A multicentre double-masked randomised non-inferiority clinical trial comparing the clinical and cost-effectiveness of intravitreal ranibizumab (Lucentis), aflibercept (Eylea) and bevacizumab (Avastin) for Macular Oedema due to Central Retinal Vein Occlusion (LEAVO)

Health Economic and Decision Modelling Analysis Plan

Abualbishr Alshreef
John Brazier
Edith Poku
Philip Hykin
Sobha Sivaprasad

School of Health and Related Research, University of Sheffield,
Regent Court,
30 Regent Street, Sheffield, S1 4DA
Email: a.o.alshreef@sheffield.ac.uk

Investigators

Health Economist:

Name: Mr. Abualbishr Alshreef
Address: School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
Email: a.o.alshreef@sheffield.ac.uk
Phone: 0114 222 0673

Lead Health Economist:

Name: Prof. John Brazier
Address: School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
Email: j.e.brazier@sheffield.ac.uk
Phone: 0114 222 0726

Systematic Reviewer:

Name: Dr. Edith Poku
Address: School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
Email: e.poku@sheffield.ac.uk
Phone: 0114 222 0692

Chief Investigator:

Name: Mr. Philip Hykin
Address: Moorfields Eye Hospital.
162, City Road, London, EC1V 2PD.
Email: Philhykin@aol.com

Co-lead:

Name: Miss Sobha Sivaprasad
Address: Moorfields Eye Hospital & UCL Institute of Ophtalmology.
162, City Road, London, EC1V 2PD
Email: sobha.sivaprasad@nhs.net

Chair of Trial Steering Committee:

Name: Miss Susan Downes
Address: Consultant Ophthalmologist, Oxford Eye Hospital,
Oxford University Hospitals
West Wing, John Radcliffe Hospital, Headley Way, Oxford, OX3 9DU
Email: susan.downes@ouh.nhs.uk

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1. BACKGROUND

This study compares three types of drugs [intravitreal ranibizumab (Lucentis), aflibercept (Eylea) and bevacizumab (Avastin)] used for treating people with an eye disease that often leads to poor vision. The eye disease is called central retinal vein occlusion (CRVO), which leads to excess fluid at the back of the eye, called macula oedema (MO). Around seven thousand patients every year in England and Wales are affected by this condition. The cause is unknown in the majority of cases, but likely factors include high blood pressure, diabetes and glaucoma. Ranibizumab, which works by tightening blood vessels to prevent them leaking, shown to reduce the fluid at the macula and improve vision. This study will determine whether bevacizumab and aflibercept work as well and are as safe as ranibizumab in improving vision for people affected with this condition. It will also determine whether aflibercept can be given less frequently than ranibizumab and whether therefore either it or bevacizumab would result in a significant cost saving if used in the NHS.

This Health Economics and Decision Modelling Analysis Plan (HEDMAP) outlines in detail the planned procedure for conducting the Health Economic Evaluation sub-study of the LEAVO trial.

2. THE DECISION PROBLEM

2.1 Aims and objectives

The primary objective of the health economic evaluation is to estimate the long-term cost-effectiveness of aflibercept (Eylea) and bevacizumab (Avastin) versus ranibizumab (Lucentis) using decision analytic modelling techniques.

A secondary objective is to calculate the short-term cost-effectiveness of aflibercept (Eylea) and bevacizumab (Avastin) compared to ranibizumab (Lucentis) in a within-trial economic evaluation (first 2 years after the initiation of the treatment).

2.2 Type of RCT, frequency and duration of follow-up

This is a phase III randomised trial with a parallel design. Participants in all three study arms will be seen at weeks 0, 4, 8, 12, 16, 20 and 24. Subsequently, participants will be seen every 4 weeks until week 96 if retreatment criteria are met. If retreatment criteria are not met at three successive visits from week 24 onwards, the visit interval will be increased to 8-weekly until week 96. Participants will also be reviewed after 100-weeks of study inclusion.

2.3 Population

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

The trial population, from which the study sample is drawn, is further defined to be adults aged 18 year or over, of less than 12 months duration who attend the 38 ophthalmology centres in the UK with expertise in retinal disorders and a proven track record in effective research.

Only one eye per patient will be included in the trial. In subjects with both eyes meeting the eligibility criteria, then the 'worst-seeing eye' will be enrolled.

2.4 Interventions (investigational treatments)

- **Arm A: Treatment:** An intravitreal injection of Aflibercept (Eylea, Bayer) (2.0mg/5µl) will be administered at baseline, 4, 8 and 12 weeks. After this the retreatment criteria is ascertained (see Protocol section 8.13).
- **Arm B: Treatment:** An intravitreal injection of Bevacizumab (Avastin, Roche) (1.25mg in 50ul) will be administered at baseline, 4, 8 and 12 weeks. After this the retreatment criteria is ascertained (see Protocol section 8.13).

2.5 Comparator (standard care)

- **Arm C: Control:** An intravitreal injection of Ranibizumab (Lucentis, Novartis) [0.5mg/50ul] will be administered at baseline, 4, 8 and 12 weeks. After this the retreatment criteria is ascertained (see Protocol section 8.13).

2.6 Sample Size, Inclusion and Exclusion Criteria

2.6.1 Sample Size

Allowing for 15% missing data at 100 weeks, 459 patients will be randomized to the three arms (equal allocation ratio; 153 per arm) for the CRVO patient group. Approximately 40 sites will be opened and recruit into this study. It is anticipated that 459 participants will be recruited over an 18 months period.

2.6.2 Inclusion Criteria

1. Subjects of either sex aged ≥ 18 years.
2. Clinical diagnosis of centre-involving MO due to CRVO
3. CRVO of ≤ 12 months duration
4. Worst-seeing eye, if both eyes are affected by CRVO of ≤ 12 months duration
5. Best corrected visual acuity in the study eye ≥ 19 and ≤ 73 early treatment diabetic retinopathy study (ETDRS) letters (approximate Snellen Visual Acuity (VA) 3/60 to Snellen VA 6/12).
6. Best corrected visual acuity in the non-study eye ≥ 14 ETDRS letters (approximate Snellen VA ≥ 2/60.
7. Spectral-domain optical coherence tomography (SD-OCT) central subfield retinal thickness > 300μm predominantly due to MO in the study eye
8. Media clarity, pupillary dilatation and subject cooperation sufficient for adequate fundus imaging of the study eye
9. In cases of bilateral CRVO, where both eyes are potentially eligible, the worst-seeing eye will be recruited unless the patient prefers otherwise

2.6.3 Exclusion Criteria

The following apply 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 previously documented diabetic retinopathy or diabetic macular oedema.
4. Moderate or severe non proliferative diabetic retinopathy (NPDR) or treated and untreated PDR or macular oedema in the non-study eye. 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- local vascular endothelial growth factor (VEGF) drugs.
6. Active iris or angle neovascularisation, neovascular glaucoma, untreated Neovasularisation Disc (NVD), Neovascularisation elsewhere (NVE) and vitreous haemorrhage or treatment for these conditions in the last 3 months.
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).
9. Uncontrolled blood pressure defined as a systolic value > 170mmHg and diastolic value > 110mmHg

10. Myocardial infarction, stroke, transient ischaemic attack, acute congestive cardiac failure or any acute coronary event < 3 months before randomisation.
11. Women of child bearing potential unless using effective methods of contraception throughout the study and for 3 months after the study has finished. Effective contraception is defined as one of the following:

    - Barrier method: condoms or occlusive cap with spermicides.
    - 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.
    - Female Contraception: have had tubal ligation or bilateral oophorectomy (with or without hysterectomy).
    - Male partner sterilisation. The vasectomised male partner should be the only partner for the female participant.
    - Use of established oral, injected or implanted hormonal methods of contraception and intrauterine device

12. Pregnant or lactating women.
13. Males who do not agree to an effective form of contraception for the duration of the study and for 3 months after the study has finished.
14. A condition that, in the opinion of the investigator, would preclude participation in the study.
15. Participation in an investigational trial involving an investigational medicinal product within 90 days of randomisation.

2.7 Health Economic Outcomes

Health economic outcomes of interest are listed as follows:

- The relative effectiveness of the investigational treatments and on quality of life (VFQ-UI, EQ-5D and EQ-5D with vision 'bolt-on') at 0, 12, 24, 52, 76 and 100 weeks.
- The relative effectiveness of the investigational treatments and standard care on resource utilization (Client Service Receipt Inventories) at 0, 12, 24, 52, 76 and 100 weeks.
- Quality-adjusted life-years (QALYs) observed over 2 year trial period in each trial arm. The central analysis will use the VFQ-UI to estimate QALYs, with EQ-5D with and without the vison bolt-ons in sensitivity analyses
- Cost of each trial arm over 2 years.
- Incremental cost effectiveness ratios (ICERs) over the 2-year trial
- The QALYs for intervention and comparator modelled over long-term.
- Total costs of intervention and comparator modelled over long-term, accounting for the costs of adverse events as well as initial intervention costs. Ophthalmic adverse events will be limited to important and serious adverse events as defined by the Food and Drugs Agency (http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm) and are summarised at the end of this section. The outcomes of interest are based on safety events reported in a worldwide survey of international vitreoretinal experts. [1]
- Long-term ICER

[1] Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal BevacizumabSafety Survey: using the internet to assess drug safety worldwide. Br J Ophthalmol. 2006;90:1344–1349

- Uncertainty surrounding the ICERs (cost-effectiveness plane, cost-effectiveness acceptability curve and frontier, probability of cost-effectiveness at willingness-to-pay thresholds of £20,000 and £30,000 per QALY).

Ocular adverse events to be included:[2]

- Infectious endophthalmitis (infection of the eye)
- Retinal detachment
- Retinal (pigment epithelium) tear
- Anterior chamber reaction (includes acute intraocular inflammation; uveitis (inflammation of the anterior chamber) and hypopyon)
- Ocular haemorrhage
- Lens damage/injury (including cataract, clouding of the lens)
- Ocular hypertension (raised intraocular pressure >21 mmHg)
- Visual loss

3. METHODS FOR WITHIN-TRIAL ECONOMIC EVALUATION

The within-trial analysis will be conducted in line with the recommendations by Ramsey et al. (2015) for cost-effectiveness analysis alongside clinical trials (1). Specifically, the analysis will use unit costs consistent with measured resource use, using VFQ-25, EQ-5D-5L (2) and EQ-5D-5L with vision 'bolt-on'(3) as the measures of health outcome, and follow the guiding principles outlined for the analysis of economic measures. The baseline analysis will be based on imputation to account for missing data, with an additional sensitivity analysis using complete cases.

3.1 Resource Use

Resource use data, including staff training, equipment, medications, and contacts with NHS healthcare practitioners, are being collected as part of the LEAVO trial. To capture all relevant aspects of resource use in the trial, customised questionnaires have been designed, which will be used at each data collection time point. Each of these resource use items will be allocated a unit cost using the following standard health economic sources:

- British National Formulary (4);
- NHS Reference Costs (5);
- PSSRU Unit Costs of Health and Social Care (6).

[2] Related publications –

(1) Poku E, Rathbone J, Everson-Hock E, Essat M, Wong R, Pandor A, Wailoo A. Bevacizumab in eye conditions: issues related to quality, use, efficacy and safety. Decision Support Unit Report for National Institute for Health and Clinical Excellence (NICE) 2012. Available at http://www.nicedsu.org.uk/Bevacizumab%20report%20-%20NICE%20published%20version%2011.04.13.pdf;

(2) Poku E, Rathbone J, Everson-Hock E, Essat M, Wong R, Pandor A, Wailoo A. Safety of intravitreal bevacizumab in ophthalmic conditions: systematic review. BMJ Open 2014;4:e005244. doi:10.1136/bmjopen-2014-005244

The references for each of these unit cost sources are provided for information. The most up-to-date version of each source at the point of analysis will be used.

3.2 Utilities

Utility scores for each patient will be calculated for the central analysis from the VFQ-25 using the VFQ-UI tariff (7) and UK EQ-5D scoring tariff (8), together with the EQ-5D-5L (2) and the EQ-5D-5L with vision 'bolt-on' mapped onto the EQ-5D-3L valuation set (15) using the mapping function (9) will be used in sensitivity analyses. QALYs for each patient will be estimated by calculating the area under the curve defined by utility scores calculated by using VFQ-UI and both EQ-5D-5L and the EQ-5D-5L with vision 'bolt-on' questionnaires, mortality and length of follow-up.

Both cost and QALYs will be calculated up to 100-week follow-up period and will be discounted at 3.5%. (10)

3.3 Analysis outputs

The combination of resource use and unit-cost data will be used to estimate a cost per patient in each arm of the trial. Similarly, QALYs per patient will be estimated separately for each arm.

An ICER will be calculated using the following formula:

$$\text{ICER} = \frac{\text{cost per patient in intervention arm} - \text{cost per patient in control arm}}{\text{QALYs per patient in intervention arm} - \text{QALYs per patient in control arm}}$$

Both deterministic and probabilistic sensitivity analysis (PSA) will be conducted. Uncertainty around the ICER will be characterised by plots on the cost-effectiveness plane and cost effectiveness acceptability curves (CEACs).

4. METHODS FOR LONG - TERM ECONOMIC EVALUATION

A systematic review of the existing literature studying the cost-effectiveness of intravitreal ranibizumab (Lucentis), aflibercept (Eylea) and bevacizumab (Avastin) will be undertaken. In addition, an economic model will be developed to compare a treatment strategy which incorporates novel techniques with a strategy that uses traditional surgery, non-foam sclerotherapy or conservative treatment.

4.1 Identifying and systematically reviewing published cost effectiveness studies

A search strategy will be developed to identify studies of cost effectiveness. The approach described is very sensitive as no study design filters are being used and will retrieve any relevant cost-effectiveness studies. Identified economic literature will be critically appraised and assessed using the Drummond checklist (11). Existing cost effectiveness analyses will also be used to identify sources of evidence to inform structural modelling assumptions and parameter values for the economic model.

4.2 Development of a health economic model

An economic evaluation will be constructed, with the primary outcome from the model being an estimate of the incremental cost per additional quality adjusted life year (QALY) gained associated with use of novel clinical techniques. The time horizon adopted will be sufficient to capture the long-term impact of the condition on costs and quality of life. The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5 %.(10)

The model structure will be determined in consultation with clinical experts. It is expected that a Markov model will be used to follow patient progression following initial treatment into post-treatment health states (reflecting the success or otherwise of treatment and adverse effects of treatment). The team of modellers have experience in a wide range of different modelling techniques, should these be required following analyses of data.(12)

Costs will be attached to discrete events as well as ongoing care appropriate to each disease state, allowing long-term costs to be estimated. Utility values will be associated with each disease/adverse event state to allow total lifetime quality-adjusted-life –years (QALYs) to be calculated. Clinical parameters (immediate treatment outcomes, adverse events, recurrence rates) will be taken from the LEAVO trial, the systematic review and meta-analysis of the literature, supplemented by clinical expert opinion where necessary.

Ideally, health related quality of life estimates will be available from the reviewed literature. In the absence of such evidence, the economic model may use indirect evidence on quality of life from alternative sources. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model. National sources as well as the reviewed literature will be used to estimate resource use and costs for use in the economic model.

Subgroup analysis will be conducted, where the subgroups will be defined based on a number of factors at baseline, including visual acuity, presence of ischaemic CRVO, disease duration and prior treatment for CRSO.

There will inevitably be some uncertainty around parameter estimates, which will be modelled by the use of appropriate distributions around the central estimates. Uncertainty surrounding the ICER will be illustrated using the cost-effectiveness plane, cost-effectiveness

acceptability curve and frontier. These will be summarised in terms of the probability that intervention is cost-effectiveness at thresholds of £20,000 and £30,000 per QALY.

Through expected value of perfect information analysis (13) and, if resources allow, expected value of partial perfect information analyses (14), we will identify whether further research is valuable, and in which areas further research is likely to be particularly valuable.

5. DELIVERABLES / OUTPUTS

- A report of methods and results to constitute a chapter of the HTA monograph.
- A peer-reviewed journal paper reporting on the cost effectiveness of intravitreal ranibizumab (Lucentis) and aflibercept (Eylea) compared to bevacizumab (Avastin)
- Potentially other papers e.g. to compare quality of life instruments.

6. TIMETABLE

	2017			2018				2019	
Activities	Q2 Apr - Jun	Q3 Jul - Sep	Q4 Oct - Dec	Q1 Jan - Mar	Q2 Apr - Jun	Q3 Jul - Sep	Q4 Oct - Dec	Q1 Jan - Mar	Q2 Apr- June
Developing problem-oriented conceptual model									
Meeting with clinicians to discuss and provide peer review of the conceptual model									
Developing a design-oriented conceptual model									
Identifying parameters required to inform the model									
Undertaking a systematic review									
Getting blinded trial data for interim analysis coding and model validation									
Developing and validating the health economic model									
Getting the trial data required for the economic evaluation (End of January)									
Within trial economic evaluation									
Model inputs and long-term analysis									
Reporting and deliverables: (HTA monograph and journal manuscripts)									

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