retinal template for calculating non-perfusion, see *Figure 25*. This was modified to a concentric ring template suited to the central Optos ultra-widefield image. The superior and inferior segments of rings 3 and 4, which are usually ungradable, were removed to ensure consistent measurements. Each cell of the grid was individually graded by determining whether or not the area of retina within the sector was perfused. A glassy, homogeneous appearance to the retina with pruning or absence of retinal capillaries was used to confirm a diagnosis of non-perfusion and each cell was graded as either 'ischaemic' (i.e. $> 50\%$ of total area non-perfused) or 'perfused' (i.e. $< 50\%$ of total area non-perfused).

The grid projected onto the angiographic grid was as follows:
Macula: the area with a radius of 3.6 mm centred on the fovea
Zone 1: the area with a radius of 8.1 mm minus the macula
Zone 2: the area with a radius of 12.6 mm minus macula and zone 1
Zone 3: the area with a radius of 17.5 mm minus macula, zone 1 and zone 2

Zones 1, 2 and 3 were further divided into superior (S), temporal (T), inferior (I) and nasal (N), giving each retinal image 13 sectors (macula, S1 to S3, T1 to T3, I1 to I3 and N1 to N3). Each sector was graded for CNP at baseline and week 100 as none, 1 to 25%, 26 to 50%, 51 to 75%, 76 to 100% and cannot grade
*≥ 2 step CNP worsening is shaded in grey in the grid below

Change in capillary non-perfusion					
Week 100 / Baseline	None	1 to 25%	26 to 50%	51 to 75%	76 to 100%
None				≥ 2 step CNP worsening	
1–25%					
26–50%					
51–75%					
76–100%					

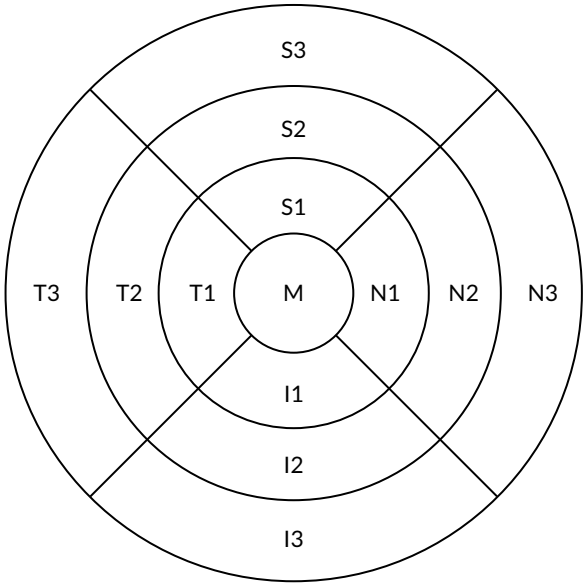

FIGURE 24 The 13-sector ETDRS retinal grid for grading retinal non-perfusion. CNP, capillary non-perfusion.

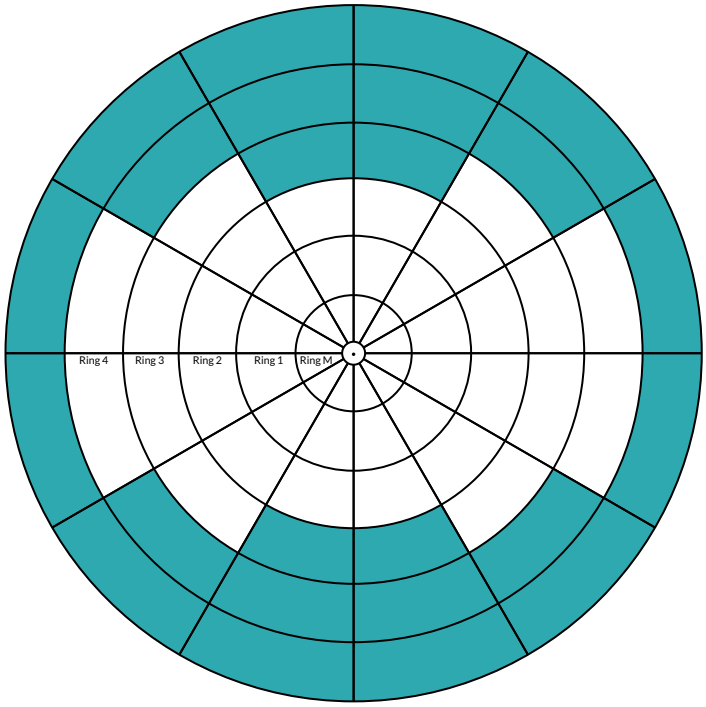

FIGURE 25 Novel concentric ring retinal template. Reproduced with permission from Nicholson *et al.*[83] This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Appendix 6 Health economics: additional information

Systematic literature review to support the long-term health economic model

Background

Description of the health problem

Central retinal vein occlusion is a vascular condition of the eye associated with significant visual loss and impaired quality of life.[36,134] RVO is the second most common cause of visual loss.[1] The obstruction causes a reduction in blood supply to the eye and results in a condition referred to as retinal ischaemia. In severe cases, blood supply may be entirely cut off, leading to non-perfusion of the retinal capillaries. Reduced perfusion of the retinal vessels triggers an increased production of VEGF and other mediators, which leads to the formation of new vessels (neovascularisation) and increased permeability and leakage in parts of the retina (MO).[37] MO is the most important cause of visual loss in patients with CRVO.[37] It is the most notable complication of CRVO, followed by retinal ischaemia.[16] Other complications of CRVO include vitreous haemorrhage, NVG and tractional retinal detachment.

Epidemiology

Prevalence rates of CRVO range from 0.1% to 0.5%, with a 15-year incidence rate of 0.1% to 0.2%.[1] A systematic review[3] reporting a pooled analysis from population-based studies (15 studies, 68,751 participants) conducted in the USA, Asia, Australia and Europe estimated that there are approximately 2.5 million (CI 1.9 million to 3.1 million) people living with CRVO. The review also demonstrated that the prevalence and incidence of CRVO increases with age.[1]

Subtypes of central retinal vein occlusion

Both CRVO and BRVO are generally classified into non-ischaemic or ischaemic type.[16] This classification is based on the area of capillary non-perfusion and is essential in the prognosis of CRVO. Although ischaemic CRVO has been defined in the Central Retinal Vein Occlusion Study[20] as 'fluorescein angiographic evidence of 410 disc areas of capillary nonperfusion on seven-field fundus fluorescein angiography', there is currently no agreed consensus on its definition. Better functional prognosis has been reported for patients with the non-ischaemic subtype than for those with ischaemic eyes.[16] Patients with ischaemic CRVO tend to have poorer vision (visual acuity of < 6/60) following treatment, whereas those with non-ischaemic CRVO may experience resolution of the condition without complications.[16]

Anti-vascular endothelial growth factor agents treatments

The introduction of therapies that target and block the activities of VEGF (referred to hereafter as anti-VEGFs) has significantly transformed the management options for patients with CRVO. Available intravitreal treatments include Lucentis (ranibizumab), Eylea (aflibercept) and Avastin (bevacizumab), the last of which is used currently used as an off-label intravitreal injection. The clinical effectiveness and safety of intravitreal anti-VEGFs in patients with ocular conditions have been studied extensively.[32,36,53,135] However, significant differences in study characteristics and methodological designs exist; furthermore, there is a lack of head-to-head comparisons and long-term data. LEAVO is a pivotal trial that shows promise in addressing some of the previously mentioned concerns.

Review methods

Aim

The aim of this review was to systematically identify evidence to inform inputs and assumptions for the long-term (> 2 years) economic model of LEAVO. Data requirements for patients with MO

secondary to CRVO treated with intravitreal injections of ranibizumab (0.5 mg/0.05 ml), aflibercept (2.0 mg/0.05 ml) or bevacizumab (1.25 mg/0.05 ml) included:

- relative clinical effectiveness and safety (including withdrawals and mortality)
- HRQoL estimates
- resource use and costs related to treatment, clinic visits, staffing and equipment
- presence of ischaemic CRVO at baseline
- prior treatment for CRVO at baseline
- trial eye OCT CST
- trial eye BCVA
- non-trial eye OCT CST
- non-trial eye BCVA
- new-onset MO
- injection frequency.

Identification of studies

The review was undertaken in line with current recommendations.[90,91]

Electronic database searches

Studies were identified through electronic database searches and supplementary searches. The following databases were searched from the date of inception up to 28 June 2018:

- MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations
- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effects
- HTA database
- NHS EED
- EMBASE
- CINAHL
- Web of Science Core Collection (Science Citation Index, Social Sciences Citation Index, Conference Proceedings Citation Index – Science and Conference Proceedings Citation Index – Social Science & Humanities).

Free-text terms and subject headings relating to MO, RVO, ranibizumab, aflibercept and bevacizumab, plus relevant synonyms for each concept, were used to develop a search strategy. The search strategy was then cross-checked against a Cochrane review of anti-VEGF for MO secondary to CRVO[32] to ensure that all relevant terms were included. Methodological search filters were applied in selected databases to identify systematic reviews, randomised trials, observational studies and economic studies (including quality-of-life studies). No search filters were applied to the CINAHL search as a limited number of references ($n = 73$) was retrieved. Furthermore, the search in Web of Science was refined by document type (review, article, proceedings paper, meeting abstract) because there are no available search filters. No additional limits were applied to the searches; details of the search strategy in MEDLINE are presented (see *Search strategy*).

Supplementary searches

Reference lists of key studies identified as potentially relevant were checked for additional references. Grey literature and authors of potentially eligible studies were also consulted. Literature-searching was iterative to ensure that sufficient data had been retrieved to populate the model. All records obtained were uploaded to an electronic bibliographic database, EndNote X8 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA].

Study selection

Study selection was informed by inclusion criteria (*Table 35*); the process was completed using a two-stage method. One researcher screened the titles and abstracts of retrieved records. Potentially relevant full-text articles were then obtained for detailed examination. A second reviewer checked selection decisions at each stage. Disagreements were resolved through consensus. In the case of multiple publications of the same study, the most recent version with up-to-date information was considered for inclusion.

Eligible data sources were studies with comparative or non-comparative study designs (systematic reviews, RCTs and non-RCTs) reporting long-term (i.e. $\geq$ 2 years) outcomes of clinical effectiveness, safety and quality of life in patients with MO secondary to CRVO who were treated with ranibizumab (Lucentis) (0.5 mg/0.05 ml), aflibercept (Eylea) (2.0 mg/0.05 ml) or bevacizumab (Avastin) (1.25 mg/0.05 ml). Patients were included if treatment was administered as a monotherapy compared with a control (e.g. another active treatment or sham injection). Prospective uncontrolled before-and-after studies were also reviewed for inclusion. In addition, studies reporting the natural history of CRVO were sought for inclusion.

The hierarchy of evidence recommendation relating to evidence of data sources for economic models by Coyle and Lee[92] (see *Recommendations for data sources*) informed the selection of full-text articles. Narrative reviews, case reports, non-human studies, editorials, expert opinions and non-English-language papers were excluded. Papers with insufficient and unclear information to ascertain the study aim(s), participant characteristics, CRVO diagnosis, treatment schedules and relevant outcome measurements were also excluded from the review.

Data extraction, quality assessment and data synthesis

Data relating to study characteristics (first author's name, publication date, study type, setting, follow-up duration), population characteristics (sample size, recruitment or identification, age, sex and comorbidities),

TABLE 35 Systematic literature review: eligibility criteria

Characteristic	Eligibility criteria
Population	Patients with MO due to CRVO, aged $\geq$ 18 years
Interventions	• Ranibizumab (Lucentis) (0.5 mg/0.05 ml) • Aflibercept (Eylea) (2.0 mg/0.05 ml) • Bevacizumab (Avastin) (1.25 mg/0.05 ml)
Comparisons	Comparisons between any of the interventions listed above Comparisons between listed interventions and no active treatment, best supportive care, placebo, sham Combination of any of the above comparisons
Outcomes	• Relative clinical effectiveness and safety (including mortality) • BCVA at baseline and change in BCVA • CRT at baseline and change in CRT • AEs as outlined in HEDMAP document • Economic data • HRQoL estimates (e.g. VFQ-25, VFQ-UI, EQ-5D, EQ-5D-5L, EQ-5D-V) • Resource use and costs related to treatment, clinic visits, staffing and equipment • Baseline visual acuity • Presence of ischaemic CRVO at baseline • Prior treatment for CRVO at baseline • Recurrence rates of MO • Injection frequency
Time horizon	> 2 years
Study design	Systematic reviews, randomised trials and observational studies reporting economic evaluations and quality of life

CRT, central retinal thickness; HEDMAP, health economics and decision-modelling analysis plan.

interventions administered and reported outcomes of interest were abstracted into summary tables by one reviewer. Reported outcomes according to study eye (primary treated eye), non-study eye (secondary treated eye), BSE and WSE or both eyes were obtained, when these were reported. Data extraction of outcomes of interest was double-checked by a second researcher. Discrepancies were resolved by discussion.

After applying the rating of hierarchies of evidence of data sources for economic models in study selection (see *Table 55*),[92] the most appropriate quality checklist endorsed the CASP[93] was used to assess the methodological quality of included studies. Tabular and narrative syntheses were presented because the available data could not be meta-analysed.

Results

Quantity and quality of available research

A total of 1338 unique records were retrieved through literature searches. Of these, three articles[24,34,94] provided potentially relevant evidence for inclusion in this review. *Figure 26* shows an outline of the selection of included studies. *Table 36* presents the available relevant data sources and their methodological ratings. A summary of excluded full-text papers with reasons for exclusion is provided in *Excluded studies with reasons*.

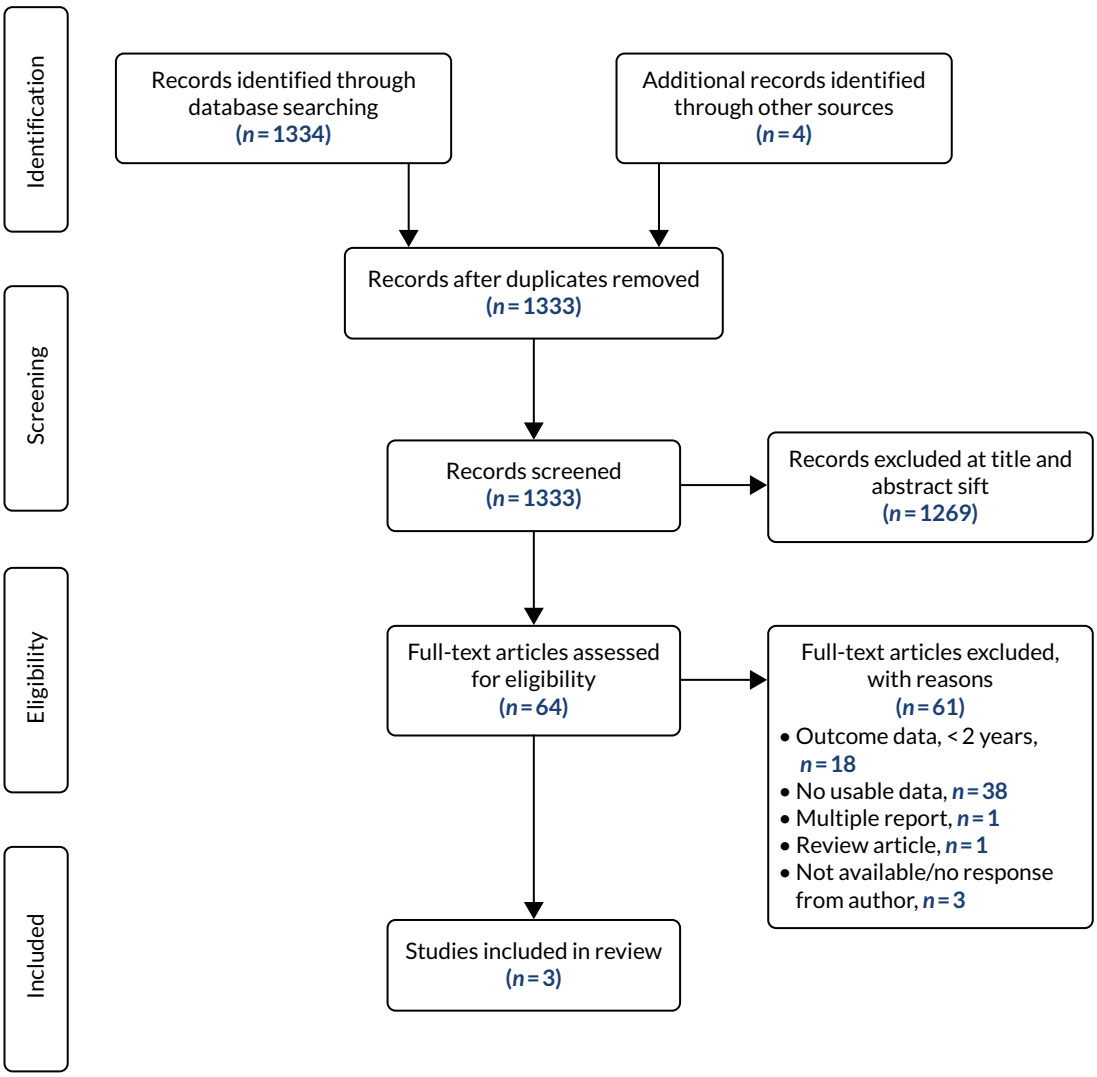

FIGURE 26 Systematic literature review: flow diagram of study selection.

TABLE 36 Systematic literature review: summary of available data sources and methodological ratings of included studies

Characteristic	Campochiaro *et al.*[34]	Novartis International AG[94]	McIntosh *et al.*[24]
Sample size (CRVO)	32 patients	1048 patients	3271 eyes
Intervention(s)	IVR	IVR	Not reported
Treatment schedule	TER	Not reported	Not reported
Study design	Non-RCT (open-label extension of CRUISE)	Non-RCT (observational, non-interventional, multicentre, open-label, single-arm study)	Systematic review of various study types
Funding	Genentech, Inc.	Novartis International AG	Allergan plc
Duration of follow-up (years)	4	5	3
Baseline characteristics of patients (mean)	• Age: 66.9 years • Duration of CRVO at baseline: 4.6 months • BCVA: 50.0 ETDRS letters • CFT: 639.8 µm	• Age: 69.7 years • Female: 41.5% • White: 78.8% • BCVA: 44.7 ETDRS letters • CFT: 551.5 µm	Not applicable
Primary study outcomes	• Mean change in BCVA • Percentage of patients with resolution of MO	• Mean change in BCVA • Mean change in CRT and the frequency and severity of ocular and systemic AEs	• Baseline visual acuity • Percentage of patients with MO at baseline • Development of neovascularisation, NVG and vitreous haemorrhage • Conversion of non-ischaemic CRVO to ischaemic CRVO • Rate of fellow eye involvement
Secondary outcomes	• Percentage of patients gaining or losing ≥ 15 letters from baseline • Percentage of patients with BCVA of ≥ 20/40 • Percentage of patients with BCVA of ≤ 20/200 • Mean change from baseline in CFT by Stratus OCT • Percentage of patients with CFT of ≤ 250 µm at each study visit • Ocular and systemic AEs	• Change in VFQ-25 scores from baseline • Number of injections • Number of visits and re-treatments • Time interval between injections • Reasons for re-treatment or treatment termination	Not reported
Evidence rating (Coyle and Lee[92])	4[a]	4;[a] 2 to 3;[b] 1[c]	3[b]
Methodological quality (CASP)	Unclear quality	Unclear quality	Good quality

CRT, central retinal thickness; IVR, intravitreal ranibizumab; TER, treat-and-extend regimen.
a Relates to clinical effect sizes and AEs.
b Relates to baseline clinical data.
c Relates to resource use.

Relative clinical effectiveness and safety

Included studies: long-term efficacy and safety

No evidence relating to the long-term (i.e. > 2 years' follow-up) head-to-head comparison of intravitreal injections of ranibizumab (0.5 mg/0.05 ml), aflibercept (2.0 mg/0.05 ml) and bevacizumab (1.25 mg/0.05 ml) in patients with MO secondary to CRVO was found. Two studies[34,94] contributed data to the review of clinical effectiveness of intravitreal ranibizumab injection:

- the RETAIN study,[34] a prospective, open-label, single-arm multicentre extension study[34]
- the LUMINOUS study,[94] a post-authorisation multicentre safety study for all licensed indications of ranibizumab.

Both studies included patients with ocular conditions other than CRVO. Hereafter, patients with CRVO in the RETAIN[34] and LUMINOUS[94] studies are referred to as 'patients', unless otherwise specified.

The RETAIN study: study and patient characteristics (central retinal vein occlusion subset) The RETAIN study enrolled a subset of patients with BRVO ($n = 34$) and CRVO ($n = 32$), originating from two pivotal multicentre Phase III RCTs[9,33,96] and a subsequent follow-up (HORIZON) trial.[38] Patients who completed CRUISE (392 participants, 95 locations)[9,33] or the BRAVO study (397 participants, 93 locations)[96] could immediately enter the RVO cohort of HORIZON.[38] HORIZON included 304 patients (intravitreal ranibizumab 0.5 mg, $n = 99$; intravitreal ranibizumab 0.3 mg, $n = 107$; and sham, $n = 98$) who had completed 12 months of follow-up in CRUISE.[9,33] From months 12 to 24, patients were reviewed every 3 months, or more frequently if needed, and were eligible to receive 0.5 mg of intravitreal ranibizumab on an 'as-needed' (pro re nata) basis.[38] The duration of follow-up for patients in HORIZON varied (mean duration 14 ± 4.7 months, range 1–24 months) because the study was terminated early following FDA approval for ranibizumab for treating RVO.[38]

The mean time from HORIZON study exit to RETAIN study entry was 92.7 days (range 68–150 days).[34] Patients with CRVO who entered the RETAIN study were representative of those enrolled in CRUISE.[34] In the RETAIN study, the mean age, visual acuity and central point thickness at baseline of enrolled patients with CRVO were 66.9 years, 50.0 ETDRS letters and 639.8 µm, respectively. Primary outcomes of the RETAIN study were mean improvement in BCVA and proportion of patients with resolved MO (defined as no intraretinal or subretinal fluid in the macula for at least 6 months after the last injection). Other reported outcomes were as follows:

- percentage of patients gaining or losing ≥ 15 letters from baseline
- percentages of patients with Snellen-equivalent BCVA of ≥ 20/40 or ≤ 20/200
- mean change from baseline in CFT, as measured by the Stratus OCT device
- percentage of patients with CFT of ≤ 250 µm at each study visit
- incidence and severity of ocular and systemic AEs.

Follow-up of patients was completed monthly for 12 months and then every 3 months for the duration of the study. At each study visit, patients were eligible to receive therapies based on treatment criteria protocol (*Table 37*).

TABLE 37 Systematic literature review: treatment criteria during follow-up visit (the RETAIN study)

Criteria	Treatment
1. Presence of intraretinal fluid involving the fovea	IVR (0.5 mg)
2. Intraretinal fluid persisting after two consecutive IVR and BCVA < 20/30	IVR (0.5mg) + scatter panretinal photocoagulation

IVR, intravitreal ranibizumab.

Scatter photocoagulation and grid laser therapy were administered as adjunctive treatments in patients who needed repeated ranibizumab injections at consecutive visits. The mean follow-up period of the RETAIN study was 49.7 months (with a maximum follow-up of 60 months).[34] Of 32 enrolled patients, 27 (84%) completed 2 years of follow-up. Reasons for loss to follow-up or withdrawal were death ($n = 2$), resolution of MO ($n = 2$) and persistence of MO ($n = 1$).[34]

Prior treatments (the RETAIN study) Patients who entered the RETAIN study had previously completed two pivotal multicentre Phase III RCTs[9,33,96] and a subsequent follow-up trial (HORIZON).[38] Patients who had received laser photocoagulation for MO 4 months before entering the study were excluded from CRUISE.[33] Further details of prior treatments in patients were not available in the extension study.[34] The mean number of prior injections with ranibizumab per eye was not reported.

Medical and ocular history (the RETAIN study) There was limited information relating to previous medical and ocular conditions in enrolled patients.

LUMINOUS: study and patient characteristics (central retinal vein occlusion subset) The LUMINOUS study was a 5-year international multicentre post-authorisation study (43 countries, 494 centres) that evaluated the long-term effectiveness and safety of ranibizumab for all its indications in the real-world setting. The study population included patients with neovascular (wet) AMD, visual impairment due to MO secondary to CRVO or BRVO, DMO and choroidal neovascularisation secondary to pathological myopia. Of the entire study population in LUMINOUS ($n = 30,153$), patients with CRVO made up 3.5% ($n = 1048$). The mean age of patients was 69.7 years. Women made up 41.5% of the subgroup with CRVO. Baseline BCVA and CFT were 44.7 ETDRS letters and 551.5 µm, respectively.

The primary outcomes were mean change in BCVA, mean change in central retinal thickness (CRT) and the frequency and severity of ocular and systemic AEs among patients during the study period. Secondary outcomes of interest included the VFQ-25 scores (change from baseline), total number of injections, number of visits and re-treatments, time interval between injections, and reasons for re-treatment or treatment termination.

Safety and effectiveness outcomes in the LUMINOUS study were presented according to various analysis sets and patient subgroups. *Table 38* shows a summary of relevant classifications.

Prior treatments (LUMINOUS) At baseline, 55.1% of patients with CRVO (primary treated eye set) had received ranibizumab. The mean number of prior injections with ranibizumab per eye was 4.5 (SD 4.29 injections) over a mean treatment duration of 38.7 weeks (SD 45.8 weeks). Additional previous intravitreal treatments other than ranibizumab were other anti-VEGFs (in 16.5% of patients, mean of 7.2 treatments per eye) and steroids (in 11.5% of patients, mean of 1.8 treatments per eye). Approximately 22.3% of all patients in the CRVO subgroup had received laser therapy, the most common type being panretinal photocoagulation.[94]

Medical and ocular history (LUMINOUS) A medical history of systemic comorbidity was reported for 4–61.3% of patients with CRVO. Previous ocular conditions were reported for 6.0–16.5% of participants.

Ongoing medical and ocular treatments (LUMINOUS) Up to 70.8% of patients [62.7% treatment-naive eyes, 75.2% of treatment non-naive (ranibizumab) eyes and 71.5% of treatment non-naive (other ocular treatments) eyes] received non-ocular medicines or non-drug treatments during the study. Ocular concomitant medicines and non-drug treatments in the primary treated eye were administered in 37.1% of patients [31.5% of treatment-naive eyes, 40.6% of treatment non-naive (ranibizumab) eyes and 36.1% of treatment non-naive (other ocular treatments) eyes].[94]

TABLE 38 Systematic literature review: summary of reported analysis sets and patient subgroups (adapted from LUMINOUS[94])

Analysis set	Definition
Enrolled set	All consenting patients with at least one baseline assessment
Safety set	Patients in the enrolled set who had received at least one dose of ranibizumab prior to study entry or during the study, and had at least one safety assessment after the first ranibizumab dose
Primary treated eye set	• All primary treated eyes in patients included in the safety set. The primary treated eye was the first eye treated with ranibizumab during the study • If both eyes were first treated on-study on the same date, or if both eyes were pretreated and did not receive treatment on-study, then the eye with the earlier diagnosis date was the primary treated eye • If both eyes had the same diagnosis date but were not treated during the study, the eye that was pretreated at study entry was regarded as the primary treated eye
Secondary treated eye set	• All secondary treated eyes in patients included in the safety set • If both eyes had the same diagnosis date, the eye that did not meet the criteria for primary treated eye was considered the secondary treated eye
Fellow treated eye set	The fellow eye referred to a non-ranibizumab-treated eye, including information prior to study entry visit/treatment history
Treatment-naive eyes	Eyes that had not been pre treated with any intravitreal treatments[a]
Treatment non-naive (ranibizumab) eye	Eyes previously treated with at least one injection of ranibizumab, regardless of other treatments
Treatment non-naive (other ocular treatments) eyes	Eyes previously treated with at least one ocular treatment other than ranibizumab

a Includes ranibizumab, VEGF inhibitor, corticosteroid focal/grid laser, panretinal laser photocoagulation and cyclodiode laser.
Adapted with permission from Novartis International AG.[94]

Table 39 presents the baseline characteristics of patients in the RETAIN study and LUMINOUS.

Efficacy outcomes

Outcomes of interest included relevant functional and anatomical outcomes reported in the RETAIN[34] study and in LUMINOUS.[94]

Visual outcomes (the RETAIN study)[34] The mean baseline visual acuity in the RETAIN study for the study population was 50.0 letters.[94] The mean improvement in BCVA was 14.0 ETDRS letters from CRUISE baseline (32 patients), resulting in a final visual acuity score of 64 letters (20/50) in patients with available data at year 4 of the RETAIN study. However, this improvement was not statistically significant when compared with the improvement of 13.1 letters ($p = 0.3$) from the end of CRUISE (i.e. the HORIZON baseline) until the end of the RETAIN study.[34] It is unclear whether this outcome is based on a per-protocol analysis because the authors also reported that patients who completed the RETAIN study had a mean BVCA of 61.3 letters (20/63), an increase of 12.6 letters from the CRUISE baseline. Overall, 43.8% of patients had a final visual acuity of 20/40 after 51.4 months of follow-up, with 53.1% of patients experiencing a 15-letter gain in visual acuity at the end of the study. Patients with resolved MO had better visual outcomes than those with unresolved MO [BCVA at the year 4 visit 73.2 letters (20/32) vs. 56.1 letters (20/80), respectively; $p = 0.1$]. A final visual acuity of $\geq$ 20/40 was reported in 64.3% of patients with resolved MO, in contrast to 27.8% of patients with unresolved MO ($p = 0.04$), translating into a visual acuity gain of 25.2 letters versus 4.3 letters ($p = 0.002$) in the respective subgroups. Six patients experienced reduced vision ranging from a loss of 3 to 33 ETDRS letters during the study. For reported visual outcomes in the RETAIN study, see *Tables 40* and *41*.

TABLE 39 Systematic literature review: baseline characteristics of the RETAIN study and LUMINOUS

Study characteristic	RETAIN study[30,34]	LUMINOUS[94]	
		All patients	Reported according to pre treatment in primary treated eye
Sample size (*n* patients)	32	1048[a,b]	• TN: 327 • TnN(R): 577 • TnN(other): 164
Age (years), mean (SD)	66.9 (SD not reported)	69.7 (12.32)[b]	• TN: 68.9 (13.03) • TnN(R): 70.5(12.13) • TnN(other): 68.3 (11.23)
Female (%)	NR	41.51[b]	• TN: 6.0 • TnN(R): 22.14 • TnN(other): 13.45
Duration of disease at baseline, mean (SD)	mean 4.6 months	391.5 (626.83) days;[a] *n* = 1048	• TN: 67.0 (121.54) • TnN(R): 551.8 (687.80) • TnN(other): 485.9 (764.32)
BCVA (ETDRS letters), mean (SD)	50	44.7 (23.88)[b]	• TN: 40.6 (23.86) • TnN(R): 49.5 (23.35) • TnN(other): 35.9 (21.74)
SD-OCT (μm), mean SD	639.8	463.5 (212.53);[a] *n* = 656	• TN: 551.5 (219.95) • TnN(R): 393.3 (184.69) • TnN(other): 510.2 (199.62)
Ocular history	NR	RVO (16.5%), glaucoma (10.4%), cataract operation (9.1%) and cataract (6.0%)	–
Medical history	NR	Cardiovascular risk factors,[c] 4–61.3%	
Percentage of patients with ischaemic CRVO	NR	NR	NR
Percentage of patients with MO	NR	NR	NR
VFQ-25 composite score, mean (SD)	NR	73.0 (20.62)	

NR, not reported; TN, treatment-naive eyes; TnN(R), treatment non-naive (ranibizumab) eye; TnN(other), treatment non-naive (other ocular treatments) eyes.
a Reported for primary treated eye.
b Reported for safety set.
c Includes hypertension (58.7–63.9%), hypercholesterolemia/hyperlipidaemia (23.9–37.0%), diabetes (18.8–24.8%) and obesity (7.6–15.3%).

Visual outcomes (LUMINOUS) The mean BCVA for all patients with CRVO (1048 patients) at baseline was 44.7 letters.[94] Baseline visual acuity for patients in the treatment-naive, treatment non-naive (ranibizumab) and treatment non-naive (other ocular treatments) subgroups were 40.6 letters, 49.5 letters and 35.9 letters, respectively. Less than 5% (30/1048) of patients provided relevant data for visual acuity outcomes beyond 2 years of follow-up. Overall, between two and eight patients across different subgroups gained > 10 or 15 letters in visual acuity, with only one patient achieving a gain of > 10 letters or a final BCVA of ≥ 73 letters in the treatment non-naive (ranibizumab) subgroup after long-term follow-up (up to 48 months).[94] *Table 42* presents the mean change in visual acuity from baseline for patients with CRVO in LUMINOUS.[94]

TABLE 40 Systematic literature review: visual outcomes – change over time (the RETAIN[34] study)

Visual outcome	Baseline	Month 6	12	18	24	30	36	42	48
Mean BCVA, score from CRUISE study entry (ETDRS)									
All patients	50.0 ($n = 32$)	63.1 ($n = 32$)	64.4 ($n = 32$)	62.8 ($n = 32$)	62.7 ($n = 32$)	62.9 ($n = 31$)	64.2 ($n = 29$)	60.8 ($n = 29$)	64.0 (20/50) ($n = 28$)
Patients with resolved MO ($n = 13$)	49.2	69.2	70.0	69.6	69.7	68.8	71.8	69.7	73.2 (20/32)
Patients with unresolved MO ($n = 15$)	50.4	55.4	60.3	54.9	54.1	55.1	56.3	52.3	56.1 (20//80)

TABLE 41 Systematic literature review: visual outcomes – final values at the end of the study (the RETAIN[34] study)

Visual outcome	Value
Mean BCVA, end of the RETAIN study, from CRUISE study entry (ETDRS), all patients	61.3 (20/63)
Mean BCVA, score, end of the RETAIN study, from CRUISE study entry (ETDRS)[a]	64.0 (20/50)
% of patients with BVCA of ≥ 20/40 ($n = 32$), mean follow-up 51.4 months	43.80
% of patients gaining ≥ 15 letters from baseline ($n = 32$), mean follow-up 51.4 months	53.10
Improvement in BCVA, from CRUISE baseline (ETDRS)[b]	12.60
Improvement in BCVA, from CRUISE baseline (ETDRS)[a]	14.00
Improvement in BCVA, at the end of CRUISE (ETDRS)[b]	13.60 ($p = 0.5$)
Improvement in BCVA, at the end of CRUISE (ETDRS)[a]	13.10 ($p = 0.3$)

a Data reported for 28 patients with CRVO for whom data were available 4 years after the CRUISE baseline.
b Data reported for patients with CRVO who completed the RETAIN study (full analysis set).

Central foveal thickness and macular oedema outcomes (the RETAIN study) The assessment of MO in the RETAIN study was based on the mean change in CFT from baseline, measured by a Stratus OCT device, at each study visit; the proportion of patients with CFT of ≤ 250 µm at each study visit; and the proportion of patients with resolved MO. Resolution of MO was defined as the absence of intraretinal or subretinal fluid in the macula for ≥ 6 months after the last injection. At study entry into CRUISE, enrolled patients had a mean baseline CFT of 639.8 µm, which reduced to 253.6 µm at month 24 ($n = 32$ patients). Of the 32 patients enrolled in the RETAIN study, 14 experienced MO resolution (43.8%). Mean CFT reported at year 4 in the RETAIN study was 171.3 µm, 263.4 µm and 220.6 µm for patients with resolved MO, patients with unresolved MO and all patients, respectively. A statistically significant difference in CFT change was noted between patients with resolved MO and those with unresolved MO ($p = 0.01$) (*Table 43a* and *b*). Patients with resolved MO had worse CFT at baseline than those with unresolved MO [mean 616.6 µm (SD 238.4 µm) vs. mean 497.9 µm (SD 218.8 µm); $p = 0.04$, respectively]. Two patients with resolved MO left the study prematurely. Of those with resolved MO ($n = 14$), eight patients (57%), two patients (14%), three patients (21%) and one patient (7%) received their last injection in years 1, 2, 3 and 4 of the follow-up period, respectively.[34]

TABLE 42 Systematic literature review: mean change from baseline visual acuity according to ETDRS letter categories (adapted from LUMINOUS[94])

Visual acuity, change in ETDRS letters	Month 12	24	36	48
CRVO, primary treated eye set				
Gain of ≥ 10 letters (%)	34.9	38.1	NR	NR
Gain of ≥ 15 letters (%)	28.8	28.1	NR	NR
Treatment naive				
Primary treated eyes with baseline and post-baseline values (*n*)	152.0	48.0	9.0	0.0
Gain of ≥ 5 letters, *n* (%)	96 (63.2)	28 (58.3)	8 (88.9)	0.0
Gain of ≥ 10 letters, *n* (%)	77 (50.7)	20 (41.7)	7 (77.8)	0.0
Gain of ≥ 15 letters, *n* (%)	66 (43.4)	13 (27.1)	5 (55.6)	Not assessed
Visual acuity of ≥ 73 letters, *n* (%)	38 (25.0)	10 (20.8)	3 (33.3)	0.0
Treatment non-naive (ranibizumab)				
Primary treated eyes with baseline and post-baseline values (*n*)	297.0	71.0	14.0	1.0
Gain of ≥ 5 letters, *n* (%)	113 (38.0)	30 (42.3)	7 (50.0)	1 (100)
Gain of ≥ 10 letters, *n* (%)	77 (25.9)	22 (31.0)	6 (42.9)	1 (100)
Gain of ≥ 15 letters, *n* (%)	59 (19.9)	19 (26.8)	4 (28.6)	Not assessed
Visual acuity of ≥ 73 letters, *n* (%)	59 (19.9)	16 (22.5)	4 (28.6)	1 (100)
Treatment non-naive (other ocular treatments)				
Primary treated eye with baseline and post-baseline values (*n*)	90.0	41.0	4.0	0.0
Gain of ≥ 5 letters, *n* (%)	48 (53.3)	20 (48.8)	2 (50.0)	0.0
Gain of ≥ 10 letters, *n* (%)	34 (37.8)	19 (46.3)	2 (50.0)	0.0
Gain of ≥ 15 letters, *n* (%)	30 (33.3)	13 (31.7)	2 (50.0)	Not assessed
Visual acuity of ≥ 73 letters, *n* (%)	9 (10.0)	3 (7.3)	0.0	0.0

NR, not reported.
Adapted with permission from Novartis International AG.[94]

TABLE 43a Systematic literature review: CFT, Stratus OCT III – change from baseline (the RETAIN[34] study)

Patient category	Baseline	Month 6	12	18	24	30	36	42	48
Mean CFT (μm), from CRUISE study entry									
All patients	639.8 (*n* = 32)	268.5 (*n* = 32)	201.4 (*n* = 32)	272.8 (*n* = 32)	253.6 (*n* = 32)	255.5 (*n* = 31)	217.4 (*n* = 29)	266.4 (*n* = 29)	220.6 (*n* = 28)
Patients with resolved MO (*n* = 13)	706.2	164.8	151.3	189.7	166.5	168.4	170.7	165.4	171.3
Patients with unresolved MO (*n* = 15)	601.7	392.4	261.3	362.3	355.8	344.8	263.5	346.5	263.4

TABLE 43b Systematic literature review: CFT, Stratus OCT III – final values at year 4 (the RETAIN[34] study)

Patients with	Mean CFT (µm)	*p*-value
Resolved MO	171.30	0.01
Unresolved MO	263.40	

Central retinal thickness and macular oedema outcomes (LUMINOUS) In the primary treated eye set, the mean CRT was 551.5 µm (SD 219.95 µm) for patients with data at baseline ($n = 224$).[94] At 36 months, CRT (seven patients) was 290.3 µm (SD 129.2 µm). Although there was a trend of CRT reducing over time, the greatest decrease was observed at month 36 in both the treatment-naive and treatment non-naive (other ocular treatments) subgroups. A similar rate of resolution was not observed in patients who had received previous injections of ranibizumab (*Table 44*).

Figure 27 shows trends in CFT change in patients included in the RETAIN[34] study and in LUMINOUS.[94]

Number of injections (the RETAIN study)[34] The mean number of injections of ranibizumab (0.5 mg) administered in the RETAIN study was 19.2 over 54 months of follow-up (28 patients). The mean number of injections administered in years 2, 3 and 4 of the study was 4.5, 3.6 and 3.3, respectively. Fewer injections were administered to patients with resolved MO than to those with unresolved MO (*Table 45a–c*). At the end of the RETAIN study, there was a statistically significant difference in the total mean number of injections received by patients with unresolved MO, compared with those with resolved MO (28.5 vs. 8.7 injections; $p < 0.01$).[34]

TABLE 44 Systematic literature review: CRT – change from baseline and values at study visits in primary treated eyes (adapted from LUMINOUS[94])

		Month			
Primary treated eye	Baseline	12	24	36	48
Treatment naive (*n*)	224	101	32	7	NR
CRT (µm) (SD)					
Value at visit	551.5 (219.95)	399.6 (218.10)	372.9 (151.35)	290.3 (129.20)	NR
Mean change	N/A	−176.4 (219.83)	−186.0 (225.46)	−257.1 (179.91)	NR
Treatment non-naive (ranibizumab) (*n*)	341	192	45	11	NR
CRT (µm) (SD)					
Value at visit	393.3 (184.69)	347.1 (159.35)	304.9 (117.71)	411.2 (172.10)	NR
Mean change	N/A	−49.0 (205.18)	−97.7 (210.46)	6.1 (249.31)	NR
Treatment non-naive (other ocular treatments) (*n*)	91	51	19	2	NR
CRT (µm) (SD)					
Value at visit	510.2 (199.62)	382.8 (147.71)	321.5 (119.54)	375.0 (77.78)	NR
Mean change	N/A	−157.4 (207.74)	−231.1 (163.44)	−277.0 (135.76)	NR

N/A, not applicable; NR, not reported.
Adapted with permission from Novartis International AG.[94]

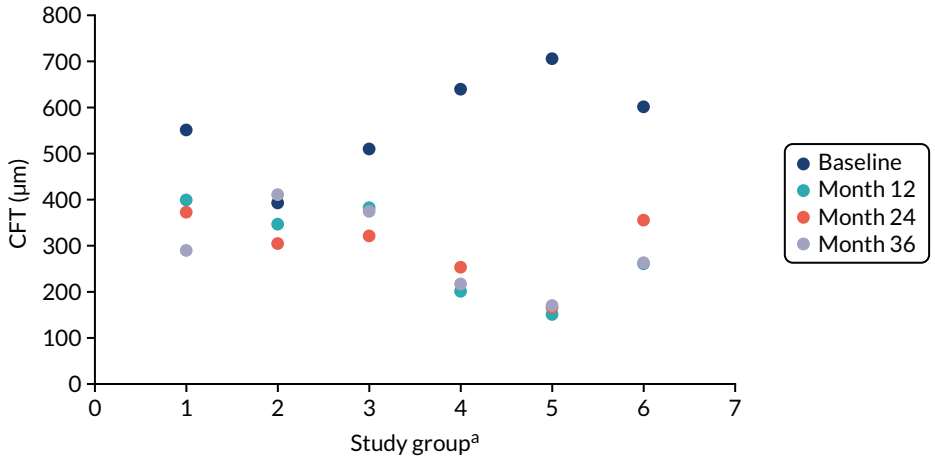

FIGURE 27 Systematic literature review: trends in CFT change over time in patients with MO due to CRVO. a, Study groups: 1, LUMINOUS, treatment naive (CRT); 2, LUMINOUS, treatment non-naive (ranibizumab) (CRT); 3, LUMINOUS, treatment non-naive (other ocular treatments) (CRT); 4, RETAIN study, all patients (CFT); 5, RETAIN study, resolved MO (CFT); 6, RETAIN study, unresolved MO (CFT).

TABLE 45a Systematic literature review: mean number of ranibizumab injections from CRUISE study entry (the RETAIN[34] study)

Mean number of injections	Baseline to month 5	Months						
		6–11	12–17	18–23	24–29	30–35	36–41	42–47
All patients	4.15 ($n = 32$)	4.0 ($n = 32$)	2.4 ($n = 32$)	2.1 ($n = 32$)	1.8 ($n = 31$)	1.8 ($n = 29$)	1.6 ($n = 29$)	1.7 ($n = 28$)
Patients with resolved MO ($n = 13$)	3.70	2.30	0.90	0.50	0.40	0.60	0.20	0.00
Patients with unresolved MO ($n = 15$)	4.30	5.30	3.80	3.30	3.00	2.80	2.80	3.10

TABLE 45b Systematic literature review: mean number of ranibizumab injections per year (the RETAIN[34] study)

Year	Mean number of injections
1	4.5
2	3.6
3	3.3

TABLE 45c Systematic literature review: total mean number of ranibizumab injections by the end of the study (the RETAIN[34] study)

Group	Mean number of injections	*p*-value
Mean follow-up 54.0 months	19.20	
Unresolved MO	28.50	0.001
Resolved MO	8.70	

Number of injections (LUMINOUS)[94] A total of 6224 ranibizumab injections were administered to patients with CRVO, of which 239 injections were administered in the secondary treated eye set. Although the majority of patients received treatment in only one eye, an estimated 3% were treated in both eyes. Treatment was administered over a mean duration of 323.5 days (primary treated eye set: 1048 patients). The mean treatment duration according to pre-treatment status in primary treated eye was 290.3 days, 337.8 days and 345.5 days for eyes that were treatment naive, treatment non-naive (ranibizumab) and treatment non-naive (other ocular treatments), respectively. The mean duration between consecutive injections (primary treated eye set) was 10.6 weeks. The shortest treatment interval was reported for treatment-naive patients (*Table 46a* and *b*). By month 48, the mean number of injections per patient was 5.9. Differences in pre-treatment status did not influence the number of injections received between subgroups.

Reasons provided for administering treatment in the primary treated eye set during the treatment period (baseline to month 60) were abnormal OCT findings (82.3%), abnormal FFA findings (8.2%), 'no further confirmation of disease activity beyond unstable visual acuity' (15.2%) and 'none of the above' (31.6%).[94] Common reasons for treatment termination in the primary treated eye set were treatment-switching to another anti-VEGF other than ranibizumab, and the decision of the treating physician or patient. Data for the secondary treated eye set were limited or not available from the report.[94]

TABLE 46a Systematic literature review: mean (SD) number of ranibizumab injections per patient, primary treated eye[a] (adapted from LUMINOUS[94])

	Up to month				
Patient category	**3**	**12**	**24**	**36**	**48**
CRVO (all) $n = 1048$	2.0 (0.99)	4.2 (2.78)	5.6 (4.55)	5.9 (5.13)	5.9 (5.25)
Treatment naive, $n = 327$	2.4 (0.87)	4.3 (2.53)	5.5 (4.18)	5.8 (4.82)	5.8 (5.01)
Treatment non-naive (ranibizumab), $n = 577$	1.6 (0.94)	4.1 (2.83)	5.5 (4.53)	5.8 (4.95)	5.8 (5.05)
Treatment non-naive (other ocular treatments), $n = 144$	2.3 (0.97)	4.5 (3.09)	6.2 (5.37)	6.6 (6.37)	6.7 (6.40)

a The mean number of injections is the total number of injections received by the end of the study. Reported only for patients with data at baseline visit.
Adapted with permission from Novartis International AG.[94]

TABLE 46b Systematic literature review: mean number of ranibizumab injections, secondary treated eye,[a] and duration between treatments (adapted from LUMINOUS[94])

Patient category	**Mean number of injections**
Mean number of injections, per patient, secondary treated eye	
CRVO (all), $n = 1048$	5.6
Mean (SD) duration between consecutive injections (weeks)	
CRVO (all), $n = 1048$	10.57 (9.16)
Treatment naive, $n = 327$	9.28 (6.83)
Treatment non-naive (ranibizumab), $n = 577$	11.12 (9.63)
Treatment non-naive (other ocular treatments), $n = 144$	11.61 (11.68)

a The mean number of injections is the total number of injections received by the end of the study. Reported only for patients with data at baseline visit.
Adapted with permission from Novartis International AG.[94]

Safety outcomes

Adverse event data were provided in two studies: the RETAIN[34] study ($n = 32$ patients) and LUMINOUS[94] ($n = 1048$ patients). Overall, the reported safety outcomes were identical in both studies. Ocular and non-ocular AEs were reported and were similar in both studies. Based on the updated health economic and decision-modelling analysis plan, only ocular AEs are reported here.

Safety outcomes (the RETAIN study)[34]

A small number of severe AEs were observed in patients with BRVO and CRVO in the RETAIN study. There was insufficient information to identify whether AEs occurred during the CRUISE or HORIZON studies or afterwards.

Ocular adverse events Four severe ocular AEs were reported, the most serious event being a superior hemiretinal vein occlusion in one patient. The remaining events were vitreous traction (two patients) and severe reaction to a local antiseptic (one patient). However, it is unclear whether or not these events occurred in patients with CRVO only. On the other hand, six patients with CRVO in the RETAIN study experienced visual loss, ranging from 3 to 33 ETDRS letters (*Table 47*). Reasons for visual loss included persisting or recurrent MO, the presence of an epiretinal membrane and poor visual improvement during the CRUISE and HORIZON studies.[34]

Safety outcomes (LUMINOUS)[94]

The mean duration of observed period for safety outcomes in the patients with CRVO was 530.0 days, with a cumulative duration of 1521.7 person-years for the primary treated eye set. Available data on systemic and ocular AEs in LUMINOUS are presented in *Tables 47* and *48*.

TABLE 47 Systematic literature review: AEs in patients in CRUISE[9] and HORIZON[38]

	Sham arm, *n* (%)			Ranibizumab (0.5 mg) arm, *n* (%)	
Ocular AE	Day 0 to month 6 ($n = 129$)	Sham/0.5 mg, months 6–12 ($n = 110$)	Sham/0.5 mg, months 12–24 ($n = 96$)	Day 0 to month 12 ($n = 129$)	Months 12–24 ($n = 99$)
Endophthalmitis	0	0	0	0	0
Rhegmatogenous retinal detachment	0	0	NR	0	NR
Retinal tear	0	2 (1.8)[a]	NR	2 (1.6)	NR
Any intraocular inflammation event (iridocyclitis, iritis, vitritis)	5 (3.9)	2 (1.8)	NR	2 (1.6)	NR
Vitreous haemorrhage	9 (7.0)[a]	2 (1.8)[a]	1 (1.0)	7 (5.4)	0
Lens damage[b]	0	0	0	0	0
Cataract[c]	0	2 (1.8)[a]	0	9 (7.0)	0
IOP increased	NR	NR	0	NR	0
MO	NR	NR	1 (1.0)	NR	2 (2.0)
Visual acuity reduced	NR	NR	3 (3.1)	NR	1 (1.0)

IOP, intraocular pressure; NR, not reported.
a One event reported as serious.
b Referred as traumatic cataract.[35]
c Cataract in some cases was possibly related to the intraocular injection procedure.
From months 12 to 24, all reported AEs were considered serious ocular events. Four severe ocular events were reported in the RETAIN study: vitreous traction ($n = 2$ patients), vitreous haemorrhage ($n = 1$) and retinal tear ($n = 1$). No further details were reported to link AEs to type of RVO or treatment group.

TABLE 48 Systematic literature review: ocular AEs according to pre-treatment status in the primary treated eye (adapted from LUMINOUS[94])

Reported AEs	All patients (*N* = 1048)	Treatment naive (*N* = 327)	Treatment non-naive (ranibizumab) (*N* = 577)	Treatment non-naive (other ocular treatments) (*N* = 144)
Ocular AEs				
Ocular AEs (all) (incidence rate per 100-person years)	164	53	87	24
Ocular AEs, % (n)				
All	10.4 (109)	11.32 (37)	9.71 (56)	11.11 (16)
Ocular SAEs	0.95 (10)	1.22 (4)	0.69 (4)	1.39 (2)
Ocular severe AEs	1.05 (11)	1.22 (4)	1.21 (7)	0
Infectious endophthalmitis	NR	NR	NR	NR
Retinal detachment	NR	NR	NR	NR
Retinal (pigment epithelium) tear	NR	NR	NR	NR
Anterior chamber reaction[a]	NR	NR	NR	NR
Conjunctival haemorrhage	0.57 (6)	0.92 (3)	0.52 (3)	0
Vitreous haemorrhage	0.38 (4)	0.31 (1)	0.52 (3)	0 (0)
Cataract	1.91 (20)	1.22 (4)	1.91 (11)	3.47 (5)
Glaucoma	0.95 (10)	1.53 (5)	0.87 (5)	0
Ocular hypertension (raised IOP of > 21 mmHg)	0.57 (6)	1.22 (4)	0.17 (1)	0.69 (1)
Increased IOP	0.86 (9)	0.61 (2)	1.04 (6)	0.69 (1)
Visual loss	0.57 (6)	0.61 (2)	0.52 (3)	0.69 (1)
Retinal ischaemia	0.19 (2)	0.31 (1)	0. (0)	0.69 (1)
Retinal neovascularisation	0.19 (2)	0 (0)	0.17 (1)	0.69 (1)
MO	0.57 (6)	0.31 (1)	0.87 (5)	0

IOP, intraocular pressure; NR, not reported.
a Includes acute intraocular inflammation, uveitis (inflammation of the anterior chamber) and hypopyon.
Adapted with permission from Novartis International AG.[94]

Ocular adverse events LUMINOUS[94] Ocular AEs were reported in 10.4% (109/1048) of patients with CRVO in the primary treated eye set [treatment naive, 11.32% (37/327); treatment non-naive (ranibizumab), 9.71% (56/577); and treatment non-naive (other ocular treatments), 11.11% (16/144)]. Among these, 0.95% of AEs were considered to be severe. Cataracts were the most common AE in the primary treated eye set, affecting 20 eyes (1.91%). The incidence of severe ocular AEs and serious ocular AEs in the primary treated eye was low (1.05% and 0.95%, respectively). Twenty-three patients (2.2%) experienced ocular AEs in the primary treated eye suspected to be related to ranibizumab and/or ocular injection. Data relating to ocular AEs in the secondary treated eye and fellow treated eye sets were not available.

Discontinuation of treatment (LUMINOUS)

Discontinuation of treatment with ranibizumab in the LUMINOUS study was reported as withdrawals (*Table 50*) and discontinuation of treatment as a result of AEs (*Table 51*).[94] It is unclear whether or not the discontinuation rates at specified time points included the proportion of patients who discontinued treatment because of AEs. Up to 87.5% (7/8) of patients stopped treatment prematurely by year 4.

TABLE 49 Systematic literature review: ocular AEs possibly related to ranibizumab and/or ocular injection in patients with CRVO (adapted from LUMINOUS[94])

Reported AEs	% (*n*)			
	All patients (*N* = 1048)	Treatment naive (*N* = 327)	Treatment non-naive (ranibizumab) (*N* = 577)	Treatment non-naive (other ocular treatments) (*N* = 144)
Ocular severe AEs, possibly treatment-related	1.05 (11)	0.38 (4)	0.67 (7)	NR
Ocular AEs, possibly treatment-related (ranibizumab or other ocular treatment)	2.20 (23)	3.36 (11)	1.56 (9)	2.08 (3)
Ocular AEs, possibly treatment-related (ranibizumab only)	0.67 (7)	0.92 (3)	0.52 (3)	0.69 (1)
Conjunctival haemorrhage	0.48 (5)	0.92 (3)	0.35 (2)	0
Cataract	0.095 (1)	0	0.17 (1)	0
Ocular hypertension	0.57 (6)	1.22 (4)	0.17 (1)	0.69 (1)
Increased IOP	0.10 (1)	0	017 (1)	0
Visual field defect	0.095 (1)	0.31 (1)	0	0

IOP, intraocular pressure; NR, not reported.
Adapted with permission from Novartis International AG.[94]

TABLE 50 Systematic literature review: discontinuation of treatment reported according to study withdrawal rates (adapted from LUMINOUS[94])

Discontinuation of treatment	Year			
	1	2	3	4
Patients (*n*)	1047	481	119	8
Withdrawals, *n* (%)	241 (23.0)	208 (43.2)	71 (59.7)	7 (87.5)
Common reasons for withdrawal[a]	• Treatment-switching to another anti-VEGF other than ranibizumab (7.3%) • Lost to follow-up (5.5%)	• Lost to follow-up (17.9%) • Treatment-switching to another anti-VEGF other than ranibizumab (8.7%)	• Lost to follow-up (25.2%) • Withdrawal of consent (10.1%)	• Lost to follow-up (42.9%) • Medical comorbidities (14.3%)[b]

a Percentages do not add up to 100 because only the most common reasons for withdrawal have been presented here.
b Hypertension and hypercholesterolaemia.
Adapted with permission from Novartis International AG.[94]

The most common reason was loss to follow-up (42.9%). Ranibizumab discontinuation because of AEs was rare. Discontinuation was more commonly related to systemic AEs (1.24%) than to ocular AEs (0.38%).[94]

Health-related quality-of-life outcomes: LUMINOUS

Data relating to the HRQoL of patients with CRVO treated with intravitreal ranibizumab were obtained from the LUMINOUS[94] study (*Table 52*). HRQoL was assessed at baseline and then at yearly intervals in the safety set, using the VFQ-25 non-preference-based scoring system.[104] Slight improvements in VFQ-25 composite scores were reported for patients in the treatment-naive and treatment non-naive

TABLE 51 Systematic literature review: discontinuation of treatment as a result of AEs in the primary treated eye by pre-treatment status (adapted from LUMINOUS[94])

AEs	% (*n*)			
	All patients (*N* = 1048)	Treatment naive (*N* = 327)	Treatment non-naive (ranibizumab) (*N* = 577)	Treatment non-naive (other ocular treatments) (*N* = 144)
Any AE (systemic and ocular)	1.62 (17)	2.14 (7)	1.56 (9)	0.69 (1)
Systemic AEs[a]	1.24 (13)	1.84 (6)	1.04 (6)	0.69 (1)
Ocular AEs	0.38 (4)	0.31 (1)	0.52 (3)	0
Details of ocular AEs				
Retinal haemorrhage	0.10 (1)	0	0.17 (1)	0
Vitreous haemorrhage	0.10 (1)	0	0.17 (1)	0
Tachyphylaxis	0.10 (1)	0	0.17 (1)	0
Retinal injury	0.10 (1)	0.31 (1)	0	0

a Same data reported for discontinuations due to serious systemic AEs.
Adapted with permission from Novartis International AG.[94]

TABLE 52 Systematic literature review: mean change in HRQoL (VFQ-25 composite score) from baseline (adapted from LUMINOUS[94])

HRQoL scores	Baseline	Month		
		12	24	36
Treatment naive, primary treated eyes with baseline and post-baseline value (*n*)	214	70	19	5
VFQ-25 composite score, mean (SD)	73.0 (20.62)	74.4 (22.89)	71.6 (19.66)	67.6 (20.89)
Mean (SD) change from baseline in VFQ-25 score		1.5 (10.47)	−2.3 (11.56)	−7.4 (23.15)
Treatment non-naive (ranibizumab), primary treated eyes with baseline and post-baseline value (*n*)	306	86	31	12
VFQ-25 composite score, mean (SD)	79.9 (7.90)	82.9 (17.85)	82.6 (17.83)	85.7 (12.20)
Mean (SD) change from baseline in VFQ-25 score		−0.8 (11.65)	−0.0 (11.89)	3.6 (10.70)
Treatment non-naive (other ocular treatments), primary treated eye with baseline and post-baseline value (*n*)	104	42	21	1
VFQ-25 composite score, mean (SD)	71.4 (20.38)	72.1 (24.49)	62.4 (21.17)	35.3
Mean (SD) change from baseline in VFQ-25 score		1.0 (9.38)	−8.3 (15.47)	−49.3

Adapted with permission from Novartis International AG.[94]

subgroups from baseline to the 12-month follow-up time point. From month 24 to month 36, small to moderate decreases in HRQoL scores were observed in a decreasing number of patients with baseline and post-baseline data (number of patients, 1 to 31 out of 214 patients included in the safety set). The mean VFQ-25 composite score at month 36 was higher than the baseline score only for patients in the treatment non-naive (ranibizumab) subgroup [mean 85.7 points (SD 12.20 points) vs. 79.9 points (SD 17.90 points), representing an improvement of 3.6 points (SD 10.70 points)].

Resource use: patients' visits and concurrent treatment

Evidence relating to resource use and costs was reported in the RETAIN[34] and LUMINOUS[94] studies. Data for the number of injections received by patients in both studies were presented earlier (see *Appendix 6*, *Table 45a* and *b*, for the RETAIN study[34] and *Appendix 6*, *Table 46a* and *b*, for LUMINOUS[94]).

Number of visits (LUMINOUS)

The authors of LUMINOUS[94] indicated that patients with CRVO (i.e. the safety set) had a mean of 11.6 visits by month 48 [treatment naive, 11.0 visits; treatment non-naive (ranibizumab), 11.4 visits; and treatment non-naive (other ocular treatments), 13.7 visits]. The comparability of number of visits at months 36 and 48 was noted (*Table 53*).[94]

Concomitant treatments

Two patients with CRVO received scatter photocoagulation in the RETAIN study.[34] However, further details were missing. On the other hand, data from LUMINOUS[94] showed that 37.1% of the CRVO primary treated eye set [31.5% of the treatment-naive eyes, 40.6% of the treatment non-naive (ranibizumab) eyes and 36.1% of the treatment non-naive (other ocular treatments) eyes] received ocular concomitant medications and significant non-drug therapies (not specified). Concurrent systemic medications and significant non-drug therapies (not specified) reported in the CRVO safety set were administered more frequently than ocular treatments [70.8% of all patients: 62.7% of treatment-naive, 75.2% of treatment non-naive (ranibizumab) and 71.5% of treatment non-naive (other ocular treatments) subgroups].[94]

Natural history (McIntosh *et al.*[24])

Evidence relating to the natural history of CRVO was obtained from a systematic review by McIntosh *et al.*[24] The review conducted literature searches up to November 2008 and included English-language articles (53 studies, 57 citations). Eligible studies were limited to observational studies of the natural history of RVO and all clinical trials evaluating interventions for CRVO. A total of 31 studies (3271 eyes) were assessed as of adequate quality and included studies evaluating patients with different CRVO subtypes [585 ischaemic eyes (20%), 1495 ischaemic subtype – unspecified (50%), 730 non-ischaemic eyes (25%) and 149 hemi-CRVO (5%)].[24]

Natural history outcomes

For reported outcomes related to the natural history of CRVO as outlined below, see *Table 54*:

- baseline visual acuity
- MO development
- MO resolution
- development of neovascularisation
- development of NVG
- development of vitreous haemorrhage
- conversion from non-ischaemic to ischaemic RVO
- fellow eye involvement.

Visual acuity observed in patients at the onset of CRVO is initially low, ranging from 20/40 to 20/200. Conversion from non-ischaemic CRVO to ischaemic CRVO occurs in up to 27% of patients. In general, patients with ischaemic CRVO present with worse vision than those with the non-ischaemic subtype.[24] Although most patients with CRVO at the time of presentation have MO, up to 73% experience resolution of this complication within 15 months of CRVO onset (i.e. post occlusion). CRVO in both eyes has been reported in 0.4% to 43% of patients. Within 1–3 years, up to 5% of patients with unilateral CRVO may develop a RVO in the fellow eye.[24]

TABLE 53 Systematic literature review: number of visits by patients according to pre-treatment status in the primary treated eye (safety set) (adapted from LUMINOUS[94])

Patients	Mean (SD) number of visits up to month			
	12	24	36	48
All patients ($N = 1048$)	7.4 (3.51)	10.8 (6.08)	11.5 (6.91)	11.6 (7.06)
Treatment naive ($N = 327$)	7.2 (3.46)	10.2 (5.72)	10.9 (6.44)	11.0 (6.63)
Treatment non-naive (ranibizumab) ($N = 577$)	7.5 (3.50)	10.7 (6.05)	11.4 (6.76)	11.4 (6.91)
Treatment non-naive (other ocular treatments) ($N = 144$)	7.9 (3.62)	12.3 (6.75)	13.6 (8.13)	13.7 (8.18)

Adapted with permission from Novartis International AG.[94]

TABLE 54 Systematic literature review: summary of evidence on the natural history of CRVO[24]

Natural history outcome	Findings	Evidence	Importance of clinical outcome[a]
VA	Initial VA generally poor (20/40) and generally decreases over time. I-CRVO has lower mean initial VA (< 20/200) and lower subsequent VA over time[b]	II	A
		II	A
Development[c] and resolution of ME	MO resolves in approximately 30% of non-ischaemic CRVO eyes	II	A
	MO resolution in up to 73% of ischaemic CRVO by 15 months post-occlusion	II	B
Development of NV	NV develops in up to 33% of NI-CRVO eyes 12 to 15 months post-occlusion	II	A
	NV develops in up to 20% of ischaemic CRVO eyes by 8 to 9 months post-occlusion	III	A
Development of NVG	NVG development occurs in 23%-60% of ischaemic CRVO by 12 to 15 months post-occlusion	III	A
Development of VH	Development of VH occurs in 10% of CRVO by 9 months post-occlusion	III	B
Conversion from NI-CRVO to I-CRVO	Conversion to i-CRVO occurs in up to 27% of niCRVO eyes within 10 weeks to 13 months post-occlusion	II	A
Fellow eye involvement	Bilateral RVO is present in 0.4% to 43% of CRVOs at presentation	II	C
	1.4% of patients with CRVO develop a CRVO in the fellow eye within 3 years	III	B
	5% of patients with CRVO develop a BRVO in the fellow eye within 30 months	III	C
	5% of patients with CRVO develop any RVO in the fellow eye within 1 year	III	B

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; MO, macular oedema; NV, neovascularisation; NVG, neovascular glaucoma; RVO, retinal vein occlusion; VA, visual acuity; VH, vitreous haemorrhage.

a Importance of clinical outcome:
Strength of evidence. A = most important or crucial to a good clinical outcome; B = moderately important to clinical outcome; C = possibly relevant but not critical to clinical outcome; I = data providing strong evidence in support of the clinical recommendation; II = strong evidence in support of the recommendation but the evidence lacks some qualities, thereby preventing its justifying the recommendation without qualification; III = insufficient evidence to provide support for or against recommendation, panel, or individual expert opinion.

b The authors also reported that the pooled mean VA decrease from baseline to ≥ 12 months was 3 letters for non-ischemic CRVO eyes and 35 letters for ischaemic eyes.

c No data. Most studies included patients with MO at baseline. Only two studies[136,137] of small study populations ($n = 3$ eyes) reported development of MO from baseline.

Reprinted from *Ophthamology*, vol. 117, McIntosh RL, Rogers SL, Lim L, Cheung N, Wang JJ, Mitchell P, *et al.*, Natural history of central retinal vein occlusion: an evidence-based systematic review, pp. 1113–23.e15, 2010,[24] with permission from Elsevier.

Discussion

The review was conducted to identify evidence to inform inputs and assumptions for the long-term (> 2 years) economic model of LEAVO, a non-inferiority clinical trial comparing the clinical effectiveness and cost-effectiveness of intravitreal injections of ranibizumab (0.5 mg/0.05 ml), aflibercept (2.0 mg/0.05 ml) and bevacizumab (1.25 mg/0.05 ml) in patients with MO secondary to CRVO. No relevant long-term comparative evidence was identified by the systematic review. Although long-term data were identified for patients treated with ranibizumab, there was a lack of long-term evidence for patients with MO secondary to CRVO who received aflibercept and bevacizumab. Three studies provided evidence that was considered potentially useful to inform the long-term model. One systematic review provided natural history data[24] and two non-randomised studies reported outcomes beyond 24 months for patients treated with ranibizumab.[34,94] Major concerns with these sources of evidence include the dearth of recent natural history evidence,[24] small sample sizes beyond 2 years of treatment,[24,34,94] and heterogeneity in clinical study design and reporting.[34,94] The RETAIN study[34] was a 4-year extension trial of a Phase III trial (CRUISE),[9,33] which followed up less than one-tenth of patients [8.2% (32/392)] enrolled in the original study. Furthermore, only 3% (30/1048) of patients evaluated in the 5-year observational, non-interventional, multicentre, open-label, single-arm study (LUMINOUS)[94] provided relevant visual acuity data beyond 2 years of follow-up.

In general, patients with CRVO have reduced visual acuity (44.7 letters[94] to 50 letters,[34] or 20/40 to 20/400[24]) and signs of MO[24] (mean SD-OCT CST, 463.5 μm[94] to 639.8 μm[34]) at the time of presentation. Although there is some evidence that treatment with intraocular ranibizumab improves visual acuity beyond 2 years (a 15-letter gain in visual acuity for 53.1% of patients; mean follow-up of 51.4 months), it is likely that greater improvement may be experienced in the earlier phase of treatment.[34] Visual acuity improved by 14.0 ETDRS letters from the CRUISE baseline (32 patients), resulting in a final visual acuity score of 64 letters (20/50) in patients with available data at year 4.[34] However, this improvement was not statistically significant when compared with the improvement of 13.1 letters ($p = 0.3$) from the end of the CRUISE study until the end of the RETAIN study.[34] Differences in treatment regimens such as fixed-dose regimen of injections every 6 months and pro re nata dosing may explain this observation. Available data suggest that earlier treatment is likely to result in greater functional improvement than delayed therapy.[35] This could explain the lack of statistically significant difference in BCVA in the CRUISE and RETAIN studies. The presence of MO was a predictor of visual acuity outcome. Improvements in visual acuity tend to be greater in patients with resolved MO than in those with unresolved MO [year 4 visit, 73.2 letters (20/32) vs. 56.1 letters (20/80); $p = 0.1$].[34] A statistically significantly higher proportion of treated patients achieved better final visual acuity of ≥ 20/40 (64.3% and 27.8% for resolved MO and unresolved MO respectively; $p = 0.04$) and greater visual acuity gain (25.2 and 4.3 ETDRS letters for resolved MO and unresolved MO, respectively; $p = 0.002$).[34]

Up to 43.8% of patients in the RETAIN[34] study had resolved MO at year 4. A statistically significant difference in CFT change was noted between patients with resolved MO and those with unresolved MO ($p = 0.01$).[34] Shorter-term real-world data comparing patients with CRVO receiving ranibizumab with patients with CRVO receiving aflibercept reported complete resolution in 50% and 42.9% of patients in the ranibizumab and aflibercept treatment groups, respectively.[35] Although clinical trials tend to provide better outcomes than real-world data,[35] fewer patients in the RETAIN[34] study experienced resolution of MO than patients in the shorter, real-world study. This may be explained by the differences in CFT at baseline: (RETAIN), 639.8 μm;[34] real-world study,[35] 573.8 μm (ranibizumab group) versus 599.1 μm (aflibercept group).

After 3 years of treatment, patients receiving ranibizumab tended to experience improved quality of life [VFQ-25 composite score, change from baseline 3.6 (SD 10.70)].[94] Reported mortality was generally low across all three included studies.[24,34,94] The rate of systemic or ocular AEs was approximately 10%. Previous studies,[24,32,34,36,51,94,135,138,139] albeit with short-term data addressing the safety of intraocular

anti-VEGF use in the treatment of MO due to CRVO, have not demonstrated major systemic and ocular AEs between anti-VEGF treatments. Although existing literature for long-term data suffers from inadequate sample sizes, inconsistent definitions and other methodological weaknesses, the findings of this review were in line with those of earlier work.

The mean number of injections of ranibizumab (0.5 mg) administered in the RETAIN study was 19.2 over 54 months of follow-up ($n = 28$ patients).[34] At the end of the RETAIN study, there was a statistically significant difference in the total mean number of injections received by patients with unresolved MO, and the total number received by those with resolved MO (28.5 vs. 8.7 injections, respectively; $p < 0.01$).[34] By contrast, by month 48, the mean number of injections per patient in LUMINOUS was 5.9. Differences in pre-treatment status did not influence the number of injections received between subgroups. This was similar to the mean number of injections reported in real-life data elsewhere evaluating 62 (62 eyes) treatment-naive patients with CRVO treated with intravitreal ranibizumab (0.5 mg) (6.8 injections) and aflibercept (0.2 mg) (6.1 injections).[35] Common reasons for treatment termination, such as treatment-switching to an anti-VEGF other than ranibizumab, could explain the observed difference in the number of injections in the RETAIN study[34] and LUMINOUS.[94] A recently published network meta-analysis found no difference between ranibizumab, aflibercept, bevacizumab and triamcinolone in improving vision.[135] The authors noted that treating physicians may tend to prefer aflibercept over other anti-VEGFs because it requires fewer injections.[94]

Visual acuity outcome is largely dependent on initial acuity.[94] In addition, visual acuity at baseline is a strong predictor of visual acuity at 3 years for eyes with good vision and eyes with poor vision, but a poor predictor for intermediate acuities.[20] Visual acuity was low in patients at the onset of CRVO, ranging from 20/40 to 20/200.[94] Conversion from non-ischaemic CRVO to ischaemic CRVO occurs in up to 27% of patients. In general, patients with ischaemic CRVO present with worse vision than patients with the non-ischaemic subtype.[94] Further evidence shows that patients with ischaemic CRVO tend to have poorer vision (visual acuity of < 6/60) following treatment, whereas those with non-ischaemic CRVO may experience resolution of the condition without complications.[16] Patients with ischaemic CRVO were not eligible for enrolment in CRUISE,[9] but there was uncertainty about the conversion rate of non-ischaemic eyes to ischaemic eyes in the extension study, RETAIN, and whether or not efficacy outcomes may have been influenced by a number of confounders (e.g. concomitant treatments and comorbidities) in the long term.

A majority of patients with CRVO have MO at the time of presentation; however, up to 73% experience resolution within 15 months of CRVO onset (i.e. post occlusion).[24] CRVO in both eyes has been reported in 0.4–43% of patients. Within 1–3 years, up to 5% of patients with unilateral CRVO may develop a RVO in the fellow eye.[24] Included studies[34,94] did not provide sufficient data to assess fellow eye involvement.

It is important to note the strengths of this systematic review, which was conducted in line with standard recommendations and informed by a multidisciplinary team comprising an information specialist, a systematic reviewer, health economists and cost-effectiveness modellers. On the other hand, a few limitations are noted here. Data relating to potential model inputs were checked by a second researcher; one researcher selected studies and performed data extraction and synthesis. The last search was carried out in June 2018. For these reasons, it is possible that key studies may have been missed.

Conclusion

Overall, the approach to identify evidence for the long-term LEAVO model was robust. There was limited evidence to inform the long-term clinical effectiveness and cost-effectiveness of anti-VEGFs used in the management of MO secondary to CRVO. A proficient understanding of comparative and long-term efficacy and safety of anti-VEGFs is needed.

Search strategy

Database searched: MEDLINE/MEDLINE In Process & Other Non-Indexed Citations.

Date range searched: from inception.

Date of search: 18 June 2018.

1. exp Macular Edema/
2. exp Macula Lutea/
3. exp EDEMA/
4. (macula* adj3 oedema).tw.
5. (macula* adj3 edema).tw.
6. 6. (CME or CMO).tw.
7. or/1-6
8. exp Retinal Vein Occlusion/
9. exp Retinal Vein/
10. ((vein* or venous or occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*) adj3 (central or retina*)).tw.
11. (CRVO or CVO or RVO).tw.
12. or/8-11
13. 7 and 12
14. exp Angiogenesis Inhibitors/
15. exp Angiogenesis Inducing Agent
16. exp Endothelial Growth Factors/
17. exp Vascular Endothelial Growth Factors/
18. exp RANIBIZUMAB/
19. (ranibizumab or lucentis or rhuFab*).tw.
20. ZL1R02VT79.rn.
21. (aflibercept or eylea).tw.
22. 15C2VL427D.rn.
23. exp BEVACIZUMAB/
24. (bevacizumab or avastin).tw.
25. 2S9ZZM9Q9 V.rn.
26. (anti adj2 VEGF*).tw.
27. (endothelial adj2 growth adj2 factor*).tw.
28. or/14–28
29. 13 and 28.

Recommendations for data sources

TABLE 55 Data components for economic models

Category	Data component[a]
1	Clinical effect sizes, AEs and complications
2	Baseline clinical data
3	Resource use
4	Costs
5	Utilities

a The data components were further divided into levels.[92]

Excluded studies, with reasons

TABLE 56 Excluded studies, with reasons

First author and year	Title	Reason(s) for exclusion/notes
Bradshaw 2016[140]	Systematic literature review of treatments for management of complications of ischemic central retinal vein occlusion	• Cost-effectiveness • No usable data
Braithwaite 2010[141]	Anti-vascular endothelial growth factor for macular edema secondary to central retinal vein occlusion	Follow-up of < 2 years
Braithwaite 2014[32]	Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion	Follow-up of < 2 years
Brand 2014[142]	Luminous: results from the 2014 interim analysis to provide further real-world evidence for clinical ranibizumab use	• LUMINOUS study • No response from authors
Brown 2010[33]	Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a Phase III study	• IVR vs. sham • Follow-up of < 2 years
Central Vein Occlusion Study Group 1997[20]	Natural history and clinical management of central retinal vein occlusion	Natural history, data available in included review reported by McIntosh *et al.*[24]
Chatziralli 2018[143]	Ranibizumab for retinal vein occlusion: predictive factors and long-term outcomes in real-life data	Natural history; full text not available
Cornel 2015[144]	Anti-vascular endothelial growth factor indications in ocular disease	Follow-up of < 2 years
Daradbounis 2014[145]	Long-term results of ranibizumab treatment in patients with macular oedema due to retinal venous occlusive disease	• IVR – efficacy • Inter-library loan, not available
Deramo 2003[134]	Vision-related quality of life in people with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire	• VFQ • No usable data
Casselholm de Salles 2019[57]	Injection frequency of aflibercept versus ranibizumab in a treat-and-extend regimen for central retinal vein occlusion: a randomized clinical trial	• Number of injections • Inter-library loan, not available
DeCroos 2014[146]	Neovascular events in eyes with central retinal vein occlusion undergoing serial bevacizumab or ranibizumab intravitreal injections: a retrospective review	• IVR and IVB • Follow-up of < 2 years
Deonandan 2017[147]	Anti-vascular endothelial growth factor drugs for the treatment of retinal conditions: a review of the safety	Follow-up of < 2 years
Edwards 2012[148]	Comparisons of the clinical effectiveness of treatments for macular oedema (MO) caused by retinal vein occlusion (RVO)	Follow-up of < 2 years
Figueroa 2012[28]	Potential anti-vascular endothelial growth factor therapies for central retinal vein occlusion	• IVR (efficacy) • Review article
Ford 2014[36]	Treatments for macular oedema following central retinal vein occlusion: systematic review	Follow-up of < 2 years
Ford 2014[135]	Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis	Follow-up of < 2 years
Freund 2015[149]	Treat-and-extend regimens with anti-VEGF agents in retinal diseases: a literature review and consensus recommendations	• Rx-pattern • No usable data
Gallego-Pinazo 2012[150]	Safety and efficacy of ranibizumab in macular edema following retinal vein occlusion	No usable data
Gerding 2015[151]	Ranibizumab in retinal vein occlusion: treatment recommendations by an expert panel	No usable data

TABLE 56 Excluded studies, with reasons (*continued*)

First author and year	Title	Reason(s) for exclusion/notes
Glanville 2014[152]	Efficacy and safety of widely used treatments for macular oedema secondary to retinal vein occlusion: a systematic review	No usable data
Heier 2012[38]	Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial	• Injection frequency (HORIZON) • No usable data
Hernando 2018[153]	Vision-related quality of life in patients diagnosed with retinal pathology	• Quality of life • Follow-up of < 2 years
Jager 2004[154]	Risks of intravitreous injection: a comprehensive review	No usable data
Jiang 2017[155]	Update on the use of anti-VEGF intravitreal therapies for retinal vein occlusions	• Summaries of IVR-related trials • No usable data
Jumper 2018[156]	Anti-VEGF treatment of macular edema associated with retinal vein occlusion: patterns of use and effectiveness in clinical practice (ECHO study report 2)	• Injections/baseline variables • No usable data
Kinge 2010[157]	Efficacy of ranibizumab in patients with macular edema secondary to central retinal vein occlusion: results from the sham-controlled ROCC study	• IVR vs. sham • No usable data
Konidaris 2018[158]	Outcomes of switching treatment to aflibercept in patients with macular oedema secondary to central retinal vein occlusion refractory to ranibizumab	• Treatment-switching from IVR to IVA • No usable data
Kornhauser 2016[159]	Bevacizumab treatment of macular edema in CRVO and BRVO: long-term follow-up. (BERVOLT study: Bevacizumab for RVO long-term follow-up)	• IVR and IVB • No usable data
Kumar 2013[160]	A clinical study to evaluate the efficacy of intravitreal anti-VEGF therapy in treating macular oedema due to retinal venous occlusions	• IVR (multiple treatments) • No usable data
Larsen 2016[55]	Individualized ranibizumab regimen driven by stabilization criteria for central retinal vein occlusion: twelve-month results of the CRYSTAL study	No usable data
Liu 2017[161]	Branch and central retinal vein occlusion: clinical pearls from trials of ranibizumab	• Review of BRAVO, CRUISE, SHORE, BRIGHTER and CRYSTAL studies • No usable data
Mohamed 2007[162]	Interventions for central retinal vein occlusion: an evidence-based systematic review	No usable data
NCT01277302 2011[163]	A study evaluating dosing regimens for treatment with intravitreal ranibizumab injections in subjects with macular edema following retinal vein occlusion	• Clinical trial record. Results available • Follow-up of < 2 years
Nghiem-Buffet 2017[164]	Treatment patterns of ranibizumab intravitreal injection and dexamethasone intravitreal implant for retinal vein occlusion in the USA	• Rx-pattern (USA, 2017) • Follow-up of < 2 years
Nicolò 2017[165]	Real-life management of patients with retinal vein occlusion using I-Macula Web platform	Follow-up of < 2 years
Nuzzi 2015[166]	Local and systemic complications after intravitreal administration of anti-vascular endothelial growth factor agents in the treatment of different ocular diseases: a five-year retrospective study	• AEs (IVB; IVR) • No usable data
Pacella 2012[167]	Testing the effectiveness of intravitreal ranibizumab during 12 months of follow-up in venous occlusion treatment	Follow-up of < 2 years
Patel 2016[168]	Central retinal vein occlusion: a review of current evidence-based treatment options	• RCTs of IVB in CRVO • Follow-up of < 2 years

continued

TABLE 56 Excluded studies, with reasons (*continued*)

First author and year	Title	Reason(s) for exclusion/notes
Penedones 2014[169]	Safety monitoring of ophthalmic biologics: a systematic review of pre- and post-marketing safety data	No usable data
Pielen 2013[37]	Efficacy and safety of intravitreal therapy in macular edema due to branch and central retinal vein occlusion: a systematic review	Follow-up of < 2 years
Poku 2014[170]	The safety of intravitreal bevacizumab monotherapy in adult ophthalmic conditions: systematic review	No usable data
Qian 2017[171]	Comparison between anti-VEGF therapy and corticosteroid or laser therapy for macular oedema secondary to retinal vein occlusion: a meta-analysis	Follow-up of < 2 years
Rayess 2016[172]	Post injection endophthalmitis rates and characteristics following intravitreal bevacizumab, ranibizumab, and aflibercept	No usable data
Regnard 2016[173]	Anti-VEGF treatment of macular edema using a treat-and-extend regimen in retinal vein occlusion in clinical practice	• Rx-pattern – injections • No usable data
Risard 2011[174]	Intravitreal ranibizumab for macular edema secondary to central retinal vein occlusion	Follow-up of < 2 years; no baseline data
Scott 2017[175]	SCORE2 report 5: vision-related function in patients with macular edema secondary to central retinal or hemiretinal vein occlusion	No usable data
Sharma 2015[176]	Baseline characteristics of Canadian patients with neovascular age-related macular degeneration (nvAMD), diabetic macular oedema (DMO) and retinal vein occlusion (RVO) enrolled in the LUMINOUS study	No usable data
Sigford 2015[138]	Global reported endophthalmitis risk following intravitreal injections of anti-VEGF: a literature review and analysis	No usable data
Sophie 2013[177]	Long-term outcomes in ranibizumab-treated patients with retinal vein occlusion; the role of progression of retinal nonperfusion	• Number of injections, resolution of MO • No usable data
Spaide 2009[39]	Prospective study of intravitreal ranibizumab as a treatment for decreased visual acuity secondary to central retinal vein occlusion	No usable data
Tabandeh 2014[178]	Endophthalmitis associated with intravitreal injections: office-based setting and operating room setting	• IVR and IVB • No usable data
Taylor 2014[179]	A United Kingdom-based economic evaluation of ranibizumab for patients with retinal vein occlusion (RVO)	• No usable data
Thulliez 2014[180]	Cardiovascular events and bleeding risk associated with intravitreal anti-vascular endothelial growth factor monoclonal antibodies: systematic review and meta-analysis	No usable data
Thulliez 2018[51]	Overview of systematic reviews and meta-analyses on systemic adverse events associated with intravitreal anti-vascular endothelial growth factor medication use	No usable data
Vorum 2016[181]	Real world evidence of use of anti-VEGF therapy in Denmark	• Rx-pattern • No usable data
Wang 2016[182]	A review of randomized trials of approved pharmaceutical agents for macular edema secondary to retinal vein occlusion	No usable data
Wecker 2017[183]	Five-year visual acuity outcomes and injection patterns in patients with pro-re-nata treatments for AMD, DME, RVO and myopic CNV	No usable data

TABLE 56 Excluded studies, with reasons (*continued*)

First author and year	Title	Reason(s) for exclusion/notes
Xu 2017[139]	Safety and complications of intravitreal injections performed in an Asian population in Singapore	No usable data
Yeh 2015[184]	Therapies for macular edema associated with central retinal vein occlusion: a report by the American Academy of Ophthalmology	• Quality of life/costs • No usable data
Yuan 2014[185]	Comparison of intravitreal ranibizumab and bevacizumab for the treatment of macular edema secondary to retinal vein occlusion	No usable data
Ziemssen 2017[186]	Demographics of patients receiving intravitreal anti-VEGF treatment in real-world practice: healthcare research data versus randomized controlled trials	No usable data

BRIGHTER, Efficacy and Safety of Ranibizumab With or Without Laser in Comparison to Laser in Branch Retinal Vein Occlusion; CNV, choroidal neovascularisation; DME, diabetic macular oedema; IVA, intravitreal aflibercept; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; SHORE, Study Evaluating Dosing Regimens for Treatment with Intraviteral Ranibizumab Injections in Subjects with Macular Edema following Retinal Vein Occlusion.

Model-based analysis methods: additional data

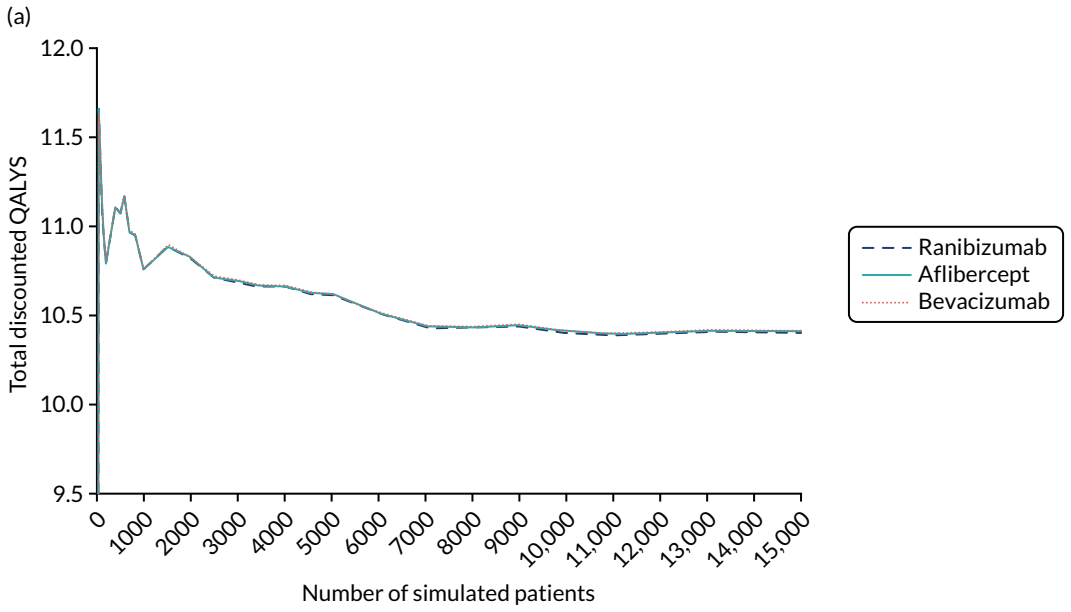

FIGURE 28 Model-based analysis: stabilisation graphs. (a) QALYs; and (b) costs. Reproduced with permission from Pennington *et al.*[95] This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure. (*continued*)

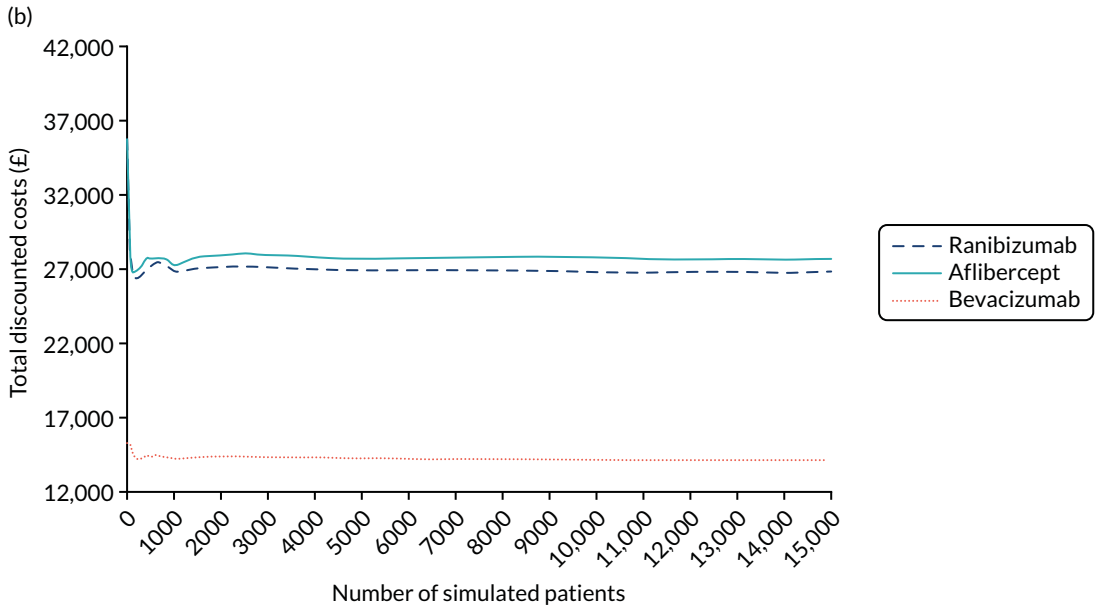

FIGURE 28 Model-based analysis: stabilisation graphs. (a) QALYs; and (b) costs. Reproduced with permission from Pennington *et al.*[95] This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Within-trial analysis methods: additional data

Table 57 presents the unit cost of each resource in the within-trial analysis.

TABLE 57 Within-trial analysis: unit costs applied for the valuation of resource use

Description	Unit cost (£)	Source	HRG code	Notes
Intervention costs				
Ranibizumab	551.00	BNF[117]	–	1.65 mg/0.165 ml solution for injection in pre-filled syringes (Novartis, supplied from routine NHS hospital stock)
Aflibercept	816.00	BNF[117]	–	2 mg/50 µl solution for injection vials (Bayer Pharmaceuticals AG, supplied from routine NHS hospital stock)
Bevacizumab	28.00	Judicial review[53]	–	Cost per pre-filled syringe 1.25 mg/0.05 ml (Roche, supplied by the Royal Liverpool and Broadgreen Pharmacy Aseptic Unit)
Baseline appointment	140.04	Department of Health and Social Care[118]	WF02B	Consultant led, ophthalmology
Follow-up appointments	105.19	Department of Health and Social Care[118]	WF02A	Consultant led, ophthalmology

TABLE 57 Within-trial analysis: unit costs applied for the valuation of resource use (*continued*)

Description	Unit cost (£)	Source	HRG code	Notes
OCT	108.21	Department of Health and Social Care[118]	BZ87A	Outpatient procedure
Colour fundus photography	116.23	Department of Health and Social Care[118]	BZ89A	• Outpatient procedure • Weighted average of ophthalmology and optometry
FFA	108.21	Department of Health and Social Care[118]	BZ87A	Outpatient procedure
Procedures and hospital admissions				
Hospital admission	337.36	Department of Health and Social Care[118]	Index: NEL_XS	Non-elective inpatients excess bed-days
Mental health admission	420.62	Department of Health and Social Care[118]	MHCC MHCCIA MHCC02	• Unit cost per occupied bed-day • Initial assessment incurred once per stay
Nose bleed	1257.40	Department of Health and Social Care[118]	CA12Z CA13A	Weighted average of elective inpatient and non-elective long stay
Outpatient procedures				
Panretinal photocoagulation	120.66	Department of Health and Social Care[118]	BZ86B	
Intravitreal steroid injection (non-study eye)	108.21	Department of Health and Social Care[118]	BZ87A	
Intravitreal anti-VEGF injection (non-study eye)	213.04	Department of Health and Social Care[118]	BZ87A WF02A	
Cyclodiode laser treatment	143.26	Department of Health and Social Care[118]	BZ95Z	
Argon laser	120.66	Department of Health and Social Care[118]	BZ86B	
Entropion repair	137.52	Department of Health and Social Care[118]	BZ45B	
Epilation	125.53	Department of Health and Social Care[118]	BZ46A	
Incision and curettage	125.53	Department of Health and Social Care[118]	BZ46A	
Left needling of bleb with 5-fluorouracil	143.26	Department of Health and Social Care[118]	BZ95Z	
Lester Jones tube insertion	125.53	Department of Health and Social Care[118]	BZ46A	
Paracentesis	143.26	Department of Health and Social Care[118]	BZ95Z	
Medial canthoplasty	137.52	Department of Health and Social Care[118]	BZ45B	
Foreign-body removal	117.21	Department of Health and Social Care[118]	BZ65Z	
Elective procedures				
Vitrectomy	2319.38	Department of Health and Social Care[118]	BZ80A–BZ84B	
Cataract surgery	1636.57	Department of Health and Social Care[118]	BZ32A–BZ34C	

continued

TABLE 57 Within-trial analysis: unit costs applied for the valuation of resource use (*continued*)

Description	Unit cost (£)	Source	HRG code	Notes
Trabeculectomy	2215.03	Department of Health and Social Care[118]	• BZ91A,B • BZ92A,B • BZ93A,B	
Tube shunt surgery	2341.09	Department of Health and Social Care[118]	• BZ90Z • BZ91 A,B • BZ92 A,B	
Blepharoplasty	2768.81	Department of Health and Social Care[118]	BZ41B	
Peripheral iridotomy	860.28	Department of Health and Social Care[118]	BZ04 A,B	Inflated costs using HCHS index
Yag capsulotomy	860.28	Department of Health and Social Care[118]	BZ04 A,B	Inflated costs using HCHS index
Low-vision aids	194.41	Department of Health and Social Care[118]	–	• Inflated to 2017/18 prices using HCHS index • Assumed that 33.3% of patients use low-vision aids
Blind registration	60.50	Meads and Hyde[122]	–	• Blind registration consists of a GP appointment to complete the BD8 form and a community occupational therapist assessment • 94.5% of eligible people will register as blind
Continuous care and support				
Care home cost	1154.00	Curtis and Burns[116]	–	• Local authority own-provision residential care for older people (aged ≥ 65 years) establishment cost plus personal living expenses • 10% of people will be funded by NHS
Home help (social services)	27.64	Curtis and Burns[116]	–	Average taken over weekday, weekend and day, night
Day centre	58.00	Curtis and Burns[116]	–	Local authority own–provision day care for older people (aged ≥ 65 years)
Health-care contacts *Visit*				
Ophthalmology consultant	95.13	Department of Health and Social Care[118]	WF01A	
GP	37.40	Curtis and Burns[116]	–	• Including direct care staff costs, and with qualification costs • Per-patient contact lasting 9.22 minutes
Practice nurse	17.79	Curtis and Burns[116]	–	• Nurse (general practice) based on band 5 patient-related work and including qualifications • Duration of contact is 15.5 minutes per surgery consultation

TABLE 57 Within-trial analysis: unit costs applied for the valuation of resource use (*continued*)

Description	Unit cost (£)	Source	HRG code	Notes
A&E/emergency department	160.32	Department of Health and Social Care[118]	VB01Z– VB09Z, VB11Z	Weighted average of all codes of those admitted and those non-admitted
Consultant at glaucoma clinic	118.02	Department of Health and Social Care[118]	WF01B	Consultant-led ophthalmology
Eye casualty				
Rapid access and optician				
Ophthalmology outpatient doctor	86.55	Department of Health and Social Care[118]	WF01B	Non-consultant-led ophthalmology
Optician or optometrist	76.50	Department of Health and Social Care[118]	WF01B	Non-consultant-led optometry
Blood sample	2.83	Department of Health and Social Care[118]	DAPS08	
Eye clinic	73.95	Department of Health and Social Care[118]	WF01A	Non-consultant-led ophthalmology
Mental health department	159.51	Department of Health and Social Care[118]	MHSTOTHA	
Diabetic community eye screening/retinopathy clinic	56.79	Department of Health and Social Care[118]	WF02B	Non-consultant-led optometry
Neurologist for double vision	284.66	Department of Health and Social Care[118]	WF01B	• Consultant-led neurology • Non-consultant-led orthoptist
High-street optician	25.00	www.boots.com/opticians-service/eyetest (accessed 7 September 2020)	–	
Eye hospital for a low-vision appointment	153.00	Department of Health and Social Care[118]	WF01A	• Non-consultant-led ophthalmology • Doubled to reflect complexity of appointment
Call				
Helpline	28.66	Curtis and Burns[116]		Band 6 specialist nurse (hospital based), 15.5-minute consultation
A&E eye department				
Staff nurse in eye clinic				
Ophthalmologist	28.20	Department of Health and Social Care[118]	WF01D	Non-consultant-led ophthalmology
Optometrist	21.61	Department of Health and Social Care[118]	WF01C	Non-consultant-led optometry
Optician				
Orthoptist	37.60	Department of Health and Social Care[118]	WF01D	Non-consultant-led orthoptist
Macular service	23.25	Curtis and Burns[116]	–	Band 5 nurse (hospital based), 15.5-minute consultation
Clinical nurse				
Eye clinic staff				
NHS 24	13.59	Turner *et al.*[187]		
GP	28.00	Curtis and Burns[116]		• Including direct staff costs and qualifications • Telephone consultation from 2015 is 7.1 minutes

continued

TABLE 57 Within-trial analysis: unit costs applied for the valuation of resource use (*continued*)

Description	Unit cost (£)	Source	HRG code	Notes
Practice nurse	6.90	Curtis and Burns[116]		• Nurse (general practice) based on band 5 patient-related work and including qualifications • Telephone consultation from 2015 with an advanced nurse is 6 minutes
Home visit				
GP	56.16	Curtis and Burns[116]		
Practice nurse	32.89	Curtis and Burns[116]	–	
Optometrist	76.50	Department of Health and Social Care[118]		
Concomitant medications				
Acetazolamide 250 mg tablets	13.87	BNF[117]	–	
Acyclovir 200 mg tablets	0.97	BNF[117]	–	
Acyclovir 400 mg tablets	2.35	BNF[117]	–	
Acular 0.5% eye drops	3.00	BNF[117]	–	
Alphagan 0.2% eye drops	2.55	BNF[117]	–	
Amikacin 100 mg/2 ml solution for injection vials	10.33	BNF[117]	–	
Artelac Night-time 0.2% eye gel	2.80	BNF[117]	–	
Aspirin 75 mg gastroresistant tablets	0.61	BNF[117]	–	
Atropine 1% eye drops	131.88	BNF[117]	–	
Azarga 10 mg/ml/5 mg/ml eye	11.05	BNF[117]	–	
Azopt 10 mg/ml eye drops	2.00	BNF[117]	–	
Betnesol-N ear/eye/nose drops	3.39	BNF[117]	–	
Bimatoprost 300 µg/ml eye drops	10.30	BNF[117]	–	
Brinzolamide 10 mg/ml eye drops	2.00	BNF[117]	–	
Brochlor 1% eye ointment	1.96	BNF[117]	–	
Celluvisc 0.5% eye drops 0.4 ml unit dose	4.80	BNF[117]	–	
Celluvisc 1% eye drops 0.4 ml unit dose	3.00	BNF[117]	–	
Chloramphenicol 0.5% eye drops	1.44	BNF[117]	–	
Clinitas 0.4% eye drops 0.5 ml unit dose	5.70	BNF[117]	–	
Clinitas Carbomer 0.2% eye gel	2.80	BNF[117]	–	
Clopidogrel 75 mg tablets	1.31	BNF[117]	–	
Co-codamol 30 mg/500 mg caplets	3.23	BNF[117]	–	
Codeine 15 mg tablets	0.77	BNF[117]	–	
Codeine 30 mg tablets	0.87	BNF[117]	–	

TABLE 57 Within-trial analysis: unit costs applied for the valuation of resource use (*continued*)

Description	Unit cost (£)	Source	HRG code	Notes
Cosopt 20 mg/ml/5 mg/ml eye drops	1.85	BNF[117]	–	
Diamox Sodium Parenteral 500 mg powder for solution for injection vials	17.71	BNF[117]	–	
Diamox SR 250 mg capsules	16.66	BNF[117]	–	
Diclofenac 0.074% mouthwash sugar-free	12.95	BNF[117]	–	
Dorzolamide 20 mg/ml eye drops	2.04	BNF[117]	–	
Dropodex 0.1% eye drops 0.4 ml unit	10.48	BNF[117]	–	
DuoTrav 40 µg/ml/5 mg/ml eye	13.95	BNF[117]	–	
Evolve Carmellose 0.5% eye drops preservative free	4.99	BNF[117]	–	
Exocin 0.3% eye drops	2.17	BNF[117]	–	
Ganfort 0.3 mg/ml/5 mg/ml eye drops	14.16	BNF[117]	–	
Hyabak 0.15% eye drops preservative free	7.99	BNF[117]	–	
Hydromoor 0.3% eye drops 0.4 ml unit dose preservative free	5.75	BNF[117]	–	
Hylo-Forte 0.2% eye drops preservative free	9.50	BNF[117]	–	
Hylo-Tear 0.1% eye drops preservative free	8.50	BNF[117]	–	
Hypromellose 0.3% eye drops	1.21	BNF[117]	–	
Ibuprofen 400 mg tablets	0.84	BNF[117]	–	
Ilube 5% eye drops	16.90	BNF[117]	–	
Iopidine 5 mg/ml eye drops	10.88	BNF[117]	–	
Lacri-lube eye ointment	3.01	BNF[117]	–	
Latanoprost 50 µg/ml/Timolol 5 mg/ml eye drops	6.37	BNF[117]	–	
Latanoprost 50 µg/ml eye drops	5.89	BNF[117]	–	
Levofloxacin 5 mg/ml eye drops	6.95	BNF[117]	–	
Liquifilm Tears 1.4% eye drops	1.93	BNF[117]	–	
Liquivisc 0.25% eye gel	4.50	BNF[117]	–	
Lumigan 100 µg/ml eye drops	11.71	BNF[117]	–	
Macushield	27.18	Amazon (Amazon.com, Inc., Bellevue, WA, USA)	–	
Maxidex 0.1% eye drops	1.42	BNF[117]	–	
Maxitrol eye drops	1.68	BNF[117]	–	
Maxitrol eye ointment	1.44	BNF[117]	–	

continued

TABLE 57 Within-trial analysis: unit costs applied for the valuation of resource use (*continued*)

Description	Unit cost (£)	Source	HRG code	Notes
Minims artificial tears 0.44% eye drops 0.5 ml unit	9.33	BNF[117]	–	
Minims fluorescein sodium 1% eye drops 0.5 ml unit dose	9.25	BNF[117]	–	
Minims oxybuprocaine hydrochloride 0.4% eye drops 0.5 ml unit dose	10.56	BNF[117]	–	
Minims phenylephrine hydrochloride 2.5% eye drops 0.5 ml unit dose	11.87	BNF[117]	–	
Minims proxymetacaine 0.5% eye drops 0.5 ml unit dose	12.12	BNF[117]	–	
Minims saline 0.9% eye drops 0.5 ml unit dose	7.43	BNF[117]	–	
Minims tropicamide 0.5% eye drops 0.5 ml unit dose	11.18	BNF[117]	–	
Mitomycin 2 mg powder for solution for injection	55.89	BNF[117]	–	
Monopost 50 µg/ml eye drops 0.2 ml unit dose	8.49	BNF[117]	–	
Moxivig 0.5% eye drops	9.80	BNF[117]	–	
Mydrilate 0.5% solution	8.08	BNF[117]	–	
Opatanol 1 mg/ml eye drops	4.68	BNF[117]	–	
Optive 0.5% eye drops	7.49	BNF[117]	–	
Ozurdex 700 µg intravitreal implant in applicator	870.00	BNF[117]	–	
Paracetamol 1 g tablets	2.49	BNF[117]	–	
Pevanti 5 mg tablets (Advanz Pharma) Prednisolone 5 mg tablets	0.67	BNF[117]	–	
Pilocarpine hydrochloride 2% eye drops	22.12	BNF[117]	–	
Pred Forte 1% eye drops	1.82	BNF[117]	–	
Predsol 0.5% ear/eye drops	2.00	BNF[117]	–	
Simbrinza 10 mg/ml/2 mg/ml eye drops	9.23	BNF[117]	–	
Sodium cromoglicate 2% eye drops	9.25	BNF[117]	–	
Tears Naturale eye drops	1.89	BNF[117]	–	
Timolol 0.5% eye drops	0.88	BNF[117]	–	
Tiopex 1 mg/g eye gel 0.4 g unit dose	7.49	BNF[117]	–	
Tobradex 3 mg/ml/1 mg/ml eye drops	5.37	BNF[117]	–	
Travatan 40 µg/ml eye drops	3.26	BNF[117]	–	
Trusopt 20 mg/ml eye drops 0.2 ml unit dose preservative free	2.04	BNF[117]	–	

TABLE 57 Within-trial analysis: unit costs applied for the valuation of resource use (*continued*)

Description	Unit cost (£)	Source	HRG code	Notes
Vancocin 500 mg powder for solution for infusion vials	5.49	BNF[117]	–	
Virgan 0.15% eye gel	19.99	BNF[117]	–	
Viscotears 2 mg/g liquid gel	2.80	BNF[117]	–	
Vitaros 3 mg/g cream	40.00	BNF[117]	–	
Xailin 0.2% eye gel	2.80	BNF[117]	–	
Xailin Fresh 0.5% eye drops 0.4 ml unit dose	4.80	BNF[117]	–	
Xailin HA 0.2% eye drops	7.19	BNF[117]	–	
Xalacom eye drops	6.37	BNF[117]	–	
Yellox 900 µg/ml eye drops	8.50	BNF[117]	–	
Zovirax 3% ophthalmic ointment	9.34	BNF[117]	–	

BNF, *British National Formulary*; HRG, Healthcare Resource Group.

Model-based analysis results: additional data

TABLE 58 Model-based analysis: deterministic results

	Total (95% CI)		Incremental (95% CI)		
Analysis	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£) (95% CI)
Base-case analysis					
Bevacizumab	14,302	10.3642			
Ranibizumab	27,015	10.3564	12,712	−0.0078	Dominated
Aflibercept	27,894	10.3607	13,592	−0.0035	Dominated
Scenario analysis: EQ-5D for utilities					
Bevacizumab	14,302	8.8834			
Ranibizumab	27,015	8.8753	12,712	−0.0081	Dominated
Aflibercept	27,894	8.8906	13,592	0.0072	1,891,888
Scenario analysis: EQ-5D-V for utilities					
Bevacizumab	14,302	8.5432			
Ranibizumab	27,015	8.5327	12,712	−0.0105	Dominated
Aflibercept	27,894	8.5464	13,592	0.0032	4,209,328

continued

TABLE 58 Model-based analysis: deterministic results (*continued*)

Analysis	Total (95% CI)		Incremental (95% CI)		ICER (£) (95% CI)
	Costs (£)	QALYs	Costs (£)	QALYs	
Scenario analysis: 100-week time horizon					
Bevacizumab	6278	1.6749			
Ranibizumab	15,881	1.6748	9603	−0.0001	Dominated
Aflibercept	16,711	1.6806	10,432	0.0057	1,820,265
Scenario analysis: 5-year time horizon					
Bevacizumab	6278	1.6749			
Ranibizumab	15,881	1.6748	9603	−0.0001	Dominated
Aflibercept	16,711	1.6806	10,432	0.0057	1,820,265
Scenario analysis: 10-year time horizon					
Bevacizumab	11,725	6.5389			
Ranibizumab	23,900	6.5400	12,175	0.0011	10,710,733
Aflibercept	24,600	6.5491	700	0.0091	77,086
Scenario analysis: bevacizumab list price from the BNF[117] (£243)					
Bevacizumab	20,947	10.3642			
Ranibizumab	27,015	10.3564	6068	−0.0078	Dominated
Aflibercept	27,894	10.3607	6948	−0.0035	Dominated

BNF, *British National Formulary*.

TABLE 59 Model-based analysis: base-case results, pairwise comparisons

Outcome	Intervention, mean (SD)	Comparator, mean (SD)	Difference, mean (95% CI)
Ranibizumab vs. bevacizumab			
Cost (£)	30,226 (9582)	18,353 (6520)	11,873 (11,458 to 12,288)
QALY	9.635 (1.395)	9.678 (1.219)	−0.044 (−0.074 to −0.013)
ICER (£)			Dominated (INMB: −14,316 to −12,067)
Aflibercept vs. ranibizumab			
Cost (£)	35,026 (11,820)	30,226 (9582)	4,800 (4445 to 5154)
QALY	9.569 (1.599)	9.635 (1.395)	−0.065 (−0.097 to −0.033)
ICER (£)			Dominated (INMB: −7917 to −5603)
Aflibercept vs. bevacizumab			
Cost (£)	35,026 (11,820)	18,353 (6520)	16,673 (16,036 to 17,310)
QALY	9.569 (1.599)	9.678 (1.219)	−0.109 (−0.161 to −0.057)
ICER (£)			Dominated (INMB: −21,864 to −18,040)

TABLE 60 Model-based analysis: EQ-5D scenario analysis results, pairwise comparisons

Outcome	Intervention, mean (SD)	Comparator, mean (SD)	Difference, mean (95% CI)
Ranibizumab vs. bevacizumab			
Cost (£)	30,226 (9582)	18,353 (6520)	11,873 (11,458 to 12,288)
QALY	8.795 (0.468)	8.782 (0.476)	0.013 (0.008 to 0.018)
ICER (£)			908,532 (659,881 to 1,476,254)
Aflibercept vs. ranibizumab			
Cost (£)	35,026 (11,820)	30,226 (9582)	4800 (4445 to 5154)
QALY	8.832 (0.478)	8.795 (0.468)	0.037 (0.032 to 0.043)
ICER (£)			128,513 (110,116 to 152,663)
Aflibercept vs. bevacizumab			
Cost (£)	35,026 (11,820)	18,353 (6520)	16,673 (16,036 to 17,310)
QALY	8.832 (0.478)	8.782 (0.476)	0.050 (0.044 to 0.057)
ICER (£)			330,697 (292,449 to 381,601)

TABLE 61 Model-based analysis: EQ-5D-V scenario analysis results, pairwise comparisons

Outcome	Intervention, mean (SD)	Comparator, mean (SD)	Difference, mean (95% CI)
Ranibizumab vs. bevacizumab			
Cost (£)	30,226 (9582)	18,353 (6520)	11,873 (11,458 to 12,288)
QALY	8.351 (1.960)	8.346 (0.731)	0.005 (–0.007 to 0.017)
ICER (£)			2,491,676 (INMB: –12,327 to –11,155)
Aflibercept vs. ranibizumab			
Cost (£)	35,026 (11,820)	30,226 (9582)	4800 (4445 to 5154)
QALY	8.639 (0.913)	8.351 (1.960)	0.018 (0.000 to 0.045)
ICER (£)			268,963 (INMB: –4930 to –3602)
Aflibercept vs. bevacizumab			
Cost (£)	35,026 (11,820)	18,353 (6520)	16,673 (16,036 to 17,310)
QALY	8.639 (0.913)	8.346 (0.731)	0.023 (–0.001 to 0.047)
ICER (£)			737,383 (INMB: –17,033 to –14,981)

Note
The INMB is at £30,000 per QALY.

TABLE 62 Model-based analysis: 100-week time horizon scenario analysis results, pairwise comparisons

Outcome	Intervention, mean (SD)	Comparator, mean (SD)	Difference, mean (95% CI)
Ranibizumab vs. bevacizumab			
Cost (£)	15,254 (3324)	6349 (638)	8905 (8650 to 9161)
QALY	1.641 (0.115)	1.641 (0.115)	0.000 (0.000 to 0.001)
ICER (£)			34,067,841 (217,070 to 10,420,696)
Aflibercept vs. ranibizumab			
Cost (£)	18,844 (4629)	15,254 (3324)	3590 (3400 to 3780)
QALY	1.646 (0.112)	1.641 (0.115)	0.005 (0.004 to 0.005)
ICER (£)			793,348 (688,418 to 926,352)
Aflibercept vs. bevacizumab			
Cost (£)	18,844 (4629)	6349 (638)	12,495 (12,119 to 12,871)
QALY	1.646 (0.112)	1.641 (0.115)	0.005 (0.004 to 0.006)
ICER (£)			2,610,554 (2,199,924 to 3,200,947)

TABLE 63 Model-based analysis: £243 list price for bevacizumab scenario analysis results, pairwise comparisons

Outcome	Intervention, mean (SD)	Comparator, mean (SD)	Difference, mean (95% CI)
Ranibizumab vs. bevacizumab			
Cost (£)	30,226 (9582)	23,530 (7372)	6696 (6400 to 6992)
QALY	9.635 (1.395)	9.678 (1.219)	−0.044 (−0.074 to −0.013)
ICER (£)			−153,559 (INMB: −9084 to −6937)
Aflibercept vs. ranibizumab			
Cost (£)	35,026 (11,820)	30,226 (9582)	4800 (4445 to 5154)
QALY	9.569 (1.599)	9.635 (1.395)	−0.065 (−0.097 to −0.033)
ICER (£)			Dominated (INMB: −7917 to −5603)
Aflibercept vs. bevacizumab			
Cost (£)	35,026 (11,820)	23,530 (7372)	11,496 (10,961 to 12,030)
QALY	9.569 (1.599)	9.678 (1.219)	−0.109 (−0.161 to −0.057)
ICER (£)			−105,573 (INMB: −16,636 to −12,905)

Within-trial analysis results: additional data

TABLE 64 Within-trial analysis: summary of missing data with the difference between treatment arms

Parameter	*n* (%)				Difference in percentage missing		
	Ranibizumab	Aflibercept	Bevacizumab	Total	Aflibercept vs. ranibizumab	Bevacizumab vs. ranibizumab	Aflibercept vs. ranibizumab
Baseline utility (EQ-5D without vision)	4 (0.03)	6 (0.04)	4 (0.03)	14 (0.03)	0.013	0.000	0.013
Baseline utility (EQ-5D-V)	12 (0.08)	19 (0.12)	18 (0.12)	49 (0.11)	0.045	0.039	0.006
Baseline utility (VFQ-UI)	6 (0.04)	6 (0.04)	4 (0.03)	14 (0.03)	0.000	−0.013	0.013
QALYs (EQ-5D without vision)	42 (0.27)	46 (0.30)	55 (0.36)	143 (0.31)	0.026	0.084	−0.058
QALYs (EQ-5D-V)	67 (0.44)	75 (0.49)	74 (0.48)	216 (0.47)	0.052	0.045	0.006
QALYs (VFQ-UI)	32 (0.21)	45 (0.29)	52 (0.34)	129 (0.28)	0.084	0.130	−0.045
Total cost	89 (0.58)	83 (0.54)	87 (0.56)	259 (0.56)	−0.039	−0.013	−0.026

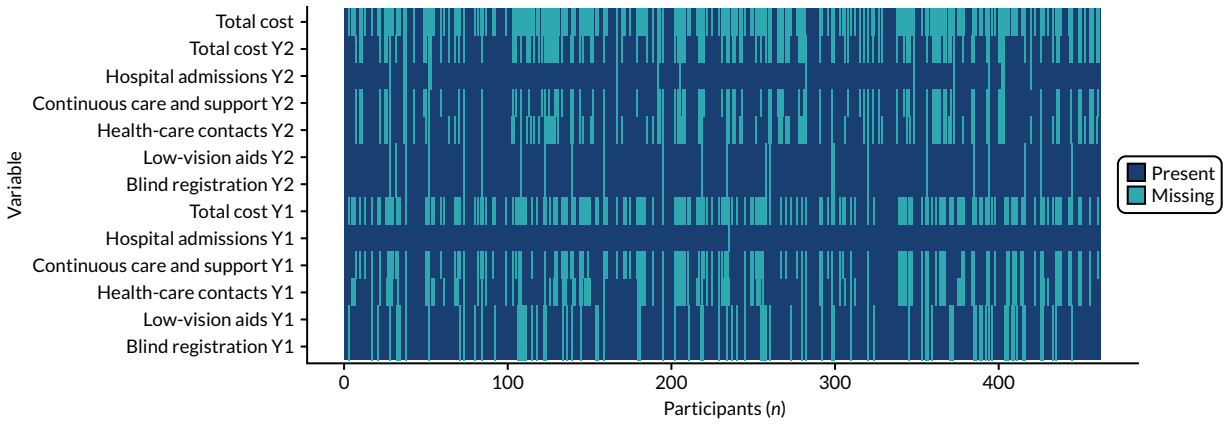

FIGURE 29 Within-trial analysis: pattern of missing cost data. Green shading indicates missing data for one or more patients. Y, year.

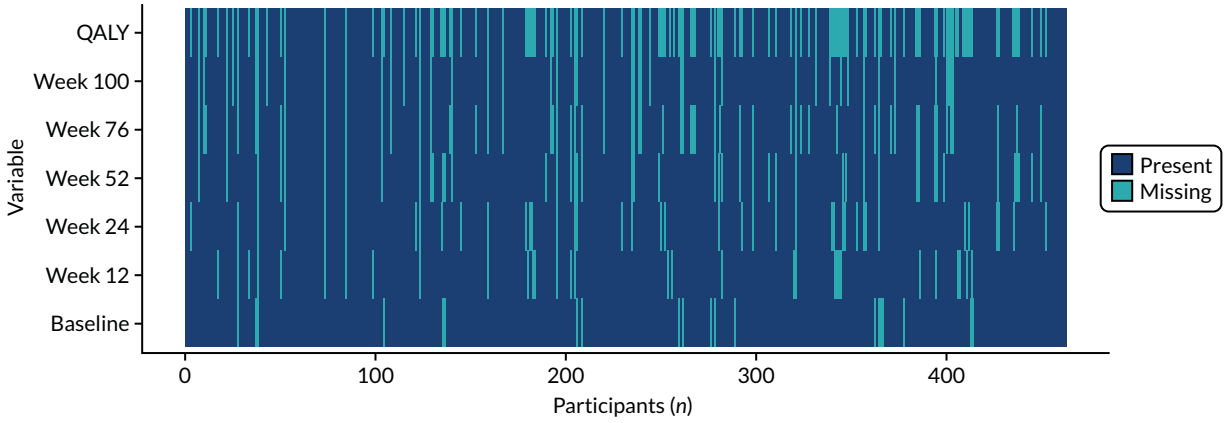

FIGURE 30 Within-trial analysis: pattern of missing VFQ-UI data. Green shading indicates missing data for one or more patients.

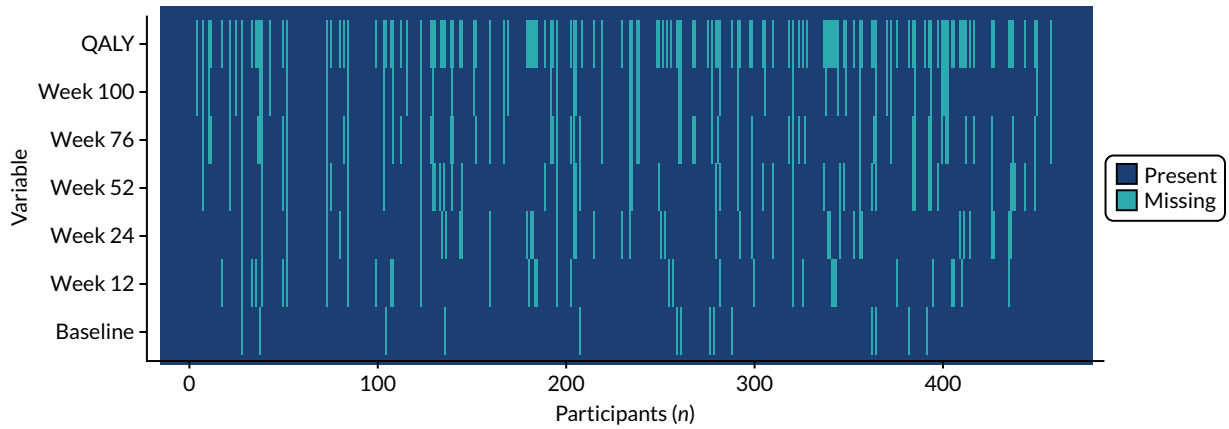

FIGURE 31 Within-trial analysis: pattern of missing EQ-5D (without the vision bolt-on) data. Green shading indicates missing data for one or more patients.

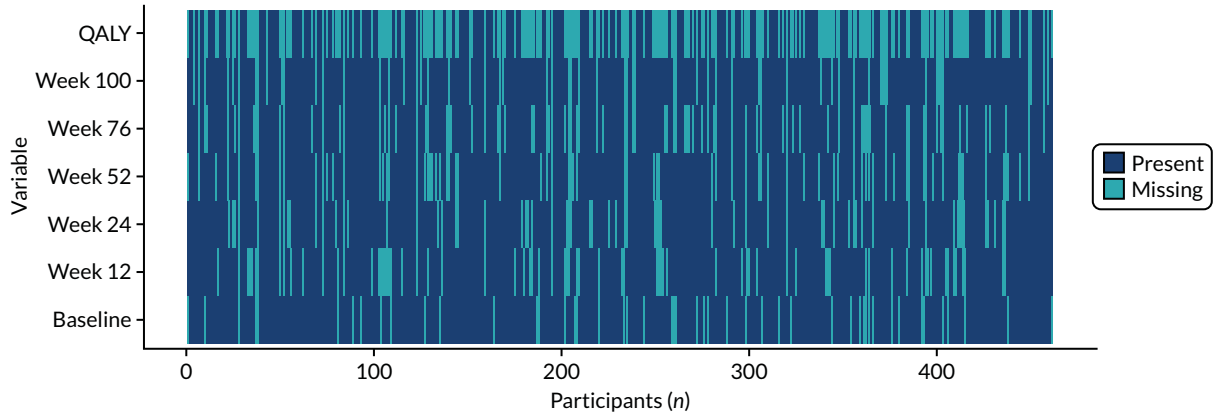

FIGURE 32 Within-trial analysis: pattern of missing EQ-5D-V data. Green shading indicates missing data for one or more patients.

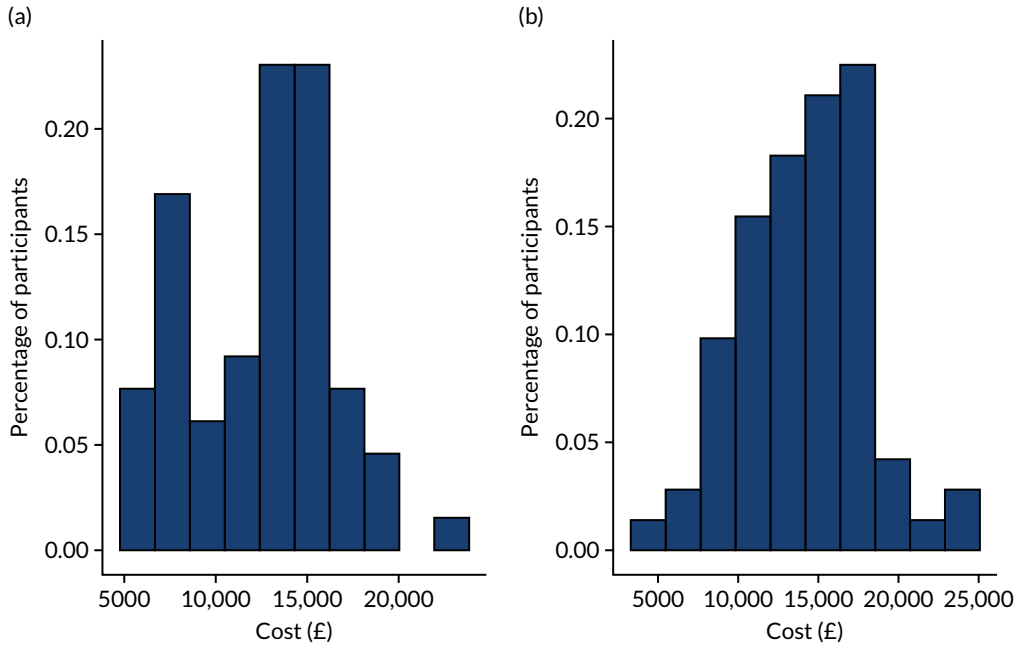

FIGURE 33 Within-trial analysis: histograms of complete-case cost data by treatment arm. (a) Ranibizumab ($n = 65$); (b) aflibercept ($n = 71$); and (c) bevacizumab ($n = 67$). (*continued*)

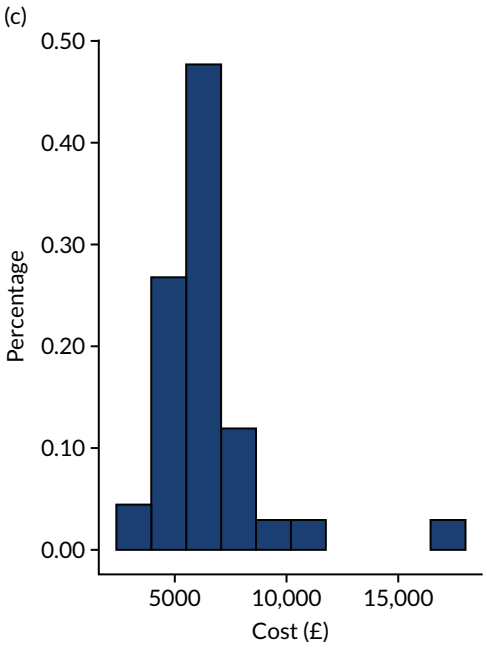

FIGURE 33 Within-trial analysis: histograms of complete-case cost data by treatment arm. (a) Ranibizumab ($n = 65$); (b) aflibercept ($n = 71$); and (c) bevacizumab ($n = 67$).

TABLE 65 Within-trial analysis: mean baseline utility and QALY estimated using the three HRQoL questionnaires

	Mean (SD); *n* patients		
HRQoL questionnaire	**Ranibizumab**	**Aflibercept**	**Bevacizumab**
VFQ-UI			
Baseline (complete case)	0.849 (0.1322); 148	0.868 (0.1295); 147	0.869 (0.1156); 148
QALY (imputed)	1.627 (0.2471); 154	1.651 (0.2374); 154	1.666 (0.2426); 154
EQ-5D (without vision bolt-on)			
Baseline (complete case)	0.790 (0.2118); 150	0.813 (0.2204); 148	0.801 (0.2055); 150
QALY (imputed)	1.472 (0.3666); 154	1.516 (0.3856); 154	1.500 (0.3757); 154
EQ-5D-V			
Baseline (complete case)	0.767 (0.2065); 142	0.783 (0.2029); 135	0.739 (0.2410); 136
QALY (imputed)	1.513 (0.3744); 154	1.560 (0.3801); 154	1.535 (0.3759); 154

Note
QALYs are adjusted for baseline utility.

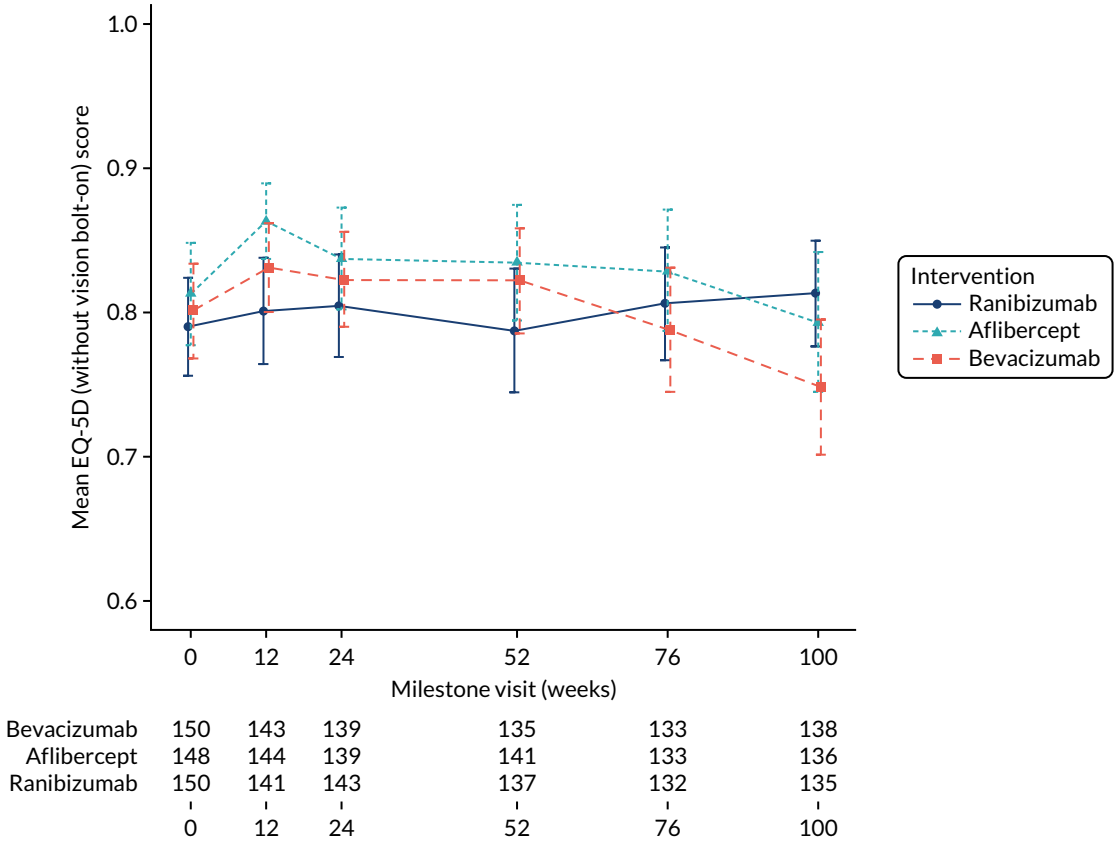

FIGURE 34 Within-trial analysis: mean utility scores using the EQ-5D (without vision bolt-on) over 100 weeks. Table shows number of observations at each time point. Reproduced with permission from Pennington *et al.*[95] This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

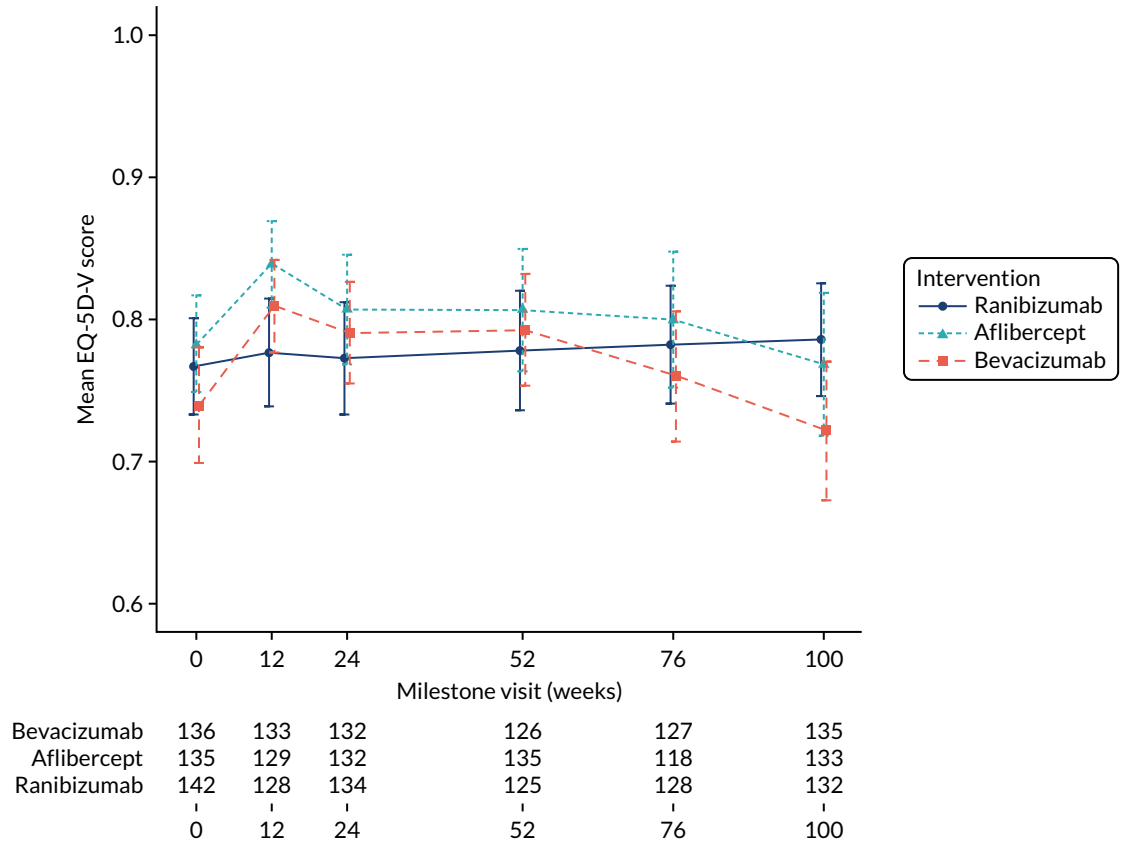

FIGURE 35 Within-trial analysis: mean utility scores using the EQ-5D-V over 100 weeks. Table shows number of observations at each time point. Reproduced with permission from Pennington *et al.*[95] This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

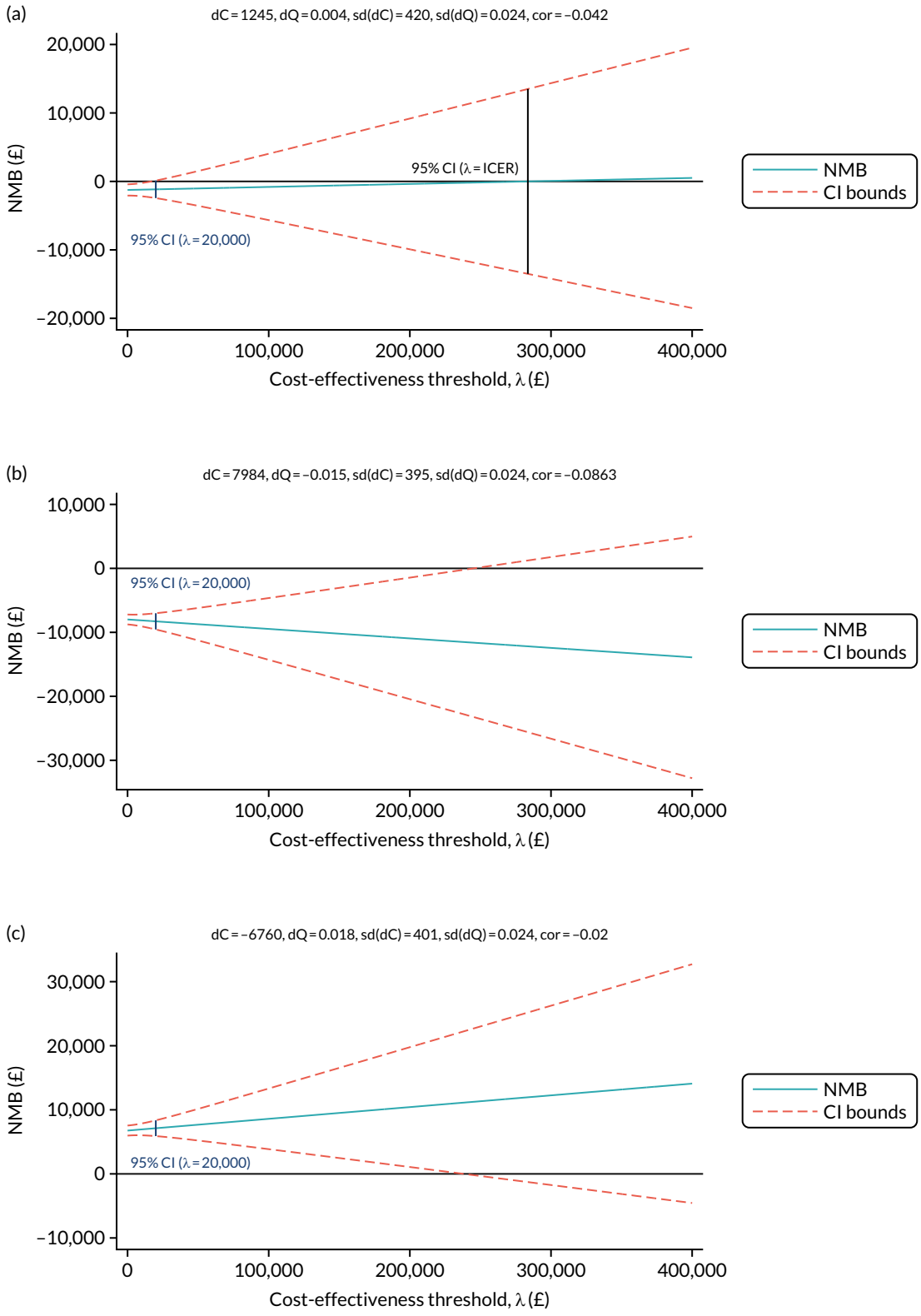

FIGURE 36 Within-trial analysis: NMB and 95% CIs. (a) Aflibercept vs. ranibizumab; (b) aflibercept vs. bevacizumab; and (c) bevacizumab vs. ranibizumab. Cor, covariance between total costs and QALYs; dC, mean difference in costs; dQ, mean difference in QALYs; sd(dC), standard error of mean differential costs; sd(dQ), standard error of mean differential QALYs.

TABLE 66 Within-trial analysis: fully incremental analyses for three HRQoL measures

	Mean total (SD)		Incremental (95% CI)[a]		ICER (£)/ dominance
	Cost (£)	QALY	Cost (£)	QALY	
VFQ-UI					
Bevacizumab	6292 (3371)	1.666 (0.2426)	–	–	–
Ranibizumab	13,014 (3605)	1.627 (0.2471)	6734 (5970 to 7498)	−0.019 (−0.065 to 0.0284)	Dominated
Aflibercept	14,328 (3773)	1.651 (0.2374)	7984 (7209 to 8759)	−0.015 (−0.0618 to 0.0322)	Dominated
EQ-5D (without vision bolt-on)					
Bevacizumab	6273 (3384)	1.535 (0.3759)	–	–	–
Ranibizumab	13,068 (3636)	1.513 (0.3744)	6769 (5987 to 7550)	−0.0102 (−0.0710 to 0.0504)	Dominated
Aflibercept	14,271 (3857)	1.560 (0.3801)	8035 (7246 to 8824)	0.008 (−0.0529 to 0.0683)	104,1476
EQ-5D-V					
Bevacizumab	6268 (3368)	1.500 (0.3757)	–	–	–
Ranibizumab	13,000 (3661)	1.472 (0.3666)	6748 (5948 to 7547)	−0.035 (−0.1172 to 0.0480)	Dominated
Aflibercept	14,273 (3720)	1.516 (0.3856)	8012 (7232 to 8793)	0.0032 (−0.0837 to 0.0902)	2,483,943

a Adjusted for baseline utility score.

TABLE 67 Within-trial analysis: scenario analysis using list price of £243 for bevacizumab

Outcome	Intervention, mean (SD); *n*	Comparator, mean (SD); *n*	Difference, mean (95% CI)[a]	Probability of being cost-effective at £20,000 (£30,000) per QALY
Aflibercept vs. ranibizumab				
Cost (£)	14,328 (3883); 154	13,013 (3673); 154	1245 (406 to 2085)	–
QALY	1.651 (0.2426); 154	1.627 (0.2471); 154	0.004 (−0.0430 to 0.0518)	–
ICER (£)			284,255	0.04 (0.10)
Bevacizumab vs. ranibizumab				
Cost (£)	8933 (3474); 154	13,013 (3673); 154	−4103 (−4949 to −3257)	–
QALY	1.666 (0.2374); 154	1.627 (0.2471); 154	0.018 (−0.0282 to 0.0648)	–
ICER (£)			Bevacizumab is dominant	1.00 (1.00)
Aflibercept vs. bevacizumab				
Cost (£)	14,328 (3883); 154	8933 (3474); 154	5342 (4552 to 6133)	–
QALY	1.651 (0.2426); 154	1.666 (0.2374); 154	−0.015 (−0.0618 to 0.0322)	–
ICER (£)			Aflibercept is dominated	0.00 (0.00)

a Adjusted for baseline utility score.

TABLE 68 Within-trial analysis: scenario analysis using complete-case data only

Outcome	Intervention, mean (SD); *n*	Comparator, mean (SD); *n*	Difference, mean (95% CI)[a]	Probability of being cost-effective at £20,000 (£30,000) per QALY
Aflibercept vs. ranibizumab				
Cost (£)	14,013 (3507); 66	12,608 (2342); 65	1405 (204 to 2606)	–
QALY	1.691 (0.1931); 66	1.656 (0.1605); 65	0.011 (–0.0413 to 0.0629)	–
ICER (£)			130,020	0.07 (0.14)
Bevacizumab vs. ranibizumab				
Cost (£)	6459 (3045); 62	12,608.2 (2342.29); 65	–6149 (–7369 to –4929)	–
QALY	1.651 (0.1507); 62	1.656 (0.1605); 65	–0.007 (–0.0596 to 0.0458)	–
ICER (£)			890,736	1.00 (1.00)
Aflibercept vs. bevacizumab				
Cost (£)	14,013 (3507); 66	6459 (3045); 62	7554 (6338 to 8769)	–
QALY	1.691 (0.1931); 66	1.651 (0.1507); 62	0.018 (–0.0345 to 0.0704)	–
ICER (£)			426,551	0.00 (0.00)

a Adjusted for baseline utility score.

TABLE 69 Within-trial analysis: scenario analysis using a 52-week time horizon

Outcome	Intervention, mean (SD); *n*	Comparator, mean (SD); *n*	Difference, mean (95% CI)[a]	Probability of being cost-effective at £20,000 (£30,000) per QALY
Aflibercept vs. ranibizumab				
Cost (£)	9214 (2235); 154	8164 (2163); 154	1002 (516 to 1487)	–
QALY	0.8798 (0.1208); 154	0.865 (0.1230); 154	0.004 (–0.0178 to 0.0256)	–
ICER (£)			256,547	0.00 (0.02)
Bevacizumab vs. ranibizumab				
Cost (£)	3621 (2017); 154	8164 (2163); 154	–4546 (–4999 to –4093)	–
QALY	0.8842 (0.1171); 154	0.865 (0.1230); 154	0.007 (–0.0143 to 0.0290)	–
ICER (£)			Bevacizumab is dominant	1.00 (1.00)
Aflibercept vs. bevacizumab				
Cost (£)	9214 (2235); 154	3621 (2017); 154	5560 (5082 to 6039)	–
QALY	0.8798 (0.1208); 154	0.8842 (0.1171); 154	–0.004 (–0.0256 to 0.0168)	–
ICER (£)			Aflibercept is dominated	0.00 (0.00)

a Adjusted for baseline utility score.

EME
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HTA
PGfAR
PHR

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