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Anti-vascular endothelial growth factor (VEGF) drugs for the treatment of retinal conditions

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ABBREVIATIONS

AE	adverse event
AMD	age-related macular degeneration
Anti-VEGF	anti-vascular endothelial growth factor
BCVA	best corrected visual acuity
CDEC	CADTH Canadian Drug Expert Committee
CI	confidence interval
CNV	choroidal neovascularization
DME	diabetic macular edema
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
MD	mean difference
ME	macular edema
NMA	network meta-analysis
OR	odds ratio
PM	pathologic myopia
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RVO	retinal vein occlusion
SAE	serious adverse event
SMD	standardized mean difference
VA	visual acuity
WDAE	withdrawal due to adverse event
Wet AMD	wet age-related macular degeneration

EXECUTIVE SUMMARY

Context and Policy Issues

Retinal conditions have become an important health policy issue due to the large number of people affected by retinal conditions and the widespread adoption of effective but costly anti-vascular endothelial growth factor (VEGF) drugs to treat these conditions. Anti-VEGFs are injected into the eye where they inhibit the abnormal angiogenesis that underlies many diseases that affect the retina and cause vision loss. Ranibizumab was approved for intravitreal injection in 2006, and in 2011, aflibercept became the second anti-VEGF approved for treating retinal conditions. A third anti-VEGF, bevacizumab, is compounded for intraocular injection and used in clinical practice to treat retinal conditions, although it is approved by Health Canada only to treat certain types of metastatic cancer.

Due to the substantial difference in the cost of intraocular administration of compounded bevacizumab and ranibizumab, there is a desire among payers, both within Canada as well as internationally, to assess reimbursement options that include the use of bevacizumab. Consequently, there is interest in assessing the relative clinical effectiveness and cost of all of the anti-VEGF drugs that are used to treat retinal conditions. Therefore, the current project was undertaken by CADTH to review published evidence regarding the relative clinical effectiveness and cost of anti-VEGF drugs for the treatment of retinal conditions. This should provide the Canadian Drug Expert Committee (CDEC) with evidence to develop recommendations regarding the reimbursement of anti-VEGF drugs by public payers in Canada for the treatment of retinal conditions.

Objectives

The objective of this report was to evaluate the comparative efficacy, safety and cost-effectiveness of anti-vascular endothelial growth factor (anti-VEGF) drugs for treating patients with the following retinal conditions.

- Neovascular (wet) age-related macular degeneration (AMD)
- Diabetic macular edema (DME)
- Macular edema due to retinal vein occlusion (RVO)
- Choroidal neovascularization (CNV) secondary to pathologic myopia (PM)

Methods

Clinical Review

A systematic review of published literature was carried out using standard methods. The systematic review was reported using the PRISMA statement,[1] as well as the PRISMA extension[2] statement for reporting of systematic reviews incorporating network meta-analyses. The systematic review methodology was pre-specified and registered with PROSPERO (CRD 42015022041).[3] The population of interest was adults (age ≥ 18 years) with any of the retinal conditions of interest (wet AMD, DME, RVO, and CNV due to PM). The interventions that were included in the review were those anti-VEGF drugs that are used in routine clinical practice in Canada to treat one or more of the conditions of interest, namely aflibercept, bevacizumab, and ranibizumab. Comparators of interest included each of the aforementioned anti-VEGF drugs as well as sham or no treatment. As the intent of this review was to carry out comparisons among the anti-VEGFs, other treatments (such as laser therapy) were not included, although studies were not excluded if other treatments were used in a balanced manner among treatment arms. The efficacy outcomes of interest included outcomes related to changes in visual acuity (specifically, best corrected visual acuity or BCVA). The three efficacy outcomes of primary

interest were therefore: (1) the change in the proportion of patients who experienced an improvement in visual acuity (as reflected by an increase in BCVA of ≥ 15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters); (2) the proportion of patients who experience worsening of vision (a decrease of ≥ 15 ETDRS letters); and (3) the average improvement in visual acuity (as reflected by the mean difference in BCVA at the end of follow-up). Other efficacy outcomes included the number of patients who progressed to legal blindness and changes in vision-related function. Safety outcomes included the frequencies of adverse events (AEs), serious AEs, withdrawals due to AEs, and mortality, as well as harms of interest such as arterial/venous thromboembolic events, bacterial endophthalmitis, increased intraocular pressure, and retinal detachment. We limited this review to parallel or cluster randomized controlled trials (RCTs).

To analyze data from the included studies, meta-analyses were conducted for each of the outcomes specified above in each of the four populations of interest (wet AMD, DME, RVO, and CNV due to PM). The meta-analysis was conducted using R (version 3.1.1).[4] Heterogeneity was quantified using the I^2 statistic. In addition to pairwise meta-analyses, we carried out an indirect comparison using a network meta-analysis (NMA), although this was possible only for the wet AMD population; there were insufficient data to allow for a NMA in any other the other three conditions of interest. The NMA was conducted using R and a random effects Bayesian model with non-informative priors to account for the observed methodological and clinical heterogeneity between the studies.

Economic Review

The approach to the economic evaluation was based on a search of the economic literature for relevant information and a systematic review of the clinical evidence. A literature search for economic evaluations of anti-VEGF therapies (ranibizumab, aflibercept, and bevacizumab) was performed by an information specialist.

The target populations for the economic analyses were adults with wet AMD, DME, RVO, or CNV due to PM. The treatments considered were intraocular injection of aflibercept, bevacizumab, or ranibizumab. The analysis was conducted from the perspective of a provincial Ministry of Health in Canada. Analyses were conducted over a two-year time horizon when possible; a one-year horizon was used where data were unavailable over two years. A 5% discount was applied to all costs in year 2.

Summary of Findings

Key Clinical Findings

The systematic review resulted in the inclusion of 30 individual RCTs (29 publications) in which the efficacy and safety of anti-VEGF drugs were evaluated in patients with wet AMD,[5-17] DME,[18-21] RVO,[22-30] or CNV due to PM.[31-33]

Wet AMD

Effects on Visual Acuity

Ranibizumab versus Bevacizumab

The results of the direct pairwise meta-analysis of ranibizumab versus bevacizumab revealed no statistically significant differences with respect to the proportion of wet AMD patients who experienced a gain of ≥ 15 ETDRS letters (meta-analysis of eight RCTs, 2,950 patients, OR: 1.13 [95% CI, 0.96 to 1.34]), a loss of ≥ 15 ETDRS letters (based on one RCT, 412 patients), or the mean difference in BCVA (seven RCTs, 2,769 patients, MD: 0.51 [95% CI, –0.82 to 1.83]).

Aflibercept versus Bevacizumab

There were no data available to compare aflibercept to bevacizumab for the outcomes of vision gain, vision loss, or mean difference in BCVA.

Ranibizumab versus Aflibercept

Direct pairwise meta-analysis revealed no statistically significant differences between ranibizumab and aflibercept with respect to the proportion of patients who demonstrated a gain of ≥ 15 ETDRS letters (two RCTs, 1,815 patients, OR: 1.01 [95% CI, 0.75 to 1.37]), loss of ≥ 15 ETDRS letters (two RCTs, 1,815 patients, OR: 1.11 [95% CI, 0.72 to 1.71]), and difference in BCVA (two RCTs, 1,907 patients, MD: 0.10 [95% CI, –5.43 to 5.64]).

Other efficacy outcomes

Ranibizumab versus bevacizumab

There was no statistically significant difference between ranibizumab and bevacizumab with respect to the number of patients who progressed to legal blindness (meta-analysis of three RCTs, 1,817 patients, OR: 0.46 [95% CI, 0.07 to 3.26]). There were no data available to allow for analysis of the other efficacy outcomes (i.e., difference in vision-related function).

Aflibercept versus bevacizumab

There were no data with which to compare aflibercept to bevacizumab for any of the other efficacy outcomes of interest.

Aflibercept versus ranibizumab

There was no statistically significant difference between aflibercept and ranibizumab with respect to vision-related function (meta-analysis of two RCTs, 1,632 patients, MD: 2.23 [95% CI, –0.61 to 5.07]). There were no data with which to compare aflibercept to ranibizumab for any of the additional efficacy outcomes of interest.

Indirect comparison of efficacy

Indirect comparisons of the anti-VEGFs via NMA were feasible only for the outcomes of vision gain, vision loss, and mean difference in BCVA in the wet AMD population. The results of the NMA suggested that there are no statistically significant differences among the anti-VEGF drugs with respect to their effects on improving vision, as reflected by the proportion of patients who report an increase in visual acuity of at least 15 ETDRS letters. Similarly, the NMA results suggested that the three anti-VEGFs are similarly efficacious in preventing deterioration of vision in patients with wet AMD, and that the anti-VEGFs appear to be similarly efficacious in improving the mean baseline BCVA. However, there was substantial uncertainty associated with the results of the NMA.

Harms

Anti-VEGFs versus placebo

Intraocular pressure was significantly higher in patients treated with ranibizumab compared to placebo (meta-analysis of two RCTs, 896 patients, OR: 4.80 [95% CI, 2.40 to 9.80]). There were no data comparing aflibercept or bevacizumab with placebo for any of the harms of interest.

Ranibizumab versus bevacizumab

There were no statistically significant differences in terms of harms (i.e., adverse events, serious adverse events, withdrawals due to adverse events and mortality) for the comparison of ranibizumab with bevacizumab.

Aflibercept versus bevacizumab

There were no data comparing aflibercept with bevacizumab for any of the harms of interest.

Aflibercept versus ranibizumab

There were no statistically significant differences in terms of harms when comparing aflibercept with ranibizumab.

DME

Effects on Visual Acuity

Ranibizumab versus bevacizumab

In patients with DME, ranibizumab was not significantly different to bevacizumab with respect to vision gain (one RCT, 412 patients, OR: 1.18 [95% CI, 0.77 to 1.79]), vision loss (one RCT, 412 patients, OR: 1.00 [95% CI, 0.20 to 5.01]), mean BCVA (meta-analysis of two RCTs, 512 patients, SMD: 0.16 [95% CI, –0.02 to 0.33]).

Aflibercept versus bevacizumab

In a single RCT with 414 participants, a significantly greater proportion of DME patients treated with aflibercept experienced an improvement of at least 15 ETDRS letter compared to bevacizumab-treated patients (OR: 0.60 [95% CI, 0.40 to 0.80]). Similarly, the difference in BCVA was greater following aflibercept treatment compared with bevacizumab treatment (MD: –4.20 [95% CI, –6.47 to –1.93]). However, there was no statistically significant difference between aflibercept and bevacizumab in the effects of these treatments on vision loss (OR: 1.01 [95% CI, 0.20 to 5.06]).

Aflibercept versus ranibizumab

In a single RCT with 414 participants, ranibizumab was associated with a significantly smaller proportion of patients who experienced a gain of ≥ 15 ETDRS letters when compared to aflibercept (OR: 0.70 [95% CI, 0.44 to 0.98]). Similarly, the mean difference in BCVA was greater following aflibercept treatment compared with ranibizumab treatment (MD: 2.10 [95% CI, 0.06 to 4.14]). However, there was no statistically significant difference between aflibercept and ranibizumab within the effects of these treatments on vision loss (OR: 1.01 [0.20, 5.06]).

Other efficacy outcomes

There were no data with which to compare any of the anti-VEGF drugs for any of the other efficacy outcomes of interest.

Harms

In DME patients, ranibizumab was associated with a significant risk of increased intraocular pressure relative to placebo (three RCTs, 910 patients, OR: 7.6 [95% CI, 2.9 to 20.4]). Other reported harms and harms of special interest (i.e., arterial thromboembolism, bacterial endophthalmitis, and retinal detachment) were not significantly different between any of the anti-VEGF drugs.

RVO

Effects on Visual Acuity

Ranibizumab versus bevacizumab

Meta-analyses of two RCTs with 173 patients, demonstrated that there were no statistically significant differences between ranibizumab and bevacizumab with respect to the proportion of patients who experienced a gain of ≥ 15 ETDRS letters (OR: 1.03 [95% CI, 0.55 to 1.94]) and the mean difference in BCVA (MD: 0.00 [95% CI, –0.30 to 0.30]). There were no data available to compare the effects of these treatments on vision loss.

Aflibercept versus bevacizumab

There were no data comparing these treatments for vision gain, loss or mean BCVA.

Aflibercept versus ranibizumab

There were no data comparing these treatments for vision gain, loss or mean BCVA.

Other efficacy outcomes

There were no data comparing any of the anti-VEGF drugs for any other efficacy outcomes of interest.

Harms

Ranibizumab versus bevacizumab

In a single RCT with 77 patients, there were no statistically significant differences between ranibizumab and bevacizumab with respect to the frequencies of serious adverse events (OR: 2.11 [95% CI, 0.18 to 24.37]) and increased intraocular pressure (OR: 0.33 [95% CI, 0.01 to 8.44].

Aflibercept versus bevacizumab

There was no data comparing these treatments for any harms of interest.

Aflibercept versus ranibizumab

There were no data comparing these treatments for any harms of interest.

CNV due to PM

Effects on Visual Acuity

Ranibizumab versus bevacizumab

In patients with CNV due to PM, there were no statistically significant differences in the effects of ranibizumab and bevacizumab on the mean difference in BCVA at follow-up (meta-analysis of two RCTs, 80 patients, SMD: –0.13 [95% CI, –0.57 to 0.31]) or the proportion of patients who experienced vision gain (one RCT, 32 patients, OR: 0.77 [95% CI, 0.19 to 3.17]) when comparing ranibizumab to bevacizumab. There was no data comparing these treatments for the outcome of vision loss.

Aflibercept versus bevacizumab

There were no data comparing these treatments in terms of vision gain, loss, or mean BCVA.

Aflibercept versus ranibizumab

There were no data comparing these treatments in terms of vision gain, loss, or mean BCVA.

Other efficacy outcomes

There was no data comparing any of the anti-VEGF drugs for any other efficacy outcomes of interest.

Harms

There were no data comparing any of the anti-VEGF drugs for any harms of interest.

Key Economic Findings

While several studies were identified in the literature, very few of them were fully applicable to the research question of this review. In addition, no studies were conducted in a Canadian context. As no overall conclusions could be inferred from the available economic literature, the results of the current clinical review were used to inform an economic analysis. Costs were based on Canadian sources, dose and frequency of administration were based on clinical input, product monograph recommended use, and clinical studies. Exploratory analyses were used to consider areas of uncertainty and possible budget impact.

Wet AMD

In wet AMD patients, bevacizumab was substantially less costly than either ranibizumab or aflibercept. Under base case pricing and assuming that ranibizumab and bevacizumab are dosed monthly while aflibercept is dosed every two months after three initial monthly doses, the cost of two years of ranibizumab therapy ($39,360 per patient) was $35,963 more than the cost of two years of bevacizumab therapy ($3,397 per patient), while two years of aflibercept ($19,364 per patient) cost $15,967 more than bevacizumab.

DME

In DME patients, bevacizumab was substantially less costly than either ranibizumab or aflibercept. Under base case pricing and when considering frequencies derived from the aflibercept product monograph and the RESTORE study, the two-year cost of aflibercept ($20,887 per patient) was $18,898 more than the two-year cost of bevacizumab ($1,989 per patient), while the two-year cost of ranibizumab ($18,160 per patient) was $16,171 more than bevacizumab.

RVO

In RVO patients, bevacizumab was substantially less costly than either ranibizumab or aflibercept. Under base case pricing, when all anti-VEGFs are assumed to have nine injections in the first year and three in the second, the two-year cost of ranibizumab ($19,920 per patient) is $18,201 more than that of bevacizumab ($1,719 per patient) while the two-year cost of aflibercept ($18,058 per patient) is $16,339 more than bevacizumab.

CNV due to PM

In patients with CNV due to PM, bevacizumab was substantially less costly than either ranibizumab or aflibercept. Under base case pricing, when all anti-VEGF drugs are assumed to have four injections over the first year of treatment, the one-year cost of ranibizumab ($6,720 per patient) is $6,140 more than the one-year cost of bevacizumab ($580 per patient), while the one-year cost of aflibercept ($6,092 per patient) is $5,512 more than bevacizumab.

Key Limitations

The main limitation of the present study was the paucity of clinical evidence to allow all pairwise combinations of anti-VEGF treatments to be analyzed for all outcomes of interest across all four conditions of interest. The paucity of data meant that there were not enough studies available to perform indirect comparisons among treatments for which head-to-head studies were unavailable. Where sufficient data were available to allow for multiple pairwise comparisons within an individual condition, in many cases the evidence available comprised only a single RCT, including vision gain, vision loss, and mean difference in BCVA for DME, vision gain and mean difference in BCVA for RVO, and vision gain for CNV due to PM. For outcomes and conditions where only one study was available, there is a high degree of uncertainty associated with conclusions related to these data.

Another key limitation is a lack of information presented regarding the appropriateness or effectiveness of switching patients among the anti-VEGFs, which was beyond the scope of the current review.

The cost minimization analyses conducted were based on the systematic review findings of similar clinical effectiveness and harms among all three anti-VEGF treatments. While the evidence base supporting similar clinical efficacy in patients with wet AMD is fairly robust, there is more uncertainty regarding harms in wet AMD and the relative clinical effects of the anti-VEGFs in the other conditions; this uncertainty is due more to a paucity of data rather than conflicting evidence. Should additional comparative clinical information become available, the cost-effectiveness of the anti-VEGF treatments in these populations may need to be re-evaluated.

Information on how treatments are administered in actual practice (dose and frequency) is not currently available for all the indications of interest. As a result, economic analyses were based on recommended dosing and dosing from the clinical studies that support similar clinical effects. Should real-world information become available, the results of the analysis may need to be revised.

Finally, reimbursement of anti-VEGF treatments varies among provincial, territorial, and federal jurisdictions, depending on the existence of retinal programs or negotiations with manufacturers, the details of which are often not publicly available. These complicate the accurate estimate of actual costs incurred by drug plans or programs.

Conclusions and Implications for Decision-Making

The results of the present study suggest that ranibizumab and bevacizumab have similar effects on visual acuity and other vision-related outcomes in patients with wet AMD, DME, RVO, or CNV due to PM. The effects of aflibercept on visual acuity were similar to those of ranibizumab and bevacizumab in patients with wet AMD. There were insufficient data to compare aflibercept to ranibizumab or bevacizumab in patients with RVO and CNV. In patients with DME, the results of one trial suggested that aflibercept might improve vision to a greater extent than ranibizumab and bevacizumab in patients with poor visual acuity, although this does not reflect a clinically meaningful difference.

Our study did not reveal any notable differences with respect to the potential for aflibercept, bevacizumab, and ranibizumab to do harm to patients with retinal conditions, both for non-specific safety outcomes as well as harms of special interest, such as bacterial endophthalmitis and retinal detachment. However, safety data were limited, and this conclusion is therefore highly uncertain. Of note, there does not appear to be any evidence in the literature to suggest that properly compounded bevacizumab is associated with more harm than ranibizumab in patients with retinal conditions.

While our study revealed that other than a potential advantage to using aflibercept within a subgroup of DME patients, there is no evidence of any major differences in the clinical effects of

the three anti-VEGFs across the conditions of interest, the results of our pharmacoeconomic analysis highlighted differences in cost among the anti-VEGFs. Consequently, the use of compounded bevacizumab where appropriate in patients with wet AMD, DME, RVO, or CNV due to PM could produce substantial cost savings to public payers.

1. CONTEXT AND POLICY ISSUES

1.1. Background and Rationale

Retinal conditions are an important health issue from both a clinical and health policy perspective. For example, age-related macular deterioration (AMD) is the main cause of irreversible blindness in persons aged 65 years or older in industrialized countries, and approximately 2 million Canadians aged 50 years or older have this condition.[34]

Angiogenesis is the process by which new blood vessels are created from pre-existing vasculature. Abnormal angiogenesis is a hallmark of diseases such as cancer and the wet form of AMD (wet AMD).[35] In the eye, angiogenesis occurs due to the carefully balanced interplay of growth-promoting and growth-inhibiting factors. Evidence suggests that vascular endothelial growth factor (VEGF) is one of the primary factors promoting abnormal angiogenesis within the eye. Elevated intraocular VEGF levels appear to be associated with intraocular neovascularization, a vascular abnormality that is common to many retinal conditions such as AMD, diabetic retinopathy, and retinal vein occlusion. This provides the rationale for pharmacological inhibition of abnormal angiogenesis to treat these retinal conditions.[36] In addition, VEGF is involved in mediating vascular permeability, which is of particular importance in the pathogenesis of DME.

In February 2004, the FDA approved bevacizumab (Avastin) for the treatment of metastatic cancer of the colon and rectum. Bevacizumab is a recombinant, humanized monoclonal antibody that reduces angiogenesis that is associated with certain metastatic cancers by inhibiting VEGF. The first anti-VEGF drug to be approved by the FDA for intravitreal use was pegaptanib (Macugen), in December 2004.[36] This approval was followed by the approval of ranibizumab (Lucentis) 18 months later, in June 2006. The latest anti-VEGF drug, approved in 2011 for intravitreal use, is aflibercept (Eylea) (Table 1). Table 1 describes anti-VEGF drugs used currently in Canada to treat retinal conditions.

TABLE 1: DRUGS AVAILABLE FOR RETINAL CONDITIONS IN CANADA

Product (Manufacturer/Distributor)	Generic Name	Health Canada-Approved Retinal Indications[a]
Eylea (Regeneron/Bayer)	aflibercept	Neovascular (wet) AMD
		Visual impairment due to ME secondary to CRVO
		DME
Lucentis (Genentech/Novartis)	ranibizumab	Neovascular (wet) AMD
		Visual impairment due to DME
		Visual impairment due to ME secondary to RVO
		Visual impairment due to CNV secondary to PM
Avastin (Genentech/Hoffmann-La Roche)	bevacizumab	NA[b]

AMD, age-related macular degeneration; CNV, choroidal neovascularization; CRVO, central retinal vein occlusion; DME, diabetic macular edema; ME, macular edema NA, not applicable; PM, pathologic myopia; RVO, retinal vein occlusion.

[a] Source of information: Health Canada Drug Product Database.[37]

[b] CADTH is not aware of regulatory filing to Health Canada for bevacizumab use in wAMD, DME, BRVO, CRVO, or CNV due to PM.

While aflibercept acts as a soluble decoy receptor that inhibits the binding and activation of certain VEGF receptors,[35] ranibizumab and bevacizumab bind VEGF directly to inhibit the binding of VEGF molecules to receptors. Bevacizumab is a recombinant humanized monoclonal antibody that acts as a non-specific VEGF inhibitor, while ranibizumab is a monoclonal antibody fragment derived from the same antibody as bevacizumab.[35] Although, to the best of CADTH's knowledge, bevacizumab has not been reviewed by Health Canada for the treatment of retinal conditions, compounded bevacizumab started to be used to treat retinal conditions within a year of it becoming available for cancer therapy.[38] After it had been approved by the FDA for an oncology indication, Dr. Phillip Rosenfeld from the University of Miami administered bevacizumab intravenously (IV) to 18 patients with neovascular AMD. Their preliminary findings suggested that the clinical benefits of IV bevacizumab were similar to those of intravitreal ranibizumab; however, Dr. Rosenfeld's group was concerned about the serious thromboembolic adverse events of bevacizumab, such as myocardial infarction (MI) and stroke, reported in patients with cancer. In the summer of 2005, Rosenfeld converted the molar amount of bevacizumab to be injected into the eye using the same low volume as ranibizumab; his group then published two successful case reports in July 2005. The first patient had AMD, whereas the second patient had central retinal vein occlusion (CRVO). The publication of these case reports led to the quick uptake of intraocular use of bevacizumab around the world.[38] Canadian physicians have successfully used compounded bevacizumab to treat patients with retinal conditions for several years prior to the approval by Health Canada of ranibizumab for intraocular injection.

Due to their effectiveness and favourable safety profile, the anti-VEGFs have quickly become established as the standard of care for the treatment of retinal conditions. However, ranibizumab and aflibercept, both of which are approved for treating several retinal conditions (Table 1) are costly therapies, particularly when compared to the cost of intraocular injection of bevacizumab. Indeed, from a payer's perspective, the use of bevacizumab in clinical practice for the treatment of AMD may be associated with expenditures that are 30 times lower than for ranibizumab.[34] Therefore, interest has grown among drug regulators and payers in reconsidering current reimbursement policies favouring use of ranibizumab over bevacizumab. For example, in November 2014, the French National Security Agency of Medicines and Health Products (Agence Nationale de Sécurité du Médicament et des Produits de Santé [ANSM]) sent a letter to the manufacturer of Avastin (bevacizumab) asking for any data it had on file regarding the use of bevacizumab in the treatment of wet AMD, as well as any information on ongoing trials on this topic. This initiative highlights possible plans at ANSM to issue a temporary authorization to use bevacizumab for treating wet AMD.[39] Other European countries have already developed reimbursement policies for bevacizumab; in Italy, bevacizumab is reimbursed by the national health service, whereas in Germany, the national association of ophthalmologists (BDOC) developed contractual agreements with several private insurance companies to reimburse bevacizumab.[34] In the US, Medicare as well as private insurers are reimbursing intravitreal use of bevacizumab.[34] In Canada, British Columbia now reimburses bevacizumab, in addition to ranibizumab and aflibercept, for three retinal disorders: wet AMD, diabetic macular edema (DME), and CRVO.[40] Two other provinces also reimburse both ranibizumab and bevacizumab. In Nova Scotia, these two anti-VEGF drugs have exceptional

drug formulary status for the treatment of AMD; however, patients must receive the treatment in a hospital or a designated eye centre.[34] In Manitoba, ranibizumab has been reimbursed since 2010; bevacizumab therapy is available at the Eye Care Centre of Excellence of Misericordia Health Centre in Winnipeg.[34,41]

With the recent approval of aflibercept for the treatment of several retinal conditions, there is interest in assessing the relative clinical effectiveness and cost of all of the anti-VEGF drugs that are used currently to treat retinal conditions. There are three policy questions for this project, which reflect the information needs of CADTH's jurisdictional clients:

1. Based on clinical evidence and cost, which anti-VEGF drug(s) should reimbursed for the treatment of neovascular (wet) AMD, DME, macular edema due to RVO, and CNV secondary to PM?
2. Are there subgroups within the aforementioned indications within which drug(s) identified in Question 1 should be reimbursed?
3. What is the preferred dosing regimen(s) for drug(s) identified in Question 1?

The current project includes a review of the relative clinical effectiveness of anti-VEGF drugs for the treatment of retinal conditions as well as an economic evaluation. This evidence will be used by the CADTH Canadian Drug Expert Committee (CDEC) to develop recommendations regarding the reimbursement of anti-VEGF drugs by public payers in Canada.

1.2. Objectives of the Report

The objective of this report was to evaluate the comparative efficacy and safety of anti-vascular endothelial growth factor (anti-VEGF) treatments for treating patients with the retinal conditions presented in Table 2.

TABLE 2: RETINAL CONDITIONS INCLUDED IN THE CURRENT REVIEW

Neovascular (wet) AMD
DME
Macular edema due to RVO*
CNV secondary to PM

* This includes both branch and central retinal vein occlusion (BRVO and CRVO).

AMD, age-related macular degeneration; CNV, choroidal neovascularization; CRVO, central retinal vein occlusion; DME, diabetic macular edema; ME, macular edema NA, not applicable; PM, pathologic myopia; RVO, retinal vein occlusion.

1.2.1. Research Questions

The research questions for this project are presented below. These questions formed the basis of the clinical and economic evaluations.

1. What is the comparative efficacy and safety of anti-VEGF drugs for treating patients with the conditions listed in Table 2?
2. What is the comparative cost-effectiveness of anti-VEGF drugs for treating patients with the conditions listed in Table 2?

2. METHODS

2.1. Systematic Review of Clinical Evidence

Methods of the systematic review were pre-specified and documented in a draft protocol. The protocol was compiled by the Drug Safety and Effectiveness Network/Canadian Institutes of Health Research-funded Methods and Applications Group for Indirect Comparisons (MAGIC) team and revised based on input from the Canadian Agency for Drugs and Technology in Health (CADTH), clinical experts, patient advocacy groups, and industry stakeholders. The draft protocol was posted on the CADTH website for public stakeholder feedback. This feedback was taken into consideration while developing the final protocol. The final protocol is presented below and is registered with PROSPERO (CRD 42015022041).[a]

The systematic review was reported using the PRISMA statement,[1] as well as the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses.[2]

2.1.1. Literature Search Strategy

We searched the following bibliographic databases from inception until November 13, 2015: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; Cochrane Central Register of Controlled Trials via Ovid, and PubMed. Grey literature (literature that is not widely available or commercially published) was identified by searching relevant websites from the following sections of the CADTH Grey Matters checklist: Clinical Trials (ongoing).[42] We used Google and other Internet search engines to search for additional Web-based materials, including conference abstracts. We obtained additional studies by reviewing the references of all included studies and based on feedback from clinical experts, patient advocacy groups, and industry stakeholders. In addition, we contacted the three manufacturers of the anti-VEGF drugs of interest for information regarding potentially relevant trials.

The literature search strategy was developed by an experienced information specialist affiliated with the MAGIC team. The search strategy was peer-reviewed by an information specialist from CADTH using the PRESS statement.[43] After minor modifications, the final literature search was conducted by the CADTH information specialist

The literature search consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords (Appendix 1). The main search concepts were anti-VEGF drugs and the relevant retinal conditions. Validated methodological filters were applied to limit retrieval to RCTs.[44] Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language, but non-English language articles were excluded during screening.

2.1.2. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria used to identify relevant studies for inclusion are described in Table 3.

[a] Note that this study is part of a larger research project addressing the comparative effectiveness of anti-VEGF drugs for retinal conditions. For more details, see http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015022041.

TABLE 3: INCLUSION AND EXCLUSION CRITERIA FOR IDENTIFYING RELEVANT STUDIES[b]

Inclusion Criteria	
Study Design	Parallel RCTs
Population	Adults[a] with any of the following: Neovascular (wet) AMD DME Macular edema due to RVO[b] CNV secondary to PM
Interventions	Aflibercept, bevacizumab, and ranibizumab
Comparators	Aflibercept, bevacizumab, ranibizumab, and placebo
Outcomes	Efficacy outcomes: Change (gain or loss) in BCVA of ≥ 15 ETDRS letters Change from baseline in BCVA Blindness (legal) Vision-related function[c] Harms outcomes: AEs SAEs WDAEs Mortality Harms of special interest: Arterial/venous thromboembolic events[d] Bacterial endophthalmitis[e] Increased intraocular pressure[f] Retinal detachment
Time Periods	All periods of time for publication and duration of follow-up are included.
Exclusion Criteria	
Study design: Quasi-RCTs, non-randomized studies, crossover trials. Population: Age < 18 years. Intervention: Administration of anti-VEGF drugs by any means other than intravitreal injection. Comparators: Surgery (e.g., cataract removal). Outcomes: No outcomes of interest.	

AE = adverse event; AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; PM = pathologic myopia; RCT = randomized controlled trial; RVO = retinal vein occlusion; SAE = serious adverse event; VEGF = vascular endothelial growth factor; WDAE = withdrawal due to adverse event.

[a] Age ≥ 18 years.

[b] Included macular edema due to central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).

[c] Assessed by validated measures.

[d] Arterial thromboembolic events included myocardial infarction (MI), unstable angina, ischemic stroke, transient ischemic attack (TIA) or any other arterial thromboembolic event that author(s) reported. Venous thromboembolic events included deep vein thrombosis (DVT), pulmonary embolism (PE), cavernous sinus thrombosis, central or branch retinal vein occlusion, or any venous thromboembolic event that author(s) reported.

[e] Defined as an inflammatory reaction of the intraocular fluids or tissues caused by microbial organisms.

[f] Increased intraocular pressure was defined as a fluid pressure of > 21 mm Hg inside the eye, which is two standard deviation over the population mean (ref: LESKE MC. THE EPIDEMIOLOGY OF OPEN-ANGLE GLAUCOMA: A REVIEW. American Journal of Epidemiology. 1983;118(2):166-91.).

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[b] Note that this study is part of a larger research project addressing the comparative effectiveness of anti-VEGF agents for retinal conditions. For more details, see http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015022041.

We included populations with wet AMD, DME, RVO, and CNV due to PM, who were being treated with aflibercept, bevacizumab or ranibizumab. The RVO population included both branch RVO and central RVO, and we intended to investigate these subgroups separately in a subgroup analysis. However, due to the limited number of included studies with RVO, subgroup analysis was not feasible.

We chose to limit our review to the highest quality evidence available by including only parallel and cluster randomized trials. Therefore, study designs that are more prone to bias, including crossover RCTs (i.e., patients receive a sequence of treatments longitudinally, which may result in carryover effects) and trials that used quasi-random methods to allocate patients to treatment groups (e.g., consecutive allocation), were excluded. With respect to interventions, the anti-VEGF pegaptanib (Macugen) was excluded, because this treatment is no longer available for use in Canada. Studies that included patients who had undergone surgical procedures (e.g., cataract surgery) were excluded due to the potential for confounding effects. Studies that included treatments other than those specified in the protocol were eligible for inclusion if the other treatments were administered to all treatment groups. Studies reported in languages other than English were excluded to allow for the project timelines to be met.

We captured BCVA data derived from Snellen and ETDRS letter charts or the logarithm of the Minimum Angle of Resolution (logMAR) chart.[45] The Snellen chart is the current standard for measurement of visual acuity in clinical practice.[45-47] The Snellen chart has letters of different sizes arranged from largest at the top to smallest at the bottom, which are read, one eye at a time, at a distance of 6 metres (20 feet). A mean BCVA of 0.41 is considered a clinically important difference.[48] The test-retest variability of the Snellen chart is large, varying from ±5 to 16.5 letters in normal patients.[49,50] The ETDRS chart is the 'gold standard' for measuring visual acuity in clinical trials.[45] The test-retest variability of the ETDRS charts are better than the Snellen charts, varying from ±3.5 to 10 letters.[51] A change of at least 10 letters (or two lines) is required to capture a true clinical change in visual acuity.[45,52]

With regards to assessment of vision-related function, the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) is a self-reported vision-targeted survey questionnaire that assesses the influence of visual impairment on health-related quality of life (HRQOL).[53] The instrument measures 12 domains (subscales) of HRQOL, including overall health; overall vision; difficulty with near-vision and distance activities; ocular pain; driving difficulties; limitations with peripheral vision and colour vision; social functioning; role limitations; dependency and mental health symptoms related to vision. Each sub-scale is scored using the average of all items within that sub-scale for an individual. Scores for each sub-scale range from 0 to 100. The average of all sub-scale scores is used to calculate an overall score. Changes in the NEI VFQ overall and sub-scale scores of 10 points or more are associated with clinically relevant changes in vision.[54] Field tests of the instrument reported it to be a reliable and valid measure in patients with age-related cataracts, AMD, diabetic retinopathy, primary open-angle glaucoma, cytomegalovirus retinitis, and low vision from any cause.[53]

3.1.3 Study selection

Citations from the literature search were imported into online systematic review software called Synthesi.SR.[55] The inclusion criteria were also imported into the software as a questionnaire (Appendix 3), which was used for level 1 screening of citations (i.e., titles and abstracts) and level 2 screening of potentially relevant full-text articles.

For level 1 screening, two training exercises were conducted to ensure high inter-rater agreement among the 14 members of the review team. For each training exercise, a random sample of 50 citations from the literature search was screened independently by all team members. The per cent agreement was calculated to determine inter-rater agreement.[56,57] Level 1 screening proceeded after 80% agreement had been achieved among the reviewers on the second training exercise. Paired reviewers conducted the level 1 screening of each citation, independently. The estimated frequency of disagreement was 8%, and this was resolved by a third reviewer. Full-text articles of potentially relevant citations identified by at least one reviewer were retrieved for level 2 screening.

A training exercise was conducted for level 2 screening using a random sample of 20 full-text articles. We proceeded to level 2 screening after 70% agreement had been achieved with the first training exercise. Paired reviewers independently screened each full-text article. The estimated frequency of disagreement was 14%. Again, any disagreement was resolved by a third reviewer. In addition, a third reviewer examined all studies that were deemed relevant at level 2 screening to ensure that they fulfilled the eligibility criteria.

2.2. Data Extraction Strategy

Study flow through the different phases of the systematic review is summarized using the PRISMA flowchart,[1] including the frequencies and reasons for exclusion at both level 1 and level 2 screening (see Appendix 4).

The review coordinator developed a data abstraction form with input from other team members, including two physicians. The team piloted and refined the form two times, each time using five randomly-selected included studies. Subsequently, paired reviewers abstracted data from the included studies, independently. Numerical data available only in figures were extracted using WebPlotDigitizer.[58] A third reviewer conducted a quality check on all data, resolving all discrepancies found in the data.

From the included studies, we extracted the following data:

- Study characteristics, e.g., parallel or cluster trial, single- or multi-centre, overall sample size, study duration
- Patient characteristics, e.g., retinal condition, overall mean age, sex, inclusion and exclusion criteria, and selected risk factors, including diabetes, mean glycosylated hemoglobin (A1C) levels, patients with A1C ≥ 8.5%, patients with hypertension, and presence of phakic lens
- Intervention characteristics; e.g., previous treatment for retinal conditions, treatment plan with anti-VEGF drugs (e.g., three monthly intravitreal injections, repeated injections if patients had vision loss ≥ 5 letters on the ETDRS chart), planned and actual dose and frequency of intravitreal injections, treatment duration

Outcomes of interest are listed in Section 2.2 and were pre-specified in the protocol. As recommended by the Cochrane Handbook,[44] only the longest duration of follow-up was abstracted.

Multiple reports of the same trial (i.e., companion reports) were identified using the trial registration identifier (e.g., ClinicalTrials.gov, NCT00593450 for the CATT trial), trial name (e.g., VIEW), or a juxtaposition of the author names, treatment comparisons, sample sizes and outcomes.[59] All companion reports were considered in the extraction of the trial data, and differences in the reported data across the reports were identified (e.g., sample sizes, study characteristics, outcome results). For each set of companion reports, two abstractors discussed

the differences, selected the data to be extracted, and if necessary, consulted an arbitrator in the selection. For each set of papers, one was considered the major publication and the subsequent report(s) were used for supplementary material only. Outcome data (e.g., mean BCVA values) available at multiple follow-up time points were extracted and data corresponding to the longest duration of follow-up were used in the meta-analysis.[44]

3.1.5. Quality appraisal of individual trials

The risk of bias in the included trials was appraised using the Cochrane risk-of-bias tool.[60] The assessment was conducted at the study-level for selection bias (i.e., random sequence generation and allocation concealment), attrition bias (i.e., incomplete outcome data), reporting bias (i.e., selective reporting), and other bias (e.g., funding source). It was conducted at the outcome-level for performance bias (i.e., blinding of patients and personnel) and detection bias (i.e., blinding of outcome assessment). The outcome-level assessment was conducted for the primary outcome as stated in the protocol for registered trials, which was vision gain (e.g., ≥ 15 ETDRS letters) or BCVA in the majority of included trials. When the primary outcome was not clearly stated, it was determined using an algorithm.[61,62] In brief, we selected the outcome that was listed in the title or objectives, most serious clinical outcome among all the trial outcomes, or first reported outcome in the results section of the trial report. The outcome-level assessment of performance or detection bias was used as a proxy for the corresponding study-level assessment (e.g., we did not assess performance bias using any of the secondary outcomes).

The risk-of-bias assessment was conducted by pairs of reviewers, independently. Conflicts were resolved by discussion or the involvement of a third reviewer. The risk of bias in individual trials was tabulated.

2.3. Clinical Data Analysis

2.3.1. Summary Measures

The odds ratio (OR) was used to summarize treatment effects based upon binary outcomes (e.g., proportion of patients with improvement in visual acuity, number of patients who progressed to blindness, thromboembolism, etc.). The OR was selected for use to allow comparison of meta-analysis (MA) estimates with the estimates derived from the NMA, for which an OR is provided as an effect measure. For dichotomous outcomes, studies reporting zero events in all groups were excluded from the data analysis, while for studies with zero events in one or more groups (but not all), 0.5 was added to all cells.

For continuous outcome measures, the standardized mean difference (SMD) was used for treatment comparisons involving trials that reported BCVA using different measurement charts (e.g., ETDRS or Snellen charts) or fractional expressions for visual acuity (e.g., 20/200, 6/60, 0.10), where the mean in each group was standardized using the corresponding standard deviations to allow the same unit of measurement. The mean difference (MD) was used when BCVA was reported consistently across trials (e.g., all trials reported ETDRS measures). The MD was used for treatment comparisons of visual functioning based upon composite scores from the National Eye Institute 25-Item Visual Function Questionnaire.

We summarized study characteristics and assessed variation in these characteristics across the included trials (e.g., methodological heterogeneity). We summarized patient characteristics and assessed clinical heterogeneity across trials (e.g., variation in mean ages, sex distributions, baseline BCVA, prior treatments of retinal conditions, inclusion and exclusion criteria).

2.3.2. Direct Comparisons

Synthesis of results

We conducted meta-analyses of pairwise comparisons of each individual anti-VEGF drug (e.g., bevacizumab versus ranibizumab). This was done separately for each of the four retinal conditions. We calculated treatment effect estimates at the individual-trial level (e.g., OR for ranibizumab relative to bevacizumab for the proportion of patients who had an improvement in BCVA of at least 15 ETDRS letters), plotted these estimates in forest plots, and visually (using width of confidence intervals) inspected variation in trial-specific estimates (i.e., within-study statistical heterogeneity). We quantified the between-trial variation using the I^2 statistic, with values of I^2 >75% indicating substantial statistical heterogeneity.[44] Pooled treatment effect estimates (and 95% confidence intervals) were derived using the meta-analytical random effects model.[63] We planned to investigate differences among the anti-VEGFs with respect to the relationship between varying dosages and/or injection frequencies versus visual acuity outcomes using subgroup analysis. However, we were unable to do so due to the small number of included studies for each outcome for the four retinal conditions of interest. The results from multiple arms of the same anti-VEGF treatments at different dosages were summed using the guidance in the Cochrane handbook.[44]

Where studies did not provide standard deviations, missing data were imputed from available data using established methods.[63] Imputation was necessary in deriving pooled estimates of treatment effect in BCVA measures and vision function (as measured by NEI VFQ-25 scores).

The meta-analysis was conducted using the "metafor" package[64] in R (version 3.1.1).[4]

2.3.3. Indirect Comparisons

We used network meta-analysis to assess the relative effectiveness of the anti-VEGF drugs via indirect comparison.[65] Although we had planned to conduct an NMA for all outcomes across all conditions, a network meta-analysis was feasible only for the wet AMD data alone, because there were insufficient data to allow for an NMA in any of the other three conditions of interest. The NMA was conducted using a Bayesian random effects model using non-informative priors to account for the observed methodological and clinical heterogeneity between the studies. The network meta-analysis was conducted via Monte Carlo simulation with 100,000 iterations using WinBugs.[66]

A common heterogeneity was assumed across treatment comparisons since the included treatments were of the same nature, which was confirmed by clinicians. We planned to assess for other assumptions in the network meta-analysis (e.g., consistency between direct and indirect evidence), but were unable to because of the small number of studies included per outcome. In addition, the network was open (i.e., no closed loops within the network). This means that direct evidence was not available for every treatment comparison, and we were therefore unable to combine direct and indirect evidence in some comparisons, or assess consistency between them. However, consistency was indirectly examined by comparing the fitted NMA results with pairwise direct and indirect estimates. We planned to conduct sensitivity and subgroup analyses for potential effect modifiers and risk of bias, but these were not feasible due to the small number of included studies available.

The NMA model convergence was assessed visually by examining trace and history plots, as well as statistically by calculating the Gelman Rubin statistic.[67] Ranking probabilities and surface under the cumulative ranking curve (SUCRA) values were obtained from the fitted NMA point estimates for vision gain, vision loss, and difference in BCVA. League tables and forest plots were used to summarize pairwise comparisons.

2.4. Pharmacoeconomic Analysis

2.4.1. Type of Economic Evaluation

To address the research question regarding the cost-effectiveness of ranibizumab, aflibercept and bevacizumab for the treatment of wet AMD, DME, RVO, and CNV, a literature search was conducted to determine whether any available economic evaluations could be used to inform the research question.

Based on the findings from the economic literature search and the CADTH clinical review, the type of economic evaluation to be conducted was determined. Where clinically meaningful differences among treatments were observed from the clinical review and/or NMA, a cost-utility analysis would be conducted for the corresponding indications. Where clinically meaningful differences among treatments are not observed, and where differences among treatments could be accounted for in health care resource use, this would be explored in a cost minimization analysis. Identified areas of uncertainty would be explored in sensitivity analyses.

2.4.2. Economic Literature Search

A literature search for economic evaluations of anti-VEGF therapies (ranibizumab, aflibercept, bevacizumab, and pegaptanib) was performed by an information specialist.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; PubMed; and the University of York Centre for Reviews and Dissemination NHS Economic Evaluations Database. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were anti-VEGF therapies (ranibizumab, aflibercept, bevacizumab, and pegaptanib) and economic evaluations.

A methodological filter was applied to limit retrieval to economic studies. The search was run on May 28, 2015. Retrieval was not limited by publication year, but was limited to English language publications. See Appendix 2 for the detailed search strategies.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist,[42] which includes the websites of health technology assessment agencies and other economics-related resources. Google and other Internet search engines were used to search for additional web-based materials.

The following inclusion criteria were used to identify citations from the formal literature search for an in-depth review:

- Economic evaluations
- Primary study or review of studies
- Comparison of aflibercept, bevacizumab, and/or ranibizumab intravitreal injections for the treatment of wet AMD, DME, RVO, or CNV due to PM
- Includes and reports costs or resource use information and cost-effectiveness results.

The following were excluded:

- Theoretical papers
- Conference abstracts
- Non-human studies

- Combination therapy
- Studies focused on pegaptanib (discontinued in Canada as of September 2014).

2.4.3. Target Population

The target population for the economic analysis matched that specified in the systematic review protocol, namely adults with any of the following:

- Neovascular (wet) AMD
- DME
- Macular edema due to RVO
- CNV secondary to PM

2.4.4. Treatments

We considered the following treatments: intraocular injection of aflibercept, bevacizumab, or ranibizumab.

2.4.5. Perspective

This analysis was conducted from the perspective of a provincial Ministry of Health in Canada.

2.4.6. Efficacy and Harms

The relative efficacy and safety of the anti-VEGFs in patients with retinal conditions were informed based on a review of the economic literature and a systematic review and analysis of clinical evidence.

2.4.7. Time Horizon

Analyses were conducted over a two-year time horizon when possible; a one-year horizon was used where data were unavailable over two years. A 5% discount was applied to all costs in year 2.

2.4.8. Data Inputs

Frequency of Treatment Administration

Wet AMD

According to the product monograph,[68] ranibizumab treatment is recommended once a month for patients with wet AMD, with an alternate schedule of one injection every three months if monthly dosing is not feasible. The aflibercept product monograph recommends that patients with wet AMD receive three monthly doses, followed by doses every two months.[69] For the purposes of these analyses, it was assumed that bevacizumab would be dosed at a frequency equal to that of ranibizumab (Table 4).

TABLE 4: FREQUENCIES OF INJECTIONS USED IN WET AMD SCENARIOS

Anti-VEGF drug	Frequency assumed	# injections in Year 1	# of injections in Year 2
Product monograph dosing; bevacizumab assumed equal to ranibizumab			
Ranibizumab	Monthly injections[68]	12	12
Aflibercept	Injections every month for 1st three months, then every other month[69]	7	6
Bevacizumab	Monthly injections (assumed)	12	12
Product monograph dosing, alternate monograph dosing for ranibizumab; bevacizumab assumed equal to ranibizumab			
Ranibizumab	Injections every month for 1st three months, then every three months[68]	6	4
Aflibercept	Injections every month for 1st three months, then every other month[69]	7	6
Bevacizumab	Injections every month for 1st three months, then every three months (assumed)	6	4

DME

The product monograph recommended dosing of aflibercept for patients with DME is monthly injections for the first five months, with bi-monthly injections thereafter.[69] In contrast, the ranibizumab product monograph specifies that ranibizumab should be given monthly for DME patients until maximum visual acuity is achieved and confirmed to be stable for three consecutive months, with monthly injections restarted after a loss of visual acuity until it is stable for another three months.[68] The ranibizumab RESTORE trial[70] was conducted under this algorithm; the mean number of injections used by patients in the ranibizumab monotherapy group was 7.0 in year 1, while patients in the extension study[71] who had started on ranibizumab monotherapy used and average of 3.9 doses of ranibizumab in year 2. It should be noted that patients in the extension study could also receive laser therapy if deemed appropriate, although the majority (75.9% in the prior ranibizumab monotherapy arm) did not receive laser therapy within the two-year extension period. To be conservative, it was assumed that bevacizumab would be used at the same frequency as aflibercept in this scenario.

A second scenario was considered incorporating the median number of injections of each anti-VEGF drug administered during the 12-month DRCR.net Protocol T trial[72] (see Table 5).

TABLE 5: FREQUENCIES OF INJECTION USED IN DME SCENARIOS

Anti-VEGF drug	Frequency assumed	# injections in Year 1	# of injections in Year 2
Product monograph dosing for aflibercept, bevacizumab assumed equal to aflibercept, ranibizumab rounded from RESTORE mean[70,71]			
Ranibizumab	Monthly injections until stable VA for three months; resume if VA lost[68]	7	4
Aflibercept	Injections every month for 1st five months, then every other month[69]	8	6
Bevacizumab	Injections every month for 1st five months, then every other month (assumed)	8	6
Median doses in DRCR.net Protocol T trial[72]			
Ranibizumab	Every 4 weeks unless strict clinical criteria met.[72] After 24 weeks, injections were withheld if no improvement or worsening seen in previous two consecutive injections and reinitiated if VA or central subfield thickness worsened subsequently.	10	N/A
Aflibercept		9	N/A
Bevacizumab		10	N/A

RVO

According to the ranibizumab product monograph, for the treatment of BRVO or CRVO, ranibizumab should be given monthly until maximum visual acuity is achieved and confirmed to be stable for three consecutive months, with monthly injections restarted after a loss of visual acuity until it is stable for another three consecutive months.[68] Aflibercept is only indicated for the treatment of CRVO, and the recommended dosing is once monthly, which may be extended up to every three months based on visual and anatomic outcomes.[69]

Clinical trial experience with anti-VEGFs beyond six months is limited. In the aflibercept CRVO trial extension of COPERNICUS,[73] dosing with aflibercept or sham was monthly for the first six months, followed by as needed aflibercept administration based on clinical criteria such as increased central retinal thickness and gain or loss of ≥ 5 letters in BCVA from previous measurement. Patients in the aflibercept group used an average of 8.7 doses in the first year, and 3.3 doses in year 2. Given the similar monograph recommendations between aflibercept and ranibizumab, suggestion from clinical experts that treatment strategy would not differ between anti-VEGF drugs, and the CADTH Common Drug Review (CDR) recommendation that up to 12 doses of ranibizumab be reimbursed for patients with CRVO (10 for BRVO),[74] a frequency of nine injections in year 1 and three in year 2 is assumed for the treatment of patients with RVO in this analysis (

Table 6).

Table 6: Frequencies of Injection Used in RVO Scenarios

Anti-VEGF drug	Frequency assumed	# injections in Year 1	# of injections in Year 2
Doses rounded from COPERNICUS aflibercept trial mean.[73] Ranibizumab and bevacizumab assumed equal to aflibercept.			
Ranibizumab	Similar to two-year COPERNICUS results[73]	9	3
Aflibercept		9	3
Bevacizumab		9	3

CNV due to pathological myopia

Of the anti-VEGFs, only ranibizumab is indicated for the treatment of CNV due to PM. The recommended dosing in the product monograph is to initiate treatment with a single injection, with further treatment recommended if monitoring reveals signs of disease activity such as reduced visual acuity and/or sins of lesion activity.[68] In the 12-month RADIANCE trial,[75] patients were randomized to receive ranibizumab guided by vision stabilization (mean number of injections was 4.6), ranibizumab guided by disease activity (mean number of injections was 3.5), or verteporfin PDT followed by ranibizumab after three months. For the purposes of this analysis, a total of four injections of each anti-VEGF drug are assumed to be given over one year for patients with CNV due to PM.

TABLE 7: FREQUENCIES OF INJECTION USED IN CNV DUE TO PM SCENARIOS

Anti-VEGF drug	Frequency assumed	# injections in Year 1	# of injections in Year 2
Doses rounded from RADIANCE ranibizumab trial.[75] Aflibercept and bevacizumab assumed equal to ranibizumab. (one year only)			
Ranibizumab	Similar to RADIANCE results[75]	4	N/A
Aflibercept		4	N/A
Bevacizumab		4	N/A

2.4.9. Costs

Ranibizumab is available in 2.3 mg/0.23 mL vials or 1.65 mg/0.165 mL pre-filled syringes, both of which are intended for single use.[68] The Ontario Drug Benefit (ODB) Formulary list price (Sept 2015[76]) for either ranibizumab formulation is $1,575 per vial or syringe. Aflibercept is available in 11.12 mg/0.278 mL vials which are also intended for single use at an ODB list price of $1,418 per vial.[69,76]

In contrast, bevacizumab is available in 100 mg/4mL vials at $600 per vial (Ontario PPS, July 2015).[77] Up to 80 1.25 mg doses of bevacizumab exist in each 100 mg vial. However, given the labour and supplies needed to fraction bevacizumab in a sterile environment and the likelihood of some wastage, for the purposes of this review it was conservatively assumed in the base case that each 100 mg vial of bevacizumab would be fractioned into 15 doses at a cost of $40 each. See Appendix 7 for cost tables including other therapies used for the treatment of retinal diseases in Canada.

While not recommended in the product monographs,[68,69] fractioning of vials of both ranibizumab and aflibercept is possible in order to reduce drug costs.[78] The British Columbia Provincial Retinal Diseases Treatment Program[79] (BC PRDTP) takes advantage of this possibility, capping

the maximum amounts reimbursed as of April 2015 to $598.33 per dose of ranibizumab, $409.00 per dose of aflibercept, and $13.13 per dose of bevacizumab for the treatment of wet AMD, DME, or RVO. Other jurisdictions in Canada are also introducing programs reimbursing bevacizumab and/or regulating the fractioning of ranibizumab and aflibercept vials in an effort to contain the rising costs of retinal disease treatment (see Appendix 20).

TABLE 8: ANTI-VEGF DRUG COSTS CONSIDERED IN CADTH COST-MINIMIZATION ANALYSES

Drug	Price per vial	BC Pricing
Aflibercept	$1,418.00	$409.00
Bevacizumab	$40.00[a]	$13.13
Ranibizumab	$1,575.00	$598.33

Base case pricing is based on ODB Formulary list prices (Sept 2015) unless otherwise indicated. BC pricing is from the Provincial Retinal Diseases Treatment Program (Apr 2015).[79]
a – Assumed, based on 15 doses fractioned from each $600.00 (PPS, Jun 2015[77]) 100 mg/4 mL vial.

As anti-VEGF drugs are administered by intravitreal injection, the physician can bill for each injection. In addition, each injection administered under certain retinal programs (e.g., the BC PRDTP) may be entitled to a program management fee of up to $125 per injection by physicians. These costs are included in the cost minimization analyses.

TABLE 9: DRUG ADMINISTRATION COSTS ASSUMED IN CADTH COST-MINIMIZATION ANALYSES

Administration costs	Base Case Pricing	BC Pricing
Intravitreal injection	$105.00[a]	131.85[b]
Program management fee	N/A	125.00[c]
Total administration cost assumed per injection	$105.00	$256.85

[a] Ontario Schedule of Benefits for Physician Services, Code E147.[80]
[b] British Columbia Medical Services Commission Payment Schedule, Ophthalmology, Code S02090.[81]
[c] British Columbia Provincial Retinal Diseases Treatment Program, program management fee.[79]

While all patients receiving intravitreal anti-VEGF treatment require monitoring (e.g., visual acuity assessment, optical coherence tomography, tonometry, fluorescein angiography, etc.) at regular or lengthening (treat and extend) intervals, the clinical experts consulted by CADTH indicated that these intervals would be determined by indication, patient response, and individual needs rather than by anti-VEGF drug choice. Monitoring and administration costs in the IVAN trial cost-effectiveness analysis were virtually identical (£16 difference over two years) between ranibizumab and bevacizumab.[82] It was therefore assumed that monitoring would be similar between anti-VEGF drugs and thus monitoring costs are not included in this analysis.

2.4.10. Exploratory Analyses

In situations where there was sufficient evidence that a difference in efficacy or harms may exist among comparators (i.e., DME), a threshold analysis was conducted to determine the minimum quality-adjusted life-year (QALY) advantage the better comparator would need to display to be considered cost-effective at a willingness to pay of $50,000 per QALY.

An exploration of the possible budget impact of introducing a reimbursement program similar to the British Columbia PRDTP was conducted.

Finally, a threshold analysis was conducted to determine the cost per dose of bevacizumab which would lead to one of the other comparators becoming a less expensive option.

2.4.11. Economic Assumptions

In all economic analyses, the following assumptions were made.

TABLE 10: ASSUMPTIONS MADE WITHIN THE ECONOMIC ANALYSES

Description
Base case frequency assumes dosing as described in the product monographs, if available. Frequency is otherwise taken from major trials in the applicable indication. Bevacizumab is assumed to be used at the same frequency as the comparator with the more frequent use if data are not otherwise available from trials.
Efficacy, harms, and tolerability are assumed to be similar between comparators based on the clinical evidence.
Monitoring frequency and costs are assumed equal between treatments.
Treatment discontinuation is considered to be similar between treatments and is not accounted for over the one- and two-year time horizons.
Costs accrued in the second year are discounted at 5%.
No switching between treatments was assumed to occur.
Publically available drug prices are a reasonable reflection of costs to public drug plans.

3. RESULTS

3.1. Clinical Data

3.1.1. Selection of Primary Clinical Studies

The clinical literature search yielded a total of 2,444 titles and abstracts (Appendix 4). Of these, 410 were identified as potentially relevant. After screening full-text articles, 29 trial reports describing 30 RCTs were included[5-33] (Appendix 4).

3.1.2. Study and Patient Characteristics

Table 11 provides a summary of the study characteristics and the detailed study table is available in Appendix 8. A total of 30 RCTs were included in the systematic review, including 13 RCTs evaluating anti-VEGF drugs in patients with wet AMD (43%), nine RCTs in patients with RVO (30%), five RCTs in patients with DME (17%), and three RCTs in patients with CNV due to PM (10%). All included studies were published between 2005 and 2015. All included studies were conducted in Europe, North America, Asia, or were multi-centre trials with international sites that included patients from different continents. Most of the included studies were multi-centre RCTs, and 40% were funded by private industry.

Table 12 summarizes the average characteristics of the 10,081 patients in the 30 included RCTs, and the detailed patient characteristics are available in Appendix 9. The mean sample size was approximately 350 patients per study (range: 28 to 1,240). More than half of the included studies did not report the age distribution of study participants. The percentage of female patients ranged from 6% to 76% across the included studies.

TABLE 11: SUMMARY OF INCLUDED STUDIES

Condition	Author and Year	Study name	Disposition	Interventions	Follow-up	Primary outcome(s)
Wet AMD	Berg 2015	LUCAS	Randomized: n = 441 Completed: n = 371	Ranibizumab (0.5/0.05 mg/mL), n=187 Bevacizumab (1.25/0.05 mg/mL), n=184	1 year	Difference in BCVA at 1 year
Wet AMD	Biswas 2011a	NR	Randomized: n = 60 Completed: n = 52	Ranibizumab (0.5/0.05 mg/mL), n= 27 Bevacizumab (1.25/0.05 mg/mL), n= 25	18 months	Change in Visual Acuity at 18 months
Wet AMD	Scholler 2014	NR	Randomized: n = NR Completed: n = 55	Bevacizumab (1.25/0.05 mg/mL), n= 26 Ranibizumab (0.5/0.05 mg/mL), n=29	2 years	Change in visual acuity in LogMAR at 2 years
Wet AMD	Heier 2012	VIEW 1	Randomized: n= 1,217 Completed: n = 1,089	Aflibercept (0.5/NR mg/mL), n=285 Aflibercept (2.0/NR mg/mL) q4weeks, n=270 Aflibercept (2.0/NR mg/mL) q8weeks, n=265 Ranibizumab (0.5/NR mg/mL), n=269	1 year	Loss of <15 ETDRS letters at 1 year
Wet AMD	Heier 2012	VIEW 2	Randomized: n =1,240 Completed:	Aflibercept (0.5/NR mg/mL), n=268	1 year	Loss of <15 ETDRS letters at 1 year

Condition	Author and Year	Study name	Disposition	Interventions	Follow-up	Primary outcome(s)
			n =1,081	Aflibercept (2.0/NR mg/mL) q4weeks, n=274 Aflibercept (2.0/NR mg/mL) q8weeks, n=270 Ranibizumab (o,5/NR mg/mL), n=269		
Wet AMD	Biswas 2011b	NR	Randomized: n =120 Completed: n = 104	Ranibizumab (0.5/0.05 mg/mL), n =54 Bevacizumab (1.25/0.05 mg/mL), n =50	18 months	Changes in BCVA and CMT at month 18
Wet AMD	Chakravarthy 2013	IVAN	Randomized: n = 610 Completed: n = 525	Ranibizumab (0.5/NR mg/mL) continuous, n=134 Ranibizumab (0.5/NR mg/mL) discontinuous, n=137 Bevacizumab (1.25/NR mg/mL) continuous, n=127 Bevacizumab (1.25/NR mg/mL) discontinuous, n=127	2 years	Difference in BCVA at year 2
Wet AMD	Kodjikian 2013	GEFAL	Randomized: n= 501 Completed: n= 374	Bevacizumab (1.25/0.05 mg/mL), n=191 Ranibizumab (0.05/0.05 mg/mL), n=183	1 year	Mean Change in visual acuity at 1 year

Condition	Author and Year	Study name	Disposition	Interventions	Follow-up	Primary outcome(s)
Wet AMD	Krebs 2013	MANTA	Randomized: n=321 Completed: n=317	Bevacizumab (1.25/NR mg/mL), n=154 Ranibizumab (0.5/NR mg/mL), n=163	1 year	Difference in BCVA at 1 year
Wet AMD	Martin 2011	CATT	Randomized: n=1,208 Completed: n=1,105	Ranibizumab (0.5/0.05 mg/mL) continuous, n=284 Ranibizumab (0.5/0.05 mg/mL) discontinuous, n=285 Bevacizumab (1.25/0.05 mg/mL) continuous, n=265 Bevacizumab (1.25/0.05 mg/mL) discontinuous, n=271	1 year	Mean Difference in BCVA at 1 year
Wet AMD	Regillo 2008	PIER	Randomized: n=184 Completed: n=183	Ranibizumab (0.3/NR mg/mL), n=59 Ranibizumab (0.5/NR mg/mL), n=61 Sham, n=63	1 year	Mean Difference in BCVA at 1 year
Wet AMD	Subramanian 2010	NR	Randomized: n= 28 Completed: n= 22	Bevacizumab (NR/0.05 mg/mL), n=15 Ranibizumab (NR/0.05 mf/mL), n=7	1 year	Mean Difference in BCVA at 1 year
Wet AMD	Rosenfeld 2006 & Chang 2007*	MARINA	Randomized: n=716	Ranibizumab (0.3/NR mg/mL),	2 years	Loss of <15 BCVA letters at year 1

Condition	Author and Year	Study name	Disposition	Interventions	Follow-up	Primary outcome(s)
			Completed: n=713	n=238 Ranibizumab (0.5/NR mg/mL), n=239 Sham, n=236		
DME	Massin 2010	RESOLVE	Randomized: n=151 Completed: n=151	Ranibizumab (0.3/0.05 mg/mL), n=51 Ranibizumab (0.5/0.05 mg/mL), n=51 Sham, n=49	1 year	Difference in BCVA at 1 year
DME	Nguyen 2012	RISE	Randomized: n=377 Completed: n=374	Ranibizumab (0.3/NR mg/mL), n=125 Ranibizumab (0.5/NR mg/mL), n= 126 Sham, n=123	2 years	Gain in >15 letters at year 2
DME	Nguyen 2012	RIDE	Randomized: n=382 Completed: n= 376	Ranibizumab (0.3/NR mg/mL), n=125 Ranibizumab (0.5/NR mg/mL), n= 124 Sham, n=127	2 years	Gain in >15 letters at year 2
DME	Wells 2015	NR	Randomized: n=660 Completed: n=660	Aflibercept (2/0.0.05 mg/mL), n=224 Bevacizumab (1.25/0.05 mg/mL), n=218 Ranibizumab (0.3/0.05 mg/mL), n=218	1 year	Mean Change of visual acuity at year 1

Condition	Author and Year	Study name	Disposition	Interventions	Follow-up	Primary outcome(s)
DME	Ekinci 2014	NR	Randomized: n = 100 Completed: n = 100	Bevacizumab (1.25/0.05 mg/mL), n=50 Ranibizumab (0.5/0.05 mg/mL), n=50	1 year	Difference in BCVA at 1 year
RVO	Epstein 2012	NR	Randomized: n = 60 Completed: n = 60	Bevacizumab (1.25/0.05 mg/mL), n=30 Sham, n=30	1 year	Gain in >15 letters at 12 months
RVO	Holz 2013	GALILEO	Randomized: n=177 Completed: n=171	Aflibercept (2.0/NR mg/mL), n=103 Sham, n =68	6 months	Difference in BCVA at 6 months
RVO	Kinge 2010	ROCC	Randomized: n= 32 Completed: n= 29	Ranibizumab (0.5/0.05 mg/mL), n= 15 Sham, n=14	6 months	Difference in BCVA at 6 months
RVO	Boyer 2012	COPERNICUS	Randomized: n = 189 Completed: n = 187	Aflibercept (2.0/NR mg/mL), n=114 Sham, n=74	2 years	Difference in BCVA at week 24
RVO	Brown 2010	CRUISE	Randomized: n = 392 Completed: n = 392	Ranibizumab (0.3/0.05 mg/mL), n=132 Ranibizumab (0.5/0.05 mg/mL), n=130 Sham, n=130	6 months	Difference in BCVA at month 6
RVO	Campochiaro 2010	BRAVO	Randomized: n = 397 Completed: n = 395	Ranibizumab (0.3/0.05 mg/mL), n=134 Ranibizumab (0.5/0.05 mg/mL),	6 months	Mean Difference in BCVA at month 6

Condition	Author and Year	Study name	Disposition	Interventions	Follow-up	Primary outcome(s)
				n=130 Sham, n=131		
RVO	Moradian 2011	NR	Randomized: n = 81 Completed: n = 81	Bevacizumab (1.25/0.05 mg/mL), n=42 Sham, n =39	3 months	Difference in BCVA at 12 weeks
RVO	Narayanan 2015	MARVEL	Randomized: n = 75 Completed: n = 75	Bevacizumab (1.25/NR mg/mL), n= 38 Ranibizumab (0.5/NR mg/mL), n= 37	6 months	Mean Difference in BCVA at 6 months
RVO	Rajagopal 2015	CRAVE	Randomized: n = 93 (then added 9 patients to the bevacizumab group without randomization) Completed: n = 98	Bevacizumab (1.25/NR mg/mL), n= 49 Ranibizumab (0.5/NR mg/mL), n= 49	6 months	Change in central foveal thickness
CNV due to PM	Gharbiya 2010	NR	Randomized: n =32 Completed: n = 32	Ranibizumab (0.5/0.05 mg/mL), n= 16 Bevacizumab (1.25/0.05 mg/mL), n=16	6 months	Difference in BCVA at 6 months
CNV due to PM	Iacono 2012	NR	Randomized: n = 55 Completed: n = 48	Bevacizumab (1.25/0.05 mg/mL), n=25 Ranibizumab (0.5/0.05 mg/mL), n= 23	18 months	Difference in BCVA at 18 months
CNV due to PM	Ikuno 2015	MYRROR	Randomized: n = 122 Completed: n=	Aflibercept (2mg), n = 90 Sham intravitreal	5.5 months	Mean change in BCVA at 24 weeks

Condition	Author and Year	Study name	Disposition	Interventions	Follow-up	Primary outcome(s)
			121	injections, n = 31		

*Chang 2007 is a companion report to Rosenfeld 2006, also reporting on the MARINA trial.

AMD, age-related macular degeneration; BRVO, branch retinal vein occlusion; CNV, choroidal neovascularization; CRVO, central retinal vein occlusion; DME, diabetic macular edema; NA, not applicable; PM, pathologic myopia.

TABLE 12: PATIENT CHARACTERISTICS

Participant Characteristics	Total # of Trials Included (n = 30) [n, %]	# of Wet AMD Trials (n = 13) [n, %]	# of DME Trials (n = 5) [n, %]	# of RVO Trials (n = 9) [n, %]	# of CNV Trials (n = 3) [n, %]
Mean Age (years)					
18 to 65	5 (16.7)	1 (7.7)	1 (20)	2 (22.2)	1 (33.3)
>65	8 (26.7)	3 (23.1)	0 (0)	5 (55.6)	0 (0)
Not reported	16 (53.3)	9 (69.2)	4 (80)	2 (22.2)	2 (66.7)
% Female					
0-25%	1 (3.3)	1 (7.8)	0 (0)	0 (0)	0 (0)
26%-50%	10 (33.3)	0 (0)	3 (60)	7 (77.8)	0 (0)
51-100%	16 (53.3)	10 (76.9)	1 (20)	2 (22.2)	3 (100)
Not reported	3 (10.0)	2 (15.4)	1 (20)	0 (0)	0 (0)

CNV, choroidal neovascularization; PM, pathologic myopia; ME, macular edema; RVO, retinal vein occlusion; AMD, age-related macular degeneration; DME, diabetic macular edema; NR; not reported

3.1.3. Critical Appraisal of Included Studies

Wet AMD

Thirteen RCTs contributed data to the evaluation of anti-VEGF drugs in patients with wet AMD (Appendix 4). With respect to random sequence generation, the risk of selection bias was either low (five studies, 38.5%) or unclear (eight studies, 61.5%). With respect to allocation concealment, the risk of selection bias was either low (six studies, 46.2%) or unclear (seven studies, 53.8%). With respect to blinding of patients, personnel and outcome assessors, the included studies were assessed to be at low risk for performance and detection biases. With respect to incomplete outcome data, nine studies were assessed to be at low risk (69.2%) and four studies at unclear risk (30.8%) of attrition bias. With respect to selective reporting, eight studies were assessed to be at low risk (69.2%) and four studies at unclear risk (30.8%) of reporting bias. Related to the potential for funding bias, eight studies were at low risk (61.5%), one study at unclear risk (7.8%) and four studies at high risk (30.8%) of other bias.

DME

Five RCTs contributed data to the evaluation of anti-VEGF drugs in patients with DME (Appendix 4). With respect to random sequence generation, the risk of selection bias was low in three studies (60%) and unclear in the other two studies (40%). With respect to allocation concealment, the risk of selection bias was low in four studies (80%) and unclear in the remaining study (20%). With respect to blinding of patients, personnel and outcome assessors, the included studies were all assessed to be at low risk for performance and detection biases. With respect to incomplete outcome data, four studies were assessed to be at low risk (80%) and the remaining study at unclear risk (20%) of attrition bias. With respect to selective reporting, four studies were assessed to be at low risk (80%) and the remaining study (20%) had an unclear risk of reporting bias. Two studies (40%) were at low risk, and the remaining three studies (60%) were at high risk of other bias.

ME due to RVO

Nine RCTs contributed data to the evaluation of anti-VEGF drugs in patients with ME due to RVO (Appendix 4). With respect to random sequence generation, the risk of selection bias was low in three RCTs (33.3%), unclear in five RCTs (55.6%), and high in one RCT (11.1%). With respect to allocation concealment, the risk of selection bias was low in one RCT (11.1%), unclear in seven RCTs (77.8%), and high in the remaining one RCT (11.1%). With respect to blinding of patients, personnel and outcome assessors, the included studies were all assessed to be at low risk for performance and detection biases. With respect to incomplete outcome data, seven RCTs were assessed to be at low risk (77.8%) and the remaining two RCTs at unclear risk (22.2%) of attrition bias. With respect to selective reporting, six RCTs were assessed to be at low risk (66.7%), one RCT at unclear risk (11.1%) and two RCTs at high risk (22.2%) of reporting bias. Five RCTs (55.6%) were at low risk, and the remaining four RCTs (44.4%) at high risk of other bias.

CNV due to PM

Three RCTs contributed data to the evaluation of anti-VEGF drugs in patients with CNV due to PM (Appendix 4). With respect to random sequence generation and allocation concealment, the risk of selection bias was low in one RCT (33.3%) and unclear in the remaining two RCTs (66.7%). With respect to blinding of patients, personnel and outcome assessors, all the included studies were assessed to be at low risk for performance and detection biases. They also were assessed to be at low risk of attrition bias. With respect to selective reporting, two RCTs were assessed to be at low risk (66.7%) and the other RCT (33.3%) at unclear risk of reporting

bias. One of each of the included studies was assessed to be at low (33.3%), unclear (33.3%), and high risk (33.3%) of other bias.

3.1.4. Direct Comparisons of Treatments

Wet AMD

The results of the pairwise comparisons of each of the active treatments for the outcomes related to visual acuity (specifically, gain or loss of ≥ 15 ETDRS letters and mean difference in the difference in BCVA) for the wet AMD population are presented in Table 13. The complete results for these and all other efficacy and safety outcomes are presented in Appendix 12 and forest plots can be found in Appendix 13

Vision gain

This outcome reports the proportion of patients who demonstrated a gain of ≥ 15 ETDRS letters.

Anti-VEGFs versus placebo
Ranibizumab was associated with a large effect on improvement of vision compared to placebo (OR: 3.9 [95% CI, 0.5 to 29.9]), although the pooled treatment effect estimate was not statistically significant in our meta-analysis of two RCTs with 900 patients. However, the effect estimates from the two studies included in the meta-analysis varied greatly, as reflected by an I^2 value of 91%. This is likely due to great variation in several aspects of these two studies (see Appendix 8 for details), including the duration of follow-up duration (12 months in one study versus 24 months in the other) as well as the number of injections (six versus 24 injections). There were no data comparing aflibercept or bevacizumab to placebo.

Ranibizumab versus bevacizumab
There was no statistically significant difference in the proportion of patients who had a gain of ≥ 15 ETDRS letters when comparing ranibizumab to bevacizumab in a meta-analysis of eight RCTs with 2,950 patients (OR: 1.13 [95% CI, 0.96 to 1.34]; see Table 13).

Aflibercept versus bevacizumab
There were no studies in which aflibercept was compared with bevacizumab for the outcome of vision gain in wet AMD patients.

Ranibizumab versus aflibercept
There was no statistically significant difference between ranibizumab and aflibercept with respect to vision gain (OR: 1.01 [95% CI, 0.75 to 1.37]; meta-analysis of two RCTs, 1,815 patients; see Table 13). The results of the two individual RCTs included in the analysis were consistent in showing no difference between ranibizumab and aflibercept.[16]

Vision loss

This outcome reports the proportion of patients who demonstrated a loss of ≥ 15 ETDRS letters.

Anti-VEGFs versus placebo
Ranibizumab was associated with a statistically significant reduction in vision loss compared to placebo (OR: 0.12 [95% CI, 0.084 to 0.17]; meta-analysis of two RCTs, 900 patients). Individually, these two RCTs showed similar statistical results with ranibizumab being statistically significantly better than placebo, despite the two RCTs having a different follow-up period (12 versus 24 months) and a different in the number of injections (six versus 24 injections).[12,14] There were no data available comparing aflibercept or bevacizumab with placebo.

Ranibizumab versus bevacizumab
Ranibizumab did not show a statistically significant difference to bevacizumab with respect to

vision loss (OR: 0.95 [95% CI, 0.70 to 1.27], meta-analysis of nine RCTs, 3,005 patients; see Table 13).

Aflibercept versus bevacizumab
There were no data available comparing aflibercept with bevacizumab for the outcome of vision loss.

Aflibercept versus ranibizumab
There was no statistically significant difference between ranibizumab and aflibercept with respect to vision loss (OR: 1.11 [95% CI, 0.72 to 1.71], meta-analysis of two RCTs, 1,815 patients; see Table 13). The results of the two individual RCTs included in the analysis were consistent and showed no difference between ranibizumab and aflibercept.[16]

Mean difference in best corrected visual acuity

This outcome reports the mean difference in best corrected visual acuity (BCVA) at follow-up.

Anti-VEGFs versus placebo
Ranibizumab was associated with statistically significant improvement in mean BCVA when compared to placebo (MD: 18.95 [95% CI, 13.83 to 24.07], meta-analysis of two RCTs, 909 patients). While both RCTs showed statistically significant benefit of ranibizumab over placebo, the magnitude of the difference was larger in one of these RCTs, likely due to a longer follow-up period and a greater number of injections.[12,14] There were no data available comparing aflibercept or bevacizumab to placebo for this outcome.

Ranibizumab versus bevacizumab
Ranibizumab was not statistically significant different to bevacizumab with respect to mean BCVA (MD: 0.51 [95% CI, –0.82 to 1.83], meta-analysis of seven RCTs, 2,769 patients).

Aflibercept versus bevacizumab
There were no data comparing aflibercept with bevacizumab in terms of mean BCVA.

Aflibercept versus ranibizumab
The effects of ranibizumab were not statistically significantly different to those of aflibercept with respect to the change in mean BCVA (MD: 0.10 [95% CI, –5.43 to 5.64], meta-analysis of two RCTs, 1907 patients; see Table 13). The results of the two individual RCTs included in the analysis were consistent and showed no difference between ranibizumab and aflibercept.[16]

TABLE 13: SUMMARY OF COMPARATIVE EFFICACY OF ANTI-VEGF DRUGS IN WET AMD PATIENTS

Outcome	Comparison	No. of RCTs*	Total Patients	I^2, *P* Value	ES	ES [95% CI]	*P* Value
Gain of ≥ 15 ETDRS letters	Ranibizumab vs. Aflibercept	2	1,815	51.88%, 0.15	OR	1.01 [0.75, 1.37]	0.94
	Ranibizumab vs. Bevacizumab	8	2,950	0.00%, 0.34	OR	1.13 [0.96, 1.34]	0.15
	Bevacizumab vs. Aflibercept	0					
Loss of ≥ 15 ETDRS letters	Ranibizumab vs. Aflibercept	2	1,815	0%, 0.73	OR	1.11 [0.72, 1.71]	0.63
	Ranibizumab vs. Bevacizumab	9	3,005	0%, 0.81	OR	0.95 [0.70, 1.27]	0.71
	Bevacizumab vs. Aflibercept	0					
Mean difference in BCVA	Ranibizumab vs. Aflibercept	2	1,907	89.13%, 0 .002	MD	0.10 [-5.43, 5.64]	0.97
	Ranibizumab vs. Bevacizumab	7	2,769	6.91%, 0.33	MD	0.51 [-0.82, 1.83]	0.45
	Bevacizumab vs. Aflibercept	0					

Other efficacy outcomes

Ranibizumab versus bevacizumab

A meta-analysis of three RCTs with 1,817 patients suggested that the effects of ranibizumab and bevacizumab were not statistically significantly different with respect to the number of patients who progressed to legal blindness (OR: 0.46 [95% CI, 0.07 to 3.26]).

Aflibercept versus bevacizumab

There were no data on any additional efficacy outcomes comparing aflibercept with bevacizumab.

Aflibercept versus ranibizumab

A meta-analysis of two RCTs with 1,632 patients suggested that ranibizumab is not significantly different to aflibercept with respect to the effects of these treatments on vision-related function (MD: 2.23 [95% CI, –0.61 to 5.07]). The results of the two individual RCTs included in the analysis were consistent and showed no difference between ranibizumab and aflibercept.[16]

Harms outcomes

Anti-VEGFs versus placebo

For each of the different anti-VEGFs, the frequency with which AEs and SAEs occurred in the included studies was not significantly different to placebo, which was also the case for clinically relevant harms such as mortality, arterial thromboembolism, bacterial endophthalmitis, and retinal detachment. The incidence of intraocular pressure was significantly higher in patients treated with ranibizumab versus placebo (OR: 4.80 [95% CI, 2.40 to 9.80], meta-analysis of two RCTs, 896 patients), Individually, the two RCTs included in this meta-analysis were consistent in reporting increased IPO in ranibizumab-treated patients compared with placebo-treated patients, despite having different follow-up periods (12 versus 24 months) and a different number of injections (six versus 24 injections).[12,14] Though not statistically significant, results from a single study of 713 patients suggest the possibility of an increased risk of bacterial

endophthalmitis (OR: 5.00 [95% CI, 0.30 to 91.90]) associated with ranibizumab treatment compared to placebo. There were no data comparing aflibercept or bevacizumab with placebo for any harms of interest.

Ranibizumab versus bevacizumab
The safety profile of ranibizumab was very similar to that of bevacizumab in terms of the nature and frequency of harms reported in wet AMD patients in the included studies, including mortality (six RCTs, 2,941 patients), serious adverse events (five RCTs, 3,026 patients), withdrawals due to adverse events (three RCTs, 1,536 patients), arterial thromboembolism (four RCTs, 2,133 patients), and venous thromboembolism (three RCTs, 2,133 patients). In a single RCT with a follow-up duration of 1,187 patient-years, three bevacizumab-treated patients reported retinal detachment and four patients reported increased intraocular pressure; none of the patients treated with ranibizumab in the same study reported such adverse events.[83]

Aflibercept versus bevacizumab
There were no data comparing aflibercept with bevacizumab for any of the harms of interest.

Aflibercept versus ranibizumab
Although more ranibizumab patients reported harms events than aflibercept patients, there was no statistically significant difference between these treatments. There were no data available on mortality or serious adverse events.

DME

The results of the pairwise comparisons of each of the active treatments for the main outcomes related to visual acuity (specifically, gain or loss of ≥ 15 ETDRS letters and mean difference in BCVA) for the DME population are presented in Table 14. The complete results for these and all other efficacy and safety outcomes are presented in Appendix 12, and forest plots can be found in Appendix 13.

Vision gain

Anti-VEGFs versus placebo
A meta-analysis of three RCTs with 910 patients suggested that ranibizumab significantly improved vision gain compared with placebo (OR: 3.90 [95% CI, 2.70 to 5.60]). There were no data comparing bevacizumab or aflibercept with placebo for this outcome.

Ranibizumab versus bevacizumab
Based on the results of a single study, the effects of ranibizumab do not appear to be significantly different to those of bevacizumab with respect to effects of these treatment on vision gain in DME patients (OR: 1.18 [95% CI, 0.77 to 1.79], 412 patients; see Table 14**Error! Not a valid bookmark self-reference.**).

Aflibercept versus bevacizumab
Comparison of bevacizumab to aflibercept in a single RCT suggested that bevacizumab had a statistically significantly smaller effect on vision gain in DME patients (OR: 0.60 [95% CI, 0.40 to 0.80], 414 patients; see Table 14**Error! Not a valid bookmark self-reference.**).

Aflibercept versus ranibizumab
Comparison of ranibizumab to aflibercept in a single RCT suggested that ranibizumab had a statistically significantly smaller effect on vision gain in DME patients (OR: 0.70 [95% CI, 0.44 to 0.98], 414 patients; see Table 14**Error! Not a valid bookmark self-reference.**)

Vision loss

Anti-VEGFs versus placebo
A meta-analysis of three RCTs with 910 patients suggested that ranibizumab treatment is

associated with a statistically significant reduction in vision loss compared to placebo (OR: 0.20 [95% CI, 0.10 to 0.40]; see Table 14**Error! Not a valid bookmark self-reference.**).

Ranibizumab versus bevacizumab
There was no statistically significant difference between the effects of ranibizumab and bevacizumab with respect to vision loss in DME patients in a single RCT (OR: 1.00 [95% CI, 0.20 to 5.01], 412 patients; see Table 14**Error! Not a valid bookmark self-reference.**).

Aflibercept versus bevacizumab
There was no statistically significant difference between the effects of aflibercept and bevacizumab with respect to vision loss in DME patients in a single RCT (OR: 1.01 [95% CI, 0.20 to 5.06], 414 patients; see Table 14**Error! Not a valid bookmark self-reference.**).

Aflibercept versus ranibizumab
There was no statistically significant difference between the effects of aflibercept and ranibizumab with respect to vision loss in DME patients in a single RCT (OR: 1.01 [95% CI, 0.20 to 5.06], 414 patients; see Table 14**Error! Not a valid bookmark self-reference.**).

Mean difference in best corrected visual acuity

Anti-VEGFs versus placebo
A meta-analysis of three RCTs with 910 patients suggested that ranibizumab had a statistically significant improvement on mean BCVA compared to placebo (MD: 9.23 [95% CI, 6.98 to 11.49]; see Table 14**Error! Not a valid bookmark self-reference.**).

Ranibizumab versus bevacizumab
Ranibizumab was not significantly different to bevacizumab with respect to mean BCVA (meta-analysis of two RCTs, 512 patients, SMD: 0.16 [95% CI, –0.02 to 0.33]; see Table 14**Error! Not a valid bookmark self-reference.**). The results of the two individual RCTs included in the analysis were consistent and showed no difference between ranibizumab and bevacizumab.[18,19]

Aflibercept versus bevacizumab
The results of a single RCT suggested that bevacizumab treatment is associated with a statistically significantly smaller improvement in mean BCVA in DME patients compared with aflibercept (MD: -4.20 [95% CI, –6.47 to –1.93], 414 patients; see Table 14**Error! Not a valid bookmark self-reference.**).

Aflibercept versus ranibizumab
The results of a single RCT suggested that aflibercept treatment is associated with a statistically significantly greater improvement in mean BCVA in DME patients compared with ranibizumab (MD: 2.10 [95% CI, 0.06 to 4.14]), when compared to ranibizumab (see Table 14**Error! Not a valid bookmark self-reference.**).

Other efficacy outcomes

Ranibizumab versus bevacizumab
There were no data comparing these treatments for any other efficacy outcomes of interest.

Aflibercept versus bevacizumab
There were no data comparing these treatments for any other efficacy outcomes of interest.

Aflibercept versus ranibizumab
There were no data comparing these treatments for any other efficacy outcomes of interest.

TABLE 14: SUMMARY OF COMPARATIVE EFFICACY OF ANTI-VEGF DRUGS IN DME

Outcome	Comparison	No. of RCTs*	Total Patients	I^2, *P* Value	ES	ES [95% CI]	*P* Value
Gain of ≥ 15 ETDRS letters	***Ranibizumab vs. Aflibercept***	***1***	***414***	***NA***	***OR***	***0.66 [0.44, 0.98]***	***0.04***
	Ranibizumab vs. Bevacizumab	1	412	NA	OR	1.18 [0.771, 1.79]	0.45
	Bevacizumab vs. Aflibercept	***1***	***414***	***NA***	***OR***	***0.56 [0.37, 0.84]***	***0.005***
Loss of ≥ 15 ETDRS letters	Ranibizumab vs. Aflibercept	1	414	NA	OR	1.01 [0.20, 5.06]	0.99
	Ranibizumab vs. Bevacizumab	1	412	NA	OR	1.00 [0.20, 5.01]	1.00
	Bevacizumab vs. Aflibercept	1	414	NA	OR	1.01 [0.20, 5.06]	0.99
Mean difference in BCVA	***Aflibercept vs. Ranibizumab***	***1***	***377***	***NA***	***MD***	***2.10 [0.06, 4.14]***	***0.04***
	Ranibizumab vs. Bevacizumab	2	512	0%, 0.70	SMD	0.16 [-0.02, 0.33]	0.08
	Bevacizumab vs. Aflibercept	***1***	***414***	***NA***	***MD***	***-4.20 [-6.47,-1.93]***	***0.0003***

Harms outcomes

Anti-VEGFs versus placebo

In terms of harms, ranibizumab was associated with a significant risk of increased intraocular pressure (OR: 7.60 [95% CI, 2.90 to 20.40], three RCTs, 910 patients). None of the other reported harms occurred significantly more frequently in ranibizumab- versus placebo-treated patients, including arterial thromboembolism, bacterial endophthalmitis, and retinal detachment. There were no trials comparing aflibercept or bevacizumab with placebo, for any of the harms of interest.

Ranibizumab versus bevacizumab

Ranibizumab and bevacizumab were similar with respect to the frequency of serious adverse events (OR: 1.26 [95% CI, 0.81 to 1.97], one RCT, 436 patients), mortality (OR: 0.80 [95% CI, 0.21 to 3.01], one RCT, 436 patients), arterial thromboembolism (OR: 1.12 [95% CI, 0.45 to 2.80], one RCT, 436 patients, and increased intraocular pressure (OR: 1.24 [95% CI, 0.65 to 2.34], one RCT, 436 patients).

Aflibercept versus bevacizumab

Aflibercept and bevacizumab were similar with respect to the frequency of serious adverse events (OR: 0.75 [95% CI, 0.48 to 1.16], one RCT, 442 patients), mortality (OR: 1.73 [95% CI, 0.41 to 7.33], one RCT, 442 patients), arterial thromboembolism (OR: 1.57 [95% CI, 0.55 to 4.47], one RCT, 442 patients), and increased intraocular pressure (OR: 0.57 [95% CI, 0.31 to 1.05], one RCT, 442 patients).

Aflibercept versus ranibizumab

Aflibercept and ranibizumab were similar with respect to the frequency of serious adverse events (OR: 0.94 [95% CI, 0.62 to 1.45], one RCT, 442 patients), mortality (OR: 1.38 [95% CI, 0.31 to 6.23], one RCT, 442 patients), arterial thromboembolism (OR: 1.75 [95% CI, 0.62 to 4.89], one RCT, 442 patients), or increased intraocular pressure (OR: 0.71 [95% CI, 0.40 to

1.25], one RCT, 442 patients).

RVO

The results of the pairwise comparisons of each of the active treatments for the main outcomes related to visual acuity (specifically, gain or loss of ≥ 15 ETDRS letters and mean change in BCVA) for the RVO population are presented in Table 15. The complete results for these and all other efficacy and safety outcomes are presented in Appendix 12, and the forest plots can be found in Appendix 15.

Vision gain

Anti-VEGFs versus placebo
There is evidence that each of the three anti-VEGFs improve vision compared to no treatment. A meta-analysis of two studies suggested that ranibizumab is superior to placebo in terms of improving vision in patients with RVO (OR: 3.80 [95% CI, 2.70 to 5.30], two RCTs with 789 patients). Both studies included in the analysis had similar results, demonstrating a consistently superior effect for ranibizumab.[27,29] According to results of a single, small RCT (60 patients), bevacizumab significantly improved vision compared to placebo (OR: 6.00 [95% CI, 1.90 to 19.00]). A meta-analysis of two studies suggested that aflibercept is associated with a statistically significantly greater improvement in vision compared with placebo (OR: 7.00 [95% CI, 3.90 to 12.60], two RCTs with 358 patients). Both of the studies included in the analysis had similar results.[23,24]

Ranibizumab versus bevacizumab
Based on a meta-analysis of two RCTs, there appeared to be no statistically significant difference between ranibizumab and bevacizumab respect to the proportion of patients with RVO who demonstrated an improvement in vision (OR: 1.03 [95% CI, 0.55 to1.94]; 173 patients; see Table 15).

Aflibercept versus bevacizumab
There were no data comparing these treatments for the outcome of vision gain.

Aflibercept versus ranibizumab
There were no data comparing these treatments for the outcome of vision gain.

Vision loss

Anti-VEGFs versus placebo
A meta-analysis of two studies suggested that ranibizumab is associated with a statistically significant reduction in vision loss compared with placebo (OR: 0.15 [95% CI, 0.07 to 0.33], two RCTs with 789 patients). Both of the studies included in the analysis had similar results, demonstrating that ranibizumab is superior to placebo.[27,29] The results of a single RCT demonstrated that aflibercept is associated with a statistically significant reduction in vision loss compared with placebo (OR: 0.05 [95% CI, 0.01 to 0.21], 187 patients). There was no statistically significant difference between bevacizumab and placebo in terms of vision loss in results from a single RCT (OR: 0.24 [95% CI, 0.04 to 1.24], 60 patients).

Ranibizumab versus bevacizumab
There were no data comparing these treatments for the outcomes of vision loss.

Aflibercept versus bevacizumab
There were no data comparing these treatments for the outcomes of vision loss.

Aflibercept versus ranibizumab
There were no data comparing these treatments for the outcomes of vision loss.

Mean difference in BCVA

Anti-VEGFs versus placebo

A meta-analysis of three studies demonstrated that ranibizumab produces a statistically significant improvement in the BCVA compared with placebo (OR: 10.70 [95% CI, 9.20 to 12.30], 818 patients). Similarly, a single RCT demonstrated that aflibercept improved mean BCVA (by 23 ETDRS letters [95% CI, 19.53 to 26.67], 187 patients) to a significantly greater degree than placebo. By contrast, a meta-analysis of two RCTs suggested that bevacizumab was similar to placebo with respect to the effect on BCVA (SMD: 0.25 [95% CI, –1.28 to 1.79], 141 patients). The results of both of these studies were not consistent: while the results of Epstein et al.[25] suggest that bevacizumab significantly improves mean BCVA compared to placebo, Moradian et al.(139} found no significant difference between the two (consistent with our meta-analysis). Moradian et al. noted that this difference may be explained by the fact that their patient population included individuals with foveal ischemia, which has been shown to limit improvement in BCVA.[25,26]

Ranibizumab versus bevacizumab

The results from meta-analysis of two RCTs comparing ranibizumab to bevacizumab suggested that these treatments are not statistically different with respect to the standardized mean difference in BCVA (SMD:
0.00 [95% CI, –0.30 to 0.30]; 173 patients; see Table 15).

Aflibercept versus bevacizumab

There were no data comparing these treatments for the outcome of change in mean BCVA.

Aflibercept versus ranibizumab

There were no data comparing these treatments for the outcome of change in mean BCVA.

TABLE 15: SUMMARY OF COMPARATIVE EFFICACY OF ANTI-VEGF DRUGS IN RVO PATIENTS

Outcome	Comparison	No. of RCTs*	Total patients	I^2, *P* Value	ES	ES [95% CI]	*P* Value
Gain of ≥ 15 ETDRS letters	Ranibizumab vs. Aflibercept	0					
	Ranibizumab vs. Bevacizumab	2	173		OR	1.03 [0.55, 1.94]	0.095
	Bevacizumab vs. Aflibercept	0					
Loss of ≥ 15 ETDRS letters	Ranibizumab vs. Aflibercept	0					
	Ranibizumab vs. Bevacizumab	0					
	Bevacizumab vs. Aflibercept	0					
Standardized mean difference in BCVA	Ranibizumab vs. Aflibercept	0					
	Ranibizumab vs. Bevacizumab	2	173	0%	SMD	0.00 [-0.30,0.30]	0.99
	Bevacizumab vs. Aflibercept	0					

Other efficacy outcomes

Ranibizumab versus bevacizumab
There were no data comparing these treatments for any other efficacy outcomes of interest.

Aflibercept versus bevacizumab
There were no data comparing these treatments for any other efficacy outcomes of interest.

Aflibercept versus ranibizumab
There were no data comparing these treatments for any other efficacy outcomes of interest.

Harms outcomes

Anti-VEGFs versus placebo
Ranibizumab appeared to be similar to placebo with respect to the frequencies of harms of interest, including mortality (one RCT, 395 patients, OR: 4.09 [95% CI, 0.14 to 122.54]), arterial thromboembolic events (one RCT, 390 patients, OR: 0.99 [95% CI, 0.09 to 11.00]), bacterial endophthalmitis (one RCT, 395 patients, OR: 1.00 [95% CI, 0.03 to 29.89]), and retinal detachment (one RCT, 395 patients, OR: 1.00 [95% CI, 0.03 to 29.89]), although no data were available to assess the effects of ranibizumab versus placebo on venous thromboembolism or increased intraocular pressure.

Similarly, there were no notable differences in the frequency with which aflibercept was associated with mortality (one RCT, 189 patients), arterial and venous thromboembolic events (one RCT, 188 patients), bacterial endophthalmitis (one RCT, 188 patients), increased intraocular pressure (one RCT, 172 patients), and retinal detachment (one RCT, 188 patients) compared with placebo. A meta-analysis of two RCTs (365 patients) suggested that aflibercept may be associated with a statistically significantly lower incidence of serious adverse events (OR: 0.26 [95% CI, 0.10 to 0.69], 365 patients) and withdrawals due to adverse events (OR: 0.14 [95% CI, 0.04 to 0.57]) compared with placebo. The results from both of the included trials were consistent.[24,25]

There were no data on any harms of interest for the comparison of bevacizumab versus placebo.

Ranibizumab versus bevacizumab
The results of a single RCT (75 patients) suggested that ranibizumab and bevacizumab are similar with respect to the frequency of serious adverse events (OR: 2.11 [95% CI, 0.18 to 24.37]) and the incidence of increased intraocular pressure (OR: 0.33 [95% CI, 0.01 to 8.44]).

Aflibercept versus bevacizumab
There were no data comparing these treatments for any harms of interest.

Aflibercept versus ranibizumab
There were no data comparing these treatments for any harms of interest

CNV due to PM

The results of the pairwise comparisons of each of the active treatments for the main outcomes related to visual acuity (specifically, gain or loss of ≥ 15 ETDRS letters and change in baseline BCVA) for the CNV population are presented in Table 16. The complete results for these and all other efficacy and safety outcomes are presented in Appendix 12, and forest plots can be found in Appendix 16.

Vision gain

Anti-VEGFs versus placebo
There was a single trial with 121 patients comparing aflibercept to placebo, which demonstrated

that aflibercept significantly increased the proportion of patients experiencing vision gain (OR: 5.94 [95% CI: 1,68 to 21.02]).

Ranibizumab versus bevacizumab
A single RCT with 32 patients assessed vision gain after treatment with ranibizumab or bevacizumab and reported no statistically significant difference between treatments (OR: 0.77 [95% CI, 0.19 to 3.17]; see Table 16).

Aflibercept versus bevacizumab
There were no data comparing these treatments for the outcome of vision gain.

Aflibercept versus ranibizumab
There were no data comparing these treatments for the outcome of vision gain.

Vision loss

Anti-VEGFs versus placebo
There were no data comparing any of the anti-VEGF drugs with placebo for the outcome of vision loss.

Ranibizumab versus bevacizumab
There were no data comparing these treatments for the outcome of vision loss.

Aflibercept versus bevacizumab
There were no data comparing these treatments for the outcome of vision loss.

Aflibercept versus ranibizumab
There were no data comparing these treatments for the outcome of vision loss.

Mean difference in best corrected visual acuity

Anti-VEGFs versus placebo
There were no data comparing any of the anti-VEGF drugs with placebo for the outcome of mean BCVA.

Ranibizumab versus bevacizumab
The results of a meta-analysis of two RCTs with 80 patients suggested that there is no statistically significant difference in the effects of ranibizumab and bevacizumab of the change in mean BCVA (SMD: –0.13 [95% CI, –0.57 to 0.31]; see Table 16).

Aflibercept versus bevacizumab
There were no data comparing these treatments for the outcome of mean BCVA.

Aflibercept versus ranibizumab
There were no data comparing these treatments for the outcome of mean BCVA.

TABLE 16: SUMMARY OF COMPARATIVE EFFICACY OF ANTI-VEGF DRUGS ON VISION GAIN IN CNV DUE TO PM PATIENTS

Outcome	Comparison	No. of RCTs*	Total patients	I^2, *P* Value	ES	ES [95% CI]	*P* Value
Gain of ≥ 15 ETDRS letters	Ranibizumab vs. Aflibercept	0					
	Ranibizumab vs. Bevacizumab	1	32	NA	OR	0.77 [0.19, 3.17]	0.72

	Bevacizumab vs. Aflibercept	0					
Loss of ≥ 15 ETDRS letters	Ranibizumab vs. Aflibercept	0					
	Ranibizumab vs. Bevacizumab	0					
	Bevacizumab vs. Aflibercept	0					
Mean difference in BCVA	Ranibizumab vs. Aflibercept	0					
	Ranibizumab vs. Bevacizumab	2	80	0%, 0.92	SMD	-0.13 [-0.57, 0.31]	0.56
	Bevacizumab vs. Aflibercept	0					

Other efficacy outcomes

Ranibizumab versus bevacizumab
There were no data comparing these treatments for any other efficacy outcomes of interest.

Aflibercept versus bevacizumab
There were no data comparing these treatments for any other efficacy outcomes of interest.

Aflibercept versus ranibizumab
There were no data comparing these treatments for any other efficacy outcomes of interest.

Harms outcomes

Anti-VEGFs versus placebo
There were no data comparing these treatments for any harms of interest.

Ranibizumab versus bevacizumab
There were no data comparing these treatments for any harms of interest.

Aflibercept versus bevacizumab
There were no data comparing these treatments for any harms of interest.

Aflibercept versus ranibizumab
There were no data comparing these treatments for any harms of interest.

3.1.5. Indirect Comparisons

Indirect comparisons of the anti-VEGFs via NMA were feasible only for the outcomes of vision gain, vision loss, and mean BCVA in the wet AMD population. The key NMA findings are reported below, while the detailed NMA tables and figures are presented in Appendix 17.

Vision gain

The results of the NMA suggested that, compared with placebo, each of the anti-VEGFs is associated with a significantly greater proportion of patients who exhibit an improvement in visual acuity of at least 15 ETDRS letters. Specifically, the ORs for vision gain versus placebo were 5.60 [95% CI, 2.00 to 13.00] for ranibizumab, 5.60 [95% CI, 1.50 to 15.40] for aflibercept, and 4.70 [95% CI, 1.50 to 11.60] for bevacizumab. As reflected by the similar magnitudes of improvement for each anti-VEGF relative to placebo, and the relative wide CIs associated with the ORs, the results of the NMA demonstrated further that there are no statistically significant differences among the anti-VEGF drugs with respect to their effects on improving vision.

However, the probability of being selected as the best treatment option to improve vision gain was 79% for ranibizumab, 73% for aflibercept, 48% for bevacizumab and 74% for placebo treatment, indicating that there was substantial uncertainty associated with the aforementioned results.

Vision loss

There were no studies in which aflibercept was compared directly to bevacizumab in patients with wet AMD, which prevented a meta-analytical approach to comparing these treatments. The multiple comparisons among the anti-VEGF drugs that were possible within the NMA allowed for an indirect comparison of aflibercept and bevacizumab. The pairwise comparisons among these and the remaining treatments in the NMA suggested that there are no statistically significant differences among the anti-VEGF drugs with respect to their effects on vision loss; that is, the NMA results suggest that the three anti-VEGFs are similarly efficacious in preventing deterioration of vision in patients with wet AMD. This conclusion was supported by the results of the ranking analysis, which demonstrated that the probability of being selected as the best treatment option to reduce vision loss was 77% for aflibercept, 62% for ranibizumab, 61% for bevacizumab, and <1% for placebo treatment.

Mean change in BCVA

Similar to the results for the efficacy outcomes above, the results of the NMA suggested that each of the three anti-VEGF drugs is significantly better than placebo in terms of the magnitude by which baseline BCVA is improved; the average gain associated with these treatments was approximately 19 [95% CI, 12 to 25] ETDRS letters. There were no statistically significant differences in the pairwise comparisons of the anti-VEGF drugs with respect to the change in BCVA, and the differences between treatments were all less than 1 ETDRS letter. This suggests that as for the other efficacy outcomes noted above, the anti-VEGFs appear to be similarly efficacious in improving the mean baseline BCVA. The results of the probability ranking support this: the probability of being selected as the best treatment option to improve mean BCVA was estimated to be 71% for ranibizumab, 64% for aflibercept, 66% for bevacizumab and 1% for placebo treatment.

3.2. Pharmacoeconomic Evaluation

3.2.1. Results from Published Literature

Overview of Literature Identified

The pharmacoeconomic literature search identified 138 articles and an additional nine were identified through grey literature, 16 of which were selected as being of potential interest. Of these 16, three were excluded for only being available as abstracts;[84-86] one for providing only information on budget impact;[87] one for having anti-VEGFs used as part of combination therapy;[88] one which compared aflibercept patients who had previously used ranibizumab to those who has used bevacizumab;[89] and, one which was based on data from the first year of a trial for which an economic evaluation including the second year was already included.[90] A breakdown of the article selection is provided in Appendix 5 .Of the nine remaining studies, four were cost-utility analyses of bevacizumab versus ranibizumab in patients with wet AMD;[82,91-93] one was a cost-utility analysis of aflibercept versus bevacizumab or ranibizumab in patients with wet AMD;[94] one was a cost-utility analysis of ranibizumab versus aflibercept in patients with DME;[95] and three were retrospective database cohort cost studies.[96-98] No economic evaluations compared the anti-VEGF treatments of interest have been published for RVO or CNV due to PM. See Appendix 21 for detailed data extraction of these nine studies.

Wet AMD

In the three retrospective cohort studies – one was a US-based study in wet AMD patients initiated on aflibercept or ranibizumab,[96] and the other two were Swiss studies of patients receiving aflibercept or ranibizumab intravitreal injections[97,98] – the authors found no statistically significant differences in the costs or frequency of injections between patients receiving ranibizumab and those receiving aflibercept. Two of the studies[96,97] had follow-up periods of only six to twelve months, while the third had a very small sample size of patients (n=5) who had initiated therapy using aflibercept.[98] All three studies were industry-funded (by the distributor of ranibizumab) and, consequently, are subject to potential bias (e.g., interest in a finding of similar frequency of injections between ranibizumab and aflibercept). However, the equal frequency of injections is consistent with the opinions of the clinical experts consulted by CADTH, in that treatment frequency is driven by individual need as determined by OCT or other assessment rather than by frequencies recommended in product monographs or used in clinical trials.

All five of the identified cost-utility analyses supported a conclusion that bevacizumab was cost-effective when compared to ranibizumab[82,91-94] or aflibercept[94] in patients with wet AMD; however, confidence in the methodology and thus the results of these studies varies. One study reported only individual cost-effectiveness ratios along with threshold analyses, leaving inputs and assumptions made about relative efficacy, QALY gains, costs per treatment arm, and utility values unclear.[92] Another reported mean QALY gains for each treatment group (21.60 QALYs gained for bevacizumab and 18.12 QALYs for ranibizumab) that appear unlikely given the analysis time horizon (20 years) and utilities reportedly used (highest health state utility possible was 0.89), and appear to assume that all QALYs gained within the model are a direct result of ranibizumab or bevacizumab treatment, yielding unrealistically low cost-effectiveness ratios (US$1,405 per QALY for bevacizumab and US$12,177 per QALY for ranibizumab versus no treatment; bevacizumab dominant over ranibizumab; $1 USD 2007 = $1.075 CDN[99]).[93]

A single cost-utility analysis, published in 2014, which compared aflibercept to bevacizumab, ranibizumab, or no treatment in wet AMD was a Dutch study incorporating results from the VIEW 1 & 2, CATT, ABC, and MARINA trials, though without performing a network meta-analysis.[94] Utilities were based on a linear regression of HUI-3 quality of life scores with visual acuity in the better seeing eye from a separate Dutch cross-sectional study undertaken by the same authors. The analysis considered the treatment of either or both eyes, regardless of whether the affected eye was the better seeing, and as a result the cost-effectiveness ratios for all comparators were substantially higher than those seen in other studies. Compared to no treatment, the cost per QALY for aflibercept (every two months) was €140,274 (€1 2012 = $1.285 CDN[99]) bevacizumab (as needed as seen in the ABC trial) was €51,062 and ranibizumab (as needed) was €181,667. No treatment had the highest probability of being cost-effective up to a willingness to pay of €44,000 per QALY. A sensitivity analysis considering treatment of only the better seeing eye (rather than treating the worse-seeing or both eyes) showed that the cost-effectiveness of aflibercept compared to no treatment was reduced from the €140,274 per QALY to approximately €20,000 per QALY. These results were only reported for aflibercept versus no treatment and only in a Tornado plot. Presumably the cost-effectiveness of both bevacizumab and ranibizumab versus no treatment were also improved in this scenario, however the extent of this and the relative cost-effectiveness between treatments was not reported.

In a cost-utility analysis by Stein et al. 2014,[91] bevacizumab and ranibizumab, administered monthly or as needed, were compared in a hypothetical cohort of 80-year-old patients with newly diagnosed wet AMD in the US, using efficacy and harms data from the CATT trial extrapolated over a 20-year time horizon. In the base case, when compared to bevacizumab as-needed, the ICUR for bevacizumab monthly was US$242,357/QALY ($1 USD 2012 = $1.000

CDN[99]) and the ICUR for ranibizumab monthly was US$10.7 million per QALY gained; while ranibizumab as-needed was dominated (more expensive and less effective) by bevacizumab monthly. When excluding physician costs and OCT scans from the cost of monthly injections, bevacizumab as-needed and ranibizumab as-needed were dominated by bevacizumab monthly, while the ICUR for ranibizumab monthly was US$10.7 million per QALY gained.

Dakin et al. 2014[82] conducted a cost-utility study as part of the IVAN trial, considering monthly and as needed dosing of both ranibizumab and bevacizumab for patients with AMD, in the UK. The analysis of ranibizumab compared with bevacizumab focused on a cost minimization as the QALY gains between the treatments were within the a priori determined threshold of 0.05 QALYs for conducting a CMA (0.02 QALYs). Researchers additionally calculated net monetary benefits for all four treatment arms at a willingness-to-pay threshold of £20,000 (£1 2011 = $1.586 CDN[99]). Total net monetary benefit for ranibizumab-monthly was £13,576, ranibizumab as-needed was £20,142, bevacizumab monthly was £28,480, and bevacizumab as-needed was £28,683. Incorporating QALY values, the authors reported that bevacizumab monthly dominated ranibizumab as-needed, while the ICUR for ranibizumab-monthly was £270,217 per QALY gained when compared with ranibizumab as-needed. A threshold analysis suggested that the cost per dose of monthly ranibizumab would need to be reduced by 91% to be cost-effective when compared with bevacizumab monthly at a willingness-to-pay threshold of £20,000.

DME

Only one economic evaluation was identified for the DME population. Regnier et al. 2015[95] conducted a cost-utility analysis comparing aflibercept (every eight weeks after five monthly doses) with ranibizumab as-needed and ranibizumab treat-and-extend strategies over a lifetime horizon for patients in the UK. Patients were treated for three years followed by a decline in visual acuity based on natural history. Transition probabilities for ranibizumab as-needed were derived from the RESTORE trial, while the relative efficacy of aflibercept in year 1 was from a published NMA by the same authors,[100] and that of ranibizumab treat-and-extend was derived by adding data from RETAIN to the NMA. Year 2 and 3 transition probabilities were assumed to be equal between treatments. After three years, transitions were based on natural history decline from the WESDR study. Base case results showed both ranibizumab arms dominating (having greater QALYs and lower cost) than aflibercept, with net monetary benefits when compared to aflibercept of £3,934 (£1 2014 [assumed] = $1.819 CDN) for treat-and-extend ranibizumab and £6,768 for ranibizumab as-needed at a willingness to pay of £20,000. However, the QALY advantage for ranibizumab in this model is not in line with newer evidence from the 2015 DRCR.net Protocol T trial,[72] which suggests that aflibercept may be more effective than ranibizumab in DME patients with low baseline visual acuity.

Of future interest, a Dutch RCT of first-line therapy with monthly ranibizumab or bevacizumab in patients with DME is reportedly underway which will incorporate a within-trial cost-effectiveness analysis.[101]

Summary of Findings in Literature

While several studies were identified in the literature, very few of them were fully applicable to the research question of this review: *what is the relative cost-effectiveness of aflibercept, bevacizumab, and ranibizumab for the treatment of wet AMD, DME, RVO, or CNV due to PM?*

All studies which included bevacizumab in patients with wet AMD concluded that it was cost-effective relative to ranibizumab as well as aflibercept, though only one study with substantial clinical uncertainties due to the lack of formal network meta-analysis included both bevacizumab and aflibercept.

No studies including bevacizumab were identified for patients with DME.

No cost-effectiveness information was identified concerning patients with RVO or CNV due to PM.

In addition, no studies were conducted in a Canadian context; the relative costs of the comparators in Canada differ substantially from that reported in many of the studies, limiting the applicability of the cost results even if the clinical findings were consistent.

As no overall conclusions could be inferred from the available economic literature, the results of the current clinical review were used to inform the economic analysis.

3.2.2. Results from Systematic Review and Meta-Analyses Applied to the Economic Analysis

Due to the absence of any relevant or useful, sufficient information within the literature identified in the economic search (see above), the results of the data analysis of the clinical evidence identified in the systematic literature review described above were used for the economic analysis. The reader is referred to Section 3.1 for the clinical data inputs for the relative efficacy and safety, respectively, of the anti-VEGF drugs included in this review. Based on these findings, there is no evidence to suggest that there are any clinically meaningful differences among the anti-VEGF treatments in each of the four conditions of interest (although see the discussion regarding the subgroup of DME patients with poor baseline visual acuity. Consequently, the approach taken for the economics was a cost minimization analysis, where differences in the frequency of administration and costs of therapies are explored.

3.2.3. Primary Economic Analysis Results

Wet AMD

Results for wet AMD cost scenarios including base case and BC pricing are outlined in Table 17. Total and incremental costs vary widely depending on pricing and frequencies of administration assumed. Under base case pricing and assuming that ranibizumab and bevacizumab are dosed monthly while aflibercept is dosed every two months after three initial monthly doses, the cost of two years of ranibizumab therapy ($39,360 per patient) is $35,963 more than the cost of two years of bevacizumab therapy ($3,397 per patient), while two years of aflibercept ($19,364 per patient) costs $15,967 more than bevacizumab. However, when bevacizumab and ranibizumab are used every three months after an initial three monthly injections, aflibercept becomes the most expensive therapy. Incremental costs for ranibizumab and aflibercept over bevacizumab are much smaller in BC pricing scenarios, in which vials are fractioned and administration fees are higher.

TABLE 17: COST MINIMIZATION RESULTS FOR ANTI-VEGF THERAPIES FOR THE TREATMENT OF WET AMD (TWO YEARS)

Drug	Drug cost per dose	# injections	Total drug cost	Total administration cost	Total cost	Incremental cost compared to bevacizumab
Base case pricing, ranibizumab and bevacizumab dosed monthly						
Bevacizumab	$40	24	$937	$2,460	$3,397	Ref
Aflibercept	$1,418	13	$18,029	$1,335	$19,364	$15,967
Ranibizumab	$1,575	24	$36,900	$2,460	$39,360	$35,963
Base case pricing, ranibizumab and bevacizumab dosed every three months after three initial monthly doses						
Bevacizumab	$40	10	$392	$1,030	$1,422	Ref
Aflibercept	$1,418	13	$18,029	$1,335	$19,364	$17,941
Ranibizumab	$1,575	10	$15,450	$1,030	$16,480	$15,058
BC pricing, ranibizumab and bevacizumab dosed monthly						
Bevacizumab	$13.13	24	$308	$6,018	$6,325	Ref
Aflibercept	$409.00	13	$5,200	$3,266	$8,466	$2,141
Ranibizumab	$598.33	24	$14,018	$6,018	$20,036	$13,710
BC pricing, ranibizumab and bevacizumab dosed every three months after three initial monthly doses						
Bevacizumab	$13.13	10	$129	$2,520	$2,648	Ref
Aflibercept	$409.00	13	$5,200	$3,266	$8,466	$5,817
Ranibizumab	$598.33	10	$5,869	$2,520	$8,389	$5,741

A 5% discount was applied to Year 2 costs. See Table 4 for explanation of frequencies used.

DME

Results for DME cost scenarios including base case and BC pricing are outlined in Table 18. Under base case pricing and when considering frequencies derived from the aflibercept product monograph and the RESTORE study, the two-year cost of aflibercept ($20,887 per patient) was $18,898 more than the two-year cost of bevacizumab ($1,989 per patient), while the two-year cost of ranibizumab ($18,160 per patient) was $16,171 more than bevacizumab. The one-year cost of aflibercept ($13,707 per patient) becomes less expensive than that of ranibizumab ($16,800 per patient) when the frequencies used in the DRCR.net trial[72] are considered, however aflibercept is still $12,257 more expensive than bevacizumab ($1,450 per patient). Incremental costs for ranibizumab and aflibercept over bevacizumab are much smaller in BC pricing scenarios, in which vials are fractioned and administration fees are higher.

TABLE 18: COST MINIMIZATION RESULTS FOR ANTI-VEGF THERAPIES FOR THE TREATMENT OF DME

Drug	Drug cost per dose	# injections	Total drug cost	Total administration cost	Total cost	Incremental cost compared to bevacizumab
Base case pricing, aflibercept and bevacizumab as per aflibercept monograph,[69] ranibizumab as in RESTORE study[70,71] – 2 years						
Bevacizumab	$40	14	$549	$1,440	$1,989	Ref
Aflibercept	$1,418	14	$19,447	$1,440	$20,887	$18,898
Ranibizumab	$1,575	11	$17,025	$1,135	$18,160	$16,171
Base case pricing, dosing frequencies as in DRCR.net trial[72] – 1 year only						
Bevacizumab	$40	10	$400	$1,050	$1,450	Ref
Aflibercept	$1,418	9	$12,762	$9,45	$13,707	$12,257
Ranibizumab	$1,575	10	$15,750	$1,050	$16,800	$15,350
BC pricing, aflibercept and bevacizumab as per aflibercept monograph,[69] ranibizumab as in RESTORE study[70,71] – 2 years						
Bevacizumab	13.13	14	$180	$3,523	$3,703	Ref
Aflibercept	409.00	14	$5,609	$3,523	$9,132	$5,429
Ranibizumab	598.33	11	$6,468	$2,776	$9,244	$5,542
BC pricing, frequencies as in DRCR.net trial[72] – 1 year only						
Bevacizumab	13.13	10	$131	$2,569	$2,700	Ref
Aflibercept	409.00	9	$3,681	$2,312	$5,993	$3,293
Ranibizumab	598.33	10	$5,983	$2,569	$8,552	$5,852

A 5% discount was applied to Year 2 costs where applicable. See Table 5 for explanation of frequencies used.

RVO

Results for RVO cost scenarios including base case and BC pricing are outlined in Table 19. Under base case pricing, when all anti-VEGFs are assumed to have nine injections in the first year and three in the second, the two-year cost of ranibizumab ($19,920 per patient) is $18,201 more than that of bevacizumab ($1,719 per patient) while the two-year cost of aflibercept ($18,058 per patient) is $16,339 more than bevacizumab. Incremental costs for ranibizumab and aflibercept over bevacizumab are much smaller in BC pricing scenarios, in which vials are fractioned and administration fees are higher.

TABLE 19: COST MINIMIZATION RESULTS FOR ANTI-VEGF THERAPIES FOR THE TREATMENT OF RVO (TWO YEARS)

Drug	Drug cost per dose	# injections	Total drug cost	Total administration cost	Total cost	Incremental cost compared to bevacizumab
Base case pricing, all drugs similar to aflibercept dosing in COPERNICUS trial[73]						
Bevacizumab	$40	12	$474	$1,245	$1,719	Ref
Aflibercept	$1,418	12	$16,813	$1,245	$18,058	$16,339
Ranibizumab	$1,575	12	$18,675	$1,245	$19,920	$18,201
BC pricing, all drugs similar to aflibercept dosing in COPERNICUS trial[73]						
Bevacizumab	$13.13	12	$180	$3,046	$3,226	Ref
Aflibercept	$409.00	12	$5,609	$3,046	$8,655	$5,429
Ranibizumab	$598.33	12	$6,411	$3,046	$9,456	$6,231

A 5% discount was applied to Year 2 costs. See Table 6 for explanation of frequencies used.

CNV due to PM

Results for CNV due to PM cost scenarios including base case and BC pricing are outlined in Table 20. Under base case pricing, when all anti-VEGF drugs are assumed to have four injections over the first year of treatment, the one-year cost of ranibizumab ($6,720 per patient) is $6,140 more than the one-year cost of bevacizumab ($580 per patient), while the one-year cost of aflibercept ($6,092 per patient) is $5,512 more than bevacizumab. Incremental costs for ranibizumab and aflibercept over bevacizumab are smaller in BC pricing scenarios, in which vials are fractioned and administration fees are higher.

TABLE 20: COST MINIMIZATION RESULTS FOR ANTI-VEGF THERAPIES FOR THE TREATMENT OF CNV DUE TO PM (ONE YEAR)

Drug	Drug cost per dose	# injections	Total drug cost	Total administration cost	Total cost	Incremental cost compared to bevacizumab
Base case pricing, all drugs similar to ranibizumab dosing in RADIANCE trial[75]						
Bevacizumab	$40	4	$160	$420	$580	Ref
Aflibercept	$1,418	4	$5,672	$420	$6,092	$5,512
Ranibizumab	$1,575	4	$6,300	$420	$6,720	$6,140
BC pricing, all drugs similar to ranibizumab dosing in RADIANCE trial[75]						
Bevacizumab	13.13	4	$53	$1,027	$1,080	Ref
Aflibercept	409.00	4	$1,636	$1,027	$2,663	$1,583
Ranibizumab	598.33	4	$2,393	$1,027	$3,421	$2,341

See Table 7 for explanation of frequencies used.

3.2.4. Exploratory Economic Analyses Results

Quality of Life Difference and Cost-Effectiveness

A key assumption for the economic evaluation is that of similar clinical effectiveness and harms among treatments. Based on the current body of evidence, the indication for which there could be a difference in in efficacy is DME, where the DRCR.net Protocol T trial[72] reported that aflibercept had a statistically significant but clinically marginal advantage over ranibizumab and bevacizumab for improvement in visual acuity in patients with low baseline vision.

To explore the likelihood of aflibercept being cost-effective compared to bevacizumab for the treatment of DME or a subpopulation of DME, an analysis was conducted to determine the minimum number of additional QALYs aflibercept would have to yield compared with bevacizumab, in order to be considered cost-effective at $50,000 per QALY, the willingness-to-pay (WTP) threshold (Table 21).

Under the base case pricing (Ontario) and aflibercept monograph-recommended dosing for DME, the use of aflibercept would need to result in at least an average gain of 0.3780 QALYs per patient over the two-year time horizon to be considered cost-effective at a WTP of $50,000 per QALY, when compared with bevacizumab, far more than that seen in the cost-effectiveness literature reviewed. This represents an unrealistically large difference in effectiveness and/or harms to generate the gain in QALYs. Scenarios incorporating BC pricing lead to substantially smaller and thus more plausible estimates of the number of additional QALYs aflibercept would need to provide (0.1086 over two years), though still larger than QALY differences found between anti-VEGF drugs in published cost-utility analyses (Appendix 21).

TABLE 21: INCREMENTAL QALY GAIN REQUIRED FOR AFLIBERCEPT TO BE CONSIDERED COST-EFFECTIVE RELATIVE TO BEVACIZUMAB AT WTP OF $50,000 UNDER DIFFERENT SCENARIOS IN PATIENTS WITH DME

Scenario	Cost of	Cost of	Incremental	QALY gain

	aflibercept	bevacizumab	cost of aflibercept	required for WTP = $50,000/QALY
Base Case Pricing, both drugs as per aflibercept monograph, two years	$20,887	$1,989	$18,898	0.3780 over two years
Base case pricing, median dosing in Protocol T,[72] one year	$13,707	$1,450	$12,257	0.2451 over one year
BC Pricing, both drugs as per aflibercept monograph, two years	$9,132	$3,703	$5,429	0.1086 over two years
BC Pricing, median dosing in Protocol T,[72] one year	$5,993	$2,700	$3,293	0.0659 over one year

See Table 18 for cost inputs. BC = British Columbia; CE = cost-effective; DME = diabetic macular edema; QALY = quality-adjusted life year; WTP = willingness to pay.

Budget impact of expanding British Columbia Provincial Retinal Diseases Treatment Program to Ontario

In the 2014-2015 fiscal year, the Ontario Drug Benefit Program (ODB) reimbursed 192,310 units of ranibizumab, the only anti-VEGF for the treatment of retinal diseases available on the ODB Formulary during the time period, at a total cost of almost $303 million, or $1,575 per unit (IMS Pharmastat, ON Public Data, Q2 2014 through Q1 2015, 8% markup removed). Aflibercept was not yet reimbursed by ODB in March 2015; it has since been added to the formulary as a limited use product for the treatment of wet AMD, DME and CRVO.

The BC PRDTP,[79] in contrast, calls for 90% of AMD and RVO patients to receive bevacizumab, with the remaining 10% to receive ranibizumab or aflibercept, while 65% of DME patients are expected to receive bevacizumab and 35% ranibizumab or aflibercept. Overall weighting is expected to be 85% bevacizumab and 15% ranibizumab or aflibercept. Maximum drug costs reimbursed under the April 2015 BC PRDTP are $13.13 per dose of bevacizumab, $598.33 per dose of ranibizumab, and $409.00 per dose of aflibercept, with an additional program management fee of up to $125 per treatment to the administering ophthalmology practice.

The following analysis explores the possible budget impact if Ontario were to adopt the BC PRDTP reimbursement strategy and pricing for anti-VEGF drugs. If 85% of the 192,310 units reimbursed by Ontario in FY 2014-2015 are assumed to be bevacizumab and the remaining 15% are assumed to be equally divided between aflibercept and ranibizumab, and after the addition of a $125 fee for each unit, the total cost to Ontario would be almost $41 million rather than almost $303 million – a potential savings d of $262 million. However, a confidential product listing agreement exists for ranibizumab in Ontario which effectively discounts the cost of ranibizumab paid by Ontario to an unknown degree; possible discounts of 0% to 50% were explored. Possible savings range from $111 million to $262 million over one year, depending on the effective discount assumed for ranibizumab (Table 22). These analyses do not include the 8% ODB markup, meaning the estimated savings are likely conservative, nor the Ontario Schedule of Benefits for Physician Services $105 intravitreal injection fee, which would be equal between scenarios. Ontario compounding costs are assumed to be similar to those in BC, and as such are considered to be included in the maximum reimbursed drug cost.

TABLE 22: POSSIBLE SAVINGS IF ODB ADOPTED BC PRDTP REIMBURSEMENT STRATEGY FOR ANTI-VEGF DRUGS

Scenario	Total Ranibizumab Drug Cost Under Various Assumed Product Listing Agreements					
	List Price[a]	90% of List Price	80% of List Price	70% of List Price	60% of List Price	50% of List Price
Ontario ranibizumab costs for FY 2014-15 at various price reductions	$302,873,730	$272,586,357	$242,298,984	$212,011,611	$181,724,238	$151,436,865
Cost if Ontario had adopted current BC PRDTP Plan[bc]	$40,713,998					
Possible savings	$262,159,731	$231,872,358	$201,584,986	$171,297,613	$141,010,240	$110,722,867

a Ontario List Price is based on total Ontario Public costs and units retrieved from IMS Pharmastat for ranibizumab from Apr 2014 through Mar 2015 minus an 8% markup (192,310 units of Lucentis; calculated cost per unit = $1574.92, i.e., equivalent to the published ODB list price of $1,575 per vial). Aflibercept was not yet reimbursed by Ontario during the analysis time period.

b PRDTP Plan weighting is assumed to be 85% bevacizumab, 7.5% ranibizumab and 7.5% aflibercept. In future clinical practice, aflibercept may have a higher use proportion than ranibizumab due to its possible clinical advantage in some patients with DME and its less expensive price per dose. A $125 fee was added per unit. Drug costs reimbursed under the April 2015 BC PRDTP is $13.13 for bevacizumab, $598.33 for ranibizumab, and $409.00 for aflibercept, with an additional $125 program management fee per treatment. Of the estimated $40.7 million, over $24 million is due to program management fees while $16.6 million is due to drug costs.

c Note that the BC PRDTP Plan does not include the CNV due to PM indication, for which ranibizumab has been approved by Health Canada and which is reimbursed by ODB beginning in July of 2015 (although not in the fiscal year of this analysis). This difference is not taken into account in this analysis as the indications for which units are reimbursed are not available.

Price at which bevacizumab ceases to be the least expensive option

In order to account for differences in the cost of bevacizumab depending on jurisdiction, compounding fees, or other variables, a threshold analysis was conducted for each scenario explored in the analyses above (see Table 17,Table 18,Table 19, and Table 20) to determine the cost per dose of bevacizumab at which it would no longer be the least expensive anti-VEGF option. Under the base case pricing assumptions, the per dose cost of bevacizumab (including drug cost and compounding fee, if applicable) would have to increase to between $722 to $1,575 (18- to 40-fold) per dose, depending on scenario and indication, before another anti-VEGF would be the least expensive option. Under BC pricing assumptions, the cost of bevacizumab would need to increase by $97 to $586 (8- to 45-fold) per dose (see Table 23).

TABLE 23: THRESHOLD PRICE PER DOSE AT WHICH BEVACIZUMAB WOULD NO LONGER BE THE LEAST EXPENSIVE COMPARATOR IN ALL EXPLORED SCENARIOS

Scenario	Price of bevacizumab dose at which it is no longer the least expensive option	Comparator which becomes the least expensive
Wet AMD		
2-year base case pricing, monthly bevacizumab	$722	Aflibercept
2-year base case pricing, bevacizumab every three months	$1,575	Ranibizumab
2-year BC pricing, bevacizumab monthly	$105	Aflibercept
2-year BC Pricing, bevacizumab every three months	$599	Ranibizumab
DME		
2-year base case pricing, bevacizumab as aflibercept monograph	$1,219	Ranibizumab
1-year base case pricing, Protocol T frequencies	$1,266	Aflibercept
2-year BC pricing, bevacizumab as aflibercept monograph	$409	Aflibercept
1-year BC pricing, Protocol T frequencies	$343	Aflibercept
RVO		
2-year base case pricing, COPERNICUS frequency	$1,418	Aflibercept
2-year BC pricing, COPERNICUS frequency	$409	Aflibercept
CNV due to PM		
1-year base case pricing, RADIANCE frequency	$1,418	Aflibercept
1-year BC pricing, RADIANCE frequency	$409	Aflibercept

4. DISCUSSION

4.1. Summary of Clinical Evidence

We conducted a review of the comparative efficacy and safety of three anti-VEGF drugs, namely aflibercept, ranibizumab, and bevacizumab, for treating wet AMD, DME, RVO, and CNV due to PM. The systematic review of clinical evidence resulted in the inclusion of 30RCTs, including 13 RCTs for wet AMD, five RCTs for DME, nine RCTs for RVO, and three RCTs for CNV due to PM. Data from the included studies were analyzed for five efficacy outcomes (vision gain, vision loss, difference in BCVA, blindness, and vision-related function) and eight safety outcomes (SAEs, AEs, withdrawals due to AEs, mortality, arterial and venous thromboembolic events, bacterial endophthalmitis, increased intraocular pressure, and retinal detachment). Pairwise comparisons between treatments were made using meta-analysis. Indirect comparisons among treatments using an NMA were feasible only for wet AMD.

4.2. Summary of Economic Findings

While the absolute costs of anti-VEGF treatments varied substantially depending on the dose frequency, indication, and pricing scenario assumed, bevacizumab was the least expensive comparator in all analyses. When considering ODB list prices, assuming single-dose units from ranibizumab and aflibercept vials, bevacizumab is the least expensive treatment even if the cost (drug cost plus any compounding costs) is increased to $700 or more per dose – i.e., bevacizumab is cost-saving even if the vials were used as single-dose units.

In terms of clinical efficacy and safety for the treatment of DME – the indication for which there is currently evidence to support a possible advantage for one of the anti-VEGF treatments over the others – aflibercept would have to confer at least 0.38 QALYs, compared with bevacizumab, over two years at base case prices to be considered cost-effective at a willingness to pay of $50,000 per QALY.

4.3. Interpretation of Results

4.3.1. Comparative Efficacy of Anti-VEGF Treatments

The results of our meta-analyses suggested that there are no statistically significant differences between ranibizumab and bevacizumab or aflibercept with respect to the effects of these treatments on visual acuity and other vision-related outcomes (such as the development of blindness) in patients with wet AMD, although pairwise comparisons were not possible for all of the efficacy outcomes included in the review. Nevertheless, indirect comparisons of the anti-VEGFs via NMA, which allowed for comparison of treatments for which direct comparative data were not available, were consistent with the direct pairwise meta-analyses in suggesting that there are no statistically significant differences among ranibizumab, bevacizumab, and aflibercept with respect to the effects of these treatments on improving visual acuity and preventing loss of vision. In addition to the absence of any statistically significant differences between the anti-VEGFs, any non-significant difference that did exist were likely attributable to methodological heterogeneity and were below the threshold of what would constitute a clinically meaningful difference. Therefore, these findings are consistent with the conclusion that there is no evidence of any clinically meaningful difference in the improvement of vision in wet AMD patients in response to treatment with ranibizumab, bevacizumab, or aflibercept.

A similar conclusion has been made by others who have examined the comparative efficacy of the anti-VEGFs in patients with wet AMD. For instance, several high-quality systematic reviews have reported that the efficacy of bevacizumab in wet AMD patients is similar to that of

ranibizumab.[102-107] Several other authors that have used direct and/or indirect comparisons (NMA) have reported that aflibercept, ranibizumab and bevacizumab were all similar in terms of their relative efficacy in wet AMD patients.[108-110]

As was the case for wet AMD, the results of our analysis did not reveal any significant differences between ranibizumab and bevacizumab with respect to the effects of these treatments on visual acuity and other vision-related outcomes in patients with DME. This suggests that these two treatment might be equally effective in DME patients, as has been reported elsewhere.[105,106] However, the comparison of aflibercept with bevacizumab and ranibizumab suggested that aflibercept might be more efficacious in improving vision compared to the other two anti-VEGF treatments. Specifically, a significantly greater proportion of patients achieved an improvement in their vision of at least 15 ETDRS letters after aflibercept treatments compared to patients treated with either bevacizumab or ranibizumab. Similarly, aflibercept-treated patients experienced a significantly greater improvement in BCVA compared to the other two anti-VEGF treatments. It is tempting to conclude, based on the aforementioned findings, that aflibercept is superior to bevacizumab and ranibizumab in terms of improving visual acuity in DME patients; however, there are several major limitations associated with the aforementioned results that suggest that such a conclusion is uncertain.

First, the statistically significantly greater improvement in the difference in BCVA attributable to aflibercept reflects an absolute relative improvement from baseline of 3.5 (95% CI, 1.4 to 5.7) ETDRS letters compared to bevacizumab and 2.1 (95% CI, 0.1 to 4.2) ETDRS letters compared to ranibizumab. It is widely accepted that the minimum threshold for improvement in visual acuity that must be exceeded for patients to perceive a meaningful improvement in vision (i.e., the minimal clinically important difference) for the ETDRS is 10 to 15 letters.[52,111,112] Therefore, while the effect size of aflibercept might be statistically significantly greater than the other treatments for improvement in visual acuity in DME patients, the magnitude of improvement of fewer than 4 ETDRS letters is substantially smaller than the threshold that would represent a clinically meaningful difference (which would require a difference of at least 10 to 15 letters). In other words, DME patients would likely not perceive a difference between aflibercept and the other anti-VEGF treatments. Indeed, the clinical experts consulted by CADTH for this review were in agreement that if there is a marginal difference between aflibercept and the other treatments in DME patients, this would not reflect a clinically meaningful improvement in practice. However, even if the slightly greater efficacy of aflibercept observed in the Protocol T study were without any major limitations, it is likely that bevacizumab remains the least costly anti-VEGF treatment in DME patients (see below). This does not, however, minimize the potential for individual patients to respond differently to different treatments, a fact that was emphasized in the patient input revived by CADTH for this review.

Second, the only differences between the three anti-VEGF treatments were derived from a single study of DME patients, namely the DRCR.net Protocol T study.[18] While our critical appraisal of this RCT did not reveal any other substantive methodological issues that threaten the validity of the results, this does not negate the possibility that the results of this study are spurious, i.e., entirely due to chance. Therefore, in the absence of independent replication of the results of the single study that has demonstrated a difference between aflibercept and the other anti-VEGF treatments, there is substantial uncertainty associated with the apparent differences observed between aflibercept and the other treatments.

Third, the apparently superior effects of aflibercept on improvement of BCVA are not completely consistent with the comparative efficacy of the anti-VEGFs on other vision-related outcomes within the same study or indeed in our analyses. Specifically, there were no differences among treatments with respect to their effect preventing vision loss (reflected in the proportion of patients whose experience a decline in BCVA of 15 of more ETDRS letters). It is unlikely that

the effects of the anti-VEGFs on preventing the macular deterioration that leads to vision loss is independent of the improvements in visual acuity caused by these drugs. Therefore, the inconsistency between the apparently greater efficacy of aflibercept versus the other anti-VEGF in terms of improving visual acuity and the absence of any such difference among treatment in terms of worsening of vision further adds to the uncertainty regarding any conclusion related to differential efficacy.

Despite the aforementioned limitations, the clinical experts consulted for this review believe that the apparent difference between aflibercept and the other anti-VEGF treatments in DME patients observed in the DRCR.net Protocol T study might drive the preferential use of aflibercept over bevacizumab and ranibizumab, although this remains to be seen in practice. Although aflibercept is a recombinant fusion protein, while bevacizumab is a recombinant monoclonal antibody and ranibizumab is monoclonal antibody fragment, the mechanism by which all three molecules inhibit angiogenesis in the eye is by inhibiting VEGF receptor activation. Therefore, there is no major difference in the mechanism of action of these molecules that would readily explain the apparent difference with respect to vision gain in DME patients. However, it has been postulated that differences in the affinity of aflibercept for other molecules that are involved in VEGF receptor binding and regulation, such as placental growth factor, might underlie the apparent differences in efficacy in DME patients between aflibercept and the other anti-VEGFs, but this has yet to be tested explicitly. If the difference in DME patients was due to a molecular mechanism, it is not clear why this difference would not be apparent in other retinal conditions, such as wet AMD, which is not the case. One hypothesis is that diabetic retinopathy is thought to be driven more by ischemia than wet AMD, which would suggest that any differences between aflibercept and the other anti-VEGFs in DME patients might not be translated in similar differences in other retinal conditions.

The results of the DRCR.net Protocol T study indicated that the significantly better effects of aflibercept on vision gain were driven by a subgroup of patients who had relatively worse visual acuity at baseline. Specifically, patients with a baseline BCVA of less than 69 ETDRS letters exhibited a significantly greater improvement in mean BCVA of 6.5 (95% CI, 2.9 to 10.1; $P < 0.001$) letters when comparing aflibercept to bevacizumab and 4.7 (95% CI, 1.4 to 8.0, $P = 0.003$) letters when comparing aflibercept to ranibizumab. By contrast, there was no statistically significant difference in the improvement in BCVA among the three treatments in patients with a baseline BCVA of > 69 ETDRS letters.[18] Therefore, it would appear that the slightly greater improvement in vision due to aflibercept treatment compared to the other anti-VEGFs in DME patients is limited to patients with relatively poor vision, and that aflibercept and the other anti-VEGF treatments have similar efficacy in patients with better visual acuity (who nevertheless still require treatment for the condition). Note, however, that even within the subgroup with poor visual acuity at baseline (< 69 ETDRS letters), the difference in improvement in BCVA compared to the other anti-VEGFs was substantially smaller than the minimal clinically relevant difference of 10 to 15 letters. Moreover, the limitations noted above for the Protocol T study as a whole apply also to any the results for the subpopulation based on visual acuity. In addition, the unbalanced use of laser therapy among the three treatment groups in this study likely was a confounding variable that further increases the uncertainty regarding any conclusion of differential efficacy within the subgroup of DME patients with poor baseline visual acuity.

Although there are limited data available for comparison of the anti-VEGFs in DME patients, Virgili and colleagues (2014) compared several different anti-VEGFs, including aflibercept, bevacizumab, and ranibizumab in a meta-analysis of two trials.[113] These authors reported no difference for the comparison of bevacizumab and ranibizumab for the outcome of mean change in visual acuity, which is consistent with the results of the Protocol T study, but were

unable to perform additional comparisons due to the paucity of available data at the time of the study.

In contrast to the data available to assess the comparative effects of the anti-VEGFs in wet AMD and DME patients, there were fewer studies available to examine the relative efficacy of the anti-VEGF drugs in patients with RVO or CNV due to PM. Of note, there were no studies in which aflibercept was compared directly to bevacizumab or ranibizumab in either of these conditions; therefore, it is not possible to determine the relative efficacy of aflibercept compared to bevacizumab or ranibizumab in patients with RVO or CNV due to PM. However, meta-analysis of two small RCTs suggested that bevacizumab and ranibizumab have similar effects on visual acuity in patients with RVO. Similarly, in patients with CNV due to PM, the effects of ranibizumab and bevacizumab on vision gain were similar in a single study, and meta-analysis of two small studies showed no statistically significant difference between the effects of ranibizumab and bevacizumab on mean BCVA. These findings are consistent with other research available in the literature. Specifically, an observational study by Cha and colleagues reported similar improvements in patients with CNV who received either ranibizumab or bevacizumab,[114] while a quasi-experimental study demonstrated similar efficacy for bevacizumab and ranibizumab in patients with RVO.[115] Whether the efficacy of ranibizumab and bevacizumab is similar to that of aflibercept in patients with RVO or CNV due to PM remains to be determined definitively. However, Ford and colleagues used a systematic review and NMA to demonstrate that the efficacy of bevacizumab is similar to that of ranibizumab and aflibercept in patients with macular edema secondary to central RVO.[116] Wang and colleagues (2013) conducted a systematic review in order to examine the evidence related to intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections for myopic choroidal neovascularization. In a meta-analysis of the mean difference in BCVA, with data from two RCTs comparing ranibizumab and bevacizumab, no significant difference between the treatments was detected.[117]

4.3.2. Comparative Safety of Anti-VEGF Drugs

For the comparative harms of anti-VEGF agents among patients with wet AMD, the results evidence from the included studies suggests that ranibizumab, aflibercept, and bevacizumab have a similar safety profile. The same results were observed for the DME and RVO indication and no statistically significant results were observed across the single trials that reported the harms outcomes of interest. For DME and RVO, a meta-analysis was not possible across all of the harms outcomes examined because there were so few studies reporting on these. For CNV due to PM, none of the included studies reported on harms, which is an area for future research. These results should be interpreted with caution. Overall, our analysis of the potential harms of aflibercept, bevacizumab, and ranibizumab revealed no statistically significant differences among the three anti-VEGFs for each of the four retinal conditions with respect to the frequency of key safety outcomes, including AEs, SAEs, WDAEs, mortality, ATEs, VTEs, bacterial endophthalmitis, increased IOP, and retinal detachment. However, it should be noted that this finding is not necessarily consistent with the conclusion that these three treatments have the same risk of causing harm or identical safety profiles, for two reasons.

First, none of the included studies were designed specifically to examine the safety of any of the anti-VEGF drugs. Therefore, these studies did not have sufficient statistical power to detect drug-specific differences in the rates of relatively rare harms such as mortality and thromboembolic events.[118]

Second, there was a paucity of data related to safety outcomes in general, particularly due to the fact that safety outcomes were reported less often than efficacy outcomes in the included studies. Therefore, there are gaps in the evidence for several safety-related comparisons

among the anti-VEGFs, including adverse events (AEs), serious AEs, withdrawals due to AEs, mortality, arterial and venous thromboembolic events, bacterial endophthalmitis, and retinal detachment, which makes any conclusions regarding the comparative safety of the anti-VEGFs uncertain. A systematic literature search revealed a published systematic review and meta-analysis of 21 RCTs that examined cardiovascular events (i.e., a composite of non-fatal myocardial infarction, non-fatal ischemic or hemorrhagic stroke, or death due to a vascular or unknown cause) and non-ocular hemorrhagic events for patients with AMD who received ranibizumab or bevacizumab versus no anti-VEGF treatment.[119] Relative to control treatments, anti-VEGF drugs did not significantly increase overall mortality, cardiovascular mortality, stroke, myocardial infarction, VTEs, or hypertension. In addition to the aforementioned study, Virgili and colleagues (2014)[113] reported that there were no statistically significant differences between all anti-VEGF treatments and either sham or photocoagulation for serious systemic adverse events, arterial thromboembolic events and overall mortality.

The relative safety of bevacizumab compared to ranibizumab is controversial. While the safety of intraocular injection of ranibizumab has been studied in several controlled trials of patients with retinal conditions, data regarding the safety of bevacizumab in the same populations are more scant.[120] The issue of the comparative safety of bevacizumab versus ranibizumab stems from (a) differences between the availability and administration of ranibizumab and bevacizumab, which has led to concerns regarding the potential for compounded bevacizumab to increase the risk of bacterial endophthalmitis, and (b) the potential elevation of risks of cardiovascular events associated with bevacizumab.

Bevacizumab is supplied in vials with a volume of 4 mL or 16 mL for intravenous administration, and for intravitreal administration, aliquots (1.25 mg per 0.05 mL[iii]) must be compounded (ideally in individual syringes) from these vials. Ranibizumab is available as single-use vials and pre-filled syringes for intraocular injection (0.05 mL per eye). Concern about the safety of compounded bevacizumab is related to the potential for bacterial growth and degradation of the active molecule, although several studies have shown no evidence of these issues in properly stored aliquots.[121-126] Despite one identified report of cases of bacterial endophthalmitis associated with contaminated batches of compounded bevacizumab,[127] we found no evidence of any significant difference with respect to the incidence of this harm in the clinical trial populations included in our study. Moreover, a recently conducted US database cohort study including more than 383,000 intravitreal injections of bevacizumab or ranibizumab found that repackaged bevacizumab did not increase the risk of endophthalmitis compared to single-use ranibizumab (adjusted OR = 0.66 [95% CI, 0.39 to 1.09]; *P* = 0 .11).[128] Therefore, while additional studies are warranted to examine the comparative safety of bevacizumab, particularly in real-world settings, the evidence available to date does not suggest that compounded bevacizumab is associated with a substantial increase in the risk of developing bacterial endophthalmitis compared to ranibizumab or aflibercept.

The concerns related to the cardiovascular safety of bevacizumab from reports that systemic bevacizumab administration in patients with metastatic colorectal cancer was reportedly associated with an increased risk of thromboembolic events,[129] despite the fact that intravitreous bevacizumab is administered at a dose that is ~150 times less than the systemic dose. Several studies have attempted to determine whether intraocular injection of bevacizumab might be associated with a similar increase in systemic cardiovascular events, particularly thromboembolism. A systematic review and meta-analysis of 21 RCTs that examined

[iii] Note that this is the most frequently reported compounding volume used in controlled studies.

cardiovascular events (i.e., a composite of non-fatal myocardial infarction, non-fatal ischemic or hemorrhagic stroke, or death due to a vascular or unknown cause) and non-ocular hemorrhagic events for patients with AMD who received ranibizumab or bevacizumab versus no anti-VEGF treatment revealed no statistically significant differences between bevacizumab and ranibizumab in the risk of a major cardiovascular or non-ocular hemorrhagic event.[119] However, this study suggested that bevacizumab treatment significantly increased the risk of venous thromboembolic events when compared with ranibizumab (OR = 3.45; 95%CI 1.25 to 9.54).[119] Three observational studies were identified that reported an increased risk of cardiovascular events in bevacizumab use compared to ranibizumab use; the first is a meeting abstract with no published full text of an observation claims database study, the study suggested increased risk of overall mortality (HR = 1.57; 99% CI 1.04 to 2.37) and hemorrhagic cerebrovascular accident (HR = 1.57; 99%CI 1.04 to 2.37), the study however was missing important information regarding essential confounders such as smoking status, lipids, and blood pressure levels;[130] the second study was a retrospective cohort of Medicare claims database, ranibizumab versus bevacizumab analysis showed an increased overall mortality with bevacizumab (HR 0.86; 95%CI 0.75 to 0.98) and an increased incident of stroke (HR 0.78; 95%CI 0.64 to 0.96), The authors of the study speculated that a selection bias might play a role in favour of ranibizumab, as patients who cannot afford ranibizumab are channelled towards bevacizumab, when the authors rerun the analysis utilizing data only from exclusive providers, statistically significant differences in overall mortality and stroke were no longer observed;[131] the third study was chart based retrospective cohort on 378 patients with wet AMD, the study suggested an increased risk of arterial thromboembolism with the use of bevacizumab compared to ranibizumab (OR = 10.16; 95%CI 2.80 to 36.93), the study, however, had a mean follow-up period of 832.63 days (SD 268.73) for bevacizumab-treated patients, but only 286.92 days (SD 205.05) for ranibizumab-treated patients, suggesting strong bias in favour of ranibizumab.[132]

In contrast to the aforementioned findings, Campbell and colleagues reported that 91,378 participants of a nest case-control study population who had ischaemic stroke, acute myocardial infarction, congestive heart failure, or venous thromboembolism were not more likely than control participants to have been exposed to either bevacizumab.[133] Another population based database on 116,388 patients with wet AMD by Campbell and colleagues showed no difference in the incidence of stroke before and after bevacizumab and ranibizumab were available for use.[134]. Two published systematic reviews and meta-analyses of RCTs comparing bevacizumab to ranibizumab showed no differences in cardiovascular related adverse events.[135,136] Several other observational studies support the lack of increased risk in cardiovascular related events with bevacizumab use, including four retrospective cohorts, [137-140] one case-control,[141] and one population database analysis.[142]

A more comprehensive summary of safety-related evidence derived from studies of intravitreal bevacizumab administration is presented in Appendix 1. According to the evidence presented in the aforementioned summary of safety-related evidence, the most credible evidence available suggests that intravitreal injection of bevacizumab is not associated with a significantly increased risk of cardiovascular harm compared to treatment with ranibizumab. Similarly, the weight of evidence available suggests that the risk of ophthalmic harm is similar for bevacizumab and ranibizumab injection. However, an important condition related to the lack of evidence of differences between bevacizumab and ranibizumab relates to the fact that this conclusion rests on appropriate preparation, storage, and handling of bevacizumab aliquots to avoid contamination, which has been reported to increase the risk of ophthalmic harm.

4.4. Patient Input

CADTH received feedback from several patient groups, including the Canadian Council of the Blind (CCB), the CNIB, and the Foundation Fighting Blindness. This is summarized in Appendix

18: Patient Input Summary. The patient input described the devastating impact caused by vision loss due to the retinal conditions under review. An important issue raised was the fact that early intervention and individualized treatment to improve long-term outcomes was essential, and that successful treatment could be jeopardized by delayed access and a lack of choice. This is directly related to two of the most important issues to patients, namely restoring vision and preventing further loss of vision.

Patients highlighted some issues that are unique to specific populations. For instance, affordability is a particular concern to many patients with DME, while predisposition to PM is a major concern to Asians of working age. While comparison of subgroups was limited in the current review by a paucity of available data (except note the discussion of DME, above), the concerns raised by patients highlight the subtleties related to patients with different retinal conditions and caution against a single approach in dealing with all retinal conditions.

According to the patient input, patients in Canada with AMD, RVO, DME, and CNV due to PM are being treated with each of the three anti-VEGF drugs included in this review, namely bevacizumab, ranibizumab, and aflibercept. Most patients appear to be undergoing treatment with ranibizumab, and most patients undergoing ranibizumab treatment were satisfied with the treatment. Patient experiences with compounded bevacizumab were conflicting: while some patients reported a negative experience with bevacizumab, others were satisfied with bevacizumab. While relatively few patients had experience with aflibercept, the experiences of patients appeared to have been positive. The patient groups cited these experiences are evidence to support the need for access to as many treatment options as possible, and the patient input emphasized treatment choice as a major issue, without identifying one anti-VEGF as the best treatment. This would appear to align with the main finding of this review, namely that there are no major or consistent differences among bevacizumab, ranibizumab, and aflibercept with respect to efficacy in treating AMD, DME, RVO, and CNV due to PM. The concept of choice for patients was related to the ability to access alternative treatments if the current treatment failed to work or caused intolerable side effects. The issue of switching among anti-VEGF drugs was beyond the scope of the current review, and it has been noted by CADTH (see Appendix 19) and others that there is little clinical evidence available to determine whether patients will respond to a different anti-VEGF drug after failing initial therapy with a different anti-VEGF drug. The clinical experts consulted by CADTH for the purpose of this review stated that they believe that in practice, for patients who fail to improve after six anti-VEGF injections (approximately six months of therapy), there may be a benefit in switching to a different anti-VEGF drug. The clinical evidence found in the issue of switching among anti-VEGF drugs is poor and comprises mainly small, observational studies, the results of which are inconsistent with respect to the effectiveness of switching among anti-VEGF drugs following the failure of initial anti-VEGF therapy.[143-147]

Side effects were of concern to patients, although side effects often do not often prompt patients to seek alternative treatments, because they feel that other options are not available to them. The results of this review suggest that the risk of harm is similar among the three anti-VEGF inhibitors, as has been reported by others. This would suggest that differences in harms among the available treatment likely will continue to be a minor factor in their treatment choice, even if additional treatment options become available. Nevertheless, as noted elsewhere, the comparative safety of these treatments should be examined in more detail using appropriately designed studies.

The high cost of treatments was noted in the patient input. This concern reflects the high cost of ranibizumab and aflibercept, rather than bevacizumab, and emphasizes the desires for patients to have access to cost-effective treatments that are safe and effective.

4.5. Strengths and Limitations

4.5.1. Strengths

A strength of this study is that the systematic review and meta-analysis were methodologically rigorous and followed the Cochrane Collaboration recommendations for the conduct of our systematic review.[44] Specific strengths of the systematic review include the use of a protocol, peer review of the literature search, comprehensive literature search, inclusion of unpublished data, and having two independent reviewers at all stages of screening, data abstraction, and quality appraisal. In addition, a third reviewer verified the data abstraction and quality appraisal, increasing the reliability and validity of results.

Another strength of the current study is that the review team included the opportunity for input from a variety of important stakeholders, including payers, patients, and clinicians. In addition, the review team itself comprised a variety of clinical and analytical expertise.

Despite the data paucity and issues related to this (see Limitations, below), a strength of the current study is that data were available for each of the three key outcomes related to efficacy, namely gain and loss of vision and change in visual acuity. Similarly, we were able to obtain data for each of the four conditions of interest.

Finally, a strength of our study is the fact that our conclusions are generally consistent with other published reports that have examined the relative effects of anti-VEGFs in patients with various retinal conditions (see above).

4.5.2. Limitations

The main limitation of the present study is the lack of a sufficient number of studies to allow for a complete analysis, i.e., to allow for all pairwise combinations to be analyzed for all outcomes of interest across all four conditions of interest. Where sufficient data were available to allow for multiple pairwise comparisons within an individual condition, there were 58 comparisons out of a possible 102 where data were available for only a single RCT, including vision gain, vision loss, and mean difference in BCVA for DME, vision gain and mean difference in BCVA for RVO, and vision gain for CNV due to PM. For outcomes and conditions where only one study was available, there is a high degree of uncertainty associated with conclusions related to these data. In cases where there was more than one study available for analysis, but fewer than three studies available (e.g., vision gain, vision loss, and mean difference BCVA for the comparison of ranibizumab versus aflibercept in the wet AMD population), there was frequently a high degree of heterogeneity. The reasons for heterogeneity included different follow-up time, different dose of the same intervention, different frequency of injection, and differences in the pathophysiology between central and branch RVO. Such heterogeneity increases uncertainty regarding conclusions for these analyses. Finally, the paucity of data meant that there were not enough studies available to perform indirect comparisons among treatments for which head-to-head studies were unavailable, except for the DME.

In addition to the effect that the paucity of available data had on our analyses, the included studies had some methodological limitations that increased the uncertainty of our conclusions. Specifically, most of the included studies did not adequately report the random sequence generation or allocation concealment, which are arguably the most important components for the conduct of RCTs. In addition, many of the RCTs were funded by private industry and there was a high risk of funding bias in these RCTs because authors of the trials were employed by the anti-VEGF manufacturer and have an inherent conflict of interest.

There is one included trial for which major concerns were noted [322]. In this trial, the authors randomized 42 patients with RVO to treatment with bevacizumab and 51 patients to ranibizumab. However, in the results section of the publication, the authors note that “an additional nine patients were included in the study but were not randomized to treatment due to financial hardship and were instead assigned to the bevacizumab group”. Since these patients were added to the bevacizumab group and comprise more than 20% of patients who received this treatment, the results are likely not trustworthy. The authors do not report the results excluding these patients.

Another limitation of the current review was that it was limited to a comparison of the relative clinical effects of the anti-VEGFs, and did not include other treatments. We did not, therefore, explicitly consider the absolute effectiveness of these treatments on outcomes of importance to patients, such as vision-related function. The reason for limiting the scope to comparison among the anti-VEGFs, as noted in the scoping document for this project, was to focus the research onto the question that is most relevant to public payers in Canada, namely the comparative effectiveness of anti-VEGFs. As noted elsewhere, future work will expand the treatments to be considered for inclusion beyond the anti-VEGFs.

It was not within scope of the current project to assess the effectiveness of anti-VEGFs in various treatment switching scenarios, in which patients are switched from one anti-VEGF to a different anti-VEGF. Therefore, another limitation of our study is the lack of information presented regarding the appropriateness or effectiveness of switching patients among the anti-VEGFs.

Another limitation of the current study is the fact that we were unable to compare the effects of differences in dosage and/or injection frequency among the anti-VEGFs on visual outcomes, because too few studies reported sufficient information to conduct such an analysis.

4.6. Pharmacoeconomic Considerations

The cost minimization analysis approach is based on the assumption of similar clinical effectiveness and harms among all three anti-VEGF treatments as found in the systematic review and meta-analyses. The evidence base supporting similar clinical efficacy in patients with wet AMD is fairly robust, while substantial gaps still exist in comparative harms information due to the nature of clinical trials (i.e., generally powered to detect primary efficacy end point differences rather than rarer adverse events). Evidence in the DME population is less clear, with one major trial reporting a statistically significant but clinically small improvement in visual acuity outcomes with aflibercept compared with bevacizumab and ranibizumab in patients with low baseline vision. In the RVO and CNV due to PM populations, direct and indirect evidence of comparative efficacy is sparse, with even more limited information regarding harms information. Should additional comparative clinical information become available, the cost-effectiveness of the anti-VEGF treatments in these populations may need to be re-evaluated.

Information on how treatments are administered in actual practice (particularly frequency) is not currently available for the indications of interest. As a result, analyses were based on recommended dosing and dosing from the clinical studies that support similar clinical effects. Should real-world information become available, the results of the analysis may need to be revised.

Reimbursement of anti-VEGF treatments differs across provincial, territorial, and federal jurisdictions depending on the existence of retinal programs or negotiations with manufacturers (e.g., confidential product listing agreements), the details of which are often not publicly available. These complicate the accurate estimate of actual costs incurred by drug plans or programs.

The exploratory analysis on the budget impact of uptake of less expensive treatment options (e.g., aflibercept or bevacizumab compared with ranibizumab, or fractioning vials) demonstrated substantial financial savings to jurisdictions. This is increasingly important with the growth in utilization of these treatments.

Considering the current clinical evidence base, the use of bevacizumab has the potential to generate cost savings to payers who are currently reimbursing ranibizumab and/or aflibercept. The average cost of treatment with ranibizumab and aflibercept ranged from $18,058 to $39,360 per patient over two years across retinal conditions, assuming base case prices. These costs are substantially higher than those of bevacizumab, which ranged from $1,422 to $3,397 per patient over two years. In fact, these results suggest that to achieve approximately equal treatment costs for with the next least expensive anti-VEGF drug, the cost of bevacizumab would have to increase from $40 to $722 to $1,575 (18- to 40-fold) per dose, or more than the cost of a full 100 mg vial of bevacizumab (i.e. even if not fractioned, bevacizumab is less expensive than the other comparators). A 2014 US budget forecasting model estimated that if all ranibizumab use was switched to bevacizumab over the ten-year period from 2010 to 2020, US$18 billion ($1 US 2014 [assumed] = $1.104 CDN)[99]) could be reduced from the Medicare Part B (medical insurance) budget, with an additional US$4.6 billion saved in patient copays.[87] While the US health care system and population size is substantially different than the Canadian, this estimate is in line with the plausible one-year savings of at least $100 million (see Table 22) in Ontario if reimbursement for anti-VEGFs more closely resembled that currently used in BC, while still allowing for 15% of patients to require ranibizumab or aflibercept. The mandate of Joint Accountability Committee of the BC Provincial Retinal Diseases Treatment Program includes the gathering, analyzing, and publication of safety and efficacy evidence regarding the drugs reimbursed under the program (see Appendix 20). These data, once publically available, will undoubtedly be of great interest to retinal disease clinicians, patients, researchers, and policy-makers.

The evidence presented in this report appears to be aligned the recommendations made previously by the CADTH CDEC for the anti-VEGFs for individual retinal conditions (see Appendix 19). As can be seen in Appendix 19, ranibizumab has been recommended for reimbursement for wet AMD, DME, RVO, and CNV due to PM. Subsequently, aflibercept has been recommended for reimbursement in the same manner as ranibizumab in each of the retinal conditions in which ranibizumab (except for CNV due to PM, for which aflibercept has not been reviewed by CDEC, and branch RVO, which is currently being reviewed by CDR – see Appendix 19: Previous CADTH Reviews of Anti-VEGF Drugs for Retinal Conditions), based on the absence of any differences in the clinical efficacy and safety of ranibizumab and aflibercept. Of note, however, were the conditions recommended by CDEC that "*Aflibercept should provide cost savings for drug plans relative to ranibizumab for the treatment of CRVO*" and that "*drug plan cost for the treatment of wet AMD with aflibercept should provide cost savings relative to the treatment of wet AMD with ranibizumab*". This reflects the belief of CDEC that the cost of treatment with aflibercept and ranibizumab should be the same, because these drugs are essentially clinically equivalent. While CDEC did not explicitly refer to bevacizumab in any of the recommendations made for aflibercept or ranibizumab, the absence of any substantive differences in the efficacy and safety of bevacizumab compared to ranibizumab and aflibercept revealed by the current study, as well as in several other studies, suggests that there is no evidence available to recommend against the reimbursement of a treatment that is as effective, but substantially cheaper than, other treatments that are being reimbursed for particular conditions. Indeed, bevacizumab is currently being reimbursed by public payers for the treatment of retinal conditions in at least four Canadian provinces, including British Columbia, Nova Scotia, New Brunswick, and Manitoba[40,41,149,150] Alberta recently introduced a new program that will allow patients to choose, and physicians to prescribe, either ranibizumab or

bevacizumab for the treatment of AMD, DME, RVO, and any other retinal condition that requires anti-VEGF treatment[151] The Alberta government will cover the cost of bevacizumab with no co-payments, and will continue to cover the cost of ranibizumab. In addition, the Retina Society of Alberta will lead a monitoring program, to assess the safety and efficacy of both treatments.[151,152]

The aforementioned developments within Canada to allow for the public reimbursement of bevacizumab for use in retinal conditions reflects a similar movement internationally, as several major jurisdictions have recently made bevacizumab available for the treatment of retinal conditions.[34] Despite the fact that bevacizumab is not approved for intraocular injection, the potential availability of bevacizumab in addition to other anti-VEGFs for the treatment of retinal conditions would meet the greatest wish expressed by patients, namely a desire to have access to a variety of different treatment options. This wish was reflected by the clinical experts consulted by CADTH for the purpose of this review, some of whom believe that where necessity requires it, the use of unapproved treatments is an essential part of medical practice that allows for better, patient-centred care. This is particularly true in the case of bevacizumab, which has been used widely to successfully treat retinal conditions without causing serious harm, yet is unlikely ever to be submitted to regulators by the manufacturer for approval specifically for the treatment of retinal conditions. There is therefore a corresponding dearth of data regarding the comparative effectiveness of bevacizumab versus other treatment in patients with retinal conditions, since most RCTs are sponsored by manufacturers. Indeed, this explains why the best available evidence of comparative effective that includes bevacizumab is the DRCR.net Protocol T trial,[72] which was sponsored by the National Eye Institute, the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institutes of Health in the USA.

4.7. Conclusions and Implications for Decision-making

The results of the present study suggest that ranibizumab and bevacizumab have similar effects on visual acuity and other vision-related outcomes in patients with wet AMD, DME, RVO, or CNV due to PM. Similarly, the effect of aflibercept on visual acuity were similar to those of ranibizumab and bevacizumab in patients with wet AMD, and that bevacizumab and ranibizumab have similar effects in patients with RVO or CNV due to PM, but there were insufficient data to compare aflibercept to the other anti-VEGFs in patients with RVO and CNV. In patients with DME, aflibercept might improve vision to a greater extent than ranibizumab and bevacizumab in patients with poor visual acuity, although this observation should be tempered by several limitations. A major limitation of the present study is the lack of data available for some conditions, particularly RVO or CNV. Therefore, comparisons of efficacy among the anti-VEGFs was not possible for all outcomes across all four of the conditions of interest, and the small number of studies available for many of the outcomes analyzed across the four conditions are uncertain, despite being consistent.

Our study did not reveal any notable differences with respect to the potential for aflibercept, bevacizumab, and ranibizumab to do harm to patients, both for non-specific safety outcomes as well as harms of special interest, such as bacterial endophthalmitis and retinal detachment. However, this finding is not necessarily consistent with the conclusion that these three treatments have the same risk of causing harm or identical safety profiles, because none of the included studies was designed specifically to examine the safety of any of the anti-VEGF drugs and there was a paucity of harms-related data available for analysis. Nevertheless, it is worth emphasizing that we failed to find any evidence to suggest that properly compounded bevacizumab is associated with more harm than ranibizumab, although failure to follow proper preparation and handling protocols can lead to an increased risk of ophthalmic harm.

In the absence of any evidence of substantial differences in the effectiveness and safety of the three anti-VEGFs, the issue of the comparative cost of these drugs might be an important determinant of reimbursement policy for the anti-VEGFs. The economic analysis suggests that, assuming the similar clinical efficacy and harms found in the included comparative clinical trials and indirect comparisons, the use of bevacizumab where possible by patients with wet AMD, DME, RVO, and CNV due to PM would represent substantial savings to public payers.

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APPENDIX 1: CLINICAL LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase <1974 to 2015 May 26> MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations Cochrane Central Register of Controlled Trials <April 2015> **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 27, 2015
Study Types:	Randomized controlled trials
Limits:	No date or language limits were used Human filter was applied Editorials & letters excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
$#	Limited truncation specifies a maximum number of characters that may follow the root word or phrase.
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.tw	Text word. Searches fields in a database which contain text words and which are appropriate for a subject search.
.kw	Author keywords
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
ai	Antagonists & inhibitors subheading in MEDLINE
vi	Intravitreal drug administration subheading in Embase
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

MULTI-DATABASE STRATEGY	
Line #	**Strategy**
1	Retinal Degeneration/
2	limit 1 to yr="1973-2009"
3	Macular Degeneration/
4	Wet Macular Degeneration/
5	((exudative or neovascular or wet) adj3 ((macula* adj2 degeneration) or (macula* adj2 deterioration) or maculopath* or (macula* adj2 dystroph*) or (macula* adj2 atroph*))).tw,kw.
6	((exudative or neovascular or wet) adj2 (AMD or ARMD)).tw,kw.
7	(wAMD or wARMD).tw,kw.
8	Diabetic Retinopathy/
9	((diabet* or DM) adj3 (maculopath* or retinopath*)).tw,kw.
10	(PDR or DME or DMO).tw,kw.
11	Macular Edema/
12	((macula* or retina*) adj3 (edema$1 or edema$1)).tw,kw.
13	(Irvine-Gass adj3 (edema$1 or edema$1 or syndrome$1)).tw,kw.
14	(cystoid macula* adj dystroph*).tw,kw.
15	Retinal Vein Occlusion/
16	(retinal vein adj3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)).tw,kw.
17	(BRVO or CRVO).tw,kw.
18	Choroidal Neovascularization/
19	((choroid* or subretinal or sub-retinal) adj1 neovasculari#ation*).tw,kw.
20	CNV.tw,kw.
21	or/2-20
22	Vascular Endothelial Growth Factor A/ai or "Receptors, Vascular Endothelial Growth Factor"/ai
23	(anti adj2 VEGF$1).tw,kw.
24	(antiVEGF$1 or VEGF inhibitor* or VEGF antagonist*).tw,kw.
25	(antivascular endothelial growth factor$1 or anti-vascular endothelial growth factor$1).tw,kw.
26	Antibodies, Monoclonal, Humanized/
27	(monoclonal antibod* and humani#ed).tw,kw.
28	(antibod* adj2 humani#ed).tw,kw.
29	Angiogenesis Inhibitors/
30	(angiogen* adj3 (inhibitor* or antagonist*)).tw,kw.
31	(anti-angiogen* or antiangiogen*).tw,kw.
32	aflibercept.tw,kw.
33	("AVE 0005" or AVE0005 or "AVE 005" or AVE005 or "Bay 86-5321" or "Bay86-5321" or Eylea or "UNII-15C2VL427D" or Zaltrap or ZIV-aflibercept).tw,kw.
34	((vasculotropin or vascular endothelial growth factor or VEGF) adj trap*).tw,kw.
35	aflibercept.rn,nm.
36	Bevacizumab.tw,kw.

MULTI-DATABASE STRATEGY	
37	(Altuzan or Avastin or "nsc 704865" or nsc704865 or "rhuMAb-VEGF" or "UNII-2S9ZZM9Q9V").tw,kw.
38	IVB injection$1.tw,kw.
39	Bevacizumab.rn,nm.
40	Pegaptanib.tw,kw.
41	("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838 or "UNII-3HP012Q0FH").tw,kw.
42	Pegaptanib.rn,nm.
43	Ranibizumab.tw,kw.
44	(Lucentis or "rhuFab V2" or "UNII-ZL1R02VT79").tw,kw.
45	IVR injection$1.tw,kw.
46	Ranibizumab.rn,nm.
47	or/22-46
48	21 and 47
49	exp Photochemotherapy/
50	Photosensitizing Agents/
51	(photochemo* or photo-chemo* or photodynamic* or photo-dynamic* or photosensiti* or photo-sensiti*).tw,kw.
52	PDT.tw,kw.
53	or/49-52
54	verteporfin.tw,kw.
55	(verteporphin or "BPD-MA" or "CL 318,952" or "CL 318952" or "UNII-0X9PA28K43" or Visudyne).tw,kw.
56	verteporfin.rn,nm.
57	or/54-56
58	53 and 57
59	(PDTV or "PDT-V" or VPDT or "V-PDT").tw,kw.
60	58 or 59
61	21 and 60
62	exp Triamcinolone/
63	((Triamcinol* adj acet*) or (Triamcincol* adj acet*) or (Triamsinol* adj acet*) or Acetospan or Adcortyl or AllerNaze or Aristocort or Aristoderm or Aristogel or Aristospan or Asmacort or Azmacort or "BRN 0060069" or "CCRIS 5231" or Cinonide or Clinacort or "Coupe-A" or "EINECS 200-948-7" or Flutex or Flutone or FX006 or Kenacort* or Kenalog* or Kenalone or Kenlog or Nasacort or "NSC 21916" or Omcilon or Oracort or Oralone or Polcortolon or Rineton or Solodelf or Tramacin or Triacet$2 or Triacort or Triamcot or Triam-Forte or Triam-Injekt or Triamonide or Trianex or Triatex or Tricinolon or Tricort* or Triderm or Triesence or Triesense or Tri-nasal or Tristoject or Trivaris or Trymex or "UNII-F446C597KA" or Volon).tw,kw.
64	triamcinolone.rn,nm.
65	triamcinolone acetonide.rn,nm.
66	Glucocorticoids/
67	(glucocorticoid* or glucorticoid*).tw,kw.
68	(anecortave or "AL 3789" or AL3789 or "EINECS 231-812-5" or "NSC 15475" or

MULTI-DATABASE STRATEGY	
	"NSC 24345" or Retaane or "UNII-Y0PC411K4T").tw,kw.
69	anecortave acetate.rn,nm.
70	exp Fluocinolone Acetonide/
71	((Fluocinolon* adj Acet*) or Alvadermo or Capex or Co-Fluocin or Cortiespec or "EINECS 200-668-5" or Flucinar or Fluocid or Flucort or Fluocet or Fluonid or Fluotrex or (Fluortriamcinolon* adj Acet*) or Flurosyn or Flusolgen or Gelidina or Iluvien or Jellin or Jellisoft or Percutina or Radiocin or Retisert or Sinalar or Synalar or Synamol or Synandone or Synandrone or Synamol or Synemol or Synsac or Tefunote or "UNII-0CD5FD6S2M").tw,kw.
72	fluocinolone acetonide.rn,nm.
73	Pregnadienediols/
74	(dihydroxypregnadiene* or di-hydroxypregnadiene* or pregnadienediol*).tw,kw.
75	exp Dexamethasone/
76	(Dexamethasone or Decaject* or Decameth or Dexasone or Dexpak or Hexadecadrol or Hexadrol or Maxidex or Millicorten or Oradexon or Ozurdex).tw,kw.
77	dexamethasone.rn,nm.
78	((intravitreal or intra-vitreal) adj3 (corticoid* or corticosteroid* or steroid*)).tw,kw.
79	or/62-78
80	exp Injections/
81	Drug Implants/
82	(depot or implant* or infus* or inject* or intravitreal* or intra-vitreal* or microsphere* or micro-sphere* or suspension*).tw,kw.
83	or/80-82
84	79 and 83
85	21 and 84
86	(controlled clinical trial or randomized controlled trial).pt.
87	clinical trials as topic.sh.
88	(randomi#ed or randomly or RCT$1 or placebo*).tw.
89	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
90	trial.ti.
91	or/86-90
92	(48 or 61 or 85) and 91
93	exp Animals/ not (exp Animals/ and Humans/)
94	92 not 93
95	(comment or editorial or interview or news).pt.
96	(letter not (letter and randomized controlled trial)).pt.
97	94 not (95 or 96)
98	97 use pmez
99	macular degeneration/
100	age related macular degeneration/
101	wet macular degeneration/
102	((exudative or neovascular or wet) adj3 ((macula* adj2 degeneration) or (macula* adj2 deterioration) or maculopath* or (macula* adj2 dystroph*) or (macula* adj2 atroph*))).tw,kw.

MULTI-DATABASE STRATEGY	
103	((exudative or neovascular or wet) adj2 (AMD or ARMD)).tw,kw.
104	(wAMD or wARMD).tw,kw.
105	diabetic retinopathy/
106	((diabet* or DM) adj3 (maculopath* or retinopath*)).tw,kw.
107	diabetic macular edema/
108	(PDR or DME or DMO).tw,kw.
109	exp macular edema/
110	((macula* or retina*) adj3 (edema$1 or edema$1)).tw,kw.
111	(Irvine-Gass adj3 (edema$1 or edema$1 or syndrome$1)).tw,kw.
112	(cystoid macula* adj dystroph*).tw,kw.
113	exp retina vein occlusion/
114	(retinal vein adj3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)).tw,kw.
115	(BRVO or CRVO).tw,kw.
116	subretinal neovascularization/
117	((choroid* or subretinal or sub-retinal) adj1 neovasculari#ation*).tw,kw.
118	CNV.tw,kw.
119	or/99-118
120	vasculotropin inhibitor/
121	(anti adj2 VEGF$1).tw,kw.
122	(antiVEGF$1 or VEGF inhibitor* or VEGF antagonist*).tw,kw.
123	(antivascular endothelial growth factor$1 or anti-vascular endothelial growth factor$1).tw,kw.
124	monoclonal antibody/
125	(monoclonal antibod* and humani#ed).tw,kw.
126	(antibod* adj2 humani#ed).tw,kw.
127	angiogenesis inhibitor/
128	(angiogen* adj3 (inhibitor* or antagonist*)).tw,kw.
129	(anti-angiogen* or antiangiogen*).tw,kw.
130	aflibercept/
131	(aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005 or "Bay 86-5321" or "Bay86-5321" or Eylea or "UNII-15C2VL427D" or Zaltrap or ZIV-aflibercept).tw,kw.
132	((vasculotropin or vascular endothelial growth factor or VEGF) adj trap*).tw,kw.
133	aflibercept.rn.
134	bevacizumab/
135	(bevacizumab or Altuzan or Avastin or "nsc 704865" or nsc704865 or "rhuMAb-VEGF" or "UNII-2S9ZZM9Q9V").tw,kw.
136	IVB injection$1.tw,kw.
137	Bevacizumab.rn.
138	pegaptanib/
139	(Pegaptanib or "EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838 or "UNII-3HP012Q0FH").tw,kw.
140	Pegaptanib.rn.

MULTI-DATABASE STRATEGY	
141	ranibizumab/
142	(Ranibizumab or Lucentis or "rhuFab V2" or "UNII-ZL1R02VT79").tw,kw.
143	IVR injection$1.tw,kw.
144	Ranibizumab.rn.
145	or/120-144
146	119 and 145
147	photodynamic therapy/
148	photosensitizing agent/
149	photochemotherapy/
150	(photochemo* or photo-chemo* or photodynamic* or photo-dynamic* or photosensiti* or photo-sensiti*).tw,kw.
151	PDT.tw,kw.
152	or/147-151
153	verteporfin/
154	(verteporphin or "BPD-MA" or "CL 318,952" or "CL 318952" or "UNII-0X9PA28K43" or Visudyne).tw,kw.
155	verteporfin.rn.
156	or/153-155
157	152 and 156
158	(PDTV or "PDT-V" or VPDT or "V-PDT").tw,kw.
159	157 or 158
160	119 and 159
161	triamcinolone/
162	triamcinolone acetonide/
163	((Triamcinol* adj acet*) or (Triamcincol* adj acet*) or (Triamsinol* adj acet*) or Acetospan or Adcortyl or AllerNaze or Aristocort or Aristoderm or Aristogel or Aristospan or Asmacort or Azmacort or "BRN 0060069" or "CCRIS 5231" or Cinonide or Clinacort or "Coupe-A" or "EINECS 200-948-7" or Flutex or Flutone or FX006 or Kenacort* or Kenalog* or Kenalone or Kenlog or Nasacort or "NSC 21916" or Omcilon or Oracort or Oralone or Polcortolon or Rineton or Solodelf or Tramacin or Triacet$2 or Triacort or Triamcot or Triam-Forte or Triam-Injekt or Triamonide or Trianex or Triatex or Tricinolon or Tricort* or Triderm or Triesence or Triesense or Tri-nasal or Tristoject or Trivaris or Trymex or "UNII-F446C597KA" or Volon).tw,kw.
164	triamcinolone.rn.
165	triamcinolone acetonide.rn.
166	glucocorticoid/
167	(glucocorticoid* or glucorticoid*).tw,kw.
168	anecortave/
169	(anecortave or "AL 3789" or AL3789 or "EINECS 231-812-5" or "NSC 15475" or "NSC 24345" or Retaane or "UNII-Y0PC411K4T").tw,kw.
170	anecortave.rn.
171	fluocinolone acetonide/
172	((Fluocinolon* adj Acet*) or Alvadermo or Capex or Co-Fluocin or Cortiespec or "EINECS 200-668-5" or Flucinar or Fluocid or Flucort or Fluocet or Fluonid or

MULTI-DATABASE STRATEGY	
	Fluotrex or (Fluortriamcinolon* adj Acet*) or Flurosyn or Flusolgen or Gelidina or Iluvien or Jellin or Jellisoft or Percutina or Radiocin or Retisert or Sinalar or Synalar or Synamol or Synandone or Synandrone or Synamol or Synemol or Synsac or Tefunote or "UNII-0CD5FD6S2M").tw,kw.
173	fluocinolone acetonide.rn.
174	pregnane derivative/
175	(dihydroxypregnadiene* or di-hydroxypregnadiene* or pregnadienediol*).tw,kw.
176	dexamethasone/
177	dexamethasone isonicotinate/
178	(Dexamethasone or Decaject* or Decameth or Dexasone or Dexpak or Hexadecadrol or Hexadrol or Maxidex or Millicorten or Oradexon or Ozurdex).tw,kw.
179	dexamethasone.rn.
180	dexamethasone isonicotinate.rn.
181	((intravitreal or intra-vitreal*) adj3 (corticoid* or corticosteroid* or steroid*)).tw,kw.
182	or/161-181
183	exp injection/
184	drug implant/
185	intravitreal drug administration/
186	vi.fs.
187	(depot or implant* or infus* or inject* or intravitreal* or intra-vitreal* or microsphere* or micro-sphere* or suspension*).tw,kw.
188	or/183-187
189	182 and 188
190	119 and 189
191	randomized controlled trial/ or controlled clinical trial/
192	exp "clinical trial (topic)"/
193	(randomi#ed or randomly or RCT$1 or placebo*).tw.
194	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
195	trial.ti.
196	or/191-195
197	(146 or 160 or 190) and 196
198	exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
199	exp humans/ or exp human experimentation/ or exp human experiment/
200	198 not 199
201	197 not 200
202	editorial.pt.
203	letter.pt. not (letter.pt. and randomized controlled trial/)
204	201 not (202 or 203)
205	204 use oemezd
206	48 or 61 or 85
207	206 use cctr
208	98 or 205 or 207

MULTI-DATABASE STRATEGY	
209	remove duplicates from 208
210	209 use pmez
211	209 use oemezd
212	209 use cctr

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	June 4, 2015
Keywords:	(intravitreal OR intra-vitreal or implant or implanted or implants or inject or injected or injects or injection or injections or Anti-VEGF or antiVEGF or VEGF inhibitor or VEGF antagonist or visudyne or verteporfin or PDT or PDTV or VPDT) AND (retinal degeneration OR wet macular degeneration OR wAMD OR neovascular macular degeneration OR exudative macular degeneration or diabetic retinopathy or DRE or Macular Edema or Retinal Vein Occlusion or Choroidal Neovascularization or BRVO or CRVO)
Limits:	Adult |Completed | Studies With Results | Interventional Studies

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based searching” (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Clinical Trials (ongoing)

APPENDIX 2: ECONOMIC LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase <1974 to 2015 May 28> MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 28, 2015
Study Types:	Economic literature
Limits:	English language

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
$#	Limited truncation specifies a maximum number of characters that may follow the root word or phrase
.ti	Title
.ab	Abstract
.tw	Text word. Searches fields in a database which contain text words and which are appropriate for a subject search
.nm	Name of substance word
.pt	Publication type
.rn	CAS registry number
.kw	Author keywords
.mp	Multi-purpose: includes Title, Original Title, Abstract, Subject Heading, Name of Substance, and Registry Word fields.
vi	Intravitreal drug administration subheading in Embase
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Strategy**
1	(Eylea* or aflibercept* or "AVE 0005" or AVE0005 or Bay 86-5321 or Bay86-5321 or VEGF Trap* or Zaltrap or Zivaflibercept or vasculotropin trap or vascular endothelial growth factor trap).tw,kw
2	862111-32-8.rn,nm.
3	(lucentis* or ranibizumab* or rhuFab V2 or rhuFabV2 or Unii-ZL1R02VT79).tw,kw
4	347396-82-1.rn,nm.
5	(Pegaptanib* or "EYE 001" or EYE001 or Macugen* or "NX 1838" or NX1838 or "UNII-3HP012Q0FH").tw,kw
6	222716-86-1.rn,nm.
7	or/1-6
8	7 use pmez
9	(Bevacizumab* or avastin* or altuzan* or nsc-704865 or nsc704865 or rhuMAb-VEGF or rhumabvegf or immunoglobulin-G1 or immunoglobulinG1).tw,kw
10	216974-75-3.rn,nm.
11	or/9-10
12	11 use pmez
13	*aflibercept/
14	(Eylea* or aflibercept* or "AVE 0005" or AVE0005 or Bay 86-5321 or Bay86-5321 or VEGF Trap* or Zaltrap or Zivaflibercept or vasculotropin trap or vascular endothelial growth factor trap).tw,kw
15	*Ranibizumab/
16	(lucentis* or ranibizumab* or rhuFab V2 or rhuFabV2 or Unii-ZL1R02VT79).tw,kw
17	*Pegaptanib/
18	(Pegaptanib or "EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838 or "UNII-3HP012Q0FH").tw,kw
19	or/13-18
20	19 use oemezd
21	*Bevacizumab/
22	(Bevacizumab* or avastin* or altuzan* or nsc-704865 or nsc704865 or rhuMAb-VEGF or rhumabvegf or immunoglobulin-G1 or immunoglobulinG1).tw,kw
23	or/21-22
24	23 use oemezd
25	macular degeneration/ use pmez,oemezd
26	age related macular degeneration/ use oemezd
27	Wet Macular Degeneration/ use pmez
28	((exudative or neovascular or wet) adj3 ((macula* adj2 degeneration) or (macula* adj2 deterioration) or maculopath* or (macula* adj2 dystroph*))).tw,kw.
29	((exudative or neovascular or wet) adj2 (AMD or ARMD)).tw,kw.
30	(wAMD or wARMD).tw,kw.
31	Diabetic Retinopathy/ use pmez,oemezd
32	((diabet* or DM) adj3 retinopath*).tw,kw.
33	(PDR or DME or DMO).tw,kw.
34	diabetic macular edema/ use oemezd

MULTI-DATABASE STRATEGY	
35	exp Macular Edema/ use pmez
36	((macula* or retina*) adj3 (edema$1 or edema$1)).tw,kw.
37	(Irvine-Gass adj3 (edema$1 or edema$1 or syndrome$1)).tw,kw.
38	(cystoid macula* adj dystroph*).tw,kw.
39	exp retina vein occlusion/ use oemezd
40	Retinal Vein Occlusion/ use pmez
41	(retinal vein adj3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)).tw,kw.
42	(BRVO or CRVO).tw,kw.
43	subretinal neovascularization/ use oemezd
44	Choroidal Neovascularization/ use pmez
45	((choroid* or subretinal or sub-retinal) adj1 neovasculari#ation*).tw,kw.
46	(CNV or mCNV).tw,kw.
47	High myopia/ use oemezd
48	exp myopia/ use pmez
49	(myopic or myopia or myopias or myopes or myopy or myope or myoptic).tw,kw.
50	intravitreal drug administration/ use oemezd
51	(Intravitreal* or intra-vitral*).tw,kw.
52	vi.fs use oemezd
53	or/25-52
54	12 or 24
55	53 and 54
56	8 or 20
57	55 or 56
58	*economics/
59	exp *"costs and cost analysis"/
60	(economic adj2 model*).mp.
61	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab.
62	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti.
63	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab.
64	(cost or economic*).ti. and (costs or cost-effectiveness or markov).ab.
65	or/58-64
66	57 and 65
67	*vasculotropin inhibitor/ use oemezd
68	(anti adj2 VEGF$1).ti.
69	antiVEGF$1.ti.
70	(antivascular endothelial growth factor$1 or anti-vascular endothelial growth factor$1).ti.
71	or/67-70

MULTI-DATABASE STRATEGY	
72	65 and 71
73	66 or 72
74	remove duplicates from 73
75	limit 74 to english language

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
University of York Centre for Reviews and Dissemination NHS Economic Evaluations Database (NHS EED)	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types restrictions. Syntax adjusted for NHS EED database.

Grey Literature

Search date:	May 28, 2015
Keywords:	Included terms for economic evaluations of anti-VEGF therapies (ranibizumab, aflibercept, bevacizumab, and pegaptanib)
Limits:	English language

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based searching” (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Internet Search

APPENDIX 3: ELIGIBILITY CRITERIA

Level 1 screening cheat sheet

Please note that answering NO to any of the screening questions will exclude the study*

Question 1: Does the study include adults with any of the retinal conditions of interest?

INCLUDE if the study population has any of the following conditions:

Wet (Neovascular/exudative) age-related macular degeneration (AMD)

AMD is a leading cause of vision loss in individuals over the age of 50 years. The macula is a small spot near the centre of the retina and is needed for sharp, central vision. Wet AMD is caused by the growth of abnormal blood vessels underneath the retina (*choroidal neovascularization*), which can leak fluid & blood and may cause swelling/damage of the macula.

Diabetic macular edema (DME)

Macular edema in diabetes results from retinal microvascular changes that compromise the blood-retinal barrier, causing leakage into the surrounding retina and, consequently, retinal edema.

Proliferative diabetic retinopathy (PDR)

Involves the growth of new blood vessels along the retina. These new blood vessels are abnormal and fragile. By themselves, these blood vessels do not cause symptoms or vision loss. However, they have thin, fragile walls. If they leak blood, severe vision loss and even blindness can result.

Macular edema due to retinal vein occlusion (RVO)

Thrombotic occlusion of the central retinal vein leads to the backup of the blood in the retinal venous system. This increased resistance venous blood flow causes stagnation of the blood and ischemic damage to the retina, which in turn results in leakage and retinal edema.

Choroidal neovascularization (CNV) secondary to pathologic myopia (PM)

Choroidal neovascularization (CNV) is one of the most important vision-threatening complications secondary to pathological myopia (PM). It involves the creation of new blood vessels in the choroid (layer between the sclera and retina), which in turn move the macula from its natural position, causing distortion of vision.

EXCLUDE if: Study population is does not have any conditions of interest

[Definitions adapted from National Eye Institute, & Principles and Practice of Ophthalmology, 2nd ed.]

Question 2: Is the study a parallel or cluster randomized controlled trial (RCT)?

INCLUDE if the study design is the following:

Parallel RCT – A trial that **randomly allocates** patients to receive either the intervention or the comparison group concurrently. Some parallel trials have more than two comparison groups and some compare different interventions without including a non-intervention control group.

Cluster RCT – A trial in which clusters of individuals (e.g., clinics, families, geographical areas), rather than individuals themselves, are **randomized** to different arms.

EXCLUDE if the study design is the following:

Crossover RCT – A trial comparing two or more interventions in which the patients, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, the patients are randomly allocated to receive them in either the order A, B or the order B, A.

Quasi-RCT – A trial which uses non-random methods to allocate patients to treatment groups, but intend to produce similar groups. Quasi-random methods include: allocation by the person's date of birth, by the day of the week or month of the year, by a person's medical record number, or just allocating every alternate person. In practice, these methods of allocation are relatively easy to manipulate, introducing selection bias.

Non-randomized study – A study in which patients were not randomly allocated to the treatment groups (i.e., observational studies)

EXCLUDE and flag if the study is relevant (i.e., likely meets inclusion criteria), but is a:

- *Systematic review/pooled analysis*
- *Conference abstract*
- *Trial protocol*
- *Non-English article*
- *Companion report/relevant post hoc analysis*

Mark as UNCLEAR if you cannot ascertain the study design from the title or abstract (in particular, if it is unclear how patients are allocated to the treatment groups, please mark as unclear).

NOTE: we will be flagging all **CATT trials** as unclear

[Definitions adapted from Cochrane Collaboration glossary]

Question 3: Does the study examine any of the following interventions of interest?

<u>INCLUDE</u> if the intervention is any of the following agents administered by intravitreal injection:

TRADE NAME	GENERIC NAME
Avastin	Bevacizumab
Eylea	Aflibercept
Lucentis	Ranibizumab
Macugen	Pegaptanib

<u>INCLUDE</u> if the intervention is any of the following:

OTHER INTERVENTIONS
photodynamic therapy verteporfin
corticosteroids (**<u>only</u>** triamcinolone acetonide intravitreal injection, dexamethasone implant, fluocinolone acetonide implant)
laser photocoagulation

<u>EXCLUDE</u> if the treatments of interest are administered by any means other than intravitreal injection

Question 4: Does the study compare a relevant intervention to any of the following:

aflibercept, bevacizumab, ranibizumab, photodynamic therapy verteporfin, corticosteroids (only triamcinolone acetonide intravitreal injection, dexamethasone implant, fluocinolone acetonide implant), laser photocoagulation, placebo).

<u>INCLUDE</u> if the intervention is being compared to any of the following:

COMPARATORS
Different doses of the same intervention drug
Bevacizumab
Aflibercept
Ranibizumab
Pegaptanib
photodynamic therapy verteporfin
corticosteroids (**<u>only</u>** triamcinolone acetonide intravitreal injection, dexamethasone implant, fluocinolone acetonide implant)
laser photocoagulation
Placebo/no treatment

<u>EXCLUDE</u> if the intervention is being compared to an agent not listed above, or surgery (e.g., cataract removal, phacoemulsification, vitrectomy, etc.)

Level 2 Screening Cheat Sheet

Please note that answering NO to any of the screening questions will exclude the study*

Question 1: Does the study include <u>adults</u> with any of the retinal conditions of interest?

☐ YES **[please answer Q2]**
☐ NO
☐ UNCLEAR

<u>INCLUDE</u> if the study population has any of the following conditions:

- Wet (Neovascular/exudative) age-related macular degeneration (AMD)
- Diabetic macular edema (DME)
- Proliferative diabetic retinopathy (PDR)
- Macular edema due to retinal vein occlusion (RVO)
- Choroidal neovascularization (CNV) secondary to pathologic myopia (PM)

<u>EXCLUDE</u> if the study population does not have any conditions of interest.

Question 2: Please specify which conditions of interest were included.

☐ Wet/neovascular/exudative age-related macular degeneration
☐ Diabetic macular edema
☐ Macular edema due to central or branch retinal vein occlusion
☐ Proliferative diabetic retinopathy
☐ Choroidal neovascularization secondary to pathologic myopia
☐ Other (please specify)

Question 3: Is the study a parallel/cluster randomized controlled trial (RCT)?

☐ YES
☐ NO
☐ NO, but relevant **[please answer Q4]**
☐ UNCLEAR

<u>INCLUDE</u> if the study design is the following:

- **Parallel RCT** – A trial that **randomly allocates** patients to receive either the intervention or the comparison group concurrently. Some parallel trials have more than two comparison groups and some compare different interventions without including a non-intervention control group.
- **Cluster RCT** – A trial in which clusters of individuals (e.g., clinics, families, geographical areas), rather than individuals themselves, are **randomized** to different arms.

<u>EXCLUDE</u> if the study design is the following:

- **Crossover RCT** – A trial comparing two or more interventions in which the patients, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, the patients are randomly allocated to receive them in either the order A, B or the order B, A.
- **Quasi-RCT** – A trial which uses non-random methods to allocate patients to treatment groups, but intend to produce similar groups. Quasi-random methods include: allocation by the person's date of birth, by the day of the week or month of the year, by a person's medical record number, or just allocating every alternate person. In practice, these methods of allocation are relatively easy to manipulate, introducing selection bias.
- **Non-randomized study** – A study in which patients were not randomly allocated to

the treatment groups (i.e., observational studies)
Mark as <u>UNCLEAR</u> if you cannot ascertain the study design (in particular, if it is unclear how patients are allocated to the treatment groups, please mark as unclear)
[Definitions adapted from Cochrane Collaboration glossary]

Question 4: please specify what category the study falls under:

- ☐ Systematic review
- ☐ Pooled analysis
- ☐ Conference abstract
- ☐ Trial protocol
- ☐ Companion report/post hoc analysis
- ☐ Non-English article

Question 5: Does the study examine any of the following interventions of interest?

- ☐ YES **[Please answer Q6]**
- ☐ YES, a combination of relevant anti-VEGF agents
- ☐ YES, a combination of anti-VEGF agent(s) with relevant comparator(s)
- ☐ NO
- ☐ UNCLEAR

<u>INCLUDE</u> if the intervention is any of the following agents administered by intravitreal injection:

TRADE NAME	GENERIC NAME
Avastin	Bevacizumab
Eylea (VEGF trap-eye)	Aflibercept
Lucentis	Ranibizumab
Macugen	Pegaptanib

<u>INCLUDE</u> if the intervention is any of the following:

OTHER INTERVENTIONS
▪ Photodynamic therapy verteporfin
▪ Corticosteroids **<u>limited to</u>** injection or implant of: - Triamcinolone acetonide (intravitreal) - Dexamethasone - Fluocinolone acetonide
▪ Laser photocoagulation

<u>INCLUDE</u> if a combination of interventions of interest were assigned

<u>EXCLUDE</u> if the treatments of interest are administered by any means other than intravitreal injection (e.g., intravenous, retrobulbar, subtenon, etc.)
<u>EXCLUDE</u> if the treatments of interests are administered pre/post-surgical procedure(s)

Question 6: Please select the examined intervention (s):

Select multiple boxes if there are separate treatment arms

☐ Aflibercept (Eylea)

☐ Bevacizumab (Avastin)

☐ Ranibizumab (Lucentis)

☐ Pegaptanib (Macugen)

☐ Any other relevant intervention [photodynamic therapy verteporfin, laser photocoagulation, intravitreal triamcinolone acetonide (injection/implant), dexamethasone (injection/implant), fluocinolone acetonide (injection/implant)]

Question 7:

Does the study compare a relevant intervention to any of the following comparators?

☐ YES **[please answer Q8]**
☐ YES, a combination of relevant anti-VEGF agents
☐ YES, a combination of anti-VEGF agent with relevant comparator(s)
☐ NO
☐ UNCLEAR

<u>INCLUDE</u> if the intervention is being compared to any of the following:

COMPARATORS
▪ Different doses of the same intervention drug
▪ Bevacizumab
▪ Aflibercept
▪ Ranibizumab
▪ Pegaptanib
▪ photodynamic therapy verteporfin
▪ Corticosteroids **<u>limited to</u>** - Triamcinolone acetonide intravitreal injection - Dexamethasone implant - Fluocinolone acetonide implant
▪ laser photocoagulation
▪ Placebo/no treatment

<u>EXCLUDE</u> if the intervention is being compared to an agent not listed above, or surgery (e.g., cataract removal, phacoemulsification, vitrectomy, etc.)

Question 8: Please specify the examined comparator:

☐ Aflibercept (Eylea) ☐ Bevacizumab (Avastin) ☐ Ranibizumab (Lucentis) ☐ Pegaptanib (Macugen) ☐ placebo ☐ no treatment ☐ Any other relevant comparator(s) [photodynamic therapy verteporfin, laser photocoagulation, intravitreal triamcinolone acetonide, dexamethasone implant, fluocinolone acetonide implant]

Question 9: Does the study report on any outcomes of interest?

☐ YES **[please answer Q10]**
☐ NO
☐ UNCLEAR

INCLUDE if the study reports on any of the following efficacy and/or harms outcomes:

Efficacy outcomes
▪ Vision **gain** in best corrected visual acuity (BCVA) of ≥ 15 ETDRS or 3 lines
▪ Vision **loss** in best corrected visual acuity (BCVA) of ≥ 15 ETDRS or 3 lines
▪ Change from baseline in BCVA
▪ Blindness (legal)
▪ Vision-related function (National Eye Institute 25-item Visual Function Questionnaire)
Harms outcomes
▪ Adverse events
▪ Serious adverse events
▪ Withdrawal due to adverse events
▪ Mortality
▪ Harms of special interest ○ Arterial/venous thromboembolic events ○ Bacterial endophthalmitis ○ Increased intraocular pressure ○ Retinal detachment

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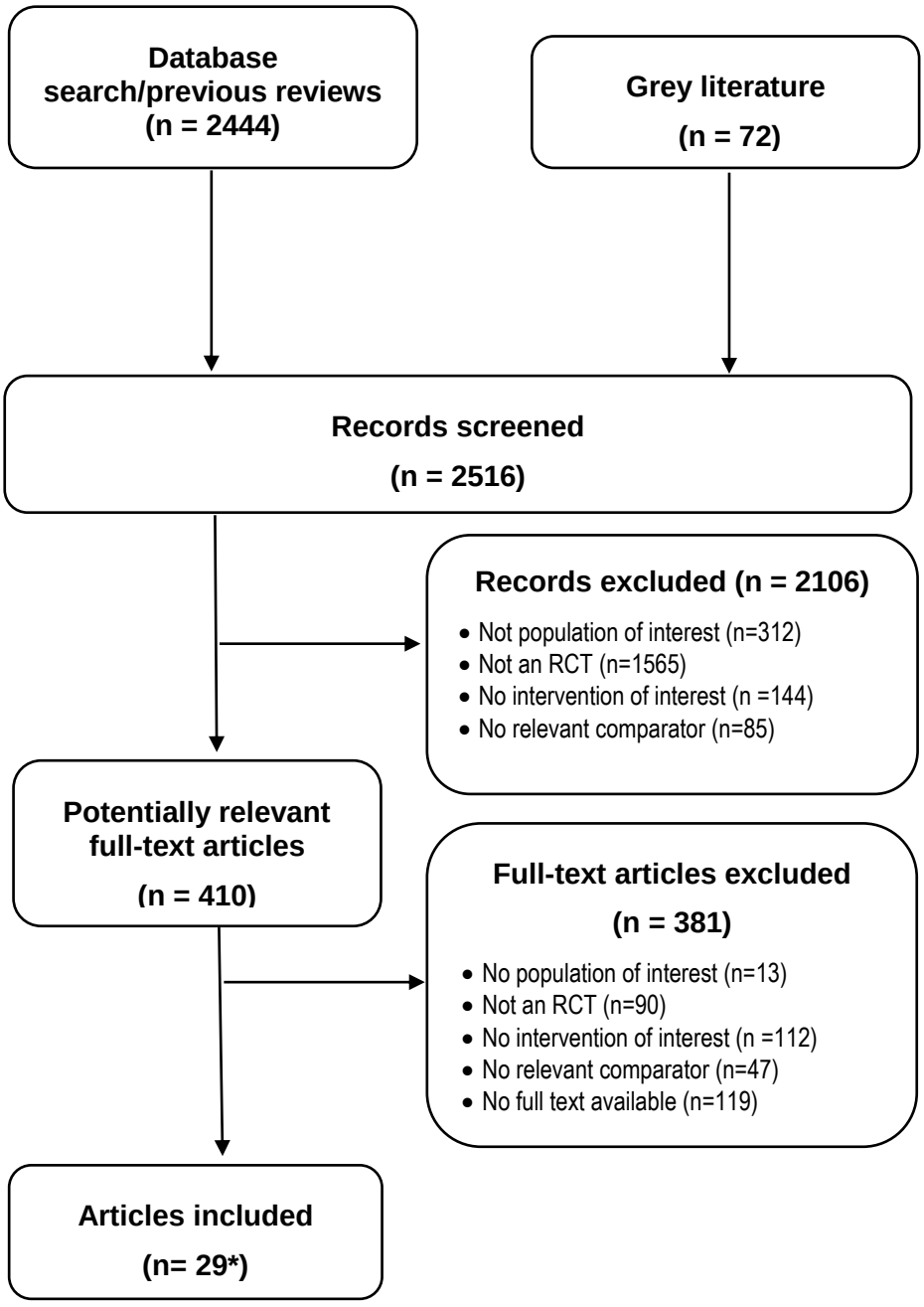
EXCLUDE if the study does not report any outcomes of interest listed above.

Question 10: Please specify the reported outcome(s):

Select multiple boxes if more than one outcome is reported

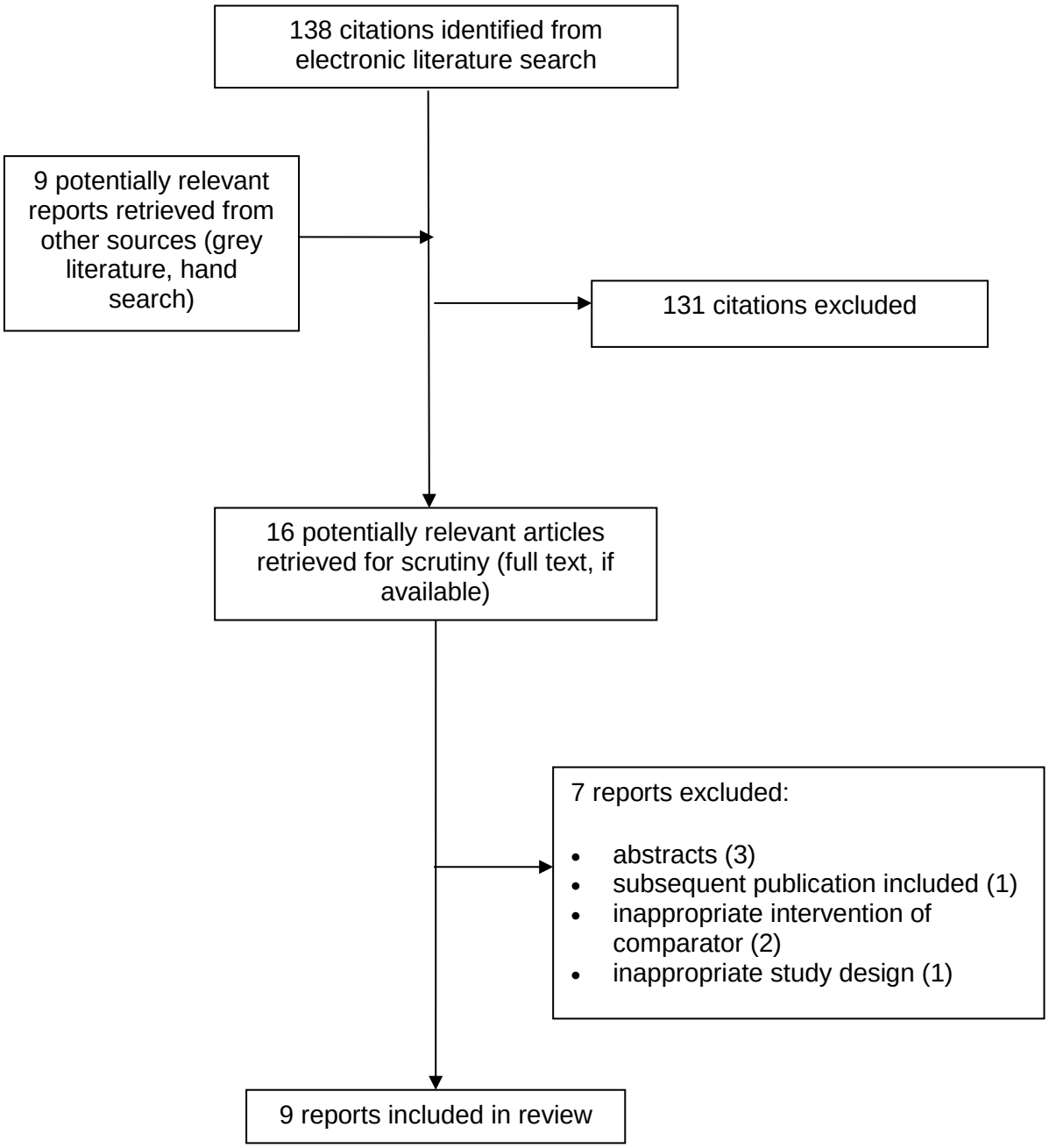
☐	Gain in best corrected visual acuity (BCVA) of ≥ 15 ETDRS letters/3 lines
☐	Loss in best corrected visual acuity (BCVA) of ≥ 15 ETDRS letters/3 lines
☐	Change from baseline in BCVA
☐	Blindness (legal)
☐	Vision-related function
☐	Adverse events (AEs)
☐	Serious adverse events (SAEs)
☐	Withdrawals due to adverse events (WDAEs)
☐	Mortality
☐	Arterial/venous thromboembolic events
☐	Bacterial endophthalmitis
☐	Increased intraocular pressure
☐	Retinal detachment

APPENDIX 4: CLINICAL STUDY SELECTION



*28 studies + 1 companion report, describing 30 RCTs

APPENDIX 5: COST-EFFECTIVENESS STUDY SELECTION



APPENDIX 6: INCLUDED STUDIES FOR CLINICAL REVIEW

Neovascular (wet) AMD

1. Berg K, Pedersen TR, Sandvik L, Bragadottir R. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. Ophthalmology. 2015 Jan;122(1):146-52.

2. Scholler A, Richter-Mueksch S, Weingessel B, Vecsei-Marlovits PV. Differences of frequency in administration of ranibizumab and bevacizumab in patients with neovascular AMD. Wien Klin Wochenschr. 2014;126(11-12):355-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24696051

3. Kodjikian L, Souied EH, Mimoun G, Mauget-Faysse M, Behar-Cohen F, Decullier E, et al. Ranibizumab versus bevacizumab for neovascular age-related macular degeneration: results from the GEFAL noninferiority randomized trial. Ophthalmology. 2013 Nov;120(11):2300-9.

4. Krebs I, Schmetterer L, Boltz A, Told R, Vecsei-Marlovits V, Egger S, et al. A randomised double-masked trial comparing the visual outcome after treatment with ranibizumab or bevacizumab in patients with neovascular age-related macular degeneration. Br J Ophthalmol. 2013 Mar;97(3):266-71. Available from: http://bjo.bmj.com/content/97/3/266.long

5. Biswas P, Sengupta S, Choudhary R, Home S, Paul A, Sinha S. Comparative role of intravitreal ranibizumab versus bevacizumab in choroidal neovascular membrane in age-related macular degeneration. Indian J Ophthalmol. 2011;59(3):191-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3120237/

6. Biswas P, Sengupta S, Choudhary R, Home S, Paul A, Sinha S. Comparing ranibizumab with bevacizumab. Ophthalmology. 2011 Mar;118(3):600.

7. Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011 May 19;364(20):1897-908. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1102673

8. Subramanian ML, Abedi G, Ness S, Ahmed E, Fenberg M, Daly MK, et al. Bevacizumab vs ranibizumab for age-related macular degeneration: 1-year outcomes of a prospective, double-masked randomised clinical trial. Eye (Lond). 2010 Nov;24(11):1708-15. Available from: http://www.nature.com/eye/journal/v24/n11/pdf/eye2010147a.pdf

9. Regillo CD, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol. 2008 Feb;145(2):239-48.

10. Chang TS, Bressler NM, Fine JT, Dolan CM, Ward J, Klesert TR. Improved vision-related function after ranibizumab treatment of neovascular age-related macular degeneration: results of a randomized clinical trial. Arch Ophthalmol. 2007 Nov;125(11):1460-9.

11. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006 Oct 5;355(14):1419-31. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa054481

12. Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet. 2013 Oct 12;382(9900):1258-67.

13. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, Kirchhof B, Ho A, Ogura Y, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Soo Y, Anderesi M, Groetzbach G, Sommerauer B, Sandbrink R, Simader C, Schmidt-Erfurth U; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012 Dec;119(12):2537-48.

DME

1. Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015 Mar 26;372(13):1193-203.

2. Ekinci M, Ceylan E, Cakici O, Tanyildiz B, Olcaysu O, Cagatay HH. Treatment of macular edema in diabetic retinopathy: Comparison of the efficacy of intravitreal bevacizumab and ranibizumab injections. Expert Rev Ophthalmol. 2014;9(2):139-43.

3. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012 Apr;119(4):789-801.

4. Massin P, Bandello F, Garweg JG, Hansen LL, Harding SP, Larsen M, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicentre phase II study. Diabetes Care. 2010 Nov;33(11):2399-405. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2963502/pdf/zdc2399.pdf

Macular edema due to RVO

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APPENDIX 7: COST TABLES

The tables presented below summarize the cost of the anti-VEGFs as well as all relevant comparators, using publicly available Canadian prices. Note that all vials are assumed to be single-use with excess medication being wasted; costs if vials are fractioned are substantially less. Administration or program management fees for intravitreal injections are not included.

TABLE 24: COST COMPARISON TABLE FOR DRUGS FOR WET AMD

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Annual Cost per Eye ($)
Aflibercept (Eylea)	40 mg/mL	0.05 mL vial	1,418.00[a]	Year 1: 2 mg monthly for three months, then 2 mg every two months Year 2: every other month	9,926 (7 injections) 8,508 (6 injections)
Ranibizumab (Lucentis)	10 mg/mL	0.23 mL vial	1,575.00[a]	0.5 mg monthly Alternate dosing: 0.5 monthly for 3 months, then 0.5 mg every 3 months	18,900 (12 injections) Year 1: 9,400 (6 injections Year 2: 6,300 (4 injections)
Verteporfin (Visudyne) with Photodynamic therapy (PDT)	2 mg/mL N/A	15 mg vial Unilateral Bilateral	1,704.00[b] 330.00[c] 500.00[c]	6 mg/m^2 body surface area IV infusion plus PDT, may be repeated if required at 3-month intervals[d]	Unilateral: 2,034 to 8,136
Non-indicated therapies					
Bevacizumab (Avastin)	25 mg/mL	100 mg vial 400 mg vial	600.00[g] 2,400.00[g]	1.25 mg monthly (assumed) 1.25 mg monthly for 3 months, then 1.25 mg every 3 months (assumed)	7,200 (12 injections) Year 1: 4,200 (6 injections) Year 2: 2,400 (4 injections)

a – Ontario Drug Benefit Formulary (Sept 2015).[76]
b – From Lucentis for mCNV CDEC recommendation report (Feb 2015).[153]
c – Ontario Schedule of Benefits for Physician Services (May 1, 2015), codes G460 and G461.[80]
d - e-Therapeutics Therapeutic Choices, Eye Disorders: wet AMD entry, revised December 2014.
e – PPS Buyer's Guide, June 2015.[77]

TABLE 25: COST COMPARISON TABLE FOR DRUGS USED FOR DME

Drug / Comparator	Strength	Dosage Form	Unit Price ($)	Recommended Treatment Dose	Annual Cost ($)
Aflibercept (Eylea)	40 mg/mL (0.278 mL vial)	Intravitreal injection	$1,418.00[a]	2 mg monthly for five doses, then every 2 months	11,344 (8 injections) 8,508 (6 injections)
Ranibizumab (Lucentis)	10 mg/mL (0.23 mL vial)	Intravitreal injection	1,575.00[a]	Treatment is continued until visual acuity is achieved (stable VA for 3 consecutive months)	11,025 (7 injections)[b] 6,300 (4 injections)[b]
Laser photocoagulation therapy	N/A	N/A	182.75[c]	As needed when retreatment criteria met, but no more frequently than every 12 weeks	731 (4 treatments) 548 (3 treatments) 183 (1 treatment)
Other treatments used that are not currently indicated					
Bevacizumab (Avastin)	100 mg/4 mL 400 mg/16 mL	Injection	600.00[d] 2,400.00[d]	1.25 mg as needed (aflibercept frequency assumed)	Up to $4,800
Dexamethasone intravitreal implant (Ozurdex)	0.7 mg	Implant device	1,295.00[e]	0.7 mg not more than every six months[f]	1,295 (1 treatment) 2,590 (2 treatments)
Triamcinolone (Kenalog, generic)	40 mg/1 mL 50 mg/5 mL 200 mg/5 mL	Injection	8.20[a] 17.80[a] 16.71[a]	4 mg every 3 months[g]	33
Triamcinolone (Triesence)	40 mg/1 mL	Intravitreal injection	44.12[h]	4 mg every 3 months[g]	176

a - Ontario Drug Benefit Formulary list price (May 2015).[76]

b - Based on rounded average use in RESTORE: 7 doses in year 1 and 4 doses in year 2.[71]

c - Ontario Schedule of Benefits for Physician Services (May 1, 2015), code E154.[80]

d - PPS, June 2015[77]

e - Quebec formulary price (Sept 2015)[154]

f - Monograph dosing for macular edema following CRVO, monograph recommends limit of 2 doses per patient[155]

g - SCORE (Standard Care vs Corticosteroid for Retinal Vein Occlusion) Study dosing

h - McKesson Canada wholesale price (Sept 2015)

TABLE 26: COST COMPARISON TABLE FOR DRUGS FOR RVO

Drug/ Comparator	Strength	Dosage Form	Unit Price ($)	Recommended Treatment Dose	Annual Cost ($)
Aflibercept (Eylea)	40 mg/mL (0.278 mL vial)	Intravitreal injection	$1,418.00[a]	2 mg monthly, interval may be extended up to 3 months based on visual and anatomic outcomes.	$12,762[b] (9 injections) $4,254[b] (3 injections)
Ranibizumab (Lucentis)*	10 mg/mL (0.23 mL vial)	Intravitreal injection	1,575.00[a]	0.5 mg monthly Treatment is continued until visual acuity is achieved (stable VA for 3 consecutive months)	14,175 (9 injections)[b] 4,725 (3 injections)[b]
Dexamethasone intravitreal implant (Ozurdex)	0.7 mg	Implant device	1,295.00[c]	0.7 mg not more than every six months[d]	1,295 (1 treatment) 2,590 (2 treatments)
Other treatments used that are not currently indicated					
Bevacizumab (Avastin)	100 mg/4 mL 400 mg/16 mL	Injection	600.00[e] 2,400.000[e]	1.25 mg monthly, aflibercept frequency assumed	5,400[b] (9 injections) 1,800[b] (3 injections)
Triamcinolone (Triesence)	40 mg/1 mL	Intravitreal injection	44.12[f]	1 mg to 4 mg every 3 months[g]	176

Note: aflibercept and dexamethasone intravitreal implant are only indicated for CRVO, not for BRVO; ranibizumab is indicated for both.
a Ontario Drug Benefit Formulary list price (Sept 2015).[76]
b Based on COPERNICUS aflibercept trial.[73]
c Quebec formulary price (Sept 2015).[154]
d Monograph recommends limit of 2 doses per patient, however, clinical practice may differ.[155]
e PPS buyer's guide, June 2015.[77]
f McKesson Canada wholesale price (Sept 2015).
g SCORE (Standard Care vs. Corticosteroid for Retinal Vein Occlusion) Study dosing.

TABLE 27: COST COMPARISON TABLE FOR DRUGS FOR CNV DUE TO PM

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Per Unilateral Treatment ($)
Ranibizumab (Lucentis)	10 mg/mL	0.23 mL vial	1,575.00[a]	0.5 mg intraocular injection as needed, not more than monthly	1 injection: 1,575
Verteporfin (Visudyne) plus photodynamic therapy	2 mg/mL reconstituted N/A	15 mg vial Unilateral procedure	1,704.00[b] 330.00[c]	6 mg/m^2 body surface area by IV infusion	1 dose (infusion + PDT): 2,034
Other treatments used that are not currently indicated					
Aflibercept (Eylea)	40 mg/mL	0.05 mL vial	1,418.00[a]	2 mg intraocular injection as needed not more than every 4 weeks	1 injection: 1,418
Bevacizumab (Avastin)	100 mg 400 mg	4 mL vial 16 mL vial	600.00[d] 2,400.00[d]	1.00 to 2.5 mg as needed not more than monthly	600

a Ontario Drug benefit Formulary List price (May 2015).
b From Lucentis for mCNV CDEC recommendation report (Feb 2015).[153]
c - Schedule of Benefits: Physician Services under the Health Insurance Act (May 1, 2014), Ministry of Health and Long Term Care, Ontario, code G460. Note that administration of bilateral PDT on the same day (code G461) is $500.[80]
d – PPS Buyer's Guide (June 2015).[77]

APPENDIX 8: DETAILED STUDY CHARACTERISTICS

First author	Year of publication	Trial name	Trial identifier	Country	Study period	Setting (multi/single centre)	Overall sample size	Study duration (months)
Berg	2015	LUCAS	NCT01127360	Norway	Mar 2009-Jul 2012	Multi	441	12
Biswas	2011	NR	NR	India	2007-2009	Multi	60	18
Campochiaro	2010	BRAVO	NCT00486018	USA	2007-2009	Multi	397	12
Gharbiya	2010	NR	ISRCTN49803272	Italy	Feb 2008-Dec 2008	Single	32	6
Iacono	2012	NR	NR	Italy	Apr 2006 - Jul 2007	Single	55	18
Moradian	2011	NR	NCT00370851	Iran	Jan 2007 - Feb 2009	Multi	81	3
Narayanan	2015	MARVEL	CTRI/2012/01/003120	India	Jan 2012 - Feb 2013	Single	75	6
Scholler	2014	NR	EK-07-192-1007/ EudraCT Nr. 2007-005157-33)	Austria	2008 - 2011	Single	55	12
Heier	2012	VIEW 1	NCT00509795	US, Canada	Aug 2007 - Sep 2010	Multi	1,217	12
Heier	2012	VIEW 2	NCT00637377	Argentina, Australia, Austria, Belgium, Brazil, Colombia, Czech Republic, France, Germany, Hungary, India, Israel, Italy, Japan, Republic of Korea, Latvia, Mexico, Netherlands,	Apr 2008 - Sep 2010	Multi	1,240	12

First author	Year of publication	Trial name	Trial identifier	Country	Study period	Setting (multi/single centre)	Overall sample size	Study duration (months)
				Poland, Portugal, Singapore, Slovakia, Spain, Sweden, Switzerland, United Kingdom				
Biswas	2011	NR	NR	India	NA	Multi	120	18
Boyer	2012	COPERNICUS	NCT00943072	US, Canada, India, Israel, Argentina, Colombia	Jul 2009 - Oct 2010	Multi	189	6
Brown	2010	CRUISE	NCT00485836	US	Jul 2007 - Jun 2009	Multi	392	6
Chakravarthy	2013	IVAN	ISRCTN92166560	UK	Mar 2008 - Oct 2010	Multi	610	24
Chang*	2007	MARINA	NCT00056836	USA	Mar 2003- Dec 2005	Multi	716	24
Ekinci	2014	NR	NR	Turkey	2011-2014	NR	100	12
Epstein	2012	NR	NCT00906685	Sweden	May 2009- Mar 2011	Single	60	6
Holz	2013	GALILEO	NCT01012973	Austria, France, Germany, Hungary, Italy, Latvia, Australia, Japan, Singapore, South Korea	2009 - 2011	Multi	177	6
Kinge	2010	ROCC	NCT00567697	Norway	2007-2008	Multi	32	6
Kodjikian	2013	GEFAL	NCT01170767	France	2009 - 2012	Multi	501	12
Krebs	2013	MANTA	NCT00710229	Austria	2008-2011	Multi	321	12

First author	Year of publication	Trial name	Trial identifier	Country	Study period	Setting (multi/single centre)	Overall sample size	Study duration (months)
Martin	2011	CATT	NCT00593450	US	2008 - 2010	Multi	1,208	12
Massin	2010	RESOLVE	NCT00284050	Switzerland	Oct 2005 - Jun 2008	Multi	151	12
Nguyen	2012	RIDE	NCT00473382	USA, South America	Jun 2007 - Jan 2011	Multi	382	24
Nguyen	2012	RISE	NCT00473330	USA, South America	Jun 2007 - Nov 2010	Multi	377	24
Regillo	2008	PIER	NCT00090623	US	2004-2007	Multi	184	24
Rosenfeld	2006	MARINA	NCT00056836	US	2003-2005	Multi	716	24
Subramanian	2010	NR	ISRCTN73359806	US	2007-2009	Single	28	12
Wells	2015	NR	NCT01627249	US	Aug 2012 - Oct 2014	Multi	660	12
Ikuno	2015	MYRROR	NCT01249664	Hong Kong, Japan, Republic of Korea, Singapore, and Taiwan	2010-2013	MULTI	122	5.5
Rajagopal	2015	CRAVE	NCT01969708	US	2011-2014	MULTI	93	6

Note: *Chang, 2007 is a companion report to Rosenfeld, 2006.

Abbreviations: RCT, Randomized Controlled Trial; NR, Not Reported, NA, Not Applicable.

APPENDIX 9: DETAILED PATIENT CHARACTERISTICS

Author + Year	Retinal Condition	# of Eyes	Overall Mean Age	Overall Mean Age Var Type	Overall Mean Age Var Value	Tx 1 - Mean Age	Tx 1 - Mean Age Var Value	Tx 2 - Mean Age	Tx 2 - Mean Age Var Value	Tx 3 - Mean Age	Tx 3 - Mean Age Var Value	Tx 4 - Mean Age	Tx 4 - Mean Age Var Value	% Female	% with Diabetes	Mean A1C Value	% with A1C >8.5%	% of Patients with Hypertension	Lens Status
Berg 2015	wAMD	NR	NR	SD	NR	78.7	7.6	78	8.2					NR	NR	NR	NR	NR	NR
Biswas 2011	wAMD	60	60	NR	NR	NR	NR	NR	NR					NR	NR	NR	NR	NR	NR
Campochiaro 2010	ME due to branch RVO	397	66	SD	NR	66.6	11.2	67.5	11.8	65.2	12.7			47	NR	NR	NR	NR	pha kic
Gharbiya 2010	CNV due to PM	32	NR	SD	NR	60.6	10.48	59.1	11.4					68.8	NR	NR	NR	NR	NR
Iacono 2012	CNV due to PM	55	NR	SD	NR	65	12	61	11					76.4	NR	NR	NR	NR	NR
Moradian 2011	ME due to branch RVO	81	57.6	SD	9.8	58.1	7.9	57.2	11.4					58	16	NR	NR	43	NR
Narayanan 2015	ME due to branch RVO	75	NR	NR	NR	53	NR	50	NR					45.3	17	NR	NR	50	NR
Scholler 2014	wAMD	55	NR	SD	NR	79.54	6.78	80.75	6.55					70.9	NR	NR	NR	NR	NR
Heier 2012	wAMD	1,210	NR	SD	NR	78.2	7.6	77.7	7.9	78.4	8.1	77.9	8.4	58.8	NR	NR	NR	NR	NR
Heier 2012	wAMD	1,202	NR	SD	NR	73	9	74.1	8.5	74.7	8.6	73.8	8.6	55.5	NR	NR	NR	NR	NR
Biswas 2011	wAMD	104	NR	NR	NR	63.48	NR	64.36	NR					52	100	NR	NR	NR	NR
Boyer 2012	ME due to central RVO	189	66.3	SD	13.83	67.5	14.3	65.5	13.6					43	NR	NR	NR	NR	NR
Brown 2010	ME due to central RVO	392	68	SD	NR	69.7	11.6	67.6	12.4	65.4	13.1			43	NR	NR	NR	NR	pha kic
Chakravarthy 2013	wAMD	NR	77.7	SD	7.4	77.8	7.6	77.7	7.3					60	NR	NR	NR	NR	NR

Author + Year	Retinal Condition	# of Eyes	Overall Mean Age	Overall Mean Age Var Type	Overall Mean Age Var Value	Tx 1 - Mean Age	Tx 1 - Mean Age Var Value	Tx 2 - Mean Age	Tx 2 - Mean Age Var Value	Tx 3 - Mean Age	Tx 3 - Mean Age Var Value	Tx 4 - Mean Age	Tx 4 - Mean Age Var Value	% Female	% with Diabetes	Mean A1C value	% with A1C >8.5%	% of Patients with Hypertension	Lens Status
Chang 2007*	wAMD	716	77	range	52-95	77	6.6 (SD)	77.4	7.6	76.8	7.7			65	NR	NR	NR	NR	NR
Ekinci 2014	DME	100	NR	NR	NR	68	9	65	14					68	100	NR	0	NR	NR
Epstein 2012 a	ME due to central RVO	60	70.5	SD	12.6	70.6	12.6	70.4	10.4					40	6.7	NR	NR	48.3	NR
Holz 2013	ME due to central RVO	171	61.5	SD	12.9	59.9	12.4	63.8	13.3					44.4	NR	NR	NR	NR	NR
Kinge 2010	ME due to central RVO	32	72	range	52-88	61	NR	64	NR					44.8	12.5	NR	NR	NR	NR
Kodjikian 2013	wAMD	501	NR	NR	NR	79.62	6.9	78.68	7.27					66	NR	NR	NR	0.57	NR
Krebs 2013	wAMD	317	NR	SD	NR	76.7	7.8	77.6	8.1					63.7	0	NA	NA		
Martin 2011	wAMD	1,208	NR	NR	NR	79.2	7.4	80.1	7.3	78.4	7.8	79.3	7.6	62	NR	NR	NR	NR	NR
Massin 2010	DME	151	NR	range	NR	63.2	37-85	62.8	32-84	65	41-82				97	7.4 (1.0) and 7.5 (1.1) for tx and sham	100	NR	NR
Nguyen 2012-RISE	DME	377	NR	SD	NR	61.7	9.8	62.8	10	61.8	9.8			43.8	NA	NR	NR	NR	NR
Nguyen 2012-RIDE	DME	382	NR	SD	NR	62.7	11.1	61.8	10.1	63.5	10.8			42.9	NA	NR	NR	NR	NR
Regillo 2008	wAMD	184	78	NR	NR	77.8	7.1	78.7	6.3	78.8	7.9			59.8	NR	NR	NR	NR-reported as AE	NR
Rosenfeld	wAMD	716	NR	SD	.	77	7	77	8	77	8	.	.	64.8	.	.	.	16.5	NR

Author + Year	Retinal Condition	# of Eyes	Overall Mean Age	Overall Mean Age Var Type	Overall Mean Age Var Value	Tx 1 - Mean Age	Tx 1 - Mean Age Var Value	Tx 2 - Mean Age	Tx 2 - Mean Age Var Value	Tx 3 - Mean Age	Tx 3 - Mean Age Var Value	Tx 4 - Mean Age	Tx 4 - Mean Age Var Value	% Female	% with Diabetes	Mean A1C value	% with A1C >8.5%	% of Patients with Hypertension	Lens Status
2006																			
Subramanian 2010	wAMD	28	78.59	SD	.	78	.	80	.	.	.	.	.	4.6	.	.	.	.	NR
Wells 2015	DME	660	61	SD	10	60	10	62	10	60	11			47	100	7.6, 7.7. 7.8 (median)	NR		
Ikuno 2015	CNV due to PM	122	58.2	SD	13.3	58.5	13.7	57.5	12.1					76	NR	NR	NR	NR	NR
Rajagopal 2015	ME due to central RVO	98	NR	NR	NR	70.6	13	72.4	11.1					55	NR	NR	NR	NR	phakic

Note: *Chang, 2007 is a companion report to Rosenfeld, 2006. **Abbreviations**: NR, Not Reported; var, variance, Tx, Treatment; AMD, age-related macular degeneration; RVO, retinal vein occlusion; CNV, choroidal neovascularization; ME, macular edema; DME, diabetic macular edema; A1C, hemoglobin A1c.

APPENDIX 10: COCHRANE RISK-OF-BIAS FIGURES

For the following figures, the legend is as follows.

1: Random sequence generation
2: Allocation concealment
3: Blinding of patients & personnel
4: Blinding of outcome assessment
5: Incomplete outcome data
6: Selective reporting
7: Other bias

FIGURE 1: QUALITY APPRAISAL FOR THE WET AMD POPULATION

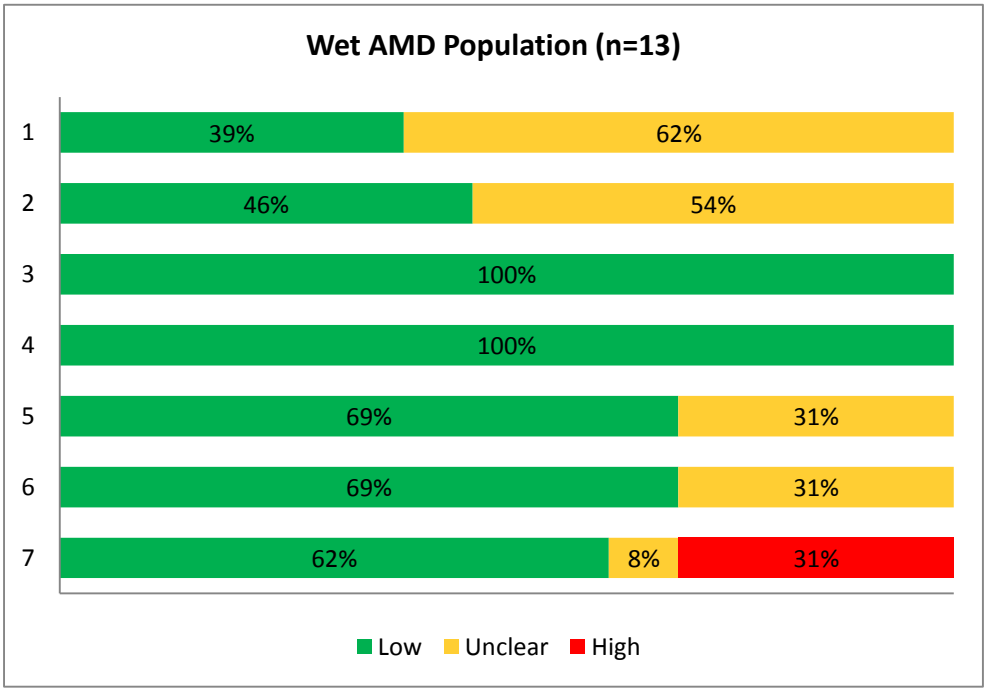


FIGURE 2: QUALITY APPRAISAL FOR THE DME POPULATION

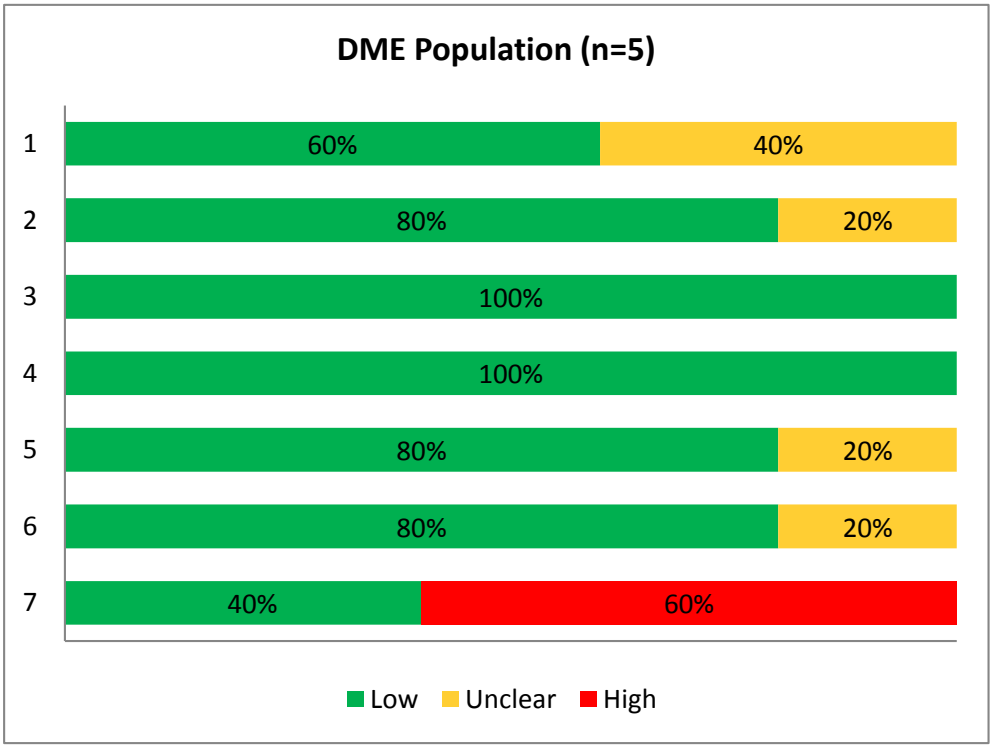


FIGURE 3: QUALITY APPRAISAL FOR ME DUE TO RVO

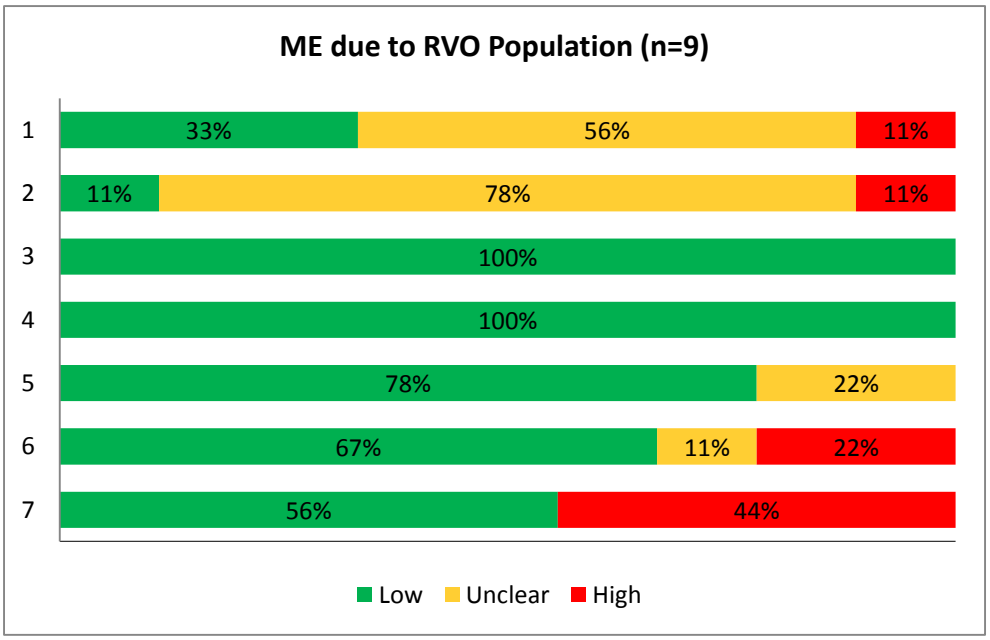
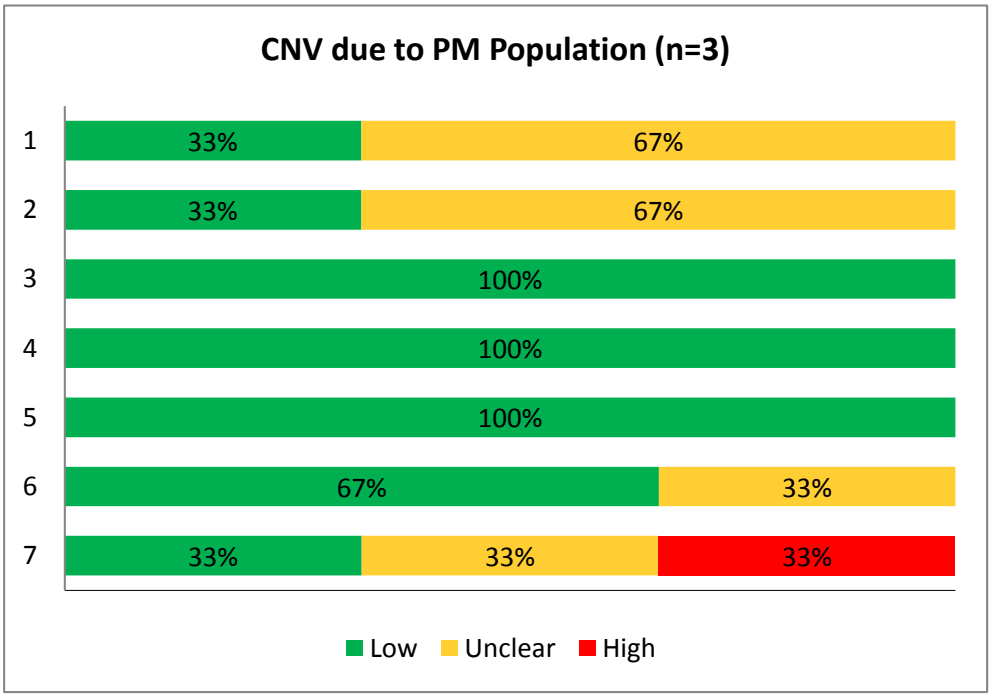


Figure 4: Quality Appraisal for CNV Due to PM



APPENDIX 11: COCHRANE RISK-OF-BIAS TABLE FOR INDIVIDUAL STUDIES

The legend for the Cochrane ROB items in the table is as follows:
1: Random sequence generation
2: Allocation concealment
3: Blinding of patients & personnel
4: Blinding of outcome assessment
5: Incomplete outcome data
6: Selective reporting
7: Other bias

	Cochrane ROB item						
STUDY	**1**	**2**	**3**	**4**	**5**	**6**	**7**
CNV due to PM (n=3)							
Iacono 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
Gharbiya 2010	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ikuno 2015	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk
DME (n=5)							
Wells 2015	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ekinci 2014	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
Nguyen 2012 – RIDE	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Nguyen 2012 - RISE	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Massin 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
ME due to RVO (n=9)							
Narayanan 2015	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Holz 2013	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk
Boyer 2012	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk
Epstein 2012	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Moradian 2011	Low risk	Low risk	Low risk	Low risk	Unclear risk	High risk	Low risk
Brown 2010	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk
Campochiaro 2010	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk
Kinge 2010	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	High risk	Low risk

STUDY	Cochrane ROB item						
	1	2	3	4	5	6	7
Rajagopal 2015	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wet AMD (n =13)							
Berg 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Scholler 2014	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Chakravarthy 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kodjikian 2013	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Krebs 2013	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Heier 2012 – VIEW 1	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Heier 2012 – VIEW 2	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Biswas 2011a	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Biswas 2011b	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
Martin 2011	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Subramanian 2010	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Regillo 2008	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	High risk
Rosenfeld 2006 (CR: Chang 2007)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	High risk

Note: CR, companion report

APPENDIX 12: DETAILED RESULTS FOR PAIRWISE META-ANALYSES

Detailed Results for Pairwise Meta-analyses								
Wet AMD								
	Comparison	**No. of RCTs***	**Total patients**	**I^2, *P* Value**	**ES**	**ES [95% CI]**	***P* value**	**Explanation for heterogeneity**
Vision gain in BCVA of ≥ 15 ETDRS letters	Ranibizumab vs. Aflibercept	2	1,815	51.88%, 0.149	OR	1.011 [0.747, 1.368]	0.943	
	Ranibizumab vs. Bevacizumab	8	2,950	0.00%, 0.336	OR	1.133 [0.955, 1.344]	0.152	
	Ranibizumab vs. Placebo	2	900	91.05%, < .001	OR	3.918 [0.514, 29.885]	0.188	Difference in # of injections (6 vs. 24) & f/u period (12 vs. 24 Mo)
	Bevacizumab vs. Aflibercept	0						
	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	0						
Vision loss in BCVA of ≥ 15 ETDRS letters	Ranibizumab vs. Aflibercept	2	1,815	0%, 0.727	OR	1.112 [0.724, 1.709]	0.628	
	Ranibizumab vs. Bevacizumab	9	3,005	0%, 0.812	OR	0.945 [0.702, 1.272]	0.707	
	Ranibizumab vs. Placebo	2	900	0.00%, 0.499	OR	0.119 [0.084, 0.169]	<.001	
	Bevacizumab vs. Aflibercept	0						
	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	0						
Mean difference in BCVA	Ranibizumab vs.	2	1,907	89.13%, 0 .0024	MD	0.103 [-5.43, 5.64]	0.9709	
	Ranibizumab vs.	7	2,769	6.91%, 0.3297	MD	0.506 [-0.82, 1.83]	0.4539	

	Ranibizumab vs. Placebo	2	909	41%,0.1930	MD	18.951 [13.83,24.07]	<0.0001	Diff injection freq (6 vs. 24) & f/u period (12 vs. 24 months)
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Blindness	Ranibizumab vs.	0						
	Ranibizumab vs.	3	1,817	0%, 1.000	OR	0.457 [0.069, 3.260]	0.449	
	Ranibizumab vs.	2	660	36.30%, 0.210	OR	0.393 [0.251, 0.613]	<.001	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Vision-related function	Ranibizumab vs.	2	1,632	72.5%	MD	2.23 [-0.61,5.07]	0.1245	
	Ranibizumab vs.	0						
	Ranibizumab vs.	1	725	NA	MD	7.9 [5.12,10.68]	<0.0001	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Adverse event (AE)	Ranibizumab vs.	0						
	Ranibizumab vs.	1	57	NA	OR	5.889 [0.281,	0.253	
	Ranibizumab vs.	1	713	NA	OR	1.700 [0.895, 3.227]	0.105	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Serious adverse event	Ranibizumab vs.	0						
	Ranibizumab vs.	5	3,026	11.85%, 0.422	OR	0.967 [0.550, 1.700]	0.288	
	Ranibizumab vs.	0						
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						

Withdrawals due to AE	Ranibizumab vs.	0						
	Ranibizumab vs.	3	1,536	0%, 0.849	OR	0.966 [0.497, 1.878]	0.908	
	Ranibizumab vs.	2	897	0% 0.849	OR	0.967 [0.550, 1.700]	0.908	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Mortality	Ranibizumab vs.	0						
	Ranibizumab vs.	6	2,941	0%, 0.729	OR	0.876 [0.551, 1.392]	0.574	
	Ranibizumab vs.	1	713	NA	OR	0.905 [0.330, 2.477]	0.846	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Arterial thromboembolic events	Ranibizumab vs.	2	1,818	0%, 0.654	OR	1.037 [0.481, 2.238]	0.8344	
	Ranibizumab vs.	4	2,133	29.65%, 0.383	OR	1.461 [0.571, 3.740]	0.429	
	Ranibizumab vs.	2	896	0%, 0.349	OR	1.256 [0.506, 3.120]	0.623	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Venous thromboembolic events	Ranibizumab vs.	1	911	NA	OR	3.997 [0.134,	0.424	
	Ranibizumab vs.	3	2,133	0%, 0.426	OR	0.626 [0.165, 2.380]	0.491	
	Ranibizumab vs.	0						
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Bacterial endophthalmitis	Ranibizumab vs.	1	911	NA	OR	2.007 [0.403, 10.001]	0.395	
	Ranibizumab vs.	2	2,502	0%, 0.457	OR	0.651 [0.142, 2.979]	0.58	
	Ranibizumab vs.	1	713	NA	OR	5.000 [0.272, 91.902]	0.279	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						

Increased intraocular pressure	Ranibizumab vs.	2	1,818	0%, 0.587	OR	2.055 [0.186, 22.708]	0.557	
	Ranibizumab vs.	1	1,185	NA	OR	0.122 [0.006, 2.304]	0.16	
	Ranibizumab vs.	2	896	0%, 0.580	OR	4.808 [2.371, 9.749]	<.001	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Retinal detachment	Ranibizumab vs.	1	907	NA	OR	4.237 [0.142,	0.405	
	Ranibizumab vs.	1	1,185	NA	OR	0.162 [0.008, 3.248]	0.234	
	Ranibizumab vs.	1	713	NA	OR	0.247 [0.008, 7.392]	0.42	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
*Note that meta-analysis was not conducted if only 1 RCT was identified. For these cases, the point estimate and 95% confidence interval was calculated from a single trial.								
DME								
	Comparison	No. of RCTs*	Total patients	I^2, ***P*** Value	ES	ES [95% CI]	***P*** value	Explanation for heterogeneity
Vision gain in BCVA of ≥15 ETDRS letters	***Ranibizumab vs.***	***1***	***414***	***NA***	***OR***	***0.656 [0.439, 0.980]***	***0.04***	
	Ranibizumab vs.	1	412	NA	OR	1.175 [0.771, 1.789]	0.453	
	Ranibizumab vs.	*3*	*1,356*	*0%, 0.655*	*OR*	*3.882 [2.706, 5.569]*	*<.001*	
	Bevacizumab vs.	***1***	***414***	***NA***	***OR***	***0.558 [0.371, 0.840]***	***0.005***	
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Vision loss in BCVA of ≥ 15 ETDRS letters	Ranibizumab vs.	1	414	NA	OR	1.010 [0.201, 5.062]	0.99	
	Ranibizumab vs.	1	412	NA	OR	1.000 [0.199, 5.013]	1	
	Ranibizumab vs.	3	910	0%, 0.524	OR	0.220 [0.118, 0.407]	<.001	
	Bevacizumab vs.	1	414	NA	OR	1.010 [0.201, 5.062]	0.99	
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Mean difference in BCVA	***Aflibercept vs.***	***1***	***377***	***NA***	***MD***	***2.1 [0.10, 4.2]***	***0.0441***	
	Ranibizumab vs.	2	512	0%, 0.7010	SM	0.16 [-0.02, 0.33]	0.0798	NA
	Ranibizumab vs.	3	910	0%, 0.5742	MD	9.23 [6.98, 11.49]	<.0001	NA
	Bevacizumab vs.	***1***	***414***	***NA***	***MD***	***-4.2 [-6.47,-1.93]***	***0.0003***	

	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Blindness	Ranibizumab vs.	0						
	Ranibizumab vs.	0						
	Ranibizumab vs.	1	249	NA	OR	3.952 [0.176, 88.514]	0.386	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Serious adverse event	Ranibizumab vs.	1	442	NA	OR	0.944 [0.616, 1.445]	0.79	
	Ranibizumab vs.	1	436	NA	OR	1.262 [0.807, 1.972]	0.307	
	Ranibizumab vs.	2	750	13.36%,	OR	0.825 [0.413, 1.649]	0.586	
	Bevacizumab vs. Aflibercept	1	442	NA	OR	0.748 [0.481, 1.162]	0.196	
	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	0						
Withdrawals due to AE	Ranibizumab vs. Aflibercept	0						
	Ranibizumab vs. Bevacizumab	0						
	Ranibizumab vs. Placebo	3	901	0%, 0.704	OR	0.814 [0.390, 1.702]	0.585	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Mortality	Ranibizumab vs.	1	442	NA	OR	1.377 [0.305, 6.225]	0.678	
	Ranibizumab vs.	1	436	NA	OR	0.796 [0.211, 3.006]	0.737	
	Ranibizumab vs.	3	901	0%, 0.785	OR	2.662 [0.832, 8.511]	0.099	
	Bevacizumab vs.	1	442	NA	OR	1.729 [0.408, 7.326]	0.457	
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Arterial thromboembolic events	Ranibizumab vs.	1	442	NA	OR	1.747 [0.624, 4.892]	0.288	
	Ranibizumab vs.	1	436	NA	OR	1.116 [0.445, 2.804]	0.815	
	Ranibizumab vs.	1	151	NA	OR	1.211 [0.227, 6.476]	0.823	

	Bevacizumab vs.	1	442	NA	OR	1.565 [0.547, 4.472]	0.404	
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Bacterial endophthalmitis	Ranibizumab vs.	0						
	Ranibizumab vs.	0						
	Ranibizumab vs.	3	901	0%, 0.884	OR	1.904 [0.307, 11.806]	0.489	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Increased intraocular pressure	Ranibizumab vs.	1	442	NA	OR	0.708 [0.400, 1.253]	0.023	
	Ranibizumab vs.	1	436	NA	OR	1.235 [0.652, 2.340]	0.517	
	Ranibizumab vs.	3	901	0%, 0.545	OR	7.637 [2.853, 20.443]	<.001	
	Bevacizumab vs.	1	442	NA	OR	0.573 [0.314, 1.045]	0.069	
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						
Retinal detachment	Ranibizumab vs.	0						
	Ranibizumab vs.	0						
	Ranibizumab vs.	3	901	0%, 0.794	OR	0.392 [0.055, 2.796]	0.35	
	Bevacizumab vs.	0						
	Bevacizumab vs.	0						
	Aflibercept vs. Placebo	0						

*Note that meta-analysis was not conducted if only 1 RCT was identified. For these cases, the point estimate and 95% confidence interval was calculated from a single trial.

RVO

	Comparison	**No. of RCTs***	**Total patients**	**I^2, *P* Value**	**ES**	**ES [95% CI]**	***P* Value**	**Explanation for heterogeneity**
Vision gain in BCVA of ≥15 ETDRS letters	Ranibizumab vs. Aflibercept	0						
	Ranibizumab vs. Bevacizumab	2	173	0%	OR	1.03 [0.555, 1.94]	0.095	
	Ranibizumab vs. Placebo	2	789	0%, 0.501	OR	3.796 [2.704, 5.331]	<.001	
	Bevacizumab vs. Aflibercept	0						

	Bevacizumab vs. Placebo	1	60	NA	OR	6.000 [1.890, 19.043]	0.002	
	Aflibercept vs. Placebo	2	358	20.92%, 0.261	OR	7.012 [3.890, 12.640]	<.001	
Vision loss in BCVA of ≥ 15 ETDRS letters	Ranibizumab vs. Aflibercept	0						
	Ranibizumab vs. Bevacizumab	0						
	Ranibizumab vs. Placebo	2	789	0%, 0.952	OR	0.153 [0.070, 0.333]	<.001	
	Bevacizumab vs. Aflibercept	0						
	Bevacizumab vs. Placebo	1	60	NA	OR	0.235 [0.044, 1.241]	0.088	
	Aflibercept vs. Placebo	1	187	NA	OR	0.047 [0.011, 0.210]	<.001	
Mean difference in BCVA	Ranibizumab vs.	0						
	Ranibizumab vs. Bevacizumab	2	173	NA	SMD	(0.00 [-0.30, 0.30])	0.99	
	Ranibizumab vs. Placebo	3	818	0.55%,0.4840	MD	10.72 [9.19,12.26]	<0.0001	
	Bevacizumab vs.	0						
	Bevacizumab vs. Placebo	2	141	94.84%,<0.0001	SMD	0.25 [-1.28,1.79]	0.7456	Diff in pathophysiology of BRVO and CRVO
	Aflibercept vs. Placebo	1	187	NA	MD	23 [19.53,26.67]	<0.0001	variability in eligibility criteria (whether other therapeutic options allowed during study)
Blindness	Ranibizumab vs.	0						
	Ranibizumab vs.	0						
	Ranibizumab vs. Placebo	2	789	68.36%,	OR	0.247 [0.075, 0.822]	0.023	
	Bevacizumab vs.	0						
	Bevacizumab vs. Placebo	1	60	NA	OR	0.266 [0.073, 0.964]	0.044	
	Aflibercept vs. Placebo	0						

Vision-related function	Ranibizumab vs.	0						
	Ranibizumab vs.	0						
	Ranibizumab vs. Placebo	1	385	NA	MD	3.95 [0.82,7.08]	0.0132	
	Bevacizumab vs.	0						
	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	1	163	NA	MD	6.1 [1.21,10.99]	0.0144	
Adverse events(AE)	Ranibizumab vs.	0						
	Ranibizumab vs.	0						
	Ranibizumab vs. Placebo	0						
	Bevacizumab vs.	0						
	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	1	188	NA	OR	0.873 [0.389, 1.958]	0.742	
Serious adverse event	Ranibizumab vs.	0						
	Ranibizumab vs.	1	75	NA	OR	2.114 [0.183, 24.368]	0.548	
	Ranibizumab vs. Placebo	0						
	Bevacizumab vs.	0						
	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	2	365	0%, 0.762	OR	0.259 [0.097, 0.693]	0.007	
Withdrawals due to AE	Ranibizumab vs.	0						
	Ranibizumab vs.	0						
	Ranibizumab vs. Placebo	0						
	Bevacizumab vs. Aflibercept	0						
	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	2	365	0%, 0.832	OR	0.140 [0.035, 0.567]	0.006	
Mortality	Ranibizumab vs. Aflibercept	0						
	Ranibizumab vs. Bevacizumab	0						
	Ranibizumab vs. Placebo	1	395	NA	OR	4.085 [0.136,	0.417	
	Bevacizumab vs.	0						

	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	1	189	NA	OR	0.158 [0.007, 3.553]	0.245	
Arterial thromboembolic events	Ranibizumab vs.	0						
	Ranibizumab vs.	0						
	Ranibizumab vs. Placebo	1	390	NA	OR	0.988 [0.089, 11.003]	0.992	
	Bevacizumab vs.	0						
	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	1	188	NA	OR	0.319 [0.028, 3.578]	0.354	
Venous thromboembolic events	Ranibizumab vs.	0						
	Ranibizumab vs.	0						
	Ranibizumab vs. Placebo	0						
	Bevacizumab vs.	0						
	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	1	188	NA	OR	0.646 [0.040, 10.490]	0.759	
Bacterial endophthalmitis	Ranibizumab vs.	0						
	Ranibizumab vs.	0						
	Ranibizumab vs. Placebo	1	395	NA	OR	0.996 [0.033, 29.886]	0.998	
	Bevacizumab vs.	0						
	Bevacizumab vs. Placebo	1				0 events		
	Aflibercept vs. Placebo	1	188	NA	OR	1.307 [0.043, 39.450]	0.878	
Increased intraocular pressure	Ranibizumab vs.	0						
	Ranibizumab vs.	1	75	NA	OR	0.333 [0.013, 8.440]	0.505	
	Ranibizumab vs. Placebo	0						
	Bevacizumab vs.	0						
	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	1	172	NA	OR	1.702 [0.512, 5.664]	0.386	
Retinal detachment	Ranibizumab vs.	0						
	Ranibizumab vs.	0						
	Ranibizumab vs. Placebo	1	395	NA	OR	0.996 [0.033, 29.886]	0.998	
	Bevacizumab vs.	0						
	Bevacizumab vs. Placebo	1				0 events		
	Aflibercept vs. Placebo	1	188	NA	OR	1.307 [0.043, 39.450]	0.878	

*Note that meta-analysis was not conducted if only 1 RCT was identified. For these cases, the point estimate and 95% confidence interval was calculated from a single trial.								
CNV due to PM								
	Comparison	**No. of RCTs***	**Total patients**	**I^2, *P* Value**	**ES**	**ES [95% CI]**	***P* Value**	**Explanation for heterogeneity**
Vision gain in BCVA of ≥ 15 ETDRS letters	Ranibizumab vs. Aflibercept	0						
	Ranibizumab vs. Bevacizumab	1	32	NA	OR	0.771 [0.188, 3.173]	0.719	NA
	Ranibizumab vs. Placebo	0						
	Bevacizumab vs. Aflibercept	0						
	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	1	121	NA	OR	5.94 [1,68, 21.02]	0.005	
Mean difference in BCVA	Ranibizumab vs. Aflibercept	0						
	Ranibizumab vs. Bevacizumab	2	80	0%, 0.9189	SM	-0.13 [-0.57, 0.31]	0.5585	NA
	Ranibizumab vs. Placebo	0						
	Bevacizumab vs. Aflibercept	0						
	Bevacizumab vs. Placebo	0						
	Aflibercept vs. Placebo	0						

APPENDIX 13: WET AMD FOREST PLOTS

These forest plots illustrate the effect sizes (95% CI) for comparative efficacy of anti-VEGF drugs for the main outcomes assessed in this review – vision gain and loss of ≥ 15 ETDRS letters, and mean difference in best corrected visual acuity (BCVA) in the wet AMD population.

VISION GAIN

FIGURE 5: RANIBIZUMAB VERSUS BEVACIZUMAB

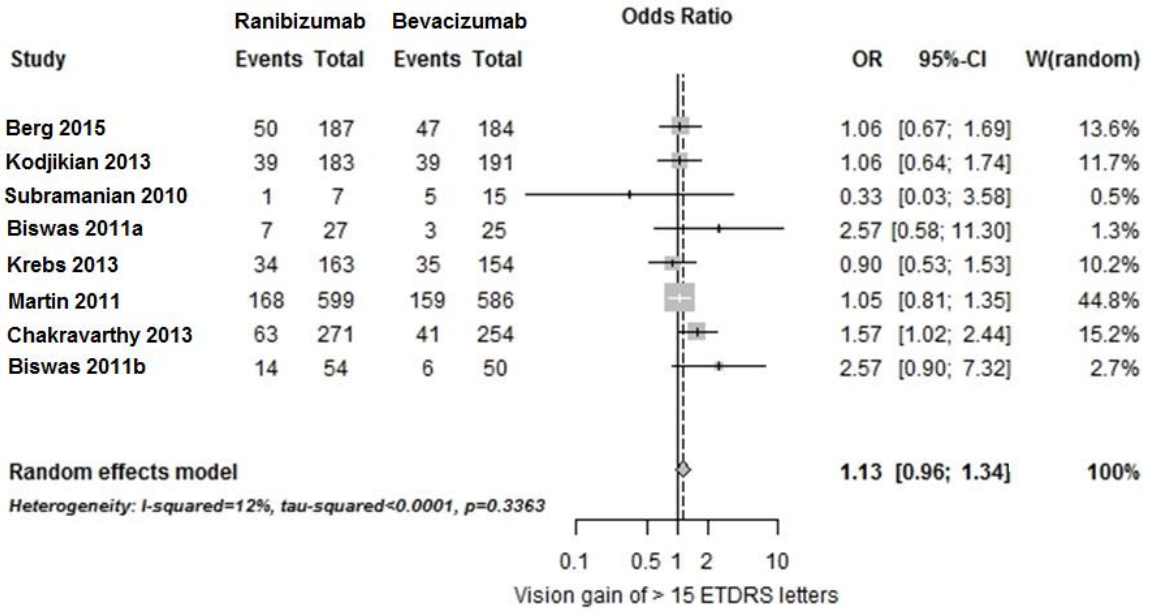
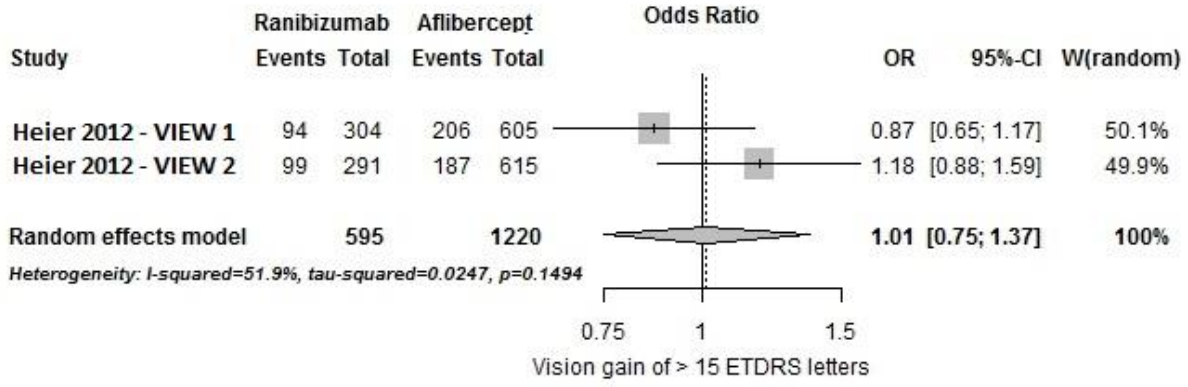
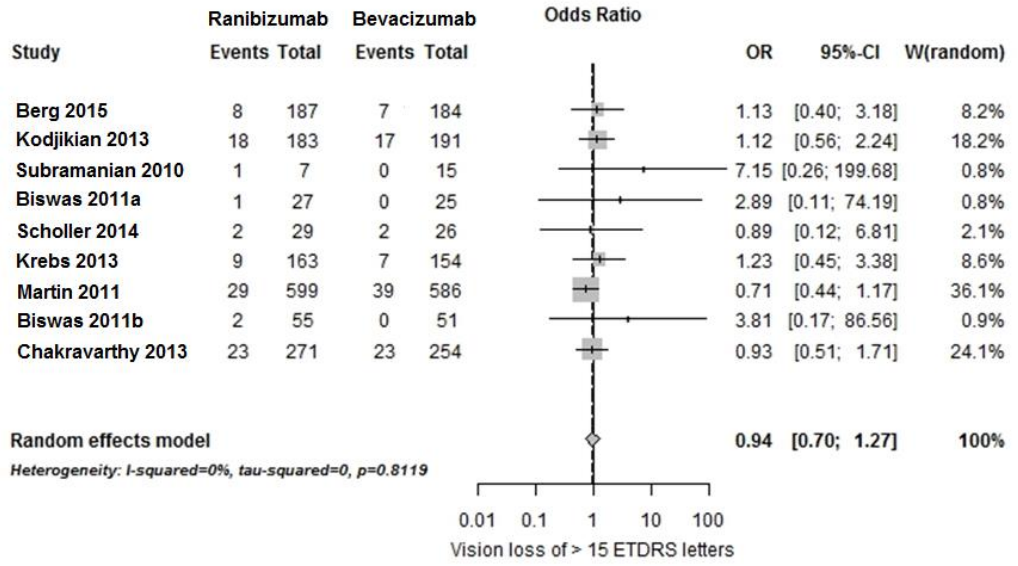


FIGURE 6: RANIBIZUMAB VERSUS AFLIBERCEPT



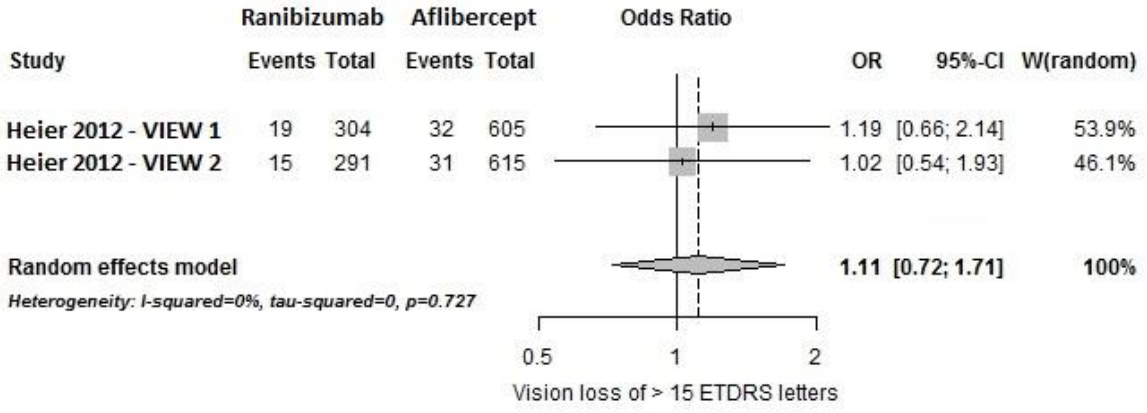
VISION LOSS

FIGURE 7: RANIBIZUMAB VERSUS BEVACIZUMAB



A.

FIGURE 8: RANIBIZUMAB VERSUS AFLIBERCEPT



DIFFERENCE IN BCVA

FIGURE 9: RANIBIZUMAB VERSUS BEVACIZUMAB

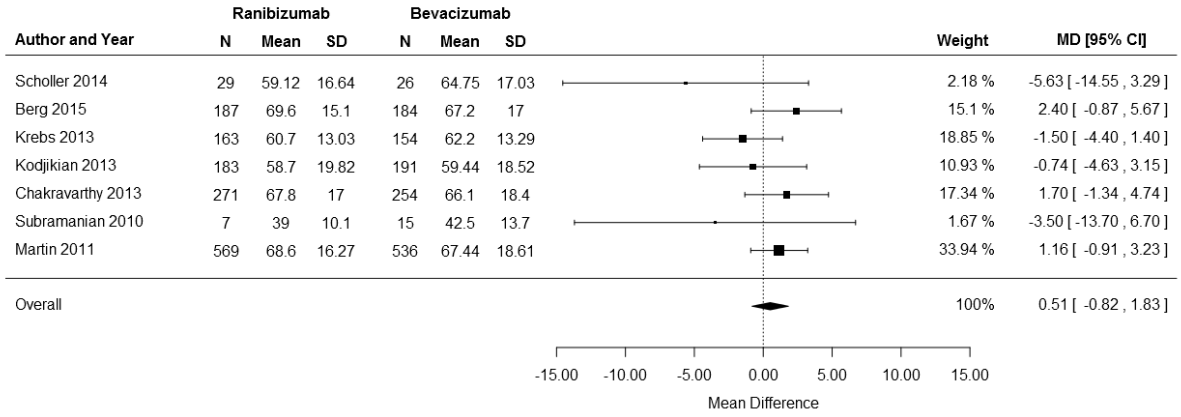
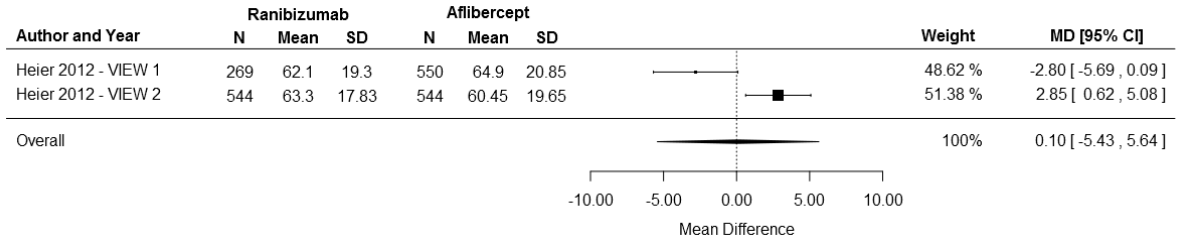


FIGURE 10: RANIBIZUMAB VERSUS AFLIBERCEPT



APPENDIX 14: DME FOREST PLOTS

VISION GAIN

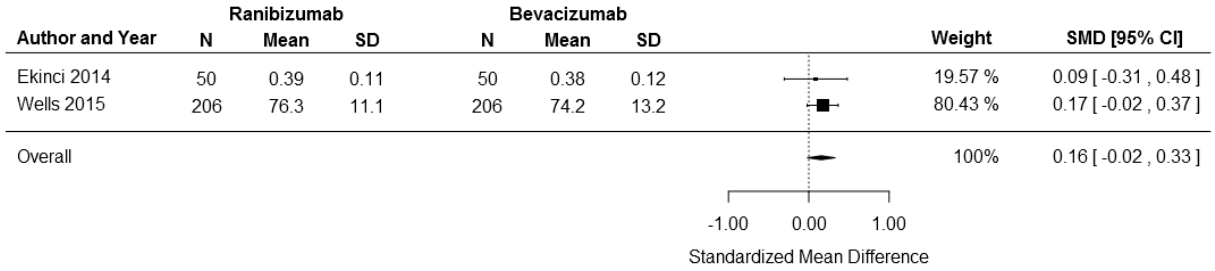
Only single RCTs reported on each of the comparisons of ranibizumab versus bevacizumab, ranibizumab versus aflibercept, and aflibercept versus bevacizumab. Please refer to Appendix 9 for the single trial estimates.

VISION LOSS

Only single RCTs reported on each of the comparisons of ranibizumab versus bevacizumab, ranibizumab versus aflibercept, and aflibercept versus bevacizumab. Please refer to Appendix 9 for the single trial estimates.

DIFFERENCE IN BCVA

FIGURE 11: RANIBIZUMAB VERSUS BEVACIZUMAB

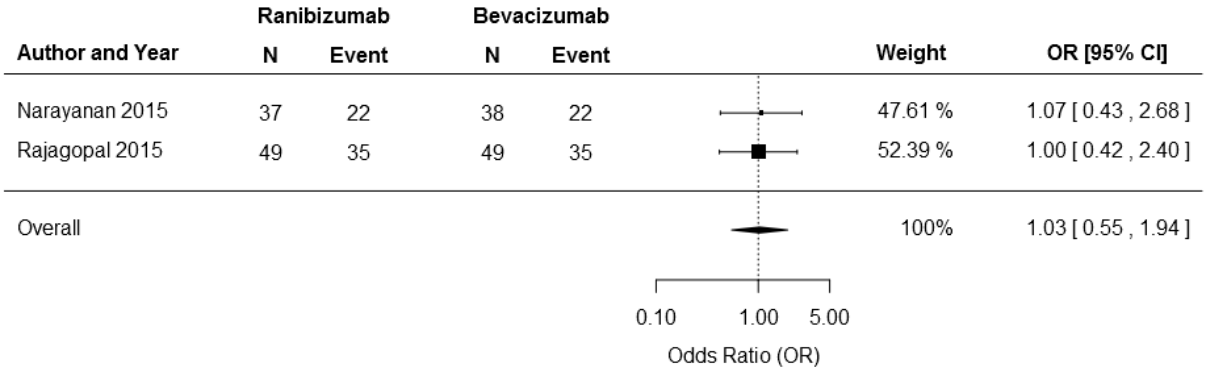


Only single RCTs reported on each of the comparisons of ranibizumab versus aflibercept, and aflibercept versus bevacizumab. Please refer to Appendix 9 for the single trial estimates.

APPENDIX 15: RVO FOREST PLOTS

VISION GAIN

FIGURE 12: RANIBIZUMAB VERSUS BEVACIZUMAB

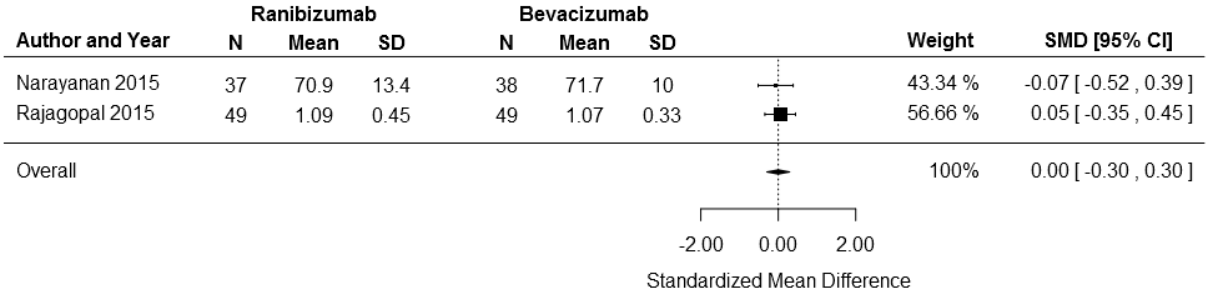


VISION LOSS

ONLY ONE RCT REPORTED ON THE COMPARISON OF RANIBIZUMAB VERSUS BEVACIZUMAB. PLEASE REFER TO APPENDIX 9 FOR THE SINGLE TRIAL ESTIMATE.

STANDARDIZED MEAN DIFFERENCE IN BCVA

FIGURE 13: RANIBIZUMAB VERSUS BEVACIZUMAB



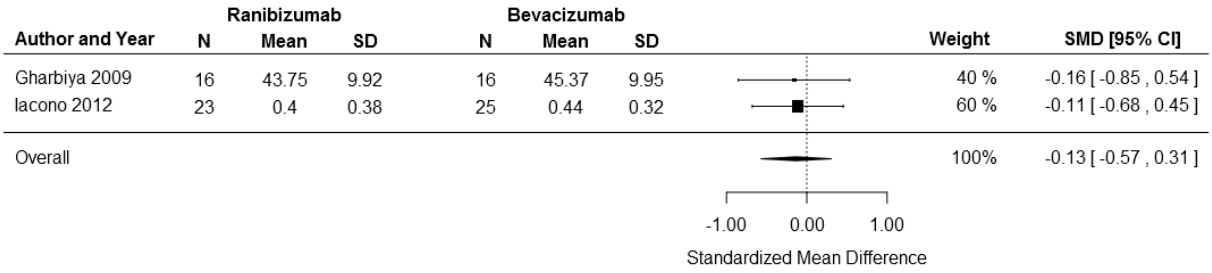
APPENDIX 16: CNV FOREST PLOTS

VISION GAIN

Only one RCT reported on the comparison of ranibizumab versus bevacizumab. Please refer to Appendix 9 for the single trial estimate.

DIFFERENCE IN BCVA

FIGURE 14: RANIBIZUMAB VERSUS BEVACIZUMAB



APPENDIX 17: NMA RESULTS

Vision Gain for Wet-AMD Population

NMA Point Estimates (± Credible Interval) for Relative Effects of Aflibercept, Ranibizumab, and Bevacizumab for the Outcome of Vision Gain for Wet AMD

Ranibizumab	1.01 [0.52,2.04]	1.19 [0.8,1.82]	5.63 [1.99,13.32]
0.99 [0.49,1.94]	**Aflibercept**	1.17 [0.54,2.63]	5.56 [1.56,15.57]
0.84 [0.55,1.25]	0.85 [0.38,1.86]	**Bevacizumab**	4.75 [1.52,11.97]
0.18 [0.08,0.5]	0.18 [0.06,0.64]	0.21 [0.08,0.66]	**Placebo**

Ranking Probability That a Treatment Will Be the Most Effective at Achieving Vision Gain of 15 or More ETDRS Letters

Treatments	Rank 1	Rank 2	Rank 3	Rank 4
Ranibizumab	0.44	0.48	0.08	0.000375
Aflibercept	0.46	0.27	0.27	0.008375
Bevacizumab	0.10	0.25	0.65	0.005125
Placebo	0.0015	0.0021	0.010	0.99

Surface Under the Cumulative RAnking (SUCRA) Curve

Treatments	SUCRA
Ranibizumab	78.82
Aflibercept	72.58
Bevacizumab	47.97
Placebo	0.64

FIGURE 15: NETWORK DIAGRAM — VISION GAIN IN WET-AMD POPULATION

Each node within the network diagram represents an intervention. A solid line connecting nodes indicates the presence of direct evidence, and a dashed line indicates presence of indirect evidence, comparing the two interventions. Node size is proportional to the number of patients included in the corresponding treatments, and line thickness indicates the number of studies included in the respective comparisons.

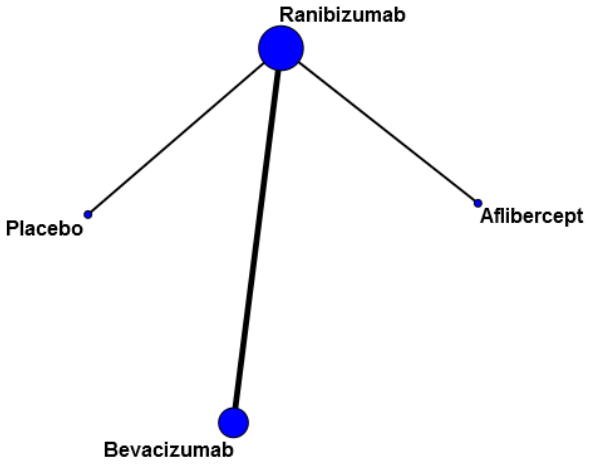
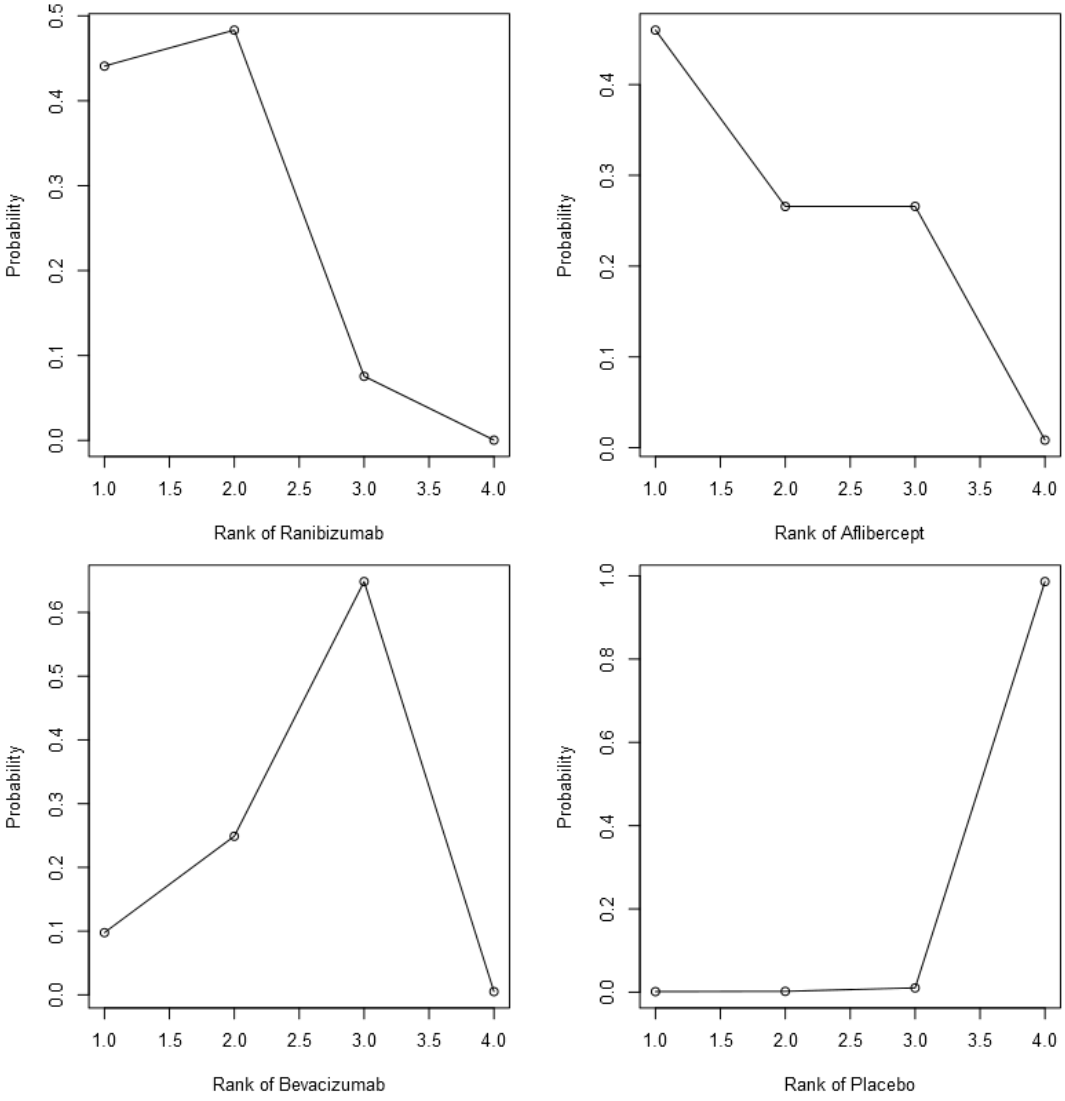


FIGURE 16: RANKING PROBABILITY PLOTS FOR VISION GAIN IN THE WET-AMD POPULATION



Vision Loss for Wet-AMD Population

NMA Estimates

NMA Point Estimates (± credible interval) for Relative Effects of Aflibercept, Ranibizumab, and Bevacizumab for the Outcome of Vision Loss for Wet AMD

Ranibizumab	1.1 [0.62,1.92]	0.99 [0.69,1.52]	0.12 [0.07,0.2]
0.91 [0.52,1.61]	**Aflibercept**	0.9 [0.48,1.89]	0.11 [0.05,0.24]
1.01 [0.66,1.44]	1.11 [0.53,2.09]	**Bevacizumab**	0.12 [0.06,0.22]
8.4 [4.97,14.18]	9.28 [4.2,19.68]	8.35 [4.55,16.34]	**Placebo**

Ranking Probability

Ranking Probability that a Treatment Will Be the Most Likely to Achieve Vision Loss of 15 or More ETDRS Letters

Treatments	Rank 1	Rank 2	Rank 3	Rank 4
Ranibizumab	0.19	0.50	0.31	0
Aflibercept	0.56	0.18	0.26	0.00038
Bevacizumab	0.25	0.32	0.43	0
Placebo	0	0	0.00038	1.00

Surface Under the Cumulative RAnking (SUCRA) Curve

Treatments	SUCRA
Ranibizumab	62.95
Aflibercept	76.47
Bevacizumab	60.57
Placebo	0.01

FIGURE 17: NETWORK DIAGRAM FOR VISION LOSS IN THE WET-AMD POPULATION

Each node within the network diagram represents an intervention. A solid line connecting nodes indicates the presence of direct evidence comparing the two interventions. Node size is proportional to the number of patients included in the corresponding treatments, and line thickness indicates the number of studies included in the respective comparisons.

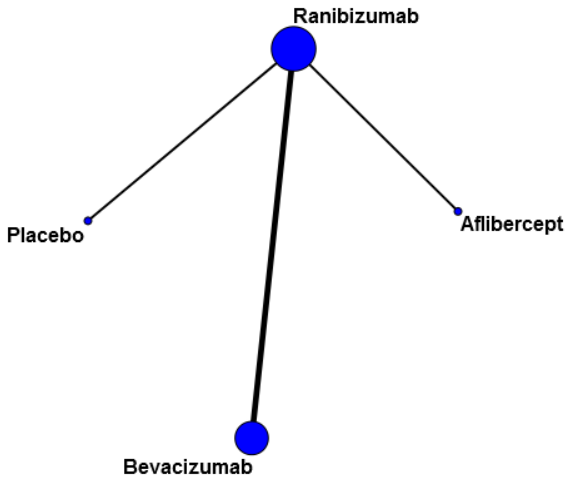
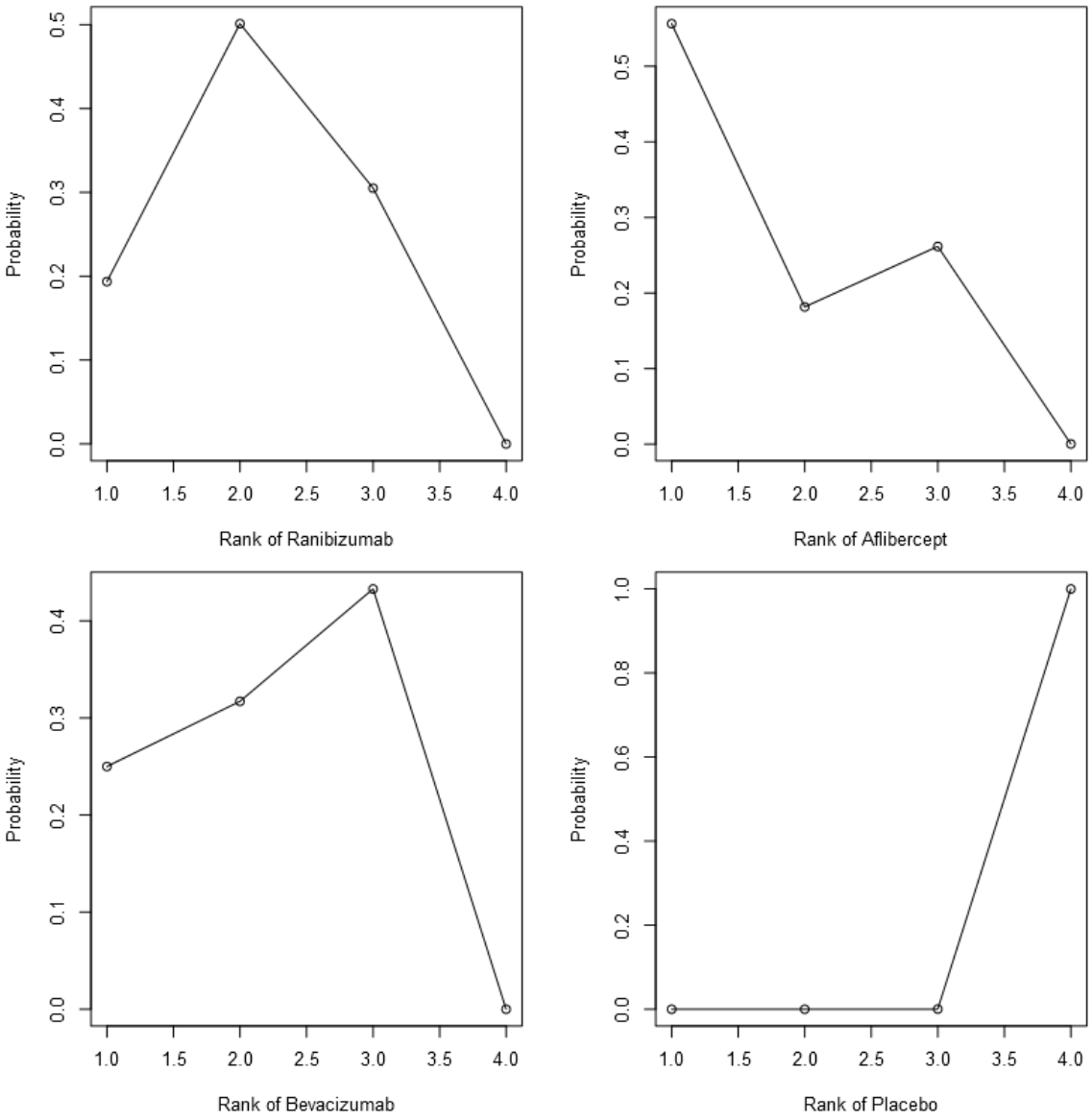


FIGURE 18: RANKING PROBABILITY PLOTS FOR VISION LOSS IN WET-AMD POPULATION



Mean Difference in BCVA for the Wet-AMD Population

NMA Point Estimates (± Credible Interval) for Relative Effects of Aflibercept, Ranibizumab, and Bevacizumab for the Outcome of Mean Difference in BCVA for Wet AMD

Ranibizumab	0.23 [-4.39,4.61]	0.11 [-2.85,2.66]	19.04 [13.28,24.28]
-0.23 [-4.61,4.39]	**Aflibercept**	-0.12 [-5.5,5.05]	18.81 [11.51,25.67]
-0.11 [-2.66,2.85]	0.12 [-5.05,5.5]	**Bevacizumab**	18.93 [12.72,24.93]
-19.04 [-24.28,-13.28]	-18.81 [-25.67,-11.51]	-18.93 [-24.93,-12.72]	**Placebo**

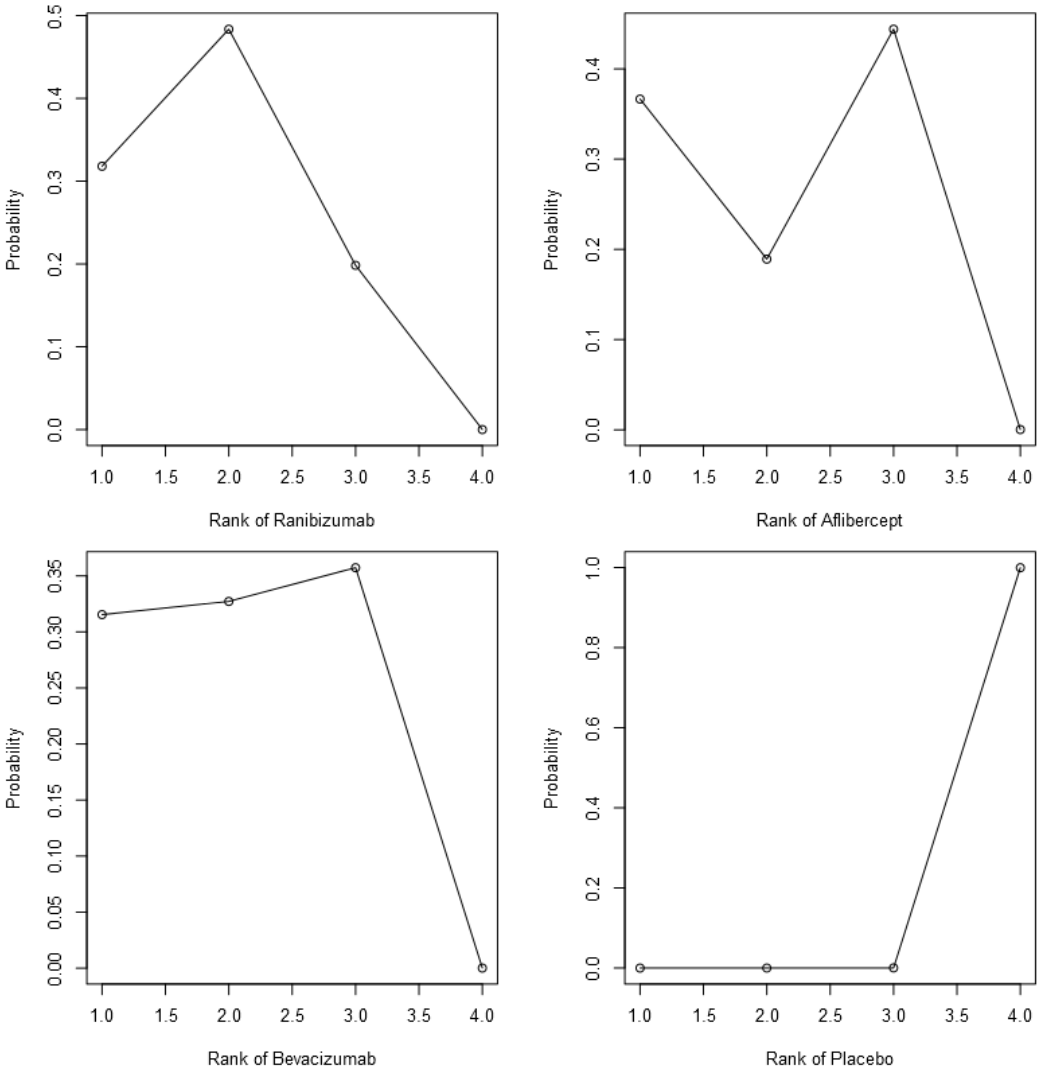
Ranking Probability that a Treatment Will Be the Most Likely to Achieve a Significant Mean Difference in BCVA

Treatments	Rank 1	Rank 2	Rank 3	Rank 4
Ranibizumab	0.318075	0.4835625	0.1983375	0.000025
Aflibercept	0.366525	0.1892	0.443925	0.00035
Bevacizumab	0.3154125	0.3272	0.3572625	0.000125
Placebo	0.0000125	0.000075	0.0004125	0.9995

Surface Under the Cumulative RAnking (SUCRA) Curve

Treatments	**SUCRA**
Ranibizumab	70.66
Aflibercept	64.06
Bevacizumab	65.26
Placebo	0.02

FIGURE 19: RANKING PROBABILITY PLOTS — MEAN DIFFERENCE IN WET AMD



APPENDIX 18: PATIENT INPUT SUMMARY

Submitting Organizations

The Canadian Council of the Blind (CCB) was founded in 1944 by blind war veterans and graduates from schools of the blind. All officers and directors are blind or visually impaired which gives a unique sensitivity to the needs of the blind community. The CCB is a registered charity pursuant to the provisions of the Income Tax Act (Canada); charity number is: 11921 8899 RR0001. The CCB has more than 70 chapters across Canada, and with more than 1,500 members, is the largest membership-based organization for the blind. **The purpose of the CCB is to give people with vision loss a distinctive and unique perspective before governments.** The CCB deals with the ongoing effects of vision loss by encouraging active living and rehabilitation through peer support and social and recreational activities. CCB promotes measures to conserve sight, create a close relationship with the sighted community and provide employment opportunities. For the 21st century, the CCB is committed to an integrated proactive health approach for early detection to improve the quality of life for all Canadians.

CNIB – The primary objective of the CNIB is to create an inclusive, accessible, barrier-free society that provides the tools blind or partially sighted Canadians require to live safe, fulfilling and independent lives. CNIB believes in making communities accessible, caring and inclusive. We believe that people living with vision loss should have no limitations placed on their ability to succeed and we work hand-in-hand with Canadians who are blind or partially sighted to advocate for a barrier-free society. As Canada's main provider of post-vision loss rehabilitation therapy, CNIB ensures its clients are able to receive the support they need throughout their journey through vision loss. Whether it be safety and mobility training, assistance with remaining gainfully employed, or gaining access to alternative formats of published works, CNIB operates across Canada providing these services to the best of the organization's ability and funded almost entirely by charitable donations received from the public.

The Foundation Fighting Blindness is Canada's leading charitable funder of sight-saving research. Our Charitable Registration Number is: 11912 9369 RR0001. **The mission of the Foundation Fighting Blindness is to lead the fight against blindness by advancing retinal disease research, education and public awareness.** We work with Canadian families affected by retinal diseases and with vision scientists at hospitals and universities across Canada. Over the past 40 years, the Foundation has contributed more than $28 million to sight-saving research. We have a rigorous process of peer review, and the systems and processes in place to support and monitor complex research projects. We do not charge membership fees and consider our community of various stakeholders (donors, educational event participants, researchers, etc.) to be our general members.

Conflict of Interest Declarations

CCB received support from the following: VIA Rail, Cannondale, Community Foundation of Ottawa, Lions Club, Keith Communications Inc., Human Resources and Skills Development Canada (HRSDC), and the following pharmaceutical companies: Bayer, Merck, Novartis, and Pfizer. **CNIB** has received unrestricted educational grants for relatively small amounts from the following pharmaceutical companies: Alcon Canada, Bayer Canada, Novartis Canada, and Pfizer Canada. **The Foundation Fighting Blindness** receives unrestricted education grants and/or fundraising event sponsorships from Novartis Pharmaceuticals, Bayer Inc, Alcon, Allergan, Rx&D Health Foundation and

Bausch & Lomb. Combined these companies contributed less than 4 per cent of the Foundation's revenues in 2014. **Together we are co-signatories on the Canadian Patient Charter for Vision Care** (included as an Appendix), which illustrates our commitment to ensuring that patients have access to the highest standard of vision care across Canada. We do not recommend specific treatments because we believe that these decisions are between the patient and her/his doctor. **We advocate for the best care.**

Condition and Current Therapy Information

Information Gathering

This collaborative submission relies on personal and organizational knowledge (across our three organizations) obtained from working with people living with AMD, DME, RVO and choroidal neovascularization secondary to progressive myopia. We also relied on: personal conversations with people living with these retinal diseases; an interview with a DME client; focus groups involving clients with DME; and an online survey for people living with wet AMD.

Impact of Condition on Patients

Each of the five retinal conditions that is being considered, including age-related macular degeneration (AMD), choroidal neovascularization (CNV), diabetic macular edema (DME), pathologic myopia (PM), and retinal vein occlusion (RVO) has a unique impact on the affected patients and their families. Although each disease has different complications, they all lead to vision loss. We therefore focus on the symptoms and problems related to central vision loss that are shared across these five diseases. **We emphasize that vision loss is a devastating diagnosis because it impacts almost every task and activity related to daily living. In every case, early diagnosis and an individualized approach to treatment are essential to effectively combat rapid vision loss.** If administered within the window of "treatability," anti-VEGF drugs can prevent further vision loss and even restore some lost sight. If this window is missed, drugs lose their effectiveness. One patient reported: "*The Lucentis booklet was very good, but too late; I should have been forewarned*."

People living with retinal diseases reported experiencing the following challenges:

Difficulties completing tasks that utilize central vision

Difficulty reading

Difficulty recognizing facial features

Difficulty or inability to drive

Loss of independence

Decreased quality of life

Depression (studies have shown that adults with vision loss experience triple the rate of depression)

Inability to maintain adequate foot care (this particularly important for people with diabetes because they also experience a range of neuropathies in the extremities)

Difficulty travelling to doctor's appointments

Difficulty gaining accessible transportation

Difficulty obtaining accessible (large print, audio, high-contrast) materials about self-care

Difficulty finding accessible information about medications and prescriptions

Difficulty with healthy eating because many kitchens are inaccessible

Difficulty maintaining a job

Difficulty paying for expensive treatments

Fear about the future

Difficult interacting with people “not seeing what they see”

Loss of friends and social supports, leading to isolation

Inability to recognize people

Worrying about their children (“I understand that there is a genetic component”)

More frequent falls and injuries

Difficulty watching TV (loss of leisure activities)

Writing (e.g., taking notes at a meeting)

Poor depth perception and balance (studies show that adults with vision loss have twice the risk of falling and four times the risk of hip fracture when compared to age-matched cohorts)

“Having to explain my limitations when out in the community”

Difficulty with housework (sewing on a button, ironing, setting oven temperature, etc.)

Difficulty with household repairs (hammering nails, using a screwdriver, using power tools, etc.)

The people we heard from emphasized that reading difficulties were particularly challenging because of the broad impact that reading has on other activities (e.g., reading signs to navigate in a new area, reading recipes in the kitchen, reading small print, such as the prescription information on medicine bottles, etc.). The majority of patients reported that the need to frequently visit their eye doctor was a significant burden. People experiencing central vision loss share many of the aforementioned difficulties, but each disease also presents additional challenges, as described below.

DME – Several groups are more vulnerable to diabetes and DME. First Nations Canadians are three to five times more likely than the general population to develop diabetes. This also makes them more likely to develop DME. Other ethno-cultural groups that have a higher risk of diabetes include Canadians of South Asian, Latin American and African descent. Diabetes and DME also have a higher prevalence in people living in poverty. Due to this economic disadvantage, access to affordable therapies is essential to the well-being and health of vulnerable Canadians. People on the lower end of the socioeconomic scale will not be able to afford new medications for DME and will suffer significant vision loss, as a result. **We have all met patients living with DME who explained the economic burden of the disease** (especially because most are below the age of 65 and therefore often not eligible for reimbursement by formularies).

CNV due to PM – This is a significant cause of vision loss globally, particularly in Asian populations. Choroidal neovascularization secondary to pathologic myopia is a major complication of pathologic myopia. This condition usually affects people under the age of

50 and can lead to severe vision loss within five years if left untreated. PM's impact on the quality of life of an otherwise healthy adult can be profound, affecting their ability to gain employment and function independently.

The impact of vision loss is conveyed by the following statistics:

Only 45% of people with vision loss have graduated from high school

Only 35% of working age adults with vision loss are employed

Almost half of adults with vision loss report gross annual incomes of $20,000 or less

A study conducted by CNIB (with 2012 data) estimated the total financial cost of vision loss in Canada due to AMD at $2.6 billion, and due to diabetic retinopathy at $776 million per year. This breaks down to $1.8 billion in direct health costs due to AMD and $412 million in direct health costs due to diabetic retinopathy, as well as $860 million in indirect costs due to AMD and $364 million in indirect costs due to diabetic retinopathy. The net cost of suffering (burden of disease) from AMD, over and above the financial costs, was estimated to be a further $1.9 billion annually and due to diabetic retinopathy was estimated at $801 million annually. In addition to these costs, CNIB recently estimated the cost of falls associated with vision loss at $25.8 million; the cost of depression due to vision loss at $175.2 million; cost of hip fractures due to vision loss at $101.7 million; and the cost of nursing home admission due to vision loss at $713.6 million. The costs of vision loss are so large, even a small reduction in vision loss leads to significant impacts.

In closing, there is a clear economic benefit to sight-saving and restoring therapies, but economics should not be the only determinant. The benefit that anti-VEGFs provide to peoples' ability to function independently – to engage in the activities of everyday life that most of us take for granted – has to be the determining factor. In Canada, people should not have to suffer blindness and the related health and psychosocial impacts because they have the inability to pay for therapies. The feedback that we received from patients is bolstered by large epidemiological studies that show the impact of vision loss on quality of life as measured by objective assessment questionnaires. **Any improvement of vision loss as a result of treatment with anti-VEGF therapies leads to improvements in quality of life.**

Patients' Experiences With Current Therapy

Currently, patients in Canada who are living with AMD, CNV, DME, PM or RVO are treated with biweekly, monthly, or bi-monthly intraocular injections with one of the following three anti-VEGF drugs: bevacizumab (Avastin); ranibizumab (Lucentis); aflibercept (Eylea). Before these treatments were available, patients reported that they had been treated with cold laser, photodynamic laser therapy, and Visudyne.

Options needed for optimal patient outcomes. We gathered information from patients who are currently receiving anti-VEGF treatments, including patients who have been treated with a different anti-VEGF drug in the past. In summary, the majority of the people who we heard from were being treated with Lucentis, and the majority of those patients reported the treatment was working well for them. Some told us that a negative experience with Avastin ("severe allergic reaction, migraine, and complete vision loss") led them to switch to Lucentis. For example, in direct conversation with two patients who initially had received seven to10 injections of Avastin then changed to Lucentis, we learned that their visual acuity improved significantly after just two injections with the latter drug, enabling them to drive. In conversation, patients who were receiving Lucentis or Eylea injections reported that they experienced only very limited eye redness and

fewer side effects then they had experienced on Avastin. Still, others reported that although they had been on both Avastin and Lucentis, they had never experienced a problem with either drug. This evidence illustrates that each patient has a unique experience and, as such, access to treatment options is important to achieving the best possible health outcomes.

Being coerced into treatments. Unfortunately, we heard from patients who felt they had no voice and no choice regarding their care. One caregiver described that she felt that her husband (who had received Avastin, Lucentis, and Eylea) was being **"*used as an experiment*."** She emphasized that she needed to speak for her husband because he was worried that if he spoke, the doctors would withhold treatment. Patients living in British Columbia refer to the "cartel" that determines their vision care. Patients described how they have been coerced into taking Avastin; they were told it was Avastin or nothing. One caregiver described how she always accompanied her husband to be sure he was not given Avastin (because he had responded poorly in one eye) – on the day when she could not make the treatment, her husband received Avastin in his good eye, which then became his bad eye. Since then, he has started taking Eylea, but the caregiver was reluctant to describe its effects because she does not know – in part, because it is so difficult to get visual acuity results from the doctor. We also learned that patients and caregivers have trouble accessing their treatment history, so they do not know what kind of anti-VEGF drug is being or has been used. **More than 10% of the respondents to our survey reported that they do not know which drug(s) they are taking.** This result was substantiated in conversations with people who described how difficult it was to ascertain which drug the doctor was using, especially because more than one type was used in one visit.

In general, the effectiveness and side effects of the different anti-VEGF drugs varies from patient to patient. Patients reported experiencing the following side effects:

Eye pain

Dizziness

Blurred vision

Headaches after the injection into the eye

Bleeding in the eye

Floaters

Lost vision/temporary blindness

Feel "little bubbles" in the eye after an injection

Elevated inner eye pressure

Greying vision

"Itchy eyeball"

Severe eye pain

Severe headaches

"Scratches on the eyeball"

These negative side effects often do not often prompt patients to seek alternative treatments because **they feel that other options are not available to them**. For example, a wet-AMD patient who had experienced negative side effects with both Avastin (migraines, vision loss [due to the drug not working], allergic reaction) and Lucentis (including elevated inner eye pressure, greying vision, blurred vision, severe headaches and severe eye pain) reported "*I was told there were no other treatment options in Canada, Eylea is only licensed in the USA*." **It should be noted that there is both research and anecdotal evidence that shows when one drug does not work, switching to another, often does work.** To maximize the treatment effectiveness, patients need access to different types of anti-VEGF treatments.

Equal access to most appropriate treatment needed. Patients are aware of the inequities in access to different anti-VEGF drugs across the country. For example, one wet-AMD patient who had received Avastin in the past and later switched to Lucentis (after it was covered) asked why the government would not pay for Eylea. One of his friends was currently taking Eylea, and he had learned that patients often require less frequent injections, which prompted him to ask: "*Wouldn't the government save money by covering Eylea?"* The same patient described that he was having a positive experience with Lucentis, but did not understand the rationale of limiting Eylea coverage. Another patient expressed her hope that Eylea would be covered so that she would need fewer injections.

The high cost of treatments is a problem. One patient described that before Lucentis was covered it had taken him several months to apply for and receive special authorization from the Alberta Blue Cross Plan. One patient reported her wish that "*our provincial government will cover eye injections and other treatments for patients under the age of 60. Because right now they do not!!!"* Another patient described how her costly treatments were not covered by OHIP, but said that it was worth it because her vision stabilized. Patients in BC described how challenging it was to try and get private coverage for Lucentis and Eylea without needing to go through the "cartel."

The most important issues to patients are restoring vision and preventing further loss of vision. To achieve these goals, patients are willing to risk almost any side effect or procedure. Patients say that their lives "*will not be worth living without vision*." Existing treatment is monthly intraocular injections – patients report fearing injections into their eyes. "*I would be very apprehensive, worried days before. I was so nervous and upset while I waited. Still what was the trade-off?*" Some patients experience pain for hours after treatment, while others do not. The unpredictable nature of these side effects adds to their unease.

Travel to and from appointments can be a major burden for patients and families. Patients, mostly seniors who are already concerned about losing their independence, must depend on family and friends to travel to a specialist to receive monthly eye injections. This is especially true in rural and remote areas. Although many doctors now elect to lengthen the treatment interval over time, the burden of the schedule may lead to suboptimal treatment decisions. *" [After five monthly injections,] I told my doctor I'd have to keep it to [every] two months. It is too hard getting there, you know winter is coming on, and it is a three-hour drive. Then we come right back. The roads are not so good either."*

Impact on Caregivers

Caregivers experience many challenges. They may be needed to act as a sighted guide for people who are blind or partially sighted, and assist them with activities of daily living such as reading, managing medications, testing blood and administering insulin. Caregivers may be asked to take people to multiple doctor's appointments. If complications arise from therapy, the requirements placed on a caregiver can increase.

Impact extends beyond the patient. It is often said that vision loss affects at least one additional family member directly. In order to provide the kind of care needed to help a person with vision loss as described above, a caregiver usually has to take time off work or stop working entirely. The social impact on the caregiver in doing this is significant and the financial cost in terms of lost productivity and earning ability has an additional impact on the economy. Caregivers reported that one of the main challenges was the need to assist with travel to and from clinic appointments. For example, caregivers reported needing to schedule time off from work for this reason. Caregivers also reported that they felt discouragement and even depression around their loved one's loss of independence and inability to do their favourite hobbies. Caregivers also reported that the frequent scheduling of appointments posed challenges for their entire family because it affected their ability to visit relatives who live far away ("*appointments cut visits short*").

Information About New Drugs

Information Gathering

Together, we drew on personal knowledge and experiences working closely with people living with vision loss. We also relied on printed sources and information gathered from presentations and professional conferences, and responses from an online survey.

What Are the Expectations for New Drugs or What Experiences Have Patients Had With New Drugs?

Based on no experience using new drug(s): The vast majority of people whom we gathered information from reported that they were very hopeful that new treatments would be developed to treat their condition. Many hope for a treatment that could be administered at home without the need for an injection. **Yet many respondents felt that they would not have access to new treatments.**

People are hoping for a treatment that is "*more successful and less painful than the present one*." Many people are hoping for a cure – recognizing that the current approaches treat the symptoms, but do not cure the disease.

Based on patients' experiences with new drug(s) as part of a clinical trial or through a manufacturer's compassionate supply: Eylea is particularly appealing to patients, who are often "panicked" about their rapid vision loss and are burdened by the need for frequent injections. The promise from the outset of reduced injection frequency is powerful. Patients are reassured that this is "*the way the drug [Eylea] is supposed to work*" rather than having their doctor watch, wait and experiment with a longer treatment interval, which is what happens with Lucentis, although patients are aware that it is supposed to be administered monthly. None of the patients we spoke with reported side effects, although ophthalmologists with patients on Eylea say the side effects are similar to existing treatments. However, the bi-monthly injection schedule means less exposure

to side effects or injection-related complications. Patients generally see Eylea as a sensible advance that will reduce drug costs for the province, as well as the burden on themselves and their families. In the words of one trial patient who was forced to switch back to monthly treatments of Lucentis at the conclusion of the Eylea trial, "*They give me one shot [of Eylea] every two months and OHIP is way ahead [financially, because they pay for fewer injections]! Why would they throw money away like that?*" Patients receiving Eylea frequently express gratitude, crediting it with saving their vision and facilitating their daily activities. Patients are hopeful for a better future, but question if they are currently receiving the best care because they do not understand how doctors are deciding to use Avastin, Lucentis or Eylea.

APPENDIX 19: PREVIOUS CADTH REVIEWS OF ANTI-VEGF DRUGS FOR RETINAL CONDITIONS

The following table summarizes selected information and data for anti-VEGF drugs reviewed by CEDAC/CDEC and is meant for general information purposes only. No formal indirect comparisons have been performed.

Generic Name (Brand Name)	Indication	Meeting Date	Final Recommendation	Reason(s)
Aflibercept (Eylea)	Macular edema secondary to branch retinal vein occlusion	TBD	TBD	TBD
Aflibercept (Eylea)	Diabetic Macular Edema	April 8, 2015	Listed in a manner similar to ranibizumab Aflibercept should provide cost savings for drug plans relative to ranibizumab for the treatment of DME.	1. Two double-blind randomized controlled trials (RCTs) (VIVID, N = 270; and VISTA, N = 310) demonstrated that aflibercept is superior to laser photocoagulation for improving visual acuity in patients with DME. 2. At the submitted price ($1,418.00 per vial), treatment with aflibercept appears to be less costly than treatment with ranibizumab ($1,575 per vial); however, the extent to which aflibercept is cost-saving depends on the frequency of administration.
Aflibercept (Eylea)	Macular edema secondary to central retinal vein occlusion	April 8, 2015	List with clinical criteria/ conditions Not previously treated with anti-VEGF Aflibercept should provide cost savings for drug plans relative to ranibizumab for the treatment of CRVO	1. Two double-blind, sham-controlled, randomized controlled studies (RCTs) (COPERNICUS, N = 188; and GALILEO, N = 171) suggest that 24 weeks of treatment with 2 mg aflibercept every four weeks is superior to sham injection for improving visual acuity in patients with CRVO. 2. At the submitted price ($1,418.00 per vial), aflibercept appears to be less costly than treatment with ranibizumab ($1,575 per vial); however, the extent to which aflibercept is cost-saving depends on the frequency of administration.

Generic Name (Brand Name)	Indication	Meeting Date	Final Recommendation	Reason(s)
Ranibizumab (Lucentis)	Choroidal Neovascularization Secondary to Pathologic Myopia	January 21, 2015	List with clinical criteria/ conditions Overall drug plan costs for ranibizumab should not exceed those currently allocated to verteporfin photodynamic therapy (vPDT) for patients with pathologic myopia and choroidal neovascularization.	1. One 12-month, double-blind randomized controlled trial (RCT) (RADIANCE; N = 277) demonstrated that treatment with ranibizumab resulted in a statistically significant improvement in best corrected visual acuity (BCVA) compared with vPDT; however, the clinical significance of this difference is uncertain as it did not exceed the minimal clinically important difference (MCID) for this end point. 2. At the submitted price ($1,575.00 per vial), ranibizumab has a lower acquisition cost than verteporfin ($1,704.00) and the administration of ranibizumab ($105 per intravitreal injection) costs less than photodynamic therapy ($330); however, overall treatment costs with ranibizumab could exceed those of vPDT if the mean number of injections per patient exceeds 4.5 in the first year.
Aflibercept (Eylea)	Wet Age-related Macular Degeneration	September 17, 2014	List with clinical criteria and / or conditions Drug plan cost for the treatment of wet AMD with aflibercept should provide cost savings relative to the treatment of wet AMD with ranibizumab.	1. Two double-blind randomized controlled trials (RCTs) (VIEW 1 and VIEW 2) demonstrated that aflibercept is non-inferior and clinically equivalent to ranibizumab for maintaining vision in treatment-naive patients with wet AMD. 2. At the submitted price, treatment of wet AMD with aflibercept appears to be less costly than treatment with ranibizumab.
Ranibizumab (Lucentis)	Macular Edema Secondary to Retinal Vein Occlusion	September 19, 2012	List with clinical criteria and / or conditions Clinically significant macular edema secondary to non-ischemic branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), not previously	1. In two double-masked randomized controlled trials (RCTs) of patients with macular edema secondary to non-ischemic BRVO or CRVO (the BRAVO and CRUISE studies respectively), compared with sham, ranibizumab resulted in statistically significantly greater improvement in best corrected visual acuity at six months. 2. The cost-effectiveness estimates for

Generic Name (Brand Name)	Indication	Meeting Date	Final Recommendation	Reason(s)
			treated with a vascular endothelial growth factor (VEGF) inhibitor. Drug plan coverage limited to 24 months duration, and typically not to exceed 10 or 12 vials for patients with BRVO or CRVO respectively	ranibizumab were sensitive to changes in assumptions regarding the durability of the treatment effect, and the frequency and duration of ranibizumab use. When CDR considered higher numbers of injections, treatment duration beyond two years, and the attenuation of ranibizumab effect following two years of treatment, the incremental cost per quality-adjusted life-year (QALY) estimates exceeded $100,000.
Ranibizumab (Lucentis)	Visual Impairment due to Diabetic Macular Edema	February 15, 2012	List with clinical criteria and / or conditions clinically significant diabetic macular edema for whom laser photocoagulation is also indicated, and A hemoglobin A1c of less than 11%, and Drug plan coverage limited to nine vials per patient.	1. In two randomized controlled trials (RCTs), ranibizumab, with or without concomitant laser photocoagulation, resulted in statistically significantly greater improvement in best corrected visual acuity at 12 months, compared with laser photocoagulation alone. 2. An economic evaluation submitted by the manufacturer reported an incremental cost-utility ratio (ICUR) for ranibizumab plus laser photocoagulation, compared with laser photocoagulation alone, of $33,317 (assuming seven vials used in year one, two vials used in year two). The analysis was sensitive to the frequency and duration of treatment with ranibizumab, with the ICUR increasing to more than $80,000 when the cost of seven vials used in year one and seven vials used in year two was considered in a more conservative scenario by the Common Drug Review (CDR).
Ranibizumab (Lucentis)	Wet Age-related Macular Degeneration	November 21, 2007	List with clinical criteria and / or conditions Drug plan coverage is limited to a maximum of 15 vials per patient used to treat the	1.Compared to verteporfin photodynamic therapy in patients with predominantly classic AMD and best supportive care in patients with minimally classic and occult AMD, ranibizumab has been shown to be more effective in stabilizing and

Generic Name (Brand Name)	Indication	Meeting Date	Final Recommendation	Reason(s)
			better seeing affected eye. Ranibizumab should not be funded in combination with verteporfin.	improving visual acuity. 2.Ranibizumab costs $1,575 per injection. The optimal duration of treatment is uncertain but it is likely that some patients will require indefinite therapy. The manufacturer submitted a cost-utility analysis comparing ranibizumab with best supportive care and/or verteporfin photodynamic therapy by lesion type. This evaluation estimated cost per quality-adjusted life year (QALY) ranging from $4,200 compared to verteporfin photodynamic therapy in predominantly classic AMD to $38,150 compared to best supportive care in occult AMD. The economic evaluation assumed that patients with predominantly classic AMD would only receive ranibizumab treatment for one year and patients with minimally classic and occult AMD would only receive treatment for two years, but that all patients treated with ranibizumab would continue to have better visual acuity than those treated with verteporfin photodynamic therapy or best supportive care after discontinuation of therapy and for the 10 year time horizon of the model. Reanalyses using baseline estimates that the committee felt were more feasible suggested less attractive estimates of cost-effectiveness. Although the model did not allow assessment of the impact of longer-term use of ranibizumab, it is likely that the cost per QALY of ranibizumab will increase substantially if patients require repeat treatment beyond that in the economic evaluation. The manufacturer did not conduct a sensitivity analysis using longer treatment durations. 3.This economic evaluation was also based on a Product Listing Agreement proposed by the

Generic Name (Brand Name)	Indication	Meeting Date	Final Recommendation	Reason(s)
				manufacturer whereby if a patient requires more than nine vials in the first year of treatment, or six vials in subsequent years, the manufacturer would cover the cost of the additional treatment. The condition in the Product Listing Agreement that drug plans would continue to cover the cost of up to six treatments per year after the first two years of therapy is inconsistent with the economic evaluation submitted by the manufacturer. It was the Committee's opinion that the product listing agreement should be consistent with the economic model submitted by the manufacturer; therefore the Committee recommends that drug plan costs be limited to a maximum of 15 vials per patient.
Pegaptanib sodium (Macugen)	Subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration	March 8, 2006	List	1. The Committee considered the results of two identically designed double-masked, randomized controlled trials (RCTs) that compared three doses of pegaptanib (0.3, 1 or 3 mg) with a sham procedure, administered into one eye per patient every six weeks for one year. When compared to the sham treated group, pegaptanib, at the approved dosage of 0.3 mg, resulted in statistically significant improvements in the number of patients who experienced loss of > 3 lines of visual acuity (55% of pegaptanib treated patients vs. 70% of sham treated patients) and the number of patients who gained > 3 lines of visual acuity (6% of pegaptanib treated patients vs. 2% of sham treated patients). The Committee considered loss of patient follow-up too great to assess outcomes beyond one year of treatment. 2. The benefits of pegaptanib on visual acuity were assessed in the study eye only and effects on visual acuity using both eyes are not clear. In

Generic Name (Brand Name)	Indication	Meeting Date	Final Recommendation	Reason(s)
				the one RCT that measured changes in quality of life, there was no significant difference between pegaptanib and sham treated patients. 3. Pegaptanib is administered by intravitreal injection and in the RCTs pegaptanib treated patients developed endophthalmitis (1.3% of patients), retinal detachment (0.7% of patients) and traumatic injury to the lens (0.6% of patients). Health Canada recently advised practitioners about an association between pegaptanib and hypersensitivity reactions, including anaphylaxis/anaphylactoid reactions. 4. Pegaptanib costs $995 per dose or $7,960 per year. The economic model submitted by the manufacturer, which was based on the assumption that patients with decreased visual acuity in one eye would have reductions in survival and quality of life, reported an incremental cost-effectiveness ratio of $59,000 per quality-adjusted life year (QALY) when compared to standard care. However, as there is no evidence that pegaptanib is associated with improvements in quality of life or survival, it is likely that the true cost-effectiveness of pegaptanib will be significantly higher than this. As such, at the current price, the committee did not consider pegaptanib to be cost-effective.

APPENDIX 20: SUMMARY OF SPECIAL RETINAL TREATMENT PROGRAMS IN CANADA

Given the expense of ranibizumab and aflibercept when used as single-use vials as recommended in product monographs and the growing prevalence of retinal conditions in the aging Canadian population, jurisdictional health care payers have begun implementing programs to take advantage of the possibility of vial fractioning as well as the availability of compounded bevacizumab as a viable comparator in an effort to reduce health care expenditure on the treatment of retinal diseases to sustainable levels.

The following program examples are not comprehensive; other retinal disease treatment programs including bevacizumab and/or regulating the fractioning of ranibizumab and aflibercept vials may exist in Canada.

Alberta

As of September 1, 2015, Alberta Health introduced the Retina Anti-VEGF Program for Intraocular Disease (RAPID) Program, which will reimburse $585.50 per dose of ranibizumab and $39.60 per dose of bevacizumab for patients with wet AMD, DME, or RVO. For other retinal indications, only bevacizumab will be reimbursed. A program fee of $104 for the first eye treated and $85.50 for the second eye per injection is also paid to participating prescribers for the implementation and management of electronic recordkeeping as well as the required reporting of serious adverse events to the program.[156] Patients will no longer be charged a $25 copay for intravitreal injections under the RAPID program.[157]

British Columbia

The British Columbia Provincial Retinal Diseases Treatment Program, updated as of April 1, 2015, reimburses ranibizumab, aflibercept, and bevacizumab for the treatment of wet AMD, DME, or RVO.[79] The program (in fiscal year 2015-16) reimburses a maximum of $598.33 per dose of ranibizumab, $409.00 per dose of aflibercept, and $13.13 per dose of bevacizumab, and requires participating ophthalmologists to acquire anti-VEGF drugs only through program-authorized compounding pharmacies as well as to follow supply chain procedures to ensure proper storage and handling of medication doses. All patients utilizing the program, upon providing informed written consent, are registered in a database to allow for clinical outcome assessment including efficacy/effectiveness and adverse events. the program requires participating ophthalmologists to submit records of any ocular adverse events experienced by their patients and any other adverse events suspected to be related to their anti-VEGF therapy. The program recommends specific expected ratios of bevacizumab to ranibizumab and aflibercept use by indication: 90% of wet AMD and RVO patients are expected to receive bevacizumab with the remaining 10% receiving ranibizumab or aflibercept, while 65% of DME patients are expected to receive bevacizumab with the other 35% receiving ranibizumab or aflibercept. Participating ophthalmologists are also entitled to a maximum of $125 per administrations as a program management fee, in addition to the fee paid for the injection procedure, up to a maximum of 2000 such administrations and providing that the global budget of the program is not exceeded.[79] Within the program, a Joint Accountability Committee has a mandate which, while including reviewing the effectiveness and costs of the program, also includes gathering, analyzing, and publishing evidence regarding the efficacy and safety of the drugs reimbursed under the program. The BC Provincial Retinal Diseases Treatment Program was used as an example throughout the economic analyses in this review (see Economics section).

Manitoba

The Winnipeg Regional Health Authority, through the Misericordia Health Centre, reimburses ranibizumab, aflibercept, and bevacizumab for the treatment of wet AMD, DME, RVO, and retinopathy of prematurity within specific clinical criteria.[158]

New Brunswick

The New Brunswick Prescription Drug Program reimburses vials of ranibizumab for the treatment of wet AMD and DME and aflibercept for the treatment of wet AMD, DME, and CRVO.[159] In addition, bevacizumab as an intravitreal injection is reimbursed as a general benefit when prescribed by an ophthalmologist.[160]

APPENDIX 21: DATA EXTRACTION FROM COST-EFFECTIVENESS STUDIES

TABLE 28: COST-UTILITY ANALYSIS OF AFLIBERCEPT VERSUS RANIBIZUMAB OR BEVACIZUMAB IN PATIENTS WITH WET AMD

Study	Elshout 2014[94]
Sponsorship	ZonMw (Netherlands org for health research and development , government & research org commissioned)
Country	Netherlands
Perspectives	Societal. Third party payer as sensitivity analysis.
Study type	Cost-utility
Comparators	Aflibercept q2m versus: Beva PRN Beva monthly Rani PRN Rani monthly No treatment
Populations	Simulated patients with characteristics based on pivotal trials and cross-sectional Dutch study of wet AMD patients. 2-eye model (affected eye is not usually better seeing)
Time horizon	2 and 5 years
Type of model	Patient-level Monte Carlo simulating 1,000 patients (no cycle)
Efficacy inputs	Pivotal trials (VIEW 1&2, CATT, ABC, MARINA).
Adverse events	Endophthalmitis, retinal detachment, lens injury, retinal hemorrhage appear to only be considered as additional costs rather than also having disutility effects.
Utilities	Dutch cross-sectional in wet AMD patient study by same authors; linear regression of HUI-3 quality of life scores with visual acuity of better seeing eye.
Resource use	Direct Dutch treatment costs (drug, diagnostic, administration, follow-up), Indirect costs from Dutch cross-sectional study (transportation, home care, nursing home, assistance services, moving house). Values inflated to 2012 euros.
Discounting	Costs: 4% per annum, outcomes: 1.5% in accordance with Dutch standards for CEA.
Outcomes	Costs and QALYs of aflibercept to comparators and all comparators to no treatment.

<table>
<tr><td>Results</td><td>Aflibercept is similarly effective to ranibizumab as needed but €9,461 less expensive over 5 years. Aflibercept is also similarly effective to bevacizumab PRN (from ABC trial), but costs €16,663 more over 5 years.

<table>
<tr><td rowspan="2">Treatment</td><td rowspan="2">Schedule</td><td colspan="2">2 years</td><td colspan="2">5 years</td><td rowspan="2">€ / QALY over no treatment</td></tr>
<tr><td>QALYs</td><td>Cost (€)</td><td>QALYs</td><td>Cost (€)</td></tr>
<tr><td>Aflibercept</td><td>Every 2 months (VIEW 1&2)</td><td>1.02</td><td>17,963</td><td>2.15</td><td>36,030</td><td>140,274</td></tr>
<tr><td rowspan="3">Bevacizumab</td><td>PRN (ABC)</td><td>1.01</td><td>8,427</td><td>2.16</td><td>19,367</td><td>51,062</td></tr>
<tr><td>PRN (CATT)</td><td>1.02</td><td>12,664</td><td>2.17</td><td>26,746</td><td>83,256</td></tr>
<tr><td>Monthly (CATT)</td><td>1.01</td><td>13,021</td><td>2.15</td><td>30,520</td><td>110,361</td></tr>
<tr><td rowspan="2">Ranibizumab</td><td>PRN (CATT)</td><td>1.01</td><td>19,919</td><td>2.16</td><td>45.491</td><td>181,667</td></tr>
<tr><td>Monthly (MARINA)</td><td>1.01</td><td>31,706</td><td>2.15</td><td>74,837</td><td>349,773</td></tr>
<tr><td>No treatment</td><td>(Literature review)</td><td>0.96</td><td>3,298</td><td>1.96</td><td>9,530</td><td>Ref</td></tr>
</table></td></tr>
<tr><td>Types of sensitivity analysis</td><td>Univariate: include one or both eyes, direct costs only, time horizon switch, altered treatment effect, costs, utilities.
Multivariate analyses were run using similar grouped assumptions. A PSA was run based on new values for appropriate probabilistic parameters</td></tr>
<tr><td>Sensitivity analysis results</td><td>CEAC curve suggested no treatment most likely to be CE up to WTP€44,000 (2-eye model), with Beva PRN most likely to be CE thereafter.

Aflib PRN became cost-equivalent to beva PRN when used every 19 weeks (CATT beva data) or every 38 weeks (ABC study data) assuming efficacy remained the same.

Cost-effectiveness of aflibercept compared to no treatment drops from €140,000 to around €20,000 (roughly extracted from tornado plot) when only better seeing eye included.</td></tr>
<tr><td>Study limitations/ considerations</td><td>Dutch setting, societal perspective
2-eye model is interesting, but may not match Canadian clinical practice
Drug efficacy taken from different trials without formal analysis by indirect comparison
Authors noted clinical trial data unlikely to reflect clinical practice.</td></tr>
</table>

TABLE 29: COST-UTILITY ANALYSES OF RANIBIZUMAB VERSUS BEVACIZUMAB IN PATIENTS WITH WET AMD

<table>
<tr><td>Study</td><td>Dakin 2014[82] CE within IVAN trial</td></tr>
<tr><td>Sponsorship</td><td>NIHR HTA Programme (full HTA not yet published)</td></tr>
<tr><td>Country</td><td>UK</td></tr>
<tr><td>Perspectives</td><td>UK National Health Service</td></tr>
<tr><td>Study type</td><td>CUA (within a factorial, non-inferior RCT) with pre-specified criteria to do CMA
• CUA for monthly versus PRN due to small incremental costs
• CMA for rani versus beva unless rani accrued QALYs ≥ 0.5 over 2 years due to large cost difference</td></tr>
<tr><td>Comparators</td><td>Ranibizumab 0.5 mg monthly or PRN
Bevacizumab 1.25 mg monthly or PRN</td></tr>
<tr><td>Populations</td><td>610 patients aged ≥ 50 years with untreated wet AMD in study eye
Setting: 23 hospital ophthalmology clinics</td></tr>
<tr><td>Time horizon</td><td>2 years. No cycle time.</td></tr>
<tr><td>Type of model</td><td>Linear regression models with nonparametric bootstrapping, Kaplan-Meier sample averaging and Rubin’s rule to combine quarterly costs and QALYs accrued by each patient to estimate mean total costs and QALYs of each of four treatment arms</td></tr>
<tr><td>Efficacy inputs</td><td>Direct QoL measures within RCT, see “Utilities”</td></tr>
<tr><td>Adverse events</td><td>SAE directly measured within RCT and assigned an instant EQ-5D utility decrement which then linearly improves to expected levels over time</td></tr>
<tr><td>Utilities</td><td>EQ-5D measured at baseline, 3, 12, and 24 months, after SAEs and after any ≥ 15 letter drop in ETDRS letters between consecutive visits. HUI3 also used at all measurements for sensitivity analysis, missing data imputed.</td></tr>
<tr><td>Resource use</td><td>Monitoring consultations, number of injections, drug costs, drug administration, hospitalizations, ambulatory consultations and medication changes for expected SAEs/AEs. Costs are reported in 2011 pounds sterling, accompanied by equivalents in US dollars (exchange rate: $1.57/pound).
Excluded protocol-driven resource use</td></tr>
<tr><td>Discounting</td><td>3.5% in year 2.</td></tr>
<tr><td>Outcomes</td><td>CUA: Cost per QALY
CMA: Drug, administration, and resource use costs (including medications and hospitalizations resulting from AEs expected to be caused by treatment). Protocol-driven costs not included (i.e., testing costs only include if they would affect treatment decisions).</td></tr>
<tr><td>Results</td><td>CMA used for ranibizumab versus bevacizumab as difference in mean QALYs between ranibizumab and bevacizumab was within the pre-specified non-inferiority margin (0.05 QALYs).

<table>
<tr><td></td><td>Mean Total 2-year cost</td><td>Mean Total 2-year QALYs</td><td>Total Net Benefit (£20,000/QALY ceiling ratio)</td></tr>
<tr><td>Monthly Rani</td><td>£18,590</td><td>1.608</td><td>£13,576</td></tr>
<tr><td>PRN Rani</td><td>£11,500</td><td>1.582</td><td>£20,142</td></tr>
<tr><td>Monthly Beva</td><td>£3,601</td><td>1.604</td><td>£28,480</td></tr>
<tr><td>PRN beva</td><td>£3,002</td><td>1.584</td><td>£28,683</td></tr>
</table>

PRN Beva 63% likely to be most CE at WTP £20,000, with 37% chance monthly beva is most CE. 50/50 at WTP £30,000.

Monthly Beva dominated PRN Rani, and monthly rani compared with PRN rani is £270,217/QALY gained. Threshold analysis: rani would need to be reduced to</td></tr>
</table>

	£63.46 (91%) per dose for monthly ranibizumab to be CE compared to monthly bevacizumab at WTP £20,000.
Types of sensitivity analysis	Univariate SA analyses include revisions to: time horizon, drug cost, wastage assumptions, administration and monitoring costs, SAE profile, utility values, and mortality assumptions.
Sensitivity analysis results	No SA resulted in rani becoming CE over bevacizumab, including halving rani price. SAs that resulted in monthly beva becoming CE compared to PRN beva included: Fluorescein angiography included only at baseline not for monitoring, using HUI3 instead of EQ-5D, altering assumptions on deaths deemed unrelated to study drugs (which prevented chance difference affecting incremental QALYs).
Study limitations/ considerations	• Uses data from a single trial, no need for indirect comparison although does not take advantage of all available data • UK setting in £, may not be transferrable to a Canadian setting • Direct HRQoL measuring without separately accounting for vision state (BVCA category)? • Substantial uncertainty around use of PRN beva and sensitivity analyses suggested that the cost-effectiveness of using continuous (monthly) treatment rather than PRN may vary between centres.

<table>
<tr><td>Study</td><td>Stein 2014[91]</td></tr>
<tr><td>Sponsorship</td><td>National Eye Institute Award, grant from National Institute of Diabetes and Digestive and Kidney Diseases, unrestricted grant and award from Research to Prevent Blindness (public charity)</td></tr>
<tr><td>Country</td><td>USA</td></tr>
<tr><td>Perspectives</td><td>Societal.</td></tr>
<tr><td>Study type</td><td>CEA/CUA</td></tr>
<tr><td>Comparators</td><td>Monthly bevacizumab
PRN bevacizumab
Monthly ranibizumab
PRN ranibizumab</td></tr>
<tr><td>Populations</td><td>Hypothetical cohort of 80-year-old patients with newly diagnosed wet AMD</td></tr>
<tr><td>Time horizon</td><td>20 years</td></tr>
<tr><td>Type of model</td><td>Markov model, 5 health states based on visual acuity plus a death state. Cycle length not stated.</td></tr>
<tr><td>Efficacy inputs</td><td>BVCA from CATT at years 1 and 2, base case assumed BCVA distribution remains at year 2 level thereafter</td></tr>
<tr><td>Adverse events</td><td>CVAs, MIs, and VTEs tracked from CATT data leading to increased costs, QoL decline and increased mortality risk (doubled after MI or CVA) for remainder of life. Also tracked blindness due to endophthalmitis. Age-adjusted mortality from US life tables incorporated.</td></tr>
<tr><td>Utilities</td><td>Utility score by BCVA category from Brown 2003, disutilities due to AEs from literature</td></tr>
<tr><td>Resource use</td><td>Direct costs of managing wet AMD (physician visits, testing, treatments, side effects/adverse event costs, professional fees, facility fees using data from CMS and Red Book. Costs adjusted to 2012 US dollars.
Number of visits and injections informed by CATT.</td></tr>
<tr><td>Discounting</td><td>3% annually.</td></tr>
<tr><td>Outcomes</td><td>Cost per QALY
ICERs</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td>Treatment</td><td>Mean Cost (US$) over 20 years</td><td>Mean QALYs</td><td>ICER versus PRN beva (per QALY)</td></tr>
<tr><td>PRN beva</td><td>$65,267</td><td>6.60</td><td>Ref</td></tr>
<tr><td>Monthly beva</td><td>$79,771</td><td>6.66</td><td>$242,357</td></tr>
<tr><td>PRN rani</td><td>$163,694</td><td>6.64</td><td>Dominated</td></tr>
<tr><td>Monthly rani</td><td>$257,496</td><td>6.68</td><td>$10,708,377</td></tr>
</table>
Base case without systemic AEs (i.e., infections considered similar between arms) increases CE of bevacizumab over ranibizumab

Base Case excluding cost of OCT & visit for monthly patients (no test as no effect on treatment decision)
<table>
<tr><td>Treatment</td><td>Mean Cost (US$) over 20 years</td><td>Mean QALYs</td><td>ICER versus monthly beva</td></tr>
<tr><td>Monthly Beva</td><td>$55,261</td><td>6.66</td><td>Ref</td></tr>
<tr><td>PRN Beva</td><td>$65,267</td><td>6.60</td><td>Dominated</td></tr>
<tr><td>PRN Rani</td><td>$163,694</td><td>6.64</td><td>Dominated</td></tr>
<tr><td>Monthly Rani</td><td>$233,108</td><td>6.68</td><td>$10,715,692</td></tr>
</table>
</td></tr>
</table>

Types of sensitivity analysis	One-way and two-way deterministic SAs: Vary rani cost and risk of systemic side effects, varying utility of severe vision loss, varying long-term effectiveness of anti-VEGF, varying drug costs, varying AE risk rates, Varying beva costs and risk of endophthalmitis, varying number of rani injections PSA (10,000 iterations)
Sensitivity analysis results	PSA: CEAC shows Beva strategies most likely to be CE at WTPs <US$600,000. PRN beva most CE 62% of simulations at WTP $100,000, with monthly beva preferred in around 18-20%. Rani CE 50% of time at WTP $1million. One- and two-way deterministic SAs support the base case results that rani is not CE compared to beva at acceptable WTP thresholds
Study limitations/ considerations	• US study, may not be generalizable to Canadian setting • All results reported in terms of WTP US$100,000 • Extrapolates 2-year data to 20-year horizon; base case visual acuity remains stable after 2 years of treatment, sensitivity analysis only reported results if bevacizumab patients declined after two years and ranibizumab patients remained stable. • 80 year old population may be higher than average age of wet AMD diagnosis in Canada, possibly leading to more conservative cost-effectiveness estimates than could be seen in clinical practice. • Uses data from single study, no issues with heterogeneity but does not take advantage of all available data. • Assumption that BCVA is an acceptable surrogate for the impact of neovascular AMD on overall HRQL

Study	Patel 2012[93]
Sponsorship	"All authors have nothing to disclose for this project", all authors employed by Veterans Affairs San Diego Healthcare System
Country	USA
Perspectives	US payer perspective
Study type	Cost-utility analysis
Comparators	Monthly 1.25 mg bevacizumab, monthly 0.5 mg ranibizumab
Populations	65-year-old cohort of hypothetical patients with wet AMD
Time horizon	20 years
Type of model	Markov model incorporating four health states: stable vision, worsening vision, improved vision, death. 3 month long cycles with half-cycle correction.
Efficacy inputs	Ranibizumab derived from MARINA and ANCHOR trials. Bevacizumab derived from four clinical trials and institutional-derived data from Veterans Affairs San Diego Healthcare System (VASDHS).
Adverse events	Mortality based on CDC, otherwise not mentioned
Utilities	Adapted for three visual acuity health state model from Brown et al. 2000, which used time-trade-off method.
Resource use	2006 VASDHS Decision Support System cost data, 2006 Medicare National Physician Fee Schedule, 2007 Red Book for drug prices, 2007 US dollars.
Discounting	3% per annum on costs only
Outcomes	Cost per QALY
Results	Bevacizumab total direct treatment cost was $30,349 per patient with mean average of 21.60 QALYS. Ranibizumab total direct treatment cost was $220,649 per patient with mean average of 18.12 QALYs. Bevacizumab CER reported as $1,405/QALY; ranibizumab as $12,177/QALY. ICER: bevacizumab dominated ranibizumab
Types of sensitivity analysis	One-way deterministic sensitivity analyses on transition probabilities, utility weights, drug costs. PSA using cohort of 10,000 simulations for transition probabilities, utility weights, drug costs.
Sensitivity analysis results	Ranibizumab would have equal cost-effectiveness to bevacizumab if its price were reduced to $44 per injection (bevacizumab is $50). Bevacizumab would have equal cost-effectiveness to ranibizumab if its price were raised to $2,666 per injection (ranibizumab is $2,000). PSA showed bevacizumab had a 95% probability of being most cost-effective at WTP = $50,000/QALY.
Study limitations/ considerations	• Absence of large-scale randomized, placebo-controlled clinical efficacy data for beva; or direct head-to-head data comparing bevacizumab to ranibizumab. • No NMA or indirect treatment comparison performed; transitions derived from different sources. Utilities adapted from different concept model. • QALY results do not seem possible given time horizon and utility values. How is a mean of 21.60 QALYs gained over 20 years, or a mean of 18.12 QALYs when the highest utility in the model is 0.89 (upper range of improved vision)? • Inappropriate calculation of cost-effectiveness ratios; using total cost divided by total QALYs assumes that all QALYs are a result of treatment. No accounting for QALYs derived if patients received placebo, best supportive care, or no treatment. • US health care system perspective; costs and clinical practice may differ substantially from Canada. • CEAC implies that bevacizumab has a 100% probability of being cost-effective at WTP = $0/QALY. This is only true relative to ranibizumab and does not consider a no-treatment scenario (which is the likely preference if WTP truly is $0).

Study	Nwanze 2012[92]
Sponsorship	National Library of Medicine, MIH, Leir Foundation, Newman's Own Foundation
Country	USA
Perspectives	Health care system
Study type	Cost-utility
Comparators	Monthly ranibizumab, PRN ranibizumab, monthly bevacizumab, PRN bevacizumab
Populations	Simulated cohort of 65 year old patients with AMD with baseline characteristics from CATT trial
Time horizon	10 years of treatment
Type of model	Markov model. No cycle time specified.
Efficacy inputs	CATT trial (first year), MARINA trial (two years of follow-up data to model the gains in vision for the monthly bevacizumab treatment groups with regression used to model to 10 years),
Adverse events	As reported in CATT trial. Mortality rates derived from the 2007 United States Life Table
Utilities	Not reported
Resource use	CATT trial for PRN frequencies, drug cost, resource utilization; related DRGs for health care costs from Healthcare Cost and Utilization Project of AHRQ for associated costs. 2011 US Dollars
Discounting	3% per annum on costs and utilities
Outcomes	Cost-effectiveness ratios for each treatment, thresholds for CE of ranibizumab versus bevacizumab regarding cost of treating AEs, frequency of AEs, relative cost of treatment, multiples of relative effectiveness
Results	Monthly Ranibizumab: $63,333/QALY PRN ranibizumab: $18,571/QALY Monthly Bevacizumab: $2,676/QALY PRN Bevacizumab: $3,333/ QALY Methodology unclear, as QALY gains are not reported. CE of PRN ranibizumab equals PRN bevacizumab when cost of treating AEs increases by a factor of 19.1, monthly ranibizumab equals monthly bevacizumab when AE cost increases by factor of 71 A 27.5% increase in the efficacy of monthly ranibizumab relative to monthly bevacizumab improves cost-effectiveness of ranibizumab to $50,000/ QALY. PRN ranibizumab needs to be 553% more effective than monthly bevacizumab to be as cost-effective, and 692% as effective as PRN bevacizumab to be as cost-effective. To meet a WTP of $50,000 per QALY, monthly ranibizumab would have to be priced at $1,560 a dose, and priced at $50.42 a dose to match the cost-effectiveness of bevacizumab.
Types of sensitivity analysis	None reported explicitly though analyses using different time horizons, different aged cohorts, lower ranibizumab prices reported, and change in efficacy.
Sensitivity analysis results	Young cohorts (50 years-old) improve the CE of ranibizumab but was insufficient to improve the CE of monthly ranibizumab to the $50,000/ QALY threshold Similarly, cost/ QALY decreases as the time horizon of the treatment is increased, implying improved cost-effectiveness as the treatment horizon increases At a 78% price reduction monthly ranibizumab meets the $50,000/QALY benchmark Authors also assessed change in efficacy

Study limitations/ considerations	• Unclear methodology and inputs as QALY gains and costs per treatment are not reported, only CERs. Utility values not reported. Relative efficacy between treatments unclear. • US costs for drugs and AE treatments, may not be transferrable to Canadian setting • Lack of long-term direct evidence

TABLE 30: COST-UTILITY ANALYSIS OF AFLIBERCEPT VERSUS RANIBIZUMAB FOR THE TREATMENT OF DME

Study	**Regnier 2015[95]**
Sponsorship	Novartis Pharmaceuticals UK
Country	UK
Perspectives	UK health care
Study type	CUA
Comparators	Aflibercept 2 mg every 8 weeks after 5 initial monthly doses Ranibizumab 0.5 mg when needed (PRN) Ranibizumab 0.5 mg treat-and-extend (T&E)
Populations	UK patients with DME; baseline characteristics based on those in RESTORE trial.
Time horizon	Lifetime (patients treated for 3 years, followed by natural history decline from the WESDR study)
Type of model	Markov – 8 health states based on visual acuity + absorbing death state. 3-month cycle length with half-cycle correction
Efficacy inputs	Efficacy for 3 years of rani PRN was from RESTORE trial. Relative efficacy of aflibercept in year 1 was from a published NMA by same authors comparing it to rani PRN. Rani T&E in year 1 was estimated by adding the RETAIN non-inferiority trial to the NMA. These efficacy parameters informed the model transition probabilities. Transition probabilities in years 2 and 3 were assumed equal between all three treatments.
Adverse events	Assumed equal.
Utilities	BSE utilities were from Czoski-Murray (range 0.497 between best and worst vision states), while for WSE a decrement of 0.1 was assumed between the best and worst vision states. Assumption for calculating utilities based on the 2013 ranibizumab for DME appraisal by NICE
Resource use	Drug costs (NICE) and monitoring costs (UK Dept of Health, NICE). Monitoring frequency was from RESTORE in year 1 and DRCR.net thereafter for rani PRN, assumed for rani T&E and from VIVID/VISTA for aflib 2q8. Costs presented in UK pounds (no date specified)
Discounting	3.5% per annum (costs and QALYs)
Outcomes	Cost per QALY, net monetary benefit
Results	Base case results showed both rani arms having greater QALYs and less cost than aflib. Rani PRN showed the highest net monetary benefit.

Drug	Total cost (£)	Total QALY	Inc cost (£)	Inc QALY	NMB (£)
Aflib 2q8	25,859	8.54	Ref	Ref	
Rani PRN	20,019	8.59	-5,841	0.05	6,768
Rani T&E	22,930	8.59	-2,930	0.05	3,934

NMB WTP = £20,000/QALY

Types of sensitivity analysis	Deterministic SAs: Rani PRN vs. aflib OR of gaining ≥ 10 letters, aflib pricing, # injections, monitoring cost, monitoring visits, OR = 1. Probabilistic SA (1,000 iterations) to test multivariate parameter uncertainty
Sensitivity analysis results	Model was most sensitive to changes in the relative OR of gaining ≥ 10 letters, as well as changes in the price of aflibercept and the number of ranibizumab injections over 3 years. Probabilistic: CEACs showed rani PRN had a 79% probability and rani T&E had a 67% probability of being cost-effective compared to aflib 2q8 at WTP = £20,000/QALY.
Study Limitations / Considerations	• Study lacks comparative efficacy data between ranibizumab 0.5 mg PRN and aflibercept 2q8 after year 1. • Newer evidence from Protocol T trial suggests aflibercept may be more effective than ranibizumab at least in DME patients with low baseline vision, which is not in line with the QALY advantage given to ranibizumab in this model. • UK costs, where ranibizumab is reportedly less expensive per vial than aflibercept, which differs from Canadian public prices. • Set in UK, which may not be generalizable to the Canadian setting • Year 1 Efficacy/transition probabilities were taken from differing sources rather than the same meta-analysis between treatment arms. • Costs appear to be from various years depending on source, no attempt to standardize to a specific year reported

TABLE 31: RETROSPECTIVE DATABASE STUDY COMPARING AFLIBERCEPT AND RANIBIZUMAB COSTS IN PATIENTS WITH WET AMD

Study	**Johnston 2013**[96]
Sponsorship	Genetech Inc.
Country	USA
Perspectives	Health care payer (90% of patients were under Medicare)
Study type	Retrospective cohort and cost analysis
Comparators	Ranibizumab, aflibercept
Populations	Patients with 12 months continuous insurance enrolment before index date, initiating first-line intravitreal anti-VEGF treatment for wet AMD between Nov 18 2011 (Eylea approval date) and Apr 30 2013
Time horizon	6 and 12 months
Type of model	Multivariable Poisson quasi-likelihood regressions to compare number of injections adjusting for a priori patient demographics and clinical characteristics. No cycle time.
Efficacy inputs	None
Adverse events	None
Utilities	None
Resource use	Measured health care expenditures on anti-VEGF injections over time period, from Truven Health Market Scan Commercial Claims and Encounters and Medicare Supplemental databases. Costs reported in US dollars (no date specified)
Discounting	None
Outcomes	Frequency of injections, expenditure on injections, interval between injections
Results	Overall mean days between injections were 42.4 for aflibercept and 40.6 for ranibizumab. 6 month analysis n=319 aflibercept, 1,054 ranibizumab. Unadjusted mean injections: 3.8 aflibercept, 3.9 ranibizumab, regression incidence rate ratio aflib versus rani was 0.97 (0.91-1.03, p=0.277) Unadjusted mean expenditure: $7,468 aflibercept, $7,816 ranibizumab. Regression cost ratio = 0.96 (0.89-1.04, p=0.338) 12 month analysis n=57 aflibercept and 374 ranibizumab Unadjusted mean injections 5.5 aflibercept, 5.8 ranibizumab, regression IRR = 0.95 (0.79-1.14, p=0.582) Unadjusted mean expenditure: $11,052 aflibercept, $11,342 ranibizumab. Regression cost ratio = 0.92, 0.74-1.13, p=0.429) Conclusions: similar use despite monograph guidelines. Similar costs.
Types of sensitivity analysis	Univariate SAs including patients using ranibizumab before aflibercept approved
Sensitivity analysis results	Similar to main analysis, with slightly fewer injections and expenditures.
Study limitations/ considerations	• US expenditures and costs; may not be generalizable to the Canadian setting • No consideration of relative health outcomes • Real-world data rather than a model • Funded by ranibizumab manufacturer, thus an interest in showing aflibercept is not used less frequently than ranibizumab. • 12 month maximum follow-up, results may differ over longer term

	• Drug coding (HCPCS) may not be accurate, relies on algorithms to determine coding before a certain date at which coding was introduced separately for aflibercept and ranibizumab. • The study is based on administrative data, which are not specifically collected for research purposes, and subject to coding and measurement errors.

TABLE 32: RETROSPECTIVE COHORT STUDIES COMPARING AFLIBERCEPT AND RANIBIZUMAB COSTS IN PATIENTS RECEIVING INTRAVITREAL INJECTIONS (NOT INDICATION-SPECIFIC)

Study	**Reich 2015**[97]
Sponsorship	Novartis (no direct involvement)
Country	Switzerland
Perspectives	Single large health insurance group in Switzerland
Study type	Cost analysis informed by retrospective database review
Comparators	Ranibizumab, aflibercept
Populations	Patients with at least 12 months of continuous insurance enrolment initiating (no aflibercept or ranibizumab in previous 12 months) ranibizumab or aflibercept treatment for one eye only through ambulatory care between Dec 1 2012 and Nov 20 2013 who had at least 6 months of follow-up
Time horizon	Six months after index date
Type of model	Multivariate linear logistic regression analysis (no cycle time)
Efficacy inputs	None
Adverse events	None
Utilities	None
Resource use	Database expenditures
Discounting	None
Outcomes	Health care expenditure (on drug, hospitalizations, physician visits, number of anti-VEGF injections); Drug costs; Number of injections
Results	Unadjusted mean health care expenditure was CHF 13,856 for ranibizumab and CHF 13,484 for aflibercept (p=0.961). Unadjusted mean anti-VEGF drug costs CHF 4,102 for ranibizumab, CHF 4,155 for aflibercept (p=0.568) Unadjusted mean number of injections in 6 months 3.86 for ranibizumab and 3.91 for aflibercept (p=0.570). Ranibizumab patients had significantly more chronic conditions and a higher number of total drug prescriptions. Multivariate regression adjusting for demographics and potential confounders determined no sig diff in number of injections between comparators.
Types of sensitivity analysis	None
Sensitivity analysis results	None
Study limitations/ considerations	• Funded by Lucentis manufacturer, interest in finding no frequency difference. • No accounting of relative efficacy or quality of life between comparators • 6-month follow-up, results may differ over longer term • Swiss costs and practices, may not be generalizable to Canadian setting • The nature of the study (retrospective database review) limited opportunity to assess impact of potential confounders (e.g., differences in demographics between groups – age – and differences in age linked to differences in the number of injections, differences in prescribing patterns) • Could not assess results by indication • Based on administrative data which are not specifically collected for research purposes, and subject to coding and measurement errors

<table>
<tr><td>Study</td><td>Schmid 2015[98]</td></tr>
<tr><td>Sponsorship</td><td>Authors employed by Helsana Health Insurance Company, Unrestricted grant from Novartis</td></tr>
<tr><td>Country</td><td>Switzerland</td></tr>
<tr><td>Perspectives</td><td>Payer perspective (assumption based on “compare the reimbursed treatment costs and clinical outcomes”)</td></tr>
<tr><td>Study type</td><td>Cost analysis informed by retrospective database review</td></tr>
<tr><td>Comparators</td><td>Ranibizumab or Aflibercept PRN based on OCT.</td></tr>
<tr><td>Populations</td><td>Patients from large public ophthalmology clinic receiving anti-VEGF treatment with underlying condition being AMD. If underlying condition differed (DME or RVO) this was noted. Primary analysis limited to AMD patients</td></tr>
<tr><td>Time horizon</td><td>Mean follow-up was 37.4 months (results were reported in costs/month)</td></tr>
<tr><td>Type of model</td><td>Multivariate linear regression model (no cycle time)</td></tr>
<tr><td>Efficacy inputs</td><td>None</td></tr>
<tr><td>Adverse events</td><td>None</td></tr>
<tr><td>Utilities</td><td>None</td></tr>
<tr><td>Resource use</td><td>Health care claims (drug, OCT, consumables, medical consultation, total number of injections).
Currency: CHF (though cost date not specified)</td></tr>
<tr><td>Discounting</td><td>None</td></tr>
<tr><td>Outcomes</td><td>Global costs, ophthalmologic costs</td></tr>
<tr><td>Results</td><td>• “two currently licensed anti-VEGF medications do not differ in clinical outcomes, injection frequency and costs.”
<table>
<tr><th>Treatment comparison (AMD) Amounts in Swiss francs</th><th>All (std dev)</th><th>Ranibizumab versus aflibercept (95% CI)*</th><th>P value</th></tr>
<tr><td>Avg global cost/month</td><td>1,712 (1,305)</td><td>-680 (-2053 to 693)</td><td>0.330</td></tr>
<tr><td>Avg ophthalmologic cost/month</td><td>1,351 (886)</td><td>-264 (-1164 to 635)</td><td>0.563</td></tr>
</table>
* adjusted for age, gender, baseline visual acuity, number of injections
• Mean injections per month were 0.43 (SD 0.31) for ranibizumab and 0.52 (SD 0.13) for aflibercept (p=0.560).</td></tr>
<tr><td>Types of sensitivity analysis</td><td>Excluding number of injections as a covariate, excluding patients with less than 6 months of follow-up,</td></tr>
<tr><td>Sensitivity analysis results</td><td>No change to results</td></tr>
<tr><td>Study Limitations / Considerations</td><td>• Small sample (241 patients with AMD included in anti-VEGF comparison).
• Only 5 patients received de novo aflibercept, 40 others were switched from ranibizumab and had a higher treatment intensity. These 40 were excluded from analysis.
• No comparison possible between drugs for DME or RVO.
• States that clinical outcomes did not differ under main findings, but does not present clinical outcome results.
• Based on administrative data which are not specifically collected for research purposes, and subject to coding and measurement errors</td></tr>
</table>

APPENDIX 22: DRUG PLAN BENEFIT LISTINGS FOR ANTI-VEGF DRUGS FOR RETINAL CONDITIONS (NOVEMBER 2015)

Bevacizumab (Avastin)													
Indication	**BCΩ**	**AB**	**SK**	**MB**	**ON**	**NB**	**NS**	**PEI#**	**NL**	**YK**	**NWT**	**NIHB/ NU**	**DND**
Neovascular (wet) age-related macular degeneration (AMD)*	NB	NB	NB	RES	NB	RES	RES	NB	UR	RES	-	EX	NB
Diabetic macular edema (DME)*	NB	NB	NB	RES	NB	RES	RES	NB	UR	RES	-	EX	NB
Treatment of visual impairment due to macular edema secondary RVO (CRVO or BRVO)*	NB	NB	NB	RES	NB	RES	RES	NB	UR	RES	-	EX	NB
Visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM)*	NB	NB	NB	RES	NB	RES	NB	NB	UR	RES	-	EX	NB
Other Uses: e.g. proliferative diabetic retinopathy (PDR)*	NB	NB	NB	EX∞	NB	RES	NB	NB	UR	RES	-	EX	NB

* No NOC granted for these indications;

Ω Coverage provided through the BC Provincial Retinal Diseases Treatment Program;

∞Retinopathy of prematurity for compassionate use in the neonatal nursery;

Avastin may be used in Ambulatory Care; indications not known or approved by PEI Pharmacare

Legend: BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; EX= Exception item for which coverage is determined on a case-by-case basis; FB= Full benefit; NB=Note a benefit; NOC = notice of compliance; RES=Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit), UR=under review; – = information not available

Ranibizumab (Lucentis)

Indication	BC[Ω]	AB	SK	MB	ON	NB	NS	PEI	NL	YK	NWT	NIHB/ NU	DND
Neovascular (wet) age-related macular degeneration (AMD)	NB	RES	RES	RES	RES	RES	RES	RES	RES	RES	-	RES	RES
Diabetic macular edema (DME)	NB	RES	RES	RES	RES	RES	RES	NB	RES	RES	-	RES	NB
Treatment of visual impairment due to macular edema secondary RVO (CRVO or BRVO)	NB	RES	RES	RES	RES	UR	RES	NB	RES	RES	-	RES	NB
Visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM)	NB	NB	RES	RES	RES	UR	NB	NB	UR	RES	-	RES	NB
Other Uses: e.g. proliferative diabetic retinopathy (PDR)*	NB	NB	NB	EX[∞]	NB	-	NB	NB	NB	RES	-	EX	NB

* No NOC granted for these indications;
[Ω] Coverage provided through the BC Provincial Retinal Diseases Treatment Program;
[∞] Retinopathy of prematurity for compassionate use in the neonatal nursery;
Legend: BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; EX= Exception item for which coverage is determined on a case-by-case basis; FB= Full benefit; NB=Note a benefit; NOC = notice of compliance; RES=Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit), UR=under review; – = information not available

Aflibercept (Eylea)													
Indication	**BC[Ω]**	**AB**	**SK**	**MB**	**ON**	**NB**	**NS**	**PEI**	**NL**	**YK**	**NWT**	**NIHB/ NU**	**DND**

Neovascular (wet) age-related macular degeneration (AMD)	NB	UR	RES	RES	RES	RES	RES	RES	RES	RES	-	EX	NB
Diabetic macular edema (DME)	NB	UR	RES	RES	RES	RES	RES	NB	RES	RES	-	EX	NB
Treatment of visual impairment due to macular edema secondary RVO (CRVO or BRVO)	NB	UR	RES	RES	RES	RES	RES	NB	RES	RES	-	EX	NB
Visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM)*	NB	-	NB	RES	NB	-	NB	NB	NB	RES	-	EX	NB
Other Uses: e.g. proliferative diabetic retinopathy (PDR)*	NB	-	NB	EX[∞]	NB	-	NB	NB	NB	RES	-	EX	NB

* No NOC granted for these indications;
[Ω] Coverage provided through the BC Provincial Retinal Diseases Treatment Program;
[∞] Retinopathy of prematurity for compassionate use in the neonatal nursery
Legend: BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; EX= Exception item for which coverage is determined on a case-by-case basis; FB= Full benefit; NB=Note a benefit; NOC = notice of compliance; RES=Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit), UR=under review; – = information not available

LISTING CRITERIA AND INFORMATION ON PROVIDER OF PRODUCT

BC	Coverage of bevacizumab, ranibizumab and aflibercept is provided through the BC Provincial Retinal Diseases Treatment Program, which is managed by the Provincial Health Services Authority (PHSA), when these drugs are prescribed and administered by retinal specialists. Coverage for these three drugs is provided for the following indications: Wet Age-related Macular Degeneration (wet AMD); Diabetic Macular Edema (DME); and Retinal Vein Occlusion (RVO). The Program has been developed with input from PHSA and representatives of the retinal specialist group in BC. Retinal specialists registered with the Program provide the Program services throughout the province. Health providers/optometrists can refer new patients directly to the Program retinal specialists for diagnosis and treatment. Program retinal specialists enter patient information/treatment data into a unique Program database. The database is used for monitoring, planning, and management of the Program and includes monitoring safety and effectiveness of each treatment dose administered. Program pharmacies provide drug product to the retinal specialist offices directly. Program pharmacies are reimbursed by the Program. The choice of drug used is up to the clinician based upon their clinical judgement and discussions with their patient.
AB	RANIBIZUMAB (LUCENTIS): "For the treatment of visual impairment due to macular edema secondary to retinal vein occlusion (RVO). Treatment to be given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on ranibizumab treatment. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to macular edema secondary to RVO and continued until stable visual

	acuity is reached again for three consecutive monthly assessments." "For the treatment of diabetic macular edema (DME), in patients with severe visual impairment as defined by: Best-Corrected Visual Acuity (using the Early Treatment Diabetic Retinopathy Study visual acuity test) of seventy-eight (78) to twenty-four (24) letters and a central retinal thickness greater than or equal to three hundred (300) micrometres meeting all of the following criteria: - clinically significant diabetic macular edema for whom laser photocoagulation is also indicated, and - a hemoglobin A1c of less than or equal to 11%." "For the treatment of neovascular (wet) age-related macular degeneration (AMD) if all of the following apply to the eye to be treated: • The best corrected visual acuity (BCVA) is between 6/12 (20/40) and 6/96 (20/320); and • There is active disease activity (choroidal neovascularization) and no permanent structural damage to the central fovea; and • The lesion size is less than or equal to twelve (12) disc areas in greatest linear dimension; and • There is evidence of recent (< three (3) months) presumed disease progression (blood vessel growth, as indicated by fluoroscein angiography, optical coherence tomography (OCT) or recent visual acuity changes); and • No concurrent verteporfin PDT treatment; and • The injection will be administered by a qualified ophthalmologist with experience in intravitreal injections. Treatment with ranibizumab should be continued only in patients who maintain adequate response to therapy. Ranibizumab should be discontinued if any of the following occur: • Reduction in BCVA in the treated eye to less than fifteen (15) letters (absolute) on two (2) consecutive visits in the treated eye, attributed to AMD in the absence of other pathology; or • Reduction in BCVA of thirty (30) letters or more compared to either baseline and/or best recorded level since baseline as this may indicate either poor treatment effect or adverse event or both; or • There is evidence of deterioration of the lesion morphology despite optimum treatment over three (3) consecutive visits." The interval between the doses should be no less than one (1) month. Note: Since October 1, 2015, with the introduction of the Retina Anti-Vascular Endothelial Growth Factor Program for Intraocular Disease (RAPID) program, patients residing in Alberta who have a retinal condition have access to both ranibizumab (Lucentis) and bevacizumab (Avastin) for the treatment of age-related macular degeneration (AMD), diabetic macular edema (DME), retinal vein occlusion (RVO) and other retinal conditions.
SK	RANIBIZUMAB (LUCENTIS): For the treatment of neovascular (wet) age-related macular degeneration (AMD) if all of the following circumstances apply to the eye to be treated:

	• The best corrected visual acuity (BCVA) is between 6/12 and 6/96 • The lesion size is less than or equal to 12 disc areas in greatest linear dimension • There is evidence of recent (< 3 months) presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, optical coherence tomography (OCT) or recent visual acuity changes) • Injection will be by a qualified ophthalmologist with experience in intravitreal injections Coverage will not be provided for patients: • With permanent structural damage to the central fovea or no active disease (as defined in the Royal College of Ophthalmology guidelines). • Receiving concurrent verteporfin PDT treatment. The interval between the doses should be no shorter than one month. Treatment with ranibizumab should be continued only in people who maintain adequate response to therapy. Ranibizumab should be permanently discontinued if any one of the following occurs: • Reduction in BCVA in the treated eye to less than 15 letters (absolute) on 2 consecutive visits in the treated eye, attributed to AMD in the absence of other pathology • Reduction in BCVA of 30 letters or more compared to either baseline and/or best recorded level since baseline and/or best recorded level since baseline as this may indicate either poor treatment effect or adverse event or both. • There is evidence of deterioration of the lesion morphology despite optimum treatment over 3 consecutive visits. For the treatment of visual impairment due to Diabetic Macular Edema (DME) for patients meeting all of the following: • Diffuse DME involving the central fovea with central fovea thickness of 300 microns or greater on optical coherence tomography (OCT) and vision less than 20/32. • Patients with focal macular edema for which laser photocoagulation is indicated should be treated with laser, except in situations where focal laser therapy treatment can not be safely performed due to the proximity of microaneurysms to the fovea. • A haemoglobin A1c of less than 11%. • Treatment to be given monthly for three consecutive treatments. Treatment should be discontinued if there is no improvement of retinal thickness on OCT or if there is no improvement in visual acuity after three consecutive treatments. • Patients responding to treatment should be monitored at regular intervals up to monthly for visual acuity AND retinal thickness. • Treatment should be resumed with monthly injections when monitoring indicates a loss in visual acuity and increase in retinal thickness and continued until stable visual acuity and improvement in retinal thickness is reached again for three consecutive monthly assessments. • Treatment should be discontinued if there is no improvement of retinal thickness or visual acuity after three consecutive treatments. • Injection will be by a qualified ophthalmologist with experience in intravitreal injections. Note: Fluorescein Angiography (FA) should be considered prior to initiation of treatment to assess perfusion and characterize the leakage, and should also be considered if the patient is not responding to treatment as expected. For the treatment of visual impairment due to clinically significant macular edema secondary to non-ischemic branch retinal vein occlusion (BRVO) or central retinal vein

	occlusion (CRVO) for patients meeting all of the following: • Diffuse RVO with macular thickness of 300 microns or greater on Optical Coherence Tomography (OCT) and a vision of 20/40 or less. • Treatment is to be given monthly until edema is resolved or there is no further improvement with three consecutive treatments. • Patients should be monitored at regular intervals up to monthly for retinal thickness and visual acuity. • Treatment should be resumed if there is a recurrence of macular edema with macular thickness greater than 300 microns or loss of visual acuity, and continued until stable visual acuity and improvement in retinal thickness is reached again for three consecutive assessments. • Treatment should be discontinued if there is no improvement after 6 months of initial treatment. • Injection will be by a qualified ophthalmologist with experience in administering intravitreal injections. For treatment of visual impairment due to choroidal neovascularization secondary to pathologic myopia. Must be administered by a qualified ophthalmologist with experience in intravitreal injections. Note: Fluorescein Angiography (FA) should be considered prior to initiation of treatment to assess perfusion and characterize the leakage, and should also be considered if the patient is not responding to treatment as expected. Grid Laser photocoagulation can also be considered for BRVO at the discretion of the treating ophthalmologist. AFLIBERCET (EYLEA) For the treatment of neovascular (wet) age-related macular degeneration (AMD) if all of the following circumstances apply to the eye to be treated: • The best corrected visual acuity (BCVA) is between 6/12 and 6/96 • The lesion size is less than or equal to 12 disc areas in greatest linear dimension • There is evidence of recent (< 3 months) presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, optical coherence tomography (OCT) or recent visual acuity changes); • Injection will be by a qualified ophthalmologist with experience in intravitreal injections Coverage will not be provided for patients: • With permanent structural damage to the central fovea or no active disease (as defined in the Royal College of Ophthalmology guidelines); • Receiving concurrent verteporfin PDT treatment. The interval between the doses should be no shorter than one month. Treatment with aflibercept should be continued only in people who maintain adequate response to therapy. Aflibercept should be permanently discontinued if any one of the following occurs: • Reduction in BCVA in the treated eye to less than 15 letters (absolute) on 2 consecutive visits in the treated eye, attributed to AMD in the absence of other pathology • Reduction in BCVA of 30 letters or more compared to either baseline and/or best recorded level since baseline, as this may indicate either poor treatment effect or adverse event or both • There is evidence of deterioration of the lesion morphology despite optimum treatment over three consecutive visits.

	For the treatment of visual impairment due to Diabetic Macular Edema (DME) for patients meeting all of the following: • Diffuse DME involving the central fovea with central fovea thickness of 300 microns or greater on optical coherence tomography (OCT) and vision less than 20/32. • Patients with focal macular edema for which laser photocoagulation is indicated should be treated with laser, except in situations where focal laser therapy treatment can not be safely performed due to the proximity of microaneurysms to the fovea. • A haemoglobin A1c of less than 11%. • Treatment should be discontinued if there is no improvement of retinal thickness on OCT or if there is no improvement in visual acuity after five consecutive treatments. • The interval between two doses should not be shorter than one month. • Patients responding to treatment should be monitored at regular intervals up to monthly for visual acuity AND retinal thickness. • Injection will be by a qualified ophthalmologist with experience in intravitreal injections. Note: Fluorescein Angiography (FA) should be considered prior to initiation of treatment to assess perfusion and characterize the leakage, and should also be considered if the patient is not responding to treatment as expected. For the treatment of visual impairment due to clinically significant macular edema secondary to central retinal vein occlusion (CRVO) for patients meeting all of the following: • Diffuse CRVO with macular thickness of 300 microns or greater on Optical Coherence Tomography (OCT) and a vision of 20/40 or less. • The interval between two doses should not be shorter than one month. • Patients should be monitored at regular intervals up to monthly for retinal thickness and visual acuity. • Treatment should be discontinued if there is no improvement after 6 months of initial treatment; • Injection will be by a qualified ophthalmologist with experience in administering intravitreal injections. Note: Fluorescein Angiography (FA) should be considered prior to initiation of treatment to assess perfusion and characterize the leakage, and should also be considered if the patient is not responding to treatment as expected.
MB	These products are funded by Manitoba Health but supplied through the Winnipeg Regional Health Authority's Intravitreal Program at the Misericordia Hospital Eye Clinic.
ON	Ranibizumab (Lucentis) Listing Criteria <u>AMD</u> For the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) in a verteporfin PDT (Visudyne)-naive eye. Initial diagnosis should be confirmed by an appropriate diagnostic procedure and administration should be done by a qualified ophthalmologist experienced in Intravitreal injections. Patients receiving concurrent administration of verteporfin PDT (Visudyne) or aflibercept (Eylea) are not eligible for reimbursement. Treatment should be initiated with a loading phase of one injection per month for three consecutive months, followed by a maintenance phase. During the maintenance phase, patients should be

	monitored for best corrected visual acuity or continued disease activity. If there is clinical or diagnostic evidence of disease activity such as a loss of greater than 5 letters in visual acuity (Early Treatment Diabetic Retinopathy Score (ETDRS) chart or one Snellen line equivalent), Lucentis may be administered. The interval between two doses should not be shorter than one month. Treatment with anti-VEGF agents should only be continued in patients who maintain adequate response to therapy. For clarity, coverage will be provided for patients responding to therapy with Eylea who switch to Lucentis. Coverage will NOT be provided for patients who have failed to respond to Eylea. DME For the treatment of patients with clinically significant diabetic macular edema (DME) for whom laser photocoagulation is also indicated; and a hemoglobin A1c of less than 11 percent. Treatment to be given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on Lucentis treatment. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to DME and continued until stable visual acuity is reached again for three consecutive monthly assessments. Treatment with anti-VEGF agents should only be continued in patients who maintain adequate response to therapy. For clarity, coverage will be provided for patients responding to therapy with Eylea who switch to Lucentis. Coverage will NOT be provided for patients who have failed to respond to Eylea. BRVO/CRVO For the treatment of patients with clinically significant macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Treatment to be given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on Lucentis treatment. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to macular edema secondary to retinal vein occlusion and continued until stable visual acuity is reached again for three consecutive monthly assessments. Treatment with anti-VEGF agents should only be continued in patients who maintain adequate response to therapy. For clarity, coverage will be provided for patients responding to therapy with Eylea who switch to Lucentis. Coverage will NOT be provided for patients who have failed to respond to Eylea. CNV For the treatment of patients with visual impairment due to choroidal neovascularization secondary to pathologic myopia.Treatment is initiated with a single intravitreal injection. Monitoring is recommended monthly for the first 2 months and at least every 3 months thereafter during the first year. If monitoring reveals signs of disease activity (e.g. reduced visual acuity and/or signs of lesion activity), further treatment is recommended at a frequency of 1 injection per month until no disease activity is seen. Aflibercept (Eylea) Listing Criteria AMD For the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) in a verteporfin PDT (Visudyne)-naive eye. Initial diagnosis should be confirmed by an appropriate diagnostic procedure and administration should be done by a qualified ophthalmologist experienced in intravitreal injections. Patients receiving concurrent administration of verteporfin PDT (Visudyne) or ranibizumab (Lucentis) are not eligible for reimbursement. Treatment should be initiated with a monthly intravitreal injection for the first 3 consecutive doses, followed by one injection every 2 months. The interval between two doses should not be shorter than one month. Treatment with anti-VEGF agents should only be continued in patients who maintain adequate response to therapy. For clarity, coverage will be provided for patients responding to therapy with Lucentis who switch to Eylea. Coverage will NOT be provided for patients who have failed to respond to Lucentis.

	DME For the treatment of patients with clinically significant diabetic macular edema (DME) for whom laser photocoagulation is also indicated; and a hemoglobin A1c of less than 12 percent. Treatment should be initiated with a monthly intravitreal injection for the first 5 consecutive doses, followed by one injection every 2 months. The interval between two doses should not be shorter than one month. Treatment with anti-VEGF agents should only be continued in patients who maintain adequate response to therapy. For clarity, coverage will be provided for patients responding to therapy with Lucentis who switch to Eylea. Coverage will NOT be provided for patients who have failed to respond to Lucentis. BRVO/CRVO For the treatment of patients with clinically significant macular edema secondary to central retinal vein occlusion (CRVO). Treatment should be initiated with an intravitreal injection once every month. The interval between two doses should not be shorter than one month. The treatment interval may be extended up to 3 months based on visual and anatomic outcomes. Prescribers are advised to periodically assess the need for continued therapy. Treatment with anti-VEGF agents should only be continued in patients who maintain adequate response to therapy. For clarity, coverage will be provided for patients responding to therapy with Lucentis who switch to Eylea. Coverage will NOT be provided for patients who have failed to respond to Lucentis.
NB	Bevacizumab (Avastin) Avastin for intravitreal injection is covered as a full benefit when prescribed by a New Brunswick ophthalmologist Ranibizumab (Lucentis) 1. Neovascular (wet) age-related macular degeneration (AMD) Initial Coverage: For the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) where all of the following apply to the eye to be treated: • Best Corrected Visual Acuity (BCVA) is between 6/12 and 6/96 • The lesion size is less than or equal to 12 disc areas in greatest linear dimension • There is evidence of recent (< 3 months) presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or optical coherence tomography (OCT) • Administration is to be done by a qualified ophthalmologist experienced in intravitreal injections. • The interval between doses should not be shorter than 1 month. Continued Coverage: • Treatment with ranibizumab should be continued only in people who maintain adequate response to therapy. Clinical Notes: • Coverage will not be approved for patients: o With permanent retinal damage as defined by the Royal College of Ophthalmology guidelines o Receiving concurrent treatment with verteporfin. • Ranibizumab should be permanently discontinued if any one of the following occurs:

	○ Reduction in BCVA in the treated eye to less than 15 letters (absolute) on 2 consecutive visits in the treated eye, attributed to AMD in the absence of other pathology ○ Reductions in BCVA of 30 letters or more compared to either baseline and/or best recorded level since baseline as this may indicate either poor treatment effect, adverse events or both. ○ There is evidence of deterioration of the lesion morphology despite optimum treatment over 3 consecutive visits. Claim Notes: • An initial claim of up to two vials of ranibizumab (one vial per eye treated) will be automatically reimbursed when prescribed by an ophthalmologist. If additional medication is required, a request should be made through special authorization. • The NBPDP will limit reimbursement to a maximum of 1 vial of ranibizumab per eye treated every 30 days. Claims submitted for greater than 1 vial, or submitted within 30 days of a previous claim will not be reimbursed. • Please refer to Quantities for Claims Submissions for the correct unit of measure. 2. Diabetic macular edema (DME) Initial coverage: For the treatment of visual impairment due to diabetic macular edema (DME) in patients who meet all of the following criteria: • clinically significant centre-involving macular edema for whom laser photocoagulation is also indicated • hemoglobin A1c test in the past 6 months with a value of less than or equal to 11% • best corrected visual acuity of 20/32 to 20/400 • central retinal thickness greater than or equal to 250 micrometers Renewal Criteria: • confirm that a hemoglobin A1c test in the past 6 months had a value of less than or equal to 11% • date of last visit and results of best corrected visual acuity at that visit • date of last OCT and central retinal thickness on that examination • if ranibizumab is being administered monthly, please provide details on the rationale Clinical Notes: • Treatment should be given monthly until maximum visual acuity is achieved (i.e. stable visual acuity for three consecutive months while on ranibizumab). Thereafter, the patient's visual acuity should be monitored monthly. Treatment should be resumed when monitoring indicates a loss of visual acuity due to DME until stable visual acuity is reached again for three consecutive months. Claim Notes: • Approval Period: 1 year • Please refer to Quantities for Claims Submissions for the correct unit of measure. Aflibercept (Eylea)

1. Neovascular (wet) age-related macular degeneration (AMD)

Initial Coverage:

For the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) where all of the following apply to the eye to be treated:

- Best Corrected Visual Acuity (BCVA) is between 6/12 and 6/96
- The lesion size is less than or equal to 12 disc areas in greatest linear dimension
- There is evidence of recent (< 3 months) presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or optical coherence tomography (OCT)
- Administration is to be done by a qualified ophthalmologist experienced in intravitreal injections.
- The interval between doses should not be shorter than 1 month.

Continued Coverage:

Treatment should be continued only in people who maintain adequate response to therapy.

Clinical Notes:

- Coverage will not be approved for patients: - With permanent retinal damage as defined by the Royal College of Ophthalmology guidelines
    - Receiving concurrent treatment with verteporfin.
- Aflibercept should be permanently discontinued if any one of the following occurs:
    - Reduction in BCVA in the treated eye to less than 15 letters (absolute) on 2 consecutive visits in the treated eye, attributed to AMD in the absence of other pathology
    - Reductions in BCVA of 30 letters or more compared to either baseline and/or best recorded level since baseline as this may indicate either poor treatment effect, adverse events or both.
    - There is evidence of deterioration of the lesion morphology despite optimum treatment over 3 consecutive visits.

Claim Notes:

- An initial claim of up to two vials of aflibercept (1 vial per eye treated) will be automatically reimbursed when prescribed by an ophthalmologist. If additional medication is required, a request should be made through special authorization.
- Reimbursement will be limited to a maximum of 1 vial of aflibercept per eye treated every 30 days. Claims submitted for greater than 1 vial, or submitted within 30 days of a previous claim, will not be reimbursed.
- Please refer to Quantities for Claims Submissions for the correct unit of measure.

2. Diabetic macular edema (DME)

Initial coverage:

For the treatment of visual impairment due to diabetic macular edema (DME) in patients who meet all of the following criteria:

- clinically significant centre-involving macular edema for whom laser photocoagulation is also indicated
- hemoglobin A1c test in the past 6 months with a value of less than or equal to 11%
- best corrected visual acuity of 20/32 to 20/400
- central retinal thickness greater than or equal to 250 micrometers

	Renewal Criteria: • confirm that a hemoglobin A1c test in the past 6 months had a value of less than or equal to 11% • date of last visit and results of best corrected visual acuity at that visit • date of last OCT and central retinal thickness on that examination • if aflibercept is being administered monthly, please provide details on the rationale Clinical Notes: • Treatment should be given monthly until maximum visual acuity is achieved (i.e. stable visual acuity for three consecutive months while on aflibercept). Thereafter, visual acuity should be monitored monthly. • Treatment should be resumed when monitoring indicates a loss of visual acuity due to DME and continued until stable visual acuity is reached again for three consecutive months. Claim Notes: • Approval Period: 1 year • Please refer to Quantities for Claims Submissions for the correct unit of measure. Central retinal vein occlusion (CRVO) For the treatment of visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO). Clinical Notes: • Treatment should be given monthly until maximum visual acuity is achieved (i.e. stable visual acuity for three consecutive months while on aflibercept). Thereafter, visual acuity should be monitored monthly. • Treatment should be resumed when monitoring indicates a loss of visual acuity due to macular edema secondary to central retinal vein occlusion and continued until stable visual acuity is reached again for three consecutive months. Claim Notes: • Approval Period: 1 year • Please refer to Quantities for Claims Submissions for the correct unit of measure.
NS	Access for Nova Scotia Provincial Pharmacare clients is through specific hospital eye clinics. The hospital pharmacy supplies the medication directly to the specialists who work in the clinic. There is a form used at this clinic by the retinal specialists for the Nova Scotia Provincial Pharmacare clients. Criteria for wet age-related macular degeneration: INITIAL PHASE Patient must meet all of the following criteria. Initial loading phase consists of one dose per month per treated eye for three months. • Best Corrected Visual Acuity (BCVA) is greater than 6/96

	• The lesion size is ≤ 12 disc areas in greatest linear dimension • There is evidence of recent (<3 months) presumed disease progression [blood vessel growth, as indicated by fluorescein angiography, optical coherence tomography (OCT), or recent visual acuity changes] • There is active disease activity and no permanent structural damage to the central fovea (as defined in the Royal College of Ophthalmologists guidelines) MAINTENANCE PHASE Patient must meet all of the following criteria. Limited to one dose per month per treated eye. • Evidence of continued disease activity • Maintaining adequate response to therapy • Absolute BCVA maintained above 6/120 • Reductions in BCVA of < 6 lines compared to either baseline and/or best recorded level since baseline Criteria for diabetic macular edema: • Clinically significant, centre involving • BCVA >6/120 Criteria for retinal vein occlusion: • Clinically significant, centre involving • BCVA >6/120 • CRVO BRVO
PEI	Same criteria for Lucentis and Eylea: For the treatment of the better seeing affected eye for patients with neovascular (wet) age-related macular degeneration (AMD) where all of the following apply to the eye to be treated: Criteria For Initial Coverage (loading dose for 3 consecutive months): a. Best Corrected Visual Acuity (BCVA) is between 6/12 and 6/96 AND b. The lesion size is less than or equal to 12 disc areas in greatest linear dimension AND c. There is evidence of recent (<3 months) presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, optical coherence tomography (OCT), or recent visual acuity changes. The interval between doses should not be shorter than one month. Administration is to be done by a qualified ophthalmologist experienced in intravitreal injections. Criteria For Continued Coverage: Treatment with ranibizumab/aflibercept should be continued only in people who maintain adequate response to therapy.

	Ranibizumab/Aflibercept should be discontinued if any of the following occur: a. Reduction in BCVA in the treated eye to less than 15 letters (absolute) on 2 consecutive visits in the treated eye, attributed to AMD in the absence of other pathology OR b. Reductions in BCVA of 30 letters or more compared to either baseline and/or best recorded level since baseline as this may indicate either poor treatment effect, adverse events, or both OR c. There is evidence of deterioration of the lesion morphology despite optimum treatment over 3 consecutive visits. Coverage will not be approved for patients: a. Receiving concurrent treatment with verteporfin. b. With permanent retinal damage as defined by the Royal College of Ophthalmology guidelines. Coverage is limited to a maximum of one vial for the better seeing affected eye in any 30 day period. Coverage must be renewed every 12 months. The request for coverage must be made by an ophthalmologist. Note: Patients must also apply for coverage through the High-Cost Drug Program. The request for coverage must be made by an ophthalmologist. Patients obtain their supply from the pharmacy which then bills the drug plan. Some ophthalmologists are using Avastin through the hospital setting in clinics for treatment of wet AMD. Avastin is not a benefit under PEI Pharmacare, but may be provided at no charge through hospital.

NL	RANIBIZUMAB (LUCENTIS 2.3 MG/0.23 ML VIAL)
	Neovascular (wet) age-related macular degeneration (AMD):
	• A diagnosis of neovascular (wet) age-related macular degeneration (AMD);
	  ○ Ocular Coherence Tomography (OCT) is recognized by the NLPDP as a relevant diagnostic test for wet AMD;
	• Evidence of recent (< 3months) disease progression (e.g. blood vessel growth, as indicated by either fluorescein angiography, OCT or recent visual acuity changes);
	• A corrected Visual acuity between 6/12 and 6/96;
	  ○ Patients falling outside of the proposed VA criterion can be considered by the NLPDP on a case-by-case basis.
	• A lesion whose size is less than or equal to 12 disc areas in its greatest linear dimension;
	• When there is no permanent structural damage to the central fovea.
	
	Note: Any NLPDP beneficiary, who meets the above criteria, will have their drug plan coverage limited to a maximum of 15 vials used to treat the better seeing affected eye.
	
	Criteria for Exclusion:
	• Patients who have “permanent retinal damage”, as defined by the Royal College of Ophthalmology guidelines, including any future amendments.

	Diabetic Macular edema (DME): For the treatment of visual impairment due to diabetic macular edema meeting all of the following criteria: • clinically significant diabetic macular edema for whom laser photocoagulation is also indicated, and • a hemoglobin A1c of less than 11%, and • drug plan coverage limited to nine vials per patient Macular edema secondary to retinal vein occlusion (RVO): For the treatment of visual impairment due to macular edema secondary to retinal vein occlusion in patients meeting both of the following criteria: • clinically significant macular edema secondary to non-ischemic branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), not previously treated with a vascular endothelial growth factor (VEG-F) inhibitor • drug plan coverage will be limited to 24 months duration AND not to exceed 10 vials for non-ischemic branch retinal vein occlusion (BRVO) or 12 vials for patients with central retinal vein occlusion (CRVO). Exclusion: Coverage is not considered for clients who have reached NLPDP coverage limits on another ophthalmic antineovascularization agent. Note: For DME and wet AMD, coverage can be considered for switching between ophthalmic antineovascularization agents if coverage limit has not been reached. Coverage will be for the number of vials remaining within the coverage limit. AFLIBERCEPT (EYLEA 2 MG/0.05 ML VIAL) Neovascular (wet) age-related macular degeneration (AMD): • A diagnosis of neovascular (wet) age-related macular degeneration (AMD); o Ocular Coherence Tomography (OCT) is recognized by the NLPDP as a relevant diagnostic test for wet AMD; • Evidence of recent (< 3months) disease progression (e.g. blood vessel growth, as indicated by either fluorescein angiography, OCT or recent visual acuity changes); • A corrected Visual acuity between 6/12 and 6/96; o Patients falling outside of the proposed VA criterion can be considered by the NLPDP on a case-by-case basis. • A lesion whose size is less than or equal to 12 disc areas in its greatest linear dimension; • When there is no permanent structural damage to the central fovea. Note: Any NLPDP beneficiary, who meets the above criteria, will have their drug plan coverage limited to a maximum of 15 vials used to treat the better seeing affected eye. Criteria for Exclusion: • Patients who have “permanent retinal damage”, as defined by the Royal College of Ophthalmology guidelines, including any future amendments.

	Diabetic Macular edema (DME): For the treatment of visual impairment due to diabetic macular edema meeting all of the following criteria: • clinically significant diabetic macular edema for whom laser photocoagulation is also indicated, and • a hemoglobin A1c of less than 11%, and • drug plan coverage limited to nine vials per patient Macular edema secondary to retinal vein occlusion (RVO): For the treatment of visual impairment due to macular edema secondary to central retinal vein occlusion in patients meeting both of the following criteria: • clinically significant macular edema secondary to central retinal vein occlusion (CRVO), not previously treated with a vascular endothelial growth factor (VEG-F) inhibitor • drug plan coverage will be limited to 24 months duration AND not to exceed 12 vials for patients with central retinal vein occlusion (CRVO). Exclusion: Coverage is not considered for clients who have reached NLPDP coverage limits on another ophthalmic antineovascularization agent. Note: For DME and wet AMD, coverage can be considered for switching between ophthalmic antineovascularization agents if coverage limit has not been reached. Coverage will be for the number of vials remaining within the coverage limit.
YK	All three drugs have the same criteria in Yukon's formulary: "On recommendation of a specialist for age-related macular degeneration, or diabetic macular edema, or visual impairment due to macular edema secondary to central vein occlusion."
NWT	-----
NIHB/NU	Ranibizumab (Lucentis): Criteria for coverage of Ranibizumab for DME and w-AMD. Note: Coverage will be limited to a maximum of 1 vial of Lucentis per eye treated every 30 days. Administered by a qualified ophthalmologist experienced in intravitreal injections. Interval between doses not shorter than 1 month. For the treatment of diabetic macular edema (DME) for patients who meet the following: • Clinically significant diabetic macular edema for whom laser photocoagulation is also indicated; AND • Have a hemoglobin A1c of less than 11% For the treatment of neovascular wet age-related macular degeneration (wAMD) where all of the following apply to the eye to be treated: • Best Corrected Visual Acuity (BCVA) is between 6/12 and 6/96. • The lesion size is less than or equal to 12 disc areas in greatest linear dimension. • There is evidence of recent (< 3 months) presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or optical coherence tomography (OCT)).

	Note: Coverage will not be approved for patients: • With permanent retinal damage as defined by the Royal College of Ophthalmology guidelines. • Receiving concurrent treatment with verteporfin.
DND	LUCENTIS: Requests for special authorization are considered for members diagnosed with neovascular (wet) age-related macular degeneration (AMD). Limited to a maximum of 15 vials per patient lifetime
CSC	Avastin or Lucentis are not listed on the CSC formulary. Requests are treated on an individual case by case basis through our non-formulary review process.

Legend: AB = Alberta, BC = British Columbia, DND = Department of National Defense; MB = Manitoba; NB = New Brunswick; NIHB = Non-Insured Health Benefits; NL = Newfoundland and Labrador; NS = Nova Scotia; NU = Nunavut; NWT = North West Territories; ON = Ontario; PEI = Prince Edward Island; SK = Saskatchewan

APPENDIX 23: ADDITIONAL SAFETY EVIDENCE FOR BEVACIZUMAB

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To provide a summary of published studies that assessed the safety of bevacizumab against other anti-VEGFs or control groups.

Methods

The literature search was performed by an information specialist. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were bevacizumab and the relevant retinal conditions. A methodological filter was applied to limit retrieval to safety data. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year, but was limited to the English language. The search was completed on November 11, 2015.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following section of the Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): advisories and warnings. Google and other Internet search engines were used to search for additional web-based materials.

In addition to the findings from our search, we also added all studies identified to us as safety-related from the stakeholder feedback. Studies were screened for inclusion according to the following criteria:

Study primary outcome was related to assessing bevacizumab safety;

Study assessment of bevacizumab safety was conducted in either a comparative fashion, or in descriptive manner along with another anti-VEGF agent;

Full-text of the study is available, conference abstracts and abstracts with no associated full-text will be excluded.

Outcomes of included studies were categorized as either ‘cardiovascular events’ (which included adverse events related to embolism, thrombosis, stroke, myocardial infarction, transient ischemic attack, bleeding, or any other systemic serious adverse event) or ‘ophthalmic events’ (related to endophthalmitis, uveitis, or retinal detachment).

Results

A flow diagram of included studies is presented in Figure 20. Findings from the review were summarized in Table 33.

FIGURE 20: FLOW DIAGRAM OF INCLUDED STUDIES

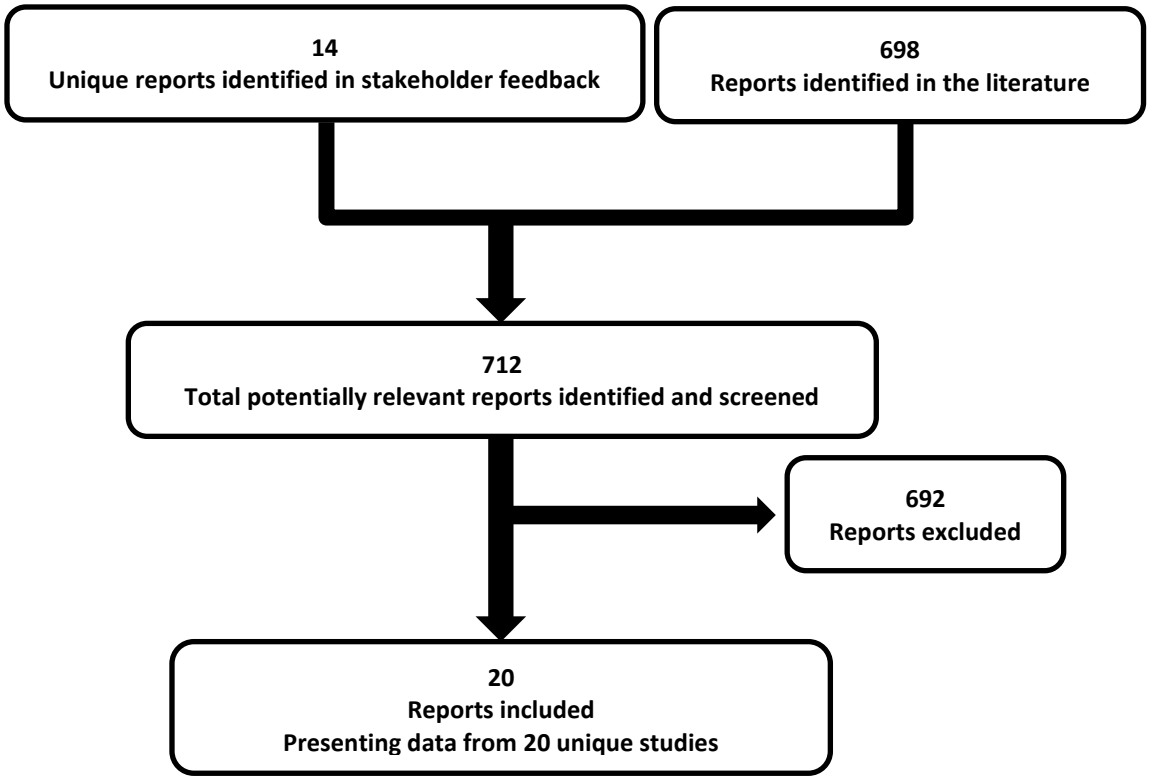


TABLE 33: OVERVIEW OF IDENTIFIED SAFETY STUDIES

Studies identified through literature search

Study	Methods	Disease	Size	Intervention	Comparison	Significant increase in the risk of cardiovascular events	Significant increase in the risk of ophthalmic events	Notes / Reference
Biagi, 2014	Database analysis	AMD	3,180 patients	Bevacizumab	Ranibizumab or pegaptanib	No	No	Bevacizumab was compared to patients that received either ranibizumab or pegaptanib / [137]
Campbell, 2012a	Population database analysis	AMD	116,388 patients	Bevacizumab	Rate of stroke hospitalization pre and post market availability	No	NA	Time series analysis for the rate of hospital admission due to ischemic stroke / [134]
				Ranibizumab		No		
Campbell, 2012b	population based, nested case-control	Retinal disease	91,378 patients	Bevacizumab	Control	No	NA	In the diabetes subgroup analysis, one significant association between MI and bevacizumab was noted when compared to ranibizumab control (OR = 1.76, 95%CI 1.03 to 3.00). / [133]
					Ranibizumab	Mostly No (see notes)		
Carneiro, 2011	Chart based, retrospective cohort	AMD	378 patients	Bevacizumab	Ranibizumab	Yes (see notes)	NA	Arterial thromboembolic events OR = 10.16 (95%CI 2.80 to 36.93) / [132]
Curtis, 2010	Population database, retrospective cohort	AMD	146,942 patients	Bevacizumab	Photodynamic therapy	No	NA	No difference in MI, bleeding, or unadjusted stroke. Adjusted HR of Ranibizumab vs. Bevacizumab in stroke HR = 0.78 (95%CI 0.64 to 0.96). Adjusted all-cause mortality HR = 0.86 (95%CI 0.75 to
				Bevacizumab	Pegaptanib	No		
				Bevacizumab	Ranibizumab	Yes		

Studies identified through literature search								
Study	**Methods**	**Disease**	**Size**	**Intervention**	**Comparison**	**Significant increase in the risk of cardiovascular events**	**Significant increase in the risk of ophthalmic events**	**Notes / Reference**
								0.98) / [131]
Fintak, 2008	Database, multicentre case-series	Retinal disease	12,585 injections	Bevacizumab Ranibizumab	NA (see notes)	NA	No (see notes)	A descriptive study of the incidence of endophthalmitis: with Bevacizumab = 0.02% (95%CI 0.00 to 0.06) with Ranibizumab = 0.02% (95%CI 0.00 to 0.07) / [161]
Fischer, 2013	Database, retrospective case-control	AMD	130 patients	Bevacizumab	Control	No (see notes)	NA	Significant increase in hospitalization rate. No significant increase in arteriothrombotic events / [141]
Gregori, 2015	Population database, case-series	Retinal disease	740,757 patients	Bevacizumab Ranibizumab Aflibercept	NA (see notes)	NA	No (see notes)	A descriptive study of the incidence of endophthalmitis: with Bevacizumab = 0.012% with Ranibizumab = 0.018% with Aflibercept = 0.03% / [162]
Hwang, 2012	Retrospective cohort	Retinal disease	916 patients	Bevacizumab	Ranibizumab	No	NA	[138]
Kemp, 2013	Population based retrospective cohort	AMD	1,267 patients	Bevacizumab	Ranibizumab	No	NA	[139]

Studies identified through literature search								
Study	**Methods**	**Disease**	**Size**	**Intervention**	**Comparison**	**Significant increase in the risk of cardiovascular events**	**Significant increase in the risk of ophthalmic events**	**Notes / Reference**
Meredith, 2015	Cohort within an RCT	AMD	18,509 injections, 1,185 patients	Bevacizumab Ranibizumab	NA (see notes)	NA	No (see notes)	Comparison was conducted for the use of topical antibiotic. Of the overall 11 eyes with endophthalmitis, 4 were treated with ranibizumab, and 7 with bevacizumab. / [163]
Moja, 2014	Systematic review of RCTs	AMD	9 studies, 3,665 participants	Bevacizumab	Ranibizumab	No	No	[136]
Ng, 2015	Population based analysis	AMD	1,182 patients	Bevacizumab (1,011 patients)	Age-adjusted incident rate of adverse events in Singapore population	No	NA	[142]
Nuzzi, 2015	Chart based retrospective cohort	Retinal disease	1,173 eyes	Bevacizumab	Ranibizumab Pegaptanib	No No	No No	[140]
Schlenker, 2015	Population-based crossover analysis with self-matched historical control data	Retinal disease	57,919 patients	Bevacizumab Ranibizumab	Control	Yes (see notes) Yes (see notes)	NA	Rate ratio of thromboembolic events versus control: Ranibizumab 1.61 (95%CI 1.39 to 1.87) Bevacizumab 1.83 (95%CI 1.61 to 2.09) / [164]
Sharma, 2012	Retrospective cohort	Retinal disease	1,584 injections, 524 patients	Bevacizumab	Ranibizumab	NA	Yes (see notes)	Odds ratio of acute intraocular inflammation in bevacizumab versus ranibizumab = 11.71

Studies identified through literature search								
Study	**Methods**	**Disease**	**Size**	**Intervention**	**Comparison**	**Significant increase in the risk of cardiovascular events**	**Significant increase in the risk of ophthalmic events**	**Notes / Reference**
								(95%CI 1.5 to 93.0) / [165]
Terzic, 2015	Retrospective case series	Retinal disease	1,101 injections	Bevacizumab	NA (see notes)	NA	No (see notes)	Descriptive study, endophthalmitis was reported in 2 out of 986 bevacizumab injections, 0 out of 55 ranibizumab injections, and 0 out of 60 aflibercept injections. / [166]
				Ranibizumab			No (see notes)	
				Aflibercept			No (see notes)	
Thulliez, 2014	Systematic review of RCTs	Retinal disease	4 trials (2,181 participants)	Bevacizumab	Ranibizumab	Mostly No (see notes)	NA	No difference in risk of major cardiovascular event and in non-ocular hemorrhage, increased risk with venous thromboembolism (OR, 3.45; 95%CI 1.25 to 9.54) / [119]
VanderBeek, 2015	Population database retrospective cohort	Retinal disease	383,810 injections (58,612 patients)	2755Bevacizumab	Ranibizumab	NA	No	[128]
Wang, 2014	Systematic review of RCTs	AMD	4 trials (2,613 participants)	Bevacizumab	Ranibizumab	No	NA	[135]

Abbreviation: AMD = age related macular degeneration; CVA = cardiovascular accident; HR = hazards ratio; MI = myocardial infarction; NA = not applicable; RCT = randomized controlled trials; RR = risk ratio; SAE = serious adverse events; OR = odds ratio; CI = confidence interval

Discussion

Bevacizumab has been used to treat retinal conditions, despite it not reviewed by Health Canada for intravitreal injection. In fact, the Canadian product monograph for Avastin contains a warning stating that "*AVASTIN is not formulated and has not been authorized for intravitreal use. Local and systemic adverse events have been reported in the post-market setting with unauthorized intravitreal use*."[167] The Avastin product monograph refers to three citations as evidence of the potentially harmful effect of intravitreal use of bevacizumab. The first citation refers to an observation claims database study by Gower et al, 2011 [130]; the second is a reference to the results of the SAEs reported in the CATT trial [10]; and the third is a reference to a selective subset of results from an observational population database retrospective cohort study by Curtis et al, 2010.[131] The aforementioned evidence is presented in Table 34.

The results of Gower et al[130] (Table 34) were presented at a scientific meeting as an abstract, and there is no associated publically available, peer-reviewed study report available. Moreover, the length of the abstract is 371 words, which is an insufficient amount of information to allow for an objective assessment of the quality of the evidence presented. Despite the lack of sufficiently detailed information, the author of the abstract reported two issues that would bias the results in favour of ranibizumab over bevacizumab. First, when expanding the data back to 2006 and allowing for unclassified drug codes, the authors admit that the differences in mortality and hemorrhagic CVA rates were attenuated. The second (more important) limitation that biases the results in favour of ranibizumab is the lack of complete information regarding important confounders, including smoking status, lipid profile, and blood pressure. These factors are well known to be associated with an increased risk of cardiovascular events, and patients less able to afford more expensive therapy with ranibizumab are channeled to bevacizumab treatment, thereby creating an unbalanced distribution of risk factors among the different treatment groups.

The CATT trial[10] (Table 34) has been discussed in detail elsewhere in this report. The emphasis on the CATT trial when highlighting the potential for an increased risk of cardiovascular harm when using bevacizumab to treat retinal conditions is due to the absence of any statistically significant difference in adverse event frequencies between bevacizumab and other treatments in any other RCT. Indeed, out meta-analysis in the current report of SAEs that included the results of the CATT trial demonstrated that bevacizumab is not associated with an elevated risk of cardiovascular harm.

Curtis et al, 2010[131] (Table 34) reported that bevacizumab was associated with a small but significantly higher risk of stroke and all-cause mortality compared to ranibizumab. However, in the same study, both ranibizumab and bevacizumab were not statistically significantly different to pegaptanib, another anti-VEGF agent, with respect to all-cause mortality and risk of MI, bleeding, and stroke. This finding violates the transitivity assumption, which would have us assume that since both interventions are not different than a common third, then they should not be different from one another. Indeed, Curtis and colleagues have clearly suggested that selection bias in favour of ranibizumab was present in the primary analysis due to the differences in socioeconomic class. When the analysis was rerun to only include exclusive treatment providers, there were no longer any statistically significant differences between bevacizumab and ranibizumab for all-cause mortality, MI, bleeding, or stroke.

TABLE 34: AVASTIN MONOGRAPH EVIDENCE AGAINST INTRAVITREAL USE

Studies supporting Avastin product monograph warning against intravitreal use								
Study	**Methods**	**Disease**	**Size**	**Intervention**	**Comparison**	**Significant increase in the risk of CV events?**	**Significant increase in the risk of ophthalmic events?**	**Notes / Reference**
Gower, 2011	Population database, retrospective cohort	AMD	77,886 patients	Bevacizumab	Ranibizumab	Yes (see notes)	Yes (See notes)	Overall mortality HR = 1.57 (99% CI 1.04 to 2.37). CVA HR = 1.57 (99%CI 1.04 to 2.37). No difference in MI. Ocular inflammation HR = 1.8 (99%CI 1.20 to 2.8)/ [130]
Martin, 2011	RCT, The CATT trial at	AMD	1,185 patients	Bevacizumab	Ranibizumab	Yes (see notes)	No	SAE RR = 1.29 (95%CI 1.01 to

	one year							1.66)/ [10]
Curtis, 2010	Population database, retrospective cohort	AMD	146,942 patients	Bevacizumab	Photodynamic therapy	No	NA	Adjusted HR of Ranibizumab vs. Bevacizumab in stroke HR = 0.78 (95%CI 0.64 to 0.96). Adjusted all-cause mortality HR = 0.86 (95%CI 0.75 to 0.98) / [131]
				Bevacizumab	Pegaptanib	No		
				Bevacizumab	Ranibizumab	Yes (see notes)		

Abbreviation: AMD = age related macular degeneration; CVA = cardiovascular accident; HR = hazards ratio; MI = myocardial infarction; NA = not applicable; RCT = randomized controlled trials; RR = risk ratio; SAE = serious adverse events; OR = odds ratio; CI = confidence interval

The product labelling for Avastin in the USA does not include as explicit a warning as appears in the Canadian monograph. Nevertheless, the post-market section of the US monograph includes the following statement: "*Eye disorders (from unapproved intravitreal use for treatment of various ocular disorders): Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort".* [168] This statement is preceded by a disclaimer from the FDA, stating that "*The following adverse reactions have been identified during post-approval use of Avastin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.*"[168] Reports related to the safety of intravitreal injections of bevacizumab led Health Canada to conduct a review in 2014 of the association between bevacizumab, ranibizumab and thrombotic microangiopathy. Health Canada concluded subsequently that the risk of thrombotic microangiopathy is applicable to the anti-VEGFs as a class and not to bevacizumab alone. [169]

Our review of the literature (Table 33) demonstrated that of five population based studies in which the safety of bevacizumab has been assessed,[131,133,134,142,164] none has reported a consistent, significant difference in the frequency of cardiovascular events between bevacizumab and ranibizumab. Contrary to these large population based-studies, Carneiro et al, 2011 [132] reported a large increase in thromboembolic events in bevacizumab compared to ranibizumab [OR = 10.16 (95%CI 2.80 to 36.93)]. However, this study has several major limitations that bias the results substantially against bevacizumab, including: (1) it was a chart-based study from a single centre; (2) it had a total of 378 patients, 26.1% of which received only bevacizumab; (3) bevacizumab-treated patients had almost double the number of intravitreal injections compared to ranibizumab-treated patients, thus exposing them to a dramatically higher risk of adverse events; and (4) bevacizumab-treated patients had more than triple the duration of follow-up compared to ranibizumab-treated patients, thus increasing the probability of experiencing an adverse event during follow-up. [132]

Of the twenty included studies that we reviewed, nine reported on ophthalmic adverse events. Only one study, Sharma et al.,[165] a retrospective cohort study, reported a statistically significant increase in the rate of acute intraocular inflammation in bevacizumab versus ranibizumab [OR = 11.71 (95%CI 1.5 to 93.0)].[165] The study compared 693 injections of bevacizumab to 891 injections of ranibizumab, all from a single centre. Very low rates of ophthalmic adverse events were detected; specifically, the study captured nine cases of acute intraocular inflammation with bevacizumab use and one case with ranibizumab use. These low rates of events in a relatively small population would explain the very wide confidence interval and reflects a high degree of uncertainty regarding the apparently higher odds ratio associated with the risk of ophthalmic events in patients treated with bevacizumab. By contrast, at least one other, much larger study failed to detect any difference in the risk of ophthalmic events between these treatments. Specifically, VanderBeek et al.,[128] a retrospective database cohort study, compared 296,565 bevacizumab injections to 87,245 ranibizumab injections in a total of 58,612 patients; the study found no statistically significant differences in the rates of endophthalmitis between bevacizumab injections and ranibizumab injections. Similarly, Gregori et al.,[162] a population based study on 740,757 anti-VEGF injections found the rate of endophthalmitis in bevacizumab injections to be 0.012%, in ranibizumab injections to be 0.018%, and in aflibercept injections to be 0.031%. In addition, there are other studies that have found the rates of ophthalmic-related events to be similar in bevacizumab to other anti-VEGFs (see Table 33).

Conclusion

The most credible evidence available suggests that intravitreal injection of bevacizumab is not associated with a significantly increased risk of cardiovascular harm compared to ranibizumab treatment. Similarly, the weight of evidence available suggests that the risk of ophthalmic harm due to intravitreal injection is similar for bevacizumab and ranibizumab. An important condition related to the lack of evidence of differences in the risk of ophthalmic harm between bevacizumab and ranibizumab relates to the fact that this conclusion rests on appropriate preparation, storage, and handling of bevacizumab aliquots to avoid contamination.

APPENDIX 24: ANALYSIS OF THE INJECTION FREQUENCY OF BEVACIZUMAB VERSUS RANIBIZUMAB

Aim

Since bevacizumab has not been reviewed or approved by Health Canada for intravitreal use in retinal conditions, there is no regulatory guidance regarding the frequency of intravitreal bevacizumab injection. The aim of this analysis was to compare the frequency at bevacizumab and ranibizumab are injected to treat retinal disease.

Methods

A random effects meta-analysis of included studies that compared bevacizumab to ranibizumab was conducted, in which the mean number of actual injections given was considered as the outcome. The main analysis was carried out irrespective of the disease type, the planned injection frequency in the protocol, and total treatment duration. To address the heterogeneity expected due to differences in the disease population, protocol, and treatment duration, subgroup analysis of studies that share the same disease population, planned frequency in the protocol, and treatment duration was also conducted. We extracted the following information from studies that compared bevacizumab to ranibizumab: disease population, the number of patients randomized to each arm, the dose of the drug, the protocol planned frequency, the actual frequency measure of injections given along with the variance measure, and the treatment duration. Studies that did not report the mean but reported the median number of injections were assessed for symmetrical data distribution. If the distribution was symmetrical, the median was assumed to be the same as the mean and the interquartile range was assumed to be 1.35 of the SD width; if the distribution was asymmetrical, the study was excluded. Studies with no reported SD that did not report any other measure of variance from which the SD can be derived from were also excluded. We reported the mean difference in the frequency of injection for each study along with the 95%CI, and the meta-analysis outcomes are reported as the weighted mean difference along with a corresponding 95%CI. Heterogeneity was assessed using the I^2 measure.

Results

A total of 15 RCTs compared bevacizumab to ranibizumab, of which four were excluded due to lack of information on the variance parameter of the number of actual injections,[9,11,17,30] and one of which was excluded due to an asymmetric distribution of the median and interquartile range.[15] Data for the remaining ten RCTs, along with the mean difference and 95% CI of the injection frequencies of bevacizumab versus ranibizumab, are presented in Table 35.

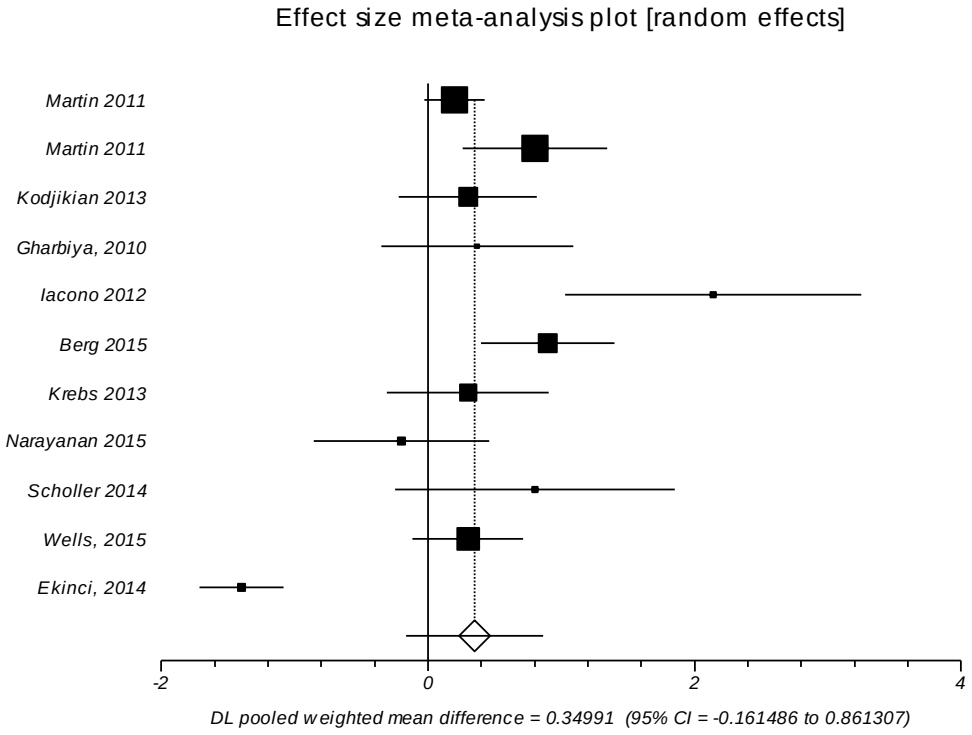
TABLE 35: SUMMARY OF INDIVIDUAL TRIALS COMPARING BEVACIZUMAB TO RANIBIZUMAB

Author, year	Treatment	Disease	Dose (mg)	Planned frequency	Population	Actual frequency, mean (SD)	Duration (months)	Mean difference (95%CI)
Martin, 2011	Bevacizumab	Wet AMD	1.25	Monthly	265	11.9 (1.2)	12	0.2 (–0.03 to 0.43)
	Ranibizumab		0.5		284	11.7 (1.5)		
	Bevacizumab		1.25	PRN	271	7.7 (3.5)		0.8 (0.26 to 1.34)
	Ranibizumab		0.5		285	6.9 (3.0)		
Kodjikian, 2013	Bevacizumab		1.25	3 monthly then PRN	191	6.8 (2.7)		0.3 (–0.22 to 0.82)
	Ranibizumab		0.5		183	6.5 (2.4)		
Berg, 2015	Bevacizumab		1.25	Monthly until OCT negative then PRN	184	8.9 (2.6)		0.9 (0.40 to 1.40)
	Ranibizumab		0.5		187	8.0 (2.3)		
Krebs, 2013	Bevacizumab		1.25	3 monthly then PRN	154	6.1 (2.8)		0.3 (–0.31 to 0.91)
	Ranibizumab		0.5		163	5.8 (2.7)		
Scholler, 2014	Bevacizumab		1.25		26	5.8 (2.3)		0.8 (–0.25 to 1.85)
	Ranibizumab		0.5		29	5.0 (1.7)		

Wells, 2015	Bevacizumab	DME	1.25	6 monthly then PRN	218	9.7 (2.3)		0.3 (–0.11 to 0.71)
	Ranibizumab		0.3		218	9.4 (2.1)		
Ekinci, 2014	Bevacizumab		1.25	3 monthly then PRN	50	5.1 (0.7)		–1.4 (–1.72 to –1.08)
	Ranibizumab		0.5		50	6.5 (0.9)		
Narayanan, 2015	Bevacizumab	RVO	1.25	PRN	38	3.0 (1.4)	6	–0.2 (–0.86 to 0.46)
	Ranibizumab		0.5		37	3.2 (1.5)		
Gharbiya, 2010	Bevacizumab	CNV due to PM	1.25		16	2.8 (1.2)		0.4 (–0.35 to 1.09)
	Ranibizumab		0.5		16	2.4 (0.9)		
Iacono, 2012	Bevacizumab		1.25		25	4.7 (2.2)	18	2.1 (1.02 to 3.25)
	Ranibizumab		0.5		23	2.56 (1.6)		

The random-effects model meta-analysis of all analyzed RCTs of bevacizumab versus ranibizumab produced a pooled weighted mean difference of 0.35 (95% CI: –0.16 to 0.86) injections, with an I^2 of 91.7%. A forest plot of this analysis is presented in Figure 21. This result suggested that there is no statistically significant difference in the mean number of bevacizumab versus ranibizumab injections in trials across different retinal conditions in which these drugs have similar efficacy. However, the high I^2 value reflects substantial heterogeneity and a correspondingly high degree of uncertainty in this result.

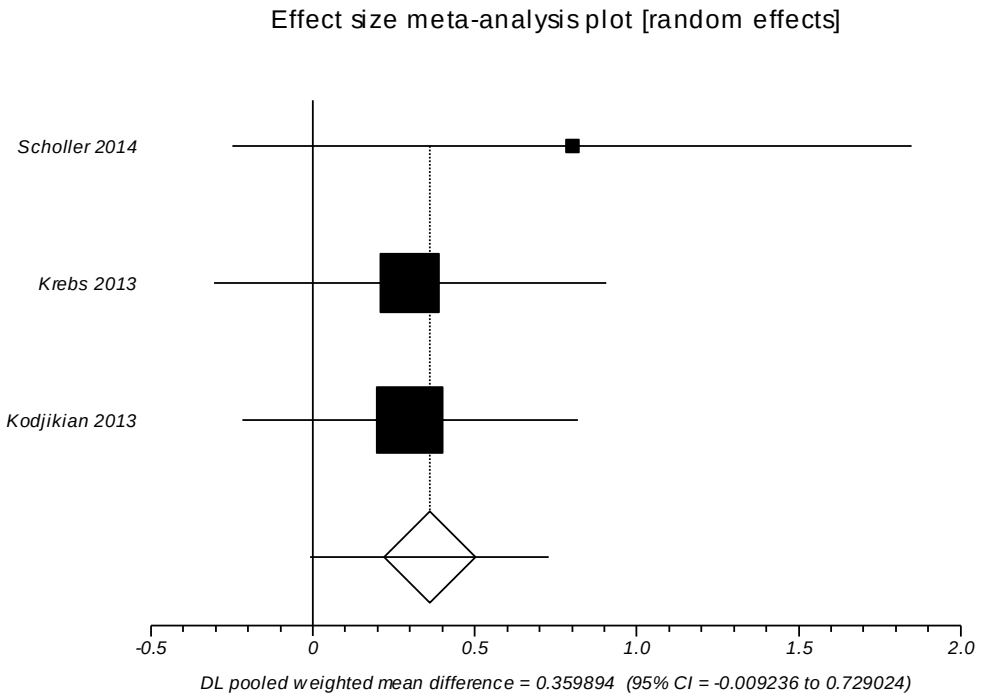
FIGURE 21: FOREST PLOT OF ALL ANALYZED TRIALS



To reduce the amount of heterogeneity, we identified a subgroup of trials that shared the same disease population, protocol planned frequency, and treatment duration. Three trials for the wet AMD population met these criteria, with a frequency protocol of a monthly injection for three months then treatment as needed, and a treatment duration of 12 months.[6-8] A subgroup analysis of these trials produced a pooled weighted mean difference of 0.36 (95% CI: –0.01 to

0.73) injections, with an I^2 of 0%. A forest plot of this analysis is presented in Figure 22. The mean difference for the subgroup analysis is almost identical to that of the primary analysis and suggests that there is no statistically significant difference in the mean number of bevacizumab versus ranibizumab injections within a subset of trials within the same population (wet AMD) and duration, but in contrast to the primary analysis, this result is associated with very low heterogeneity.

FIGURE 22: SUBGROUP ANALYSIS OF TRIALS OF WET AMD POPULATION



Discussion

Due to the absence of regulatory guidance regarding the frequency at which bevacizumab can be used to treat retinal conditions, we examined whether the frequency of injection of bevacizumab in trials that compared bevacizumab and ranibizumab and demonstrated similar efficacy of these two drugs. The primary pooled analysis suggests that there was a weighted mean difference of 0.35 injections for the comparison of the number of injections administered in the clinical trials evaluating bevacizumab to ranibizumab for the treatment of wet AMD, DME, RVO, or CNV due to PM, and that this difference was not statistically significant. Although there

was a high degree of heterogeneity associated with this result, this was not surprising given the fact that the included trials spanned four different types of retinal disease as well as different treatment durations. Indeed, a secondary analysis of a subgroup of trials carried out within the same disease type (wet AMD) for the same duration produced a mean difference between injection frequency for the two treatments that was almost identical to that in the primary analysis (MD = 0.36), and was similarly not statically significantly different between treatments, but with zero heterogeneity. Individually, most trials showed no statistically significant differences in the frequency of injection, and even in those in which there was a statistically significant difference, the mean differences in injection frequency between the two drugs ranged from 1.4 fewer bevacizumab injections to 2.1 more bevacizumab injections. This narrow range across different studies that spans 0 further support the hypothesis that the recommended frequency of ranibizumab injection can be used as a proxy for guiding the frequency of bevacizumab injections.

The analysis presented above has several limitations. First, a relatively small number of studies contributed to the analysis: the ten RCTs included in this analysis represented 11 different comparisons between bevacizumab and ranibizumab, and this number was insufficient to allow for subgroup analyses that controlled for each potential effect-modifier. Second, most of the RCTs were for patients with wet AMD, suggesting that the pooled estimate may be less generalizable to other disease populations.

Conclusion

The results of a meta-analysis of RCTs suggests that the frequency at which bevacizumab is injected to improve visual acuity in patients with retinal conditions is not statistically significantly different to the frequency of ranibizumab injections that achieves a similar effect on visual acuity in the same patient populations. This suggests that the recommended frequency of ranibizumab injection may be used as a reasonable proxy to guide the frequency of bevacizumab injections.