TREATING RETINAL DISEASES IN THE ERA OF ANTI-VEGF THERAPIES

A Position Paper Regarding the CADTH Therapeutic Review

“Anti-Vascular Endothelial Growth Factor Drugs for the Treatment of Retinal Conditions – Recommendations Report”

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Disclosures

Members of the Drafting Committee were volunteers and received no compensation for their time or work on this Position Paper. All members disclosed any affiliations with the manufacturers of the available anti-VEGF agents. These disclosures are detailed in Appendix A.

Note to readers:

While CADTH’s recommendations may be considered by all of the provinces (with the exception of Quebec) and have the potential to impact many Canadians, the focus of this paper is Ontario.
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EXECUTIVE SUMMARY

The Canadian Agency for Drugs and Technologies in Health (CADTH) recently released a report entitled Anti-Vascular Endothelial Growth Factor Drugs for the Treatment of Retinal Conditions – Recommendations Report. This report included three recommendations to guide jurisdictions in their decision-making around reimbursement of these agents. CADTH’s report is timely, as retinal diseases are an important public health issue affecting an increasing number of people. The advent of anti-VEGF therapies has dramatically changed the treatment paradigm for a number of common and serious retinal diseases, leading to significantly improved prognosis and outcomes, including visual improvements and health-related quality of life, for many Canadians.

In 2014, the Ontario Ministry of Health and Long-term Care (MOHLTC) published its Quality-Based Procedures [QBP] Clinical Handbook for Integrated Retinal Care. The QBP Clinical Handbook was developed through collaborative efforts between the Ministry and an Advisory Group comprised of retina experts. Given the volume of intravitreal injections in Ontario, the Advisory Group spent considerable time exploring diagnostic and care pathways and developing evidence-based best practice recommendations with a goal of encouraging high-quality care for retinal diseases that involve intraocular injections.

A key focus for the MOHLTC is the provision of patient-centred care. At the heart of this tenet is the ability for physicians to determine the most appropriate evidence-based treatment for the unique characteristics of each patient – there is no “one-size fits all” solution for complex ocular diseases. CADTH’s recommendations, if implemented, would have a significant impact on this core principle. The following key concerns are highlighted in the Position Paper:

- Bevacizumab does not have Health Canada approval for any ophthalmic indications and the product monograph carries an explicit warning against its intravitreal use.
- As two anti-VEGF agents have Health Canada approval for ophthalmic use (aflibercept and ranibizumab), the CADTH recommendation to preferentially use an agent without federal approval for intravitreal use appears to have been made on the basis of cost alone.
- The CADTH recommendations to use bevacizumab as the preferred initial agent for all patients with all retinal diseases and subgroups are not evidence based or patient-centred. The various treatment paradigms for different diseases are both complex and time-sensitive.
- The CADTH recommendation that one treatment approach be applied to four different diseases is unsupported by the evidence and runs contrary to the Ministry QBP Clinical Handbook, which highlights in detail the different evidence-based paradigms for treating age-related macular degeneration (AMD), diabetic macular edema (DME), branch retinal vein occlusion (BRVO), and central retinal vein occlusion (CRVO).
- CADTH’s definition of an inadequate treatment response for all retinal conditions considered is based solely on visual acuity and does not reflect the number of functional and anatomical criteria that are typically used to determine treatment success in the clinical setting.
- There is risk to patients if appropriate treatment is delayed. Clear and compelling evidence from the major trials has demonstrated that there is a window of opportunity to optimize visual outcomes. As delays in receiving the most appropriate treatment can result in intractable vision loss, it is critical that patients have access to the most appropriate agent at the right time.
- Significant problems have been reported with compounding and storage of bevacizumab, which raises concerns about its safety in the event of widespread use. The risk of a devastating complication, such as endophthalmitis, is increased when a drug is repurposed and used in a fashion not intended or indicated by the manufacturer.

The authors of this Position Paper recognize that there is a place for bevacizumab among the therapeutic options for retinal diseases, and, therefore, ask the Ontario government to immediately enter into a sustained dialogue to develop a scientifically and clinically sound framework for the use of anti-VEGF agents that recognizes that efficacy and safety are paramount when it comes to providing truly patient-centred care. Working together, all interested parties can align the implementation of such a framework with the core principles of the Ontario Excellent Care for All Act and also build on the collaborative work done by the Ministry and its Advisory Group on the QBP Clinical Handbook.

It is not only possible, but also vital to balance physicians, and patients’ need for access to the right drug at the right time with the need for pharmacovigilance of compounded products and the reality of cost considerations for the taxpayer. Current and future generations of Ontarians deserve this.
INTRODUCTION

The introduction of anti-vascular endothelial growth factor (VEGF) medications has fundamentally changed the way in which retinal disease is treated, providing optimism for patients through sight-preserving options. These medications are known to improve vision, prevent blindness and improve quality of life.

The Canadian Agency for Drugs and Technologies in Health (CADTH) recently carried out “a therapeutic review of the relative efficacy and safety of anti-VEGF drugs for treating retinal conditions, followed by an analysis of treatment costs.” The Agency reviewed the available anti-VEGF medications – aflibercept (Eylea), bevacizumab (Avastin) and ranibizumab (Lucentis) – and in May 2016, released its final report entitled Anti-Vascular Endothelial Growth Factor Drugs for the Treatment of Retinal Conditions - Recommendations Report, which included three recommendations to guide jurisdictions in their decision-making around reimbursement of these agents.

As retina subspecialists from the seven academic centres in Ontario, the authors of this Position Paper recognize that CADTH’s report is timely, as retinal diseases are an important public health issue affecting an increasing number of Canadians. The release of this report provides an important opportunity for retina specialists to enter into a sustained dialogue with the Ontario government to develop a framework for anti-VEGF therapy in the province that optimizes outcomes for patients by focusing on the safety and efficacy of the available anti-VEGF agents. The authors believe that all patients, regardless of whether they have private health insurance, deserve access to approved evidence-based treatments that are safe and efficacious. There is also recognition that governments need to provide cost-effective options.

As experts in the treatment of retinal diseases, and focused on optimal patient outcomes, the physicians on this Drafting Committee seek to enter into a sustained dialogue with the Ontario government. The goal of this dialogue is to review the potential impact of the CADTH recommendations and to consider them in light of the existing Ministry QBP Clinical Handbook in order to develop a mutually agreed-upon framework for the use of anti-VEGF medications for retinal conditions. It is hoped that this Position Paper will further raise awareness about the complexities of treating retinal diseases, with the expectation that evidence-based patient-centred care will be at the forefront of any decisions moving forward.

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PERSONAL AND SOCIETAL IMPACTS OF VISION LOSS IN CANADA

According to the Canadian National Institute for the Blind (CNIB), an estimated half a million Canadians are living with significant vision loss. Of these, approximately 187,000 live in Ontario. An aging population will experience an increase in eye disease; the four most common causes of blindness (which include age-related macular degeneration [AMD] and diabetic retinopathy) increase with age. By 2036, the number of Canadian seniors is predicted to be more than double the number observed in 2009 and will vary between 9.9 and 10.9 million persons. In addition, the increasing prevalence of obesity can be expected to result in an increase in diabetes and hence diabetes-related ocular complications.

A statement prepared by the Canadian Council of the Blind (CCB), the CNIB and the Foundation Fighting Blindness (FFB) and published on the CADTH website, strongly expresses the negative impacts of vision loss on the individual and society as a whole. Vision loss is a devastating outcome, dramatically impacting a person’s quality of life, affecting independence, the ability to work or gain an education, relationships, and mental health. According to the National Coalition for Vision Health, vision loss increases the incidence of other problems. “Compared to people of the same age without vision problems, people with vision loss are admitted to nursing homes three years earlier; experience twice the number of falls, experience three times the incidence of depression, have four times as many hip fractures, and have double the mortality rate.” In a study on the impact of bilateral wet AMD in elderly patients, compared with control subjects, patients with AMD reported four times the need for assistance with activities of daily living, worse vision-related functioning (45%), worse overall functioning (13%), more anxiety (30%) and depression (42%), and double the rates of falls. The impact of AMD on quality of life varies depending on the severity of vision loss, thus highlighting the value of any preservation of sight. Patients with mild, moderate, and very severe AMD reported quality of life decreases of 17%, 40%, and 63%, respectively.

On a broader scale, the impact of vision loss on productivity and health care costs is serious and significant. The direct and indirect health care cost of vision loss in Canada was estimated at $15.8 billion and projected to increase to $30.3 billion by 2032. A study conducted by the CNIB (based on 2012 data) estimated the total annual financial cost of vision loss in Canada due to AMD alone at $2.6 billion ($1.8 billion in direct health costs and $860 million in indirect costs), and due to diabetic retinopathy at $776 million ($412 million in direct health costs and $364 million in indirect costs). A study conducted in the United Kingdom, estimated that the healthcare utilization costs for AMD patients in that country were seven times higher than for control subjects. Net annual costs of human suffering (burden of disease), over and above financial costs, have been estimated to be a further $1.9 billion annually for AMD and $801 million for diabetic retinopathy. In addition to these costs, the CNIB estimated the cost of associated complications of vision loss: falls $25.8 million; depression $175.2 million; hip fractures $101.7 million; and the cost of nursing home admissions $713.6 million.

Timely administration of the most effective treatment for retinal diseases, therefore not only improves patients’ functional ability and their potential to remain productive in society, but also decreases the social and economic burdens on society at large.

“Timely administration of the most effective treatment for retinal diseases, therefore not only improves patients’ functional ability and their potential to remain productive in society, but also decreases the social and economic burdens on society at large.”
PATIENT-CENTRED CARE FOR RETINAL DISEASES

One of the key focuses for the Ontario Ministry of Health and Long-term Care is the provision of patient-focused care. At the heart of this tenet is the ability for physicians, in dialogue with patients, to determine the most appropriate evidence-based treatment. Physicians determine personalised treatment regimens and care plans on the basis of a number of different patient factors – there is no “one-size fits all” solution for complex ocular diseases. These factors include disease severity and likely rate of progression, baseline vision, status of the fellow eye, comorbidities, distance from the treating centre, and patient preferences and values. Physicians must also consider cumulative risk with ongoing treatment and seek opportunities to maximize efficacy while reducing risk. Furthermore, if patients experience side effects or limited effectiveness with one agent, switching to another agent may offer a better outcome. An essential component for the provision of patient-centre care is the ability for physicians to prescribe the right treatment to the right patient at the right time.

Patient-centred care is intimately linked to the concept of informed consent. The Canadian Patient Charter for Vision Care states that “Patients have a right to make an informed consent to treatment, which includes being provided with the necessary information about potential benefits, side-effects and approved alternatives.” Accordingly, it is not only necessary, but also appropriate that patients receive complete and transparent explanations for why they may be prescribed one agent over another, including whether any treatment options are being influenced by cost considerations rather than scientific evidence. Ophthalmologists must therefore not be incentivized in any way (whether through direct financial incentives or quantity restrictions in the distribution of any one agent) to prescribe one anti-VEGF drug over another.

ANTI-VEGF DRUGS FOR THE TREATMENT OF RETINAL DISEASES

Vascular endothelial growth factor (VEGF) plays a key role in the pathogenesis of many blinding retinal conditions, such as diabetic macular edema (DME), AMD and retinal occlusive diseases such as branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). Blocking the action of VEGF within the eye has been proven to restore and improve visual function in these conditions. Anti-VEGF drugs are injected directly into the vitreous cavity of the eye. Once in the eye, they bind to VEGF, preventing the adverse effects of this molecule on visual function. The advent of anti-VEGF therapies has dramatically changed the treatment paradigm for a number of common and serious retinal diseases, leading to significantly improved prognosis and outcomes for many Canadians.

As CADTH states in its report, “retinal conditions have become an important health policy issue due to the large number of people they affect, and the widespread adoption of effective but costly anti-VEGF drugs to treat these conditions.” The diseases that respond to anti-VEGF therapy are very prevalent in our aging population.

Diabetic macular edema (DME)

Diabetic retinopathy is the leading cause of vision loss among working-age adults, with DME being the most common cause of vision loss among people with diabetic retinopathy. It is estimated that 50% of people with diabetic retinopathy will develop DME, with prevalence rates varying by type of diabetes and ethnicity. 

Age-related macular degeneration (AMD)

Each year, approximately 17,000 Canadians receive a diagnosis of AMD, making it the leading cause of vision loss in Canada, affecting two million Canadians over the age of 50 years. With the aging of the Canadian population, the incidence and prevalence of AMD is expected to triple by 2034. While only ten to 15 percent of AMD progresses to wet AMD, it is this form that causes 90% of the severe vision loss related to the disease.

Retinal vein occlusion (RVO)

While the prevalence of RVO increases with age, ascertaining the actual incidence and prevalence of RVO is complex, as many patients are asymptomatic and are only diagnosed opportunistically. Depending on the age of patients and population studied, branch retinal vein occlusion (BRVO) is estimated to be three to six times more prevalent than central retinal vein occlusion (CRVO). Data from eleven population-based studies estimate prevalence rates of 0.52% for any RVO, 0.44% for BRVO, and 0.08% for CRVO. In terms of visual impairment due to macular edema secondary to RVO, records from a Southwestern Ontario database reveal an annual incidence of 0.056% and 0.021% secondary to BRVO and CRVO, respectively. Importantly, in this real-world Canadian setting, RVO was associated with hypertension and dyslipidemia, both highly prevalent vascular disease risk factors.

Of the three anti-VEGF drugs available in Canada (aflibercept, bevacizumab, ranibizumab), only two (aflibercept and ranibizumab) are approved by Health Canada for use in retinal diseases (see Table 1). Bevacizumab is used off-label for the treatment of retinal conditions. Patients living with these retinal diseases are typically treated every one to three months with intra-ocular injections of these drugs. Within any class of medications or for any given patient, different agents within the same class may have variable efficacy or side-effect profiles. Careful selection and sometimes trial and error are needed to determine the most appropriate agent for an individual patient. This is also true for anti-VEGF agents, as all patients and all retinal diseases do not respond equally to each agent.
COMMENTARY ON CADTH’S RECOMMENDATIONS

CADTH Recommendation #1

For the treatment of patients with wet AMD, DME, RVO, or CNV due to PM, bevacizumab is the preferred initial anti-VEGF therapy, based on similar clinical effectiveness and lower cost compared with other anti-VEGF treatments. Ranibizumab or aflibercept can be used as alternative treatment options in patients who experience thromboembolism following the initiation of bevacizumab treatment or who are at a high risk of cardiovascular adverse events (see Note 2).

Note 1: For all retinal conditions considered, an inadequate response to treatment is defined as not achieving any improvement in best corrected visual acuity (BCVA) at three months or not achieving an improvement in BCVA at six months of at least 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters compared with the baseline (pre-treatment) BCVA.

Note 2: Individuals are considered to be at a high risk of cardiovascular adverse events if there is clinical evidence of atherosclerosis or they have had a previous myocardial infarction, have undergone coronary or arterial revascularization, or have a history of cerebrovascular disease (including transient ischemic attack) or peripheral arterial disease.

CADTH Recommendation #2

There is no specific recommendation pertaining to anti-VEGF therapy for subgroups of patients within any of the conditions of interest.

Bevacizumab is not approved by Health Canada for intraocular use

Patients and healthcare professionals alike depend on Health Canada’s drug approval and pharmacosurveillance processes. Health Canada’s Health Protection and Food Branch is the national authority that regulates, evaluates and monitors the safety, efficacy, and quality of therapeutic and diagnostic products available in Canada. Health Canada issues a Notice of Compliance (NOC) to a manufacturer upon the satisfactory review of a submission for a new drug or indication, which signifies compliance with the Food and Drug Regulations. This extensive review process includes the results of the preclinical and clinical studies, details regarding the production of the drug, packaging and labelling details, and information regarding therapeutic claims and side effects. Health Canada’s Good Pharmacovigilance Practices (GVP) guidelines set forth the regulatory requirements related to the reporting of adverse drug

Table 1. Anti-VEGF medications approved by Health Canada

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<th>Brand name (Manufacturer/distributor)</th>
<th>Generic name</th>
<th>Health Canada-approved indications</th>
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| Eylea (Regeneron/Bayer)               | aflibercept  | • Neovascular (wet) age-related macular degeneration  
|                                       |              | • Visual impairment due to macular edema secondary to central retinal vein occlusion  
|                                       |              | • Visual impairment due to macular edema secondary to branch retinal vein occlusion  
|                                       |              | • Diabetic macular edema |
| Lucentis (Genentech/Novartis)         | ranibizumab  | • Neovascular (wet) age-related macular degeneration  
|                                       |              | • Visual impairment due to diabetic macular edema  
|                                       |              | • Visual impairment due to macular edema secondary to retinal vein occlusion  
|                                       |              | • Visual impairment due to choroidal neovascularization secondary to pathologic myopia |
| Avastin (Genentech/Hoffmann-La Roche) | bevacizumab  | • Metastatic carcinoma of the colon or rectum  
|                                       |              | • Unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer  
|                                       |              | • First recurrence platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer  
|                                       |              | • Recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer  
|                                       |              | • Glioblastoma after relapse or disease progression |

Note: The Canadian product monograph includes the following warning: “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.”
Bevacizumab does not have Health Canada approval for ophthalmic indications and the product monograph carries an explicit warning against its intravitreal use. As two anti-VEGF agents have Health Canada approval for ophthalmic use (aflibercept and ranibizumab), the recommendation to preferentially use an agent without approval for intravitreal use appears to have been made on the basis of cost alone.

**Efficacy**

Recommendation #1 to use bevacizumab as the preferred initial agent for all patients with all retinal diseases, and Recommendation #2 suggesting that all subgroups can be managed the same are not evidence-based assertions. For example, in the subgroup of patients with DME, the only head-to-head trial of the three anti-VEGF agents in this disease demonstrated that after one and two years of treatment there were differential responses to the different anti-VEGF agents. While patients in all three anti-VEGF groups experienced improved vision from baseline to two years, bevacizumab was inferior to the other two agents in terms of reducing abnormal retinal swelling (i.e. decreasing macular edema), and in terms of visual acuity in those patients with worse baseline vision. For patients with DME with poorer baseline vision, the recommendation to begin therapy with bevacizumab is neither evidence based, nor in the patients’ best interest, as this approach may delay access to a more effective agent.

There is no one-size-fits-all treatment for different retinal diseases. The various treatment paradigms for different diseases are both complex and time-sensitive. The CADTH recommendation that one treatment approach be applied to four different diseases is unsupported by the evidence and runs contrary to the Ministry’s own conclusions. The Ministry QBP Clinical Handbook highlights in detail the different evidence-based paradigms for treating AMD, DME, and RVO. For each disease, the QBP Clinical Handbook proposes a treatment paradigm that provides guidance on patient eligibility criteria, guidelines for initiating treatment, guidelines for the conduct of therapy (e.g. injection intervals, follow-up and surveillance required to guide therapy) [such as visual acuity, intraocular pressure, fundus examination, optical coherence tomography (OCT) [measurement of retinal thickness] and criteria for continuation and discontinuation of therapy.

While the QBP Clinical Handbook offers a rational approach for each disease based on an individual patient’s response to treatment, CADTH has offered the following definition of an inadequate response for all retinal conditions considered: “not achieving any improvement in best corrected visual acuity (BCVA) at three months or not achieving an improvement in BCVA at six months of at least 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters compared with the baseline (pre-treatment) BCVA.” It is important to note that the ETDRS chart is a research tool that is not used in the clinical setting, as it is not practical. In clinical practice, most patients do not experience an improvement equivalent to 15 ETDRS letters, and the better a patient’s baseline (i.e. pre-treatment) vision, the lower the expected magnitude of visual improvement. Clinical practice guidelines and many studies use a number of functional and anatomical criteria in addition to visual acuity to determine “treatment success.” These include the presence or absence of blood, and/or the amount of reduction or presence of fluid on OCT imaging. Importantly, with progressive diseases, stability of vision over time can rightly be considered treatment “success.”

Delaying treatment with the appropriate drug can have significant and life-changing consequences for patients. All the major AMD trials have demonstrated that the biggest gain for patients occurs in the first three months of treatment. However, the CADTH definition of an inadequate response to treatment would suggest that an ophthalmologist would have to use an inferior drug for three to six months before switching, thereby missing the window of opportunity to improve vision. Furthermore, as patients with wet AMD in one eye have greater than a 50% risk of developing the disease in the fellow eye within two to five years, saving vision in the first eye is critical, as it is not possible to predict which eye will ultimately retain better vision. As stated in the QBP Clinical Handbook, “It is important that patients who have the most potential to benefit are treated rapidly, yet it is also important to modify or discontinue treatment if it is not producing the expected response.”

While there are no trial data comparing the three anti-VEGF agents for RVO or pathologic myopia (PM), there is clear and compelling evidence from the major RVO trials of a window of opportunity to optimize visual outcomes. A delay in receiving treatment of six months resulted in intractable vision loss that could not be recaptured. In these trials, patients with BRVO or CRVO were randomized to either sham injections or to one of two doses of ranibizumab. After six months, those in the sham injection arms were crossed over to a ranibizumab treatment arm. While treatment with ranibizumab as needed for six months then resulted in rapid reduction in edema, this later-treated group did not achieve the same visual gains as did the two groups initially treated with ranibizumab.

**Safety**

Significant problems have been reported with compounding and storage of bevacizumab, which does raise serious concerns about its safety in the event of widespread use. The risk of an adverse event or a devastating complication, such as acute ocular inflammation or endophthalmitis, is increased when a drug is repurposed and used in a fashion not intended or indicated by the manufacturer. A retrospective chart review of a consecutive series of intravitreal injections in Kingston, Ontario examined the rates of serious ocular adverse events in patients who had received bevacizumab (n = 693) vs. ranibizumab (n = 891) over a 22-month period (June 2006 to March 2008). Patients who had received bevacizumab were 12 times more likely to have developed severe intraocular inflammation following each injection compared with patients who had received ranibizumab. At the 2009 Annual Meeting of the Canadian Ophthalmological Society, data were presented on three
outbreaks of serious ocular adverse events in patients who had been treated with bevacizumab.\textsuperscript{38,40-42} In 2011, Health Canada issued an alert about “clusters of cases of bacterial infection and eye inflammation in the eye resulting in blindness or near blindness in three locations in the United States in patients who were injected in the eye with Avastin \textsuperscript{(bevacizumab)}. These cases appeared to be due to contamination after repackaging single-use Avastin \textsuperscript{(bevacizumab)} vials into several syringes.”\textsuperscript{43} This alert also cautioned that “reporting rates determined on the basis of spontaneously reported post-market adverse reactions are generally presumed to underestimate the risk associated with health product treatments.”\textsuperscript{43} The risk of infection can be mitigated by careful preparation, but clusters of sterile endophthalmitis have also been seen in Canada\textsuperscript{38} and internationally\textsuperscript{44,45} and likely relate more to the intra-ocular use of a drug that has not been formulated for this purpose. These infections and episodes of severe and devastating inflammation may occur because of impurities that can be tolerated intravenously, but not in the eye.\textsuperscript{38,44}

It should be noted that the delivery of bevacizumab in major trials occurred through the use of a single vial for each bevacizumab injection under strict preparation and trial protocol conditions. Each batch of repackaged bevacizumab was subjected to sterility, purity and potency testing, limiting the ability to generalize safety conclusions from these trials to real-world vial-splitting practices.

CADTH highlighted and supported the need for a system to ensure the proper handling, storage and distribution of bevacizumab to decrease the risk of microbial contamination.\textsuperscript{46} Clinicians and patients require transparency and accountability around such a compounding program, which would need to be overseen and monitored at the provincial level. Quality assurance and pharmacovigilance procedures would need to include bioavailability, potency, sterility and purity testing. This system would also need to include the ability to measure and monitor patient outcomes and adverse events. As part of the provincial investment in pharmacovigilance, issues around liability for the safety and the efficacy of the product would have to be addressed.

**CADTH Recommendation #3**

The frequency and dose of intravitreal injections of the anti-VEGF drugs should be determined by the treating ophthalmologist, but should not exceed that recommended for a particular retinal condition by the product monograph (if available) or that used in randomized clinical trials.

CADTH appropriately recommends that the frequency of injections should be determined by the treating ophthalmologist. The QBP \textit{Clinical Handbook} also supports this by stressing the need to make individualized treatment decisions based on each individual patient’s response to treatment. However, the specification in the above CADTH recommendation to limit injection frequency based on the product monograph (not available for bevacizumab) or by randomized clinical trials (which each have a different treatment protocol) is clearly aimed at cost containment rather than on optimizing outcomes through patient-centred care. It is also important to note that the rigid limitations that are necessarily used in clinical trials can be problematic in real-world clinical practice, where it may not always be possible to adhere to stringent monthly or bi-monthly intervals. Many factors influence patients’ abilities to schedule and attend appointments, including distance from the treating ophthalmologist, competing appointments and treatments for comorbidities, and reliance on others for transport. Ophthalmologists need the flexibility to offer treatment regimens that consider the whole patient and their unique circumstances and that reflect an ever-evolving evidence base.

## CONCLUSIONS

The authors of this Position Paper recognize that there is a place for bevacizumab among the therapeutic options for retinal diseases, and, therefore, ask the Ontario government to immediately enter into a sustained dialogue to develop a scientifically and clinically sound framework for the use of anti-VEGF agents that recognizes that efficacy and safety are paramount when it comes to providing truly patient-centred care.

By working together, we can build on the collaborative work undertaken by the Ministry and its Advisory Group on the QBP \textit{Clinical Handbook}. We believe it is possible to balance physicians and patients’ need for access to the right drug at the right time with the need for pharmacovigilance of compounded products and the reality of cost considerations for the taxpayer. There must also be flexibility in the system to reflect the evolving evidence base. Importantly, these goals are aligned with the four core principles of the \textit{Ontario Excellent Care for All Act}:

- Care is organized around the person to support their health;
- Quality and its continuous improvement is a critical goal across the health system;
- Quality of care is supported by the best evidence and standards of care; and
- Payment, policy and planning support quality and efficient use of resources.\textsuperscript{2}

**THIS IS WHAT CURRENT AND FUTURE GENERATIONS OF ONTARIANS DESERVE.**
APPENDIX A – DISCLOSURES

The physicians on the Drafting Committee made the following disclosures regarding any affiliations (financial or otherwise) within the past two years with the manufacturers of the anti-VEGF medications that are currently available in Canada.

Varun Chaudhary, MD, FRCSC
- Grant/research support: Bayer, Novartis
- Participation in clinical trial: Bayer, Novartis
- Honoraria/consulting fees/in-kind compensation: Bayer, Novartis
- Membership on an advisory panel, committee or board of directors: Bayer, Novartis

Robert Devenyi, MD, FRCSC, FACS
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- Honoraria: Bayer, Novartis
- Membership on advisory panel: Bayer, Novartis

Peter J. Kertes, MD, CM, FRCSC
- Grant/research support: Bayer, Novartis
- Participation in clinical trial: Bayer, Novartis
- Honoraria: Bayer, Novartis
- Membership on advisory panel: Bayer, Novartis

Wai-Ching Lam, MD, FRCSC
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- Participation in clinical trial: Novartis
- Consulting fees: Bayer, Novartis
- Membership on advisory panel: Bayer, Novartis

Sanjay Sharma, MD, FRCSC
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- Consulting fees: Bayer, Novartis
- Membership on advisory panel: Bayer, Novartis

Tom Sheidow, MD, FRCSC
- Clinical trials: Bayer, Novartis
- Advisory board member: Bayer, Novartis

David Wong, MD, FRCSC
- Grant/research support: Bayer, Novartis
- Participation in clinical trial: Bayer, Novartis
- Honoraria/consulting fees/in-kind compensation: Bayer, Novartis
- Membership on an advisory panel, committee or board of directors: Bayer, Novartis

APPENDIX B – GLOSSARY

Branch retinal vein occlusion (BRVO)
With BRVO, thickened arteries in the retina compress and block (occlude) a branch retinal vein, causing nerve cells within the retina to die. Many patients will experience edema (swelling) of the macula. While BRVO is painless, vision often becomes progressively blurry, misty or distorted.47

Branch retinal veins
Branch veins are the smaller tributary veins in the retina that flow into the central retinal vein.

Central retinal vein
Blood, which carries oxygen, is transported to the retina via an artery that enters the eye through the optic nerve (the central retinal artery). Blood is drained from the eye by the central retinal vein. The vein may become blocked (occluded), which impedes blood flow in the eye (known as central retinal vein occlusion).

Central retinal vein occlusion (CRVO)
With CRVO, the main vein in the retina becomes blocked (occluded) by a blood clot, which compromises the circulation in the eye. The walls of this vein begin to leak blood and excess fluid into the retina. When this fluid collects in the macula (macular edema), vision becomes blurry.47

Choroid
The choroid is a thin layer of connective tissue that lies between the white outer coating of the eye (the sclera) and the retina. This tissue is densely packed with blood vessels and provides nourishment to the retina.

Choroidal neovascularization (CNV)
With CNV, new blood vessels that originate in the choroid grow into or under the retinal pigment epithelium or subretinal space. CNV causes painless vision loss. It occurs mostly common secondary to wet AMD, but there are other causes as well.

Diabetic macular edema (DME)
DME is the most common cause of visual loss in people with diabetes. It is caused by fluid leaking from retinal blood vessels, causing the macula to swell. Vision loss can range from mild to severe.47

Endophthalmitis
Endophthalmitis is an infection inside the eyeball. Infectious (exogenous) endophthalmitis is more common and occurs after penetration of the eyeball (for example, surgery, injection, trauma) or from the spread of an external eye infection into the eye. Endogenous endophthalmitis occurs when infectious organisms enter the inside of the eye via the bloodstream. Sterile endophthalmitis is a severe inflammatory reaction in the eye that is non-infectious and typically occurs in response to impurities or toxins that are introduced into the eye at the time of injection.
or surgery. The prognosis of endophthalmitis varies depending on the cause and severity of the infection, and the amount of resultant inflammation and scarring. While mild cases may have excellent visual outcomes, severe infections may result not only in loss of sight, but even loss of the entire eye.48

**Macula**

The macula is the small central area of the retina that is responsible for central and fine vision. A healthy macula is essential for many everyday tasks such as driving, facial recognition, reading and writing, and the ability to distinguish colours.

**Neovascular (wet) age-related macular degeneration (AMD)**

There are two types of AMD – dry, which includes the visually disabling geographic atrophy, and the less prevalent, but more visually disabling neovascular (wet) AMD. In wet AMD, abnormal fragile blood vessels (see CNV above) grow and leak fluid under and into the macula. This damages the retina and slowly destroys central vision.47

**Optical coherence tomography (OCT)**

OCT is a non-invasive test that takes cross-sectional images of the retina. By mapping and measuring the thickness of the various parts of the retina, OCT provides objective measurements that are useful for diagnosing, following, and guiding treatment of retinal conditions.49

**Pathologic myopia (PM)**

PM is a severe form of near-sightedness in which the eyeball is much longer than normal. PM can cause vision loss at any age, but it occurs most commonly between the ages of 30 and 40. In people under 50 years of age, PM is an important cause of CNV.50

**Retina**

The retina, located at the back of the eye, is comprised of multi-layers of cells that sense light. It serves a function similar to the film in a camera. Depending on where damage occurs in the retina, different aspects of vision are affected.

**Retinal pigment epithelium**

The retinal pigment epithelium is sandwiched between the choroid and the retinal visual cells (the rods and cones). It serves many functions, including light absorption. Damage to the retinal pigment epithelium will impair vision.
APPENDIX C – REFERENCES


