University of York
Centre for Reviews and Dissemination

AVID

Anti-VEGF drugs compared with laser photocoagulation for the treatment of diabetic retinopathy: a systematic review and economic analysis

Protocol

PROSPERO Registration number: CRD42021272642

October 2021

Funded by NHS National Institute for Health Research

Organizational details

Collaboration

This individual participant data network meta-analysis is collaborative project between the research team based at York University, and clinical experts from around the UK. This group will jointly conduct the project and publish its findings. In addition, all trial investigators who contribute individual level data from their trials to the project will be invited to collaborate on the project including co-authorship of publications that use the data provided.

The project is led by its advisory group, which includes trial investigators responsible for the largest trials, clinical advisors, methodological advisors, research team members and patient stakeholder representatives.

Research team

The IPD-NMA and economic analyses will be carried out by a research team based at the Centre for Reviews and Dissemination (CRD) at the University of York, UK, working under the direction of Mark Simmonds. Team members will include: Melissa Harden, Matthew Walton, Rob Hodgson, Alexis Llewellyn and Ruth Walker.

The IPD-NMA and the economic evaluation and VOI analyses will be undertaken as two separate but interlinked projects. The IPD meta-analysis will focus on clinical effectiveness and have universal relevance; the economic evaluation and VOI will take a UK and NHS perspective.

Advisory group

The project will be supported by an advisory group, which includes three independent clinical experts, three methodologists and will include two patient experts/PPI partners.

Advisory group members currently include:

Prof. Tunde Peto (Queens University Belfast)
Prof. David Steel (University of Newcastle)
Prof. John Lawrenson (City, University of London)
Mr Tom Rush (Patient representative)
Prof. Lesley Stewart (CRD, York)
Prof. Sofia Dias (CRD, York)
Dr Laura Bojke (Centre for Health Economics, York)

This group will provide advice and guidance over the course of the project.

Funding

The project is funded by the NIHR Health Technology Assessment Programme (grant number NIHR321948). Views expressed in this protocol are those of the research team and advisory group and do not necessarily represent those of the NHS, the NIHR or the Department of Health.

Patient and public involvement

Two PPI partners will be involved throughout the project through their advisory group roles

and by commenting on project materials. Both will be invited to attend the results meeting and will work with us in developing plain language summaries of project findings tailored to patient and public audiences. They will contribute particularly to dissemination and knowledge translation activity including co-presenting project findings. The two PPI partners and three further patient representatives will be involved as members of the patient panel, which will meet three times during the project. Their perspective on patient experience and the outcomes that matter most to patients will be particularly helpful in informing the design of the decision model, to contextualise project findings and to aid dissemination to patients.

Patient representatives will be recruited through contact with diabetes and diabetic retinopathy advocacy groups (such as Diabetes UK, JDRF, the Macular Society) or from patients known to the clinicians. Diabetes UK have given their support for this project. The intention is to obtain a diverse PPI panel, with diversity in ethnicity and socioeconomic status, in line with diabetes incidence.

Publication policy

The results will be published in an academic journal, authored by the collaborative group, which will include all trial investigators who provide individual level data for analysis, all members of the IPD-NMA research team and all members of the advisory group. Each contributing trial may nominate one member to join the group. Individuals outside of the group who provide input to, or feedback on the project will also be acknowledged in the publication. The protocol will be published by the research team on behalf of the forming advisory group.

The linked economic analysis, which will have a UK perspective, will be published by the research team with acknowledgement of the role of the full collaborative group and additional authors as appropriate and defined by contribution.

Results meeting

Results of the IPD-NMA and economic analysis will be presented and discussed at a meeting of the collaborative group. Trial investigators who have provided data for analysis will be invited to attend via the internet. The meeting will be held in summer 2023, with the date and venue to be confirmed.

Ethical approval

This project uses existing data provided by contributing trials and addresses the same clinical question to which trial participants consented originally. Data supplied will contain no identifying names or numbers and will be held securely under controlled access.

The Chair of the University of York Health Sciences Research Governance Committee has therefore confirmed that ethics review is not required.

Plain Language Summary

Diabetic retinopathy is an eye disease occurring in people with diabetes. It causes abnormal blood vessels to grow on the retina at the back of the eye, which can lead to major sight loss over time. The current treatment is to use laser light surgery to prevent the growth of these abnormal blood vessels. Recently a new class of drugs called anti-vascular endothelial growth factor (anti-VEGF) drugs have been successfully used to treat other eye conditions but their value for diabetic retinopathy is less certain; with some concerns over their side effects and whether they are effective in the long-term.

It is of critical importance that people with diabetic retinopathy, or people who may develop it, have access to the best possible treatments. This will enable them to retain good visual health so that they can continue to work, drive, read, see what is going on around them, and remain independent for as long as possible. This project aims to support this by determining what is best practice for the treatment of diabetic retinopathy, in collaboration with leading clinicians and patient representatives.

This project aims to determine whether anti-VEGF therapy is of value, by conducting a thorough review and re-analysis of all the clinical trials where anti-VEGF has been used to treat diabetic retinopathy. As there are several types of anti-VEGF drug, a specialist statistical technique called network meta-analysis will be used, which allows fair and objective comparisons to be made between different drugs. To investigate which types of patient might benefit most from anti-VEGF, the original data from larger trials will be requested and reanalysed, focussing on analysing the CLARITY trial, conducted in the UK, which compared the anti-VEGF drug aflibercept to laser treatment and included over 200 patients.

To evaluate whether anti-VEGF therapy is economically viable for the NHS a review of all relevant economic evidence will be performed, and a new economic analysis of anti-VEGF treatment, based on the findings of the project, will be undertaken.

In collaboration with clinical experts and patient representatives the findings of the project will be considered, and overall decisions made as to whether, and how, anti-VEGF drugs might be used, and whether more trials or investigations are needed before they could be recommended. The findings of the project will be published in an overall report, and in journal articles. Key clinical and patient groups will be made aware of the project, and it will be promoted via suitable social media. Plain language and more technical summaries will be made available online to promote understanding of this research.

Background

Diabetes is a major cause of poor health, impairing the sight of more than 1,700 people in the UK each year (1). Diabetes accounts for approximately 10% of the NHS budget, or £9.8 billion (2).

Diabetic retinopathy is a "chronic progressive, potentially sight-threatening disease of the retinal microvasculature" (3, 4) and is a major form of sight loss. Prevalence in type 1 diabetes is around 48%, and 28% in type 2 diabetes (4). Older people, men, South Asian groups, and more deprived populations are at higher risk (5). Diabetic retinopathy develops in stages. The most severe form: proliferative retinopathy, presents a very high risk of severe bleeding, retinal detachment and vision loss, depending on stage at presentation (6, 7).

Laser photocoagulation is the primary treatment for proliferative diabetic retinopathy (PDR). Laser is applied to the retina to prevent the proliferation of new blood vessels. Panretinal photocoagulation (PRP) is delivered over the entire periphery of the retina, by placing 1,200-1,600 burns per session, usually over two or three treatment sessions. It is known to be effective and long-lasting (8) but can have side effects including central scotomata and peripheral visual field loss, blurred vision and impaired night time and colour vision (9).

Anti-vascular endothelial growth factor (anti-VEGF) drugs are used to treat various eye conditions. NICE has recently approved ranibizumab and aflibercept for the treatment of diabetic macular oedema (10, 11). Anti-VEGF treatments are injected into the eye, under local anaesthetic, at regular intervals. They may have adverse effects including: ocular hypertension, retinal detachment, endophthalmitis and other intraocular inflammation, and cataracts (12). Use of anti-VEGF agents to treat PDR would substantially increase the costs of treatment. It is uncertain whether anti-VEGF will be cost-effective for treatment of oedema if multiple injections are needed over many years (11), and the same issue may apply to retinopathy. There are also concerns that effects may not be long-lasting, and patients may have worse outcomes than with laser photocoagulation if not carefully followed up (13) (14).

Current evidence and knowledge

The most recent review of anti-VEGF treatments for PDR was published in 2020 (15). It included 12 studies, but meta-analyses included at most 4 trials. It concluded that there is insufficient evidence to recommend anti-VEGF therapy as an alternative to PRP. A Cochrane review from 2014 (16) considered proliferative retinopathy in 18 trials, but only 4 (with 373 patients) were comparisons of anti-VEGF drugs with photocoagulation. It concluded there was low-quality evidence that anti-VEGF drugs improved visual acuity. It noted problems with short follow-up times, and selective outcome reporting, which could be resolved with access to IPD. Another review in 2015 (17) included 22 trials; 8 were comparisons of anti-VEGF with photocoagulation. It concluded that "anti-VEGF agents before PRP results in superior functional and structural outcomes at 3 months to 4 months."

These appear to be the only three systematic reviews of anti-VEGF therapy for diabetic retinopathy (15-17). Two are out of date, with limited evidence; the third is up to date (15), but none collected IPD nor used NMA to fully investigate the efficacy of different treatments. Initial searches suggest that at least 10 trials in proliferative retinopathy have been conducted since 2015, including the UK CLARITY trial (18). (See Table 1)

A recent cost-effectiveness analysis suggested that ranibizumab may not be cost effective for patients with retinopathy but without macular oedema (19). Another review (20) found

substantial variation in the methods used across studies, making results difficult for decision makers to interpret. It concluded: “there is a pressing need for more advanced and standardised approaches to assessing the cost effectiveness anti-VEGF pharmacotherapies”. Consistent modelling approaches are needed to support decision-making regarding funding and reimbursement decisions and further economic evidence is needed to inform practice.

The cost-effectiveness of aflibercept and ranibizumab for treating diabetic macular oedema has been assessed by NICE. Both treatments have been approved for use, with a confidential discount in price. These assessments note that anti-VEGF may cease to be cost-effective if many injections are needed, or if more than one anti-VEGF is used, and that there has been no comparison of the cost-effectiveness of different anti-VEGF drugs (10, 11).

Rationale for a new systematic review with IPD meta-analysis

There is no current NICE guidance for the use of anti-VEGF drugs in diabetic retinopathy, including for proliferative retinopathy.

International Council of Ophthalmology guidelines on diabetic eye care (21) support laser photocoagulation and 'appropriate use of anti-VEGF drugs' for the management of diabetic retinopathy. However, there remains uncertainty regarding the cost effectiveness and long-term durability of anti-VEGF therapy.

There is a growing body of evidence in favour of the various anti-VEGF drugs, so a thorough systematic assessment of the relevant evidence, network meta-analysis and economic analysis is needed to assess the value and rank of all relevant anti-VEGF interventions.

Patients included in trials of anti-VEGF drugs in diabetic retinopathy vary substantially in the nature and severity of their diabetic retinopathy. Using IPD trials will enable investigation of which patients are most likely to benefit, or suffer harm, from anti-VEGF treatment, and help identify where anti-VEGF drugs might be of most benefit to the NHS, by incorporating data on individual patient characteristics and outcomes not available in publications. This project will seek IPD from trials judged most likely to provide useful data, rather than seeking data from all trials, to minimise time required for the project while still gaining the research benefits of using IPD. The IPD can be combined with evidence on the costs and longer-term consequences of anti-VEGF treatment, to assess if they are appropriate for use in the UK.

Aims and Objectives

This project will evaluate whether anti-VEGF drugs are clinically- and cost-effective for the treatment of diabetic retinopathy and its complications, either as a replacement for, or in addition to photocoagulation, within the UK NHS.

Key objectives

1. To systematically review all RCTs of anti-VEGF drugs and laser photocoagulation for diabetic retinopathy
2. To obtain IPD for large trials comparing anti-VEGF drugs to photocoagulation
3. To perform network meta-analyses to compare and rank all treatments, incorporating the IPD collected.

4. Where RCT evidence is limited, to identify high quality observational evidence, focusing on long-term and safety outcomes, relevant to a UK context, to inform the economic analysis.
5. To systematically review and critique UK-relevant cost-effectiveness models for anti-VEGF and laser photocoagulation therapies.
6. To develop a de novo economic model, informed by the review of existing economic evaluations, which will incorporate the network meta-analysis results.
7. In collaboration with patients and clinicians, to examine the evidence collected, consider its suitability for the UK health service, or identify priority areas where additional evidence is required.

Protocol development and registration

This protocol has been registered in PROSPERO (CRD42021272642). To ensure transparency, the full protocol is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-analysis Protocols (PRISMA-P) 2015 statement (22). The protocol will be submitted for publication in a suitable open access journal.

It is anticipated that this protocol will be updated, particularly as decisions are made regarding what IPD to request, and what non-randomised evidence will be sought. Any protocol updates will be used to clarify components of the project; we do not intend to deviate from the protocol set out here. Any updates will be lodged with the funding body.

A log of feedback received from the advisory group and PPI partners on this protocol will be maintained along with an audit trail of any consequential changes made to the protocol and PROSPERO record, to safeguard against perception of undue influence or academic bias.

Methods

Reviews will be conducted following CRD's guidance on undertaking systematic reviews (23) and reported according to the principles of the overarching PRISMA statement and extensions for NMA and for IPD meta-analysis (24) (25, 26).

The technologies of interest are anti-VEGF drugs for the treatment of diabetic retinopathy. All types of anti-VEGF drugs are eligible (including aflibercept, bevacizumab, ranibizumab and their biosimilars). The primary alternative therapy, to which anti-VEGF drugs will be compared, is laser photocoagulation therapy.

Three linked reviews of anti-VEGF therapies and laser photocoagulation will be undertaken:

1. A systematic review of all completed RCTs
2. A targeted review of observational evidence for long-term and safety outcomes
3. A review of all cost-effectiveness analyses of anti-VEGF and laser coagulation therapies

Inclusion and exclusion criteria

We will aim to include all relevant trials irrespective of whether they are published or unpublished, where they have been carried out, or which language they have been managed and reported in.

Population

People with diabetic retinopathy (proliferative and non-proliferative) will be included. Patients with a principal indication for treatment of diabetic macular oedema will be excluded.

Intervention

- Any anti-VEGF therapy
    - Including aflibercept, bevacizumab, ranibizumab and their biosimilars
- Anti-VEGF with, or subsequent to, laser photocoagulation

Comparators

- Laser photocoagulation (in any form, and any laser type)
- Sham treatment, or other control interventions

Outcomes

Key outcomes are based on the CORE outcomes established for macular degeneration (27), as there are none for retinopathy and include any of the following:

- Visual acuity measurement
- Functional impact on vision, e.g.
    - driving vision (approx. 0.3logMAR)
    - blind level vision (approx. 1.0logMAR)
    - clinically important vision loss (0.3logMAR or worse)
- Number of treatments
- Need for subsequent treatment (e.g. vitrectomy)
- Complications and adverse effects
    - E.g. Raised intraocular pressure, vitreous haemorrhage, retinal detachment, cataract formation, systemic AEs.
- Progression of retinopathy (non-proliferative to proliferative)
- Peripheral vision and visual field changes
- Treatment withdrawal
- Quality of life (NEI-VFQ-25, EQ-5D, SF-36)

Study design

The main systematic review will include only RCTs.

High quality non-randomised observational studies will be sought to supplement the RCT evidence, should the review of RCTs find that evidence is limited or absent for some identified outcomes. The focus will be on identifying evidence required to inform the economic analysis, that is of importance to patients. This is anticipated to include evidence on:

1. Longer-term visual acuity and other vision outcomes (beyond the duration of typical RCTs)
2. Adverse events and other harm data, which may not be adequately examined in RCTs.

3. Quality of life

This non-randomised evidence will include follow-up and extension studies of the RCTs as well as independent high-quality observational studies (based on ROBINS-I assessment).

Cost-effectiveness studies in this area will be identified and assessed for their suitability to inform the structure and parameter inputs of the *de novo* economic model. If necessary, economic evaluations in other ophthalmological conditions may be sought to these ends.

Trial identification

Bibliographic searches

An experienced information specialist will design and run comprehensive, systematic searches of bibliographic databases to identify all relevant studies for each of the reviews set out above. As a minimum, the following databases will be searched: MEDLINE, EMBASE and CENTRAL using a search strategy that combines relevant text-word searches for terms that appear in the titles or abstracts of database records, with relevant indexed keywords (e.g. MeSH terms). Trial registries (including clinicaltrials.gov) will be searched for ongoing or unpublished studies.

No language limits will be applied. Records identified from the database searches will be downloaded and imported into EndNote bibliographic software and de-duplicated. Reference lists of relevant systematic reviews will also be searched manually.

An example MEDLINE strategy is provided in Appendix A. This will be translated for use with the other databases. Full details of all databases and search strategies will be finalised and detailed in the protocol. Update searches will be conducted towards the end of the project to ensure that we identify any recently published studies.

Screening

Two researchers will independently screen all titles and abstracts retrieved from electronic database and other searches. Full text publications will be retrieved for potentially relevant trials. Full text articles will be screened by two reviewers for final inclusion.

Where no full paper exists and/or trial eligibility is uncertain, study authors will be contacted and asked to provide further information.

Two researchers will independently assess the relevance of each trial using the fullest available information. Any discrepancies in screening decisions will be resolved by consensus and discussion with a senior team member or advisory group members, as required.

'Near miss' studies that do not meet all of the inclusion criteria and have therefore been excluded will be tabulated and their bibliographic details listed with reasons for exclusion in the final project report and PRISMA diagram.

Data collection

Published data

A data extraction form will be developed in advance and piloted by two reviewers using a selection of included studies. Data on interventions used, patient characteristics outcomes

reported, and all outcome data will be extracted for all included studies from included publications by one reviewer and checked by a second. Where studies are reported in multiple publications data will be extracted from the most recent, complete publication; data will be extracted from other publications if they report additional outcome data.

Individual participant data

The collection and analysis of IPD will enhance this project by enabling data across trials to be recoded, harmonised and analysed in a consistent manner, and to allow investigation of the impact of patient characteristics (such as type of retinopathy) on treatment efficacy.

It is anticipated that the number of included RCTs will be too large to request data from them all within the timeframe and budget of this project. Therefore, we intend to request IPD from a subset of RCTs that compare anti-VEGF to laser photocoagulation. The exact choice of trials will be decided based on the total size of the complete RCT data, how recent and relevant trials are, trial size and quality, and power calculations to identify the gains in information that IPD could provide and its contribution to the overall treatment network (28). IPD is expected to be available from the UK CLARITY trial of aflibercept (232 participants) (18); its authors have in principle agreed to provide IPD. Data from the large PROTOCOL S trial of ranibizumab (305 participants) (29) has been made publicly available [public.jaeb.org/drcrnet/stdy], and this repository will be used for the IPD analysis. The trialists have confirmed that they can support this project.

Included RCTs will be categorised by size, intervention and location to identify and prioritise those for which we will request IPD. Corresponding authors will be contacted to request IPD. In order to encourage participation, all trialists that supply IPD will be invited to nominate one representative to join the project advisory panel, should they wish, and they will also have the option to be a co-author of the primary paper reporting the IPD-NMA results.

Data coding and transfer

A formal data sharing agreement will be created for each trial supplying IPD, to ensure appropriate transfer and use of the data. A data request form will be created by the project team to specify exactly which data are requested for analysis, along with a suggested coding for the data. An example of the data to be requested is given in Appendix B. Trialists may either recode the data themselves or send their data without editing, in which case it will be re-coded by the research team. All data will be anonymised to remove any personal identifiers, location data and any other data which might permit identification of specific patients before transfer of data to York. All data will be transferred using secure encrypted transfer methods and will be stored on a secure area of the university server, accessible only to designated members of the project team.

Action in case IPD are not available

The project plans 16 months to identify and receive IPD to maximise the opportunity to obtain all requested IPD. At the 12-month advisory group meeting the progress in obtaining IPD will be discussed, and a decision made on whether to proceed with seeking any outstanding IPD, and how to progress with the project.

Decisions on how to proceed with IPD collection after 12 months will be made based on the proportion of the total trials and participants for which IPD has already been obtained (or where trialists have agreed to provide the IPD but it has not been received). For example, if

a large proportion of the requested IPD has been obtained or promised by 12 months a decision may be made to continue seeking to obtain any outstanding trials. By contrast, if few trials have been obtained it may be preferred to focus on obtaining only those larger trials most likely to influence the analyses.

Decisions will be also be made on a trial-by trial basis. For example, it may be appropriate to cease trying to collect IPD where trialists have been entirely unresponsive to requests, particularly for smaller or older trials. Instead, the focus may move to obtaining data from larger, more influential trials where trialists have responded positively, but where there have been delays in supplying IPD.

Data storage and confidentiality

IPD will be received via secure online transfer or by encrypted email. All data will be anonymous and held in a password-protected area of the CRD server. No attempt will be made to re-identify participants and in the unlikely case of re-identification, confidentiality will be maintained. Access will be limited to staff working directly on the project. Copying data to home computers, laptop computers, cloud services or storage devices will be prohibited.

Critical appraisal, data checking and quality assurance

All IPD will be checked on receipt. Data will be examined for internal consistency and integrity of randomization (e.g. temporal distribution of randomisations, baseline balance of important prognostic factors). Patterns of missing data will be examined. Baseline data will be tabulated and compared with the trial publication and any inconsistencies noted. One researcher will run data checks, which will be independently checked by a second person. Findings of all data checking will be discussed with senior members of the research team. Each individual trial will be analysed (primary outcomes only) and compared with corresponding published analyses (bearing in mind that there may be reasonable discrepancies, if for example previously excluded participants have been reinstated in the analyses, or additional follow up provided). Any problems, uncertainties or queries will be passed back to the responsible trial investigator for explanation and discussion.

Risk of bias in RCTs will be assessed using the most recent Cochrane risk of bias tool (30). For non-randomised evidence an adaptation of the ROBINS-I tool (31) will be used to assess risk of bias and study quality. Risk of bias assessment will be performed by one reviewer and checked by a second.

Data analysis

A detailed statistical analysis plan (SAP) will be developed when the extent of available data is known, but before starting meta-analysis. Analyses will be conducted on an intention–to-treat basis. The overall structure of the data analysis is laid out in Figure 1.

Outcomes and effect modifiers

Main outcomes

- Visual acuity
    - Best corrected visual acuity, mean change in BCVA (from logMAR or EDTRS charts)
- Impact of vision impairment
    - Mobility, well-being, reading ability, driving ability, functional blindness
- Clinically important vision loss
- Number of treatments
- Need for subsequent treatment (e.g. vitrectomy)
- Complications and adverse effects
    - E.g. Raised intraocular pressure, vitreous haemorrhage, retinal detachment, cataract formation, systemic AEs.

The advisory group and PPI representatives will be consulted to identify further outcomes of practical interest.

Additional outcomes

- Progression of retinopathy (non-proliferative to proliferative)
- Peripheral vision, visual field changes
- Treatment withdrawal
- Quality of life (NEI-VFQ-25, EQ-5D, SF-36)

Potential effect modifiers

- Type of retinopathy (proliferative, non-proliferative retinopathy grade, presence of maculopathy)
- Low and high-risk PDR
- Vitreous haemorrhage or tractional retinal detachment
- Type 1 vs Type 2 diabetes
- Age, gender, ethnicity

Outcome measures

For continuous outcomes mean differences between treatment arms will be reported. Dichotomous outcomes will be analysed by calculating the risk ratio for the effect of anti-VEGF compared to the control treatment. Odds ratios may be used where analyses based on risk ratios do not converge. Hazard ratios will be analysed for time-to-event outcomes.

Published data meta-analysis

An initial meta-analysis will be conducted using outcome data as extracted from publications, prior to full collection of IPD. Effect estimates will be pooled across studies using standard DerSimonian-Laird random effect meta-analysis. Forest plots will be produced. Heterogeneity will be assessed in terms of I^2 (32) and by inspecting the between-study heterogeneity standard deviation (τ) relative to the treatment effect size.

Separate meta-analyses will be conducted for each anti-VEGF drug (aflibercept, bevacizumab, ranibizumab). Meta-analyses will be performed at all time points after

treatment where sufficient data are reported. Where data permits, analyses will be performed on both a by-patient and a by-eye basis. A pooled analysis across all drugs may be considered if there is little heterogeneity across drug types.

Network meta-analyses of published data will be performed using standard Bayesian models (33, 34) to compare and rank the interventions. Where feasible, subgroup analysis and meta-regression will be used to identify possible impact of key patient characteristics as listed above.

This published data analysis will support the project, and the subsequent IPD analysis and economic analysis by:

1. Identifying the broad effectiveness of anti-VEGF early in the project, to be discussed at the 12-month meetings.
2. Supporting the IPD collection process, by identifying trials most likely to influence network meta-analysis results, or where published data are insufficient to investigate the impact of patient characteristics.
3. Identifying outcomes and treatments where RCT data are limited or absent, to target the searching for non-randomised evidence
4. Providing data to support the initial development of the economic model.
5. Ensuring that IPD analyses are correct. For example, by identifying possible errors in the IPD supplied, its coding, or analysis.

Network meta-analysis of IPD

All supplied IPD will be recoded into a common format (either by trialists or the project team) and checked for validity and consistency with published results.

Network meta-analyses will be performed to identify the comparative effectiveness of the interventions and to rank them; we will consider all visual, quality of life and safety outcomes. These analyses will be conducted combining both IPD and aggregate data (where IPD is unavailable or was not sought). To achieve this, we will use multi-level network meta-regression. This extends the standard Bayesian methods of network meta-analysis to allow inclusion of IPD in combination with aggregate data (35, 36). It also permits extending analyses to investigate the potential impact of the patient factors listed above (e.g. type of retinopathy) on the effectiveness of anti-VEGF therapy, and on the ranking of the different treatments (35). This approach permits considerable flexibility in modelling the IPD; for example, permitting sharing of regression parameters across different treatments. This will ensure we are able to make fullest use of both the IPD and aggregate data.

Networks of treatment comparisons will be drawn for each outcome to check that they are connected. The contrast-based Bayesian models proposed in Dias et al, which appropriately account for correlations in trials with more than 2 arms, will be used. Care will be taken to properly account for correlations when data are given as relative treatment effects from RCTs with 3 or more arms (hence providing 2 or more relative effects) (37, 38).

Network consistency will be checked by comparing the model fit and between-study heterogeneity from the NMA models to an unrelated mean effects model (similar to a model performing direct meta-analysis for each treatment comparison, but with a shared heterogeneity parameter) (37). Where inconsistency is identified, it will be explored by inspecting the characteristics of the included studies (participant and design characteristics)

that may contribute to inconsistency. Where feasible, node-split models will be fitted to provide further evidence of the location and impact of potential inconsistency (39).

Threshold analysis

Where feasible, the potential impact of unpublished or ongoing trials on the NMAs will be investigated using threshold analysis. Threshold analysis investigates where in an NMA results might not be robust to changes in the observed evidence (40). Threshold analysis will be applied to the NMAs and used in conjunction with the risk of bias assessments to identify which comparisons lack robust RCT evidence. Results of the analysis will be presented graphically in forest plots and using tables, where appropriate. The results will be used to broadly classify the evidence on interventions and comparisons as:

- Robust (further RCTs or non-randomised evidence unlikely to change conclusions)
- Fairly robust (only substantial new evidence would change conclusions)
- Not robust (even limited new evidence could alter conclusions)
- Highly uncertain (new evidence could substantially change conclusions)

This classification will inform where future research may be beneficial and guide the economic value of information analysis.

Further IPD meta-analysis

The Bayesian NMAs described above will be the primary analyses in this project. Given the complexity and novelty of the approach, they will be supported by use of frequentist IPD meta-analyses, in order to compare results from different approaches.

This analysis will use “one-stage” mixed model methods (41). Aggregate data will be combined with IPD using “pseudo-IPD” methods (42, 43), where partial IPD is reconstructed based on data reported in publications. The impact of patient characteristics (such as type of retinopathy) will be analysed by including interaction terms in the models (44). One-stage models will compare all treatments in the same model, to match the network meta-analysis (45). As trials have reported outcomes at different and varying times, how treatment effectiveness varies over time will be modelled using repeated measures analysis and suitable models to evaluate time trends, such as fractional polynomial models.

Meta-analysis approach should IPD be unavailable

As this project will not collect IPD from all studies, focussing instead on collecting IPD for targeted studies only, it will be necessary to perform analyses combining IPD (where supplied) with published data (for trials without IPD). This joint analysis approach will also be used should we be unable to obtain IPD from some of the trials for which we request it. The meta-analysis methods described above will combine all IPD with aggregate data where IPD are unavailable, or not sought. This will maximise the value of any IPD collected, even where some trials do not provide IPD. Sensitivity analyses will be performed to compare analyses based on IPD to those based on published data alone.

Should no IPD, or very limited IPD, be obtained (e.g. only one trial, or a very small proportion of the total data) the project will use the published data meta-analysis described above as the primary analysis. If limited IPD have been obtained, summary effect estimates from publications will be replaced by summary estimates estimated from IPD, and the meta-analyses re-performed.

Non-randomised evidence

The results of the network meta-analyses will be used to identify outcomes where non-randomised evidence might resolve uncertainty, inform economic modelling and aid UK decision-making. This is anticipated to be, but not limited to:

1. Longer-term visual acuity and other vision outcomes (beyond the duration of typical RCTs)
2. Adverse events and other harm data, which may not be adequately examined in RCTs.
3. Quality of life

The non-randomised studies will be combined in network meta-analyses, where there are sufficient data, and including any RCTs that do provide relevant data. As this project will not seek IPD for non-randomised studies, conventional DerSimonian-Laird random effects meta-analyses will be performed. Sensitivity analyses will be used to identify differences between randomised and non-randomised evidence.

Where outcome data are too limited for meta-analysis, a narrative synthesis approach will be used, tabulating and plotting results and summarising across studies.

Relative and absolute differences

Absolute differences will be calculated by applying the resulting risk ratios or hazard ratios to appropriate baseline incidences (calculated from suitable meta-analyses across the trial control arms). Numbers needed to treat and numbers needed to harm will similarly be calculated for a range of plausible baseline measures.

Economic analysis

A review of cost-effectiveness studies will identify and critique previous modelling approaches and inputs in diabetic retinopathy and other conditions with a similar disease course, if necessary. It will include a broad range of studies, including cost-effectiveness and cost-utility studies, and be used to assess the suitability of existing models. The review will inform the structure and parameters of our *de novo* economic model.

Model structure

The clinical experts in the project team and the PPI panel will be consulted (at both first and second meetings) to identify key outcomes most relevant to patient quality of life as well as other clinical factors and issues relevant to patient experience, which will guide the overall structure of the economic decision model. It is anticipated that the model will focus on the evolution of best-corrected visual acuity (BCVA) and functional outcomes such as driving vision, and the impact of treatment on these outcomes.

Where data permit, we will model BCVA in both eyes, allowing some degree of co-dependency between eyes (where one is affected with diabetic retinopathy and the other not), and the impact of vision changes on health-related quality of life (HRQoL). The cycle length in the model will be determined by the intervals at which data were collected in the identified RCTs and in line with the licensed retreatment interval for the comparators.

If feasible, an individual or cohort simulation approach will be used. Research conducted at CRD shows that such an approach allows increased flexibility over Markov modelling (46, 47). A simulation approach makes it simpler to model vision in both eyes and to incorporate the fact that costs and quality of life are a function of overall visual acuity rather than of eye specific acuity (48). It also simplifies the inclusion of natural history into a patient's progression and so is better able to reflect disease pathology. Where appropriate data are available, a simulation approach can also be used to link patient characteristics to model outcomes, ensuring that the model appropriately reflects heterogeneity in disease pathology and patient outcomes.

The model will be designed to include alternative 'stopping' rules, or a maximum time on treatment. The stopping rule will ensure that patients in the model discontinue treatment if their visual acuity improves to or falls below a pre-specified threshold. The model will use a lifetime time horizon.

The model will present analyses for each anti-VEGF drug (aflibercept, bevacizumab, ranibizumab and biosimilars); compared to laser photocoagulation therapy. Where appropriate, treatment sequences and combinations of treatments will be considered.

Key parameters and populating the model

Clinical effectiveness

Clinical effectiveness data will be drawn from the IPD network meta-analyses. If required, this will be linked to medium- and long-term outcomes based on the identified non-randomised evidence.

We intend to conduct an analysis of the IPD to predict BCVA change from baseline over each model cycle as a function of key baseline characteristics, accounting for the correlation between baseline BCVA and BCVA change in each cycle. If the available IPD are insufficient for credible analyses, clinical effectiveness data will be drawn from the meta-analysis of aggregate data. If it is not possible to perform analysis of aggregate data for any particular outcome, then the corresponding parameter value may be obtained from an individual trial, selected based on its sample size and relevance to the decision problem. The safety profile of each comparator will also be considered, if found to be relevant.

Demographic and clinical parameters

The key parameters will be the characteristics of the population under consideration, which will be used to inform the risk equations for treatment effectiveness, and for long-term disease progression and mortality. These will be based on the supplied IPD (where relevant to the UK) and identified through a review of the epidemiological literature, and will be selected to represent the diabetic retinopathy population in the UK, if possible.

Health-related quality of life

The period of time for which the average patient is alive within the model will be adjusted to quality adjusted life years (QALYs) using an appropriate utility or preference score. A review of utility scores will be carried out to identify appropriate values for people with diabetic retinopathy and other similar conditions, and the PPI panel will be consulted to determine the acceptability of these utilities. Quality of life will be an outcome of the network meta-analyses and, if relevant data are identified, this will be used in the model.

It is anticipated that HRQoL will be modelled as a function of visual acuity in the patient's best-seeing eye (BSE) and in their worst-seeing eye (WSE). Previous economic analyses have been criticized for failing to account for the bilateral nature of ophthalmologic conditions on HRQoL. Research in other conditions associated with central vision loss conducted at CRD was among the first to explore how HRQoL is a function of overall rather than of eye specific acuity (49).

Resource use and unit costs

Resource utilisation data and unit costs will be sought from published sources, national surveys, and consultation with clinical experts and service providers. All resources used will then be costed by applying unit costs, in UK pounds sterling, for the financial year 2021–2022 (or appropriate year). Such costs will include the cost of the treatment itself, as well as other costs such as GP visits, inpatient stays, outpatient visits, resources associated with supporting a patient with blindness, and other concomitant medications that are associated with diabetic retinopathy.

Time horizon and discounting of future outcomes

The model will take a lifetime horizon to ensure that all costs and benefits of anti-VEGF treatment are captured. The model will incorporate a discount rate of 3.5% per annum for costs and health benefits, in line with current NICE Guidance.

Modelling uncertainty

Uncertainty in the data used to populate the economic model will be characterised. A probabilistic model will be developed, with each input entered as an uncertain parameter with an assigned probability distribution representing its uncertainty. This will be presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.

Scenario analysis will be used to test the robustness of the cost-effectiveness results to changes in the structural assumptions of the model. Sensitivity analyses will also be used to evaluate the impact of key methodological assumptions on the results.

Value of information analysis and identifying key areas of uncertainty

We will undertake a Value of Information (VOI) analysis to establish the value of undertaking further research to resolve decision uncertainty and to identify the key sources of uncertainty in the decision problem. VOI analysis allows us to quantify the expected benefits of further research by estimating the value of reducing uncertainty in decisions. The consequences of making an incorrect decision due to uncertainty will be compared to the costs of conducting new research (e.g. a clinical trial) in order to establish the value of the new research. The expected value of perfect information (EVPI) places an upper bound on the value of research to resolve uncertainty. If further research is worthwhile, information on the fixed costs of a trial and the marginal sampling costs of enrolment into the trial can be used to inform sample size of the trial. This will help inform recommendations for primary research and determine whether a new trial is a good investment.

Software

Meta-analyses will be conducted in R. The newly developed *multinma* package will be used for network meta-regression; *meta* and *metafor* packages for standard meta-analysis; and *lme4* for frequentist IPD analyses. The economic model will be developed in R or Excel as appropriate.

Dissemination and projected outputs

A targeted dissemination strategy for the project will be developed, in consultation with the advisory group and PPI representatives. The exact choice of dissemination activities will be informed by the key results of the research with regards to effectiveness and cost-effectiveness of anti-VEGF treatment, and where evidence remains uncertain. We will take account of the needs and preferences of the specific audiences to be targeted, specifically patients (as informed by PPI representatives), clinicians, researchers, regulatory bodies, and the wider public.

Alongside the production of a full final report for the NIHR HTA Programme, dissemination activities will include the submission of papers for peer-reviewed publication and conference abstracts to appropriate ophthalmology and diabetes journals and societies. We will utilise the CRD website and social media to disseminate findings (e.g. @crd_york Twitter and Facebook accounts). All dissemination activities will involve signposting those interested in further details to the full NIHR HTA report.

To ensure proper engagement with, and dissemination to, patients and clinicians we aim to collaborate with key patient representative groups, including Diabetes UK, and other advocacy groups (JDRF, the Macular Society, RNIB). Through them, and our clinical experts, PPI representatives will be engaged in the full progress of the project (see Project management section below). The clinical experts on the project team and providers of IPD will also be involved in the project advisory group, to ensure experts in the fields of diabetic retinopathy treatment are engaged in the project. We will ensure that dissemination output for patients and the general public are accessible to people with sight loss, including producing large-print documents and spoken-word outputs. Outputs intended for the general public may be translated into other languages to make them fully accessible to relevant minority groups (such as South Asians). The advisory group will decide whether and how to translate outputs.

In collaboration with our PPI representatives and key representative organisations, including Diabetes UK, we will produce brief plain-language evidence summaries. These will be aimed at key audiences (particularly patients and clinicians) providing a concise critique of the quality of the evidence and strength of the findings, that can be disseminated via patient and clinical networks, and online. We will also develop an infographic to summarise the results of the project in a concise and accessible way. This will be used to disseminate our findings at conferences and meetings (where it will be used as a flyer or handout), and distributed via digital media such as Twitter and Facebook. A short video, providing an overview of the project, will also be developed.

CRD has particular expertise in working with NICE in the assessment of the clinical and cost-effectiveness of new interventions. This expertise will be used to ensure that project outputs can fully support and direct future regulatory guidance on the use of anti-VEGF treatments.

References

1. Public Health England. Public Health Outcomes Framework statistical summary May 2020. 2020; Available from: https://www.gov.uk/government/publications/public-health-outcomes-framework-may-2020-data-update/public-health-outcomes-framework-statistical-commentary-may-2020.
2. Diabetes UK. The cost of diabetes. 2014 [17/09/2020]; Available from: https://www.diabetes.org.uk/resources-s3/2017-11/diabetes%20uk%20cost%20of%20diabetes%20report.pdf.
3. The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines. 2013 [04/09/2020]; Available from: https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-301-FINAL-DR-GUIDELINES-DEC-2012-updated-July-2013.pdf.
4. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology. 2008 Nov;115(11):1859-68.
5. Mathur R, Bhaskaran K, Edwards E, Lee H, Chaturvedi N, Smeeth L, et al. Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: a cohort study in the Clinical Practice Research Datalink 2004-2014. BMJ Open. 2017 Feb 28;7(2):e014444.
6. Four risk factors for severe visual loss in diabetic retinopathy. The third report from the Diabetic Retinopathy Study. The Diabetic Retinopathy Study Research Group. Arch Ophthalmol. 1979 Apr;97(4):654-5.
7. Parikh R, Shah RJ, VanHouten JP, Cherney EF. Ocular findings at initial pan retinal photocoagulation for proliferative diabetic retinopathy predict the need for future pars plana vitrectomy. Retina. 2014 Oct;34(10):1997-2002.
8. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991 May;98(5 Suppl):766-85.
9. Royle P, Mistry H, Auguste P, Shyangdan D, Freeman K, Lois N, et al. Pan-retinal photocoagulation and other forms of laser treatment and drug therapies for non-proliferative diabetic retinopathy: systematic review and economic evaluation. Health Technol Assess. 2015 Jul;19(51):v-xxviii, 1-247.
10. NICE. Aflibercept for treating diabetic macular oedema. Available from: https://www.nice.org.uk/guidance/ta346/resources/aflibercept-for-treating-diabetic-macular-oedema-pdf-82602611201221.
11. NICE. Ranibizumab for treating diabetic macular oedema. Available from: https://www.nice.org.uk/guidance/ta274/resources/ranibizumab-for-treating-diabetic-macular-oedema-pdf-82600612458181.
12. Royal National Institute of Blind People (RNIB). Anti-VEGF treatment. Available from: https://www.rnib.org.uk/eye-health/eye-conditions/anti-vegf-treatment.
13. Wubben TJ, Johnson MW, Anti VTISG. Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Retinopathy: Consequences of Inadvertent Treatment Interruptions. Am J Ophthalmol. 2019 Aug;204:13-8.
14. Obeid A, Su D, Patel SN, Uhr JH, Borkar D, Gao X, et al. Outcomes of Eyes Lost to Follow-up with Proliferative Diabetic Retinopathy That Received Panretinal Photocoagulation versus Intravitreal Anti-Vascular Endothelial Growth Factor. Ophthalmology. 2019 Mar;126(3):407-13.
15. Gao S, Lin Z, Shen X. Anti-Vascular Endothelial Growth Factor Therapy as an Alternative or Adjunct to Pan-Retinal Photocoagulation in Treating Proliferative Diabetic Retinopathy: Meta-Analysis of Randomized Trials. Front Pharmacol. 2020;11:849.
16. Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I, Pijoán JI, Buil-Calvo JA, Martinez-Zapata MJ. Anti-vascular endothelial growth factor for proliferative diabetic retinopathy. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2010.
17. Simunovic MP, Maberley DA. ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR PROLIFERATIVE DIABETIC RETINOPATHY: A Systematic Review and Meta-Analysis. Retina. 2015 Oct;35(10):1931-42.
18. Sivaprasad S, Prevost AT, Vasconcelos JC, Riddell A, Murphy C, Kelly J, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. Lancet (London, England). 2017;389(10085):2193-203.
19. Hutton DW, Stein JD, Bressler NM, Jampol LM, Browning D, Glassman AR, et al. Cost-effectiveness of Intravitreous Ranibizumab Compared With Panretinal Photocoagulation for Proliferative Diabetic Retinopathy: Secondary Analysis From a Diabetic Retinopathy Clinical Research Network Randomized Clinical Trial. JAMA ophthalmology. 2017;135(6):576-84.
20. Maniadakis N, Konstantakopoulou E. Cost Effectiveness of Treatments for Diabetic Retinopathy: A Systematic Literature Review. PharmacoEconomics. 2019;37(8):995-1010.
21. Wong TY, Sun J, Kawasaki R, Ruamviboonsuk P, Gupta N, Lansingh VC, et al. Guidelines on Diabetic Eye Care: The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings. Ophthalmology. 2018 Oct;125(10):1608-22.

22. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015 2015/01/01;4(1):1.
23. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. [17/09/2020]; Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf.
24. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009 Aug 18;151(4):264-9, W64.
25. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015 Jun 2;162(11):777-84.
26. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA. 2015 Apr 28;313(16):1657-65.
27. Rodrigues IA, Sprinkhuizen SM, Barthelmes D, Blumenkranz M, Cheung G, Haller J, et al. Defining a Minimum Set of Standardized Patient-centered Outcome Measures for Macular Degeneration. Am J Ophthalmol. 2016 Aug;168:1-12.
28. Simmonds MC, Higgins JP. Covariate heterogeneity in meta-analysis: criteria for deciding between meta-regression and individual patient data. Stat Med. 2007 Jul 10;26(15):2982-99.
29. Writing Committee for the Diabetic Retinopathy Clinical Research N, Gross JG, Glassman AR, Jampol LM, Inusah S, Aiello LP, et al. Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. JAMA. 2015 Nov 24;314(20):2137-46.
30. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898.
31. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016 Oct 12;355:i4919.
32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60.
33. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods. 2012 Jun;3(2):98-110.
34. Lu G, Ades AE. Assessing Evidence Inconsistency in Mixed Treatment Comparisons. Journal of the American Statistical Association. 2012;101(474):447-59.
35. Phillippo DM, Dias S, Ades AE, Belger M, Brnabic A, Schacht A, et al. Multilevel network meta-regression for population-adjusted treatment comparisons. J R Stat Soc Ser A Stat Soc. 2020 Jun;183(3):1189-210.
36. Calibration of multiple treatment comparisons using individual patient data. Available from: https://gtr.ukri.org/projects?ref=MR%2FP015298%2F1.
37. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making. 2013 Jul;33(5):641-56.
38. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010 Mar 30;29(7-8):932-44.
39. van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Res Synth Methods. 2016 Mar;7(1):80-93.
40. Phillippo DM, Dias S, Welton NJ, Caldwell DM, Taske N, Ades AE. Threshold Analysis as an Alternative to GRADE for Assessing Confidence in Guideline Recommendations Based on Network Meta-analyses. Ann Intern Med. 2019 Apr 16;170(8):538-46.
41. Simmonds M, Stewart G, Stewart L. A decade of individual participant data meta-analyses: A review of current practice. Contemp Clin Trials. 2015 Nov;45(Pt A):76-83.
42. Papadimitropoulou K, Stijnen T, Riley RD, Dekkers OM, le Cessie S. Meta-analysis of continuous outcomes: Using pseudo IPD created from aggregate data to adjust for baseline imbalance and assess treatment-by-baseline modification. Res Synth Methods. 2020 Nov;11(6):780-94.
43. Riley RD, Simmonds MC, Look MP. Evidence synthesis combining individual patient data and aggregate data: a systematic review identified current practice and possible methods. J Clin Epidemiol. 2007 May;60(5):431-9.
44. Stewart GB, Altman DG, Askie LM, Duley L, Simmonds MC, Stewart LA. Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice. PLoS One. 2012;7(10):e46042.
45. Simmonds MC, Higgins JP. A general framework for the use of logistic regression models in meta-analysis. Stat Methods Med Res. 2016 Dec;25(6):2858-77.
46. Claxton L, Hodgson R, Taylor M, Malcolm B, Pulikottil Jacob R. Simulation Modelling in Ophthalmology: Application to Cost Effectiveness of Ranibizumab and Aflibercept for the Treatment of Wet Age-Related Macular Degeneration in the United Kingdom. Pharmacoeconomics. 2017 Feb;35(2):237-48.

47. Claxton L, Malcolm B, Taylor M, Haig J, Leteneux C. Ranibizumab, verteporfin photodynamic therapy or observation for the treatment of myopic choroidal neovascularization: cost effectiveness in the UK. Drugs Aging. 2014 Nov;31(11):837-48.
48. Pennington BM, Hernandez-Alava M, Hykin P, Sivaprasad S, Flight L, Alshreef A, et al. Mapping From Visual Acuity to EQ-5D, EQ-5D With Vision Bolt-On, and VFQ-UI in Patients With Macular Edema in the LEAVO Trial. Value Health. 2020 Jul;23(7):928-35.
49. Hodgson R, Reason T, Trueman D, Wickstead R, Kusel J, Jasilek A, et al. Challenges Associated with Estimating Utility in Wet Age-Related Macular Degeneration: A Novel Regression Analysis to Capture the Bilateral Nature of the Disease. Adv Ther. 2017 Oct;34(10):2360-70.

Figure 1: Outline of data collection and statistical analysis

Red arrows indicate order of action.
Blue arrows indicate where an analysis will influence later data collection

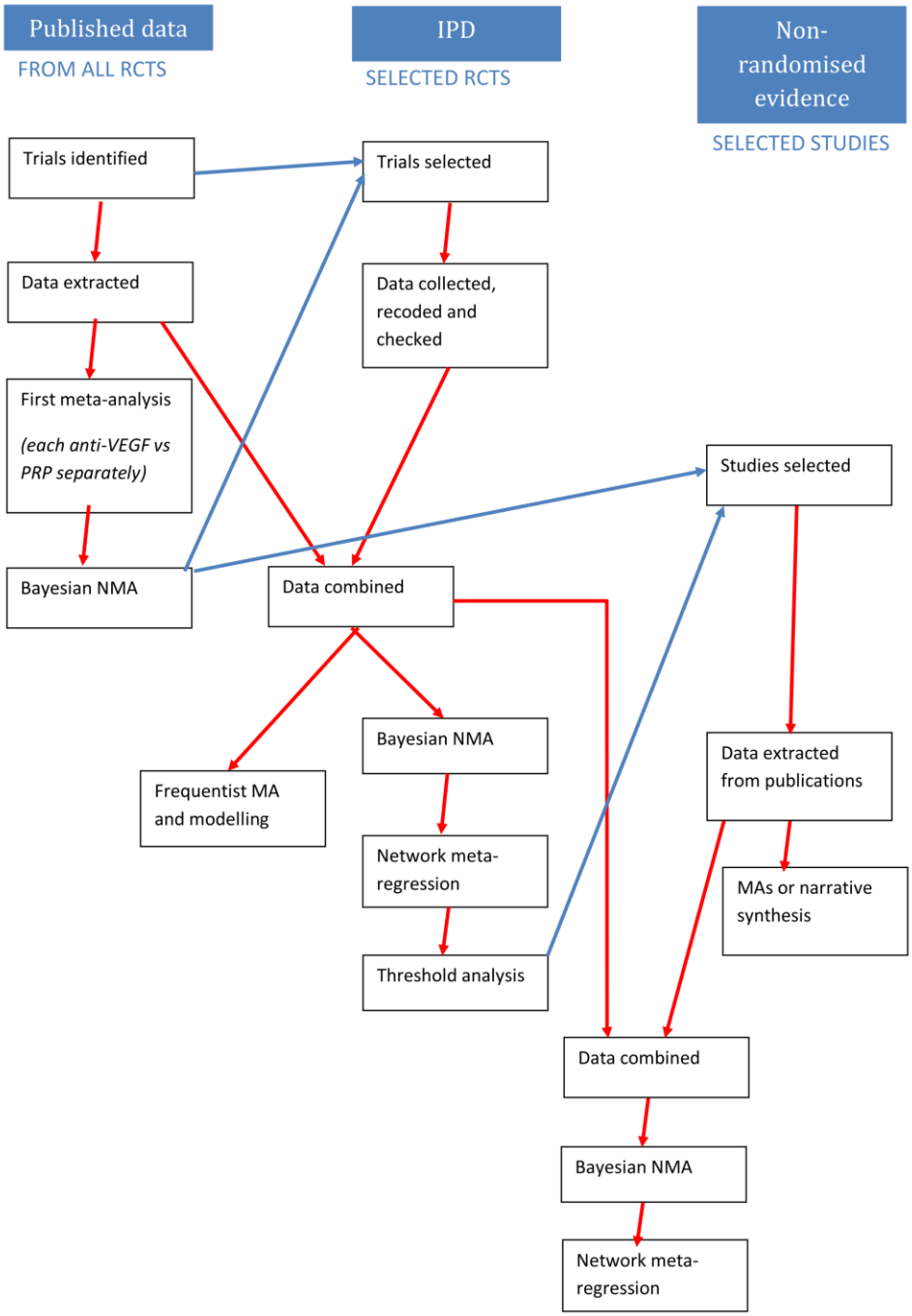

Table 1: Potential eligible randomised controlled trials

Table 1 presents a provisional list of randomized controlled trials potentially eligible for inclusion in this review. Trials listed here may not necessarily be included as not all have been fully assessed for eligibility. This list will be updated as new trials are identified by further bibliographic searches and from other sources.

Trial	Key Paper(s)	Anti-VEGF used	Comparator	Location	Sample size	Main outcome(s)
Ahmad	Ahmad 2012	Bevacuzimab (+PRP)	PRP	India	54 eyes	NVD/NVE area
RIDE & RISE	Nguyen 2012 / Gonzales 2019	Ranibuzumab	Sham injection	USA/ South America	Unclear*	Various
Ferraz	Ferraz 2015	Ranibuzumab (+PRP)	PRP	Brazil	60 persons	BCVA
PROTEUS	Figuera 2018 /2016	Ranibuzumab (+PRP)	PRP	Portugal	87 persons	NVD/NVE area
Roohipoor	Roohipoor 2016 / 2019	Bevacuzimab (+PRP)	PRP	Iran	33 persons	Subfoeval CT, BVCA
CLARITY	Various (e.g. Sivaprasad 2017)	Aflibercept	PRP	UK	232 persons	BCVA
Sameen	Sameen 2017	Bevacuzimab (+PRP)	PRP	Pakistan	76 eyes	BCVA
Ali	Ali 2018	Bevacuzimab (+PRP)	PRP	Pakistan	60 eyes	BCVA
DRCRN Protocol S	Various (e.g. Gross 2018)	Ranibuzumab	PRP	USA	305 persons	Various
Messias	Messias 2018	Ranibuzumab (+PRP)	PRP	Brazil	43 eyes	BCVA
PRIDE	Lang 2019	Ranibuzumab (+PRP)	PRP	Germany	106 persons	NVD/NVE area

** Only an unspecified subset of patients had diabetic retinopathy*

Appendix A: MEDLINE search strategy

1 (*Diabetes Mellitus/ or *Diabetes Complications/) and exp *Retinal Diseases/ (1884)
2 Diabetic Retinopathy/ (26180)
3 ((diabet* or DM) adj3 (retinopath* or vitreoretinopath* or vitreo-retinopath* or chorioretinopath* or chorio-retinopath* or maculopath*)).ti,ab,kw. (26964)
4 (((proliferat* or PDR or pre-proliferat* or preproliferat* or non-proliferat* or nonproliferat* or NPDR or background) adj3 (retinopath* or vitreoretinopath* or vitreo-retinopath* or chorioretinopath* or chorio-retinopath*)) and (diabet* or DM)).ti,ab,kw. (7161)
5 (new blood vessel* and diabet*).ti,ab,kw. (243)
6 (((retin* or subretina* or sub-retina* or interretina* or inter-retina* or vitreoretin* or vitreo-retin* or chorioretin* or chorio-retin* or choroid* or macula* or intraocular or intra-ocular or intravitreal or intra-vitreal) adj4 (damage* or deteriorat* or degenerat* or disease* or edema or oedema or neovasculari?ation*)) and diabet*).ti,ab,kw. (11788)
7 ((retinal vein* adj3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or emboli*)) and diabet*).ti,ab,kw. (1281)
8 or/1-7 (39822)
9 exp Vascular Endothelial Growth Factors/ai (8958)
10 exp Receptors, Vascular Endothelial Growth Factor/ai (3201)
11 (anti adj2 VEGF*).ti,ab,kw. (7764)
12 (anti-VEGF* or antiVEGF*).ti,ab,kw. (7881)
13 ((anti vascular or anti-vascular or antivascular) adj2 endothelial growth factor*).ti,ab,kw. (4682)
14 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).ti,ab,kw. (9982)
15 (vascular proliferation adj4 inhibit*).ti,ab,kw. (31)
16 or/9-15 (25019)
17 Angiogenesis Inhibitors/ (26476)
18 exp Angiogenesis Inducing Agents/ai (118)
19 (angiogen* adj2 (antagonist* or inhibit*)).ti,ab,kw. (13679)
20 ((antiangiogen* or anti angiogen* or anti-angiogen*) adj2 (agent* or drug* or effect*)).ti,ab,kw. (9964)
21 (angiostatic adj2 (agent* or drug*)).ti,ab,kw. (102)
22 ((neovasculari?ation or vasculari?ation) adj2 inhibit*).ti,ab,kw. (1149)
23 or/17-22 (41148)
24 Aflibercept*.ti,ab,kw,rn. (2693)
25 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).ti,ab,kw. (280)
26 Bevacizumab/ (12526)
27 Bevacizumab*.ti,ab,kw,rn. (19832)
28 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).ti,ab,kw. (1590)
29 (IVB adj2 inject*).ti,ab,kw. (294)
30 Ranibizumab/ (3947)
31 Ranibizumab*.ti,ab,kw,rn. (5435)
32 (Lucentis or "rhuFab V2").ti,ab,kw. (426)
33 (IVR adj2 inject*).ti,ab,kw. (122)
34 Pegaptanib*.ti,ab,kw,rn. (649)
35 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).ti,ab,kw. (137)
36 or/24-35 (24761)
37 8 and (16 or 23 or 36) (4189)
38 randomized controlled trial.pt. (541863)
39 controlled clinical trial.pt. (94353)
40 randomized.ab. (531653)
41 placebo.ab. (220832)
42 drug therapy.fs. (2365878)
43 randomly.ab. (364519)
44 trial.ab. (565429)
45 groups.ab. (2238084)
46 or/38-45 (5099909)
47 37 and 46 (2714)
48 exp animals/ not humans.sh. (4878861)
49 47 not 48 (2621)

Appendix B: Data items to be collected

Trial level data items to be collected

- Trial registration number, if available
- Method of randomisation
- Trial location(s)
- Date trial started
- Date trial closed
- Anti-VEGF used
- Control arm details
  - E.g. type of laser therapy
- For each treatment arm
  - Dosage and scheduling of treatment (numbers of injections / sessions)
- Details of planned co-interventions

Individual-level data items to be collected

Baseline data

- Participant unique ID (does not include participant name or identifier)
- Date of randomization
- Age at randomization
- Sex
- Ethnicity
- Use of vision aids
  - Glasses prescription
  - Mobility aids
- Employment status
- Diabetes type
- Vision at time of randomisation
  - BVCA
  - Reading ability
- Type of retinopathy
  - proliferative (low or high risk)
  - non-proliferative retinopathy grade
  - presence of maculopathy
  - Vitreous haemorrhage or tractional retinal detachment

Outcomes

- Date or timing of each assessment
- Date or timing of last follow up
- Number of treatments received
- Employment status
- Visual acuity
  - Best corrected visual acuity
  - mean change in BCVA
- Other vison
  - Reading ability
  - vision for driving ability
  - vison for functional blindness
  - clinically significant vision loss
- Use of mobility aids

- Need for subsequent treatment
  - vitrectomy
- Complications and adverse effects
  - Raised intraocular pressure
  - vitreous haemorrhage
  - retinal detachment
  - cataract formation
  - systemic AEs
- Progression of retinopathy
- Peripheral vision
- Visual field changes
- Treatment withdrawal
- Quality of life (NEI-VFQ-25, EQ-5D, SF-36 or any scale)