LEAVO: CLINICAL STUDY REPORT

Title Page:

Study Title (short)	LEAVO
Study Title (full)	A Multicentre Phase III 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).
Name of test drug/investigational product	Intravitreal ranibizumab, aflibercept & bevacizumab
Indication studied	Macular oedema secondary to central retinal vein occlusion
Name of the sponsor	Moorfields Eye Hospital NHS Foundation Trust, 162, City Road, London EC1V 2PD
Sponsor Representative	Ms Maria Hassard, Moorfields Eye Hospital,
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A Multicentre Phase III 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).

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List of Key Words

Macula oedema, central retinal vein occlusion, bevacizumab, ranibizumab, aflibercept, VEGF, anti-VEGF, cost-effectiveness, retinal non-perfusion, randomised controlled trial, non-inferiority, clinical effectiveness, visual acuity, intravitreal, safety, adverse events.

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Competing Interest Statement

Philip Hykin has received grants, personal fees and non-financial support from Bayer, Novartis and Allergan; A Toby Prevost is part of the Public Health Research Funding Board and has received a lecture fee from Bayer; Sobha Sivaprasad is part of the HTA Commissioning Board and has received research grants, personal fees, and non financial support from Bayer, Novartis, Allergan, Roche, Heidelberg Engineering, Optos and Boehringer Ingelheim; Laura Flight has received grants from the NIHR; Rebekah Pennington has

received research grants from Roche; Yit Yang has received personal fees from Novartis, Bayer, Allergan and Roche; Simon Harding has received grants to his employer from the NIHR UK and Roche Pharma; Andrew Lotery has received travel grants, speaker fees attended advisory board meetings of Novartis, Bayer and Allergan. Usha Chakravarthy has received grants from the NIHR, was part of the HTA Prioritisation Committee and received personal fees from Allergan and Novartis;. JV, CM, JK, JR, AA, RP, BH, EL, AM, EP, JB have no conflicts of interest. All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

Abstract

Background: The licensed agents, ranibizumab and aflibercept and unlicensed bevacizumab are used to treat macula oedema (MO) due to central retinal vein occlusion (CRVO) but their relative clinical and cost effectiveness and impact on the UK NHS and Personal Social Services has never been directly compared over the typical disease treatment period

Objective: To compare the clinical and cost effectiveness of the three intravitreal anti-vascular endothelial growth factor agents for the management of MO due to CRVO.

Design: A three-arm, double masked, randomised controlled non-inferiority trial. 463 patients with visual impairment due to MO related to CRVO were treated with repeated intravitreal injections of ranibizumab (n=155) aflibercept (n=154) and bevacizumab (n=154). The primary outcome was increase in best corrected visual acuity (BCVA) letter score from baseline to 100 weeks in the study eye. The null hypotheses that aflibercept and bevacizumab are each inferior to ranibizumab were tested with a non-inferiority margin of -5 ETDRS visual acuity letters over 100 weeks. Secondary outcomes included additional visual acuity, and imaging outcomes, Visual Function Questionnaire (VFG)-25, EQ-5D with and without a vision bolt on and drug side effects . Cost-effectiveness was estimated using treatment costs and VFQ – Utility Index (VFQ-UI) to measure quality adjusted life years (QALYs).

Setting: 44 UK National Health Service ophthalmology departments, 2014-2018.

Result: Adjusted mean change in BCVA letter score was ranibizumab +12.5 (SD 21.1), aflibercept +15.1 (18.7), and bevacizumab +9.8 (21.4) at 100 weeks. Aflibercept was non-inferior to ranibizumab in the ITT population (adjusted mean BCVA difference 2.23 letters; 95% CI -2.17 to 6.63, p=0.0006) but not superior. The study was unable to demonstrate that bevacizumab was non-inferior to ranibizumab in the ITT population (adjusted mean BCVA difference -1.73 letters; 95% CI -6.12 to 2.67; p=0.071). A post-hoc analysis was unable to demonstrate that bevacizumab was non-inferior to aflibercept in the ITT population (adjusted mean BCVA difference was -3.96 letters; 95% CI –8.34 to 0.42; p=0.32). All PP population results were the same. Fewer injections were required with aflibercept, 10.0 versus ranibizumab, 11.8 (difference in means -1.8; 95% CI -2.9 to -0.8) and there were no new safety concerns.

Post-hoc analysis showed more bevacizumab compared to aflibercept injections were required (difference in means 1.6 (95% CI: 0.5 to 2.7).The model- and trial-based cost-effectiveness analyses estimated that bevacizumab was the most cost-effective treatment at £20,000-£30,000 per QALY.

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

Conclusion and relevance: The study showed aflibercept to be non inferior to ranibizumab .However, we cannot rule out the possibility that bevacizumab, is worse than ranibizumab and aflibercept by 5 visual acuity letters. Bevacizumab is an economically attractive treatment alternative and would lead to substantial cost savings to the NHS and other healthcare systems. However, uncertainty about its relative effectiveness should be discussed in detail with individual patients, and more broadly with their representative groups and fund holders before considering treatment.

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

Current Controlled Trials ISRCTN 13623634.

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Alphabetical list of abbreviations

Abbreviation	Definition
A&E	Accident and Emergency
AIC	Akaike Information Centre
ALDVMM	Adjusted-Limited Dependent Variable Mixture Model
AMD	Age-related Macular Degeneration
ANCOVA	Analysis of Covariance
APTC	Anti-Platelet Trialists` Collaboration
BCVA	Best Corrected Visual Acuity
BIC	Bayesian Information Centre
BNF	British National Formulary
BP	Blood Pressure
BSE	Better Seeing Eye
CARF	Central Angiographic Resource Facility
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CFP	Colour Fundus Photograph
CI	Confidence Interval
CRF	Case Report Form

CRVO	Central Retinal Vein Occlusion
CSRI	Client Service Receipt Inventory
CST	Central Subfield Thickness
COST	Cone Outer Segment Tips
CUA	Cost Utility Analysis
CVI	Certificate Visual Impairment
CVOS	Central Vein Occlusion Study
DMEC	Data Monitoring and Ethics Committee
DMO	Diabetic Macula Oedema
DRIL	Disorganisation of Inner Retinal Layers
EC	European Commission
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELM	External Limiting Membrane
EMA	European Medicines Agency
EQ-5D	EuroQoL Five Dimension
EQ-5D-V	EuroQoL Five Dimension with vision bolt on
ERM	Epiretinal Membrane
ETDRS	Early Treatment Diabetic Retinopathy Study
EudraCT	European Clinical Trials Database
EZ	Ellipsoid Zone
FDA	U.S. Food and Drug Administration
FFA	Fundus Fluorescein Angiography
GBP	Great British Pound
GCP	Good Clinical Practice
GP	General Practitioner
HCHS	Hospital and Community Health Services

HRF	Hyper Reflective Foci
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IMP	Investigational Medicinal Product
INMB	Incremental Net Monetary Benefits
IQR	Inter Quartile Range
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to treat
KCTU	King's Clinical Trials Unit
LEAVO	A Multicentre Phase III 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.
LME	Linear Mixed Effects
MAE	Mean Absolute Error
MAR	Missing At Random
MHRA	Medicines and Healthcare products Regulatory Agency
MO	Macular Oedema
NEI – VFQ - 25	National Eye Institute Visual Function Questionnaire-25
NetwORC UK	Network of Ophthalmic Reading Centres UK
NHS	National Health Service
NICE	National Institute for Health & Care Excellence
NICE TA	National Institute for Health & Care Excellence Technology Appraisal
NIHR	National Institute of Health Research
NMB	Net Monetary Benefit
nvAMD	Neovascular Age Related Macular Degeneration
NVD	Neovascularisation disc

NVE	Neovascularisation elsewhere
NVA	Neovascularisation of the angle
NVG	Neovascular glaucoma
NVI	Neovascularisation of Iris
OCT	Optical Coherence Tomography
PAS	Patient Access Scheme
PIN	Patient Identification Number
PIS	Patient Information Sheet
PP	Per protocol
PPI	Patient and Public Involvement
PRN	Pro Re Nata
PROM	Patient Reported Outcome Measures
PRP	Panretinal photocoagulation
QALY	Quality-adjusted Life Year
QoL	Quality of Life
RAPD	Relative Afferent Pupillary Defect
RCT	Randomised Control Trial
R&D	Research and Development
RMSE	Root Mean Square Error
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SD-OCT	Spectral-domain optical coherence tomography
SE	Standard Error
SFTP	Secure File Transfer Protocol
SOP	Standard Operating Procedure

SUR	Seemingly Unrelated Regression
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VFQ-UI	Visual Function Questionnaire-Utility Index
VMT	Vitreomacular Traction
WSE	Worst Seeing Eye

Plain English Summary

The eye is like a camera with the retina, at the back of the eye, the camera film. The centre of the retina, the macula is important because it allows us to see fine details. Swelling of the macula due to fluid leakage as a result of blockage of the blood vessel that normally drains blood from the retina is a common cause of visual problems. It affects about 6,500 people each year in the UK

Three drugs, repeatedly injected into the eye in tiny amounts every 4 to 8 weeks have been shown to improve vision in this condition. Two, ranibizumab and aflibercept are licensed for use in this condition but the third, bevacizumab is not, even though it is much cheaper and widely used.. No trials have compared the three drugs over the typical two year treatment period of the disease. . The LEAVO study was designed to do this.

All three drugs improved vision a lot but bevacizumab, the unlicensed alternative was slightly less effective than ranibizumab but aflibercept was as good. The drugs did not cause many side effects and there were no differences between the drugs. . All three led to similar improvements in quality of life.

Since aflibercept cost more than ranibizumab and both cost much more than bevacizumab, they may not be good value for money. If patients, their representatives and funders all agreed, it may be possible to treat MO related to CRVO with bevacizumab, with the other agents available if needed, and save money.

Word Count: 253

Scientific Summary

Background

Approximately 5200 cases of visual impairment due to central retinal vein occlusion (CRVO) related macular oedema occur yearly in England and Wales and require treatment with repeated intraocular injection of anti-vascular endothelial growth factor (VEGF) agents. Treatment typically last for two years. Two agents ranibizumab (0.5mg/0.05ml (Novartis, Basel, Switzerland) and aflibercept 2mg/0.05ml (Bayer Pharma AG, Berlin, Germany) are both licensed and recommended by the National Institute of Health and Care Excellence.

As an alternative low-cost option, unlicensed bevacizumab 1.25mg/0.05ml (Roche, Basel, Switzerland) is utilised globally. All three anti-VEGF agents are also used in other retinal disorders. Despite clinical evidence that bevacizumab is non-inferior to ranibizumab and cost-effective in neovascular age related macular degeneration and diabetic macular oedema, it is not used in the NHS. The reasons include lack of clinical evidence in certain indications, concerns whether high quality bevacizumab could be manufactured on the scale required for NHS use, and that it is not licensed or recommended by NICE. Therefore, in 2012 the NICE Decision Support Unit recommended further comparative studies of these agents in retinal diseases, resulting in the development of the LEAVO clinical trial in 2014. No new anti-VEGF agents or other treatments have since superseded anti-VEGF agents in vein occlusion related macula oedema. Since LEAVO was initiated, the US SCORE2 trial reported non-inferiority of bevacizumab to aflibercept with respect to visual acuity at 6 months on 362 patients with macula oedema due to CRVO or hemiretinal vein occlusion. A systematic review

of anti-VEGF therapy confirmed there were no RCTs comparing all three anti-VEGF agents in vein occlusion. The LEAVO trial is therefore the first RCT that evaluated the comparative clinical and cost-effectiveness of the three anti-VEGF agents in CRVO related macula oedema over the typical duration of the disease.

Objectives

The research questions addressed in this trial were

i. is bevacizumab non-inferior to ranibizumab in eyes with macula oedema due to CRVO in terms of best corrected visual acuity (BCVA) at 100 weeks?
ii. is aflibercept non-inferior to ranibizumab in eyes with macula oedema due to CRVO in terms of the best corrected visual acuity at 100 weeks?
iii. what is the short-term and long-term cost-effectiveness of aflibercept and bevacizumab versus ranibizumab in the treatment of macula oedema due to CRVO ?

Methods

Design

A multicentre, prospective, three-arm, parallel-group, double-masked, randomised, non-inferiority trial to evaluate the clinical and cost-effectiveness and side effect profile of three anti-VEGF agents in the management of CRVO related macula oedema over 100 weeks.

Setting

The ophthalmology departments of 44 UK NHS Trust Hospitals.

Participants

Adults with visual impairment due to CRVO related macula oedema of less than 12 months duration with visual acuity letter score in the study eye between 19 (~3/60 Snellen) and 78 (~6/9 Snellen) and spectral domain optical coherence tomography (OCT) central subfield thickness (CST) ≥ 320μm.

Interventions

Eligible patients were randomly allocated (1:1:1) to repeated intravitreal injection of ranibizumab, aflibercept or bevacizumab using the method of minimisation, with factors visual acuity (19-38, 39-58 and 59-78 ETDRS letters), disease duration (< 3 months, 3-6 months or >6 months) and treatment naïve or not, via a web-based randomisation service. Participants in all study arms had mandated injection at baseline, 4, 8 and 12 weeks. From week 16 to 96, treatment was given if one or more pre-defined retreatment criteria were met including a decrease in visual acuity of more than five letters between the current and most recent visit attributed to an increase in OCT CST, an increase in visual acuity of more than five letters between the current and most recent visit, OCT CST ≥ 320μm due to intra- or subretinal fluid and OCT CST increase >50μm from the lowest previous measurement. From week 24, the visit interval could be increased from 4 to 8 weeks if retreatment criteria were not met at three consecutive visits. Retreatment was withheld if visual acuity was >83 letters and could be suspended if there was minimal response to three consecutive injections and 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 & 100 weeks, change in OCT CST from baseline to 52 and 100 weeks, OCT CST <320µm at 52 and 100 weeks, and the number of injections by 100 weeks. Adverse events were recorded throughout the weeks.

Statistical analysis

The standard deviation was anticipated to be 14.3 based on 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 ETDRS letters for each intervention compared to 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 aflibercept and ranibizumab and between bevacizumab and ranibizumab groups primarily at the 100-week point adjusting for baseline using a linear mixed effects model 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 12, 24, 52, 76 and 100 weeks) of treatment group, disease duration (<3, ≥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 against the non-inferiority margin of -5 letters. The per protocol (PP) population was defined as a subset of the ITT 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 within the PP 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 ITT and PP analysis models primarily at 100 and secondarily at 52 weeks (and implicitly one-sided $p<0.025$ for both). Analyses were completed according to the ITT strategy under a missing at random assumption together with principled sensitivity analysis in the full ITT and PP 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 ITT 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 Anti-Platelet Trialists` Collaboration (APTC) events were reported as proportions and compared between groups with Wilson's 95% confidence interval for rare events. All superiority tests were two-sided at the 5% significance level and effect sizes 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

study supplemented with evidence from external sources. Cost-effectiveness was expressed in terms of the incremental cost per quality-adjusted life year (QALY), estimated using the Visual Functioning Questionnaire-Utility Index (VFQ-UI), EuroQol-Five Dimension (EQ-5D) and EQ-5D with vision bolt-on (EQ-5D V). 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 in 586 patients and 463 were randomly assigned to receive ranibizumab (n=155), aflibercept (n=154) or bevacizumab (n=154). Baseline characteristics were similar between treatment groups. A total of 454 and 443 participants were included in the pre-specified ITT and PP linear mixed effect models and the 100 week visit was completed by 135 (87.1%) patients in the ranibizumab, 133 (86.4%) in the aflibercept and 139 (90.3%) in the bevacizumab groups respectively.

Clinical results

The mean gain in visual acuity letter score was ranibizumab +12.5 (SD 21.1), aflibercept +15.1 (18.7), and bevacizumab +9.8 (21.4) at 100 weeks. At 100 weeks, the study was unable to demonstrate that bevacizumab was non-inferior to ranibizumab in both the ITT (adjusted mean BCVA difference was -1.73 letters; 95% CI -6.12 to 2.67; p=0.071) and PP population (adjusted mean BCVA difference was -1.67 letters; 95% CI -6.02 to 2.68 letters; p=0.066). Aflibercept was non-inferior to ranibizumab in both ITT (adjusted mean BCVA difference was 2.23 letters; 95% CI -2.17 to 6.63, p=0.0006) and PP populations (adjusted mean BCVA difference was 3.49 letters; 95% CI -0.91 to 7.88 letters p< 0.0001) but not superior. . At 52 weeks, aflibercept and bevacizumab were non-inferior to ranibizumab. The proportion of patients in the three groups with a ≥15 BCVA letter gain was similar: 47% ranibizumab, 52% aflibercept and 45% bevacizumab. There were no differences across groups in the proportion of patients with ≥10 BCVA letter gain or <15 BCVA letter loss. The adjusted difference in OCT CST at 100 weeks was aflibercept vs ranibizumab: -29.3 (95% CI -60.9, 2.3) and bevacizumab vs ranibizumab: 21.9 (95% CI -9.7, 53.4) However, there was a significantly greater proportion of patients with OCT CST <320μm at 52 weeks for aflibercept (76%), compared to ranibizumab (63%), a 12.4% mean difference (95% CI 1.7 to 23.1). This also occurred at 100 weeks, aflibercept (81%) compared to ranibizumab group (66%), 15.3% mean difference (95% CI 4.9 to 25.7), but only between bevacizumab and ranibizumab at week 24, -18.7% (95% CI -30.1, -7.4). The corresponding proportions at 52 weeks and 100 weeks for bevacizumab were respectively -10.7% (95% CI -22.3, 0.9) and -7.4% (95% CI -18.9, 4.1).

By 100 weeks, ranibizumab group patients had received a mean of 11.8 injections compared to 10.0 in the aflibercept and 11.5 in the bevacizumab groups. The difference between aflibercept and ranibizumab groups was significant at week 24 (mean difference -0.4 (95% CIs -0.6, -0.2), week 52 -1.1 (95% CIs -1.6 to -0.5) and week 100 -1.9 (95% CI -2.9 to -0.8)), but not for aflibercept. There was one case of infectious endophthalmitis in the bevacizumab group. The frequency of all ocular adverse and APTC defined events occurred with an expected and similar frequency between groups

Aflibercept had become 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 bevacizumab was not non-inferior to aflibercept in both the ITT (adjusted mean BCVA difference was -3.96 letters; 95% CI –8.34 to 0.42; p=0.32) and PP populations (adjusted mean BCVA difference was -5.15 letters; 95% CI -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 licenced products ranibizumab and aflibercept.

The model-based economic analysis found that all three anti-VEGF agents generated similar QALYs. Aflibercept generated the highest costs, followed by ranibizumab and then bevacizumab. Using the VFQ-UI, bevacizumab generated more QALYs than ranibizumab and aflibercept. The mean difference in QALYs between ranibizumab and bevacizumab was -0.044 (95% confidence interval (CI): -0.074 to 0.013) and the mean difference in costs was £11,873 (95% CI: £11,458 to £12,288), so bevacizumab was said to dominate ranibizumab, and the 95% CI for the incremental net monetary benefit (INMB) at £30,000 per QALY was -14,316 to -12,067. The mean difference in QALYs between aflibercept and bevacizumab was -0.109 (95% CI: -0.161 to -0.057) and the mean difference in costs was £4,800 (95% CI: £4,445 to £5,154)), so bevacizumab was said to dominate aflibercept, and the 95% CI for the INMB at £30,000 per QALY was -21,864 to -18,040. The mean difference in QALYs between aflibercept and ranibizumab was -0.065 (95% CI: -0.097 to -0.033) and the mean difference in costs was £4,800 (95% CI: £4,445 to £5,154), so ranibizumab was said to dominate aflibercept, and the 95% CI for the INMB at £30,000 per QALY was -7,917 to -5,603. 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% for them to have comparable costs with bevacizumab (at £28 per injection over a patient's lifetime.

In the within trial base case analysis, the difference in mean total costs between aflibercept and ranibizumab was £1,245 (95% CI: £421 to £2,070), between bevacizumab and ranibizumab arms was -£6,760 (95% CI: -£7,546 to -£5,973) and between aflibercept and bevacizumab was £7,984 (95% CI: £7,209 to £8,759). Bevacizumab was dominant (less costly and with no difference in benefit) compared to ranibizumab, with a probability of cost-effectiveness of 1.00 at the £20,000 per QALY threshold. Aflibercept was more costly with a mean QALY difference of 0.004 (95% CI: -0.0430 to 0.0518) compared to ranibizumab with an incremental cost-effectiveness ratio (ICER) of £283,595 per QALY gained and a probability of cost-effectiveness of 0.04 at the £20,000 per QALY threshold. 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 both the £20,000 and £30,000 per QALY threshold.

Conclusions

All three anti-VEGF agents are effective therapies for macula oedema secondary to CRVO with no differences from a safety perspective. While aflibercept was demonstrated non-inferior to ranibizumab, the study was

unable to demonstrate that bevacizumab was non-inferior to either of them, implying we cannot rule out the possibility that it may be worse by 5 visual acuity letters. However patients' health related quality of life assessments were similar across arms, and bevacizumab is the most cost-effective option. The study results are therefore divergent. We believe that bevacizumab could only be introduced into the NHS as a first line agent for this condition after review of these results and agreement with patients, their representatives and fund holders . 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 are available to them as an option if response to bevacizumab is less than expected. If adopted, bevacizumab would result in substantial savings to the NHS, and potentially to healthcare systems around the world.

Trial Registration

This trial is registered as ISRCTN: 13623634.

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Chapter 1: Introduction

1.1 Background

Retinal vein occlusion (RVO) is the second commonest retinal vascular disorder[1,2] after diabetic retinopathy and comprises branch retinal vein occlusion, hemiretinal vein occlusion and central retinal vein occlusion (CRVO). The latter has a prevalence of 0.08% to 0.41%[3–5] and a 15 year cumulative incidence of 0.5%.[6,7] Approximately 6,860 people develop CRVO every year in England and Wales of whom 5,150 develop visual impairment due to macula oedema (MO) which is unlikely to improve spontaneously[8–11] and therefore potentially eligible for treatment (www.NICE.org).[12,13]

CRVO is characterised by retinal haemorrhages, venous dilatation and tortuosity in all four quadrants of the retina[2,7]. 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 macular oedema[14] although the raised hydrostatic pressure per se likely 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 left untreated. CRVO may be bilateral in 5% of cases and the risk of developing RVO in the contralateral eye is approximately 5% in 12 months.[7,8]

CRVO has two distinct clinical subtypes.[7,8] Non-ischaemic CRVO is characterised by a visual acuity of 6/30 or better, no RAPD, mild to moderate retinal venous dilatation and tortuosity, and intraretinal haemorrhage and macula oedema. Ischaemic CRVO is characterised by a visual acuity of 6/36 or worse, the presence of a relative afferent pupillary defect and intraretinal haemorrhage with venous dilatation and tortuosity greater than the Central Vein Occlusion Study standard photograph[15] with complications that include MO, macula ischaemia, retinal ischaemia, iris and retinal neovascularisation and neovascular glaucoma.[16] Optical coherence tomography (OCT) confirms and characterises the MO and fluorescein angiography the extent of macular and retinal ischaemia and the presence of retinal neovascularisation, with both investigations guiding management.[7,8] Novel morphological OCT biomarkers for CRVO have been identified which may provide important diagnostic and prognostic information, although none have been utilised in a large prospective clinical trial to date.[17–19] Conventional seven field FFA is semi quantitative 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 sub-type.[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 has 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 to 20% of cases present with an ischaemic CRVO and non-ischaemic CRVO convert to the ischaemic subtype in 25 to 34% in 3 years.[20,24] Neovascular complications such as iris neovascularisation are typically managed with 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 of Diabetic Retinopathy Study (ETDRS) letters. This is thought to represent a meaningful difference between two treatments based on: i. most patients in a busy clinic setting can reliably distinguish an 8 letter (1.5 line) difference on an ETDRS visual acuity chart but may perform better than this is a clinical trial setting[25], ii. a 5 letter (one 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 it is a meaningful difference[68], iii. the choice of a five-letter margin was 32% higher than the available estimated 12-month placebo-controlled effect of 6.6 letters for ranibizumab, the standard (comparator) treatment for LEAVO. This margin choice was therefore consistent with maintaining assay sensitivity sufficiently to be able to declare non-inferiority (See LEAVO SAP, Stand Alone Documents).and iv. such a 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 of LEAVO study design, and we wanted to ensure the LEAVO study would be as similar as possible to alternative comparable studies of anti-VEGF therapy in CRVO (SCORE2).

1.2 CRVO related macular oedema and anti-VEGF therapy

Visual impairment is due primarily to MO in CRVO, is typically significant, resolution is only likely to occur in the mildest non ischaemic cases[24] and 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 and patients who present with an initial visual acuity ≥ 6/12 will likely retain good vision whilst 80% of those who present with visual acuity ≤ 6/60 do not improve to better than 6/60.[20] The natural history arm of the (CVOS) showed no change in mean baseline visual acuity over 3 years,[20] a finding supported by the sham arm in the CRUISE,[9] GALILEO and COPERNICUS[10,26–29] licensing trials for ranibizumab and aflibercept in which patients who were initiated on treatment six 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 of MO is repeated intravitreal injections of anti-VEGF agents to block the action of VEGF thereby reducing capillary permeability.[9,30–36] Early studies excluded patients with ischaemic CRVO[31,37] as it was questionable whether there would be significant improvement in vision with anti-VEGF therapy. More recent studies did not[38] and this is the approach we adopted in the LEAVO study to ensure our study population fully reflected a general UK population likely to present for treatment.

To date three anti-VEGF agents have been used in treating MO due to CRVO:
Ranibizumab is a humanized, affinity-matured VEGF antibody fragment that binds to and neutralizes 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) [2,39,40] and was licensed by the FDA and EMA for MO due to CRVO in 2012. This was based on the CRUISE study data[9] that showed monthly intraocular ranibizumab therapy improved mean BCVA by +15 ETDRS letters at 6 months and a PRN regimen

with monthly monitoring improved mean BCVA by +14 letters at 12 months.[9] In an open label extension (HORIZON) from months 12 to 24, the mean visual acuity in CRVO patients reduced by 4.1 letters with an average of 3.5 injections in 12 months.[36] Ranibizumab was well tolerated with 6.5% of patients having some degree of cataract after 2 years and < 1% having any rise in intraocular pressure.[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. It was FDA and EMA licensed for CRVO in 2014 based on the GALILEO and COPERNICUS studies that showed a mean gain of +16.2 letters BVCA at 12 and +13.0 at 24 months with 60% gaining ≥ 15 letters at 12 and 49.1% at 24 months.[2,27–29] Despite these results and that it was non-inferior to ranibizumab when given 8 weekly after a loading phase in nvAMD suggesting improved cost effectiveness,[41] no clinical trial had been undertaken to directly compare it with ranibizumab or bevacizumab even though NICE recommended it for MO due to CRVO (NICE TA305).[12]

Cumulative safety data to date have not shown an increased risk of any ocular or systemic adverse events compared to other drugs used for these indications.

Bevacizumab is a monoclonal antibody that also inhibits VEGF, and is EMA licensed for the treatment of cancer but is used off-label in the eye. However, it was of crucial importance to fully assess its suitability for intraocular use because: (i). it is substantially cheaper when divided by a compounding pharmacy into multiple doses from a single 4ml vial than ranibizumab or aflibercept, (ii) it was found by the Decision Support Unit (DSU)[42] to be used in NHS trusts across the UK for nvAMD, DMO and RVO and other less common indications such as choroidal neovascularisation due to myopia and retinal dystrophies, (iii) it is widely used in UK private practice, (iv) there have been concerns about the possible systemic side effects following intraocular injection of bevacizumab.[2] Bevacizumab was found to be non-inferior to ranibizumab in terms of macular dysfunction and final visual acuity over two years in two large clinical trials, the IVAN and CATT studies.[43,44] These studies also found there was no increased risk of local or systemic side effects with bevacizumab compared to ranibizumab, although there were more hospitalisations with bevacizumab due to serious adverse events, these were thought unrelated to bevacizumab by the investigators.[45]

Two independent reviews[46,47] had previously suggested an increase in bevacizumab related side effects raising the need to compare the safety of bevacizumab directly with ranibizumab. The NICE TAG 283: Lucentis (ranibizumab)[13] and the TAG 305: Eylea (aflibercept)[12] for MO secondary to CRVO recommended that further head to head trials including bevacizumab were needed for RVO that carefully examined clinical and cost effectiveness. It was therefore proposed to conduct the LEAVO trial in MO due to CRVO to (i) compare the clinical effectiveness of ranibizumab, aflibercept and bevacizumab in a pragmatic trial over 24 months that followed patients over the natural history of the disease (ii). compare the cost-effectiveness of the agents in a trial that closely resembled clinical practice (iii). describe the safety profile of each agent for ocular and systemic adverse events over 24 months.

1.3 Evidence update post–LEAVO trial 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 in many countries. Despite convincing case series and early trials employing bevacizumab, full scale RCTs were commissioned and completed by the UK NIHR and the US NIH to compare bevacizumab

with ranibizumab in nvAMD[43,44] prior to licensing of aflibercept. There have been no randomised controlled trials (RCTs) comparing all three agents for nvAMD. Nevertheless, after review of all the available evidence the NICE Guideline Committee reported that all three agents had equivalent efficacy and side effects[48] and systematic reviews found that there were no differences in the risk of vision threatening complications or systemic adverse events.[49,50]

Despite this, bevacizumab has not achieved widespread usage in the UK. The reasons for this include no clear position on the issue from NHS England or the MHRA, likely conflicts of interest amongst 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 Care Commissioning Groups, who had adopted a policy that bevacizumab should be the preferred option for the treatment of nvAMD, ruled this was lawful.[51] 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 where the three anti-VEGF agents have been compared is diabetic macular oedema. The visual gains at two years in eyes with moderate and severe visual loss (VA ≤ 20/50) occurred earlier and were greater in eyes receiving aflibercept therapy. However for patients with mild initial visual impairment visual gains were similar across treatment arms suggesting bevacizumab could be used in this sub group.[52]

There remains a lack of robust data on long-term comparisons of outcomes with anti-VEGF agents for MO due to CRVO. After initiation of the LEAVO trial, the secondary outcome of the randomized, double-masked, phase 3 licensing trials on aflibercept for CRVO, the COPERNICUS and GALILEO studies, become available. These showed that the visual and anatomic improvements after fixed monthly dosing through to week 24 and continued PRN dosing with monthly monitoring from weeks 24 to 52 were largely maintained up to 100 weeks if monitored every 8 weeks and diminished if monitored quarterly from weeks 52 to 100. [27–29] The 12-month single arm study of an individualized dosing regimen of ranibizumab driven by stabilization criteria in 357 patients with CRVO also resulted in significant gain in visual acuity (CRYSTAL).[53] The mean number of injections by 12 months was 8.8 injections with better outcomes in eyes with CRVO of less than 3 months duration and lower baseline visual acuity. The visual outcomes were similar in eyes with and 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.[54]

Whilst these trials compared each anti-VEGF agent to sham treatment for MO due to CRVO, RCTs comparing these agents over a longer term have been limited. An RCT comparing aflibercept and ranibizumab on a treat and extend regimen over 18 months showed that the frequency of injections was significantly less in the aflibercept arm compared to the ranibizumab arm.[55] The SCORE2 study group randomised 362 patients with macular oedema due to central retinal 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.[56] The participants who responded well to either monthly aflibercept or bevacizumab for 6 months in the SCORE2 study were further randomised to receive either monthly injections or treat-and-extend regimens of aflibercept or bevacizumab respectively. The 12 months outcome showed that the treat and extend arm of each anti-VEGF agent required up to two less injections from 6 to 12 months than the

monthly mandated treatment arms although the difference in visual outcomes showed significant variability.[57] A RCT comparing aflibercept and bevacizumab on a one plus pro re nata basis found that the aflibercept arm required fewer injections at 12 months.[58]

The COMRADE C was a Phase IIIb, multicentre, double-masked, randomized clinical trial that compared a ranibizumab loading phase followed by pro re nata dosing versus dexamethasone 0.7 mg given only at baseline for MO due CRVO and showed a favourable outcome of ranibizumab.[59] A recent systematic review evaluating the effectiveness and adverse effects of ranibizumab, aflibercept and bevacizumab in three common retinal conditions including retinal vein occlusion reported that none of the seventeen included studies reported a clinically important difference (≥ 5 letters) in visual acuity gains between agents. There was insufficient evidence to compare bevacizumab and ranibizumab in retinal vein occlusion. Overall, the authors reported that no agent had a clear advantage over another for effectiveness or safety but both aflibercept and ranibizumab were significantly less cost-effective than repackaged bevacizumab in two trials.[60]
A further systematic review and network analysis of eleven RCTs of the three anti-VEGF agents in retinal vein occlusion showed that there were no statistically significant differences in the proportion of patients who gained at least 15 letters in best-corrected visual acuity (BCVA), mean change from baseline in BCVA, and mean change from baseline in central macular thickness (CMT) at 6 months.[61] However, to date there are no RCTs that compare all 3 anti-VEGF agents for this condition over the at least two year duration of the disease.

The LEAVO trial is the first RCT evaluating the comparative clinical and cost-effectiveness and relative safety of these three anti-VEGF agents in CRVO related MO over 100 weeks. In summary, if bevacizumab was shown in the LEAVO study 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 supporting evidence of its equivalence to the licensed medications in multiple indications and lend substantial support to the case for bevacizumab use in nvAMD and other retinal diseases.

1.4 Clinical Trial Objectives

The objective was to compare the relative clinical 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. It was intended to determine if bevacizumab or aflibercept were as effective as ranibizumab in reducing visual loss from MO due to CRVO, whether they have an equivalent side effect profile and whether either could be considered or recommended for NHS treatment based on non-inferior clinical effectiveness and superior cost-effectiveness.

Primary Objectives[2]

1. To determine whether bevacizumab is non-inferior to ranibizumab in treating visual loss due to MO secondary to central retinal vein occlusion
2. To determine whether aflibercept is non-inferior to ranibizumab in treating visual loss due to MO secondary to central retinal vein occlusion

Secondary Objectives[2]

1. To determine the difference between arms in mean change in best corrected visual acuity at 52 weeks.
2. 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 ETDRS letter loss (severe visual loss) at 52 and 100 weeks.
3. To determine the difference between arms in the proportion of participants with ≥73 ETDRS letters or better than 6/12 Snellen equivalent (i.e. approximate driving visual acuity), ≤58 ETDRS letters (≤6/24) and ≤ 19 letters (≤3/60)(Certificate of Visual Impairment CVI partial and severe visual impairment) at 52 and 100 weeks.
4. To determine the difference between arms in the mean change in OCT CST and macular volume at 52 and 100 weeks.
5. To determine the difference between arms in the proportion of participants with OCT CST <320µm (Spectralis or equivalent) at 52 and 100 weeks (key guide to subsequent NHS clinical practice).
6. To determine the differences between arms in the mean number of intravitreal injections performed per participant at 100 weeks.

7&8 To determine any differences in the relative effectiveness of the investigational treatments and comparator on quality of life and resource utilization, reported as Incremental Cost Effectiveness Ratios (ICERs) at 52 weeks and 100weeks

9. To detect any differences in the prevalence of local and systemic side effects at 100 weeks
10. To determine differences between arms at 100 weeks in the proportion i. of persistent non-responders (see Section ii. of participants that develop a change in retinal non-perfusion compared to screening, iii. of participants that develop anterior and posterior segment neovascularisation).
11. To determine differences between arms in mean change in best corrected visual acuity at 100 weeks due to i) baseline visual acuity stratified as ≤38 letters, 39-58 letters, 59-78 letters, ii) duration of disease stratified as: <3 months, 3-6 months and > 6 months, iii) treatment stratified as naïve vs previous treatment iv) quantity of retinal ischaemia (<10, ≥10 and < 30, and ≥ 30 DA of non-perfusion).
12. To determine 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

2.1 Trial design

The LEAVO study was a phase III randomised controlled double-masked non-inferiority clinical trial to evaluate the relative clinical and cost-effectiveness of intravitreal bevacizumab and aflibercept compared to ranibizumab in MO due to CRVO. The intention was to randomise 459 patients with MO due to CRVO in at least one eye 1:1:1 to ranibizumab [0.5mg/50ul], aflibercept [2.0mg/50ul] and bevacizumab [1.25mg/50ul], all administered by repeated intravitreal injection and followed for 100 weeks. The study was conducted across 44 Ophthalmology centres in the UK National Health Service with expertise in retinal disorders and a proven track record in effectiveness research.[2]

2.2 Participants

The trial population, from which the study sample was drawn, were adults aged 18 year or over with MO secondary to CRVO of less than 12 months duration who attend one of the 44 NHS Ophthalmology centres. The complete inclusion and exclusion criteria were:

2.2.1 Selection of Participants[2]

2.2.1.1 Inclusion Criteria

1. Subjects of either sex aged ≥ 18 years.
2. Clinical diagnosis of centre-involving macular oedema (MO) due to central retinal vein occlusion (CRVO)
3. CRVO of ≤ 12 months duration
4. Best corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score (approximate Snellen equivalent) in the study eye between 78 (20/32) and 19 (20/400).
5. Optical Coherence Tomography (OCT) central subfield thickness >320μm (Spectralis™, Heidelberg) [or equivalent for alternative OCT device] predominantly due to MO secondary to CRVO in the study eye.
6. Media clarity, pupillary dilatation and subject cooperation sufficient for adequate fundus imaging of the study eye.
7. BCVA ETDRS letter score (approximate Snellen equivalent) in the non-study eye ≥ 14 (20/600).

2.2.1.1 Exclusion Criteria

The following applied to the study eye only and to the non-study eye only where specifically stated:

1. Macular oedema considered to be due to a cause other than CRVO (e.g. diabetic macular oedema, Irvine-Gass syndrome).
2. An ocular condition is present that, in the opinion of the investigator, might affect macular oedema or alter visual acuity during the course of the study (e.g. vitreomacular traction)
3. Any diabetic retinopathy or diabetic macular oedema at baseline clinical examination of the study eye.

4. Moderate or severe non proliferative diabetic retinopathy (NPDR) or quiescent, treated or active proliferative diabetic retinopathy (PDR) or macular oedema in the non-study eye. Note: Mild NPDR only is permissible in the non-study eye.
5. History of treatment for MO due to CRVO in the past 90 days with intravitreal or peribulbar corticosteroids or in the last 60 days with anti-VEGF drugs or >6 prior anti-VEGF treatments in the previous 12 months.
6. Active iris or angle neovascularisation, neovascular glaucoma, untreated NVD, NVE and vitreous haemorrhage or treatment for these conditions in the last 1 month.
7. Uncontrolled glaucoma [>30mmHg], either untreated or on anti-glaucoma medication at screening.
8. Any active periocular or intraocular infection or inflammation (e.g. conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis).

2.2.1.3 Systemic exclusion criteria:

1. Uncontrolled blood pressure defined as a systolic value > 170mmHg and diastolic value > 110mmHg.
2. Myocardial infarction, stroke, transient ischaemic attack, acute congestive cardiac failure or any acute coronary event < 3 months before randomisation
3. Women of child bearing potential unless using effective methods of contraception throughout the study and for 6 months after their last injection for the trial. Effective contraception is defined as one of the following:[62]
    a. Barrier method: condoms or occlusive cap with spermicides.
    b. True abstinence: When it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception).
    c. Have had tubal ligation or bilateral oophorectomy (with or without hysterectomy).
    d. Male partner sterilisation. The vasectomised male partner should be the only partner for the female participant.
    e. Use of established oral, injected or implanted hormonal methods of contraception and intrauterine device.
4. Pregnant or lactating women.
5. Males who do not agree to an effective form of contraception for the duration of the study and for 6 months after their last injection for the trial.
6. Hypersensitivity to the active ingredients aflibercept, bevacizumab or ranibizumab or any of the excipients of these drugs.
7. Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.
8. A condition that, in the opinion of the investigator, would preclude participation in the study.
9. Participation in an investigational trial involving an investigational medicinal product within 90 days of randomisation.

2.2.1.4 Re-screening of patients[2]

Patients could be rescreened in the following circumstances:

1. Patients that 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.
2. Individuals that did not meet other modifiable inclusion criteria, e.g. blood pressure, could be re-screened 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 fluorescein angiography, if the rescreening visit was within 10 weeks of the original screening visit, otherwise this too had to be repeated. If a patient was found to be eligible on re-screening and was randomised, their initial entry on the eCRF system had to be updated rather than creating a 'new' patient on the system. This avoided 'double counting the patients in the CONSORT diagram.'

2.2.2 Recruitment

The study recruited from 44 UK Ophthalmology centres over 24 months. Recruitment was competitive, however each site was allocated a minimum target number of patients to recruit and encouraged to exceed this where possible. Sites were set up strategically, larger sites with greater capacity were initiated first to maximise early recruitment and to ensure the recruitment period was fully utilised. Eligible patients were invited to participate via their local clinics, or via an invitation letter. Within each site patients were identified from subspecialty retina clinics, general clinics, and eye casualty clinics and at which clinical examination and discussion of a study were undertaken and the patient information sheet (PIS) provided.[2]

2.3 Study procedures

2.3.1 Informed consent procedure

The Principal Investigator or designated sub-investigator were responsible for ensuring that a patient was fully consented following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. Patients were advised that any data collected were held and used in accordance with the Data Protection Act 1998. Patients were given at least 24 hours after receiving the PIS to consider taking part. The PI or designee recorded in the medical notes date the patient information sheet was given to the patient and 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 prior to taking consent from the participant and consent denoted enrolment into the trial. A copy of the signed informed consent form was given to the patient. The original signed form was retained at the study site and a copy placed in the medical notes. If new safety information resulted in significant changes in the risk/benefit assessment, or there were significant changes to the protocol or patient information sheet, subjects were re-consented as appropriate.

2.3.2 Randomisation

Only one eye was randomised into the trial. In 95% of cases, one eye was affected by CRVO and was the 'worst seeing eye' and was randomised. On rare occasions, patients had bilateral CRVO that met the

eligibility criteria. In these cases the worst-seeing eye was randomised unless the patient opted for randomization of the 'better seeing eye'. The plan was to recruit 459 adult patients with MO due to CRVO 1:1:1 at the level of the individual using the method of minimisation incorporating a random element. The three stratifying factors were visual acuity (stratified by screening BCVA letter score (≤38 [approximate Snellen equivalent ≤6/60], 39–58 [approximate Snellen equivalent 6/48 to 6/24], ≥59 [approximate Snellen equivalent ≥ 6/18]), duration of disease from date of CRVO diagnosis to commencement of therapy (< 3 months, 3-6 months and > 6 months) and treatment naïve vs 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 the patient on the MACRO eCRF system (InferMed Macro), after consent had been signed. Randomisation was via a bespoke web based randomisation system hosted at the Kings College Clinical Trials Unit. A unique PIN was generated in the Macro program and recorded on all source data worksheets and used to identify the patient throughout the study.[2,62] Authorised site staff were allocated a username and password for the randomisation system by the Trial Manager. All authorised staff members, who were typically the PI or designee logged into the randomisation system and entered the patients' details, including unique PIN. Once a patient was randomised, the system automatically generated emails to key staff within the study. Unmasked e-mails sent to site pharmacies alerted them to a patient's treatment arm: ranibizumab, aflibercept or bevacizumab. The pharmacy department used the email to cross check the trial prescription to ensure that the correct medication was being dispensed for the correct patient. Additional masked emails were generated from the randomisation system to key trial site staff,[62] and unmasked e-mails to the emergency unmasking service (eSMS Global) and unmasked trial management staff.[2]

2.3.3 Masking

Masking of treatment allocation: the randomization process informed only the pharmacy at the local trial site of the subjects' treatment allocation, with a copy to the emergency unmasking service (eSMS Global) and unmasked trial management staff. The study drug the patient received was transferred in a masking bag to the dedicated injection room. Prior to leaving the Pharmacy a unique seal was attached to the bag. The non-transparent masking bag, designed to securely and safely transport medication, had a safe zipped compartment containing a pre-printed form detailing the participants unique PIN, date of birth, date drug dispensed and injection batch number. Prior to the participant entering the injection room, the unmasked injector broke the seal, and took the drug out of the masking bag. In the case of bevacizumab, this was 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 patient, who was then invited into the room, to lie on the injection bed and the injection administered to the patient. Ranibizumab was provided in a unique prefilled syringe by the manufacturer during the course of the trial and vials ceased to be available. In this situation, the unmasked injector took care not to allow the subject sight of the syringe either before or after the injection had been given. This was done by performing the injection with the patient lying down and the injection given via the pars plana in any quadrant of the eye with the syringe being brought to and taken away from the injection site via the patients inferotemporal field of vision so that it was not passed

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 patient, without specifying the treatment, and also signed the pre-printed form within the masking bag. The empty drug syringe with needle and vial were disposed of in the injection room. The masking bag and completed pre-printed form were returned to pharmacy. The drug outer packaging was disposed of in the injection room.[2]

The clinical assessment team including the site PI, optometrist i.e. assessor of the primary outcome, site trial co-ordinator, the clinical investigator, clinical assessment study nurse and ophthalmic technician therefore remained masked throughout the study as there was no record of the subjects' treatment arm in the source notes or case report form. Similarly, co-ordinators or administrators completing questionnaires in person with participants or in extreme circumstances only by telephone at specific time points had details of subject study number only. If at any time, information regarding treatment allocation was shared with the outcome assessors, then this was recorded in the Trial Master File, the person (s) involved met with the site PI to ensure no repetition occurred and undertook not to convey this information either to the participant or others involved in the project. Certain secondary outcomes e.g. interpretation of fluorescein angiography occurred at the remote NetwORC UK Reading Centre where the assessors were masked as to the treatment allocation. These masking procedures avoided both performance and detection bias. We 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 was required for reporting to the DMEC. Both trial statisticians attended both the open and closed DMEC meetings.

2.3.4 Screening and baseline assessment

The patient had to receive the PIS not less than 24 hours before the screening assessment. The screening and baseline visits could be performed on the same day provided all test results were available. The 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 (**appendix 3**).

2.3.5 Milestone and non milestone visits

Study milestone assessments, at which key research data were collected, occurred at baseline and weeks 12, 24, 52, 76 and 100. These visits, as well as treatment visits at weeks 4 and 8 were calculated and agreed with the participant prior to randomization (with flexibility of 0 to +14 days for weeks 4, 8 and 12, and -14 to +14 days for weeks 24, 52, 76 and 100 from the date of randomization). It was mandatory for all participants to attend all milestone visits, even if a milestone visit fell less than 4 weeks after a treatment visit or if the participant was following an 8 weekly follow up schedule and the next milestone visit fell within the 8 week interval. The intervening study treatment visits were deliberately flexible to allow normal clinical practice treatment follow up to be accommodated. All data from the study milestone visits were entered into the eCRF. For regular treatment visits only BCVA, OCT CST, whether an injection was given, and if no injection was given the reason it was not given were entered into the eCRF. At these visits refracted visual acuity and

health economic questionnaires were performed, colour photography undertaken at baseline, weeks 52 and 100 and fluorescein angiography at baseline and week 100, in addition to the clinical examination and optical coherence tomography tests performed at all other study visits (**appendix 3**).

2.4 Study assessments and methods

2.4.1 Participant demographics, medical and ophthalmic history

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

2.4.2 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.[63,64] Refracted visual acuity was done in both eyes at screening,[62] 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** Assessment of the Primary Outcome).

2.4.3 Standard ophthalmic examination

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

2.4.4 Spectral Domain Optical Coherence Tomography (SD- OCT)

The central sub-field thickness and total macular volume in both eyes were recorded in the eCRF from the SD-OCT thickness map at every visit, and if applicable, at the point of withdrawal. [62] Any SD-OCT machine could be used for the study but the same model of SD-OCT had to be used for each individual throughout the period of the study. SD-OCTs at screening, weeks 52 and 100 only were transferred to and read by masked graders at the Independent Reading Centre at NetwORC UK. The NetwORC UK provided each site with a study imaging protocol on how to acquire and transfer SD-OCTs, and CFPs and FFAs (see below) to them. Initial grading of all OCTs at baseline, week 52 and 100 was performed by the NetwORC UK Reading Centre. The grading took into account intraretinal oedema, classified as diffuse, cystic and mixed, subretinal fluid as present or absent, and vitreoretinal interface abnormalities as present, either as an epiretinal membrane or vitreomacular traction or absent. Following the contract variation, additional grading parameters were assessed at NetwORC UK, Belfast in collaboration with specialised retinal graders at Moorfields Eye Hospital, utilising additional definitions and analyses that had been developed whilst the study was in progress.[1,65,66]

Only images captured with Spectralis™ OCT had sufficient detail to support the enhanced grading definitions. Retinal morphology was assessed using the Spectralis™ Heidelberg Macular Raster OCT of 31 line scans, 30 x 25mm in size, at an inter-scan distance of 240 micron or equivalent for alternative devices. Macula oedema was graded using the entire line scan series and the central 1500um i.e. 7 scans were employed for vitreo-macular interface abnormality and subretinal detachment or equivalent**.** The remaining parameters were graded using the central 1000um only, i.e. central 5 line scans only unless otherwise specified below. A magnification of 300% was used to assess the ellipsoid layer (EZ), disorganisation of the inner retinal layers (DRIL),[65,66] and hyper reflective foci (HRF)[67,68] with 100% magnification for the remaining parameters. HRF, ELM, EZ and COST were only graded as positive 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 please see **Appendix 5.1** and **Figures 22 & 23**.

2.4.5 Colour Fundus Photography (CFP)

Non stereo, 7-field conventional or wide-angle CFP was performed at screening, week 52 and week 100 in the study eye. CFP confirmed the diagnosis of CRVO and assisted interpretation of features identified on fundus fluorescein angiography e.g. 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 study visit as per investigator discretion. CFP was transferred to and read by masked graders at the Independent Reading Centres in NetwORC UK. Either a colour camera capable of taking 7-field CFP or wide angle system was used but the same model of camera was used for each individual throughout the period of the study. The colour photographs were graded by the NetwORC UK Reading Centre, Belfast .[2,].

2.4.6 Fundus fluorescein angiography (FFA)

Non stereo, 7-field conventional or wide angle FFA was performed at screening and week 100 in the study eye. Any FFA system capable of taking 7-field FFA pictures or a wide angle system was allowable but the same system had to be used in the same individual throughout the study. [2,]. FFA was used to quantify the degree of retinal ischaemia and for identification of retinal neovascularization (see **Appendix 5.1**). Pseudo anonymized FFA images were transferred to the NetwORC UK Reading Centre where the standard NetwORC UK thirteen sector grid (**figure 24**) was applied over the wide angle or montaged seven field angiography pictures at baseline and 100 weeks. The first 100 gradings were double graded. Discrepancies were adjudicated. Subsequently 1 in every 8 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 in excess of 0.8. Any graders that did not achieve this were required to undergo additional training. Each sector within the grid was semi-quantified in terms of percentage 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 (**figure 24**). This technique was used in preference to the ischaemic index which estimates the ratio of ischaemic vs. total retinal area but is very susceptible to image quality and only applicable to wide angled images.[22] Therefore, during the study we used concentric ring method which displays superimposed concentric circles centered n

the fovea.[23,69,70] The innermost circle was one 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 (Ring 1, Ring 2, Ring 3, and Ring 4) are placed at increments of 2.5 DD in radius from the foveal centre. Each of these rings are subdivided into 12 equal segments.[23] To calculate the size of the concentric rings required, we assumed that the mean axial length was 24mm and excluded 2mm from this to account for the cornea and part of the anterior chamber. In our model eye, the radius was 11mm (22mm in diameter), and therefore the full circumference would have been 69.1mm (π=3.142). The wide angled imaging system (Optos^{TM}) was able to image 200 degrees of the retina and we used this to calculate the average diameter of retina obtained in a single central image. This was calculated to be 38.4mm. Using the disc diameter as 1.8mm, this meant the diameter of the image was 21.3 DD. A diameter of 21.3 DD resulted in the need for a macular + 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 due to the nature of the ultra-wide field image having better clarity in the horizontal meridian. The method used is represented in **figure 25**.

2.4.7 Health Economic Questionnaires

The following quality of life and resource use questionnaires were administered at baseline, 12, 24, 52, 76, 100 weeks and at the point of withdrawal: VFQ-25, EQ-5D with and without vision 'bolt-on' and a bespoke resource use questionnaire (see **Stand Alone Documents**).

2.4.8 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 for the study.[2]

2.4.9 Definition of end of trial

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

2.5 Treatment procedures

2.5.1 Treatment schedule

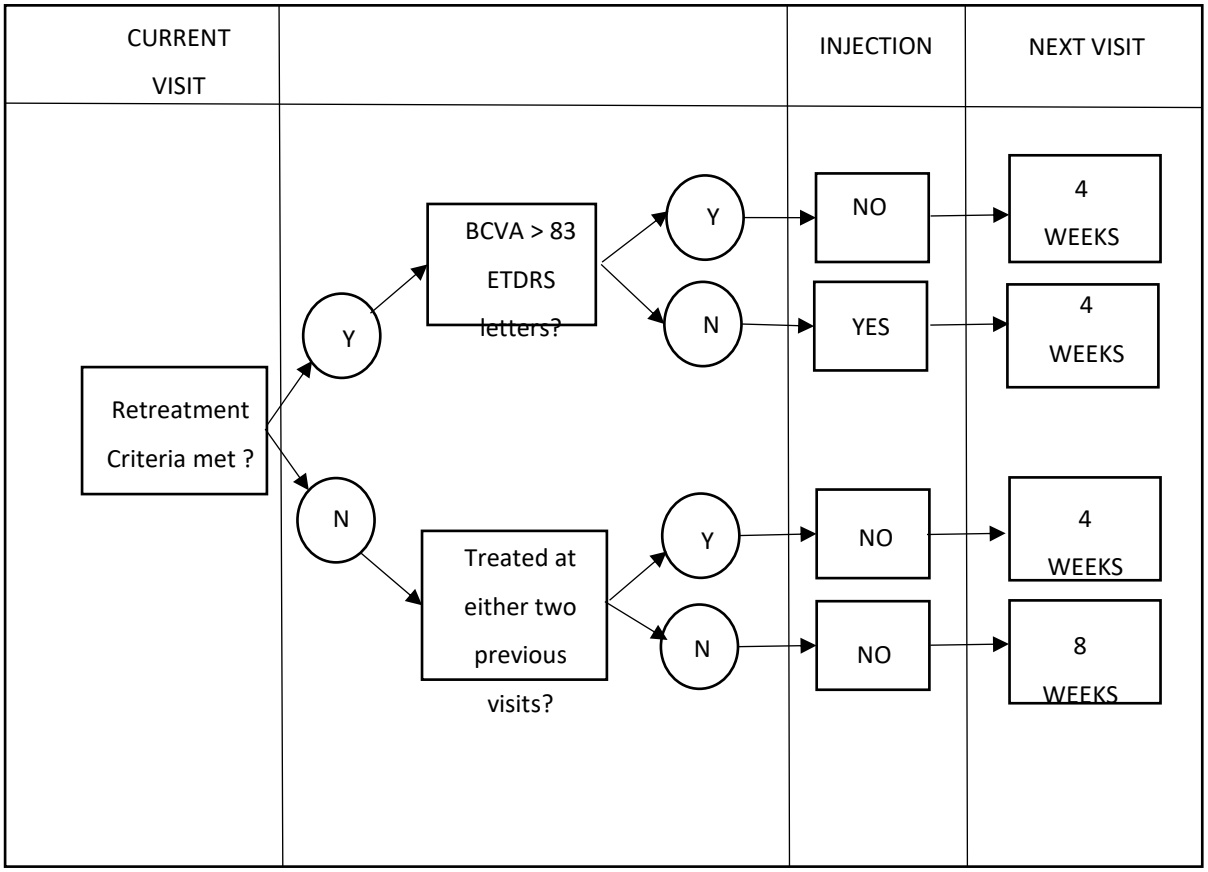
After mandated administration in all three study arms at baseline, 4, 8, and 12 weeks, further PRN intervention was administered at weeks 16 and 20 if retreatment criteria were met and VA ≤ 83 letters. Whether a treatment was given or not, the patient was reviewed in 4 weeks. From week 24 to week 96, intervals were initially 4 weekly (with a -14 to + 14 day visit window) with the potential to increase to 8 weekly (with a -14 to + 14 day visit window) 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 > 83 letters and if present at any retreatment visit from 16 weeks onwards, then treatment was not given at that visit and the participant reviewed in 4 weeks if 'success' was fulfilled at week 16 or 20 weeks and either at 4 or 8 weeks at any other time point depending on their pre-existing visit interval. If at any subsequent visit, retreatment criteria were met and BCVA ≤ 83 ETDRS letters then retreatment was commenced (**figure 1**) At each visit between weeks 24 and 96 inclusively, 'Non responder treatment suspension' criteria could be met. If so, the PI or his 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 retreatment criteria were met at an 8 weekly or unscheduled visit, then 4 weekly visits were resumed. Treatment could be 'Deferred' in certain circumstances but the participant was asked to still attend the milestone visits.

2.5.2 Re-treatment criteria: criteria were met if one or more of the following is present[2]

1. a decrease in visual acuity of ≥ 6 letters between the current and most recent visit attributed to an increase in OCT CST OR
2. an increase in visual acuity of ≥ 6 letters between the current and most recent visit OR
3. OCT CST >320μm (Spectralis or refer to appendix 1) due to intraretinal or subretinal fluid OR
4. OCT CST increase > 50μm from the lowest previous measurement.

Figure 1: Retreatment Algorithm for study weeks 24 to 96[2]



2.6 Investigational medicinal products (IMPs)

2.6.1 Comparator: Ranibizumab (0.5mg/50µl)

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

2.6.2 Intervention: Aflibercept (2.0mg/50ul)

Aflibercept is a fusion protein that includes the key binding domains of human VEGF receptors 1 and 2 with human IgGFc and acts as a dummy receptor for all VEGF isoforms and placental growth factor preventing increased permeability and MO in CRVO. At the time of the initiation of this study, It was EMA licensed and NICE has recommended it for nvAMD, The NICE TA305 was published in

February 2014[12] and NICE recommends this drug as first line use for CRVO related MO . It was supplied in a glass vial to each Site Hospital Pharmacy direct from the manufacturer as part of routine hospital stock.[2]

2.6.3 Intervention: Bevacizumab (1.25mg/50µl)

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. For this study it was supplied in a sealed package containing a prefilled plastic syringe to each study site by the pharmacy from the Liverpool and Broadgreen Pharmacy Aseptic Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L78XP. [2]

2.6.4 Site Pharmacy Storage, Ordering and Handling Procedures of IMPs

A study medication dispensing and return log was maintained by the study site pharmacies. Administration records from these sites were retained by the pharmacy department and monitored by the Trial Manager, to ensure that accurate CRF data were recorded. The randomization system was linked to the IMP supply. The site pharmacy was also responsible for appropriate storage, dispensing, disposal and recall and destruction logs in accordance with Good Manufacturing and Good Clinical practice and the site hospital pharmacies approved policies for IMP accountability and management. Furthermore, each site pharmacy maintained a record of study drug administration based on the pre-printed form signed by the unmasked investigator that was returned to the pharmacy at each centre.[2]

2.6.5 IMP accountability

Used and unused Trial Study Medication & Study Medication Accountability: Each masking bag contained a pre-printed form which had the details of the participant's unique pin number, date of birth, date drug dispensed and injection batch number. After performing the intravitreal injection, the unmasked injector signed this form to confirm the drug had been given to the allocated patient and 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 pharmacy. Pharmacy departments in each site maintained a study medication dispensing log, including date dispensed, batch number, expiry date and return log. The latter was compiled from the form signed by the unmasked injector. In addition, the study specific prescriptions were maintained in the pharmacy file for audit purposes. Any administration errors were reported to the CI and trial statistician. In the event that an injection was not given as scheduled, reasons were documented in the patients' notes and CRF. The study monitor checked the pharmacy records against the eCRF. All records were reconciled at the end of the study with the Investigator Site File. [2]

2.6.6 Description and justification of route of administration and dosage of IMP

The approved route of administration, i.e. by intravitreal injection through the pars plana of the eye, were used in all cases under sterile conditions in a designated treatment area in accordance with the Guidelines for Intravitreal Injection of the Royal College of Ophthalmologists (RCOphth) and any approved procedures for the individual site hospital. The injection could only be performed by the unmasked injector(s), who were on the hospital site LEAVO study Delegation Log and experienced in intravitreal injection procedures. The dosage of ranibizumab, 0.5mg/50ul and aflibercept, 2.0mg/50ul used in this trial were the EMA approved and NICE recommended doses of these agents for intraocular use. The dosage for bevacizumab, 1.25mg/50ul was the dosage used in the IVAN and CATT clinical trials of treating wet AMD and the standard dose used in clinical practice. Post injection checks were in accordance with local hospital policy and included VA, IOP or optic nerve head perfusion check or a combination of the above. The interval between two doses of all three drugs was not recommended to be less than 4 weeks. [2]

2.7 Management of complications

Complications such as the development of ischaemic CRVO, NVA, NVI, NVG, NVE and NVD in the study eye were recorded as adverse events. Diagnosis and management of these complications of CRVO in the study was based on investigator discretion and local practice. Laser therapy formed the mainstay of therapy and was recorded as a concomitant procedure. [7,8]

2.8 Recording and reporting of adverse events and reactions

2.8.1 Routine Reporting

The MHRA definitions of adverse and serious adverse events were adopted for this trial. Adverse events were reported by the site in the adverse events log in the eCRF. All SAEs, SARs & SUSARs were recorded and reported on the serious adverse event 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 site assessed relationship of the SAE to either study intervention. 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 SARs 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 timescale.

All Principal Investigators were informed of all SAEs assessed as fulfilling criteria as a SUSAR (i.e., possibly, probably or definitely related to either study intervention and unexpected as per the SPC or the protocol).[2]

2.8.2 Planned "hospitalisations", non-emergency procedures and AE reporting

There were some AEs that met the definition of serious which did not require reporting on an SAE report form. Common ophthalmology and non-ophthalmology related events which resulted in *planned, non-emergency* hospital admissions for the investigation or treatment of those events and which were not possibly, probably or definitely related to the IMPs did not need to be reported on an 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 study visit, to ensure the independent data monitoring committee received accurate reports relating to the occurrence and treatment of adverse events.[2]

2.9 Pregnancy

In the event that a female participant became pregnant, this was reported to KCTU via fax or email (Fax: 020 7848 5229, email: ctu@kcl.ac.uk) using a pregnancy form 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]

2.10 Data management

2.10.1 Confidentiality

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

2.10.2 Data collection tools and source document identification

Written informed consent was obtained prior to screening and other study specific being procedures performed. SAE data were collected on paper SAE report forms and emailed or faxed to the KCTU. Summary details of SAEs were transcribed to the adverse event 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 the patients NHS

medical notes in the recruiting site. During the trial, critical clinical information were written in the medical notes to ensure informed medical decisions could be made in the absence of the study team. Trial related clinical letters were copied to the medical notes during the trial. It was the responsibility of the Principal Investigator and his team to ensure 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 to ensure source data verification could be undertaken throughout the study.[2]

2.10.3 Data handling and analysis

All study data and site files were kept at site in a secure location with restricted access.
The study employed an eCRF created using the InferMed MACRO database system. Data was managed via this system. The eCRF was created in collaboration with the trial statistician and the CI and maintained by the KCTU. It was hosted on a dedicated secure server within KCL. This system is regulatory compliant and has a full audit trail, data discrepancy functionality, database lock functionality, and supports real time data cleaning and reporting. The Trial Manager was responsible for providing usernames and passwords to permitted local study personnel. Only those authorised by the Trial Manager were able to use the system.[2,62]

2.11 Quality assurance

The study 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 was monitored by the Trial Manager. The Trial Manager provided study training, ongoing study 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 within 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]

2.12 Database lock and record keeping

Prior to database lock, the Trial Manager reviewed any outstanding warnings on the eCRF and resolved or close these as appropriate before database lock. Local study personnel resolved any queries that arose. Once all queries were resolved no further changes were made to the database unless specifically requested by the Study Office in response to the statistician's data

checks. The study PI reviewed all the data for each participant and provided e-mail sign-off to verify that all the 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 on 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 study 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 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 study.[2]

2.13 Statistical Considerations

2.13.1 Sample size calculation

Bevacizumab and aflibercept were hypothesised to be substantially inferior to ranibizumab, if in each case, the mean of the primary outcome (change in best corrected ETDRS visual acuity letter score) was worse by a margin of five letters, a previously used non-inferiority margin,[71,72] representing the minimum VA change a patient may distinguish. A similar CRVO population[9] reported a standard deviation of 14.3 in the ranibizumab 0.5mg arm and the 12-month lost to follow-up was 8.4% in the ranibizumab arms. In the absence of 24-month data, we assumed a comparable standard deviation (SD) of 14.3 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 for the difference in treatment means was wholly above the five letter margin in each case. Assuming equal efficacy, there was 80% power to reject each null hypothesis and 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 randomized to the three arms (equal allocation ratio; 153 per arm) for the CRVO patient group. Sample size calculations were performed using nQuery Advisor 4.0 software. The primary method of analysis was a linear mixed effects 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 patients we anticipated could be missing the 100 weeks primary outcome endpoint.[2]

2.13.2 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 and commented on by the DMEC and approved by the 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.

2.13.2.1 Target Population

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

2.13.2.2 Trial Population

The trial population, from which the study sample was drawn, was further defined to be adults aged 18 year or over, of less than 12 months duration who attend the 44 ophthalmology centres in the UK with expertise in retinal disorders and a proven track record in effective research. Only one eye per patient was included in the trial.

2.13.3 Hypotheses

The hypotheses referred to the populations of relevant patients rather than study subjects.
The *Working hypothesis*: The so-called "working hypothesis" was the hypothesis which 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 to 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.

2.13.4 Treatment arms

The trial was randomised with equal allocation of participants in a 1:1:1 ratio to the three arms (see **Randomisation 2.3.2**)

2.13.5 Trial Samples

2.13.5.1 Intention-to-Treat (ITT)

The achieved trial sample comprised those patients who consented to participate and were actually randomised into this trial.[62] These patients were the study subjects. This randomised trial sample was also the trial intention-to-treat (ITT) population. The intention-to-treat principle states that every subject will be analysed according to the treatment group to which they were randomised. In this trial,

subjects' data were analysed according to the *Intention-to-Treat Strategy*, 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 eligibility (inclusion/exclusion) error, post-randomisation withdrawal, and whether the correct study treatments were received, or other interventions received.[62]

2.13.5.2 Per Protocol (PP)

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 4 treatments correctly assessed and received during the first 6 visits up to week 20. For each of the first four visits, a correct treatment was defined as receiving the injection. For the 5th and 6th visits, a correctly assessed and received treatment was defined to be the receipt of an injection where this was indicated to be required by the retreatment criteria or the non-receipt of an injection where this was indicated by the retreatment criteria.

The main reason for having a per protocol set comes from the fact that this is a non-inferiority trial and so the use of the full analysis set is generally not conservative (ICH E9 section 5.2.3[73]). As Lesaffre 2008[74] 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 AD 2003[75] state that "*The perceived conservative nature of the PP 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 to a placebo-controlled trial.[62]

Prominence: Non-inferiority was only declared if both ITT and the PP analyses were supportive of a non-inferiority conclusion. The Committee on Proprietary Medical Products Points-to-Consider and several other papers support this.[62] The requirement to declare noninferiority in both the ITT and the PP analyses promoted the adherence to treatment protocol and the minimisation of exclusions, maintaining power.

2.13.6 Outcomes

2.13.6.1 Primary outcome

The primary outcome was BCVA in the study eye measured in ETDRS letter score at 4 meters 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 more than 3 standard deviations below the mean at that timepoint (including all measurements) and taken within 3 months of occurrence of a vitreous haemorrhage or another cause unrelated to maculopathy secondary to CRVO (such as neovascular glaucoma).

2.13.6.2 Secondary Outcomes

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

i. Continuous outcome variables

i. Visual Acuity and Clinical Outcomes

1. Change from baseline in ETDRS letter score measured at 4 metres at 52 weeks.
2. Change from baseline in mean OCT central subfield thickness (CST) at 52 and 100 weeks.
3. Change from baseline in macular volume at 52 and 100 weeks.
4. Number of injections performed in the study eye at 100 weeks
5. Change in retinal non-perfusion as assessed by mean disc area of non-perfusion at 100 weeks.

ii. Patient reported outcomes

1. National Eye Institute visual function questionnaire (VFQ25) composite score, distance, and near subscales at 52 and 100 weeks.
2. Quality of life (EQ-5D with and without vision bolt-on) at 52 and 100 weeks.

iii. Economic reported outcomes (this is detailed in the health economics analysis plan)

1. Quality of life scales (VFQ25 and EQ5D with and without vision bolt-on) at 0, 12, 24, 52, 76 and 100 weeks.
2. Resource utilization at 0, 12, 24, 52, 76 and 100 weeks.

ii. Categorical outcome variables:

i. Visual Acuity and Clinical Outcomes

1. Participants with ≥15 ETDRS letter improvement (appreciable visual gain), ≥ 10 letter improvement, <15 letter loss and ≥ 30 ETDRS letter loss (severe visual loss) at 52 and 100 weeks.
2. Participants with ≥73 ETDRS letters or better than 6/12 Snellen equivalent (i.e. approximate driving visual acuity), ≤58 ETDRS letter (≤6/24) and ≤19 letters (≤3/60) (CVI partial and severe visual impairment) at 52 and 100 weeks.
3. Participants with OCT CST <320µm (Spectralis or refer to protocol appendix 1) at 52 and 100 weeks (key guide to subsequent NHS clinical practice).
4. Participants with the anatomical OCT features: diffuse intraretinal oedema, intraretinal cystic change, subretinal fluid, vitreomacular interface abnormality (either VMT or ERM) over time and at 100 weeks.
5. Participants with a change in retinal non perfusion at 100 weeks.

ii. Safety and tolerability

Prevalence of local and systemic side effects at 100 weeks.

1. Participants that are persistent non-responders and that develop anterior and posterior segment neovascularisation at 100 weeks.

2.13.8 Subgroup variables

Two subgroup variables were considered: i) baseline visual acuity (low, moderate, high: ≤38 letters, 39-58 letters, 59-78 letters), ii) disease duration (<3 months, ≥3 months) and iii) ischaemic vs non-ischaemic. These were based on the fact that visual gain in the low vision group may be higher than that achieved by the high 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.

2.13.9 Outcomes requiring derivation

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

EQ-5D with and without vision bolt-on: 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 5 dimensions (Mobility, Self-care, Usual activities, Pain/Discomfort, Anxiety/Depression. Each dimension has 5 response categories (EQ-5D-5L) corresponding to e.g. “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 (EQ-VAS), which records the respondent’s self-rated health on a vertical scale where the endpoints are labelled ‘Best imaginable health state’ (marked as 100) and ‘Worst imaginable health state’ (marked as 0). The EQ-5D with bolt-on was similar to the EQ-5D-5L but another dimension was added (vision) in order to overcome perceived inadequacies in a particular population.

More information is given in Section 4.4.3.1

2.13.10 Defining Outliers

Outliers are observations that have extreme values relative to other observations observed under the same conditions. An outlier was defined here as a data-point being at least four standard deviations from the mean of its distribution of values observed across other patients. A “bivariate outlier" for checking was defined as a pair of successive serial data-points of the same measure for a patient whose difference was at least four standard deviations from the mean of all patients’ such differences. Simple plots of successive pairs of serial measures were used through the 24-month period to assist in identifying outliers for data checking.[62]

2.13.11 Handling outliers

Outliers were identified for further investigation by looking at the distributions of the data through histograms, scatter plots or box-plots. Univariate tests for the compatibility of the distribution with a normal distribution were not undertaken since they can be too sensitive to departures that are often not relevant for the comparison of means (Central Limit Theorem).
Once an outlier was found, a blinded member of the team with sufficient clinical experience was involved in the decisions as to whether a data value was impossible versus implausible versus plausible. If the outlier was impossible, then it was set to missing. If an outlier was clinically plausible, the outlier remained. If an outlier was clinically implausible (but possible), it was not ignored or deleted but was retained for ITT analysis. If outliers remained in the distribution of a variable, then data transformations or nonparametric methods of analysis were considered. Sensitivity analysis was undertaken to check whether the outlier was influential by obtaining results with and then without inclusion of the outlier. If the conclusions were changed, then this was noted.[62]

2.13.12 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 may be chance-generated and not for hypothesised reasons. Continuous variables such as OCT central subfield thickness and VFQ-25 were summarised using means and standard deviations (SD) and/or medians and interquartile range (IQR) for variables presenting a skewed distribution. Categorical variables such as proportion of patients gaining ≥15 BCVA or participants with OCT CST < 320μm were described using numbers and percentages.

2.13.13 Comparison of rates of adherence and follow-up

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

2.13.14 Analysis covariates

The ICH E9 guideline recommends that consideration is 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 (3 levels) and disease duration (2 levels). This excluded the third stratifier of Previous Treatment (Eye treatment naïve versus has

received previous treatment) due to very low numbers with previous treatment, and this was approved in the statistical analysis plan[125] by the Trial Steering Committee..

Baseline

The corresponding baseline measure for a continuous outcome is also often predictive of the outcome at follow-up. Therefore "baseline", if collected, was included as an additional covariate when modelling continuous outcomes.[62] This was the case for visual acuity and CST.

2.13.15 Statistical Model

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

2.13.16 Primary outcome analysis

The primary efficacy measure was the change from baseline in refracted best corrected visual acuity (BCVA) in the study eye, using the ETDRS letter score at 100 weeks. As the analysis approach for continuous outcomes below makes advantage of covariate-adjustment for the baseline of the outcome, the primary endpoint could equivalently be regarded to be each participant's 100-week measurement. This is convenient because then those with a 100-week outcome, but whose baseline measurement is missing, are not regarded to be missing the endpoint. The primary outcome may therefore be referred to below as the 100-week visual acuity, rather than the change in this from baseline to 100 weeks.

The primary outcome was analysed using a linear mixed effects (LME) model incorporating the 5 post-baseline measurements of the refracted BCVA outcome (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 timepoint, 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", the baseline of the outcome and its missing indicator required for the missing indicator method. The other fixed effects included 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, at the primary timepoint of 100 weeks, and estimated at 24 and 76 weeks.[62]

2.13.16.1 Intention to treat strategy

Outcome data was valid and included if the BCVA measure was refracted. All randomised subjects who provided at least one post-baseline valid measurement were included.[62]

2.13.16.2 Per protocol analysis

For the analysis of the primary outcome, the mixed effects model was re-fitted in a reduced per protocol population already described above.[62] 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.

2.13.16.3 Concluding non-inferiority

Non-inferiority was only concluded if this was declared by both the ITT analysis and the PP analysis at 100 weeks. Non-inferiority was also assessed secondarily in ITT and PP populations at 52 weeks from the same models. Non-inferiority was declared if the estimated 95% confidence interval for the difference in means lies wholly above the margin of -5 letters in both ITT and PP analysis models primarily at 100 weeks and secondarily at 52 weeks.

2.13.16.4 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 need for correction for multiple testing.[62] In addition, it was planned that if both investigative treatments were considered non-inferior to the standard treatment at 100 weeks then superiority of the investigative treatments was assessed to each other.

2.13.16.5 Subgroup analysis

The two subgroup variables were assessed by extending the primary outcome model to have an interaction between arm and each categorical subgroup variable.[62] Subgroup variables with more than two categories that are ordinal were entered as linear in the interaction. The treatment effects were presented within each subgroup category with a 95% confidence interval.

2.13.16.6 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 should 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 PP population and a less compliant ITT population, the focus was on handling of missing data.[62]

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 Intention to Treat Strategy in which a second analysis examined the sensitivity of the results to missing data in the full randomised, Intention to Treat, population. This met the ideal of ITT. The approach to missing data taken for the trial followed the published implementation paper of

the ITT strategy. This was then also applied again to the PP population so that the non-inferiority conclusion could be re-assessed under the sensitivity analysis.[62]

For the sensitivity analysis, we pre-specified 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".[76] In other words, this range could be thought of as how much a typical subject with missing data may on average have had a different estimated treatment effect compared to the corresponding subject with the outcome data observed (given the same baseline covariates and follow-up data in the LME model). The range (-20 to +20) was chosen to represent both negative and positive departures that could potentially arise as the "net effect" of alternative reasons which may be unknown; such as dropout due to no anticipated further improvement, or dropout due to no improvement so far together with no anticipated achievable improvement.[62]

This range of 40 letters (from -20 to +20) was generously wide for exploring sensitivity of the main results to departures from the MAR 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 to completers.

At the end of the trial, the fractions of individuals with missing data 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 to those observed, δ, will take values by passing across the range -20 to +20. Three scenarios were undertaken within the sensitivity analysis.[76–78] These reflected whether departures from the MAR assumption applied within the intervention arms only (aflibercept and bevacizumab), within the control arm only (ranibizumab), or within 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).[62]

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 $(f_i-f_c)\delta$

2.13.16.7 Sensitivity analysis to use of concomitant treatments

The use of concomitant treatments was monitored by the DMEC.[62] If necessary, a sensitivity analysis was also planned to be undertaken to examine the robustness of the 100-week per protocol analysis to the use of concomitant treatments.

2.13.17 Secondary outcome analysis

Secondary outcome analyses, **Table 1,** were on an ITT basis only. All tests were two-sided at the 5% significance level and interpreted cautiously with a focus on interpreting effect sizes with 95% confidence intervals. Safety outcomes were reported as unadjusted patient proportions and rates within and between arms with 95% confidence intervals using exact methods where appropriate. Significance tests were used sparingly and restricted where possible to addressing stated hypotheses.

2.13.17.1 Analysis of continuous outcomes

As for the primary outcome, the analysis of continuous secondary outcomes were compared between arms at 100-weeks using the linear mixed effect model adjusting for all randomisation stratifiers, except with baseline BCVA represented by its minimization categories, and where collected, the baseline of the outcome with the associated missing indicator. Time was represented as categorical contrasts in main effect form and in interaction with all other fixed effects. For skewed outcomes, 95% confidence intervals were obtained using the nonparametric bootstrap percentile method.[62]

2.13.17.2 Analysis of binary outcomes

For the binary outcomes, such as the proportion of participants with ≥15 ETDRS letter improvement, differences between two proportions with 95% confidence intervals have been used. Safety outcomes have been reported as unadjusted patient proportions and rates within and between arms with 95% confidence intervals using exact methods where appropriate.[62]

Table 1: Analyses used for Secondary Outcomes

Types of variables	Outcomes	Methods
Continuous	Best Corrected Visual Acuity at 52 weeks	Linear mixed effects model
	Mean OCT central subfield thickness (CST) at 52 and 100 weeks	Linear mixed effects model
	Macular volume at 52 and 100 weeks	Linear mixed effects model
	VFQ25 composite score, distance and near subscales at 52 and 100 weeks	Linear mixed effects model
	Number of injections by 100 weeks	Difference in means with 95% CI
	Change in retinal non-perfusion at week 100 as	Difference in medians

	assessed by disc areas of non-perfusion (in approx. 27 sites)	with 95% CI
Categorical	Participants with ≥15 and ≥ 10 ETDRS letter improvement, <15 letter loss and ≥ 30 ETDRS letter loss (severe visual loss) at 52 and 100 weeks	Differences in proportions with 95% CI
	Participants with ≥73 ETDRS letters or better, ≤ 58 ETDRS letter and ≤19 letters at 52 and 100 weeks	Differences in proportions with 95% CI consistent with a chi-squared test
	Participants with OCT CST <320µm at 52 and 100 weeks	Differences in proportions with 95% CI consistent with a chi-squared test
	Persistent non-responders participants at 52 and 100 weeks	Differences in proportions with 95% CI
	Participants that develop ocular neovascularisation at 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, ellipsoid zone disruption, disorganization of inner retinal layers 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

2.14 Safety meta-analysis

It was not possible to perform a safety meta-analysis due to the lack of comparative outcome data for anti-VEGF therapy in CRVO. Two other comparative studies were completed during the LEAVO study, the multicentre SCORE2 clinical trial that compared aflibercept and bevacizumab given by mandated monthly injection over 6 months and a small comparative study of aflibercept vs bevacizumab in 50 patients with MO due to CRVO followed for 12 months. This latter trial did not publish any tabulated adverse event data and was discounted. A direct comparison was made with the SCORE2 safety

data by comparing it with the first six months of LEAVO study safety data and this is presented in the results (Section 3.6)

2.15 Public Patient Involvement

As a result of consulting the User Involvement Officer, Research Design Service London, prior to study start up we i. consulted the Diabetes Research Network online Lay Member Panel, ii. met with the CEL LCRN Lay Member Group, iii. formed a Service User Advisory Group of Retinal Vein Occlusion patients. They were asked to comment on the non-expert summary, a brief Powerpoint overview of the project, asked specific questions and to give comments. Overall they were very supportive, felt the study was of benefit to patients, would definitely participate although they felt the dexamethasone intravitreal implant (Ozurdex) , originally intended to be a study arm, should be excluded due to limited efficacy and side effect profile. In addition they thought aflibercept should be included as this may reduce frequency of visits, invasive procedures e.g. dilating and checking the non study eye at each visit should be avoided where possible, and that they would wish to help in the development of the Patient Information Sheet . This feedback led to us remove Ozurdex from the project, include aflibercept as a third trial arm, minimise study research visits to 6 in two years, not dilate the non study eye at each visit to help the patients work and commute after their study visit and 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, attended every meeting and actively contributed to each. Once the LEAVO study clinical and health economic outcomes were available, the members of the CRVO service users group at Moorfields, additional retinal vein occlusion patients, members of the renamed Barts Health / QMUL lay panel and patients with a history of eye disease from their extended users group were sent a cover letter and Questionnaire regarding the study that had been reviewed and agreed with the Barts Health / QMUL lay panel chairperson and MEH BRC PPI lead. The results are presented in Chapter 3.7. A member of the Royal National Institute for the Blind served as a member of the Trial Steering Committee.

2.16 Trial Committees

2.16.1 Trial Steering Committee (TSC)

The TSC was the Committee, responsible for monitoring the overall integrity, conduct and safety of the trial. It monitored its progress; investigated any serious adverse events; and took account of regular reports from the DMEC and communication from the TMG. Ultimate responsibility for any decision required on the trial's continuation lay with the TSC. The Committee included an Independent Chair, a Professor of Statistics, an Independent Ophthalmologist and General Physician, Consultant in Public Health, Senior Department of Health 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 Chair. For Committee Members see **appendix 2**. A Moorfields Eye Hospital (Sponsor) representative was invited to each meeting [2]

2.16.2 Data Monitoring and Ethics Committee (DMEC

An independent DMEC of three persons, 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 provide advice and recommendations on trial conduct to the Trial Steering Committee. The study 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]

2.16.3 Trial Management Group (TMG) 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: Chief Investigator, Co-Lead, Trial Manager, Data Manager, the Lead and Trial Statisticians and Senior Members of KCTU. Other members of the wider research team were also invited on a meeting by meeting basis depending on the scope covered. Monitoring of study conduct and data collected was performed by a combination of central review and site monitoring visits to ensure the study was conducted in accordance with GCP. Study site monitoring was undertaken by the Trial Manager, Assistant Trial manager and an experienced Kings CTU Trial Monitor. The main areas of focus were consent, serious adverse events, and essential documents in study site files.

Site monitoring included:

- Reviewing all consent forms within the site file and medical notes.
- Source data verifying serious adverse events against medical records and a proportion of the primary outcome measure.
- Checking essential documents in the investigator site file and study files.

Central reviews included:

- Ensuring accuracy and completeness of all applications for study authorisations and submissions of progress/safety reports, prior to submission
- Ensuring all documentation essential for study initiation is 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, REC 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.

2.17 Approvals, Reporting and Compliance

The study was approved by the National Research Ethics Committee Service London South East (14/LO/1043), Clinical Trials Authorisation was given by the Medicines and Healthcare Products Regulatory Agency (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 study and KCTU collaborated with the sponsor to ensure efficient delivery of the study. The trial was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement.

2.18 Summary of changes made to Protocol

After initial substantial amendments (SA1 to SA3) at commencement of the study clarified handling of several key issues e.g. pregnancy and contraception and nurse injectors, subsequent substantial amendments mainly dealt with addition of sites or change in principal investigators (**table 28**). Substantial amendment 6, approved by the REC on 11/2/2016 included changes to the Protocol, in particular the eligibility criteria to increase recruitment to the study. The key change requested by the Trial Team was to increase the upper limit of permissible visual acuity at screening from 73 (6/12) to 78 (6/9) letters. This was to increase recruitment across all study sites since as the protocol stood, patients in clinical practice with a visual acuity of 6/9 may have been excluded from the trial as visual acuity was too good and go onto receive treatment in the NHS and be lost to the study. This change would potentially allow patients with VA = 6/9 to enrol in the study. The DMEC and TSC statisticians were however concerned this may introduce a ceiling effect if an abnormally high 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 they stated they could not agree to such a change without additional data from other studies being obtained by the CI to determine whether a significant ceiling effect would likely occur. After consultation with the relevant study Sponsors and /or CIs, the Chief Investigator and co lead were able to provide the DMC and TSC unpublished results from recent clinical trials, (CRYSTAL study of retinal vein occlusion and US DRCR.net Protocol T Study of diabetic macular oedema) 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 to proceed. Additional changes to the eligibility criteria were approved including an increase in the number of anti-VEGF injections a participant could have received prior to randomisation from three to six. The rescreening interval was reduced from 4 to 2 weeks as a number of participants who failed initial screening sought treatment elsewhere before rescreening was possible.

Chapter 3: Clinical Results

3.1 Participant flow

The original contract commenced 1st May 2014 with recruitment due to start on 1st November 2014. An early contract variation was requested by the LEAVO study team and approved by the NIHR for the contract to commence on 1st June 2014 and recruitment to start from 1st December 2014. Recruitment was predicted to take 18 months (see Figure 3) and therefore to finish on 31st May 2016 with last patient last visit to take place by the 31st May 2018 and the study to close on 31st October 2018. The first patient was duly randomised on 12th December 2014 but the last was only randomised on 16th December 2016 i.e. almost exactly 24 months later. As a result, a contract variation was sought to extend the study by six months so the last patient last visit would occur by 30th November 2018 and the study to close on 30th April 2019. The last patient last visit was actually on 21st November 2018.

Therefore between December 2014, and December 2016, 586 patients were assessed across 44 UK NHS Hospitals for eligibility. 123 patients were excluded as 117 were ineligible, 1 withdrew consent and 5 did not proceed for other reasons. Thus 463 were 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, hospital sites and within baseline visual acuity strata. The PP population consisted of 145 patients in the ranibizumab, 146 in the aflibercept and 152 in the bevacizumab arm. For the ITT population, the 100 week visit was completed by 135 patients in the ranibizumab, 133 in the aflibercept and 139 in the bevacizumab arms respectively and for the PP population the same visit was completed by 133 ranibizumab, 128 aflibercept and 139 bevacizumab arm patients respectively (**figure 2**).

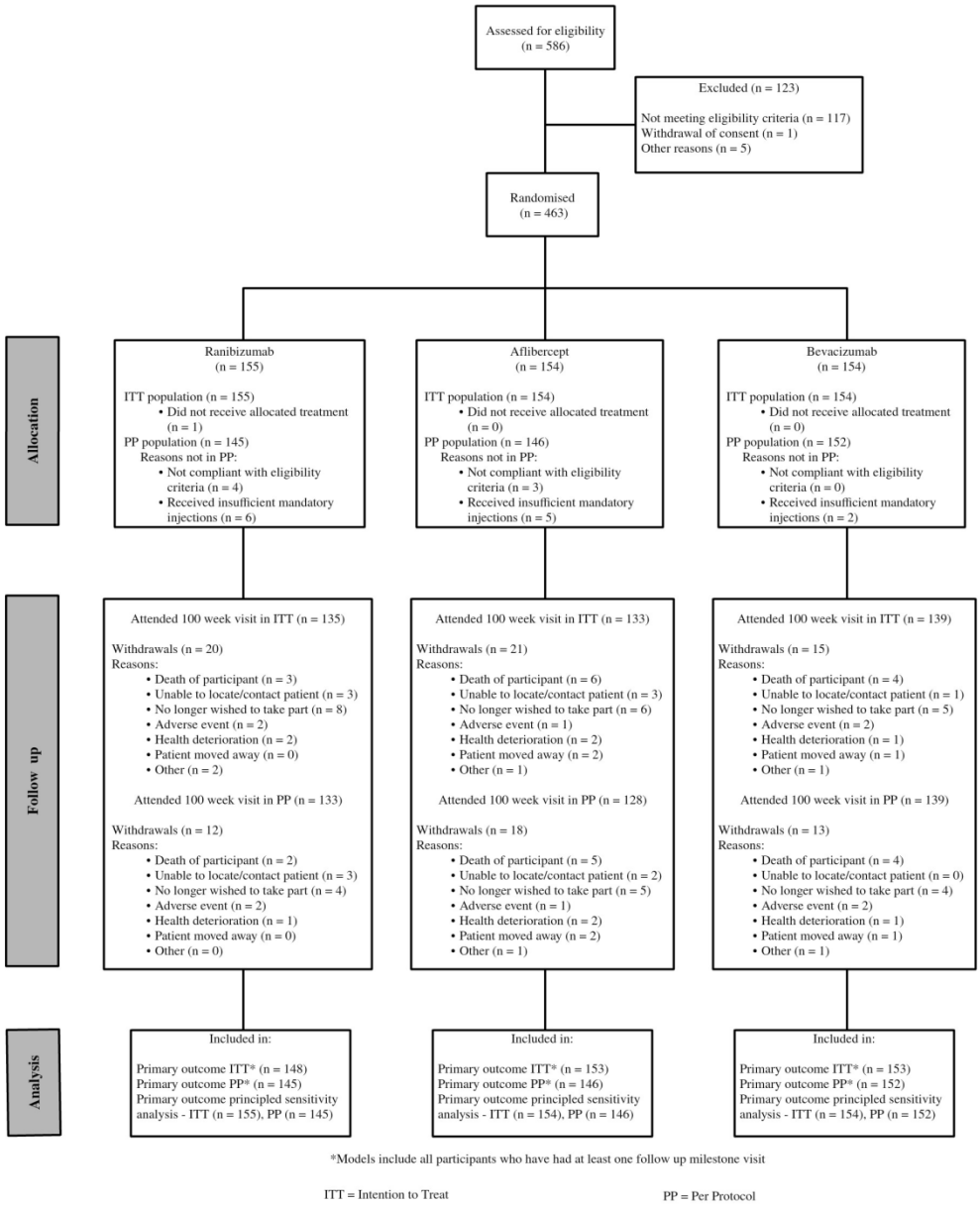
3.2 Recruitment

3.2.1 Overview

The National Institute of Health Research (NIHR) acknowledges the need for experienced trial management and recommends the involvement of a specialised clinical trials unit to conduct the study. We were fortunate to have the multidisciplinary team from KCTU participate in the study. As a LEAVO study collaborator they provided a trial manager, deputy trial manager and experienced monitors in addition to a senior and junior statistician and the expertise of their core team including the CTU Operations Manager, Senior Data Manager and Trial Methodologist. All these members attended the Trial Management Meetings, Trial Steering Committee and Data Management Meetings where appropriate. In addition they were all available for advice and guidance on a daily basis and working

in conjunction with the Trial Manager were ultimately the cornerstone of the study. [62] They recognised the need to open as many sites as quickly as possible and their Senior Team spent many hours with

Figure 2: The LEAVO Consort Diagram



the Trial Manager ensuring she was fully familiar with the study and able to begin site initiations prior to the commencement of recruitment on 1st December 2014. The largest and most experienced sites e.g. Moorfields and Leeds were initiated first. Unfortunately a few weeks before initiation of the first site the original Trial Manager was absent on sick leave and 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 study delays. Fortunately, an experienced Asst. 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 study protocol and procedures and we fell significantly behind with site initiations and recruitment. The low point was 39 patients 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 of 2015 and the number of site initiations increased, such that we initiated only 8 sites in the first 4 months of recruitment compared to 13 in the succeeding 2 months. As a result actual recruitment kept pace with predicted recruitment in October, November and December 2015. By November 2015 i.e. after twelve months of recruitment we had 38 sites open against a target of 40 and 176 patients recruited against a target of 268 (66%). An additional 8 extra sites were subsequently initiated to give 46 greenlighted sites open in the first quarter of 2016. By May 31st 2016, when recruitment should have completed we had 320 patients recruited against a target of 459 (70%) and by December 2018 we had completed recruitment almost exactly six months behind schedule (**figure 3**). The number of patients recruited each month by site is given in **table 4** and the number of patients every site recruited per trial am is presented in **table 5**.

3.2.2 Barriers to recruitment and corrective strategies

A number of barriers to recruitment were identified:

i. Availability of trial staff e.g. masked injectors and trial co-ordinators. Despite fulfilling our initial study site requirements, several sites were unable to provide sufficient clinician unmasked injector cover e.g. Rugby, due to limited staff availability, and sufficient research co-ordinator time for the study e.g. Addenbrookes and Hillingdon, the latter in some cases as NHS support costs attributable to the LEAVO study were not available to the local study 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 the LEAVO study. We also approached a number of local Ophthalmology CLRNs to provide additional co-ordinator time for the study based on CLRN support costs and received very helpful support from Rupert Bourne, CLRN National Lead for Ophthalmology in this regard.

ii. Difficulties with the Protocol. The following changes were made to the Protocol, (see **table 28**)

a. increasing the upper limit of VA eligibility at baseline from 73 (~6/12) to 78 letters (~6/9) (see Section 2.16 for detail). Patients in clinical practice with a visual acuity of 6/9 were being excluded from the trial as visual acuity was too good and they were receiving NHS treatment instead. The change allowed patients with VA = 6/9 to enrol in the study.

b. the inclusion criteria for diabetic retinopathy in the study 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’. This was changed to prevent patients being excluded from the study who presented with a documented history of diabetic retinopathy, which may not have been reliable, rather than clinical evidence based on the study screening examination.

c. The number of prior allowable anti-VEGF injections was increased from three to six to allow patients who had had longer term treatment for MO due to CRVO i.e. six injections to be considered for the study.

d. Patients who had had recent pan-retinal photocoagulation for NVE, NVD or NVI were considered eligible for the study within one month of treatment rather than three, as treatment within one month would not have had an adverse outcome on anti-VEGF therapy a month later.

e. 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 e.g. 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 re-screening as the protocol originally stated they typically opted for NHS treatment in the interim and so being able to re-screen after 2 weeks prevented them being lost to NHS care.

iii. 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 twelve, 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 patients. Nevertheless these additional sites made a very significant contribution to the last six months of recruitment.

iv. Site equipment: several sites had issues with equipment, in particular wide angled FA imaging and IT support that allowed communication with the Kings CTU randomisation software and MACRO study 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.

v. Although we had held an investigator meeting prior to study 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 Study Optometrist to any site to undertake optometry certification.

vi. Other measures we used to try to maximise recruitment included: a) a monthly newsletter to every site detailing progress[62] and acknowledging each site that had recruited one or more patients in the previous month b). an e-mail from the CI to each site team every two months encouraging further recruitment c). a thank you e-mail to each site from the CI after each patient was recruited d). reward vouchers each month to the site recruiting the most patients and ‘best site of the month’ e.) very prompt replies to any site with queries on any aspect of the study. We think this latter 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.

Table 2: The number of participants recruited by each site by calendar month

Year	2015																									
Month	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	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
Kings College Hospital									1						1		2				1				1	6
Wolverhampton Eye Infirmary															4	2	2		4	3	2	2	1	1		21
St. Pauls Eye Unit, Liverpool												2	2				2	1	2				2	2		13
Southampton University Hospital					2		4					3				2		1	1					1		14
Royal Victoria Infirmary, 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							2	1	4	3	1	1	4													16
Kent and Canterbury Hospital								1										1	1					1		4
Frimley Park Hospital					2			1	1		1	1	2	3	1		1		1	1						15
Whipps Cross Hospital														1												1
James Paget Hosp., Gt Yarmouth									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 Hospital. Leeds		1	2	1			2	1			1	1	1	1		1				1				1		14
Hillingdon Hospital							1				1						2		2						1	7
Maidstone Eye, Ear & Mouth Unit											2		1	2	1		1		2	2	1	1	1			14
Central Manchester Hospital								1	1					1		1	2				2	1				9
RVI, Newcastle									2	2		3	1			2	1	1								12
Luton & Dunstable Hospital												1	1	1						1	1					5
UHW, Cardiff Eye Unit													1	1		1							2			5
Sunderland Eye Infirmary						1		1	2	1	3		3		1			3				2	2	2		21

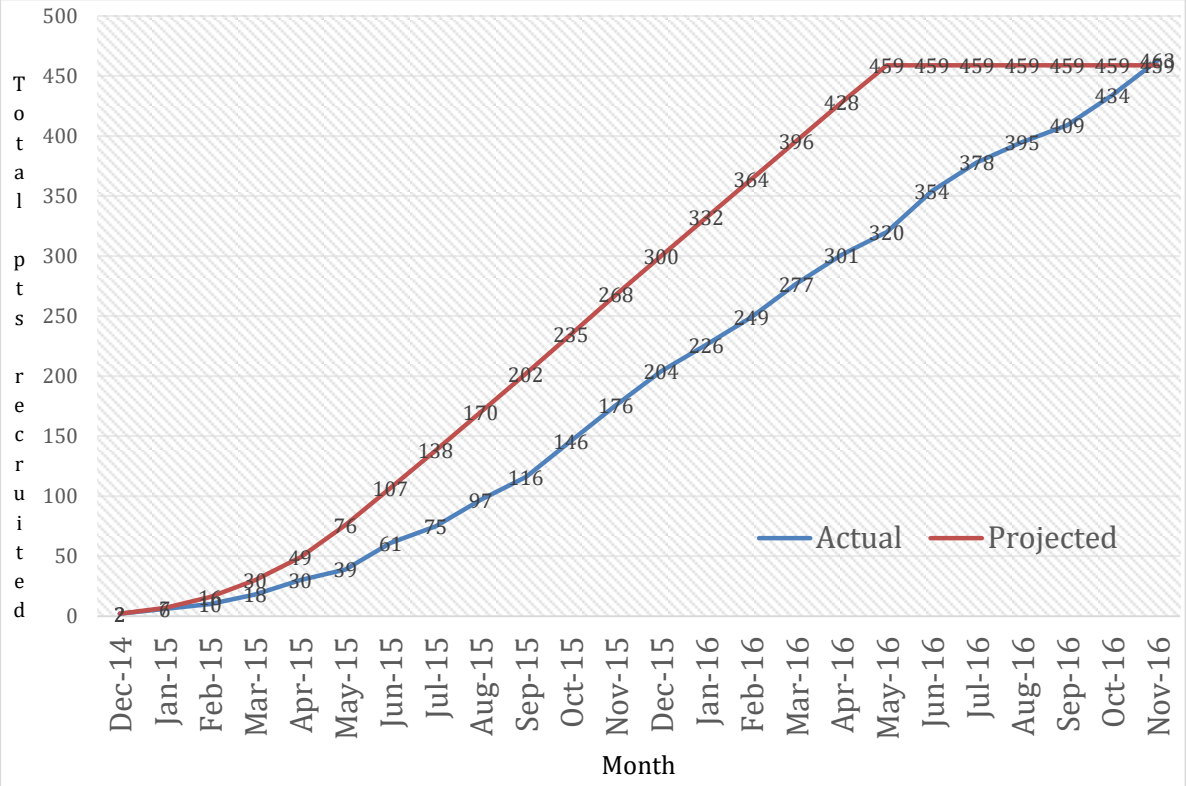
Royal Glamorgan Hospital											1	2	1	1	1	1		2	3				1	1		14
Sheffield Teaching Hospital									1		2		1	1	3	1		2		1			1			13
Addenbrooke's Hospital											1		1						2	2		1	1	3		11
Gartnavel Hospital, Glasgow																	1		1		1	1			1	5
Bolton Hospital														1	1	1			2				1			6
Calderdale 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 Hosp., South Tees																			1					2		3
Princes Alex. 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:	Ranibizumab	Aflibercept	Bevacizumab	Total
Moorfields Eye Hospital	25	24	28	77
Kings College Hospital	3	2	1	6
Wolverhampton Eye Infirmary	8	6	7	21
St Pauls Eye Unit	5	6	2	13
Southampton University Hospital	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, Eye Clinic	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 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 Hospital, Leeds	6	4	4	14
Hillingdon Hospital	2	2	3	7
Maidstone, Eye, Ear and Mouth Unit	5	5	4	14
Central Manchester Hospital	2	4	3	9
Royal Victoria Infirmary, Newcastle	5	3	4	12
Luton and Dunstable Hospital	1	2	2	5
UHW, Cardiff Eye Unit	3	1	1	5
Sunderland Eye Infirmary	8	7	6	21
Royal Glamorgan Hospital	5	6	3	14
Sheffield Teaching Hospitals	3	4	6	13
Addenbrooke's Hospital	2	5	4	11
Gartnavel Hospital, Glasgow	0	3	2	5
Bolton Hospital	3	2	1	6
Calderdale Royal Hospital	2	3	1	6
Leicester Royal Infirmary	2	1	2	5
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, London	1	4	5	10
James Cook Hospital, South Tees	2	1	0	3
Princess Alexandra Hospital	1	1	2	4
Total	155	154	154	463

Figure 3: Actual vs. predicted recruitment per month[62]



3.2.3 Withdrawals

Table 29 shows the numbers of participants who did not complete week 100 visit in the three arms and the week of their last visit. **Table 30** details the number of weeks all withdrawal patients participated in the study and the reason for withdrawal. Withdrawals were balanced across treatment arms and overall more patients completed their week 100 visit, 87.9% (407/463) than predicted for the sample size calculation, 85%.

3.3 Baseline data

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

Table 3: Baseline ocular and systemic characteristics in each group

	Total N=463	Ranibizumab N=155	Aflibercept N=154	Bevacizumab N=154
Age, 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, n (%)	226 (48.8)	81 (52.3)	67 (43.5)	78 (50.6)
Mean (SD) BCVA letter score in the study eye*†				
	54.1(14.8)	53.6(15.1)	54.1(15.3)	54.4 (14.2)
BCVA letter score in the study 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)*				
	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 study 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 study eye, n (%)*				
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, (study eye) n (%)*				
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)
OCT (study eye)* ‡				
Central subfield thickness (µm), mean (SD)	693.6 (209.8)	731.3 (227.6)	673.2 (189.4)	676.1 (207.0)
Total volume (mm^3), mean (SD)	12.7 (2.8)	13 (2.9)	12.3 (2.6)	12.8 (2.9)
Lens Status, (study 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*				
Systolic (mmHg) mean (SD)	143.0 (16.8)	143.1 (17.6)	142.6 (17.0)	143.1 (15.7)
Diastolic (mmHg) mean (SD)	79.7 (10.4)	80.1 (10.2)	79.1 (10.6)	79.9 (10.6)

* Not recorded for one ranibizumab patient randomized in error.

†For one participant in each arm the baseline best refracted visual acuity test was incomplete /test was not performed.

‡For Total Volume, data was further missing for two ranibizumab patients and one bevacizumab patient.

3.4 Derivation of the Intention-to-treat model and Per-protocol populations

Patients included in the pre-specified intention-to-treat linear mixed effect model were derived as follows: (1) The BCVA data were available for 407 of 463 randomly assigned patients (ranibizumab arm = 135, aflibercept = 133, bevacizumab = 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 have 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 patient was excluded due to presence of retinal detachment within 3 months of BCVA recordings and BCVA was more than 3SD below the mean at that time point (including all measurements). (3) Therefore, no patients were removed on this basis from the linear mixed effect model analysis and the ITT and PP populations were not modified by this (4) A total of 20 patients did not meet the PP definition, so 443 patients constituted the PP population (**Figure 3,** Consort Diagram). [62]

Table 4: Unadjusted refracted BCVA available at each milestone visit

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

1. Data are unadjusted Means (SD), N

3.5 Outcomes and Estimations

3.5.1 Primary outcome

The mean gain in BCVA letter score was ranibizumab +12.5 (SD 21.1), aflibercept +15.1 (18.7), and bevacizumab +9.8 (21.4) at 100 weeks (**figure 4**). Firstly, the primary outcome at 100 weeks was unable to show that bevacizumab was non inferior in terms of BCVA in both intention-to-treat and per-protocol populations, **table 9**. The 95% CI for the adjusted difference between arms at 100 weeks lay below the pre-specified acceptable margin of -5 letters **(figure 5).** Secondly, aflibercept was non-inferior to ranibizumab in terms of BCVA in both the intention-to-treat and per-protocol populations but not superior (**table 9, figure 5**). The 95% CI for the adjusted difference between arms at 100 weeks lay above the pre-specified acceptable margin of -5 letters **(figure 5).** The mean BCVA letter score at 24 weeks had decreased by approximately three letters across groups following pro re nata (PRN) injections at weeks 16 and 20 where fewer injections were given (ranibizumab injections: 123, aflibercept: 76, bevacizumab: 121), but increased gradually thereafter across groups to week 100, during which period patients were seen at least 8 weekly and injected promptly if retreatment criteria were met (**figure 4**). Such peak and trough changes in visual acuity were closely by mirrored by OCT trough and peak central subfield thickness results over the two year period (**figure 12**).

Figure 4: Adjusted mean best corrected visual acuity letter score across groups to 100 weeks

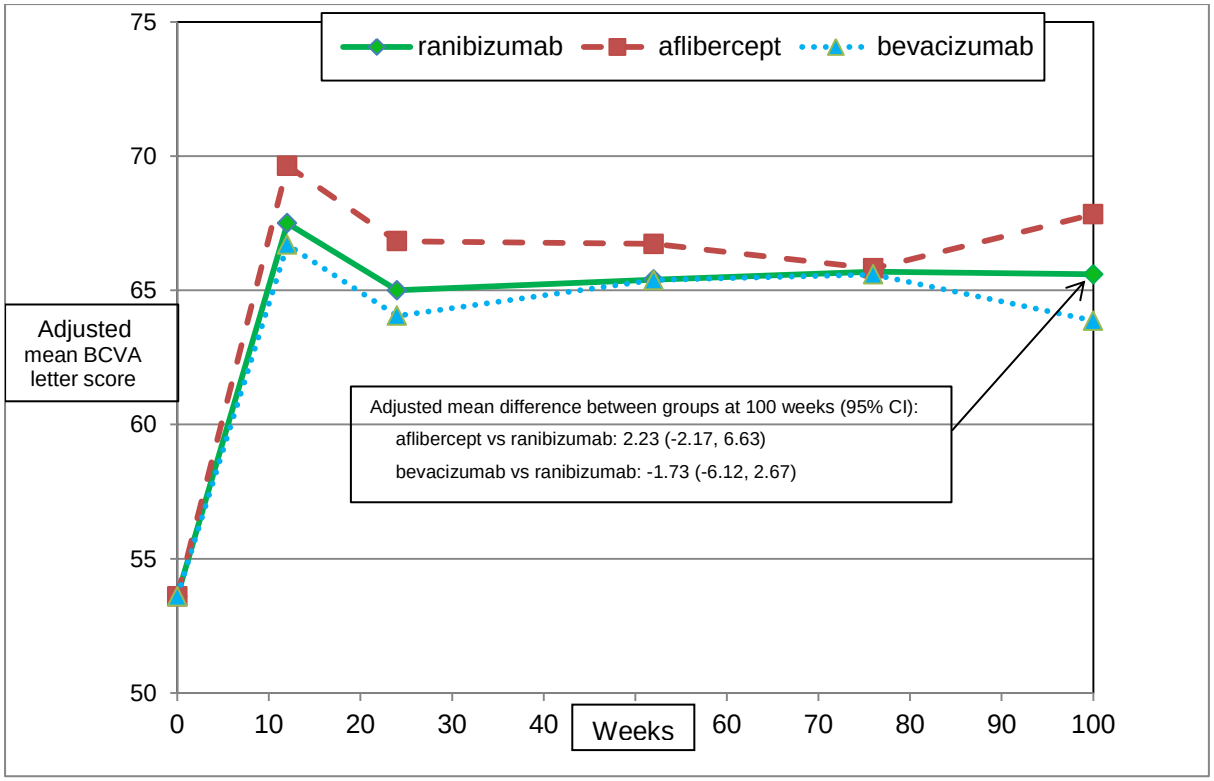


Table 5: Primary Outcome at 100 weeks

Mean (SE[§]) BCVA at screening		Mean (SE) (N) BCVA at 100 weeks		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 versus Ranibizumab ITT						
Aflibercept	Ranibizumab	Aflibercept	Ranibizumab			
54.1 (1.2)	53.6 (1.2)	68.4 (1.6) (133)	65.6 (1.7) (135)	2.23 (-2.17, 6.63)* ‡	0.0006	0.32
Aflibercept versus Ranibizumab PP						
Aflibercept	Ranibizumab	Aflibercept	Ranibizumab			
55.0 (1.2)	53.6 (1.3)	69.5 (1.5) (128)	65.7 (1.7) (133)	3.49 (-0.91, 7.88)*†	<0.0001	0.12
Bevacizumab versus Ranibizumab ITT						
Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab			
54.4 (1.1)	53.6 (1.2)	64.6 (1.8) (139)	65.6 (1.7) (135)	-1.73 (-6.12, 2.67) ‡	0.071	0.44
Bevacizumab versus Ranibizumab PP						
Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab			
54.4 (1.2)	53.6 (1.3)	64.6 (1.8) (139)	65.7 (1.7) (133)	-1.67 (-6.02, 2.68)†	0.066	0.45

* Non-inferior relative to Ranibizumab.

‡ The linear mixed-effects model incorporates 454 participants (n=148 ranibizumab, n=153 aflibercept and n=153 bevacizumab) with best corrected visual acuity at 100 weeks.

†The linear mixed-effects model incorporates 443 participants (n=145 ranibizumab, n=146 aflibercept and n=152 bevacizumab) with best corrected visual acuity at 100 weeks.

The 95% CI for the adjusted difference between arms at 100 weeks lay above the pre-specified acceptable margin of -5 letters

The principled sensitivity analysis for missing data supported the primary outcome results **(Figures 6 and 7)**. The sensitivity analysis for outliers was not done as there were no outliers in the ITT and PP populations (see SAP, Stand Alone Documents). The sensitivity analysis for concomitant treatments taken by one patient within the trial supported the primary outcome results.

Figure 5: Forest Plot of the Primary Outcome at 100 weeks

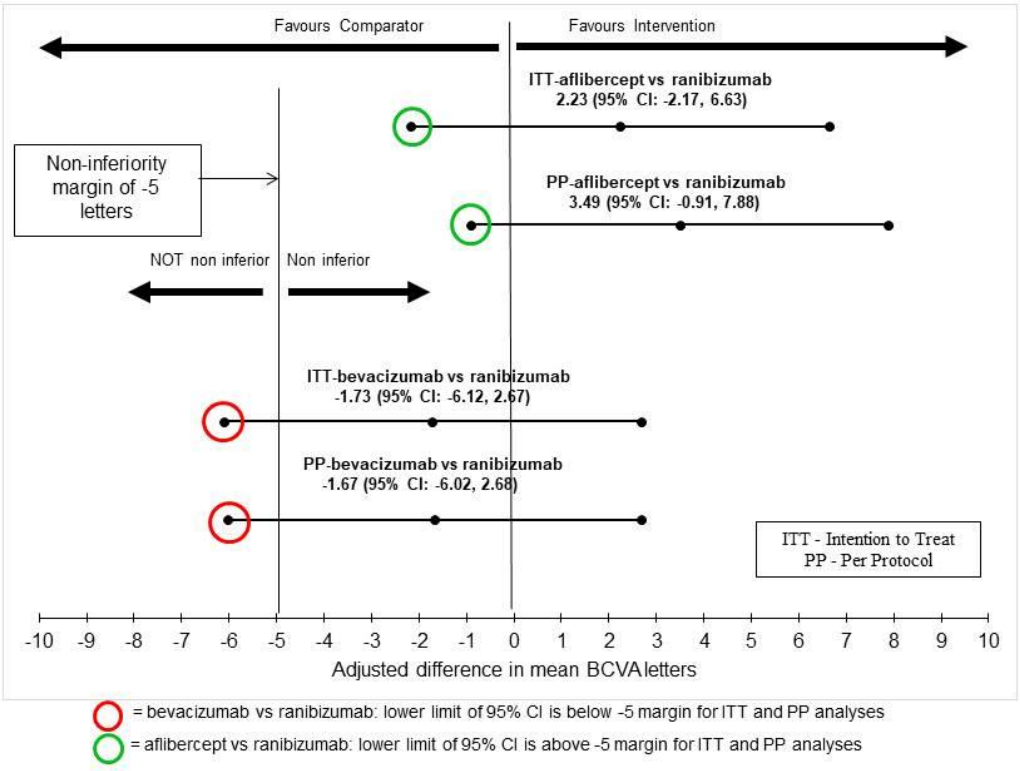
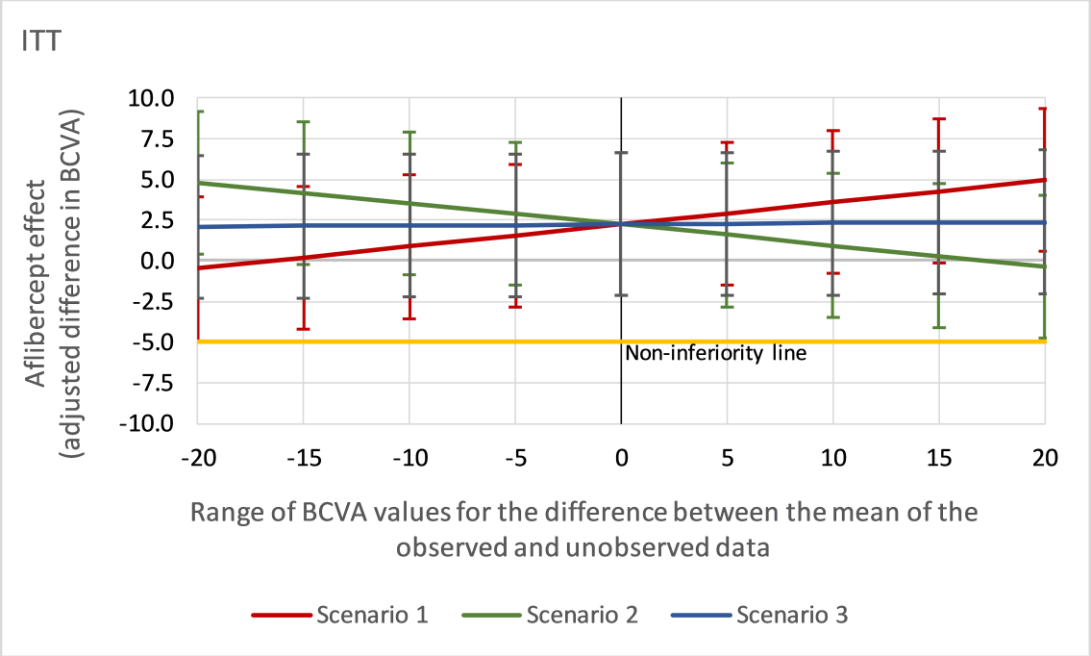


Figure 6: Sensitivity analysis for the missing at random assumption in the primary outcome analysis assessing non-inferiority of aflibercept

The sensitivity analysis assessed the impact on the treatment effect considering the mean outcome in those with unobserved data could range from minus 20 to plus 20 best corrected visual acuity (BCVA) letter score from patients with observed data (horizontal axis), in aflibercept patients only (Scenario 1), or in ranibizumab only (Scenario 2), or in both patient groups equally (Scenario 3). 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 lay above the non-inferiority margin of -5 supporting the non-inferiority of aflibercept in both intention-to -treat (ITT) and per protocol (PP) populations.



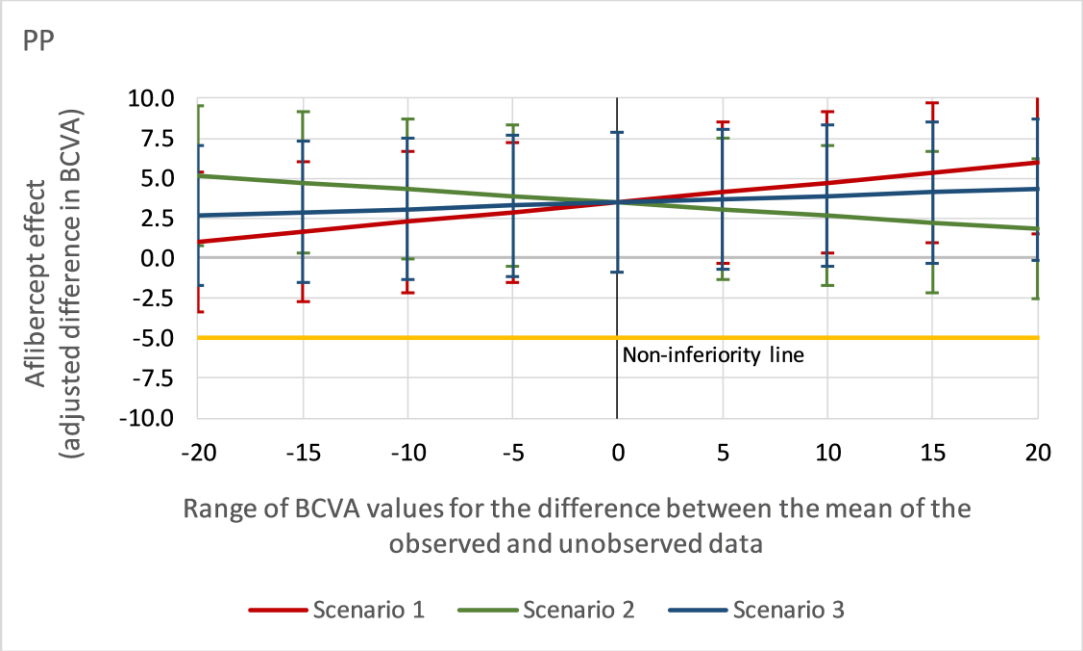
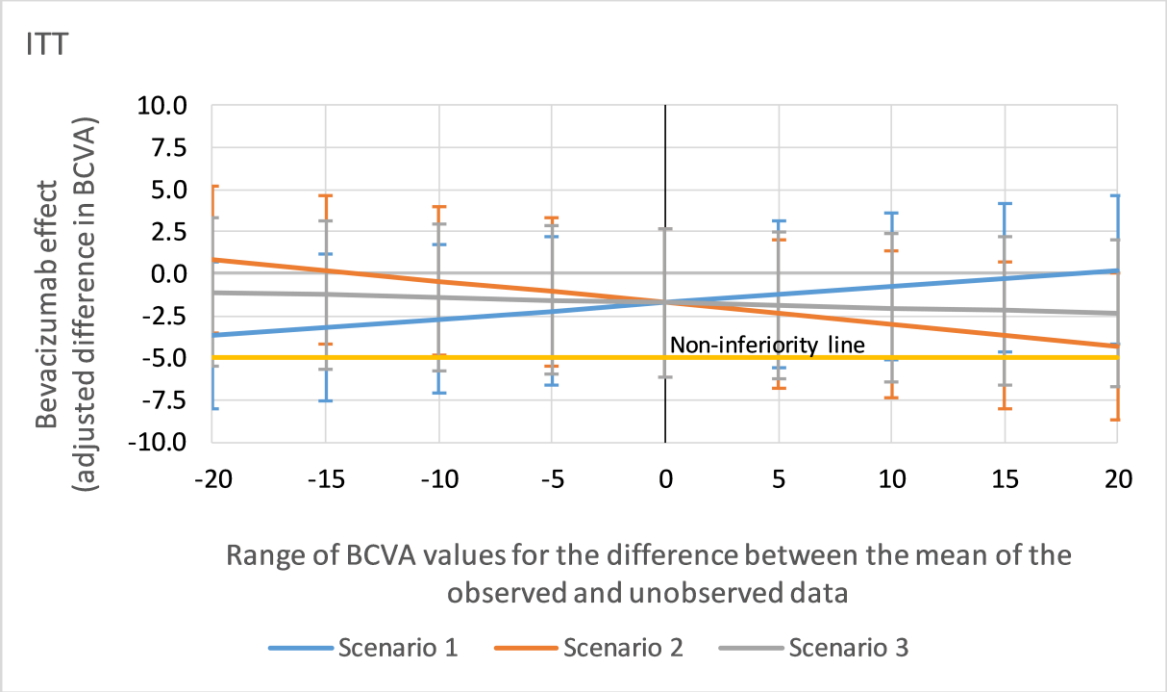
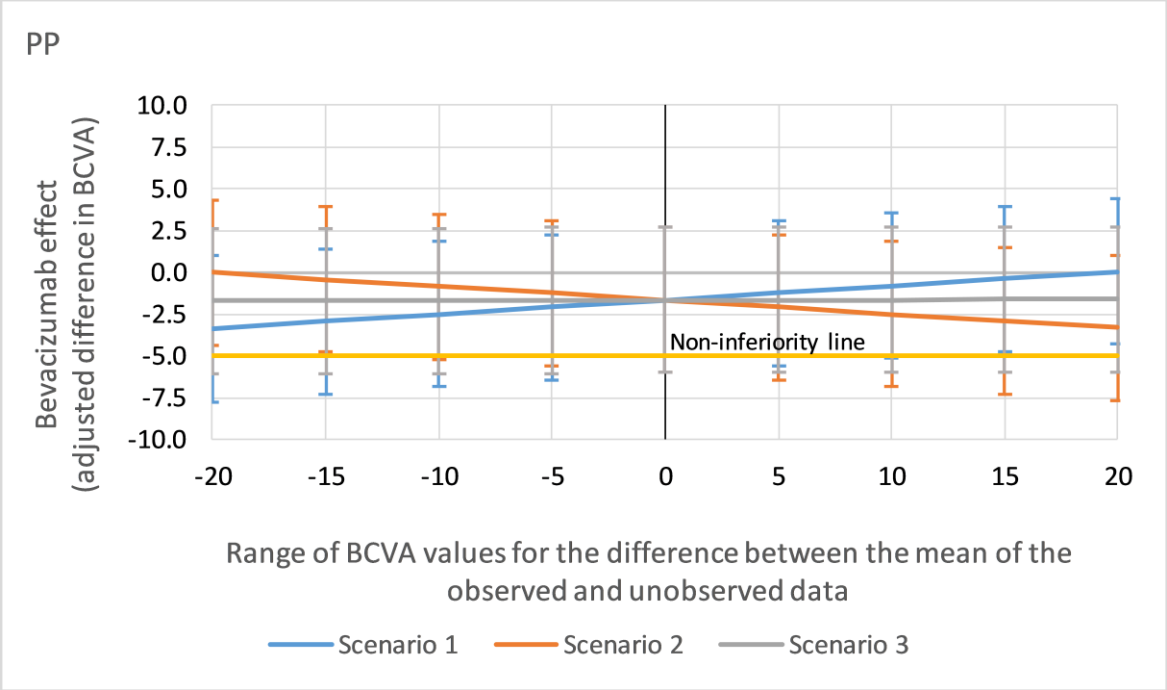


Figure 7: Sensitivity analysis for the missing at random assumption in the primary outcome analysis assessing non-inferiority of bevacizumab

For scenario 3, and within most of the ranges of Scenarios 1 and 2, the lower confidence interval limit lay below the non-inferiority margin of -5, support the main analysis conclusion of a lack of non-inferiority of bevacizumab. The difference in 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 compared to 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 ITT and PP populations.





3.5.2 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 pre-specified acceptable non inferiority margin of -5 letters at 52 weeks for both aflibercept and bevacizumab

Table 6: Adjusted BCVA at 52 weeks

Mean (SE) BCVA at screening		Mean (SE) (N) 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 versus Ranibizumab ITT						
Aflibercept	Ranibizumab	Aflibercept	Ranibizumab			
54.1 (1.2)	53.6 (1.2)	67.2 (1.5) (n=139)	65.4 (1.6) (n=139)	1.33 (-2.62, 5.28)*‡	0.0008	0.51
Aflibercept versus Ranibizumab PP						
Aflibercept	Ranibizumab	Aflibercept	Ranibizumab			
55.0 (1.2)	53.6 (1.3)	68.4 (1.4) (n=133)	65.5 (1.7) (n=137)	2.15 (-1.81, 6.1)*†	0.0002	0.29
Bevacizumab versus Ranibizumab ITT						
Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab			
54.4 (1.1)	53.6 (1.2)	66.4 (1.6)(n=135)	65.4 (1.6) (n=139)	-0.02 (-3.97, 3.94)*‡	0.0067	0.99
Bevacizumab versus Ranibizumab PP						
Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab			
54.4 (1.2)	53.6 (1.3)	66.4 (1.6) (n=135)	65.5 (1.7) (n=137)	0.05 (-3.88, 3.98)*†	0.0058	0.98

*Non-inferior relative to Ranibizumab

‡The linear mixed-effects model incorporates 454 participants (n=148 ranibizumab, n=153 aflibercept and n=153 bevacizumab) with best corrected visual acuity at 52 weeks.

†The linear mixed-effects model incorporates 443 participants (n=145 ranibizumab, n=146 aflibercept and n=152 bevacizumab) with best corrected visual acuity at 52 weeks

The proportion of patients 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% gaining ≥10 letters at 100 weeks (**figure 9**).

Figure 8: Percentage of patients in each group with ≥15 ETDRS letters BCVA improvement at 52 and 100 weeks

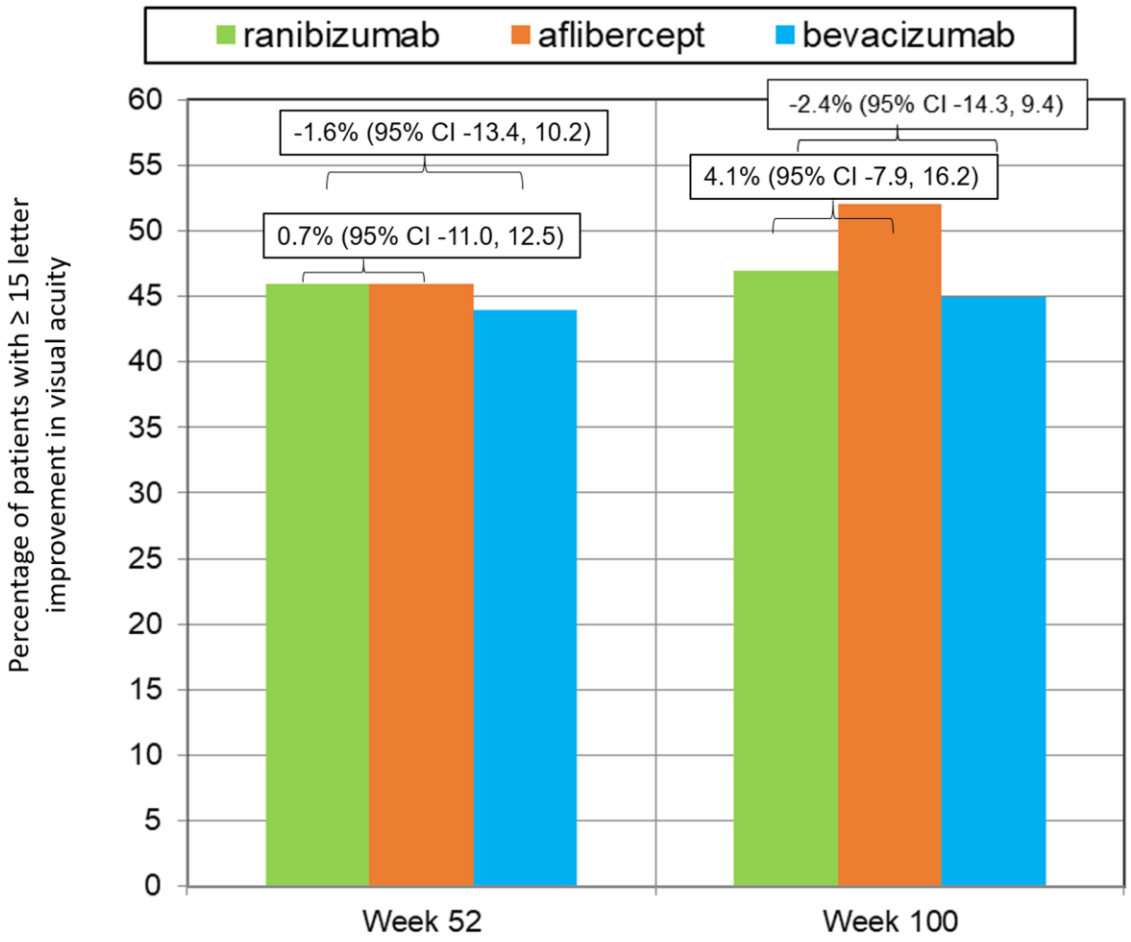
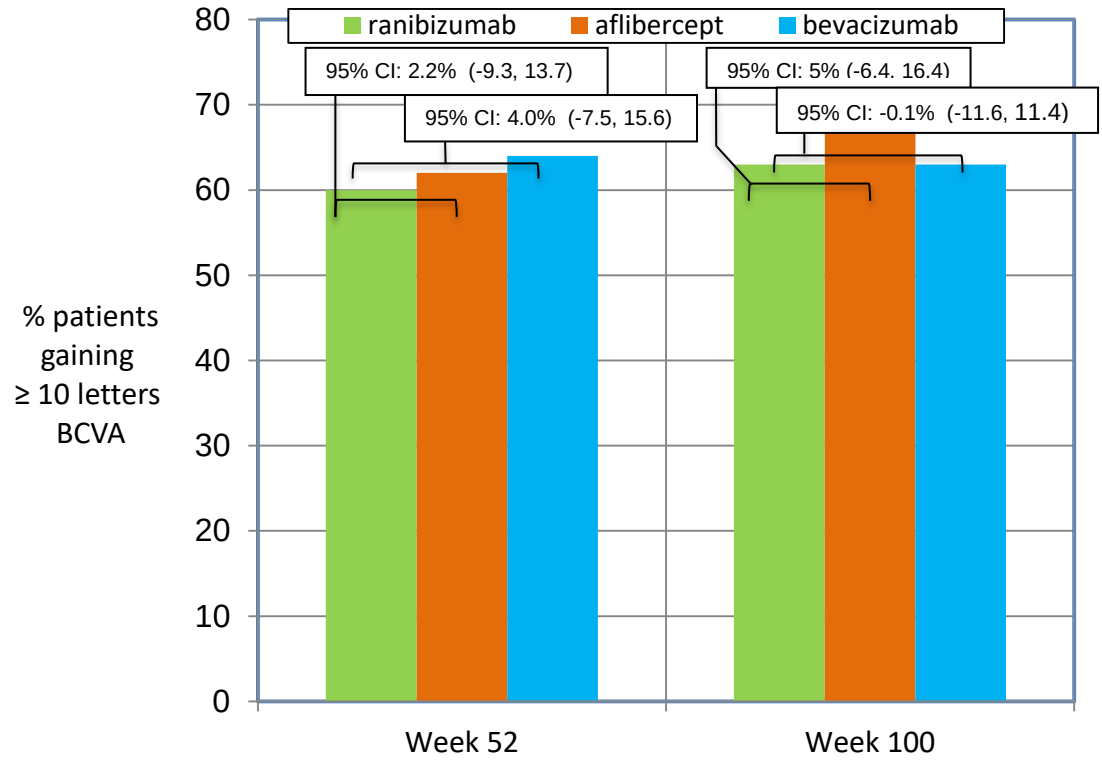


Figure 9: Percentage of patients in each group with ≥10 ETDRS letters improvement at 52 and 100 weeks



The number of patients with a < 15 letter loss was 90%, 93%, and 90% in the ranibizumab, aflibercept and bevacizumab groups respectively **(figure 10)** and ≥ 30 letter loss in best corrected visual acuity was less than 6% in each group (**figure 11**).

Figure 10: Percentage of patients per group with <15 ETDRS letter loss at 52 and 100 weeks

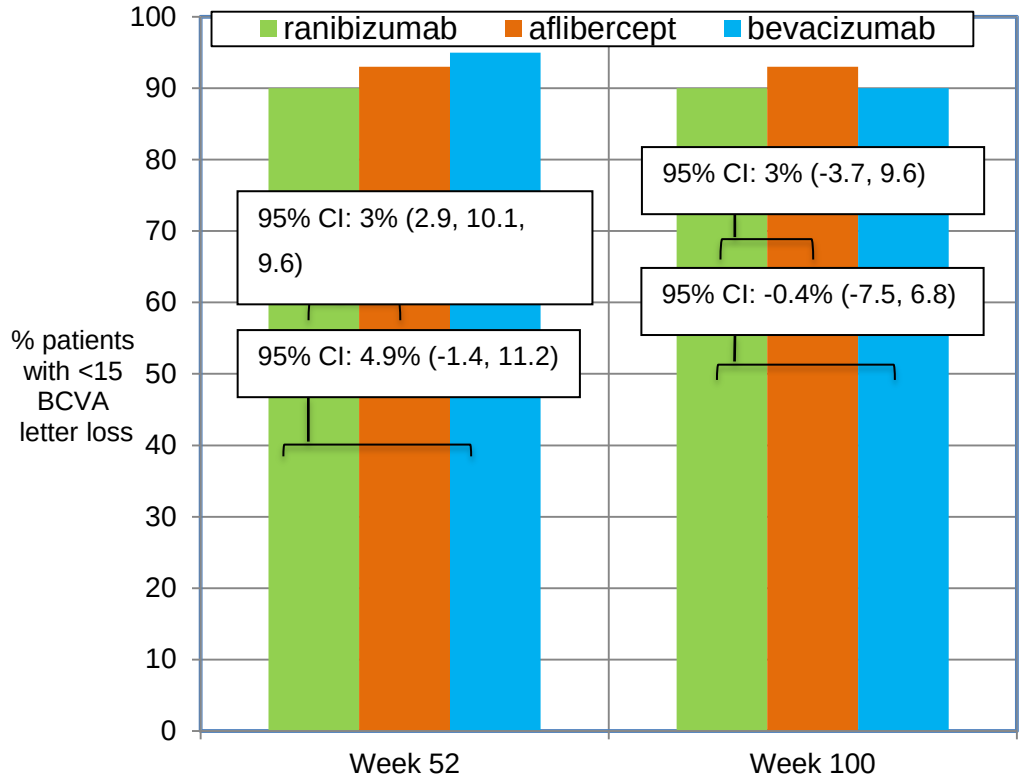
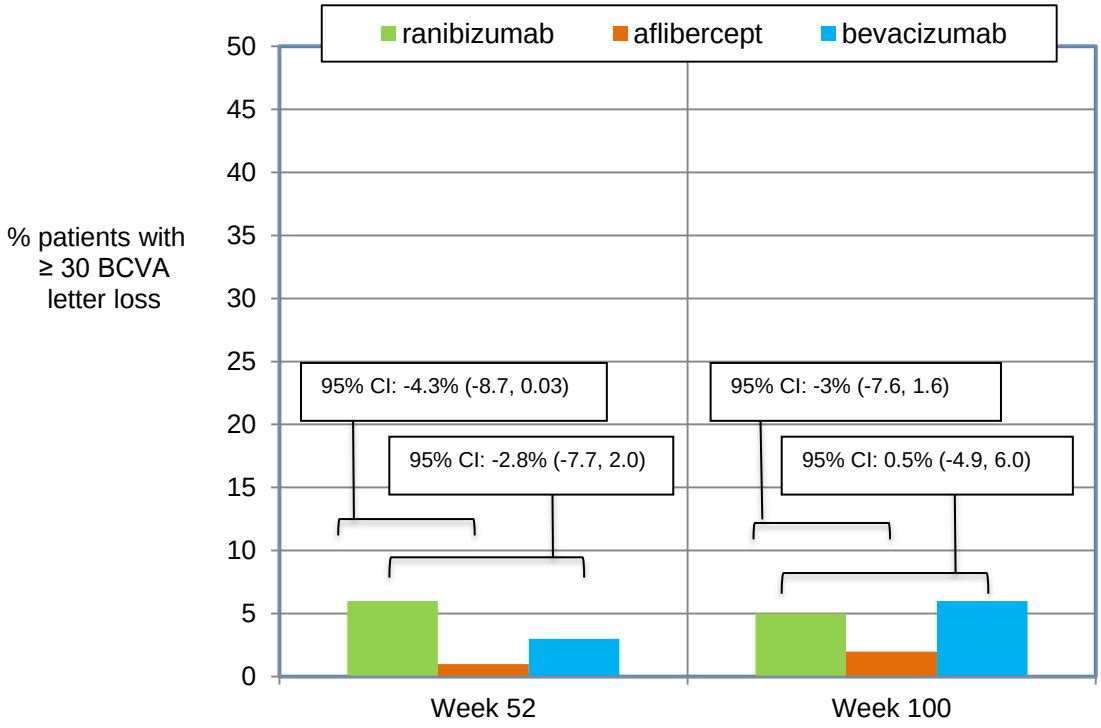


Figure 11: Percentage of patients per group with ≥ 30 ETDRS letter loss at 52 and 100 weeks



There were no meaningful differences in the percentage of participants in each group with pre-specified categorical outcomes e.g. less than 19 letters i.e. eligible for blind registration **table 7**).

Furthermore, there were no subgroup differences in final visual acuity outcome by baseline stratifiers (**tables 8, 9, 10).**

Table 7: Categorical visual acuity outcomes by treatment group

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

Table 8: Visual acuity outcomes stratified by baseline visual acuity

	Mean (SE) at screening		Mean (SE) (N) at 100 weeks		Adjusted difference between groups (95% CI)
Aflibercept versus ranibizumab ITT a)					p=0.91†
	Aflibercept	Ranibizumab	Aflibercept	Ranibizumab	
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, 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, 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, 10.7)
Aflibercept versus ranibizumab PP b)					p=0.97†
	Aflibercept	Ranibizumab	Aflibercept	Ranibizumab	
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, 15.7)
BCVA 39-58 letters	51.1 (0.8)	51.5 (0.7)	67.2 (2.6)	65.2 (2.8)	2.0 (-5.4, 9.5)

			(n=46)	(n=45)	
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, 10.4)
Bevacizumab versus ranibizumab ITT a)					p=0.81†
	Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab	
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, 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, 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, 5.5)
Bevacizumab versus ranibizumab PP b)					p=0.82†
	Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab	
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)

a) The linear mixed-effects model incorporates 454 participants (148 ranibizumab, 153 aflibercept and 153 bevacizumab)

b) The linear mixed-effects model incorporates 443 participants (145 ranibizumab, 146 aflibercept and 152 bevacizumab)

† p-value from interaction test for differential effect between subgroup categories

Table 9: Visual acuity outcomes stratified by disease duration at baseline

	Mean (SE) at screening		Mean (SE) (N) at 100 weeks		Adjusted difference between groups (95% CI)
Aflibercept versus ranibizumab ITT a)					p=0.14†
	Aflibercept	Ranibizumab	Aflibercept	Ranibizumab	
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, 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, 21.4)
Aflibercept versus ranibizumab PP b)					p=0.21†
	Aflibercept	Ranibizumab	Aflibercept	Ranibizumab	
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, 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, 21.2)
Bevacizumab versus ranibizumab ITT a)					p=0.33†
	Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab	
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, 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, 5)
Bevacizumab versus ranibizumab PP b)					p=0.32†
	Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab	
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, 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, 4.8)

a) The linear mixed-effects model incorporates 454 participants (148 ranibizumab, 153 aflibercept and 153 bevacizumab)

b) The linear mixed-effects model incorporates 443 participants (145 ranibizumab, 146 aflibercept and 152 bevacizumab)

† p-value from interaction test for differential effect between subgroup categories

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

	Mean (SE) at screening		Mean (SE) (N) at 100 weeks		Adjusted diff. between groups (95% CI)
Aflibercept versus ranibizumab ITT a)					p=0.15†
	Aflibercept	Ranibizumab	Aflibercept	Ranibizumab	

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, 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, 24.3)
Aflibercept versus ranibizumab PP b)					p=0.25†
	Aflibercept	Ranibizumab	Aflibercept	Ranibizumab	
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, 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, 23.8)
Bevacizumab versus ranibizumab ITT a)					p=0.85†
	Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab	
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, 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, 12.7)
Bevacizumab versus ranibizumab PP b)					p=0.73†
	Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab	
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, 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, 13.6)

a) The linear mixed-effects model incorporates 454 participants (148 ranibizumab, 153 aflibercept and 153 bevacizumab)

b) The linear mixed-effects model incorporates 443 participants (145 ranibizumab, 146 aflibercept and 152 bevacizumab)

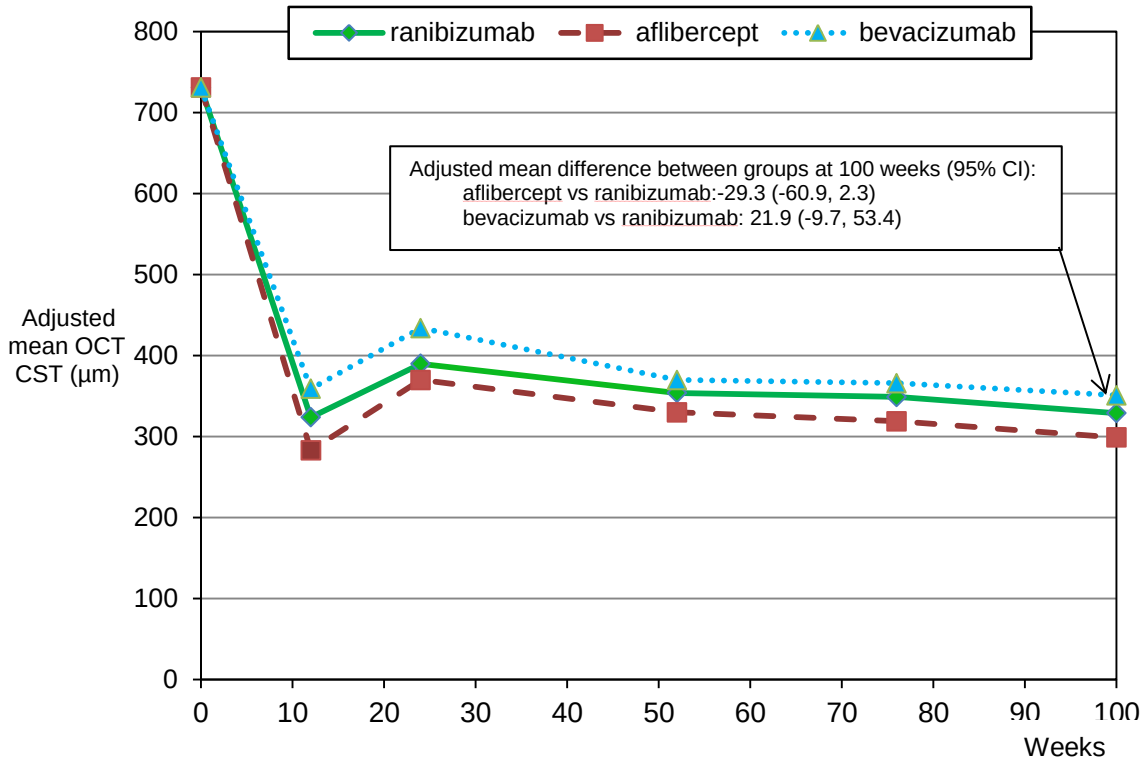
† p-value from interaction test for differential effect between subgroup categories

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

3.5.3 OCT outcomes

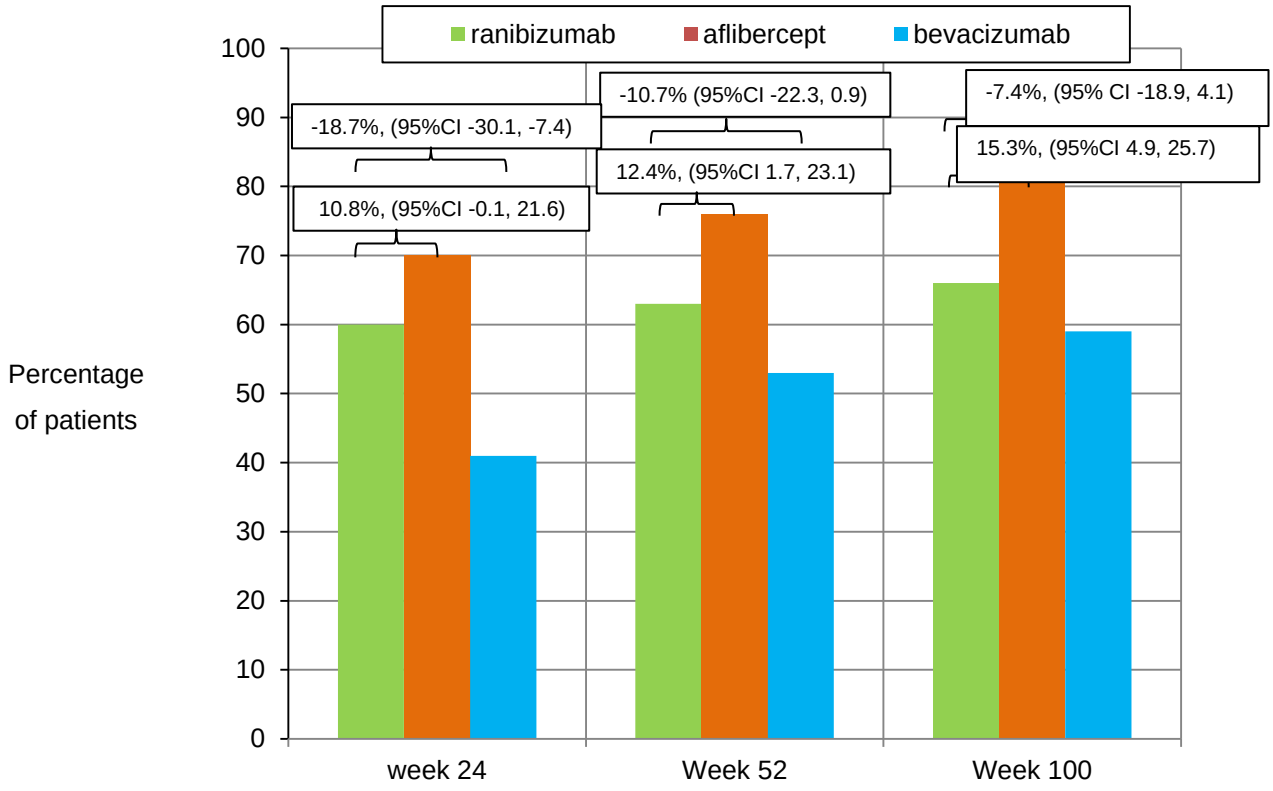
The mean reduction in OCT CST from baseline to 100 weeks was for ranibizumab -405µm, (95% CI -450, -360), aflibercept -378µm, (95% CI -412, -343) and bevacizumab group -334µm (95% CI -374, -293). There were no clinically relevant differences across treatment groups for the adjusted difference in CST at 100 weeks, aflibercept vs ranibizumab: -29.3 (95% CI -60.9, 2.3) and bevacizumab vs ranibizumab: 21.9 (95% CI -9.7, 53.4). The adjusted mean OCT CST across groups increased by approximately 50µm following PRN 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 study group at 100 weeks (**table 31**).

Figure 12: Adjusted mean optical coherence tomography central subfield thickness across groups to 100 weeks



There was a significantly greater proportion of patients with OCT CST <320µm at 52 weeks for aflibercept (76%), compared to ranibizumab (63%), a 12.4% difference (95% CI 1.7 to 23.1), which also occurred at 100 weeks, aflibercept (81%) compared to ranibizumab group (66%), 15.3% difference (95% CI 4.9 to 25.7), but only between bevacizumab and ranibizumab at week 24, -18.7% (95% CI -30.1, -7.4) (**figure 13**).

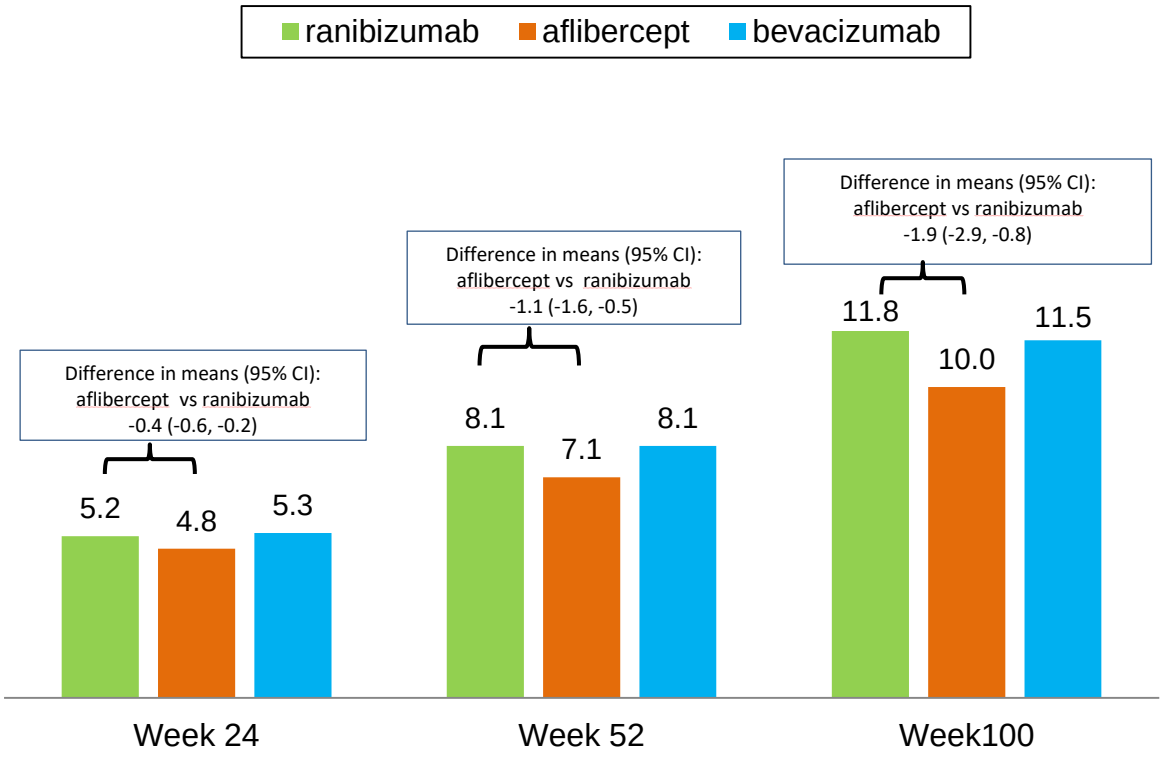
Figure 13: Percentage of patients with OCT < 320um at 52 and 100 weeks



3.5.4 Injection Number

By 100 weeks, ranibizumab group patients had received a mean of 11.8 injections compared to 10.0 for aflibercept and 11.5 for the bevacizumab groups. The difference between aflibercept and ranibizumab groups was meaningful as early as week 24 (mean difference -0.4 (95% CIs -0.6, -0.2), week 52 -1.1 (95% CIs -1.6 to -0.5) and week 100 -1.9 (95% CI -2.9 to -0.8)) (**figure 14**)

Figure 14: Mean number of injections across treatment groups by weeks 24, 52 and 100



3.5.5 Post hoc bevacizumab vs aflibercept analysis

After approval by the DMEC, a post hoc analysis was unable to demonstrate bevacizumab to be non-inferior to aflibercept in the ITT analysis at 52 weeks (adjusted mean difference -1.35 letters; 95% CI -5.29 to 2.59) and at 100 weeks (adjusted mean BCVA difference was -3.96 letters; 95% CI –8.34 to 0.42; p=0.32). The results of the PP analysis were similar. At 100 weeks, there was a significant difference of 1.6 (95% CI: 0.5 to 2.7) in the mean number of injections received by patients randomised to bevacizumab compared to aflibercept.

3.5.6 Retinal Imaging

3.5.6.1 OCT Imaging

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

Table 11: OCT anatomical outcomes for macula oedema, subretinal fluid and vitreomacular traction abnormality by treatment group

	All	Ranibizumab	Aflibercept	Bevacizumab
Macula Oedema				
Baseline				
null	7	3	1	3
no evidence	5 (1%)	2 (1%)	2 (1%)	1 (1%)
diffuse	19 (4%)	8 (5%)	8 (5%)	3 (2%)
cystic	90 (20%)	25 (16%)	33 (22%)	32 (21%)
mixed	342 (75%)	117 (77%)	110 (72%)	115 (76%)
Week 52				
null	53	21	13	19
no evidence	147 (36%)	56 (42%)	62 (44%)	29 (21%)
diffuse	64 (16%)	18 (13%)	24 (17%)	22 (16%)
cystic	103 (25%)	27 (20%)	35 (25%)	41 (30%)
mixed	96 (23%)	33 (25%)	20 (14%)	43 (32%)
Week 100				
null	67	22	24	21
no evidence	150(38%)	55(41%)	59 (45%)	36 (27%)
diffuse	55 (14%)	17 (13%)	19 (15%)	19 (14%)
cystic	87 (22%)	26 (20%)	29 (22%)	32 (24%)
mixed	104 (26%)	35 (26%)	23 (18%)	46 (35%)
Subretinal detachment				
Baseline				
null	26	9	8	9
no evidence	126 (29%)	39 (27%)	45 (31%)	42 (29%)
questionable	9 (2%)	6 (4%)	1 (1%)	2 (1%)
definite	196 (43%)	62 (41%)	63 (41%)	71 (48%)
Week 52				
null	55	22	13	20
no evidence	352(86%)	113 (85%)	124(88%)	115(86%)
questionable	0(0%)	0(0%)	0(0%)	0(0%)
definite	56(14%)	20(15%)	17(12%)	19(14%)
Week 100				
null	67	22	24	21
no evidence	342(86%)	118(89%)	111(85%)	113(85%)

questionable	0(0%)	0(0%)	0(0%)	0(0%)
definite	54(14%)	15(11%)	19(15%)	20(15%)
VItreomacular Interface Abnormality				
Baseline				
null	9	3	1	5
no evidence	250(55%)	87(57%)	88(58%)	75(50%)
questionable	8(2%)	3(2%)	2(1%)	3(2%)
definite	196(43%)	62(41%)	63(41%)	71(48%)
Week 52				
null	53	21	13	19
no evidence	221(54%)	73(54%)	76(54%)	72(53%)
questionable	4(1%)	0(0%)	3(2%)	1(1%)
definite	185(45%)	61(46%)	62(44%)	62(46%)
Week 100				
null	67	22	24	21
no evidence	219(55%)	74(56%)	77(59%)	68(51%)
questionable	9(2%)	4(3%)	4(3%)	1(1%)
definite	168(42%)	55(41%)	49(38%)	64(48%)

Null= not available due to patient withdrawal or image not taken or not saved. Ungradable= grader unable to grade due to poor image quality or feature(s) obscured e.g. by overlying macula oedema.

Spectral domain OCT (Spectralis^{TM}) image grading was undertaken for additional parameters including disorganisation of the retinal inner layers (DRIL), cone outer segment tip (COST) visibility loss, ellipsoid zone (EZ) disruption, loss of external limiting membrane (ELM) integrity and presence of intraretinal hyper reflective foci (HRF). Of 463 patients, 337 were enrolled at sites where Spectralis OCT^{TM} was available, of whom 267 had gradable images at baseline, week 52 and 100 (**table 12**). There was no difference in 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 represented better visualisation with time as macula oedema 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.

Table 12: Morphological grading of novel OCT parameters

	All N=267	**Ranibizumab N=92**	**Aflibercept N=89**	**Bevacizumab N=86**
Disorganisation of inner retinal layers (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%)
Hyper reflective foci (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%)
External limiting membrane (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%)
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%)
Ellipsoid zone (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%)
Cone Outer Segment Tips (COST)				
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%)

3.5.6.2 Fluorescein angiography image analysis

Of 463 patients at baseline, 461 underwent FFA. At 100 weeks, 407 completed the ITT analysis of whom 377 underwent FFA, and 30 did not as they declined, had experienced an adverse reaction to the dye at baseline, or there were intravenous cannulation / technical difficulties. Of the 377, 53 could not be graded for other reasons e.g. the patient had received panretinal photocoagulation before or during the study and in 14 all images were ungradable, leaving 310 patients with gradable images (**table 13**). The percentages of patients in each arm with ≥2 step worsening in one or more quadrants appeared more frequent in the aflibercept arm compared to bevacizumab but as the number of

affected quadrants increased the result across arms tended to converge. Overall the data showed no meaningful difference between treatment groups in terms of the number of patients with at least 2-step worsening of non perfusion in one or more quadrant.

Table 13: Change in capillary non-perfusion (CNP) based on fluorescein angiography image characteristics available at baseline and week 100

No. of sectors with ≥ 2 step CNP worsening	Ranibizumab 105 (%)	Aflibercept 96 (%)	Bevacizumab 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%)

The novel concentric ring method for analysing non-perfusion in disc areas and developed by the LEAVO group during the study was applicable in 235 of 463 patients randomised who underwent wide angled Optos fluorescein angiography. Of these 187 had images successfully performed at both entry and exit and of these 40 were not graded as they received PRP during the study (n=11), there were poor quality images either at baseline or exit (n=23) or the images were not corrected for peripheral angular distortion (n=6) leaving 147 gradable images. Of these 102 were gradable in more than 85% of the assessed area, were converted into disc areas of non perfusion and form the basis of the comparison in **table 14.**

Table 14: i. Amount of retinal non-perfusion per arm and ii. Comparison of the changes from baseline in the amount of retinal non-perfusion between arms

14.i	**Amount of retinal non-perfusion (Median (IQR))†**			
Retinal area	**All (n=103)***	**Ranibizumab (n=40)**	**Aflibercept (n=33)***	**Bevacizumab (n=30)**

	Cells	DAs	Cells	DAs	Cells	DAs	Cells	DAs
Baseline								
Total area	3 (1.5, 5)	29.3 (14.2, 49.1)	2 (1, 5.8)	20.7 (9.5, 54.3)	4 (1.8, 6)	30.2 (17.2, 56.9)	3 (2, 5)	30.2 (20.7, 46.8)
Posterior (M+R1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0.25)	0 (0, 0.5)	0 (0, 0)	0 (0, 0)
%(n) subjects with posterior >0	16% (16)	16% (16)	18% (7)	18% (7)	24% (8)	24% (8)	3% (1)	3% (1)
Peripheral (R2 to R4)	3 (1.5, 5)	29.3 (14.2, 49.1)	2 (1, 5.8)	20.7 (9.5, 54.3)	3 (1.8, 6)	30.2 (16.8, 56.9)	3 (2, 5)	30.2 (20.7, 46.8)
M	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
R1	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
R2	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0 (0, 7.78)	0 (0, 0)	0 (0, 0)
R3	1.5 (0, 3)	14.2 (0, 28.4)	1 (0, 2.4)	9.5 (0, 22.5)	2 (0, 3)	18.9 (0, 28.4)	2 (0, 3)	18.9 (0, 28.4)
R4	2 (0.5, 2)	20.7 (5.2, 20.7)	1 (0.5, 2)	10.4 (5.2, 20.7)	2 (0.8, 2)	20.7 (7.8, 20.7)	2 (0.8, 2)	20.7 (7.8, 20.7)
Week 100								
Total area	3.5 (2, 7)	33.6 (20.7, 64.6)	3 (1.5, 7.8)	30.2 (15.5, 65.5)	4.5 (2, 9.8)	42 (20.7, 88.6)	3 (2, 5)	30.2 (20.7, 49.2)
Posterior (M+R1)	0 (0, 0)	0 (0, 0)	0 (0, 0.8)	0 (0, 3.9)	0 (0, 2)	0 (0, 6.8)	0 (0, 0)	0 (0, 0)
%(n) subjects with posterior >0	23% (23)	23% (23)	25% (10)	25% (10)	31% (10)	31% (10)	10% (3)	10% (3)
Peripheral (R2 to R4)	3.5 (2, 6.6)	33.6 (20.7, 60.1)	3 (1.5, 6.9)	30.2 (15.5, 61.2)	4.3 (2, 8.6)	42 (20.7, 77.1)	3 (2, 5)	30.2 (20.7, 49.2)
M	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0.9)	0 (0, 1.6)	0 (0, 0)	0 (0, 0)
R1	0 (0, 0)	0 (0, 0)	0 (0, 0.4)	0 (0, 2)	0 (0, 1)	0 (0, 5.2)	0 (0, 0)	0 (0, 0)

R2	0 (0, 1.1)	0 (0, 8.8)	0 (0, 1.8)	0 (0, 13.6)	0 (0, 2.9)	0 (0, 22.4)	0 (0, 0.5)	0 (0, 3.9)
R3	1.5 (0, 3)	14.2 (0, 28.4)	1.3 (0, 3)	11.8 (0, 28.4)	2 (0.1, 4)	18.9 (1.2, 37.9)	1.5 (0, 2.5)	14.2 (0, 23.7)
R4	2 (1, 2)	20.7 (10.4, 20.7)	1.8 (1, 2)	18.1 (10.4, 20.7)	2 (1.6, 2)	20.7 (16.8, 20.7)	2 (1, 2)	20.7 (10.4, 20.7)
	Cells	DAs	Cells	DAs	Cells	DAs	Cells	DAs
Change in total area	0.0 (-0.5, 2.0)	0.0 (-5.1, 19.4)	0.0 (-0.5, 2.0)	0.0 (-5.6, 16.6)	0.75 (-0.13, 2.63)	6.5 (0.0, 22.5)	0.0 (-1.38, 1.50)	0.0 (-13.2, 15.2)
Change in posterior	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.38)	0.0 (0.0, 2.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
%(n) subjects with an increase in posterior	17% (17)	18% (18)	18% (7)	18% (7)	25% (8)	28% (9)	7% (2)	7% (2)
Change in peripheral	0.0 (-0.5, 2.0)	0.0 (-5.1, 18.4)	0.0 (-0.6, 1.6)	0.0 (-5.7, 16.6)	0.5 (0.0, 2.1)	5.4 (0.0, 20.8)	0.0 (-1.4, 1.5)	0.0 (-13.2, 15.2)

†Medians(IQR) except written otherwise

*Data were missing for one aflibercept patient at 100 weeks.

14.ii	**Difference in medians (95% CI)* Aflibercept - Ranibizumab**		**Difference in medians (95% CI)* Bevacizumab - Ranibizumab**	
	Cells	**DA**	**Cells**	**DA**
Change in total area	0.8 (-0.5, 1.8)	6.5 (-1.1, 10.8)	0.0 (-1.0, 0.5)	0.0 (-8.6, 4.6)
%(N) patients with an increase in posterior	7.5% (-11.6%, 27.0%)	10.6% (-8.9%, 30.6%)	-10.8% (-25.6%, 3.9%)	-10.8% (-25.6%, 3.9%)
Change in peripheral	0.5 (-0.3, 1.5)	5.4 (-2.4, 13.8)	0.0 (-1.0, 0.5)	0.0 (-9.5, 4.7)

*95% confidence intervals for the changes were obtained using the nonparametric bootstrap percentile method with 100,000 samples.

The median value of baseline non perfusion for all patients was 29.3 disc areas (IQR 34.9) mostly in the peripheral retina. There was more non perfusion in the periphery and notably in the posterior pole in the ranibizumab (18%) and aflibercept (24%) than bevacizumab (3%) groups. This baseline imbalance between groups was seen at week 100 particularly in the percentage of patients showing an increase in posterior non perfusion which may simply reflect higher baseline non-perfusion and

therefore more likelihood to progress. A detailed appraisal of this data is currently being undertaken and will form the basis of a further report.

3.5.7 Treatment Allocation Guess Form

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

3.5.8 Safety outcomes

There was one case of infectious endophthalmitis in a study eye that followed trabeculectomy bleb infection rather than intravitreal injection. The frequency of all ocular adverse events and Anti-Platelet Trialists` Collaboration (APTC) defined events were similar between study arms (**table 15**). The proportion of patients who were persistent non-responders defined as not more than a 5 letter gain in VA and OCT CST decrease of less than 50 µm after 24 weeks was ranibizumab 1/139, aflibercept 5/133 and bevacizumab 5/135 at 52 weeks with only one bevacizumab patient at 100 weeks**.** During the study, 25 (5.4%) eyes developed an ischaemic CRVO, 13 (2.8%) anterior segment neovascularisation and 6 (1.3%) retinal neovascularisation with no difference across arms (**table 15**). Eight ranibizumab, 7 aflibercept and 8 bevacizumab arm patients required panretinal photocoagulation. There were two pregnancies reported in the study, 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.

Table 15: Ocular adverse events and APTC events

	Total (n=463)	Ranibizumab (n=155)	Aflibercept (n=154)	Bevacizumab (n=154)	Difference (95% CI) Aflibercept vs Ranibizumab	Difference (95% CI) Bevacizumab vs Ranibizumab
Ocular adverse events						
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 Neovascularization	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%)
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%)

Systemic serious adverse events occurred with an expected and similar frequency between groups (**table 15**) and there were no meaningful differences between groups in the frequency of adverse events within the same body system (**table 16**).

Table 16: Comparison between arms of serious adverse events by body system

Body system	Total N (%) N = 463	Ranibizumab N (%) N = 155	Aflibercept N (%) N = 154	Bevacizumab N (%) 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%)
Endocrine	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%)
Neoplasia	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%)

3.6 Comparison with SCORE2 Safety Data

Although it was not possible to perform a safety meta-analysis due to the lack of comparative outcome data in CRVO as described in the methods, the data from the SCORE2 study during the initial comparative six months was compared with the first six months of LEAVO safety data (**table 17**). There were a higher number of conversions to ischaemic CRVO recorded in LEAVO compared to SCORE 2. This may have been erroneous due to LEAVO recording conversion to ischaemic CRVO as a direct question in each study visit sheet, due to early enrolment in LEAVO vs SCORE 2 and treatment naive status of most LEAVO patients at randomisation. There were more vitreous haemorrhages recorded in LEAVO compared to SCORE2 and more vascular deaths in SCORE2 than LEAVO. The prevalence of these events was low and it was not thought there were any meaningful differences between the two studies in the number or type of adverse events.

Table 17: Comparison of LEAVO and SCORE2 AEs at six months

		LEAVO			SCORE2	
	Event	**Ranibiz-umab**	**Afliber-cept**	**Bevaci-zumab**	**Afliber-cept**	**Bevaci-zumab**
Study eye	Infective endophthalmitis	0	0	1	-	-
	Non-infectious endophthalmitis	0	0	0	0	1
	Neovascular glaucoma	1	1	0	1	0
	Conversion to iCRVO	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 not limited to study eye	Participants with any AE	108	99	115	82	98
	Total no of all AEs	301	337	323	184	263
	Participants with any SAE	19	7	14	14	14
	Total no of all SAEs	20	10	14	18	25

3.7 Patient Public Involvement

The Lay Panel Members co-developed the contents and wording of the questions in the following questionnaire. The feedback regarding the final questionnaire content was positive , i.e. it was an important study to have done, the text was easy to follow and the questions clear. The results were under embargo pending publication at the time the questionnaire which was sent to patients (n=22, 7 with a history of retinal vein occlusion [but not LEAVO patients] 15 with a history of diabetic eye disease and 3 regular lay panel members). The results of the PPI LEAVO study questionnaire are given below and presented in **table 18**.

Q1. 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?
Yes 100%, No 0%, May be 0%

Q2. 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).
Yes 27%, No 59%, May be 9% Not answered 5%

Q3. 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?
Yes 91%, No 0%, May be 9%

Q4: 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?
Yes 50%, No 36%, May be 14%

Q5. 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 like drive, read books and magazines, work machinery, use power tools would you be happy to be given Avastin?

Yes 68%, No 27%, May be 5%

Q6. 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?

Yes 100%, No 0%, May be 0%

Table 18: Study Results: Post trial Patient Questionnaire Feedback

	Question 1	Question 2*	Question 3	Question 4	Question 5	Question 6
Yes	**22**	**6**	**20**	**11**	**15**	**22**
Maybe	**0**	**2**	**2**	**3**	**1**	**0**
No	**0**	**13**	**0**	**8**	**6**	**0**

*one nil response

Chapter 4: Health Economic Evaluation

4.1 Introduction

Economic evaluation forms an important part of Health Technology Assessment (HTA) by evaluating the cost-effectiveness of interventions to determine whether they represent value for money. In England, the National Institute for Health and Care Excellence (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.[79,80] Our analyses use NICE's preferred methods in conjunction with other good practice guidelines[81,82] to evaluate the cost-effectiveness of intravitreal ranibizumab, aflibercept and bevacizumab for macular oedema (MO) due to central retinal vein occlusion (CRVO).

NICE's preferred method for cost-effectiveness analysis, of interventions delivered in NHS setting, is cost-utility analysis (CUA).[79,80] 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 zero and one, where one represents perfect health and zero represents death (utilities below zero are permitted, reflecting health states considered to be worse than death).

CUA is used to compare two or more interventions, using incremental analysis. The outcome of a CUA is an incremental cost-effectiveness ratio (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 CUA can be used in decision-making, to determine whether interventions represent good value for money. The simplest decisions concern dominance. An intervention is said to "dominate" the comparator (and the comparator is "dominated") where 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 saves costs and improves outcomes. In the situation where an intervention is more costly and leads to more QALYs than the comparator, a decision rule is required to determine whether the gain in QALYs is worth the additional cost. In this case, the ICER can be compared to a threshold representing the maximum the funder is willing to pay for 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 below £20,000 per QALY are generally considered to be cost-effective, while decisions regarding interventions with ICERs between £20,000 and £30,000 per QALY will need to consider additional factors such as uncertainty, innovation, whether the HRQoL benefits have been adequately captured, whether the treatment meets specific criteria for life-extending treatments at the end of life, and the NHS' non-health

objectives. Above £30,000 per QALY, a stronger case is required for NICE to consider the intervention to be cost-effective.[79]

4.2 Overview of health economics methods

4.2.1 Interventions

A full health economic evaluation was conducted comparing three interventions for MO due to CRVO using data collected as part of the LEAVO study. The interventions are:
Interventions (investigational treatments)

- **Arm A: Treatment:** An intravitreal injection of aflibercept (2.0mg/50µl) administered at baseline, 4, 8 and 12 weeks as mandated injections. From week 16 to 96, treatment was given if one or more retreatment criteria were met as specified in the study protocol.[83] Beyond the 100 week trial period, injections were given based on treatment continuation rules specified in section 5.1.1
- **Arm B: Treatment:** An intravitreal injection of bevacizumab (1.25mg/50ul) administered at baseline, 4, 8 and 12 weeks as mandated injections. From week 16 to 96, treatment was given if one or more retreatment 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 (0.5mg/50ul) administered at baseline, 4, 8 and 12 weeks as mandated injections. From week 16 to 96, treatment was given if one or more retreatment criteria were met. Beyond the 100 weeks trial period, injections were given based on treatment continuation rules.

4.2.2 Method of economic evaluation

The economic evaluation is comprised of 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 patients' lifetimes, extrapolating clinical outcomes beyond the trial period and relating these to costs and QALYs. The within-trial analysis evaluates the three interventions within the trial period, using the individual patient-level cost and HRQoL data collected during the trial. The economic evaluation uses cost utility analysis. The methods for the economic evaluation were pre-specified in a health economic and decision modelling analysis plan (and associated addendum) documents prior to database lock.[84,85]
The within-trial analysis provides the short-term cost-effectiveness evidence using individual patient-level data on quality of life and costs; and therefore, avoids extrapolation uncertainty. The model-based analysis provides the long-term cost-effectiveness evidence (extrapolating outcomes and costs beyond the trial period) and this is the preferred approach for resource allocation decision-making (in

line with NICE's Guide to methods of Technology Appraisal). To support the development of the economic model, a systematic literature review was undertaken to identify evidence to inform inputs and assumptions.

4.2.3 Settings

4.2.3.1 Perspective

The economic evaluation uses the NHS and Personal Social Services (PSS) perspective, consistent with the NICE Methods Guides.[79,80] Included costs are those incurred by the NHS and PSS: so include costs for healthcare resource use and interventions. Societal costs, lost productivity and patient's personal expenditure (such as travel costs) are excluded.

4.2.3.2 Discounting

Future costs and health outcomes are discounted to reflect time preference. The discount rates for both costs and QALYs is 3.5% per year, consistent with the NICE Methods Guides.[79,80]

4.2.3.3 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"[79] Using a lifetime horizon reflects the long-term differences between the interventions in terms of effectiveness, time on treatment/discontinuation, and safety outcomes.

4.2.4 Presentation of results

4.2.4.1 Incremental and pairwise analyses

The economic evaluation reports fully incremental analyses, consistent with the NICE Reference Case,[79,80] and pairwise analyses to allow comparison of each pair of interventions. For the model-based analysis, the fully incremental analysis is presented within the main report and for the within-trial analysis, pairwise comparisons are also presented in the main report.

4.2.4.2 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 Section 4.5).
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 Section 4.5) and

probabilistic sensitivity analysis is presented as an additional scenario using base case settings (see Section 4.7).

4.2.5 Quality assurance

The model was developed by two economic modellers. When one economic modeller added coding or inputs to the model, the other 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 checked for errors by a second health economist.

4.3 Overview of systematic literature review

4.3.1 Objectives

A systematic literature review was undertaken in line with current recommendations.[86,87] The aim of this review was to identify evidence to inform inputs and assumptions for the long-term (>2 years) economic model of the LEAVO study. Data requirements for patients with macular oedema (MO) secondary to central retinal vein occlusion (CRVO) treated with intravitreal injections of ranibizumab (0.5mg/50ul), aflibercept (2.0mg/50µl) and bevacizumab (1.25mg/50ul) included:

- Relative clinical effectiveness and safety (including withdrawals and mortality)
- Health related quality of life 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,
- Study eye optical coherence tomography central sub-field thickness (OCT CST),
- Study eye best corrected visual acuity (BCVA),
- Non-study eye OCT CST,
- Non-study eye best corrected visual acuity (BCVA),
- New onset macular oedema,
- Injection frequency.

4.3.2 Methods

4.3.2.1 Literature searching

Eight electronic databases were searched: MEDLINE; MEDLINE In-Process; Cochrane Library; Health Technology Assessment (HTA) database; NHS Economic Evaluation Database (NHS EED); EMBASE; Cumulative Index to Nursing and Allied Health Literature (CINAHL); Web of Science. Searching of databases was conducted from date of inception up 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. To identify systematic reviews, randomised trials, observational studies, and economic studies (including quality of life studies), appropriate search filters were applied in selected databases

4.3.2.2 Study selection, data extraction, critical appraisal and synthesis

Study selection was completed by using a two-stage process based on pre-specified eligibility criteria. 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)[0.5mg/50ul], aflibercept (Eylea)[2.0mg/50µl] and bevacizumab (Avastin)[1.25mg/50µl], as a monotherapy versus 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[88] in study selection, the most appropriate methodological quality checklist endorsed by the Critical Appraisal Skills Programme (CASP)[89] was applied for quality assessment of included studies. 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 clinical and methodological heterogeneity of included studies precluded meta-analysis of available evidence.

4.3.3 Results

A total of 1,338 unique records were retrieved through literature searches and supplementary searching. Of these, three articles[24,32,90] provided evidence of limited relevance for informing or validating the LEAVO economic model. A summary of included studies is presented in **table 19**.

4.3.3.1 Included studies

None of the studies provided a head-to-head comparison of the clinical effectiveness outcomes of interest. Two non-randomised studies, the RETAIN study (n=32 patients)[32] and LUMINOUS study (n= 1,048 patients),[90] provided long-term clinical effectiveness data for ranibizumab only. Patients in RETAIN had previously completed two pivotal multicentre US-based Phase III randomised controlled trials (CRUISE, for patients with CRVO, and BRAVO, for patients with BRVO)[9,31,91] and a subsequent follow-up trial[36] The mean follow-up period of RETAIN was 49.7 months (with a maximum follow-up of 60 months).[32] The LUMINOUS study was a five-year international multicentre post-authorisation study (n=43 countries; 494 centres) which evaluated the long-term effectiveness and safety of ranibizumab for all its indications in the real-world setting. Patients with CRVO made up 3.5% (n=1, 048) of the entire study population in LUMINOUS (n=30,153 patients). Evidence relating to the natural history for CRVO was obtained from a systematic review (n=31 studies; 3,271 eyes).[24]

4.3.3.2 Summary of findings

No clinical effectiveness evidence relating to the long term (i.e. >2years follow-up) head-to-head comparison of intravitreal injections of ranibizumab (0.5mg/50ul), aflibercept (2.0mg/50µl) and bevacizumab (1.25mg/50ul) in patients with MO secondary to CRVO was identified. 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.[32,90] 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 follow-up intervals were less frequent.[32] Improved long term outcomes were observed in patients with early MO resolution (resolved MO versus unresolved MO, at year four: mean BCVA, 73.2 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/32) versus 56.1 ETDRS letters (20/80); mean CFT, 171.30 versus 263.40 µm, respectively).[32] Less than 5% (n=30/1,048) of patients provided relevant data for visual acuity outcomes beyond two years of follow-up in the LUMINOUS study. Therefore, the observed general trend in improved vision (gain of 10 or 15 letters in visual acuity, n=2 to 8 patients; gain of > 10 letters or a final BCVA ≥ 73 letters, n=1 patient, at 48 months) and MO (mean change from baseline, -257.1 (179.91) µm, n=7 patients, at 36 months) needs to be interpreted with caution.[32] 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 adverse events following long-term ranibizumab was mixed due to inadequate sample sizes, inconsistent definitions and reporting. The review also found that most patients with CRVO present with MO.[24] Of the 32 patients enrolled in RETAIN, 14 experienced MO resolution (43.8%).[32] A statistically significant difference in change in central foveal thickness was noted between patients with resolved MO and unresolved MO (263.4 µm versus 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.* [32]

The mean number of injections of ranibizumab, 0.5 mg administered in RETAIN was 19.2 over 54 months of follow-up (n=28 patients).[32] The mean number of injections per patient administered in year two, year three and year four of the study was 4.5, 3.6 and 3.3 respectively. In contrast, the mean number of injections per patient was 5.9 in LUMINOUS, by month 48.[90] A total of 6,224 ranibizumab injections were received by patients with CRVO.[90] While the majority of patients received treatment in only one eye, an estimated 3% were treated in both eyes.[90] Differences in prior intravitreal treatment status did not influence the number of injections received between respective subgroups.

Available evidence suggests that after three years of treatment, patients receiving ranibizumab tend to experience improved quality of life (NEI VFQ 25 composite score, change from baseline +3.6 (SD=10.70)).

The LUMINOUS study[90] reflected real-world management to a greater degree compared to the RETAIN study.[32] This could explain the higher rate of withdrawals observed.

Table 19: Summary of included studies in systematic review

Study reference	Campochiaro 2014 [30]	Novartis 2017 [87]	McIntosh 2011 [23]
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	Not applicable
Treatment schedule	TER	Not reported	Not applicable
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	Novartis	Allergan Inc
Length of follow-up (years)	4	5	3

Study reference	Campochiaro 2014 [30]	Novartis 2017 [87]	McIntosh 2011 [23]
Baseline characteristics			
Mean age	66.9 (SD, not reported)	69.7 (12.32)	Not applicable
% females	Not reported	41.5%	Not applicable
Duration of CRVO at baseline, months	4.6	12.6 (20.2)	Not applicable
BCVA	50	44.7 (23.88)	Not applicable
SD-OCT, (μm) mean, SD	639	463.5 (212.5)[β]	Not applicable
% patients with ischaemic CRVO	Not reported	Not reported	Not applicable
NEI-VFQ 25 composite score	Not reported	73.0 (20.62)	Not applicable
Previous ocular history	Not reported	RVO (16.5%) glaucoma (10.4%) cataract operation (9.1%)	Not applicable

Study reference	Campochiaro 2014 [30]	Novartis 2017 [87]	McIntosh 2011 [23]
		cataract (6.0%)	
Previous medical history	Not reported	Cardiovascular risk factor* , 4 to 61.3%	Not applicable
Outcomes			
Primary study outcomes	Mean change in BCVA Percentage of patients with resolution of macular oedema	Mean change in BCVA Mean change in central retinal thickness Ocular and systemic adverse events	Baseline VA Percentage of patients with MO at baseline Development of neovascularisation, neovascular glaucoma 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	Change in National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) scores, from baseline	Not reported

Study reference	Campochiaro 2014 [30]	Novartis 2017 [87]	McIntosh 2011 [23]
	baseline Percentage of patients , BCVA≥20/40 Percentage of patients, BCVA ≤20/200 Mean change from baseline in central foveal thickness (CFT) by Stratus OCT Percentage of patients with CFT ≤ 250 µm at each study visit, Ocular and systemic adverse events	Number of injections, Number of visits and re-treatments, Time interval between injections Reasons for re-treatment or treatment termination.	
Quality assessment of included studies			
Evidence rating (Coyle and Lee)(Coyle and Lee,	4§	4§; 2 to 3◊; 1 ∞	3◊

Study reference	Campochiaro 2014 [30]			Novartis 2017 [87]									McIntosh 2011 [23]
2002)													
Methodological quality (CASP)	Unclear quality			Unclear quality									Good quality
Results													
Visual acuity													Not reported
Mean BCVA from baseline	Mean follow-up	51. 4 months		Month 24		Month 36				Month 48			
		61.3 (20/63)											
% patients, BVCA ≥20/40		43.8		Not reported		Not reported				Not reported			
% patients, gain ≥ 15 letters		53.1		28.1		Not reported				Not reported			
Macular oedema													
Mean retinal thickness	Time-point	Month 48 (CFT)		Month 24 (CRT)			Month 36 (CRT)			Month 48 (CRT)			
	All patients	Patients with resolved	Patients with unresolv	TN	TnN (R)	TnN (other)	TN	TnN (R)	TnN (other)	TN	TnN (R)	TnN (other)	Not reported

Study reference	Campochiaro 2014 [30]			Novartis 2017 [87]									McIntosh 2011 [23]
		MO	ed MO										
	220.6 (n=28)	171.3 (n=13)	263.4 (n=15)	372.9 (n=32)	304.9 (n=45)	321.5 (n=19)	290.3 (n=7)	411.2 (n=11)	375.0 (n=2)	Not reported	Not reported	Not reported	
		p=0.01											
% patients, CFT ≤ 250 µm	All patients	43.8% (n=14/32)		Not reported									Not reported
Resource use													
Mean number of injections per patient (Ranibizumab)	Time-point	Month 24	Month 36	Month 48	Month 24			Month 36			Month 48			Not reported
					TN	TN (R)	TnN (other)	TN	TnN (R)	TnN (other)	TN	TnN (R)	Tn N (other)	
		4.5	3.6	3.3	5.5	5.5	6.2	5.8	5.8	6.6	5.8	5.8	6.7	
Total number of injections (Ranibizumab)	All patients (n=32)			19.2	All patients (n=1,048)						6,224: Approx. 3% were treated in both eyes			
	Patients with resolved MO			28.5	Not reported									
	Patients with unresolved MO			8.7										

Study reference	Campochiaro 2014 [30]	Novartis 2017 [87]				McIntosh 2011 [23]
Mean duration between consecutive injections (weeks)	Not reported	All patients	TN	TnN (R)	TnN (other)	
		10.57	9.28	11.12	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).				
Adverse events						
Ocular events	4 severe ocular AEs were reported (BRVO and CRVO patients)	All ocular AEs	10.4% (109/1048)			Not reported
		Ocular serious AEs	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 [Δ]	Not reported			
		Conjunctival haemorrhage	0.57% (6/1048)			
		Vitreous haemorrhage	0.38% (4/1048)			

Study reference	Campochiaro 2014 [30]	Novartis 2017 [87]		McIntosh 2011 [23]
		Cataract	1.91% (20/1048)	
		Glaucoma	0.95%(10/1048)	
		Ocular hypertension (raised intraocular pressure >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)	
		Macular oedema	0.57% (6/1048)	
Systemic adverse events	13 severe systemic AEs reported including 2 deaths Lack of clarity about the incidence of remaining systemic events in patients with CRVO.	All systemic AEs	10.69% (112/1048)	Not reported
		Serious systemic AE	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)	

Study reference	Campochiaro 2014 [30]	Novartis 2017 [87]			McIntosh 2011 [23]
Health-related quality of life					
Mean change in health-related quality of life (NEI-VFQ 25 composite score) from baseline	Not reported	Time-point	Month 24	Month 36	Not reported
			-8.3 (15.47)	-49.3	
Natural history					
Baseline visual acuity	50.0 ETDRS letters	44.7 ETDRS letters			Initial VA generally poor (20/40) in all patients. Patients with ischaemic CRVO tend to have lower mean initial VA (20/200)

Study reference	Campochiaro 2014 [30]	Novartis 2017 [87]	McIntosh 2011 [23]
			Generally, initial VA decreases over time. Ischaemic CRVO is associated with lower subsequent VA over time.
Development and resolution of MO	Not reported	Not reported	MO resolution occurs in approximately 30% to 31% of non-ischaemic CRVO eyes by 15 months post-occlusion
			MO resolves in up to 73% of ischaemic CRVO by 15 months post-occlusion.
Development of NV	Not reported	Not reported	33% of non-ischaemic CRVO eyes develop NV by 12 to 15 months post-occlusion.
			Up to 20% of ischaemic CRVO

Study reference	Campochiaro 2014 [30]	Novartis 2017 [87]	McIntosh 2011 [23]
			eyes develop NV by 8 to 9 months post-occlusion
Development of NVG	Not reported	Not reported	NVG develops in 23% to 60% of ischaemic CRVO by 12 to15 months post-occlusion
Development of VH	Not reported	Not reported	VH develops in 10% of CRVO by 9 months post-occlusion
Conversion from NI-CRVO to I-CRVO	Not reported	Not reported	Up to 27% of non-ischaemic CRVO eyes convert to ischaemic CRVO within 10 weeks to 13 months post-occlusion
Fellow eye involvement	Not reported	Not reported	Bilateral RVO is present in 0.4% to 43% of CRVOs at presentation

Study reference	Campochiaro 2014 [30]	Novartis 2017 [87]	McIntosh 2011 [23]
			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

Abbreviations: BCVA, best corrected visual acuity; CASP, Critical Appraisal Skills Programme; CFT, central foveal thickness; CRVO, central retinal vein occlusion; ETDRS Early Treatment Diabetic Retinopathy Study; HRQOL, health-related quality of life; IVR, intravitreal ranibizumab; n/a, not applicable; NV, neovascularization; NVG, neovascular glaucoma; RVO, retinal vein occlusion; SD-OCT, Spectral Domain Optical Coherence Tomography TER, treat-and-extend regimen; TN, Treatment-naïve eyes; TnN(R), Treatment non-naïve (ranibizumab) eye; TnN(other), Treatment non-naïve (other ocular treatments) eyes; VH, vitreous haemorrhage

$^{\beta}$ Reported for primary treated eye

§Relates to clinical effect sizes and adverse events; ◊ Relates to baseline clinical data; ∞ Relates to resource use.

* Includes hypertension, (58.7% to 63.9%); hypercholesterolemia/hyperlipidemia, (23.9% to 37.0%); diabetes, (18.8 % to 24.8%); obesity, (7.6% to 15.3%)

Study reference	Campochiaro 2014 [30]	Novartis 2017 [87]	McIntosh 2011 [23]
[△] includes acute intraocular inflammation; uveitis (inflammation of the anterior chamber) and hypopyon			

4.3.4 Conclusion

Overall, there was limited evidence to adequately compare the long-term clinical 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.

4.4 Methods: model-based analysis

4.4.1 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).

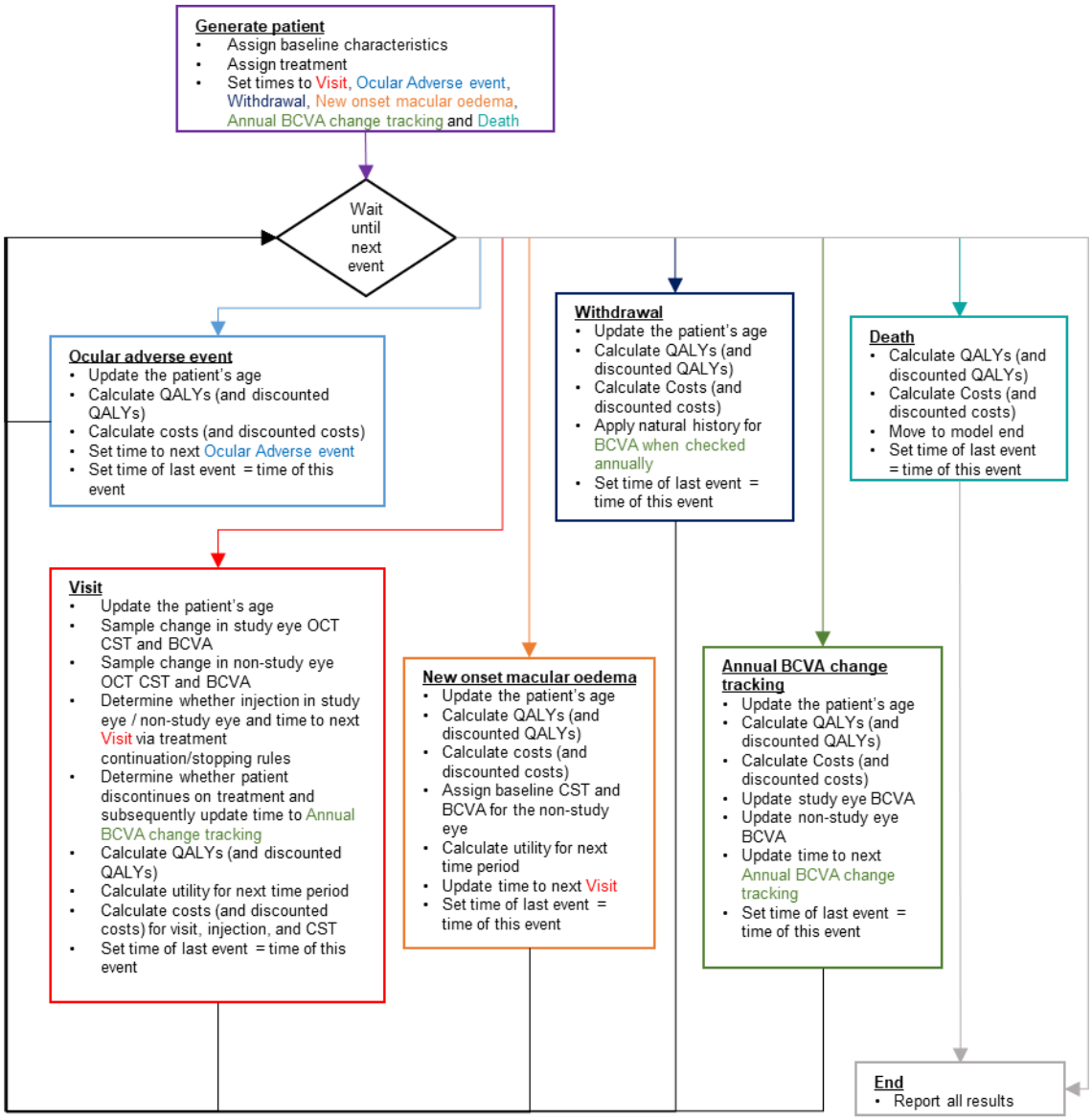
A discrete event simulation model has five key advantages in this application:

1. Health states are not required – each individual patient's visual acuity can be tracked over time on a continuous scale.
2. The study eye and non-study 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 2.5.1) from LEAVO can be used.
4. The follow-up visits 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 run in Simul8 Professional Edition (SIMUL8 Corporation, Boston, MA, USA). Once a patient is simulated, has baseline characteristics and an intervention assigned, their times to events are set – these times may be fixed or sampled from a distribution (see Section 4.4.2 for times to each event). 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 (Visit to ophthalmologist, Ocular adverse event, Withdrawal, New onset macular oedema in the non-study eye, Annual change in visual acuity, Death, Model End) is explained in more detail in the following subsections.

Figure 15: Health Economic Model structure



BCVA, Best Corrected Visual Acuity; CST, Central Subfield Thickness; OCT, optical coherence tomography; QALYs, Quality-Adjusted Life Years.

4.4.1.1 Model event: 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 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 rule as specified in the LEAVO study protocol.[83]

- All patients (except those who have withdrawn) attend visits and have a mandated injection at baseline, 4, 8, and 12 weeks.
- All patients attend visits at week 16 and 20, but only have an anti-VEGF injection if their BCVA>83 letters and they meet the retreatment criteria:
    - Decrease in visual acuity of ≥6 letters between the previous and current visit and an increase in OCT CST, or
    - Increase in visual acuity of ≥6 letters between the previous and current visit, or
    - OCT CST>320μm, or
    - OCT CST increase of>50μm from lowest previous visit
- From week 24 to 96, the same retreatment criteria as at week 16 and 20 are applied. If the patient does not meet the retreatment 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 the LEAVO study (PH, SS, AL, YY, MW) and guidance from the Royal College of Ophthalmologists.[8] The following rules are applied:

- If the patient has not had an injection since year one, they do not receive an injection and do not visit the ophthalmologist again.
- Within the first five years, the same retreatment criteria as in the LEAVO study are applied, to determine whether a patient has an injection, but the time to the next visit is increased to 12 weeks. If the patient does not meet the retreatment 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 five 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 to one year.

4.4.1.2 Model event: ocular adverse event

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

4.4.1.3 Model event: 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 receive treatment. As patients cannot withdraw more than once, the time to withdrawal is set to infinity.

4.4.1.4 Model event: new onset macular oedema in non-study eye

Patients may develop MO in the non-study 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 score for the non-study eye. This is sampled from the baseline characteristics for the study-eye, for patients of the same sex and similar age.

Patients who develop MO in the non-study eye are assumed to receive the same intervention in their non-study eye to which they were assigned for their study eye. Patients who are still on their assigned treatment (and have not discontinued due to treatment continuation rules or withdrawal) will receive treatment in both eyes, while patients who have discontinued or withdrawn from treatment in their study eye will receive treatment only in the non-study eye. Where a patient is still receiving treatment in their study eye, their initial visit for the non-study eye will occur at the same time as the next visit for the study eye. After this point, the same treatment continuation rule is applied to each eye to determine when the next visit for each eye occurs. Where a patient is not still receiving treatment in their study eye, the patient immediately has a visit for the non-study eye and follows treatment continuation rules for that eye only.

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

4.4.1.5 Model event: 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 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 to one year.

4.4.1.6 Model event: death

When a modelled patient dies, they move immediately to the Model End event.

4.4.1.7 Model event: end

Once a modelled patient reaches the Model End their costs and QALYs are reported.

4.4.2 Model inputs

4.4.2.1 Baseline characteristics

The model uses the baseline characteristics of LEAVO patients, to preserve the relationship between characteristics. Each modelled patient has the baseline age, sex, study and non-study eye BCVA and CST of one of 452 LEAVO patients for whom all of these variables were available at baseline. This approach is consistent with other simulation models in ophthalmology.[92]

4.4.2.2 Central subfield thickness and visual acuity

The retreatment 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 trial 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. Gender is found not be a significant predictor of CST or BCVA, so is excluded. Intervention is not a significant predictor of CST or BCVA, but is included to reflect numerical differences between the interventions.

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

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

Where

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

And

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

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, 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 only available at 12, 24, 52 and 76 weeks. To estimate CST and BCVA in the economic model, these covariates are used at week 12, 24, 52, 76 and 100 visits. For other visits, the following approach is used:

Weeks 4 and 8: CST and BCVA are calculated at week 12, and linear interpolation is used to estimate CST and BCVA at week 4 and week 8 visits.

Visits from 16 to 100, excluding weeks 24, 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 the LEAVO study, and so models which restricted these covariates to be the same at week 76 and 100 were compared to 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 and eyes from which treatment has ended or been withdrawn. The same assumption is used for treated eyes where the most recent injection was at least one year ago.

CST is not modelled for the non-study eye, unless the patient develops MO in the non-study eye. In this case, CST and BCVA for the non-study eye are modelled using the same approach as the study eye.

BCVA is modelled for untreated eyes using natural history data. The Beaver Dam study was a large population-based study that recorded BCVA in patients over five years This study reports[93] the letters gained or lost in the left and right eye for people aged under 55, 56-65, 65-74 and 75 and over and has been used in previous CRVO economic models.[49] Combining the right and left eye data, the annual average decrease in BCVA is -0.02 (standard error (SE): 0.04) for ages 55-64, 0.26 (SE: 0.04) for ages 65-74, and 0.76 (SE: 0.06) for ages 75+. There is no change for people aged fewer than 55. These data appear consistent with a study of the natural history in CRVO, which reports that increasing age was positively associated with visual acuity deterioration, and over two to five years, in eyes with non-ischaemic CRVO MO, 14% improved, 47% stayed the same, and 39% worsened.[94]

4.4.2.3 Ocular adverse events

The model considers the same ocular adverse events as are 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 IOP elevation. As relatively few patients experienced these adverse events in the LEAVO study (for example, 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 adverse event, using the data for all ocular adverse events (and applying a cost per average adverse event –see section 4.4.4.4). Where the date of the adverse event was missing, multiple imputation was used to impute the date based on the trial arm and whether an adverse event 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 adverse event and time to subsequent adverse events (p=0.128), and the number of subsequent adverse events was small, so the time to first adverse event is used as the time to first or subsequent adverse events in the model.

Although the time to adverse event 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 adverse event rates for any of the three interventions beyond the trial period (see Section 4.3), external validation is not possible. The Weibull is therefore used to model

the time to adverse events. All three interventions have the same shape parameter of 0.745, demonstrating that the probability of having an ocular adverse event decreases over time.

4.4.2.4 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). AIC and BIC are similar between parametric models, and no external validation was possible due to 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.

4.4.2.5 New onset macular oedema

Eight of 463 patients in LEAVO either had new onset MO recorded as an adverse event or received an anti-VEGF injection in the non-study eye. This is a small number of observations to fit parametric models to using survival analysis, it is instead 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.[95]

4.4.2.6 Mortality

As only 13 patients died in LEAVO, 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[96] for the general UK population[97] to represent the increased mortality associated with CRVO.

4.4.2.7 Number of simulated patients

A drawback of individual-level simulation approach is introducing first order uncertainty (also known as stochastic uncertainty), where mean cost and benefit outcomes may vary between different model runs even if the same input parameters for a given individual (patient) are used[98] To reduce this type of uncertainty, a total of 7,000 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. **Figure 28** in Appendix 6 shows that total costs and QALYs are stable when 7,000 patients or more are to be sampled.

4.4.3 Health-related quality of life

The model considers patients' BCVA over their lifetime. To include patients' utility 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, where 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 dataset that contains

both the clinical measure and the utility measure. The LEAVO study provided this dataset for BCVA and three measures of utility.

4.4.3.1 Health-related quality of life measures

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

1. National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25)[99]
2. EQ-5D[100]
3. EQ-5D V[101]

As specified in the health economic analysis plan and trial protocol, the NEI VFQ-25 was chosen as the primary measure with the EQ-5D (with and without vision bolt-on) used in secondary analyses.[9,12] The EQ-5D has been shown to perform poorly in eye disorders including age-related macular degeneration (AMD).[102] While it may not meet NICE reference case, non-EQ-5D utility values have been used in economic evaluations in many cases, including eye conditions.[103]

Each HRQoL questionnaire was collected at the six milestone visits of the LEAVO study; baseline, 12, 24, 52, 76 and 100 weeks. Utility scores from the NEI VFQ-25 were calculated using the Visual Function Questionnaire – Utility Index (VFQ-UI) for each patient.[104] This tariff uses six items (questions 6, 11, 14, 18, 20, and 25) representing six of the NEI VFQ-25 subscales.[105] The EQ-5D health states were converted on to the three level scale, as this is preferred by NICE, using the crosswalk.[106,107] Utility scores for the EQ-5D V were calculated by first taking the EQ-5D-3L score and then subtracting the vision bolt-on score as a utility decrement applied to the individual patient-level data.[101]

4.4.3.2 Mapping from BCVA 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 worse seeing eye (WSE), according to whether BCVA was higher in the study or non-study eye.

Standard statistical models are often a poor fit to the distribution of utility data[108] (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.

ALDVMMs were estimated with one to four components (classes). Models were fitted for the three utility measures. The independent variables used to predict utility within the components were age, sex, BSE BCVA and WSE BCVA. The interaction between BSE and WSE was considered as a variable, but its inclusion worsened model fit and therefore 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. Within each utility measure, the mean error, MAE and RMSE were generally similar for models with two, three and four components where component membership was predicted by BSE and WSE. The AIC and BIC, which penalises 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 EQ-5D and EQ-5D V have two components. The parameters for the models are shown in **table 32.**

The utility within 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:

$$a = \frac{u_u - u}{\sigma} \quad (4)$$

3) Parameter b is calculated as:

$$b = \frac{u_l - u}{\sigma} \quad (5)$$

4) Parameter c is calculated as:

$$c = \varphi(a) - \varphi(b) \quad (6)$$

5) Parameter d is calculated as:

$$d = \Phi(a) - \Phi(b) \quad (7)$$

6) If parameter c is between -0.00000001 and 0.00000001 parameters c is set to zero and d is set to one.
7) The expected utility within the component is calculated as:

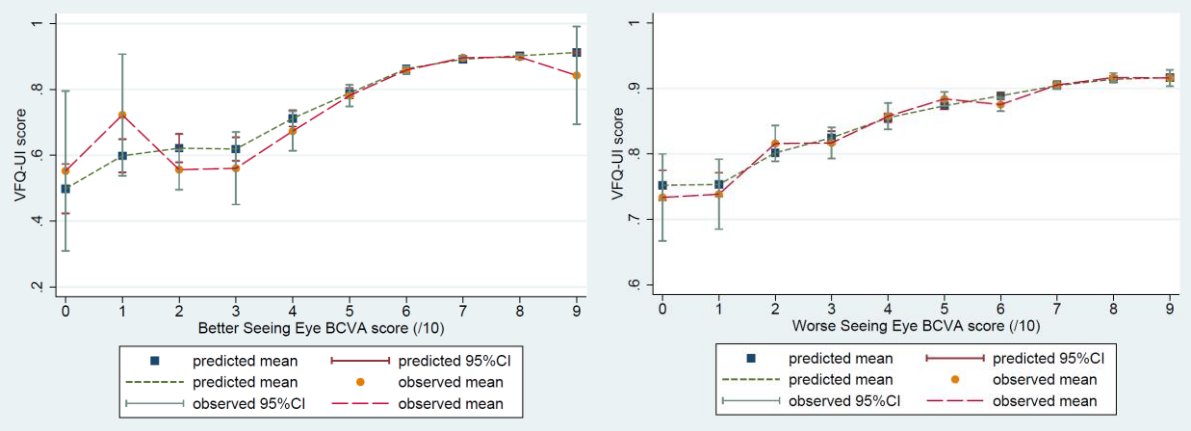
$$\left(1 - \Phi(a) + \left(\Phi(a) - \Phi(b)\right)\right) \times \left(u + \left(\sigma \times \frac{c}{d}\right)\right) + \left(u_l \times \Phi(b)\right) \quad (8)$$

Where u_u is the highest feasible utility next to one, 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 zero and standard deviation one, and Φ is the cumulative distribution function for the normal distribution with mean zero and standard deviation one.

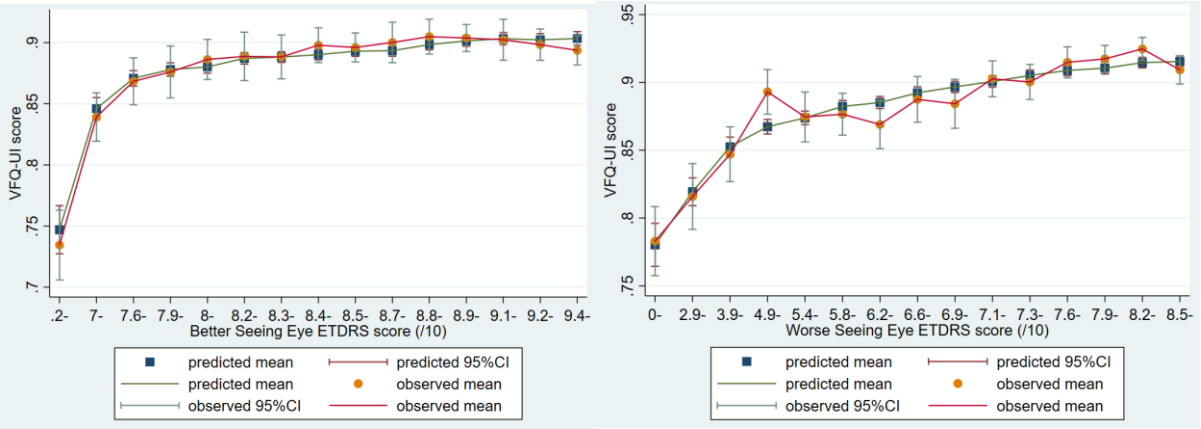
The probability of belonging to each component is calculated by the exponentiation of the product of the between-components by the individual patient's characteristics. For the last component this will equal one. The probabilities are then normalised by dividing by the sum of all probabilities.

The expected utility within each component is multiplied by the probability of belonging to each component. The sum of these gives the patient's utility. The relationship between visual acuity and utility for BSE and WSE is provided in Figure 16. An Excel tool which calculates a patient's utility score (VFQ-UI, EQ-5D, EQ-5D-V) based on our mappings is provided.[109]

Figure 16: VFQ-UI mapping, comparison of observed and predicted scores



CI, confidence interval; ETDRS, Early Treatment for Diabetic Retinopathy Study' VFQ-UI, Visual Functioning Questionnaire-Utility Index



4.4.4 Resource use and costs

Costs are calculated using GBP for 2017/18, where costs are not available for this year they are inflated using the hospital and community health services (HCHS) index.[110]

4.4.4.1 Intervention costs

The list price for the ranibizumab injection is £551.00 and for the aflibercept injection is £816.00.[111] 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. The list price for bevacizumab is £243.00, however, this is the cost for a large infusion vial of the drug.[111] As discussed in Chapter 2.6.3, during the LEAVO study the injections of bevacizumab were separated from the larger bottle into pre-filled syringes by the Liverpool and Broadgreen Pharmacy Aseptic Unit. [83] This compounding of the drug was deemed to be legal in a judicial review in 2018, which cited the price per injection as being £28[53] . It is assumed this 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.

4.4.4.2 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 optical coherence tomography examination (OCT) (if performed) and the drug cost of the injection.

The cost for the initial visit is £140.04 – a first multi-professional consultant-led outpatient ophthalmology visit. Subsequent visits cost £105.19 - a follow-up multi-professional consultant-led outpatient ophthalmology visit.[112] Patients who are receiving treatment in both eyes incur 1.5 times the visit costs, to represent clinician advice that approximately half of all patients would have both eyes treated in a single visit, while the other half would require two separate visits.

The cost for the OCT exam is £108.21 – a minor vitreous retinal outpatient ophthalmology procedure [H43]. This is incurred for each eye where re-treatment criteria are assessed.

4.4.4.3 Disease management costs

A bespoke resource use questionnaire was developed to capture resource use relating to the patient's eye condition during the 100 week study. Patients were asked to complete the questionnaire at baseline, 12, 24, 52, 76 and 100 weeks. Although resource use questionnaires can be vulnerable to recall bias, the questionnaire captured nine of the ten questions recommended as core items in standardised resource measures[113] collecting information relating to hospital admissions, healthcare contacts and continuous care and support of patients.

The model includes resource use for:

- Visits to the eye consultant, General Practitioner (GP), GP practice nurse, Accident and Emergency (A&E), eye A&E and optometrist
- Low vision appointments
- Phone 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 fewer than ten observations were excluded. Patients who developed new onset MO or who had an adverse event were excluded from the analysis to avoid double counting the resource use associated with these events.

Ordinary least squares regression was performed to estimate the relationship between WSE BCVA and resource use per three month period (higher BCVA predicted less resource use). Where 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 phone calls with healthcare professionals or number of hours of care received, over the previous three or six months. However, the duration of each visit was not recorded and therefore average estimates were used based on the NHS national reference costs or the costs of health and social care, where relevant.[110,112]

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 the patient was then used to adjust the cost by adding or subtracting the difference between the number of bed days reported by the patient 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 patient costs were only counted once using the information provided by the patient relating to length of stay. If no reason was recorded for the admission the cost of a non-elective excess bed day was used.[112]

4.4.4.4 Adverse event costs

As the model considers any ocular adverse event, modelled patients who experience ocular adverse events incur the average cost for an ocular adverse event, based on the proportion of patients in LEAVO experiencing each ocular adverse event. This is calculated by multiplying the number of each type of ocular adverse event by the cost for treating that ocular adverse event, and dividing the total by the number of patients experiencing ocular adverse events in LEAVO. The cost per ocular adverse event is the same for the three interventions, £317.96. Costs for each ocular adverse event are from NHS Reference Costs[112] or the British National Formulary.[111]

4.4.4.5 Blindness costs

Modelled patients may become blind when the BCVA score of both eyes is at 35 letters or below, consistent with the definition of severely sight impaired from the RNIB[114] and previous models in MO.[49,107] Blindness was tracked at Visit and Annual BCVA change, both of which are events where BCVA scores can change. BCVA scores can fluctuate through a patient's lifetime meaning that the patient can experience more than one blindness *episode* through their life.

Two sets of costs associated with blindness are defined from literature; one-off costs and recurrent costs.[107,115] Whenever 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, depression, and hip replacement.

Costs of blindness registration, daily community care, and weekly residential care are £60.50, £27.64, and £115.40 respectively.[110] Low vision rehabilitation and hip replacement unit costs are estimated at £153 and £4,170 respectively.[112] Low vision aids costs and annual costs of depression are estimated from Meads et al 2003 and TA460 respectively,[116,117] both of which are inflated to 2018 values using the hospital and community health services (HCHS) indices.[110]

The proportion of blind patients receiving each service are taken from Colquitt et al 2008.[115]

4.4.5 Addressing uncertainty

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

Patient Access Schemes (PASs) are in place for ranibizumab and aflibercept, offering a discount on the list price.[13,49] However, the level of discount is confidential so unknown. We therefore consider threshold analyses, to determine the level of discount that would be needed for the decision about the most cost-effective intervention to change.

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 (presented in Appendix 6) uses point estimate (mean) inputs, probabilistic sensitivity analysis simultaneously samples all uncertain inputs from their associated distributions. Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) 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% confidence intervals around the mean and total costs and QALYs are presented using the standard error, 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.[118]

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 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 to zero for a defined cost per QALY threshold.[118] Using the tutorial provided by Hatswell et al (2018) 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 as to 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.

4.5 Methods: within-trial analysis

4.5.1 Method of economic evaluation

The methods for the within-trial analysis were pre-specified in a health economic analysis plan prior to database lock.[84] The primary outcome for the within-trial health economic analysis was to establish the short-term cost-effectiveness of

- aflibercept compared to ranibizumab,
- bevacizumab compared to ranibizumab ,
- aflibercept compared to bevacizumab.

A fully incremental analysis (ranking the alternative treatment options by total costs and ruling out dominated and extended dominated options from the comparison) was also performed. The economic analysis used individual patient-level data collected as part of the LEAVO study. 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 intention-to-treat (ITT) population was used, including all of the patients randomised to each treatment group. Analyses were conducted using Stata version 15 (Stata 2017) and R (R 2019).

4.5.2 Health related quality of life

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

4.5.3 Resource use

The costing approach included identification of resource use, measurement and valuation.[116] Resource use associated with delivery of the intervention, hospital admissions, healthcare contacts, continuous care and support, concomitant medications and procedures and costs associated with blindness were measured.

4.5.3.1 Identification of resource use

The within-trial analysis included costs related to the patient's eye condition, as collected in the resource use questionnaire (see section 4.4.4.3), delivery of the intervention and concomitant medications.

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

Ocular adverse events were captured using the resource use questionnaire and from data relating to concomitant procedures and medications. To capture relevant costs associated with blindness, the costs of blind registration and low vision aids were applied to patients who became partially or severely sighted during the study. A patient was deemed to be partially or severely sighted if their BCVA score was less than or equal to 58 letters in both eyes.[113] These costs were applied once during the course of the study; the first time the patient met this criteria, as low vision aids are thought to be incurred biannually[48] It is assumed that the same proportion of patients 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.

4.5.3.2 Measurement of resources

The costs of medications were costed according to standard NHS sources where available.[111]

4.5.3.3 Valuation of resources

Unit costs, were applied to each resource use event at the individual patient level to calculate their total cost of resource use over the 100 week study period.

Intervention costs

The drug costs are the same as in the model-based analysis.[112]

4.5.4 Analytical methods

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

4.5.4.1 Missing data

Missing data can give misleading estimates of a within-trial cost-effectiveness analysis. A complete-case analysis uses only patients with no missing data in the key cost and benefit outcomes. This is undesirable as it reduces the sample size and affects the power of the study.[117] To handle missing data from the trial, the following assumptions were made:

- When a patient died, their utility scores at all subsequent milestone visits were set to 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 study, if a withdrawal appointment was carried out, cost and utility data were assigned to the nearest milestone visit and all subsequent costs were set to zero and utilities recorded as missing.

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

1. Proportion of missing data by treatment arm, at each follow-up period, to assess whether or not missing data differed by arm.
2. 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 one QALY imputation model included covariates age, gender, ethnicity, previous treatment, baseline utility, time since diagnosis, baseline BCVA in the study eye and baseline BCVA in the non-study eye. The year two QALY imputation model also included the imputed year one QALY data, as per recommendations by Faria et al.[117] The year one cost imputation model included the same covariates as the year one QALY model, as well as baseline resource use and site. The year two cost imputation model also included the imputed year one 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 with missing data, for which imputation was performed across all observations.

4.5.4.2 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.[119] The SUR model estimated the full variance-covariance matrix, which was further used to address uncertainty.[120] The regression equation for total costs included the randomisation arm. The regression equation for QALY included the randomisation arm and baseline utility to control for imbalances in baseline utility between treatment arms[119]. The model assumed a Normal distribution for both costs and QALYs.[120] Marginal effects in each treatment arm were calculated using the SUR without adjusting for baseline utility.

4.5.5 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,
- Standard error (SE) of the mean differential QALYs,
- Difference in mean total costs,
- SE of mean differential total costs,
- Covariance between total costs and QALY.

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

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

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 BNF (£243).
5. Complete case analysis – the CUA carried out using complete case data from the LEAVO study only.

6. 52 week analysis – the CUA carried out using imputed data up to the 52 week milestone visit from the LEAVO study.

4.6 Results: model-based analysis

4.6.1 Base case analysis

Results are presented in **table 20**. In the base case, bevacizumab generates the most QALYs, followed by ranibizumab and aflibercept. Aflibercept generatles the highest costs, followed by ranibizumab and bevacizumab. The confidence intervals 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 (is more effective and less costly than) both ranibizumab and aflibercept. The 95% confidence intervals for the net monetary benefit 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 (see

Figure 17) display the variation in the incremental costs and QALYs in the probabilistic samples. These are akin to presenting the standard deviation – while they display the dispersion in the set of values, they do not present the uncertainty around the mean. The 95% confidence intervals using the standard error present the uncertainty around the mean, and find that there is a difference in incremental QALYs for the three comparisons.

The CEAC (**figure 18**) shows that at £20,000-£30,000 per QALY, bevacizumab has the highest probability of being cost-effective (99.6% and 98.4%). 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.

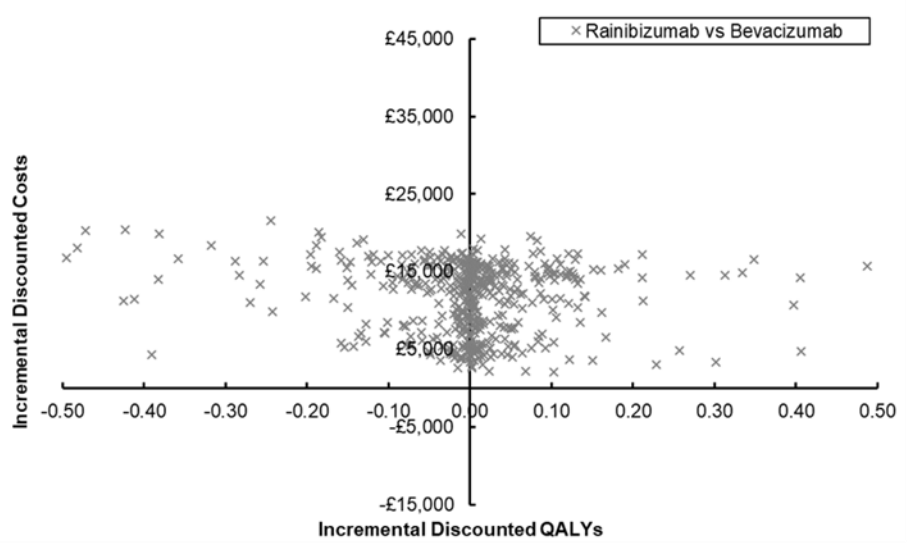
Table 20: Model-based analysis: base case and scenario analysis results

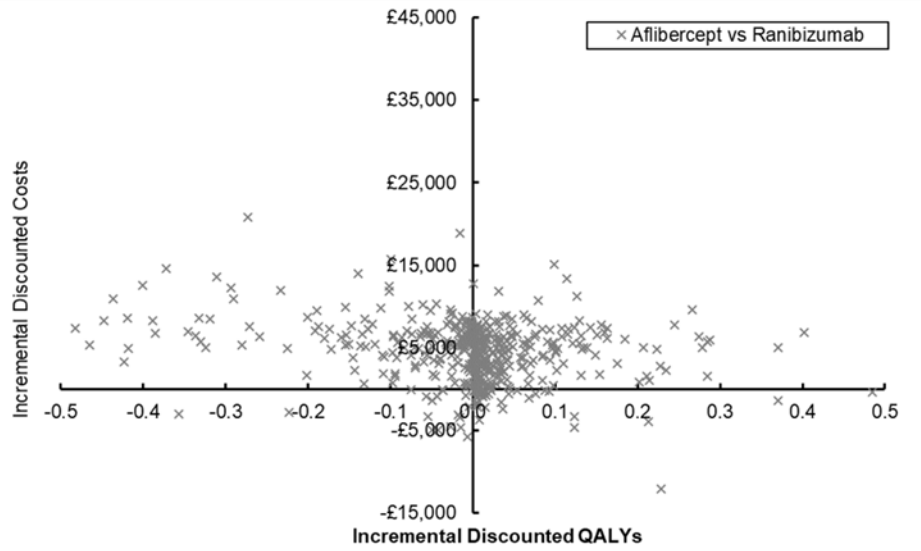
	Total Costs (95% CI)		Incremental Costs (95% CI)		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	(95% CI)
Base case analysis					
Bevacizumab	18,353 (17,782 to 18,925)	9.678 (9.572 to 9.785)			
Ranibizumab	30,226 (29,386 to 31,066)	9.635 (9.512 to 9.757)	11,873 (11,458 to 12,288)	-0.044 (-0.074 to -0.013)	Dominated (INMB: -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: -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)	4,800 (4,445 to 5,154)	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: -12,327 to -11,155)
Aflibercept	35,026 (33,990 to 36,062)	8.369 (8.289 to 8.449)	4,800 (4,445 to 5,154)	0.018 (0.000 to 0.035)	268,963 (INMB: -4,930 to -3,602)
Scenario analysis: 100 week time horizon					
Bevacizumab	6,349 (6,293 to 6,405)	1.641 (1.631 to 1.651)			
Ranibizumab	15,254 (14,962 to 15,545)	1.641 (1.631 to 1.651)	8,905 (8,650 to 9,161)	0.000 (0.000 to 0.001)	34,067,841 (217,070 to 10,420,696)

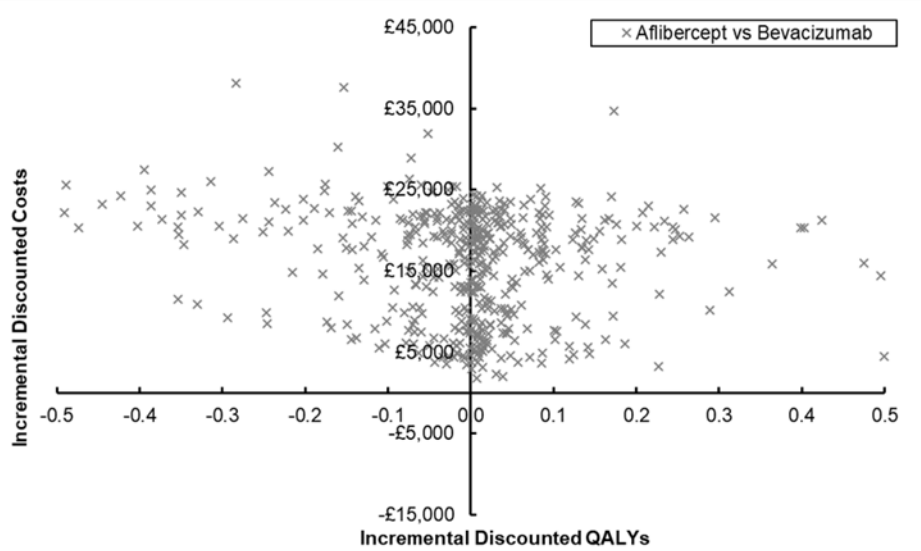
Aflibercept	18,844 (18,438 to 19,249)	1.646 (1.636 to 1.655)	3,590 (3,400 to 3,780)	0.005 (0.004 to 0.005)	793,348 (688,418 to 926,352)
Scenario analysis: Bevacizumab list price from BNF (£243)					
Bevacizumab	23,530 (22,884 to 24,176)	9.678 (9.572 to 9.785)			
Ranibizumab	30,226 (29,386 to 31,066)	9.635 (9.512 to 9.757)	6,696 (6,400 to 6,992)	-0.044 (-0.074 to -0.013)	Dominated (INMB: -9,084 to -6,937)
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: -16,636 to -12,905)

BNF, British National Formulary; CI, confidence interval; EQ-5D, EuroQol-5 Dimension; EQ-5D V, EuroQol-5 Dimension with Vision bolt-on; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit at £30,000 per QALY; QALY, quality-adjusted life year,

Figure 17: Model-based analysis: Cost-effectiveness scatterplots

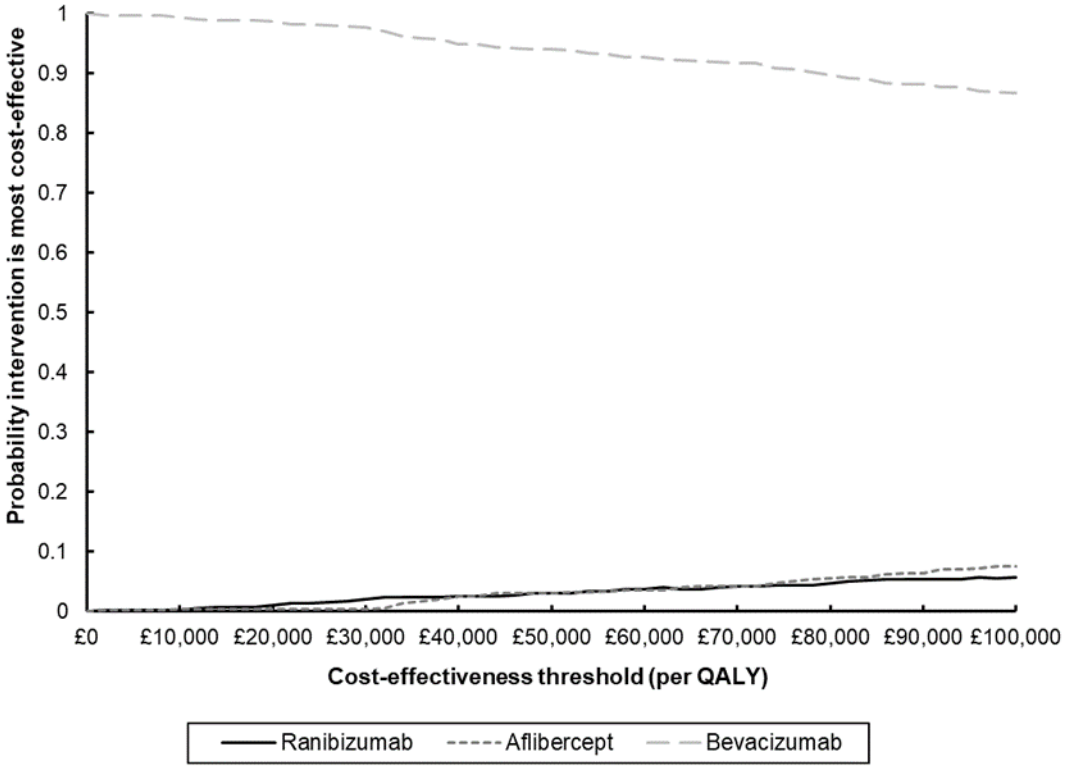






QALY, quality adjusted life year

Figure 18: Model-based analysis: Cost-effectiveness acceptability curve



The difference in QALYs is due to the difference in the effectiveness of the three interventions (see Chapter3, **table 4**) 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 21**. The study eye CST and visit costs are higher for bevacizumab than aflibercept and ranibizumab because patients require more injections. However, the drug costs are lower for bevacizumab because the cost for the injection is much lower.

Table 21: Model-based analysis: base case disaggregated costs

Costs (£) (95% Confidence Interval)	Ranibizumab	Aflibercept	Bevacizumab
1. Treatment costs			
a. Study eye Intervention costs	11,785 (11,387 to 12,184)	17,156 (16,582 to 17,730)	634 (614 to 654)
b.Study eye CST & visit costs	5,427 (5,351 to 5,503)	5,372 (5,299 to 5,444)	5,622 (5,542 to 5,701)
c. Non-study eye drug costs	771 (750 to 792)	1,051 (1,021 to 1,081)	40 (39 to 41)
d. Non-study eye CST & visit costs	268 (262 to 274)	249 (242 to 255)	276 (270 to 282)
2. Disease manage costs	9,588 (9,049 to 10,127)	10,058 (9,435 to 10,681)	9,283 (8,807 to 9,759)
3. Ocular AE costs	1,322 (1,238 to 1,405)	109 (101 to 117)	1,392 (1,301 to 1,483)
4. Blindness costs	1,065 (918 to 1,212)	1,031 (886 to 1,176)	1,107 (957 to 1,257)
Total costs	**30,226 (29,386 to 31,066)**	**35,026 (33,990 to 36,062)**	**18,353 (17,782 to 18,925)**
AE, adverse event; CST, central subfield thickness			

4.6.2 Scenario analyses

Table 26 presents the results of scenario analysis. In the scenarios using 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 EQ-5D, aflibercept generates the most QALYs followed by ranibizumab. This is different to 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 (£110,116 to £152,663). Using EQ-5D V, the results indicate the same trends, but the confidence interval for the incremental effectiveness of ranibizumab compared to bevacizumab contains zero, indicating the

difference is not statistically significant. The confidence interval around the incremental net monetary benefit (INMB) is presented for this comparison, as the ICER may contain dominated results where ranibizumab is less effective than bevacizumab. Aflibercept is more effective than bevacizumab and ranibizumab, but is not cost-effective.

Using a 100 week time horizon, as per the LEAVO study, bevacizumab is slightly less effective than ranibizumab and aflibercept, but the ICERs for ranibizumab and aflibercept versus bevacizumab are £34,067,841 and £2,610,554 per QALY. However, in this analysis, the 95% confidence interval for the incremental QALYs for ranibizumab versus bevacizumab contains 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 but the cost of bevacizumab has increased. However, bevacizumab remains significantly cheaper than ranibizumab and aflibercept, demonstrated by the confidence intervals for the incremental costs not containing zero. Bevacizumab continues to dominate ranibizumab and aflibercept.

In deterministic analysis using a five and ten year time horizon, bevacizumab remains the most cost-effective intervention at £20,000-£30,000 per QALY.

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

4.7 Results: within trial analysis

A total of 462 patients were included in the health economic analysis, with one patient excluded as they were randomised in error. Thirteen people died and 42 patients withdrew or were lost to follow-up during the study and their subsequent costs and QALYs adjusted as described in Section 4.5.1.

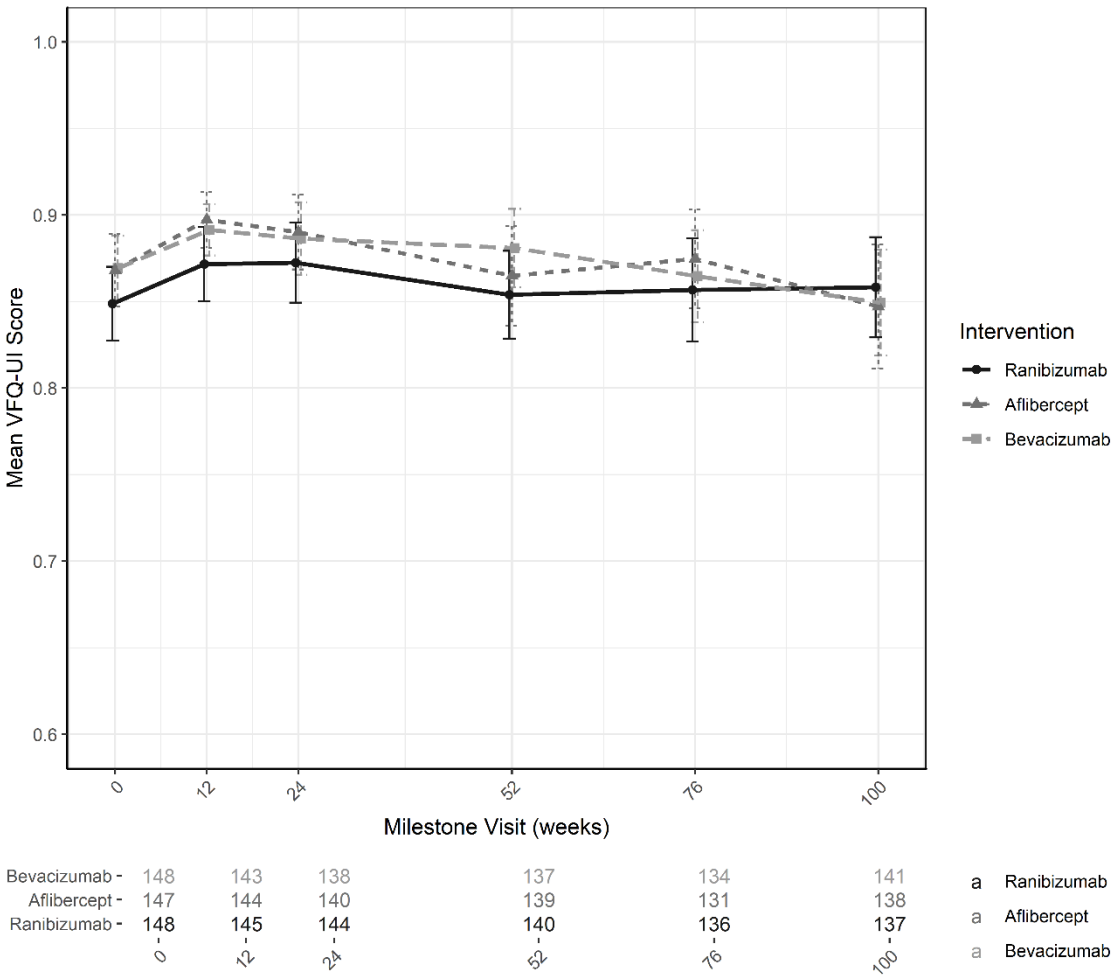
4.7.1 Data completeness

Over the 100 week data collection period, data were missing for some patients for baseline utility, QALY parameters for the three quality of life measures and total costs. The highest proportion of missing data was recorded for total costs at 56%. There were only small differences in the proportion of missing data between the treatment arms.

4.7.2 Utilities

Figure 19 summarises the mean VFQ-UI utility score at each milestone visit with 95% confidence intervals. 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.

Figure 19: Within-trial analysis: Mean utility scores calculated using VFQ-UI over 100 weeks



4.7.3 Costs

Table 22 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.

Table 22: Within-trial analysis: Disaggregated costs for complete cases and total costs based on multiple imputation at 100 weeks.

Cost per patient (£)	Ranibizumab Mean (SD); N	Aflibercept Mean (SD); N	Bevacizumab Mean (SD); N	Aflibercept vs Ranibizumab Mean (95% CI)	Bevacizumab vs Ranibizumab Mean (95% CI)	Aflibercept vs Bevacizumab Mean (95% CI)
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 (-116.66,215.4)	44.34 (-121.69,210.37)	-5.03 (-171.06,161)
Continuous Care and Support	7.11 (54.99);99	38.76 (172.27);88	10.43 (82.93);90	31.66 (-0.75,64.07)	3.32 (-28.89,35.54)	-28.33 (-61.5,4.83)
Health Care Contacts	729.36 (815.88);91	710.46 (920.25);92	740.14 (1,065.62);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 (-134.43,94.23)	35.15 (-79.37,149.67)	-55.24 (-169.76,59.28)
Intervention	10,991.74 (3,973.57);154	12,445.31 (4,231.59);154	4,784.99 (1,247.34);154	1,453.57 (687.9 to 2,219.23)	-6,206.74 (-6,972.41 to -5,441.08)	7660.31 (6,894.65 to8,425.98)
Total Costs	13,014 (3,605); 154	14,328 (3,773);154	6292 (3371);154	1,245 (421 to 2,070)	-6,760 (-7,546 to-5,973)	7,984 (7,209 to 8,759)

4.7.4 Base case analysis

In the base case analysis (see Table 29) the difference in mean total costs between aflibercept and ranibizumab was £1,245 (95% CI: 421 to 2070), between bevacizumab and ranibizumab arms was -£6,760 (95% CI: -7546 to -5973) and between aflibercept and bevacizumab was £7,984 (95% CI: 7209 to 8759). Bevacizumab was dominant (less costly and with no difference in benefit) compared to ranibizumab, with a probability of cost-effectiveness of 1.00 at the £20000 per QALY threshold. Aflibercept was more costly with a mean QALY difference of 0.004 (95% CI: -0.0430 to 0.0518) compared to ranibizumab with an ICER of £283,595 per QALY gained and a probability of cost-effectiveness of 0.04 at the £20,000 per QALY threshold. 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 £20,000 and £30,000 per QALY threshold.

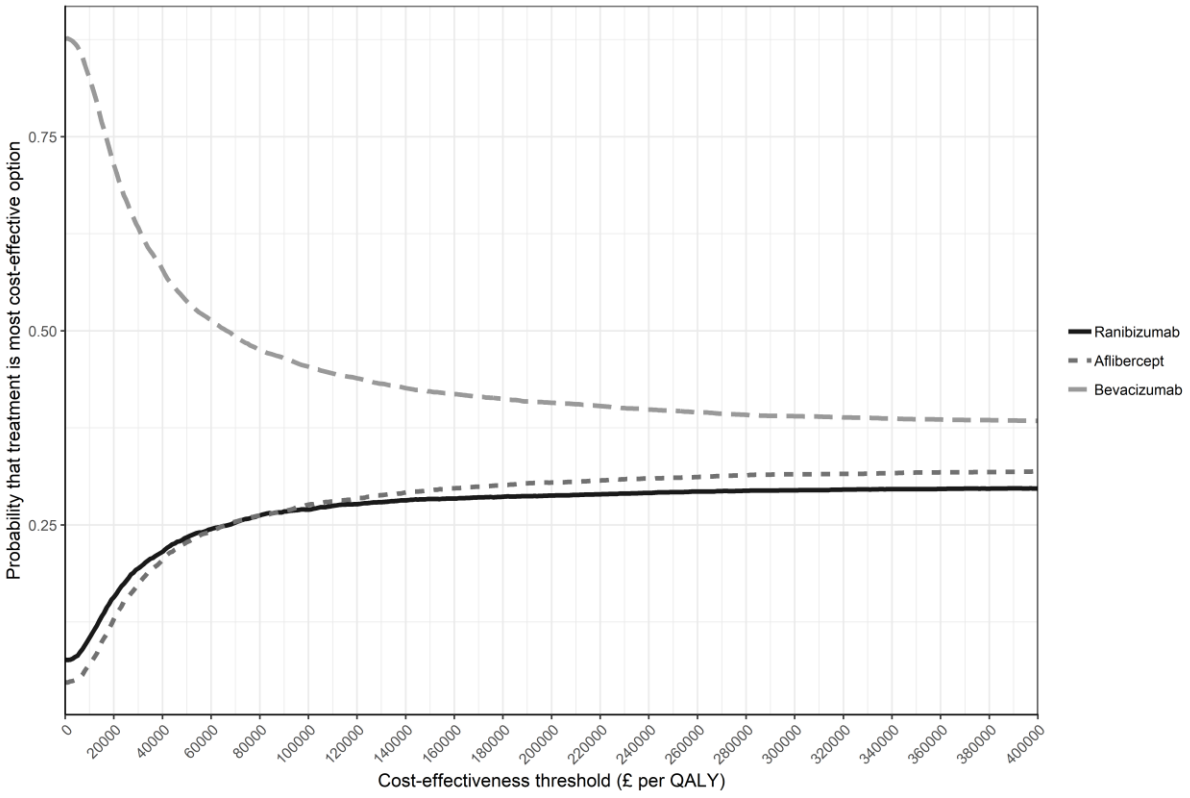
Table 23: Within-trial analysis: Base case results using imputed 100 week data based on the VFQ-UI [a] adjusted for baseline utility score

	Outcome	Intervention Mean (SD); N	Comparator Mean (SD); N	Difference [a] Mean (95% CI)	Probability CE £20000 (£30000)
Aflibercept vs Ranibizumab	**Cost (£)**	14,328 (3,773);154	13,014 (3,605); 154	1,245 (421 to 2,070)	-
	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 (£)**	6,292 (3,371);154	13,014 (3,605); 154	-6,760 (-7,546 to -5,973)	-
	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 (3,773);154	6,292 (3,371);154	7,984 (7,209 to 8,759)	-
	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)

4.7.5 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 option compared to alternative treatments, for a range of threshold values. Bevacizumab has the highest probability of being the most cost-effective of the three treatments for all thresholds considered. The confidence ellipses graphs shown in **figure 21** represents 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 to 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 to 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.

Figure 20: Within-trial analysis: Cost-effectiveness acceptability curve



4.7.6 Scenario analysis

The results from secondary analyses using the EQ-5D with and without the vision bolt-on to estimate QALYs are summarised in **table 24**. While the three HRQoL measures (VFQ, EQ-5D, EQ-5D V) generated slightly different results, the differences between the three interventions in terms of QALY was small, and uncertain in each analysis. The overall conclusion regarding the most cost-effective treatment remains unchanged. Bevacizumab consistently dominates ranibizumab and while aflibercept might be slightly more effective than bevacizumab and ranibizumab it was more costly, resulting in a low probability of cost-effectiveness in both cases at the £20,000 per QALY threshold.

Table 24: Within-trial analysis: Results from secondary analyses using EQ-5D with and without vision bolt on to estimate QALY [a] adjusted for baseline utility score

EQ-5D without vision bolt-on					
	Outcome	**Intervention Mean (SD); N**	**Comparator Mean (SD); N**	**Difference [a] Mean (95% CI)**	**Probability CE £20000 (£30000)**
Aflibercept vs Ranibizumab	**Cost (£)**	14,271 (3,857); 154	13,068(3,636);154	1,196 (406 to 1,986)	-
	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 (£)**	6,273 (3,384);154	13,068(3,636);154	-6,783 (-7,575 to -5,990)	-
	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 (3,857); 154	6,273 (3,384);154	8,035 (7,246 to 8,824)	
	QALY	1.560 (0.3801);154	1.535 (0.3759);154	0.008 (-0.0529 to 0.0683)	
	ICER (£)			104,1476	0.00 (0.00)
EQ-5D with vision bolt-on					
	Outcome	**Intervention Mean (SD); N**	**Comparator Mean (SD); N**	**Difference [a] Mean (95%**	**Probability CE £20000**

				CI)	(£30000)
Aflibercept vs Ranibizumab	**Cost (£)**	14,273 (3,720); 154	13,000 (3,661); 154	1,325 (499 to 2,151)	
	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 (£)**	6,268 (3,368);154	13,000 (3,661); 154	-6,713 (-7,499 to -5,926)	-
	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 (3,720); 154	6,268 (3,368);154	8,012 (7,232 to 8,793)	-
	QALY	1.516 (0.3856); 154	1.500(0.3757);154	0.0032 (-0.0837 to 0.0902)	-
	ICER (£)			248,3943	0.00 (0.00)

Results from the fully incremental analysis showed that bevacizumab dominates all alternative treatment options (less costly and more effective), and therefore, ranibizumab and aflibercept are ruled out by dominance.

Table 25 summarises the results from scenario analyses when a discount rate of 30% and 50% is applied to the drug costs of ranibizumab and aflibercept. These findings suggest that the within trial cost-utility base case analysis results are not sensitive to these discount rates. While the probability of aflibercept being cost-effective compared to 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 compared to ranibizumab and aflibercept was more costly and less effective compared to bevacizumab.

Table 25: Within-trial analysis: Results from scenario analyses using discount rates of 30% and 50% applied to aflibercept and ranibizumab reflecting patient access schemes available in the UK [a]adjusted for baseline utility score

Discount of 30% applied to aflibercept and ranibizumab drug costs					
	Outcome	**Intervention Mean (SD); N**	**Comparator Mean (SD); N)**	**Difference [a] Mean (95% CI)**	**Probability CE £20000 (£30000)**
Aflibercept vs Ranibizumab	**Cost (£)**	11,727 (2,900) ;154	10,893 (2,848) ;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 (£)**	6,227 (2,700) ;154	10,893 (2,848) ;154	-4,656 (-5,280 to -4,033)	-
	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 (2,900) ;154	6,227 (2,700) ;154	5,476 (4,837 to 6,116)	
	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					
	Outcome	**Intervention Mean (SD); N**	**Comparator Mean (SD); N**	**Difference [a] Mean (95% CI)**	**Probability CE £20000 (£30000)**
Aflibercept vs Ranibizumab	**Cost (£)**	10,042 (2,553) ;154	9,499 (2,538) ;154	497 (-71 to 1,053)	-
	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 (£)**	6,201 (2,419) ;154	9,499 (2,538) ;154	-3,288 (-3,842 to -2,734)	-
	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 (2,553) ;154	6,201 (2,419) ;154	3,809 (3,252 to 4,365)	-
	QALY	1.651 (0.2426)	1.666 (0.2374) ;154	-0.015 (-0.0618 to 0.0322)	-
	ICER (£)			Aflibercept is dominated	0.00 (0.00)

4.8 Summary of findings from the economic evaluation

4.8.1 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 assuming that bevacizumab vials cannot be split, incurring a higher cost per injection. The cost-savings associated with bevacizumab are due to the much lower drug cost. In order to have comparable costs with bevacizumab and therefore have a chance of being cost-effective, the PAS discounts on aflibercept and ranibizumab 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.

4.8.2 Main findings from the within-trial analysis

The within trial health economic analysis found that there is strong evidence that bevacizumab is considerably cheaper than ranibizumab and aflibercept even when potential discount rates are applied to the two licenced products. There was no evidence to suggest a difference in health-related quality of life between the three alternative treatments, regardless of the HRQoL questionnaire used to measure utility, however, the estimates of QALY difference are uncertain. Bevacizumab is the most cost-effective option compared to ranibizumab and aflibercept. Aflibercept is highly unlikely to be cost-effective in the short term (100 weeks) compared to 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.

4.8.3 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 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: £6,349, trial: £6,292), 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 a 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 excluding concomitant medications and procedures (although these make up less than £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 a patient 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 are receiving the intervention where they did not in LEAVO.

The model results follow the same trend as the trial, in that the number of injections was lower for aflibercept than for bevacizumab or ranibizumab, but the absolute number of injections in each arm is higher. The re-treatment criteria in the model dictates that patients will be retreated if their CST is above 320µm, and the CST data used in the model suggest that on average, bevacizumab and aflibercept patients have CST above this threshold throughout the trial duration. Variation between individual patients may have led to a greater proportion of patients within the trial having CST below the threshold than in the model. Alternatively, the difference may arise because the re-treatment criteria in the trial stipulated that patients should have CST above 320µm 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 CST above 320µm for other reasons who were not treated, but would be assumed to be treated in the model. Additionally, patients in LEAVO may have missed appointments, which would lead to decreased injection frequency.

There are also differences between the QALYs in the model 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 BSE or WSE did not correlate with EQ-5D scores below zero, and so the models 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, so includes the deaths of three patients for ranibizumab, six for aflibercept, and four for bevacizumab. The model instead links mortality to baseline age, sex and the presence of CRVO: since 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.[13,49] The within-trial analysis captures these costs and includes blind registration and low vision aid costs using the same estimates as the severely sighted patients. 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

5.1 Summary and interpretation of findings

5.1.1 Clinical effectiveness and side effect profile

The results of this prospective multicentre phase III randomised trial demonstrate that repeated intravitreal injections of the three anti-VEGF agents markedly improved 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 study was unable to demonstate that bevacizumab was non-inferior to ranibizumab as the lower 95% confidence interval extended beyond the non-inferiority margin of -5 letters. The results were consistent in that both the ITT and PP 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 it was non-inferior to the latter.
In clinical terms, the result confirms aflibercept aswell as ranibizumab use in macular oedema due to CRVO which was important to demonstrate as both are used widely in UK clinical practice but had not been directly compared previously in this condition. . Bevacizumab, on the other hand could be worse than ranibizumab and aflibercept or it could be no worse. Practically this means, 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 a patient 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 patients in each group achieving key secondary endpoints such as gain in 15 or more BCVA letters, or remaining stable i.e. experiencing less than 15 letters loss of visual acuity. The former means that for patients commencing therapy, there is a 45 to 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 advice from a patient perspective, to note that less than four percent of patients in the bevacizumab arm experienced a significant loss of vision of 30 letters or more, in keeping with data pertaining to ranibizumab and aflibercept in this and prior studies.[27–29,31]

As anticipated visual acuity improved rapidly during the initial monthly mandated injection phase but there was a small mean decrease in visual acuity that occurred across all 3 arms of the study

between weeks 16 and 24 which coincided with the pro re nata injection phase at week 16. Previous studies had employed a protocol of six mandated monthly injections from week 0 to week.[9,21,27,28,56] During the stage of study design, we reviewed available data and believed that four mandated injections would be sufficient as the increase in visual acuity had plateaued in the CRUISE study by four months.[9] This may have been due to the study enrolling a carefully selected population of non ischaemic CRVO, likely to respond well to therapy. However we now recognise that subsequent studies[27,28,56,57] which introduced broader and more generalisable eligibility criteria, indicate that the initial gain in visual acuity takes longer to maximise. Thus our findings suggest 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 patients at week 24 could have been some 3 or more letters higher and more in keeping with gains at 6 months in other studies.[27,28,56]

It is also worth noting that SCORE2[56] and other studies e.g. COPERNICUS[27,28] did not maintain such early gains through 1 and 2 years most likely because follow up in year two was too infrequent to identify and treat those patients who needed regular medication. Notably, the final gain in VA at week 100 compared to baseline is higher in LEAVO than any other previously reported study in this condition and could possibly have been even higher.

We believe this reflects the importance of timely monitoring in the second year of the study, which should initially be 4 to 8 weekly in keeping with the LEAVO protocol. Longer intervals of follow up in other studies likely led to loss of initial visual gains.[27,32,36] It is possible that 4 to 8 weekly follow-up could be extended in 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 study in that aflibercept group values were higher than ranibizumab 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 the baseline to 12 week mandated injection phase. However the CST increased by approximately 50µm over the next three visits as the number of injections performed reduced markedly. This was because intense treatment during the mandated phase meant retreatment criteria were frequently not met at visits 16 and 20 weeks leading to a rebound increase in CST by week 24, which closely mirrored the decrease in visual acuity. However, as patients entered the remaining 18 months of the study, their visits were regularly structured every 4 to 8 weeks resulting in patients who met criteria for retreatment being promptly treated. This meant 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 where OCT data did not closely reflect visual acuity changes.[56] A previously unreported finding was that a significantly greater percentage of patients in the aflibercept arm compared to ranibizumab arm had OCT CST <320um at weeks 52 and 100. This suggests that

aflibercept is more effective at resolving MO in the longer term compared to ranibizumab, a finding previously reported in exudative AMD and diabetic macular oedema.[41,52] Interestingly, bevacizumab was no less effective than ranibizumab in this regard unlike in other retinal disorders.[52]

Less injections were required for aflibercept compared to ranibizumab over 100 weeks, a difference that has only been previously reported in a treat and extend protocol.[55] 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 fewer aflibercept injections were required compared to bevacizumab. This likely reflects higher binding affinity of aflibercept to the VEGF molecule and prolonged duration of action. This coupled with a greater visual acuity gain and more patients achieving a normal thickness OCT at 2 years would be potential advantages of aflibercept over ranibizumab for MO due to CRVO.

The OCT morphological grading showed no meaningful differences between groups at baseline and 100 weeks.

FA 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.

There were no new safety concerns identified in the LEAVO study to suggest any discrepancies in the overall safety profile of the three anti-VEGF agent, in keeping with previous reports. The chance of severe visual loss whilst undergoing anti-VEGF therapy remained low, i.e. in the order of 5% over 2 years and has been noted in all previous studies.[9,27–29,55,56] This is typically due to development of an ischaemic CRVO i.e. an increase in severity of the original occlusion to a point where retinal blood inflow leading 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 co-incidentally limited the risk of neovascularisation .

When this study 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 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 being performed during the LEAVO study. In practice, only the comparative US SCORE2 study[56] and a small aflibercept versus bevacizumab trial have been conducted.[58] In addition the SCORE2 investigators re-randomised their patients at six months depending on whether they met predefined criteria of being good or poor responders.[57] Thus a comparison was not possible beyond six months and the comparative prevalence of adverse events of anti-VEGF agents used in the two studies up to six months showed no difference. No study to date in multiple conditions including nvAMD, DMO,[60]

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 this issue would be a barrier to the use of this drug in the National Health Service. The recent Judicial Review by Lord Justice Whipple emphasised this point and commented that ensuring enough compounding pharmacies were available to ensure the large scale safe production of significant amounts of the drug remained a key issue.[51]

After the study 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 study initiation, additional patients with RVO, the Barts Health / QMUL Lay Panel, and Barts Heath diabetic patients with 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 the difference was so small that it would be very unlikely to prevent them from carrying out their regular daily activities. All said they would be more likely to agree to this if a licensed alternative was available should they not respond as expected to bevacizumab and provision would likely need to be made for this.

5.1.2 Limitations

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

5.2 Generalisability (external validity)

The study was undertaken at a wide range of UK Ophthalmic Centres throughout the United Kingdom. The study eligibility criteria were purposely as broad as possible to ensure recruitment of a population that represented patients presenting for NHS standard care. Unlike prior studies, patients with visual acuity below 6/60 or a relative afferent pupillary defect were not excluded. The protocol was amended to extend the upper limit of VA from 74 (6/12) to 78 (6/9) letters to allow patients with MO but relatively good vision to enrol in the study 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 study, e.g. a patient could undergo cataract surgery if his/her clinician deemed this necessary. The 4 to 8 weekly second year follow-up regimen ensured first year visual acuity gains were maintained and we feel this was an important part of the study protocol for NHS centres to replicate. The centres involved in the study 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 study, no special expertise or equipment beyond sub-speciality retinal expertise was necessary. We believe the study is potentially applicable to all UK and

overseas ophthalmic centres. We do not believe there are any related outcomes that the trial did not assess that may affect applicability and we believe the two year primary outcome and follow-up intervals were appropriate. The concentrations of anti-VEGF therapy in the plasma after four weeks are immeasurably low and since patients did not receive injections after week 96 we would not anticipate any harms occurring beyond week 100 relevant to the study. The only exception to this might be pregnancy but in both cases in which this occurred in the study, these were followed to term with the delivery of normal neonates. Clearly, not all patients in clinical care will respond the same as the trial cohort but we would expect discrepancies only in magnitude rather than direction and mostly related to non-adherence to a robust treatment protocol. Overall the patient feedback from the study 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 study protocol.

5.3 Overall Evidence

5.3.1 Comparative Clinical Data

The only previous well powered comparison of anti-VEGF drugs for MO secondary to CRVO prior to the LEAVO study was SCORE2[56] which randomised 361 patients to aflibercept vs bevacizumab and treated monthly from baseline to month 5 (6 injections). The primary outcome was at 6 months. This differed to the LEAVO study where patients received monthly injections from baseline to month 3 (4 injections) followed by PRN treatment at mandated visit weeks 16 and 20 with milestone visual acuity assessments at 6 months. Larger mean BCVA letter gains were achieved in the first six months of SCORE2 compared to LEAVO, aflibercept: SCORE2 mean +18.9 vs LEAVO mean +13.4 (SD 16.4). This may be explained by the longer initial period of mandated monthly injections in SCORE2,[56] or 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) versus 74 (6/12) in SCORE2. It is unknown whether the initial BCVA gains in SCORE2 could have been maintained through two years as the initial patients cohorts were re-randomised at 6 months depending on good and poor response to initial therapy.[57] The CRYSTAL study was a prospective single arm study of ranibizumab therapy in CRVO with MO that followed patients for two years with at least an 8 week review in year two. Although it 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 targeting of patients in need of treatment is of key importance.[54] LEAVO is therefore 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.

5.3.2 Health Economics Analysis

The cost-effectiveness analysis found that bevacizumab was the most cost-effective intervention 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 that bevacizumab led to substantially lower costs. The finding that bevacizumab was the most cost-effective intervention was robust to scenario analyses varying assumptions and data inputs. If bevacizumab were 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 £5,561 per year compared with aflibercept or £4,546 compared with ranibizumab. If the estimated 5,700 people diagnosed with MO due to CRVO each year in England and Wales (Royal College of Ophthalmologists) were treated with bevacizumab instead of aflibercept, the NHS would save £31,697,700 within one year (£25,912,200 if treated with bevacizumab instead of ranibizumab). Since the cost savings are due to a difference in intervention costs, this result would hold across other healthcare systems, as long as the cost per injection for bevacizumab is lower than aflibercept and ranibizumab.

This study provides evidence on the cost-effectiveness of anti-VEGF treatment in MO due to CRVO, where 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 to bevacizumab in other retinal conditions (neovascular age-related macular degeneration and diabetic macular oedema). The cost-effectiveness findings for MO in the LEAVO trial are consistent with these findings.

The analyses adhered to good practice guidelines,[79,82,116,117] and had the strengths of being based on data from a well-conducted multicentre randomised trial with good retention rates over 100 week follow-up. A key strength of the economic evaluation is using three different HRQoL outcome measures, including both disease-specific (VFQ-UI and EQ-5D) 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 versus EQ-5D) **.** The argument is that generic measures are not sensitive to particular disease-specific improvements; and therefore, the VFQ-UI was seen as a better alternative for the LEAVO study population. In addition, bolt ons to generic measures such as EQ-5D-V was proposed as an alternative approach to retain comparability across different diseases areas while improving sensitivity. In this study, we used the three alternative approaches and 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. Using a discrete event simulation facilitates the use of a continuous BCVA scale, and avoids arbitrarily grouping patients. This enables detection of small differences in visual acuity, which are linked to utility and costs, to ensure the differences between the three treatments are reflected. The model structure further enables consideration of both eyes, and their relationship with utility. The utility mappings follow best practice guidelines[108] and up-to-date statistical methods to capture the

distributions of utility. The inclusion of age and sex as variables within the utility mappings improved the model fit. In this study 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 study 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 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 amounts of missing data in the health economic analysis, but, the multiple imputation model for the trial-based analysis suggests the results are robust. Resource use questionnaires are vulnerable to recall bias. However, in LEAVO study this was designed especially for the study. 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 complete case analysis provided similar conclusions and bevacizumab remained the most cost-effective option.

The primary outcome in LEAVO study concerned visual acuity in the study eye. The model-based analysis considered both the study and non-study eye and their relation to utility. However, consideration should be given to the relationship between these outcomes and the reality for patients – while clinical measures assess visual acuity in two eyes 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 assessment of visual acuity in the study eye, and this may explain why the differences in the utilities and QALYs between arms are 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 standard errors could have been used which is robust in the presence of correlation between observations for each individual. This does not change the estimated coefficients from the ALDVMM, only affects the standard errors used in the probabilistic sensitivity analyses.

Chapter 6: Conclusions

6.1 Implications for Healthcare

The LEAVO study was unable to demonstrate that bevacizumab was non inferior i.e. 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 was equivalent in clinical effectiveness to the licensed medications for the management of this condition. No differences were detected in side effect profile in this study, 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 impact on their regular daily activities as appraised in this study. 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 recognisable 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 better sighted eye. Therefore this finding is not applicable to other retinal conditions such as nvAMD and DMO where a larger proportion of patients have bilateral visual impairment.

Compared to 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 multi-technology 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 healthcare systems. However since the study could not demonstrate that bevacizumab was non-inferior to the licensed medication, the study results would need to be discussed in detail with patients, their representatives and fund holders before proceeding. The post study patient questionnaire suggests approximately two thirds of patients may be amenable to this approach assuming the licensed medications were available in reserve.

6.2 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, the key factors that would dissuade others and whether these could be mitigated against. This would likely require full involvement of patients, patient advocate groups and fund holders to determine if bevacizumab could be introduced in this way. Further larger scale clinical trials may also be justified in this condition.

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All authors reviewed, revised and approved the final version of the manuscript.

Philip Hykin* (Consultant Ophthalmic Surgeon) was Chief Investigator and was responsible for obtaining funding, study concept, study design, protocol development, data collection, analysis and interpretation, and for critical revision of this manuscript for important intellectual content.

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Publications

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). http://www.thelancet.com/protocol-reviews/14PRT-065.

Data Sharing Statement

Consent was not obtained for data sharing with a third party. The presented data are anonymized and risk of identification is low.. All data requests should be submitted to the corresponding author Mr Philip Hykin for consideration. Access to anonymised data may be granted following review to any researcher who provides an ethics approved study protocol and access will help achieve the aims of the protocol. Three years after the study has been published, the data will be deposited with the R&D department, Moorfields Eye Hospital.

Disclaimers

This report presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the MRC, NETSCC, the EME programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the EME programme or the Department of Health.

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Appendices

Appendix 1: LEAVO Study Group and Resource Centres

LEAVO Study Group

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

Table 26: The LEAVO Study Group

Sites	Principal Investigators
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 & Broadgreen University Hospitals NHS Trust, Liverpool.	**Michael Briggs**
University Hospital Southampton NHS Foundation Trust, Southampton.	**Andrew Lotery**
Royal Victoria Hospital 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 & Midlands Eye Clinic, 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 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, County Durham.	**Komala Vadivelu**
St James's University Hospital, Leeds.	**Martin McKibbin**
Ophthalmology Department, Hillingdon Hospitals NHS Foundation Trust, London.	**Sheena George**
Maidstone & Tunbridge Wells NHS Trust, Kent.	**Goncalo Almeida**
Central Manchester Hospital, Manchester University NHS Foundation Trust, Manchester.	**Yvonne D'Souza**
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 Hospital 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 & Norwich University 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,	**Philip Severn**

South Tees.	
Princess Alexandra Hospital, Harlow, Essex.	**Priya Prakash**

Resource Centres

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Appendix 2: 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 & 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 Foundaton Trust, London, UK), Vanessa Burgess*, NHS* Lambeth Clinical Commisssiong Group, London, UK), Alison Powling (Community Diabetes, Bartshealth NHS Trust, London, UK), Mrs Melba Ryde (lay representative). Data monitoring committee members: Sarah Walker (Chairperson, Oxford University, Oxford, UK), Consuela Moorman (Stoke Mandiville NHS Trust, UK),
Baljean Dhillon (Centre for Clinical Brain Sciences, University of Edinburgh).

Appendix 3: Additional Data Tables and Figures

Table 27: Complete study assessment schedule from baseline to week 100

	Screening	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28-48	Week 52	Weeks 56-72	Week 76	Weeks 80-96	Week 100	Withdrawal Visit
Variable treatment visits									4-8 weekly		4-8 weekly		4-8 weekly		13-97 weeks
Informed consent	X														
Inclusion/Exclusion criteria [X1 if on different day]	X	X1													
Randomisation		X													
Urine pregnancy test in women of child bearing age.	X														
Patient demographics, medical and ophthalmic history	X														
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Best corrected ETDRS visual acuity in both eyes [X2 = with refraction]	X2	X	X	X	X2	X	X	X2	X	X2	X	X2	X	X2	X2
Standard ophthalmic examination both eyes	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT both eyes	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Wide-angle or 7 field colour fundus photography	X									X				X	X
Wide angle or 7 field fundus fluorescein angiography	X													X	X
VFQ-25 and EQ-5D with and without vision 'bolt-on'		X			X			X		X		X		X	X
Resource use questionnaire		X			X			X		X		X		X	X
Treatment allocation guess form														X	X
Administer IMP [X3 = pro re nata treatment}		X	X	X	X	X3	X3	X3	X3	X3	X3	X3	X3		

Table 28: Summary of LEAVO study substantial amendments to the Protocol

Amend-ment No.	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 PIS	Substantial	24/07/2014	04/09/2014	N/A	**Protocol and PIS**: Changes to ensure 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, PIS, ICF Also includes minor amendments to the protocol	Substantial	27/02/2015	10/11/2014	N/A	**Protocol:** Changes to inclusion and exclusion criteria; treatment allocation guess form; retreatment criteria; criteria for restarting therapy; management of ischemic CRVO, neovascular glaucoma, angle or iris neovascularisation; expectedness; secondary outcome. PIS: To reflect that VA will form part of the routine eye exam; guidance on contraception ICF: To reflect new PIS
SA#3	New PI at existing site; removal of site; addition of new site;	Substantial	16/03/2015	17/02/2015	N/A	PIS: Amended following review of new SPCs; allows sites to use nurse injectors ICF: To reflect new PIS
SA#4	Adding Sites: Calderdale Royal Hospital, Leicester Royal Infirmary, Norfolk and Norwich University NHS Trust Cheltenham General Hospital	Substantial	N/A	02/06/2015	N/A	None
SA#5	Adding Sites: Hull Royal Infirmary, Gartnavel General Hospital, Hull Royal Infirmary, Western Eye Hospital, James Cook Hospital, Princess Alexandra Hospital, Aberdeen Royal Infirmary,New PI at existing site: Cheltenham General Hospital	Substantial	N/A	04/08/2015	N/A	None
SA#6	Changes to protocol; PIS; ICF	Substantial	14/03/2016	11/02/2016	16/05/2016	Protocol: Changes to inclusion and exclusion criteria; rescreening; injectors; statistical changes; miscellaneous

						PIS: Changes to clarify who performs the injections; who prescribes antibiotic drops ICF: To reflect new PIS
SA#7	New PI at existing site: Darlington memorial Hospital	Substantial	N/A	11/08/2016	N/A	None
SA#8	New PI at existing site: Canterbury Hospital	Substantial	N/A	19/06/2017	20/06/2017	None
SA#9	Change of SPC regarding Reference Safety Information	Substantial	02/08/2017	25/07/2017	22/08/2017	None
SA#10	New PI at existing site: Darlington memorial Hospital	Substantial	N/A	16/07/2018	16/07/2018	None
SA#11	New PI at existing site: Torbay Hospital	Substantial	N/A	04/09/2018	04/09/2018	None

Table 29: Last visit week of withdrawal patients

Week	Ranibizumab	Aflibercept	Bevacizumab	Total
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 30: Reason for and time to withdrawal

Date withdrawn	Date randomised	Weeks in trial	Reason for withdrawal	Trial arm
30/06/2015	09/04/2015	12	Health deterioration	
14/09/2015	24/06/2015	12	Participant no longer wishes to take part	Aflibercept
06/11/2015	10/09/2015	8	Unable to locate/ contact participant	
06/11/2015	25/09/2015	6	Participant no longer wishes to take part	
08/12/2015	08/12/2015	0	Other	
08/01/2016	31/03/2015	40	Other	

12/04/2016	19/05/2015	47	Participant no longer wishes to take part	
26/05/2016	01/09/2015	38	Participant no longer wishes to take part	Aflibercept
01/06/2016	23/12/2015	23	Participant no longer wishes to take part	
07/06/2016	13/10/2015	34	Adverse event	
21/06/2016	23/09/2015	39	Patient moving away from area	Aflibercept
22/07/2016	16/06/2015	57	Participant no longer wishes to take part	
29/07/2016	18/04/2016	15	Other	
19/08/2016	09/06/2016	10	Death of participant	
30/08/2016	29/01/2016	31	Unable to locate/ contact participant	Aflibercept
26/09/2016	03/11/2015	47	Health deterioration	
12/10/2016	17/06/2015	69	Patient moving away from area	
17/10/2016	28/08/2015	59	Participant no longer wishes to take part	
19/10/2016	11/12/2015	45	Participant no longer wishes to take part	
29/10/2016	18/02/2016	36	Death of participant	Aflibercept
31/10/2016	14/04/2016	29	Death of participant	
08/11/2016	25/04/2016	28	Participant no longer wishes to take part	Aflibercept

09/11/2016	08/04/2015	83	Unable to locate/ contact participant	Aflibercept
26/11/2016	26/01/2016	44	Participant no longer wishes to take part	
18/12/2016	13/06/2016	27	Death of participant	Aflibercept
03/01/2017	26/08/2016	19	Death of participant	Aflibercept
03/01/2017	26/08/2015	71	Health deterioration	Aflibercept
12/01/2017	17/09/2015	69	Unable to locate/ contact participant	Aflibercept
01/02/2017	13/04/2016	42	Participant no longer wishes to take part	
09/02/2017	06/11/2015	66	Participant no longer wishes to take part	
20/02/2017	23/10/2015	69	Other	Aflibercept
02/03/2017	28/04/2016	44	Participant no longer wishes to take part	
09/03/2017	22/10/2015	72	Death of participant	
10/03/2017	23/10/2015	72	Participant no longer wishes to take part	
21/03/2017	27/10/2015	73	Adverse event	Aflibercept
15/05/2017	03/03/2016	63	Death of participant	
25/05/2017	31/12/2015	73	Participant no longer wishes to take part	Aflibercept
19/06/2017	16/10/2015	87	Death of participant	Aflibercept

01/08/2017	12/10/2015	94	Death of participant	
05/09/2017	22/03/2016	76	Health deterioration	
14/09/2017	25/02/2016	81	Adverse event	
10/11/2017	14/11/2016	52	Participant no longer wishes to take part	Aflibercept
13/11/2017	02/06/2016	76	Unable to locate/ contact participant	
17/11/2017	21/10/2015	108	Unable to locate/ contact participant	
27/11/2017	14/06/2016	76	Death of participant	Aflibercept
04/12/2017	28/10/2016	57	Death of participant	
17/01/2018	28/10/2016	64	Death of participant	
01/03/2018	17/06/2016	89	Participant no longer wishes to take part	
29/03/2018	23/06/2016	92	Participant no longer wishes to take part	Aflibercept
05/05/2018	18/10/2016	81	Death of participant	Aflibercept
04/06/2018	10/10/2016	86	Patient moving away from area	Aflibercept
13/08/2018	24/11/2016	90	Adverse event	
13/09/2018	11/10/2016	100	Participant no longer wishes to take part	
05/10/2018	29/11/2016	96	Health deterioration	Aflibercept

13/11/2018	30/11/2016	102	Adverse event	
27/11/2018	04/11/2016	108	Unable to locate/ contact participant	

Table 31: Comparison of OCT macular volume at 52 and 100 weeks

Mean (SE) at screening		Mean (SE) (N) at 52 weeks Mean (SE) (N) at 100 weeks		Adjusted difference between groups (95% CI) at 52 weeks† Adjusted difference between groups (95% CI) at 100 weeks†
Aflibercept versus ranibizumab				
Aflibercept	Ranibizumab	Aflibercept	Ranibizumab	
12.3 (0.2)	13.0 (0.2)	9.1 (0.2) (N=140)	9.2 (0.2) (N=138)	-0.1 (-0.6, 0.4)
		8.6 (0.1) (N=133)	8.9 (0.1) (N=135)	-0.2 (-0.6, 0.3)
Bevacizumab versus ranibizumab				
Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab	
12.8 (0.2)	13.0 (0.2)	9.4 (0.2) (N=135)	9.2 (0.2) (N=138)	0.2 (-0.3, 0.7)
		9.1 (0.2) (N=135)	8.9 (0.1) (N=135)	0.3 (-0.2, 0.7)

†The linear mixed-effects model incorporates 455 participants (n=149 ranibizumab, n=153 aflibercept and n=153 bevacizumab and) with both CST and macular volume at either 52 weeks or 100 weeks.

Table 32: The Input Parameters for the Health Economic Models

Parameter	Distribution	Mean (standard error)	Source (mean)	Source for standard error
Intervention and related costs				
Ranibizumab injection	N/A	£551.00	BNF 2019	N/A
Aflibercept injection	N/A	£816.00	BNF 2019	N/A
Bevacizumab injection	N/A	£28.00	Judicial review (2018)	N/A
CST cost	Gamma	£108.21	Department of Health (2018) NHS codes BZ87A	Quartile data of the NHS codes Department of Health (2017)
First visit cost	Gamma	£140.04	Department of Health (2018)	

			NHS codes WF02B	
Follow-up visit cost	Gamma	£105.19	Department of Health (2018) NHS codes WF02A	
Costs associated with resource use				
A&E visit cost	Gamma	£160.23 (£9.34)	Department of Health (2018) Weighted average for NHS codes VB01Z to VB11Z	Quartile data of the NHS codes (weighted) Department of Health (2017)
Visit Cost of ocular A&E	Gamma	£118.02 (£2.67)	Department of Health (2018) NHS codes WF01B	Quartile data of the NHS codes Department of Health (2017)
Visit Cost of eye consultant	Gamma	£95.13 (£1.85)	Department of Health (2018) NHS codes WF01A	
Call cost to ophthalmologist	Gamma	£28.20 (£4)	Department of Health (2018) NHS codes WF01D	
Visit Cost of optometrist/optician	Gamma	£76.50 (£10.5)	Department of Health (2018) 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 (2018)	10% assumption around the mean
Visit Cost of practice nurse	Gamma	£17.79 (£1.78)		
Call cost to GP	Gamma	£28.00 (£2.8)		
Resource use parameters (3 monthly)				
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		
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 (2008)	10% assumption around mean
Percentage requiring hip replacement	Beta	5% (0.5%)	Colquitt et al (2008)	10% assumption around mean
Percentage requiring low vision aids	Beta	33% (0.05%)	Colquitt et al (2008)	Margrain et al (1999
Percentage requiring low vision rehabilitation	Beta	11% (1.1%)	Colquitt et al (2008)	10% assumption around mean
Percentage requiring residential care	Beta	30% (3%)	Colquitt et al (2008)	10% assumption around mean
Percentage requiring treatment for depression	Beta	39% (5.8%)	Colquitt et al (2008)	Galaria et al (2000)
Percentage requiring blindness registration	Beta	95 % (0.05%)	Colquitt et al (2008)	Owen et al (2003)
Cost of community care (annual)	Gamma	£10,060.95 (£1,006.10)	Curtis and Burns 2018	10% assumption around mean
Cost of hip replacement (annual)	Gamma	£4,170.00 (£417.00)	Department of Health (2018) Code HT14C	10% assumption around mean
Cost of low vision aids (one-off)	Gamma	£194.41 (£19.44)	Meads 2003, Curtis and Burns (2018)	10% assumption around mean

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	£6,000.80 (£600.08)	Curtis and Burns 2018	10% assumption around mean
Cost of treatment for depression (annual)	Gamma	£2,430.58 (£243.06)	NICE, 2017 (TA460)	10% assumption around mean
Cost of blindness registration (one-off)	Gamma	£60.50 (£6.05)	Curtis and Burns 2018	10% assumption around mean
Adverse events				
Cost of adverse event	Gamma	£317.96 (£2.58)	Department of Health (2018)	Weighted variance from NHS reference costs
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	Lognormal	0.83 (2.89)	Bertelsen et al (2013)	Calculated from confidence intervals
Female: aged 50-59	Lognormal	1.49 (1.86)	Bertelsen et al	Calculated from

			(2013)	confidence intervals
Female: aged 60-69	Lognormal	1.94 (1.27)	Bertelsen et al (2013)	Calculated from confidence intervals
Female: aged 70-79	Lognormal	0.94 (1.25)	Bertelsen et al (2013)	Calculated from confidence intervals
Female: aged 80 and over	Lognormal	1.04 (1.23)	Bertelsen et al (2013)	Calculated from confidence intervals
Male: aged 0-49	Lognormal	1.49 (1.88)	Bertelsen et al (2013)	Calculated from confidence intervals
Male: aged 50-59	Lognormal	1.71 (1.54)	Bertelsen et al (2013)	Calculated from confidence intervals
Male: aged 60-69	Lognormal	1.17 (1.3)	Bertelsen et al (2013)	Calculated from confidence intervals
Male: aged 70-79	Lognormal	1.24 (1.14)	Bertelsen et al (2013)	Calculated from confidence intervals
Male: aged 80 and over	Lognormal	1.26 (1.22)	Bertelsen et al (2013)	Calculated from confidence intervals
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	Normal	0.00069 (0.001)		

injection at 52 weeks			
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)	
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)	

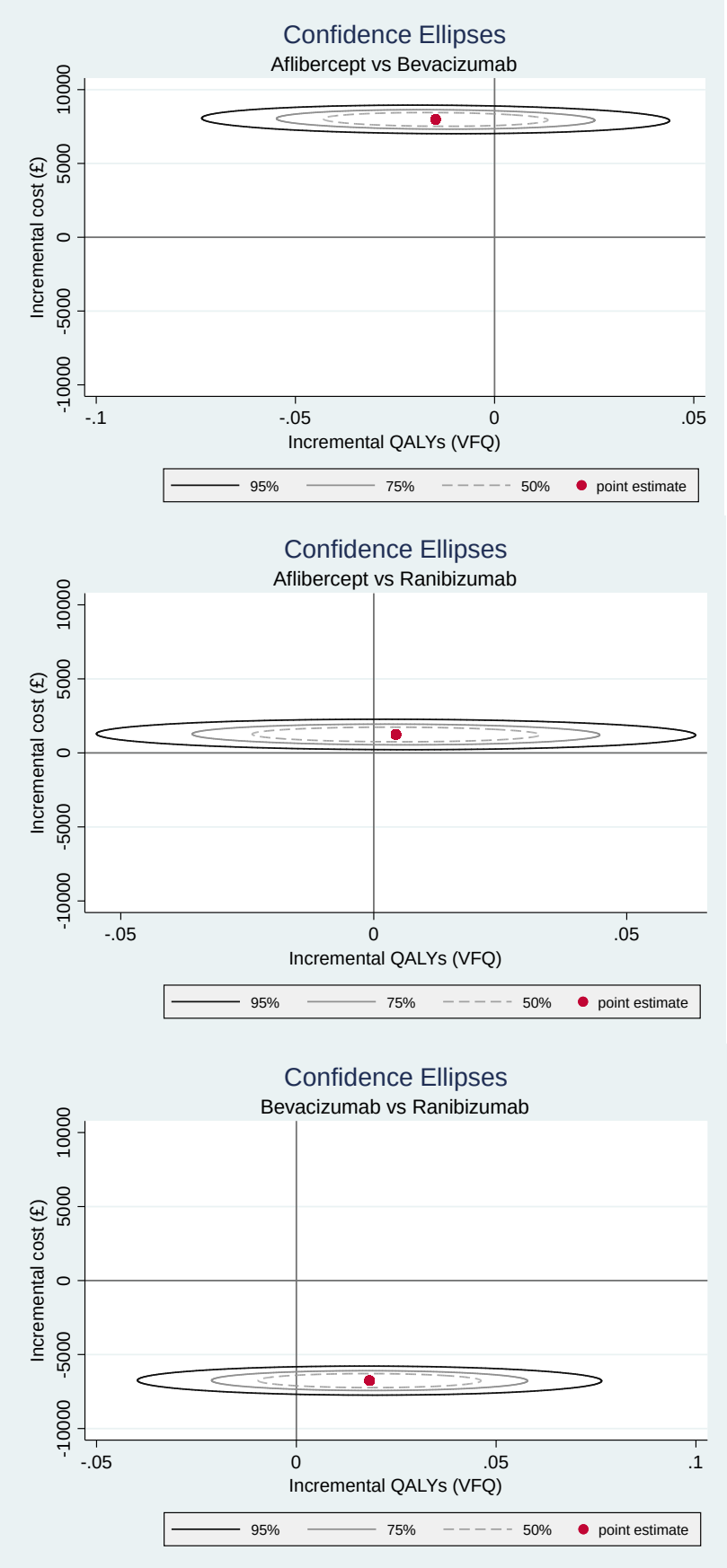
CST: number of injection at 24 weeks	Normal	-0.0594 (0.056)		
CST: number of injection at 52 weeks	Normal	0.06798 (0.027)		
CST: number of injection at 76+ weeks	Normal	0.06327 (0.022)		
CST: intercept	Multinormal	3.76348		
CST: slope	Multinormal	-2.75221		
Annual BCVA change				
Age 55-64: mean	Normal	0.0200 (0.002)	Klein et al (1996)	10% assumption around mean
Age 55-64: standard deviation	Normal	0.0400 (0.004)	Klein et al (1996)	10% assumption around mean
Age 65-74: mean	Normal	-0.2600 (0.026)	Klein et al (1996)	10% assumption around mean
Age 65-74: standard deviation	Normal	0.0400 (0.004)	Klein et al (1996)	10% assumption around mean
Age 65-74: mean	Normal	-0.7600 (0.076)	Klein et al (1996)	10% assumption around mean
Age 65-74: standard deviation	Normal	0.0602 (0.060)	Klein et al (1996)	10% assumption around mean
Utility parameters: VFQ-UI				
Component 1: BSE/10	Multinormal	-0.00025	Analysis of LEAVO	
Component 1: WSE/10		-0.00033		
Component 1: Age/10		0.00922		
Component 1: Male		0.00110		
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		0.25197		

membership: BSE/10			
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
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	
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	

A&E, Accident and Emergency; BCVA, best corrected visual acuity; BSE, Better Seeing Eye; CST, central subfield thickness; EQ-5D, EuroQol-Five Dimension; EQ-5D V, EQ-5D with vision bolt-on; GP, General Practitioner; N/A, Not applicable; VFQ-UI, Visual Functioning Questionnaire-Utility Index; WSE, Worse Seeing Eye

Figure 21: Within-trial analysis: Confidence ellipses VFQ; VFQ-UI measure



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 the 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, study number and detail of study eye and non-study eye to be refracted, but with no previous subject records or worksheet forms. Best corrected visual acuity (BCVA) was measured following refraction at screening, 12, 24, 52, 76 and 100 weeks (and unscheduled visits if they are to be considered as milestone visits including a withdrawal visit) in all subjects in both eyes. At all other visits VA was recorded by masked personnel using the refraction results found at the previous refraction visit.

4.1.Equipment and Room Set-Up

ETDRS chart R was used for refraction. The lightbox was illuminated with 2 Cool Daylight 20 watt fluorescent tubes. New tubes were kept on for 96 hours before use. Room lights were turned off, and the chart lights 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 (+/- 5 cm) from the floor. Full aperture trial lenses were used with a trial frame.

4.2.Refraction

The right eye was refracted first with the subject sat at 4 metres from the chart. The fellow eye was occluded with a pad and tape. At the baseline visit the initial acuity was measured with the subjects' own spectacles or unaided if the subject 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 6/60, (4 letters read correctly), or better refraction was performed at 4 metres. If the acuity was less than 6/60, refraction was performed at 1 metre. 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 improves or makes no difference to the VA. This was continued until the offered plus blurred the VA. Minus was added only if the subject read at least one more letter and the plus rechecked. The cylinder axis was rechecked using a round letter on a row 1 or 2 lines above the lowest row the subject can read. The cylinder power was rechecked using a round letter on the lowest row the subject can read. The sphere was refined as before offering plus, minus then plus. The refraction recorded was the 4 metre result. If the subject was tested at 1 metre +0.75 DS was taken from the result to adjust for the 4 metre distance. The procedure was repeated for the left eye.

4.3.Protocol for measuring ETDRS Acuities

BCVA was measured using ETDRS chart 1 for the right eye, chart 2 for the left eye. Subjects were not shown the charts until the test begun. Each eye was tested at 4 metres initially, even if the refraction was performed at 1 metre. The right eye should be tested first, followed by the left. The subject was seated at 4 metres 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 placed in the trial frame. What was required of the subject was then explained i.e. there are 5 letters on each row, they letters should be read slowly, there are no numbers on the chart, even if they are unsure of a letter they should guess, they can't go back and change their mind once they have attempted the next letter, they can move their head or eye to give the best possible VA as long as they don't lean forward.

The subject 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. Subjects were permitted to change their mind on a letter provided the subsequent letter has not already been read. If the subject gave a choice of 2 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 subject if a letter has been identified correctly. If the subject lost their place, the examiner pointed to the next line to be read, but then moved away from the chart. The subject was asked and encouraged to move onto the next line as long as they correctly identify at least one letter on the previous line. The test was stopped when the subject could no longer guess, provided mistakes had been made on previous guesses. Ideally the aim was for 4 letters missed on a row.

If a subject could not read 20 letters or more at 4 metres, the test was repeated at 1 metre. In this case, only the first six rows needed to be attempted. +0.75DS was added to the prescription in the trial frame to correct for the closer test distance. A rigid measuring device was used to ensure that the distance was correct, and care was taken to ensure that the patient did not move forward during testing. The visual acuity score was the number of letters read correctly at 4 metres, plus the number of letters read correctly at 1 metre. If the subject did not need to be tested at 1 metre, i.e. they read 20 or more letters at 4 metres, then the score was the number of letters read correctly at 4 metres, plus 30. The subject was given the credit for the 30 letters at 1 metre, 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 the subject could not read any letters on the ETDRS chart at 1 metre, then their ability to detect hand movements or light perception was measured.

4.4 Testing for Hand Movements Vision

The examiner should hold their hand steady approximately 0.5 metre in front of the subject with all fingers outstretched. A light should be shone directly on the hand from behind the subject. Ensure the fellow eye is completely occluded with a pad and tape. The examiner should move their hand from side to side or up and down at a constant speed of one back and forth presentation per second. The subject should be asked, “In which direction am I moving my hand?” This should be repeated 5 times. 4 out of 5 correct responses indicates hand movement vision. If not, test for light perception.

4.5 Testing for Light Perception / No Light Perception

Light Perception should be measured with an indirect ophthalmoscope in a darkened room. The indirect ophthalmoscope should be focused at 1 metre with the rheostat on maximum voltage. Direct the beam in and out of the eye at least 4 times, and ask the subject to respond when they see the light. Light perception should be recorded if the examiner is convinced that the subject sees the light. If not, the acuity is ‘No light perception’.

Appendix 5: Optical Coherence Tomography (OCT) & Fundus Fluorescein Angiography (FFA) Image Grading

Normal macula cross sectional architecture with Spectralis OCT is shown in Figure 22 and key abnormal morphological features in Figure 23.

Figure 22: Normal macula architecture with Spectralis OCT

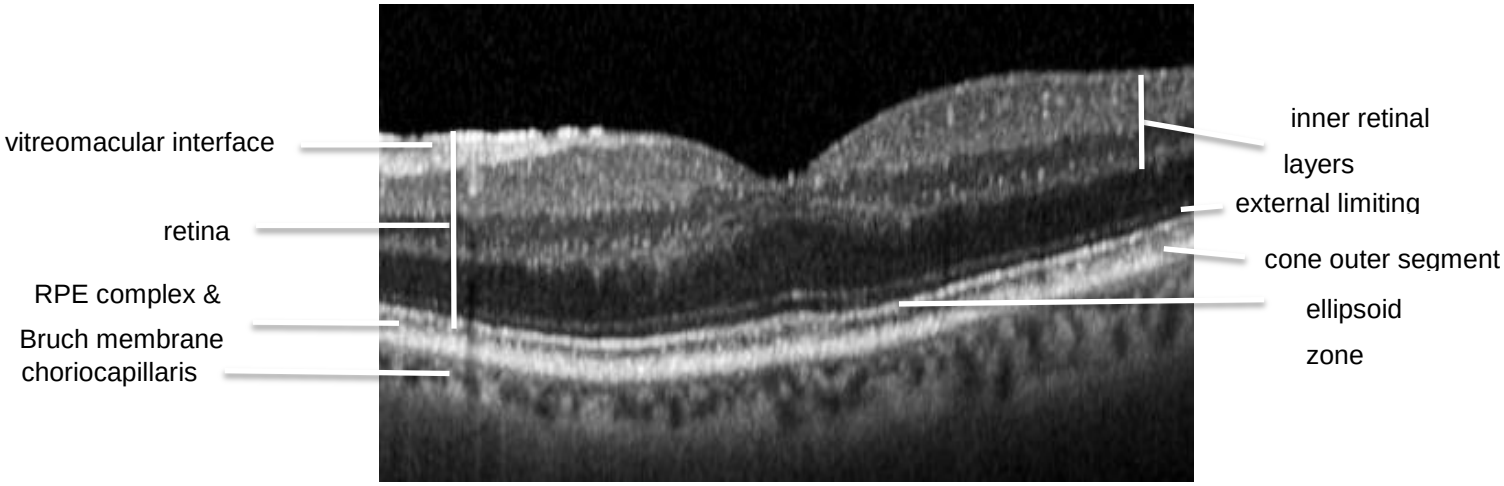
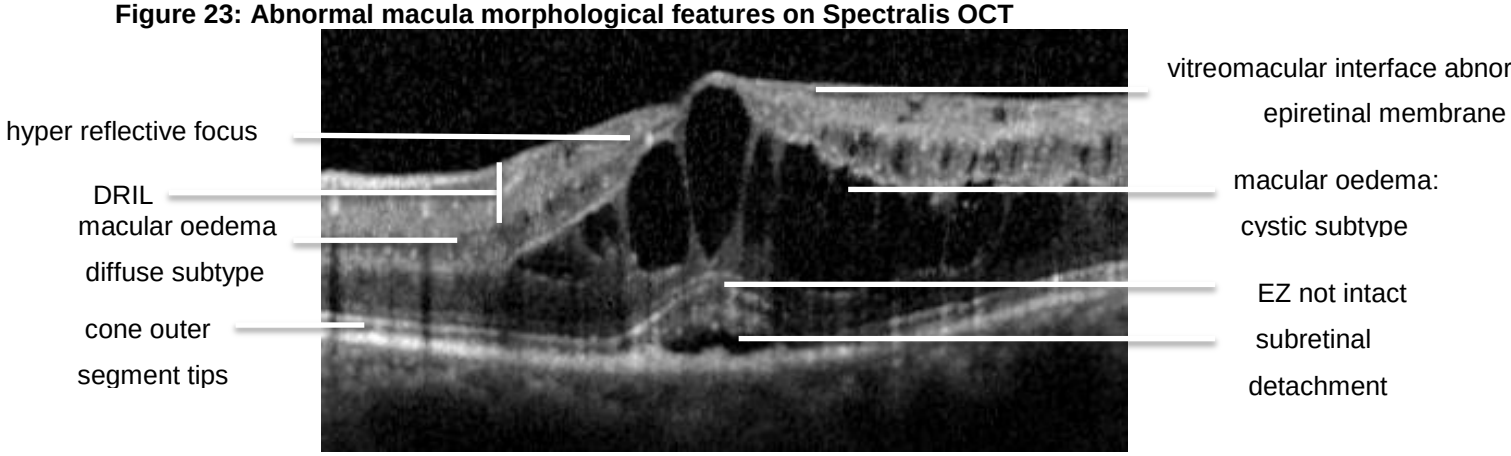


Figure 23: Abnormal macula morphological features on Spectralis OCT



5.1 Specific Grading of Individual Morphological OCT features

a. vitreomacular interface abnormality: i**. 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, a visible membrane tuft or edge. ii**. 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.
b. disorganisation of the inner retina layers (DRIL) 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 5 line scans. The total amount of DRIL in each line scan was added and the average extent per line scan calculated. If the total exceeded 50%, DRIL was considered positive. Lesser amounts and no DRIL were considered absent and if shadowing prevented assessment it was deemed ungradable. The averaged horizontal extent of DRIL per line scan was recorded.
c. macular oedema (MO) was classified as i**. DRT** (diffuse retinal thickening) defined as sponge-like retinal swelling with reduced intra-retinal reflectivity and the absence of hypo reflective spaces. ii. **CMO** (cystoid macula oedema): defined as intra-retinal cystoid spaces of low reflectivity with highly reflective septa separating cystoid-like cavities. Intra-retinal cysts were further defined based on the greatest horizontal diameter of the largest cyst (small cysts, <250 mm, medium cysts ≥250 mm and <500 mm, and large cysts ≥500 mm. **iii. the mixed** pattern was graded present if DRT and CMO were present together.
d. hyper reflective foci intraretinal abnormally bright dots distributed throughout all retinal layers, without a characteristic intra-retinal location and optimally visualised under 'black on white' options. Any number of HRF were graded as 'present' and 'absent' if none were visible[M13,M14]
e. external limiting membrane (ELM)
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 due to shadowing of oedematous retina.
f. ellipsoid Layer (EZ): the ellipsoid layer 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 defined as disrupted or complete absence of the band based on continuity under high contrast settings, or ungradable due to shadowing of oedematous retina.
g. cone outer segment tips (COST): the COST line was defined as the hyper reflective band between the RPE 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.

h. subretinal detachment (SRD)

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.

5.2 Fluorescein angiography grading

5.2.1 Standard fluorescein angiography grading

The standard 13 sector ETDRS retinal grading grid is shown in 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.

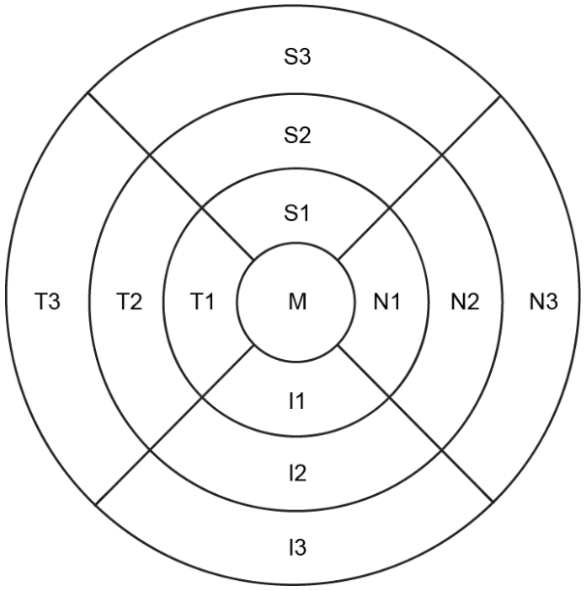
Figure 24:: 13 Sector ETDRS retinal grid for grading retinal non-perfusion

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, S1to 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 as shown 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 to 25%					
26 to 50%					
51 to 75%					
76 to 100%					



5.2.2 Novel concentric ring template for calculating retinal non perfusion

The novel concentric ring retinal template for grading non-perfusion is shown in **figure 25**. It was modified to use a concentric ring template suited to the central Optos ultra-widefield image. The superior and inferior segments of Ring 3 and 4 which are usually ungradable were removed to ensure consistent measurements. Each cell of the above grid was individually graded by determining whether the area of retina within the sector was perfused or not. A glassy, homogenous appearance to the retina with pruning or absence of retinal capillaries was used to confirm a diagnosis of non-perfusion and each cell was either graded as 'ischaemic' i.e > 50% of total area non perfused or 'perfused' i.e. <50% of total area non perfused.

Figure 25: Novel concentric ring retinal template

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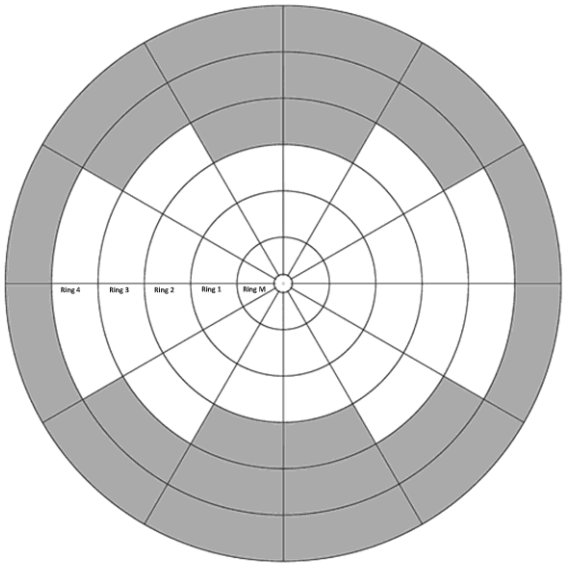

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