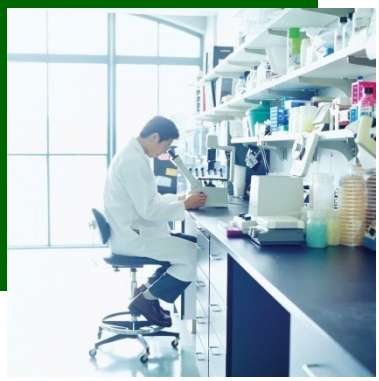
Provincial Health Services Authority

Provincial Retinal Diseases Treatment Program

Phase IV:

Quality Review Report



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Provincial Health Services Authority
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CHAPTER ONE: INTRODUCTION - WHAT IS THIS QUALITY REVIEW ABOUT?

In the past 10 – 15 years, the treatment of retinal disease has changed dramatically. The use of intravitreal injections (also known as intra-ocular injections or injections into the eye) of anti-vascular endothelial growth factor (anti-VEGF) medications have "revolutionized the treatment of numerous retinal disorders" [1, 2] in a positive manner, preserving vision in ways not previously observed.

Since 2009 British Columbia's (B.C.'s) Provincial Retinal Diseases Treatment Program (PRDTP) has provided intravitreal drug treatment therapies for B.C. patients diagnosed with one of three approved retinal disease indications — wet age-related macular degeneration (AMD), diabetic macular edema (DME) and retinal vein occlusion (RVO). Since its start, the program has provided 100% coverage for a number of drugs for the treatment of retinal diseases when the drugs are prescribed and administered by retinal specialists. Through the provincial program, B.C. patients who have been diagnosed with one of three approved indications, have access to a group of anti-VEGF medications including, bevacizumab (Avastin), ranibizumab (Lucentis) and aflibercept (Eylea). This program also provides coverage for verteporfin (Visudyne) with photodynamic therapy for AMD. The Provincial Health Services Authority (PHSA) manages the provincial program on behalf of the Ministry of Health (MoH). Currently, thirty retinal specialists deliver the care and patients can access a retinal specialist by direct referral from their health providers and optometrists (data for twenty-nine retinal specialists who worked over course of the review are included in the study).

Before anti-VEGF treatments were available, the vision-related prognosis of patients with retinal disease patients was very poor. Without treatment, a systematic review of the natural history and prognosis of AMD found that these patients experience a steady deterioration in vision over the first two years. The review estimated the vision deterioration to be 1-line of visual acuity (VA) lost at three months, 2.7-lines lost after one year and 4-lines lost after two years. Further, the proportion of AMD patients who become legally blind (VA worse than 20/200), increases from a 20% at baseline to 75% by three years. [3]

Clinical studies have shown clear benefits of anti-VEGF treatment compared with sham treatment on various VA outcomes, including improving vision, reducing vision deterioration and preventing blindness. For example, in the MARINA 2006 and PIER 2008 studies, AMD patients in the anti-VEGF treatment group gained at least 15 letters at one year (26.6% with anti-VEGF treatment versus 6.6% with sham). As well, fewer patients treated with anti-VEGF drugs were legally blind (VA 20/200 or worse) at one year as compared to the sham group (14.3% with anti-VEGF treatment versus 44.9% with sham). [2,4-5]

In terms of the demonstrating non-inferiority between Avastin and Lucentis, a Cochrane Database Systematic Review published in 2019 assessed ten head-to-head randomized studies and found little or no difference in various VA outcomes between the two drugs.[4] This review included the CATT study (one- and two-year results) published in 2011 and 2013, which concluded that vision improvement is the same for Avastin as it is for Lucentis, and also included the IVAN study (two year results), published in July 2013 finding similar efficacy results with the CATT study. [6-7] The clinical effectiveness of Avastin was

also studied in the British Columbia's PRDTP. This retrospective cohort study of patients in BC with AMD showed that, when controlled for potential confounders, a gain in vision similar to what was observed in the CATT study over one year. Such gains were greatest by month three and were generally maintained thereafter. [8] A therapeutic review conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) in 2016 recommended that for the treatment of patients with wet AMD, DME, or RVO, Avastin is the preferred initial anti-VEGF therapy, based on similar clinical effectiveness and lower cost compared with other anti-VEGF treatments.[9]

Despite the noted visual benefits of anti-VEGF medications, the long-term implications of this treatment, including its effects on managing intra-ocular pressure (IOP) and risk of glaucoma, are still being evaluated. Temporary increases in pressure inside the eye (known as intra-ocular pressure or IOP) observed shortly after injections, are currently thought to be caused by the mechanical effect of injecting a volume of fluid into the eye; however, in most cases the pressure normalizes in 30 to 60 minutes after the injection [10-12]. With respect to longer-term effects on pressure, concerns are raised in the literature regarding a cumulative effect on IOP rise after multiple intraocular injections of anti-VEGF agents. A number of studies have investigated the longer-term effect of increasing IOP on the subsequent need for interventions to manage glaucoma. When reviewing the literature, however, variations in the study methods, exclusions, study sizes and available information regarding additional risk factors (e.g. inclusion/exclusion of patients in the study with increased IOP, or inclusion/exclusion of patients in the study with pre-existing ocular hypertension treatment) make it difficult to extract clear risk information for comparison purposes. Some research results are contradictory regarding the link between these injections and risk of increased IOP or glaucoma; however, what is clear in the literature, including from the emerging research about what the potential mechanisms for longer term increased IOP, is "that repeated intravitreal anti-VEGF injections may decrease the function of the aqueous outflow system and be associated with the development of glaucomatous disease." The recently published large chart review of 1,078 patients seen between 2005 and 2012 by Wingard et al, showed "a significant risk for glaucoma or sustained OHT (ocular hypertension) development in patients undergoing repeated treatments with anti-VEGF intravitreal injections for exudative AMD" [13].

Locally, in B.C., there has been ongoing attention to the question regarding the effect of anti-VEGF injections on increased pressure in the eye. As a component of the PRDTP quality improvement program, an investigation of anti-VEGF drugs and glaucoma requiring surgery in B.C. was conducted following reported cases of elevated IOP after anti-VEGF use. Three phases of analysis were completed before Phase IV, to be reported below. A summary of Phases I-III are summarized below and available on the PRDTP website:[1]

- Phase I (March 2018) linked data from the PRDTP database to the PHSA Surgical Patient Registry (SPR) (procedures performed in operating rooms) to identify glaucoma surgery. The preliminary data indicated the overall rate of PRDTP patients requiring glaucoma surgery, in the four years studied (2013-2017), was 1.4% across all program-covered indications.
- Phase II (June 2018) focused on all patients in the PRDTP database who received their first injection between 2011 and the end of 2015). This study included more procedures as it

[1] Provincial Retinal Disease Treatment Program website: http://www.phsa.ca/our-services/programs-services/provincial-retinal-disease-treatment#Quality--Improvement

included operating rooms *and* procedure rooms *and* physician office procedures. Linked data from the MoH dataset specifically the Medical Services Plan (MSP) billing data was used with PharmaNet. The two-year rate of glaucoma laser procedure or surgery using these expanded definitions (i.e. not solely operating rooms for this phase) was 2.1% average across *all* patients. For clarity, this was a composite endpoint of patient-level data of first event of either laser procedure or surgery, and was not a combined endpoint of laser and surgery. Higher risk, was associated with RVO, male sex, history of prior glaucoma and number of injections received. There was no increased risk related to pharmacy or drug used.

- Phase III (March 2019) was designed to more specifically look for the direct effect of treatment and therefore more precision in identifying the sub-group studied was used. Patients with a previous history of glaucoma were excluded. Over a two year follow-up, operating room surgeries that could be determined by linking the PRDTP database, SPR data and MSP data were used. Phase III found that the overall two-year glaucoma surgery rate was 0.5% over the years of 2011 to 2015; however, a higher number of injections given to a patient per year were associated with an increased risk. More specifically, for a subset of patients (11% of the patients) receiving 10-13 injections per year, the two-year rate was 2.4%.

Following the Phase III results, the MoH and PHSA issued a news release to inform patients of the possible risk of glaucoma surgery following treatments, stating the most conservative (highest) estimate of risk across *all* patients, the 2.1% risk noted in Phase II. MoH and PHSA committed to further study and the Phase IV analysis, presented here, represent the results on the next phase of quality review.

CHAPTER TWO: KEY STUDY QUESTIONS - WHAT IS BEING LEARNED FROM THIS REVIEW?

The Phase IV Quality Review was completed to answer three main study questions which were prompted by the previous results and supported by queries from the ophthalmologic community in B.C.. The ultimate goal of the review was to understand the risk of glaucoma-related outcomes in B.C., to explain that risk in a meaningful manner to patients; to identify any modifiable risk factors that were potentially influencing outcomes; and to recommend changes to them, making treatment for retinal disease as safe as possible.

The three specific study questions for this review included:

1. Is there evidence of an increase in ocular hypertension, laser procedure or glaucoma surgery rates among patients receiving anti-VEGF injections between 2009 and 2018?
2. What is the risk to patients over time from the first anti-VEGF injection to the development of ocular hypertension, laser procedure, or glaucoma surgery?
3. What are the factors associated with higher risk of ocular hypertension, laser procedure or glaucoma surgery?

As noted in these study questions, three outcomes of interest were examined: evidence of 1) ocular hypertension, 2) laser procedure and 3) glaucoma surgery. While measuring “glaucoma” in the broadest sense as an outcome would have been ideal, this quality review required reliable and available data. It is recognized that these measures may not definitively identify every patient with potential increased intra-ocular pressure; however, these outcome measures were of high quality and represented a reasonably close proxy. Outcome measures are discussed in more detail later in this report.

CHAPTER THREE: WHAT METHODS WERE USED IN THE PHASE IV QUALITY REVIEW?

The analysis utilized data from the PHSA and the MoH. All data were anonymized. The PRDTP database (from 2009-2018) provided data regarding the details of anti-VEGF injections. The Surgical Patient Registry (SPR) provided data regarding the eye surgeries performed between 2009 and 2018 in operating rooms (OR). In addition, data from the period 2004 – 2018 was utilized from the following sources: the Medical Services Plan (MSP) data for glaucoma diagnosis and procedure information; PharmaNet data for glaucoma drug prescriptions; Vital Statistics data to capture death information; Client Roster (CR) data to capture demographic data; Chronic Disease Registry (CDR) data to identify patients with diabetes. Details regarding the data sources are included in **Appendix A**.

Creating oversight and working teams

A first step in the Phase IV quality review process was to create a team to oversee the review process. **Appendix B** presents the members of the three groups involved: the Quality Working Group oversaw all aspects of the review including establishing the study questions and clinical and data definitions, review of all analyses and preparation of conclusions and summary reports; the Analytic Subgroup representing a diverse group of epidemiologic and analytic experts from PHSA, University of British Columbia (UBC) and Vancouver Coastal Health Authority (VCH), planned and executed the analysis. The external reviewers were engaged to assess and contribute to the plan for the review and then to serve as out-of-province peer reviewers to the process. A timeline of the project meetings (**Appendix B)** was posted on the PRDTP website and updated on a regular basis during the review period.

Establishing the outcomes of interest

Glaucoma is a chronic, progressive deterioration of the optic nerve and is typically caused or worsened by raised IOP inside the eye. The primary treatment of glaucoma is lowering of IOP to prevent or to slow down the damage to the optic nerve. In order to lower pressure, glaucoma treatment typically starts with medications and/or laser techniques, and if these fail or are not tolerated, the patient may receive surgical treatment.

Measuring “glaucoma” as a disease across its full continuum would have been ideal as an outcome; however, this diagnosis is a broad categorical term with a range of diagnostic features; in addition, from a data perspective no specific diagnostic code is consistently and reliably used to enable the use of this term. Therefore, after thorough review, the Quality Working Group identified three primary outcome measures which together served as a reasonably close proxy for “glaucoma”: ocular hypertension (higher than normal eye pressure as measured by the need to be prescribed glaucoma medication); (glaucoma) laser procedure; and, glaucoma surgery. While all three measures are referred as outcome measures, they all reflect an intervention (e.g., medication, procedure, surgery).

Note that the three outcomes were investigated separately and misclassification may occur when patients with increased IOP did not report having any one of the three outcome measures. In theory,

this misclassification would reduce the estimate of risk. Clinician experts advised however, that this would be unlikely given the frequency of monitoring by retinal specialists in the PRDTP program.

For each of these outcomes, very explicit definitions were established to ensure accurate examination of the data. The Quality Working Group discussed these definitions at length prior to starting the review to ensure that the results would be as fulsome and as valid as is possible with the extensive data available. In addition, sensitivity analyses were conducted on the definitions to evaluate variations in the definitions. Explicit data definitions were desirable so that future comparisons with other jurisdictions would be possible. The detailed data definitions, including the explicit medications used in the data definition for ocular hypertension, are provided in **Appendix C**.

To put the B.C. results into B.C. context, two study cohorts were created, including the **Program Cohort** (B.C. patients who received anti-VEGF injections in the PRDTP for approved indications - AMD, DME, RVO) and the **Non-Program Cohort** (excluding patients in the Program Cohort and including all B.C. patients who have been identified by either condition in the MSP data Claim specialty code 06: Ophthalmology and/or ICD9 diagnosis code: 365.XX Glaucoma). Essentially the Non-Program Cohort was made up of all additional patients who saw an ophthalmologist in B.C., excluding those patients in the PRDTP program. This group was clearly very different than the Program Cohort in that the Non-Program Cohort included all reasons for seeing an ophthalmologist which could have included, for example, younger individuals with eye injuries and other transient conditions for which no linkage to the outcomes of interest was expected. However, as a reference group was desirable, the Non-Program Cohort was utilized for the review.

Establishing the analytic approach

Before starting the analysis, the data sets were obtained in keeping with appropriate data sharing agreements from the MoH. The data extract was then linked.

The analytic approach followed the following steps: define the available variables; conduct descriptive analysis of the Program Cohort and the Non-Program Cohort; conduct univariate analysis on selected factors and outcomes; and, based on the univariate analysis, conduct multivariable analysis using 2 year follow-up to investigate trends in outcome rates over time; up to 5 year follow-up to examine the association of variation among retinal specialists in relation to risk of outcomes; and up to 9.5 year follow-up to assess association of all factors and outcomes. **Appendix D** provides additional detail regarding the steps in this analysis, the statistical methods of the multivariable approach, the framework for analysis by study question and the study design flowchart.

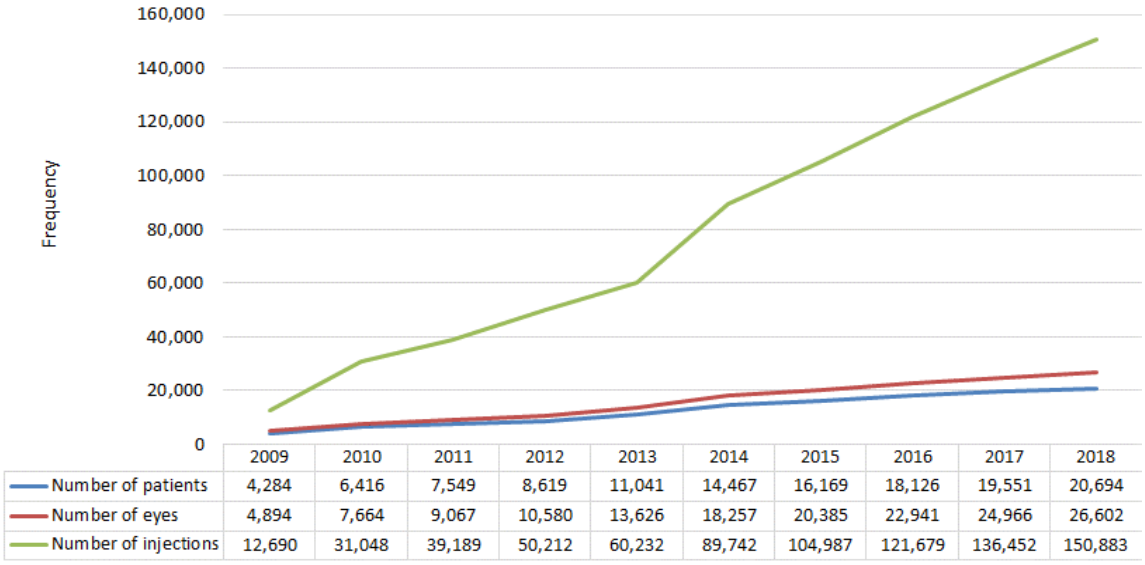
CHAPTER FOUR: RESULTS

What was found in the initial descriptive analysis?

First, a descriptive review of the data provided information about the patients included in the study and set the stage for further analysis.

The PRDTP program increased from 4,284 active patients per year in 2009 to 20,694 active patients per year in 2018, having served 41,051 unique patients over the course of the program to 2018. In total 52,770 patient eyes received 795,027 injections over the 2009 to 2018 period. The frequency of injections also increased over the period, specifically after the introduction of DME and RVO as indications for treatment in 2013. In 2018, 63% of injections were for AMD, 24% were for DME and 13% were for RVO. As well in 2018, 86% of injections were of Avastin, 13% were of Eylea and 1% were of Lucentis.

Exhibit 1: Number of PRDTP Patients, Patient Eyes and Injections by Year (2009-2018)



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Number of patients	4,284	6,416	7,549	8,619	11,041	14,467	16,169	18,126	19,551	20,694
Number of eyes	4,894	7,664	9,067	10,580	13,626	18,257	20,385	22,941	24,966	26,602
Number of injections	12,690	31,048	39,189	50,212	60,232	89,742	104,987	121,679	136,452	150,883

Data source: PRDTP data (2009-2018)

Note: PRDTP commenced as a program mid-way through June 2009 with approval for treatment of AMD indication. RVO and DME indications were subsequently approved in 2013.

Exhibit 2: (New) Patient Characteristics by Year of Enrollment

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	All
# of New Patient	4284	3150	2949	2989	3693	4640	4667	5040	4940	4699	41051
Age (mean±SD)	79 ±10	77 ±12	77 ±12	76 ±12	74 ±13	73 ±13	73 ±13	73 ±13	73 ±14	73 ±14	74 ±13
Male	39.1%	40.1%	42.4%	43.9%	46.9%	49.3%	46.6%	47.5%	49.3%	48.0%	45.7%
Previous Glaucoma Surgery	0.5%	0.6%	0.4%	0.6%	0.8%	1.5%	1.2%	1.1%	1.0%	1.2%	0.9%
Previous Laser	3.4%	2.6%	3.0%	3.5%	3.5%	4.6%	4.6%	4.5%	4.2%	4.5%	4.0%
Previous Ocular Hypertension	12.8%	12.9%	10.9%	10.0%	10.7%	11.7%	10.7%	10.6%	11.0%	9.8%	11.1%
AMD	94.1%	91.1%	84.0%	79.9%	61.7%	49.6%	52.8%	51.4%	52.3%	54.1%	64.7%
DME	4.0%	5.7%	11.0%	12.6%	22.2%	29.9%	25.2%	27.0%	27.3%	24.7%	20.2%
RVO	1.9%	3.2%	4.9%	7.5%	16.1%	20.6%	22.0%	21.6%	20.4%	21.2%	15.1%

Note: Patient indication over the entire treatment period is reviewed. Where multiple indications are provided for a patient, indication is attributed based on the following hierarchy: RVO, DME and then AMD. A small number of DME/RVO patients were treated and coded as AMD prior to MoH approval of these indications in 2013.

Data Source: PRDTP, MSP, SPR, Client Roster, PharmaNet, Vital Statistics, Chronic Disease Registry (2009-2018).

Exhibit 3: Total Injections by Indication and Injected Drug Type (2009-2018)

	All	Injection Drug Type					
		Avastin		Eylea		Lucentis	
	N	n	%	n	%	n	%
AMD	580,449	501,819	86.5	33,738	5.8	44,892	7.7
DME	139,402	116,064	83.3	18,461	13.2	4,877	3.5
RVO	75,176	64,490	85.8	7,900	10.5	2,786	3.7
All Indications	795,027	682,373	85.8	60,099	7.6	52,555	6.6

Data Source: PRDTP data (2009-2018)

Summary of findings:

With respect to the findings of the first stage of descriptive analysis, a number of key observations from the range of analyses completed were made:

- Addition of program coverage for RVO and DME indications midway through the study period (2013) appeared to impact analysis of year-over-year trends. Further analysis by indication (AMD, RVO, DME) will be important given differences in the underlying patient populations.

- Conclusions by drug type injected (Avastin, Lucentis, Eylea, switchers[2]) may be challenging given small sample sizes for the sole use of Lucentis and the sole use of Eylea and statistically significant correlations with other factors (e.g., indication for use of one drug over another).
- On average, 11.1% of patients had ocular hypertension prior to entering the PRDTP, indicating that previous history of elevated IOP was an important factor for consideration.
- The number of injections per patient eye increased over the study period making it a variable of continued interest.

In addition, with respect to the Non-Program Cohort, patient characteristics were reviewed. In keeping with what would be expected given the data definition, the Non-Program Cohort was younger (33% were less than 50 years of age compared to only 6% of the Program Cohort being less to 50 years) and had a lower rate of pre-existing diabetes. Importantly, the Non-Program Cohort had a much lower level of pre-existing ocular hypertension (0.3% compared to 11.1% in the Program Cohort). In addition, it was noted that given the number of injections provided per year, the Program Cohort was more likely to report more frequent visits to a retinal specialist/ophthalmologist, increasing the likelihood that one of the outcomes could be identified compared to the Non-Program Cohort (detection bias). Overall, these findings highlight that the Program Cohort and Non-Program Cohort are *not* comparable with respect to what we see in the outcomes. The Non-Program Cohort, however, could serve as a reference group approaching what would be seen in the general population of B.C and without these retinal diseases.

[2] A switcher uses more than one drug over the course of treatment.

Quality Review Results - Study Question 1:

Is there evidence of an increase in ocular hypertension, laser procedure or glaucoma surgery rate among patients receiving anti-VEGF injections between 2009 and 2018?

To answer this question, two different sets of analyses were completed. First, crude (unadjusted) cumulative incidence rates over time were evaluated for both the Program Cohort and Non-Program Cohort. It should be noted that the results were expected to be different between the two groups given differences previously noted between the two groups, including pre-existing ocular hypertension in 11.1% of the Program Cohort versus 0.3% of the Non-Program Cohort. Second, multivariable cause-specific hazards modeling examined the time trend in two-year glaucoma surgery rates, using 2010 as the baseline year as it is the first full year of PRDTP data.

Exhibits 4, 5 and 6 present results of the univariate and multivariable analysis for the glaucoma surgery outcome.

Exhibit 4: Glaucoma Surgery Crude Cumulative Incidence per 100 *Patient Eyes* by Follow-up Year – Program Cohort (2009-2018)

Number of Follow-up Years	Year of First Anti-VEGF Injection									
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
1 year	0.1	0.2	0.1	0.2	0.2	0.4	0.4	0.7	0.6	0.4
2 years	0.4	0.4	0.5	0.7	0.6	0.9	1.1	1.4	1.2	.
3 years	0.6	0.6	0.8	1.0	1.2	1.5	1.7	1.8	.	.
4 years	1.0	0.8	1.1	1.4	1.8	1.8	2.0	.	.	.
5 years	1.1	1.0	1.3	1.6	2.2	2.2	.	.	.	.
6 years	1.2	1.3	1.6	2.0	2.5	.	.	.	.	.
7 years	1.3	1.5	1.8	2.0	.	.	.	.	.	.
8 years	1.4	1.7	2.2	.	.	.	.	.	.	.
9 years	1.4	1.8	.	.	.	.	.	.	.	.
10 years	1.5	.	.	.	.	.	.	.	.	.

Data Sources: PRDTP, MSP, SPR, Vital Statistics (2009-2018).

Exhibit 5: Glaucoma Surgery Crude Cumulative Incidence per 100 *Patients* by Follow-up Year – Program vs. Non-Program Cohort (2009- 2018)

Program Cohort:

Number of Follow-up Years	Year of First Anti-VEGF Injection									
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
1 year	0.3	0.3	0.2	0.3	0.6	0.8	0.9	1.0	1.1	0.8
2 years	0.7	0.6	0.8	1.0	1.1	1.6	1.8	2.1	2.1	.
3 years	1.0	0.9	1.3	1.6	2.0	2.3	2.9	2.9	.	.
4 years	1.5	1.3	1.8	2.2	2.8	2.8	3.6	.	.	.
5 years	1.7	1.7	2.1	2.7	3.4	3.3	.	.	.	.
6 years	1.9	2.1	2.6	3.3	4.0	.	.	.	.	.
7 years	2.3	2.5	3.0	3.3	.	.	.	.	.	.
8 years	2.5	2.8	3.2	.	.	.	.	.	.	.
9 years	2.6	2.9	.	.	.	.	.	.	.	.
10 years	2.7	.	.	.	.	.	.	.	.	.

Non-Program Cohort:

Number of Follow-up Years	Year of First Visit to Ophthalmologist									
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
1 year	0.1	0.0	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.1
2 years	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	.
3 years	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	.	.
4 years	0.1	0.1	0.1	0.1	0.1	0.1	0.1	.	.	.
5 years	0.2	0.1	0.1	0.1	0.2	0.2	.	.	.	.
6 years	0.2	0.2	0.2	0.2	0.2	.	.	.	.	.
7 years	0.2	0.2	0.2	0.2	.	.	.	.	.	.
8 years	0.3	0.2	0.2	.	.	.	.	.	.	.
9 years	0.3	0.2	.	.	.	.	.	.	.	.
10 years	0.3	.	.	.	.	.	.	.	.	.

Data Sources: PRDTP, MSP, SPR, Vital Statistics (2009-2018).

Exhibit 6: Glaucoma Surgery Multivariable Cause-specific Hazards Model Examining Time Trend in Two-Year Cumulative Incidence Rates - Program Cohort (2009-2017)

Factor: Year of First Injection (Comparison Year = 2010)	**2-Year Cumulative Incidence Rate**	**95% Confidence Intervals**			
		Hazard Ratio	**Lower Limit – Higher Limit**		**p-value**
2009 vs 2010	0.37	1.07	0.52	2.18	0.8613
2010 vs 2010	0.35	1.00			
2011 vs 2010	0.47	1.34	0.66	2.74	0.4184
2012 vs 2010	0.68	1.88	0.98	3.59	0.0564
2013 vs 2010	0.61	1.52	0.81	2.88	0.1963
2014 vs 2010	0.93	2.09	1.16	3.78	0.0144
2015 vs 2010	1.05	2.45	1.37	4.39	0.0026
2016 vs 2010	1.35	3.10	1.75	5.48	0.0001
2017 vs 2010	1.15	3.07	1.69	5.56	0.0002

Data Sources: PRDTP, MSP, SPR, Client Roster, PharmaNet, Vital Statistics, Chronic Disease Registry (2009-2018).

Note: - These hazard ratios are adjusted for patient baseline characteristics including age, sex, and indication for injection, prior ocular hypertension, and prior laser procedure. Patients who had had glaucoma surgery prior to first injection were excluded. 2017 cumulative incidence rate is underestimated due to insufficient follow-up.

Similar crude cumulative incidence rate analyses at the patient level were completed for the outcome of ocular hypertension and laser procedures.

The results of all three outcomes' results are summarized below.

Summary of findings:

Question 1, crude cumulative incidence rates were calculated and their trends over time were examined.

The two year follow-up crude cumulative (unadjusted for factors that could influence outcome) incidence rates were as follow:

- Glaucoma surgery two year crude cumulative incidence rate was between 0.4% -0.7% for those patients with the first injection in 2009 and between 1.2% - 2.1% for those patients with the first injection in 2017. A range is provided given limitations in the data both at the lower and upper ends. The lower end of each of these ranges represented the incidence when only eye-level data was used (meaning we could be sure the injection and the surgery occurred in the same eye); this excludes glaucoma surgery cases where eye-level information is missing. The upper end of each of these ranges represented the incidence when patient level data was used (meaning the injection and the surgery may or may not have occurred in the same eye).

- Laser procedure crude cumulative incidence rate was measured at the patient level (no eye level data available) and the two year crude cumulative incidence rate was 0.8% in 2009 and 2.3% in 2017.
- Ocular hypertension crude cumulative incidence rate was measured at the patient level (no eye level data available) and the two year crude cumulative incidence was 3.7% in 2009 to 8.2% in 2017.

The increase in the incidence rate mainly after 2013 may have been influenced by the introduction of DME and RVO as approved indications in 2013, as a particular increase was seen around that time period. The multivariable analysis, however, adjusted for patient baseline characteristics (including indication) and continued to show increased glaucoma surgery risk in the Program Cohort during the period of 2014 to 2017 suggesting factors other than indication for treatment were influencing the change over time.

The Non-Program Cohort demonstrated lower incidence rates that were low over time for all three outcomes and relatively stable over time for all three outcomes. These differences were not surprising given the very important distinctions between the two patient populations.

Quality Review Results – Study Question 2:

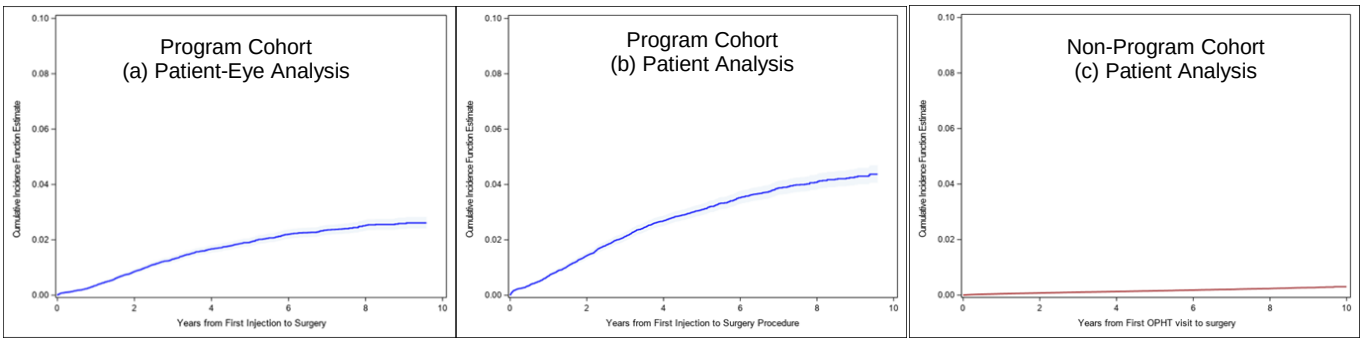
What is the risk to patients over time from the first anti-VEGF injection to the development of ocular hypertension, laser procedure, or glaucoma surgery?

To answer this question, the cumulative incidence rate was calculated to estimate the incidence rate of the outcome occurring while taking death or loss to follow-up into account (which would preclude the subsequent occurrence of the outcome). As the average age of patients in the PRDTP was 74 years of age, it is important to take death or loss to follow-up into account. This approach allowed incidence to be estimated in a population as a function of follow-up time and provided important information on the absolute risk of an event.

The following exhibits demonstrate the results with respect to the glaucoma surgery outcome. Additional exhibits are available with respect to the additional two outcomes and are consistent thematically with glaucoma surgery. The crude cumulative incidence rates with two-year follow-up by primary retinal physician are provided in **Appendix E** for all three outcomes.

Keeping in mind the known differences between the Program Cohort and Non-Program Cohort (including the pre-existing ocular hypertension in 11.1% of the Program Cohort before their first injection versus 0.3% of the Non-Program Cohort having ocular hypertension before their first visit), the following results were observed:

Exhibit 7: Crude Cumulative Glaucoma Surgery Incidence Rate – Program Cohort (eye level and patient level) and Non-Program Cohort (2009-2018)



	Number of Follow-up Years	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years	7 Years	8 Years	9 Years
Program	**Eye-level**	0.35%	**0.85%**	1.30%	1.67%	1.92%	2.20%	2.36%	2.52%	2.59%
	Patient-Level	0.69%	**1.43%**	2.12%	2.69%	3.09%	3.53%	3.87%	4.09%	4.27%
Non-Program	**Patient-Level**	0.05%	**0.08%**	0.10%	0.13%	0.15%	0.18%	0.21%	0.24%	0.27%

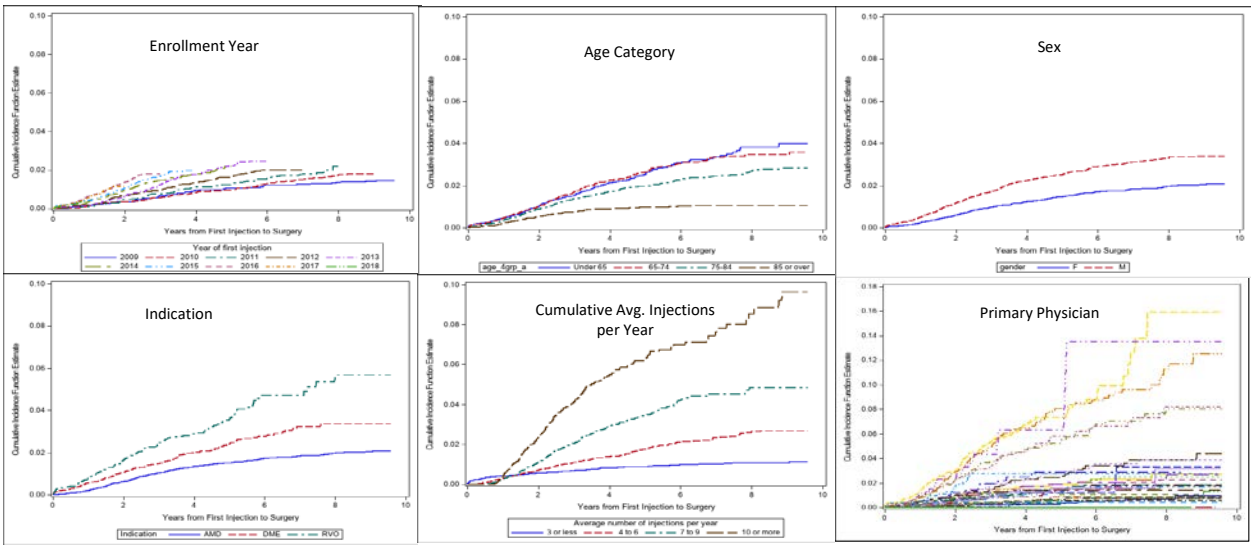
Note: Patients treated with glaucoma surgery prior to their first injection (Program Cohort) or prior to their first visit to ophthalmologist (Non-Program Cohort) are excluded.

Data Sources: PRDTP, MSP, SPR, Vital Statistics (2009-2018).

Exhibit 7 notes both eye-level data and patient level data. The patient level data reflects patients who have received anti-VEGF treatment and then went on to have glaucoma surgery; however, the patient may have had the injection in one eye and the surgery in the other eye and thus the *patient* level outcomes may reflect an over-estimate of the incidence rate. The eye-level data reflects the incidence based on linked data where the injection and the surgery both occurred in the same eye. This eye level data *should* reflect a more accurate estimate of incidence rate; however, because of incomplete data linkage due to missing fields and perhaps missing surgeries, the most conservative approach is to state a range of risks between the eye-level data and the patient-level date rates. Thus, for example, the two-year cumulative incidence rate of glaucoma surgery in the Program Cohort was between 0.85% and 1.43%. Note that sensitivity analysis was conducted on the results by patient and by patient-eye and comparable results were found across all factors studied.

Given these crude cumulative rates, with the goal of understanding the factors influencing them, univariate crude cumulative incidence rates were calculated for various factors that may influence risk (patient and non-patient related factors):

Exhibit 8: Crude Cumulative Glaucoma Surgery Incidence Rates (eye level) – Program Cohort – Selected Factors (2009-2018)



Data Sources: PRDTP, MSP, SPR, Vital Statistics (2009-2018).

This important set of figures outline a number of factors that may influence the crude cumulative incidence rate for glaucoma surgery. The selected factors reviewed one by one indicated the following:

- **Enrollment year:** There were statistically significant differences by enrollment year with 2009 and 2010 reporting the lowest rates. Incidence rates increased with year of enrollment (p<.001). 2009 was the first year over which patients were enrolled presumably contributing to these low rates.
- **Age group:** In the Program Cohort, those greater than 85 years of age reported the lowest rates and those less than 74 years of age reported the highest incidence rates (p<.001).
- **Sex:** The Program Cohort reported higher incidence rates in males compared to females (p<.001).
- **Indication:** RVO reported statistically significantly higher incidence rates followed by DME and wAMD (p<.001).
- **Cumulative average number of injections per follow-up year:** Increasing frequency of injections was associated with increasing incidence rates (p<.001). It is critical to note that this metric describes the number of injections "per year of follow-up". This means, for example, that a patient followed for three years with an average of 6 injections per follow-up year would have had approximately 18 injections over the three year period. A limitation of this cumulative average number of injections per follow-up year is that the spacing between injections may have varied over the years of follow-up and also may have been subject to between patient variation.
- **Primary Retinal Physician:** There were statistically significant differences in incidence rates across primary retinal physicians (p<.001). The primary retinal physician is the retinal specialist

physician from whom a given patient receives the majority of their injections, recognizing that over the course of their follow-up they may see more than one retinal specialist.

Summary of findings:

To answer this question, the crude cumulative incidence rate was calculated to estimate the incidence rate of the outcome occurring while taking death or loss to follow-up into account (which would preclude the subsequent occurrence of the outcome). This allows incidence to be estimated in a population as a function of follow-up time and provides important information on the absolute risk of an event.

The risk for glaucoma surgery, as measured by 2-year incidence rate of glaucoma surgery was between 0.85% (based on eye level data) to 1.43% (based on patient level data). While this incidence rate was lower than what was previously identified in the Phase II Quality Review (which was 2.1% for composite endpoint of glaucoma laser procedure orsurgery), these rates cannot be directly compared. Compared with Phase II methods, the Phase IV analysis separately evaluated surgeries from laser procedures, included more patients, had a longer study follow-up period, included a more robust definition of glaucoma surgery verified by MSP and SPR (excludes laser and office procedures), and , importantly, used additional data sets allowing for examinations of the association between eye-specific risk factors and the outcome which could influence the comparison to the previous phase. With these methodological differences, there is greater confidence of the risk estimate findings from Phase IV compared to Phase II.

For those patients for whom up to 9 year follow-up was possible, the crude cumulative incidence rates after 9 years of follow-up was between 2.59% (based on eye-level data) and 4.27% (based on patient level data). This is a crude measure and does not take into account confounding factors.

Of the factors reviewed through the cumulative incidence univariate analysis, a number of factors were associated with increased risk for the three outcomes of interest that is ocular hypertension, laser procedure, or glaucoma surgery over time. The patient-related factors of age < 75 years, male sex, RVO and DME as indications for treatment and, higher average number of injections per follow-up up year were associated with increased risk. With respect to non-patient related factors, the year of the patients' enrollment (enrolling after 2013), and specific primary retinal physician treating the patient were all factors shown to be predictors of increased risk.

These factors are further examined in the multivariable analysis to evaluate associations between risk factors and outcomes in response to review Study Question 3.

Quality Review Results – Study Question 3:

What are the factors associated with higher risk of ocular hypertension, laser procedure, glaucoma surgery?

Before describing the approaches used for the multivariable modelling, univariate analysis of selected factors by outcome was first conducted using a Cox regression model. Then, to address Study Question 3, controlling for baseline characteristics (i.e., age, sex, indication, previous history of the outcome of interest prior to injection), a multivariable cause-specific hazards model examined the factors associated with the outcomes using:

- **Up to 9.5 year follow-up:** To examine the association of select factors on the risk of outcomes, recognizing that additional follow-up time allows for the possibility of time related biases including disease severity which can also affect the risk of outcomes.
- **Up to five year follow-up:** To examine the associations of variation among retinal specialists in relation to the risk of the outcomes as had emerged from the univariate analysis. A five year time frame was used for the retinal physician analysis to decrease the number of patients lost to follow-up and improve the robustness of the estimate.

After controlling for baseline characteristics, the association of the following factors with the outcomes was examined: Patient-related factors including injected drug type, cumulative average injections per follow-up year; Non patient-related factors including physician practice location and primary retinal physician.

Exhibit 9 shows the results of the first step of the analysis for Study Question 3.

Exhibit 9: Univariate Cox Regression Analysis by Outcome with up to 9.5 Years of Follow-up (2009-2018)

Factor	Time to Glaucoma Surgery (n=52,770 patient eyes)					Time to Ocular Hypertension (n=34,995 patients)					Time to Laser Procedure (n=37,992 patients)				
	No. of patient eyes (%)	Hazard Ratio	95% Confidence Limits Lower	Upper	p-value	No. of patients (%)	Hazard Ratio	95% Confidence Limits Lower	Upper	p-value	No. of patients (%)	Hazard Ratio	95% Confidence Limits Lower	Upper	p-value
Age at injection (per 10 years)	74.5 ±13.0 Mean ± STD	0.85	0.81	0.88	<.001	73.9 ± 13.0 Mean ± STD	0.97	0.95	0.99	0.0096	74.2 ±12.9 Mean ± STD	0.95	0.91	0.98	0.0004
Sex															
Female	28809 (54.6)	1	.	.	.	18936 (54.1)	1	.	.	.	20542 (54.1)	1	.	.	.
Male	23961 (45.4)	1.77	1.54	2.03	<.001	16059 (45.9)	1.26	1.19	1.34	<.0001	17450 (45.9)	1.24	1.11	1.39	<.001
History of diabetes															
No	30233 (57.3)	1	.	.	.	20728 (59.2)	1	.	.	.	22513 (59.3)	1	.	.	.
Yes	22537 (42.7)	1.3	1.13	1.49	<.001	14267 (40.8)	0.94	0.89	1.00	0.0635	15479 (40.7)	0.92	0.82	1.04	0.199
Prior laser procedure															
No	51165 (97)	1	.	.	.										
Yes	1605 (3.0)	6.22	5.13	7.55	<.001										
Prior history of ocular hypertension															
No	47146 (89.3)	1	.	.	.						34692 (91.3)	1	.	.	.
Yes	5624 (10.7)	4.02	3.47	4.65	<.001						3300 (8.7)	3.62	3.17	4.12	<.001
Injected drug type															
Switcher	12876 (24.4)	1	.	.	.	9617 (27.5)	1	.	.	.	10417 (27.4)	1	.	.	.
Avastin	38783 (73.5)	0.92	0.8	1.06	0.245	24834 (71.0)	0.85	0.80	0.91	<.0001	26975 (71.0)	0.78	0.7	0.88	<.001
Eylea / Lucentis	1111 (2.1)	0.4	0.19	0.84	0.016	544 (1.5)	0.37	0.26	0.54	<.0001	600 (1.6)	0.48	0.26	0.9	0.021
Indication															
AMD	33112 (62.7)	1	.	.	.	21858 (62.5)	1	.	.	.	23684 (62.3)	1	.	.	.
DME	12647 (24.0)	1.27	1.08	1.49	0.003	7604 (21.7)	0.98	0.91	1.06	0.6854	8106 (21.3)	0.93	0.8	1.09	0.383
RVO	7011 (13.3)	2.13	1.81	2.52	<.001	5533 (15.8)	1.73	1.61	1.87	<.0001	6202 (16.3)	1.56	1.35	1.81	<.001
Cumulative avg number of injections per follow-up year															
≤ 3	24383 (46.2)	1	.	.	.	13439 (38.4)	1	.	.	.	14754 (38.8)	1	.	.	.
> 3 - ≤ 6	13817 (26.2)	0.92	0.78	1.07	0.282	8683 (24.8)	0.87	0.81	0.94	0.0002	9513 (25.0)	0.83	0.72	0.95	0.007
> 6 - ≤ 9	9497 (18.0)	1.90	1.63	2.22	<.001	6341 (18.1)	1.41	1.31	1.51	<.0001	6867 (18.1)	1.61	1.41	1.84	<.001
>9	5073 (9.6)	3.67	3.13	4.3	<.001	6532 (18.7)	2.10	1.97	2.25	<.0001	6858 (18.1)	2.52	2.23	2.84	<.001

Data Sources: PRDTP, MSP, SPR, Client Roster, PharmaNet, Vital Statistics, Chronic Disease Registry (2009-2018).

Results from this univariate analysis showed consistent themes and trends across all three outcomes. In reviewing these results, the blue shaded hazard ratio columns for each of the three outcomes identified the increased risk associated with the individual factors of interest. As expected, prior laser procedure presented in the Exhibit above showed the following result: the hazard ratio shown for patients who had a prior laser procedure (that is, they had had a laser procedure before ever receiving an anti-VEGF injection through the PRDTP) was 6.22 meaning patients who have had laser procedure have approximately 6 times the risk of glaucoma surgery compared with patients with no prior history of laser procedure.

Statistically significant differences were identified with respect to the following factors when each were considered on their own, that is, through the univariate analysis: Age: increased risk < 75 years of age; Sex: increased risk among males; Diabetes diagnosis: increased risk for glaucoma surgery; Prior laser procedure: increased risk of glaucoma surgery; Prior history of ocular hypertension: increased risk of glaucoma surgery and of laser procedure; Injected drug type: increased risk with those who were switchers (i.e., a switcher used more than one drug over course of treatment); Indication: increased risk for RVO indication; Cumulative average number of injections per follow-up year: increased risk with increasing injections per year of follow-up (specifically >6 average injections per follow-up year).

Exhibit 10: Multivariable Fine and Gray Sub-Distribution Hazards Model Results by Outcome with up to 9.5 Years of Follow-up (2009-2018)

Factor		Time to Glaucoma Surgery				Time to Ocular Hypertension				Time to Laser Procedure			
		Hazard Ratio	95% Hazard Ratio Confidence Limits Lower – Higher		p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits Lower – Higher		p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits Lower – Higher		p-value
Age	per 10 years	0.80	0.75	0.85	<.0001	1.01	0.98	1.04	0.6061	0.88	0.84	0.93	<.0001
Sex	Male vs. Female	1.66	1.43	1.94	<.0001	1.26	1.18	1.34	<.0001	1.23	1.10	1.39	0.0004
Indication	DME vs. AMD	1.20	0.97	1.49	0.0871	1.08	0.99	1.19	0.0852	0.86	0.72	1.03	0.1014
	RVO vs. AMD	1.79	1.47	2.18	<.0001	1.94	1.79	2.11	<.0001	1.51	1.29	1.77	<.0001
Prior ocular hypertension	Yes vs. No	3.59	2.99	4.31	<.0001					4.07	3.55	4.67	<.0001
Prior laser procedure	Yes vs. No	3.01	2.35	3.84	<.0001								
Cumulative average # of injections per follow-up year for Avastin only drug:	>3 - ≤6 vs. ≤3	1.92	1.50	2.46	<.0001	1.62	1.46	1.80	<.0001	2.11	1.70	2.62	<.0001
	>6 - ≤9 vs. ≤3	4.74	3.72	6.02	<.0001	2.53	2.27	2.83	<.0001	3.98	3.21	4.93	<.0001
	>9 vs. ≤3	9.94	7.66	12.91	<.0001	3.88	3.49	4.31	<.0001	6.67	5.42	8.21	<.0001

Note: These hazard ratios are adjusted for patient baseline characteristics including age, sex, indication for injection, prior ocular hypertension (for laser procedure and glaucoma surgery outcomes), prior laser procedure (for glaucoma surgery outcome). History of diabetes factor was removed from multivariable analysis due to the collinearity with DME indication. The higher hazard ratios and wider confidence intervals must be interpreted with caution due to a smaller number of events in this group.

Data Sources: PRDTP, MSP, SPR, Client Roster, PharmaNet, Vital Statistics, Chronic Disease Registry (2009-2018).

When the multivariable Fine and Gray sub-distribution hazards model analysis were completed, similar findings and trends to the univariate analysis were noted. The multivariable analysis investigated the effect of baseline patient characteristics, frequency of injections per follow-up year and injected drug type.

With respect to the specific type of an injection (Avastin, Lucentis or Eylea), data for patients who were treated with Lucentis only or Eylea only were excluded due to a small sample size. Univariate and multivariable analyses by drug type did use data from patients that were treated with Lucentis and Eylea in combination with Avastin over the course of their treatments period. The univariate analyses indicated that "switchers" (that is, patients who were treated with more than one drug type over the course of their treatment) experienced increased risk in comparison to those who had Avastin only injections. Data from the switcher group is challenging to interpret as this is a heterogeneous group compared with the pure Avastin patient users (i.e., the combination of drugs within the switchers group represented a variety of combinations of drug types given in varying orders and for varying durations). After discussion through the Quality Working Group, it was determined that drawing conclusions from this heterogeneous switcher group was challenging and potentially subject to bias. Therefore, the analysis above in Exhibit 10 included Avastin only injections. Results indicate that more frequent injections per year of follow-up increases the risk of all three outcomes.

The next area for analysis focused on studying variations across physicians using up to five year follow-up time frames. Physicians, all of whom were retinal specialists, and their practice locations or groups were considered in this analyses. Physicians were denoted to be the primary retinal physician ("Primary Retinal Physician") for the patients for whom they provided the majority of their treatments. To

evaluate the effect of primary retinal physician on outcomes, the *initial* multivariable model was adjusted for baseline patient characteristics only (including age, sex, indication, and prior ocular hypertension and/or laser procedure) (see Exhibit 11). Then, to investigate the influence of selected practice differences on primary retinal physician the model added cumulative average number of injections per follow-up year, followed by injected drug type (see Exhibit 12).

Exhibit 11: Multivariable cause-specific Hazards Model Results by Outcome (controlling for baseline patient characteristics) with up to Five Years of Follow-up – Primary Retinal Physician (2009-2018)

	Time to Glaucoma Surgery (*n*=52,770 patient eyes)				Time to Ocular Hypertension (*n*=34,995 patients)				Time to Laser Procedure (*n*=37,992 patients)			
Primary Retinal Physician vs BC Average	Hazard Ratio	95% Confidence Limit Lower	Upper	p-value	Hazard Ratio	95% Confidence Limit Lower	Upper	p-value	Hazard Ratio	95% Confidence Limit Lower	Upper	p-value
24	0.20	0.07	0.59	0.0037	1.07	0.90	1.27	0.4597	0.81	0.52	1.27	0.3536
1	0.26	0.13	0.52	0.0001	0.78	0.67	0.91	0.0015	0.84	0.61	1.15	0.2788
8	0.36	0.15	0.84	0.0184	0.49	0.37	0.65	<.0001	1.02	0.68	1.54	0.9217
9	0.38	0.20	0.72	0.0031	0.69	0.57	0.82	<.0001	0.58	0.38	0.88	0.0102
17	0.39	0.17	0.93	0.0338	0.51	0.38	0.68	<.0001	0.27	0.12	0.63	0.0026
14	0.41	0.20	0.85	0.0159	0.59	0.47	0.74	<.0001	1.34	0.96	1.86	0.0840
3	0.41	0.22	0.77	0.0059	0.66	0.55	0.79	<.0001	0.68	0.47	0.98	0.0380
27	0.54	0.25	1.19	0.1288	0.84	0.66	1.06	0.1365	0.86	0.52	1.41	0.5484
2	0.58	0.24	1.41	0.2251	0.39	0.27	0.56	<.0001	0.14	0.04	0.53	0.0039
5	0.75	0.46	1.22	0.2516	0.70	0.57	0.85	0.0004	0.64	0.42	0.98	0.0418
12	0.82	0.53	1.25	0.3567	0.64	0.53	0.77	<.0001	0.67	0.44	1.00	0.0492
13	0.86	0.58	1.30	0.4836	0.43	0.35	0.52	<.0001	0.66	0.46	0.94	0.0202
7	0.96	0.66	1.40	0.8250	0.75	0.64	0.88	0.0004	1.12	0.84	1.50	0.4356
20	1.00	0.64	1.57	0.9948	1.44	1.26	1.65	<.0001	0.34	0.19	0.60	0.0002
21	1.10	0.56	2.15	0.7846	1.68	1.40	2.03	<.0001	0.97	0.58	1.63	0.9197
29	1.11	0.61	2.03	0.7316	1.46	1.20	1.79	0.0002	0.81	0.43	1.53	0.5128
25	1.11	0.68	1.82	0.6817	0.98	0.80	1.20	0.8352	1.14	0.76	1.71	0.5299
6	1.16	0.63	2.13	0.6444	1.03	0.82	1.30	0.7948	0.59	0.31	1.12	0.1045
15	1.23	0.87	1.74	0.2312	0.63	0.53	0.75	<.0001	1.02	0.75	1.39	0.8860
11	1.27	0.84	1.92	0.2619	0.97	0.81	1.16	0.7419	0.52	0.32	0.84	0.0079
4	1.47	0.96	2.26	0.0799	1.30	1.09	1.56	0.0040	0.93	0.64	1.36	0.6991
10	1.62	1.08	2.43	0.0195	1.07	0.87	1.30	0.5275	1.90	1.40	2.59	<.0001
23	1.75	1.04	2.96	0.0359	1.50	1.20	1.86	0.0003	5.89	4.56	7.60	<.0001
28	2.46	1.46	4.16	0.0007	0.65	0.47	0.92	0.0134	0.75	0.34	1.64	0.4680
16	3.94	2.97	5.23	<.0001	2.33	2.07	2.63	<.0001	2.44	1.90	3.13	<.0001
18	3.95	3.02	5.18	<.0001	2.17	1.92	2.46	<.0001	2.41	1.88	3.09	<.0001
26	4.34	2.84	6.63	<.0001	3.74	3.20	4.36	<.0001	5.04	3.69	6.89	<.0001
22	5.05	3.89	6.57	<.0001	2.72	2.41	3.07	<.0001	4.39	3.54	5.45	<.0001
19	5.25	4.20	6.56	<.0001	2.34	2.10	2.62	<.0001	3.85	3.17	4.68	<.0001

Important Notes:
- Physician names are coded with a number.
- The data are sorted from lowest to highest Glaucoma Surgery Hazard Ratio.
- These hazard ratios are adjusted for patient baseline characteristics including age, sex, indication for injection, prior ocular hypertension (for laser and surgery models), prior laser surgery procedure (for surgery models). This means that differences between physician hazard ratios cannot be explained on the basis of these factors.
- Patients were excluded from the risk analysis if they had the event of interest prior to the first injection date.
- Red font denotes statistically increased risk; Blue font denotes statistically decreased risk; black font denotes not statistically different from provincial average. Data Sources: PRDTP, MSP, SPR, Client Roster, PharmaNet, Vital Statistics, Chronic Disease Registry (2009-2018).

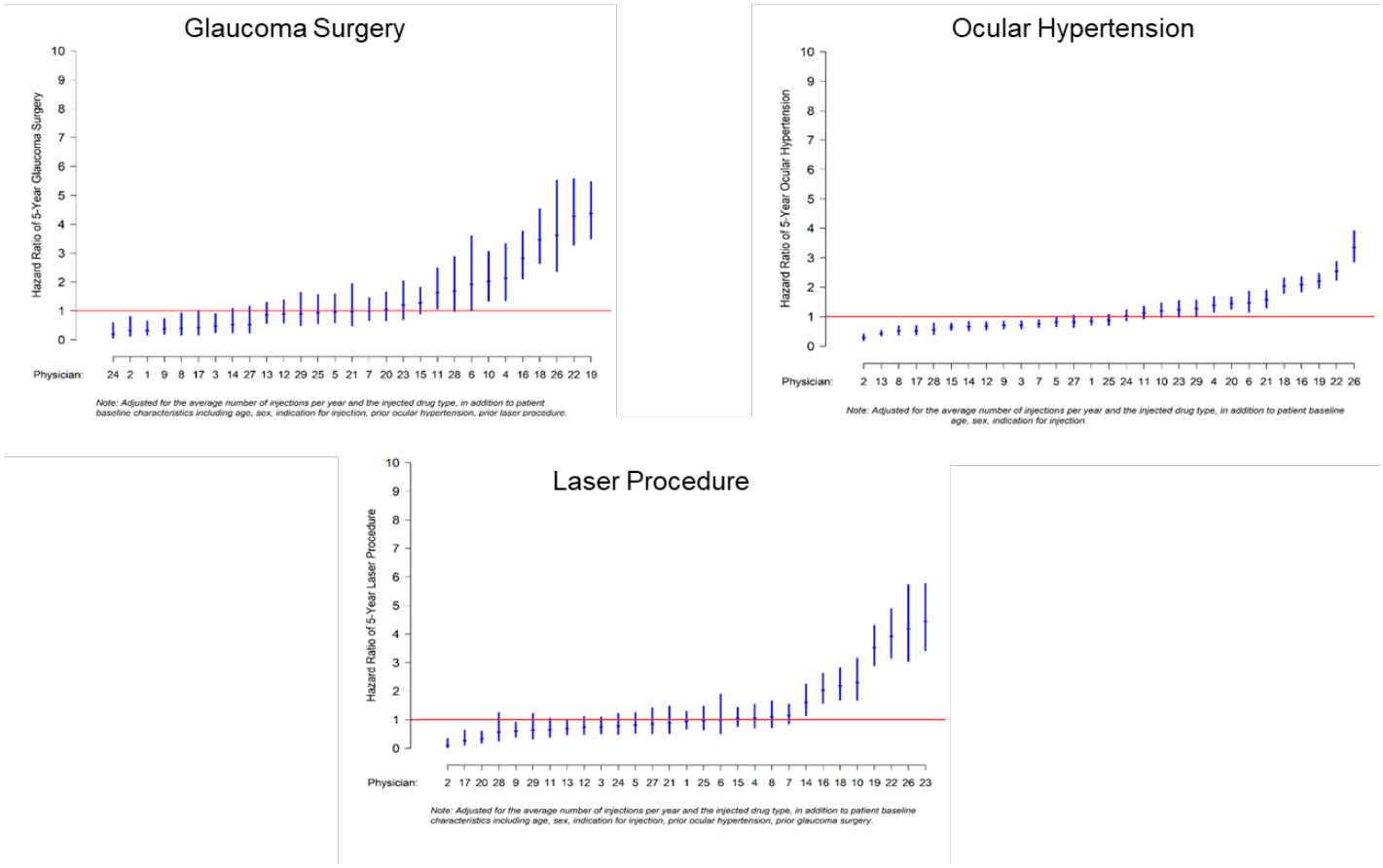
Exhibit 12: Multivariable cause-specific Hazards Model Results by Outcome (controlling for baseline patient *and non-patient characteristics*) with up to Five Years of Follow-up – Primary Retinal Physician (2009-2018)

	Time to Glaucoma Surgery (*n*=52,770 patient eyes)				Time to Ocular Hypertension (*n*=34,995 patients)				Time to Laser Procedure (*n*=37,992 patients)			
Primary Physician vs BC Average	Hazard Ratio	95% Confidence Limit Lower	Upper	p-value	Hazard Ratio	95% Confidence Limit Lower	Upper	p-value	Hazard Ratio	95% Confidence Limit Lower	Upper	p-value
24	0.19	0.06	0.58	0.0035	1.03	0.86	1.23	0.7553	0.77	0.50	1.21	0.2590
2	0.32	0.13	0.80	0.0142	0.29	0.20	0.41	<.0001	0.09	0.02	0.34	0.0004
1	0.32	0.16	0.64	0.0012	0.84	0.72	0.98	0.0297	0.94	0.69	1.29	0.7017
9	0.38	0.20	0.72	0.0031	0.70	0.59	0.84	0.0001	0.60	0.40	0.91	0.0163
8	0.39	0.17	0.92	0.0322	0.51	0.38	0.68	<.0001	1.10	0.73	1.65	0.6525
17	0.42	0.18	1.00	0.0510	0.51	0.39	0.69	<.0001	0.27	0.11	0.63	0.0024
3	0.47	0.25	0.89	0.0209	0.71	0.59	0.85	0.0002	0.75	0.51	1.08	0.1206
14	0.52	0.25	1.08	0.0799	0.66	0.52	0.83	0.0004	1.61	1.15	2.24	0.0054
27	0.52	0.24	1.15	0.1080	0.82	0.64	1.03	0.0932	0.85	0.52	1.41	0.5317
13	0.86	0.57	1.29	0.4670	0.43	0.35	0.52	<.0001	0.69	0.48	0.98	0.0371
12	0.89	0.58	1.37	0.6038	0.68	0.56	0.81	<.0001	0.74	0.49	1.11	0.1390
29	0.90	0.50	1.63	0.7315	1.27	1.04	1.55	0.0214	0.63	0.33	1.20	0.1631
25	0.94	0.56	1.55	0.7991	0.87	0.71	1.06	0.1710	0.97	0.65	1.46	0.8879
5	0.96	0.59	1.57	0.8747	0.82	0.67	0.99	0.0431	0.81	0.53	1.24	0.3365
21	0.98	0.50	1.93	0.9536	1.57	1.30	1.89	<.0001	0.88	0.53	1.47	0.6241
7	0.99	0.68	1.45	0.9660	0.75	0.64	0.89	0.0006	1.15	0.86	1.54	0.3471
20	1.04	0.66	1.64	0.8608	1.45	1.26	1.66	<.0001	0.33	0.19	0.59	0.0002
23	1.20	0.71	2.03	0.4990	1.23	0.99	1.54	0.0606	4.44	3.43	5.76	<.0001
15	1.27	0.90	1.80	0.1723	0.65	0.55	0.76	<.0001	1.05	0.77	1.43	0.7711
11	1.63	1.07	2.48	0.0227	1.12	0.93	1.34	0.2214	0.64	0.40	1.05	0.0746
28	1.69	0.99	2.88	0.0537	0.55	0.39	0.78	0.0006	0.57	0.26	1.24	0.1571
6	1.92	1.03	3.59	0.0403	1.47	1.16	1.85	0.0012	0.99	0.52	1.88	0.9674
10	2.02	1.35	3.05	0.0007	1.20	0.98	1.46	0.0752	2.30	1.69	3.14	<.0001
4	2.13	1.37	3.31	0.0008	1.39	1.16	1.67	0.0004	1.05	0.72	1.53	0.8132
16	2.82	2.12	3.75	<.0001	2.08	1.85	2.35	<.0001	2.03	1.58	2.61	<.0001
18	3.46	2.65	4.52	<.0001	2.04	1.80	2.31	<.0001	2.19	1.70	2.81	<.0001
26	3.61	2.37	5.51	<.0001	3.35	2.87	3.91	<.0001	4.18	3.05	5.72	<.0001
22	4.28	3.29	5.56	<.0001	2.54	2.25	2.87	<.0001	3.93	3.16	4.88	<.0001
19	4.37	3.50	5.46	<.0001	2.20	1.97	2.46	<.0001	3.53	2.90	4.29	<.0001

Important Notes:
- Physician names are coded with a number. - The data are sorted from lowest to highest Glaucoma Surgery Hazard Ratio.
- These hazard ratios are adjusted for patient baseline characteristics including age, sex, indication for injection, prior ocular hypertension (for laser and surgery models), prior laser surgery procedure (for surgery models), cumulative average number of injections per follow-up year and injected drug type. This means that differences between physician hazard ratios cannot be explained on the basis of these factors.
- Patients were excluded from the risk analysis if they had the event of interest prior to the first injection date.
- Red font denotes statistically increased risk; Blue font denotes statistically decreased risk; black font denotes not statistically different from provincial average.

Data Sources: PRDTP, MSP, SPR, Client Roster, PharmaNet, Vital Statistics, Chronic Disease Registry (2009-2018).

Exhibit 13: Multivariable Cause-specific Hazards Model Graphs by Outcome (controlling for baseline patient *and non-patient characteristics*) with up to Five Years of Follow-up - Primary Retinal Physician (2009-2018)



Important Notes:

- Physician names were coded. The data are sorted by primary physician from the lowest to the highest Hazard Ratio.
- These hazard ratios were adjusted for patient baseline characteristics including age, sex, indication for injection, prior ocular hypertension (for laser and surgery models), prior laser surgery procedure (for surgery models), cumulative average number of injections per follow-up year and injected drug type. This means that differences between physician hazard ratios could not be explained on the basis of these factors.
- Patients were excluded from the risk analysis if they had the event of interest prior to the first injection date.

Data Sources: PRDTP, MSP, SPR, Client Roster, PharmaNet, Vital Statistics, Chronic Disease Registry (2009-2018)

The multivariable analysis was also conducted stratifying the analysis by primary retinal physician location. The mapping of physician practice location with primary retinal physician identified examples where physicians with increased risk were located in the same location as physicians with decreased risk. The one location where all physicians reported increased risk, the physicians shared patients which is unlike all other locations where physicians practice in the same location but do not share patients. Given that the location effect may have been confounded by the physician effect, data were summarized in the report by primary retinal physician only.

Summary of findings

Multivariable models examined the factors associated with the outcomes using up to 9.5 years of follow-up to examine the association of select factors on the risk of the outcomes. The association of variation among retinal physicians on the risk of the outcomes using up to five years of follow-up was also examined.

The multivariable analyses reported consistent findings across all three outcomes and where similar factors could be tested, results were consistent with Phase II findings. These results included:

- **Age <75 years, male sex, and RVO indication were risk factors for patients/eyes to develop ocular hypertension, require laser procedure or glaucoma surgery.**
- **Patients with pre-existing ocular hypertension or prior laser procedure were more likely to receive glaucoma surgery.**
- **The data analysis did not support that drug type is associated with increased risk of the three outcomes analyzed.**
    - It is first important to note that VEGF-drug treatments are known and reported in the literature and drug product monographs to cause increase in intraocular pressure and in some cases lead to glaucoma.
    - In this review, there was no clear association of one specific drug type compared to another drug type with increased risk of the three outcomes of interest. Specifically, there is no association that Avastin has increased risk of the three outcomes of interest.
    - The analysis on drug type should be interpreted given the following: (a) the number of patients only on Lucentis/Eylea were very low limiting direct comparisons, (b) analysis by drug type needs to account for indication and number of treatments. That is, more patients on Avastin had RVO and also received higher number of treatments. As indicated, both RVO and higher treatment numbers were found to increase the risk for the outcomes of interest.
- **The cumulative average number of injections per follow-up year per eye was identified as an independent risk factor. Increasing number of injections resulted in increased risk across all three outcomes (noting again that, for example, 6 injections per year of follow-up at 9 years would mean an average of 54 injections for that given patient group).**
- **The same primary retinal physicians were identified to have a decreased risk consistently across all three outcomes of interest.**
- **The same primary retinal physicians were identified to have an increased risk consistently across all three outcomes of interest.**
- **These primary retinal physician differences were evident even when baseline patient characteristics and treatment factors (e.g., number of injections they provided and/or drug type injected) were taken into account.**

Subsequent analyses were completed examining the potential risk of dispensing pharmacy (where the drugs were compounded and dispensed) as a factor affecting outcomes. The outcomes could not be attributed to the dispensing pharmacy. Given the variation of risk of glaucoma surgery among the 29

retinal specialists, the potential role of the syringe as a contributing factor to this variation was also examined. The data did not indicate this to be a factor as all physicians used the same syringe type over the course of the review.

Finally, a subsequent analysis was conducted to investigate the cumulative glaucoma surgery incidence rates for visiting clinics as compared to other clinics. In rural and smaller urban communities where locum physicians might see patients, a statistically decreased risk of glaucoma surgery was observed.

CHAPTER FIVE: SUMMARY OF FINDINGS

Context and approach

In the past 10-15 years, the treatment of retinal disease has changed dramatically. Before effective treatments became available, the natural history and vision prognosis of retinal disease patients was very poor, with 20% of patients legally blind (VA worse than 20/200) at presentation (baseline) and increasing to 75% by three years.[3] The use of intra-vitreal injections of anti-VEGF agents, considered the mainstay therapy, have revolutionized the treatment of retinal disorders. They are the first-line therapy for AMD, RVO and DME and are one of the most important treatments due to the demonstrated benefit for vision improvement, stabilization, and preventing vision loss.[2] AMD is the leading cause of severe vision loss among seniors while the leading cause of visual disability and loss in working-aged people is diabetic retinopathy (where 80% are related to DME). There is compelling evidence from clinical studies in AMD patients that anti-VEGF drugs not only preserve but also improve vision as compared to sham treatment. [2,4-5]

Avastin is the predominant drug used in the BC program, which is aligned with the CADTH 2016 therapeutic review recommendation for anti-VEGF treatments for retinal diseases to preferentially use Avastin over Lucentis and Eylea due to its demonstrated clinical efficacy and lower cost.[8] The therapeutic equivalency (non-inferiority) of Avastin to Lucentis has been demonstrated through ten head-to-head randomized studies, including the CATT study and IVAN study.[2,6,7] Through a retrospective cohort study of British Columbians treated through this program, the clinical effectiveness of bevacizumab was found to be similar to the efficacy results found in the CATT.[9]

While some risks of anti-VEGF injections have been noted in the literature, they are used extensively in many countries and are viewed as generally safe; however, as with all treatments, some risks are present. These risks are not prevalent and include complications such as serious internal eye infection and retinal detachment. Evidence suggests that there is a risk for glaucoma or sustained ocular hypertension (raised IOP) in patients undergoing repeated treatments with anti-VEGF drugs. Therefore, the results of this study are not unique. [12]

One component of BC's PRDTP focuses on program quality improvement and as part of this, an investigation of anti-VEGF and glaucoma requiring surgery was conducted following reported cases of elevated intraocular pressure after anti-VEGF use. Three phases of quality review were completed prior to this Phase IV quality review.

Based on the data available in the previous analysis, Phase II analysis indicated a two-year rate of 2.1% for the composite endpoint of first event of either glaucoma laser procedure or surgery in PRDTP patients. An increased risk was associated with RVO, male sex, patients with prior glaucoma, but not age. Risk increased with a higher number of injections received. There was no increased risk related to dispensing pharmacy. As well, there did not appear to be a link between which drug was used for treatment and glaucoma surgery. The rates were reported at a patient-level and therefore, may have over-estimated the overall risk as the surgery may have occurred in an eye that had not been treated with anti-VEGF medications. Furthermore, the analysis was limited to a two-year follow-up. However, the MoH and the PHSA issued a news release to inform patients of a possible risk of glaucoma surgery following treatments stating the more conservative (highest) estimate of risk across all patients and a

risk of 2.1% over two-years. The MoH and PHSA committed to further study this important question and the Phase IV Quality Review results represent that next phase of work.

This report (Phase IV) built on Phases I-III and included additional patients, a longer follow-up period, additional data linkage to increase the information available on the patient populations, and broader involvement from a working group of clinical experts and methodologists to inform the analysis.

The questions asked in this Phase IV Quality Review and methods used have been summarized previously in this report with further detail provided in the appendices. However, it is important to point out a limitation with respect to glaucoma as a disease and the specific outcomes used in this quality review. The ultimate goal of this work was to understand the risk of glaucoma. Glaucoma is a chronic progressive deterioration of the optic nerve and is typically, though not always, worsened by raised IOP inside the eye. Glaucoma can be mild to severe and be of different types. While measuring "glaucoma" in the broadest sense as an outcome would have been ideal, this quality review required available and reliable data. It was recognized that the three measurable outcomes identified (ocular hypertension, laser procedure, glaucoma surgery) may not definitively identify every patient with potential increased IOP; however, the three outcome measures were based on high quality data and were deemed to represent a reasonably close proxy. It is possible that program patients could have had an elevated IOP and might not have been treated with medications, laser or surgery; however, clinician experts advised that would be unlikely given the frequency of monitoring by retinal specialists in the PRDTP.

The important findings:

Program size and description:

- The PRDTP was found to have grown from 4,284 active patients in 2009 to 20,694 active patients in 2018, having served 41,051 unique patients over the course of the program to 2018. In total 52,770 patient eyes had received 795,027 injections over the 2009-2018 period.
- The frequency of injections also increased over the period, specifically after the introduction of DME and RVO in 2013. In 2018, 63% of injections were for wAMD, 24% for DME and 13% for RVO. As well in 2018, 86% of injections were Avastin, 13% were Eylea and 1% were Lucentis.
- 11.1% of the patients treated in the program had ocular hypertension before their first injection.
- Variability in the outcomes cannot be attributed to the syringe or filtering differences as all physicians were using the same type of syringe and all patients were receiving the same syringe. (It should be noted that a syringe change to Norm-Ject syringes for a small sub-set of the retinal specialists working in the PRDTP and filtering of drug with all pharmacy providers was instituted after end of the study period and therefore do not impact these study results).

Was there evidence of an increase in intra-ocular pressure, laser procedure and or glaucoma surgery over time since the program started (between 2009 and 2018) for patient receiving these treatments?

- The two year follow-up crude (unadjusted for factors that could influence outcome) cumulative incidence rates were calculated and the results indicated that while the absolute rates for the PRDTP

patients remained relatively low, there was an increase from the time the program started to 2017 when the last patients for whom a two year follow-up could be calculated received treatment.

  - Glaucoma surgery two year crude cumulative incidence rate was between 0.4% -0.7% in 2009 and between 1.2% - 2.1% in 2017. The lower end of each of these ranges represented the incidence when eye-level data was used (meaning the injection and the surgery occurred in the same eye). The upper end of each of these ranges represented the incidence rate when patient level data was used (meaning the injection and the surgery may or may not have occurred in the same eye.) Because of some missing data in the eye-level analysis, and to be as conservative as possible in these estimates, the range using both eye-level and patient-level results are shown.
  - When the data that was stratified by year of entry was examined as a whole (i.e., entire follow-up period analyzed), the crude cumulative glaucoma surgery incidence rate at two years was 0.85 % (eye level) to 1.43% (patient level). The crude incidence rate was calculated not year by year (as above) but across all years of data available (i.e., for any patient that had two-years of follow-up regardless of when they commenced treatment).
  - Laser procedure crude cumulative incidence rate was measured at the patient level (no eye level data available) and the two year crude cumulative incidence rate was 0.8% in 2009 and 2.3% in 2017.
  - Ocular hypertension crude cumulative incidence rate was measured at the patient level (no eye level data available) and the two year crude cumulative incidence rate was 3.7% in 2009 and 8.2% in 2017.

- The changing two year crude cumulative incidence rates over time may have been influenced by the introduction of DME and RVO as indications for treatment in 2013, as a particular increase was seen around that time period. The multivariable analysis, however, adjusted for patient baseline characteristics (including indication), continued to show increased glaucoma surgery risk in the Program Cohort during the period of 2014 to 2017 suggesting factors other than indication for treatment were influencing the change over time.
- It is of noteworthy that over the same period of time, ocular hypertension in the Non-Program Cohort (all British Columbians who saw an ophthalmologist for any reason, but were not in the program and who were known to be younger with less history of independent risk factors) saw an increase in ocular hypertension incidence rate from 1.9% at two years of follow-up to 2.7% at the end of five years of follow-up.
- The incidence rates provided in Phase II reported 2.1% for two-year composite endpoint of first event of either glaucoma surgery or laser procedure. Phase IV analysis, utilized an expanded number of patients and years of follow-up as well as additional data linkage creating a more robust analysis, and indicated a two-year glaucoma surgery rate of 0.85 to 1.43%.

What was the risk to patients over time from their first anti-VEGF injection to the development of ocular hypertension, laser procedure or glaucoma surgery?

- To answer this question cumulative incidence rates were calculated to estimate the incidence of the outcome over time. For glaucoma surgery events, both eye level cumulative incidence rates and patient-level cumulative incidence rates were calculated.
- As noted above, when the data was analyzed as a whole (across all years), the crude cumulative glaucoma surgery incidence rate at two years was in the range of 0.85 % (eye level) to 1.43% (patient level). By the fifth year, these rates increased to the range of 1.92% to 3.09% and by 9 years, though based on a smaller sample size of patients followed for that duration, the rate was in the range of 2.59% to 4.27%.
- Results from all the analysis, using different time points and across all three outcomes, were consistent.

What are the factors associated with a higher risk of ocular hypertension, laser procedure and glaucoma surgery?

- Models were primarily used to answer this question based on earlier univariate analyses findings. All three outcomes were examined and the results were quite consistent across all three outcomes of ocular hypertension, laser procedure and glaucoma surgery.
- The analysis indicated there is increased risk for glaucoma surgery, laser procedure and ocular hypertension among patients with AMD, DME and RVO in the PRDTP Cohort in comparison to the Non-Program Cohort.
- Within the PRDTP Cohort, there were statistically significant differences with respect to the increased risk of all three outcomes (ocular hypertension, glaucoma surgery, laser procedure) with patients whose age was less than 75 years, who were of male sex, who were treated for the RVO indication and who had higher injection frequency. Increased glaucoma surgery risk was also associated with patients with pre-existing ocular hypertension or who had prior laser procedure before starting injections.
- The data analyses do not support that drug type (Avastin, Lucentis, Eylea) is associated with increased risk of the three outcomes analyzed.
- The analysis that examined the possible role of the dispensing pharmacies also did not demonstrate attributable differences related to pharmacy that prepared and dispensed the anti-VEGF drugs.
- No analyses were undertaken that specifically examined the effect of the syringe as all physicians used the same type of syringe. Differences between physicians' rates could not be explained on the basis of syringe. It should be noted that a change in syringe for a sub-set of retinal specialists occurred after the study period in 2019 and therefore do not affect these analyses in any manner.
- Even after controlling for patient and non-patient characteristics, a small number of physicians consistently were associated with increased risk across all three outcomes and a small number of

physicians consistently were associated with lower risk across all three outcomes. These findings persisted once patients who received treatments from multiple physicians are removed.

Comparison of the study findings to the current literature

Most of the published studies on this topic are case reports or case series describing patients with mainly ocular hypertension. Case series evidence are considered the weakest epidemiologic study design as their lack of a control group does not allow them to compute glaucoma rates. Only one epidemiologic study in the United States (Atchison) has quantified the risk of glaucoma and glaucoma surgeries in the United States. However, this study was not a population-based study but only captured data from a selected group of ophthalmology practices in the United States. For the outcome of glaucoma surgery, no information was provided as to the manner by which data on glaucoma surgeries were ascertained. [(14)]

To our knowledge this is the first large population-based study that has examined the risk of three outcomes of ocular hypertension, laser procedure and glaucoma surgery over a span of close to ten years in approximately 41,000 B.C. residents. Publication of future population-based studies, similar to this study and on this topic, will allow for a more informed comparison to B.C. data.

Phase IV Quality Review study limitations

There are some limitations associated with this review.

It was not possible to compare the PRDTP group to a control group (e.g., patients with retinal disease that did not receive anti-VEGF treatments). Given this, it is challenging to differentiate between the effect of progressing underlying disease not associated with treatment from the effect that may be associated with anti-VEGF treatments. Investigating the risk across different outcomes, adjusting for some of the measured confounders, as well as utilizing different follow-up time periods mitigates some of this bias; however, an active control group might allow the possibility that patients who are followed for a longer period of time might be more prone to time related biases such as confounding by disease severity. Lack of an active control group also makes it difficult to differentiate the effect of the injection to the effect of the disease.

This review was not designed to compare B.C.'s program with other similar retinal drug treatment programs. Such an analysis would be needed to put the B.C. results into relative perspective and similar data ascertainment, linkage, methodology and analytics would be required. There is agreement that such a review with another jurisdiction would be desirable using the same methodology and definitions to permit comparison. While no direct comparisons are available, high level comparisons to the literature can be made, including:

- The crude cumulative incidence rate of ocular hypertension defined as use of glaucoma eye drop medications at the end of two-years follow-up in the PRDTP Phase IV Review was reported at 7.0% (AMD, DME and RVO patients). Studies in the literature reported incidence rates of elevated IOP following anti-VEGF treatment, defined as with or without glaucoma medication treatment of the elevated IOP, between 5.7% (AMD patients only with median follow-up of 2.5 years) to 7.8% (DME patients only with follow-of of 6-12 months).[(15-16)]

- The crude cumulative incidence rate of glaucoma surgery at the end of two-years follow-up in the PRDTP Phase IV Review for AMD patients only was reported between 0.6% (eye-level analysis) to 0.9% (patient-level analysis). One study in the literature reported incidence rates of glaucoma surgery following anti-VEGF treatment at 0.6% (AMD patients only; median follow-up time frame 2.5 years). [16]

The review was not able to address potential additional clinical care factors that might influence a physician to treat or not treat symptoms associated with glaucoma. Factors, such as IOP, visual field, optic disc status, eye-related comorbidities are not captured in the database but important for a retinal specialist's choice of treatment strategy and may influence clinical outcomes.

To take into consideration the incidence of death given the average age of the population, a fixed time covariate model was selected. The impact of number of injections over time on the outcome was measured as the cumulative average number of injections per follow-up year. Further analysis on the effect of the number of injections on risk should consider other multi-variable approaches such as time-dependent covariate analysis, to reflect the frequency and intensity of injections over time.

While measuring "glaucoma" in the broadest sense as an outcome would have been ideal, this quality review required available and reliable data. The three measurable outcomes identified (ocular hypertension, laser procedure, glaucoma surgery) may not definitively identify every patient with potential increased IOP; however, the outcome measures were based on high quality data and were deemed to represent a reasonably close proxy. The outcome measures represent an intervention that occurred, for example, ocular hypertension reflects treatment of ocular hypertension through medication. It is possible that program patients could have raised IOP and not be treated with medications, laser or surgery; however, clinician experts advised that this would be unlikely given the frequency of monitoring by retinal specialists in the PRDTP program. As well there may be patients who had severe glaucoma while in the program however, were not candidates for surgery and therefore, were not captured in the surgery outcome.

Three additional important issues could not be explored within the context of this review and are worthy of subsequent follow-up. Consideration could be given to the potential differences in the management approach, including threshold for intervention regarding a raised IOP by the retinal surgeon and /or the glaucoma specialist to whom they may refer. In addition, differences in the care process during the provision of the anti-VEGF treatment itself could not be explored within the current data set but could be considered for future attention. Finally, it is recognized that patient factors like age and drug dose effects do not alone explain medication response. New genomic technologies have helped clinicians understand why some patients respond in a particular manner or to a particular anti-VEGF agent while others do not. Such technologies have not been employed yet to date with this patient population; however, this could be an area that researchers may be prompted to explore based on these findings.

CHAPTER SIX: ACTION PLAN

ACTION PLAN SUMMARY:

1. **Ensure that patients, the public, and the ophthalmology clinical community are aware of the general benefits and risks associated with the PRDTP drug treatments as confirmed through the program quality reviews:**
   Through public communication of the quality review findings, to continue to reassure the patients, public and ophthalmology clinical community that the program is safe and effective to improve vision and prevent blindness. The results from the quality reviews did not find an association between the glaucoma outcomes evaluated and the drug treatments used in the program or how they were prepared.

2. **Provide support to program retinal specialists with quality review results and other tools to support patient care:**
   Through the provision of provider-specific quality review results and the development of a risk assessment tools to support use in patient care.

3. **Initiate reviews of provider practices to identify best practices and address potentially modifiable risk factors:** Through practice reviews of selected providers (those with higher and lower rates of the outcomes of interest), in collaboration with health authorities, to identify best practices to address modifiable practices to reduce risk;

4. **Complete additional quality reviews:**
   Through conducting comparative safety assessment of the BC analysis key findings with another comparable jurisdiction. Further opportunities and the use of other research expertise should be explored to improve the prospective data collection and evaluation methods to better control for biases inherent in uncontrolled studies;

5. **Continue to enhance program data collection, monitoring, reporting, and oversight around the program's quality measures related to effectiveness, safety, and program changes:**
   Improve data measures collected to continue to enhance the robust PRDTP dataset and continue ongoing monitoring, reporting, and oversight of the PRDTP program, including assessments of significant changes made to the program or affecting the program; and

6. **Share the findings from the PRDTP Quality Review Studies (Phase I, II, III and IV) at scientific and medical forums:**
   Results from these comprehensive reviews should be shared broadly at scientific and medical forums so others can be informed, can review, and learn from BC's program.

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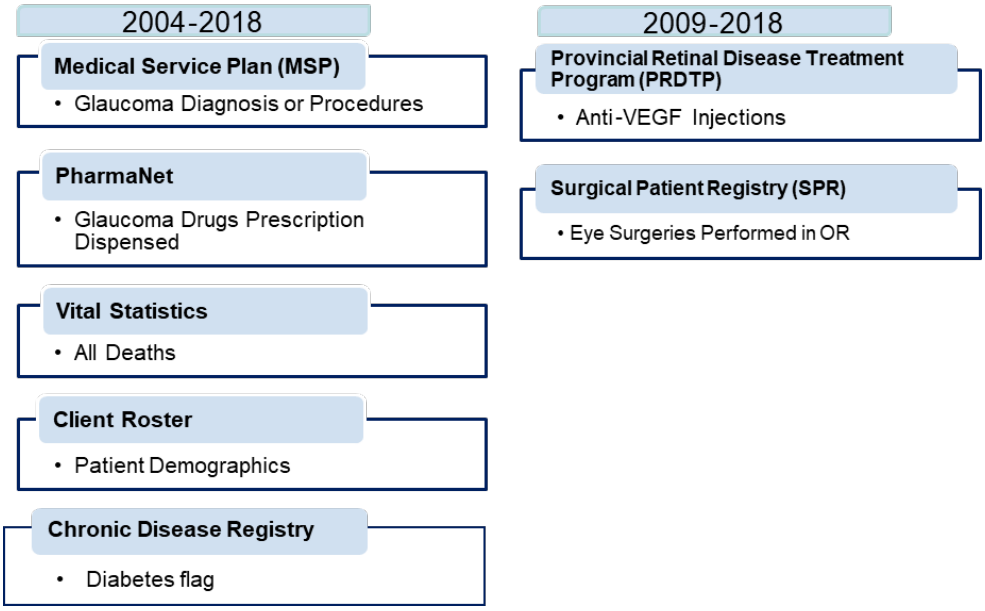
APPENDIX A: PHASE IV DATA SOURCES

Exhibit 14: Phase IV Quality Review – Data Sources



1. **Provincial Retinal Disease Treatment Program (PRDTP) data**: Includes all anti-VEGF injection records under the Provincial Retinal Disease Treatment Program (PRDTP) between June 1, 2009 and December 31, 2018. Data set identifies the Program Cohort and PRDTP treatment details. Data fields include:
    - Physician MSP no.
    - Locum MSP no.
    - Date of birth
    - Gender
    - Visual acuity
    - Responsibility for payment
    - Indication
    - Eye
    - Date of informed consent for injection
    - Date of informed consent for info release
    - Date of injection
    - Pharmacy/supplier
    - Drug type
    - Adverse reaction
    - Method of preparation
    - Date of symptom onset
    - Clinic location
    - Date of injection/treatment

2. **Medical Services Plan (MSP) data:** Includes all MSP claims with speciality =6 (Ophthalmology) or diagnosis codes indicating glaucoma (i.e., 365XX) between January 1, 2004 and December 31, 2018. Data set identifies the outcomes of interest, namely laser procedure and glaucoma surgery. Data fields include:
    - Client age
    - Client gender
    - Client month and year of birth
    - Client health authority/local health authority
    - Service date
    - Fee item
    - Service code
    - Paid service
    - ICD9 diagnostic code
    - Claim type
    - Client province
    - Service place
    - Practitioner number
    - Claim specialty
3. **PharmaNet data:** Includes Glaucoma drugs list provided by PRDTP, every prescription dispensed in community pharmacies in B.C. between January 1, 2004 and December 31, 2018. Data set identifies glaucoma medications pre and/or post injection. Data set identifies the outcome of interest, namely ocular hypertension. Data fields include:
    - Gender
    - Patient health authority/local health authority
    - Pharmacy identification number
    - Pharmacy health authority/local health authority
    - Practitioner number
    - Practitioner licencing body identifier/body
    - Practitioner local health area
    - Recent MSP billing practitioner
    - Recent college practitioner specialty description
    - DINPIN
    - Canadian brand name
    - Chemical/generic name
    - Drug strength
    - Dosage form description
    - Unit of drug form
    - Date of service
    - Quantity dispensed
    - Days' supply

4. **Vital Statistics data:** Includes all deaths between January 1, 2004 and December 31, 2018 in B.C. Data set is utilized to conduct survival analysis and analyze patient outcomes. Data fields include:
    - Sex
    - Postal code
    - Year/month/date of death

5. **Client Roster (CR) data**: Includes demographic detail on all patients between January 1, 2004 and December 31, 2018. Data set is utilized to match patient between data sources. Data fields include:
    - Calendar year
    - Sex
    - Postal code
    - Year/month/date of birth

6. **Surgical Patient Registry (SPR) data:** Includes all surgeries performed in an operating room in B.C. by an ophthalmologist between January 1, 2009 and December 31, 2018. Data set is utilized to verify that glaucoma surgery was performed in an operating room and to confirm the eye surgery was performed on. Data fields include:
    - Health authority
    - Facility
    - Surgeon MSP
    - Gender
    - Decision/referral/initial visit date
    - Patient postal code
    - Procedure code/description
    - Secondary procedure code/description
    - **Procedure side**
    - Diagnosis code
    - Date of surgery
    - Emergency code

7. **Chronic Disease Registry (CDR) data:** Includes all patients diagnosed with diabetes in B.C. based upon an algorithm applied by the MoH between 2004 and 2018. Data set is utilized to identify patients with diabetes given their increased risk of developing glaucoma. Data fields include:
    - Date of diabetes

The linkage key for the Program and Non-Program is the Personal Health Number (PHN). This was replaced with a Study ID.

APPENDIX B: PROJECT STUDY TEAM AND PROJECT TIMELINE

Exhibit 15: Project Study Team for PRDTP Phase IV Quality Review

Quality Working Group

- Ophthalmologist, Retinal Specialist, Vancouver geography and Clinical Assistant Professor, Department of Ophthalmology and Visual Sciences, Faculty of Medicine, University of British Columbia
- Ophthalmologist, Retinal Specialist, Fraser Health geography
- Ophthalmologist, Retinal Specialist, Interior Health geography
- Ophthalmologist, Glaucoma Specialist, Island Health geography
- Ophthalmologist, Retinal Specialist, President of the Association of British Columbia Retinal Specialists
- Associate Professor, PhD, Department of Ophthalmology and Visual Sciences, Faculty of Medicine, University of British Columbia
- Ophthalmologist, Professor and Department Head, Department of Ophthalmology and Visual Sciences, Faculty of Medicine, University of British Columbia
- Vice President, Public Health, Chief Medical Health Officer, Vancouver Coastal Health
- Epidemiologist and Harm Reduction Lead, BCCDC and Professor, Division of Epidemiology, Biostatistics and Public Health Practice, School of Population and Public Health, University of British Columbia
- Regular Presenters from Analytic Sub-group (guests):
  - Director, Data Solutions and Biostatistical Analysis, PHSA
  - Senior Biostatistician, PHSA
  - Epidemiologist/Biostatistician, Public Health Surveillance Unit, Vancouver Coastal Health
- Executive Vice President, Clinical Policy, Planning & Partnerships, PHSA (ex-officio)
- Secretariat support /resources including as required:
  - Interim Program Facilitator, PRDTP, PHSA (minute taker)
  - Chief Data Governance & Analytics Officer, PHSA
  - Executive Director, Drug Intelligence, Outcomes and Strategy, Pharmaceutical Services Division, Ministry of Health
  - Pharmacist, Decision Support and Specialty Medicines, Drug Intelligence, Outcomes and Strategy, Pharmaceutical Services Division, Ministry of Health

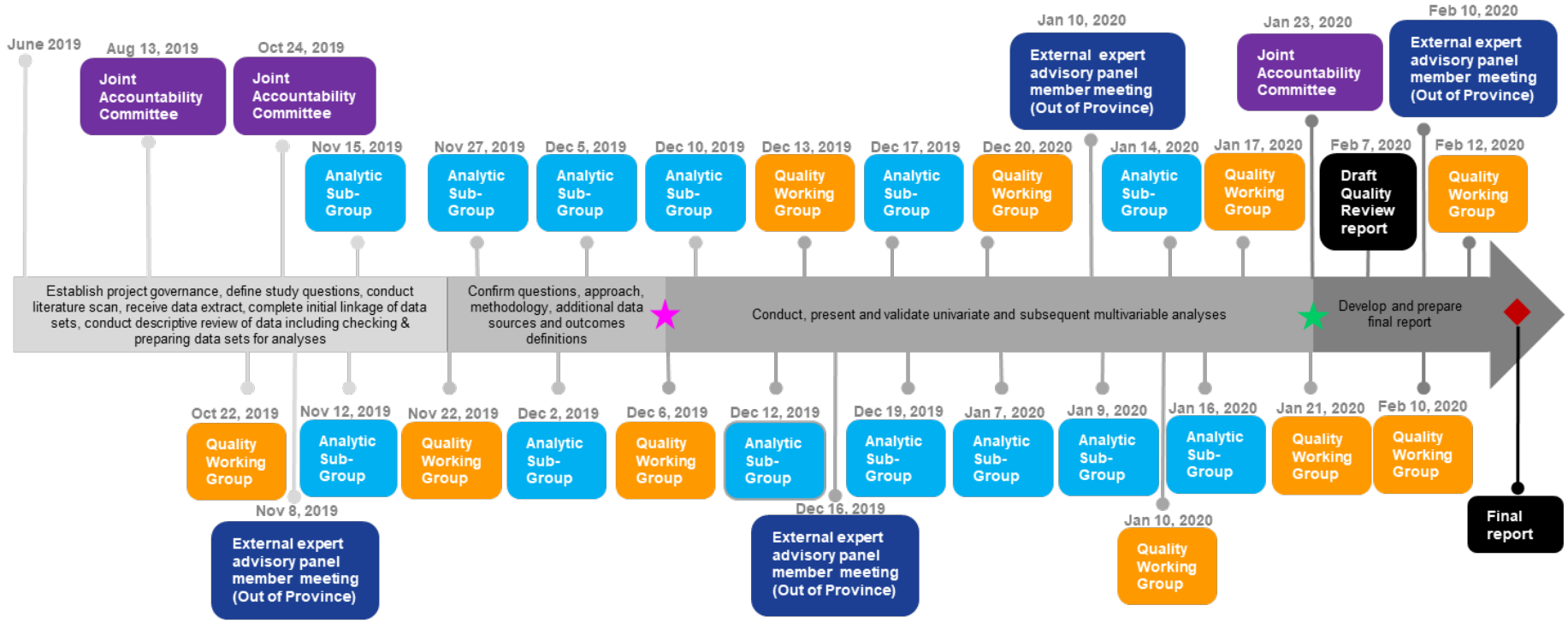
Analytics Sub-Group

- Associate Professor, PhD, Department of Ophthalmology and Visual Sciences, Faculty of Medicine, University of British Columbia
- Professor and Department Head, Department of Ophthalmology and Visual Sciences, Faculty of Medicine, University of British Columbia
- Epidemiologist/Biostatistician, Public Health Surveillance Unit, Vancouver Coastal Health
- Senior Scientist Statistician, BC Centre for Disease Control, PHSA
- Biostatistician, PHSA
- Biostatistician, PHSA
- Biostatistician/Data Quality Coordinator, PHSA
- Director, Data Solutions and Biostatistical Analysis, PHSA
- Senior Biostatistician, PHSA

External Expert Advisory Panel (Out of Province)

- Ophthalmologist, Department of Ophthalmology, Queen's University & Kingston Health Sciences Centre, Kingston, Ontario
- Ophthalmologist, Ivey Eye Institute, St. Joseph's Hospital, London, Ontario

Exhibit 16: Phase IV Quality Review Project Meeting Schedule and Key Milestones



Key Milestones:

- ★ Validated and approved modelling approach, analyses methodology and outcomes definition with revisions
- ★ Review and obtain acceptance on all analyses and findings
- ◆ Complete final quality review report

APPENDIX C: OUTCOME DEFINITIONS

As noted on pages 5 and 6 of this report, the primary outcome measures are used as a proxy for glaucoma. Reliable measure of Intra-Ocular Pressure (IOP) is not available. As such, the three primary outcome measures were defined as follows:

- **Ocular Hypertension:** occurs when the pressure inside the eye (IOP) is higher than normal. Higher than normal eye pressure can cause glaucoma.
    - For the purposes of this study, ocular hypertension was defined as at least two glaucoma medication prescriptions dispensed; one medication dispensed and another refilled within 30-days after the end of the previous prescription (either the same or a different medication). Note a sensitivity analysis evaluated the time period between two-consecutive prescriptions and determined that the 30-day timeframe was an appropriate definition.
    - The following list of medications (generic drug name) were identified by the MoH Pharmaceutical Division and confirmed by the ophthalmology members of the Quality Working Group as treatment of elevated intraocular pressure due to glaucoma or ocular hypertension:

Bimatoprost	Levobunolol Hcl
Brimonidine Tartrate	Methazolamide
Brimonidine Tartrate / Timolol	Pilocarpine Hcl
Brinzolamide	Pilocarpine Nitrate
Brinzolamide / Brimonidine Tart	Pilocarpine Nitrate / Pf
Brinzolamide / Timolol Maleate	Timolol / Hydrochlorothiazide
Dipivefrin Hcl / Levobunolol Hcl	Timolol Maleate
Dorzolamide / Timolol / Pf	Timolol Maleate / Pilocarpin Hcl
Dorzolamide Hcl	Timolol Maleate / Travoprost
Dorzolamide Hcl / Pf	Travoprost
Dorzolamide Hcl / Timolol Maleat	Travoprost (Benzalkonium)
Latanoprost	
Latanoprost / Pf	
Latanoprost / Timolol Maleate	

    - This outcome was measured at the patient level as data does not permit measuring at the patient eye level.

- **Laser Procedure:** a procedure performed to lower intraocular pressure in patients with glaucoma.
    - Laser procedure was defined as MSP fee item code 22114 - laser trabeculoplasty.
    - The outcome was measured at the patient-level as data does not permit measuring at the patient eye-level.
- **Glaucoma Surgery:** several types of variations/combinations of surgeries can facilitate the lowering of IOP.
    - Glaucoma surgery was defined as MSP fee item codes:
        - 2177 - Glaucoma – peripheral iridectomy (isolated proced.)
        - 2178 - Glaucoma - filtering procedure, non-microscopic
        - 2180 - Glaucoma – goniotomy
        - 2184 - Glaucoma – cyclodialysis
        - 2187 - Glaucoma - filtering procedure, microscopic
        - 22070 - Molteno implant (includes phase 1 and phase 2)
        - 22185 - Glaucoma - cycloablative procedures
        - 22187 - Glaucoma - complicated trabeculectomy
    - The outcome was measured at the patient-level and the patient eye-level. Patient eye comparisons were possible when MSP data were linked with SPR data and surgery was performed in an operating room.

Note: As stated in the body of the report, MSP data could not sufficiently and reliably define glaucoma as a diagnosis; therefore these three proxies were used for identifying glaucoma as an outcome.

APPENDIX D: GENERAL APPROACH

The General Approach included:

1. Define additional variables
    - Program Cohort and Non-Program Cohort
    - Crude cumulative incidence rate
2. Conduct descriptive analysis
    - PRDTP data
    - Select patient characteristics
3. Conduct univariate analysis on selected factors and outcomes:
    - Age
    - Sex
    - Indication
    - Year of enrollment
    - Cumulative average number of injections per follow-up year
    - Patient's prior history
    - Physician/practice location
4. Based on univariate analysis, conduct multivariable analysis using:
    - Up to 2 year follow-up to investigate trends in outcome rates over time
    - Up to 5 year follow-up to assess variations across physicians/community
    - Up to 9.5 year follow-up to assess associations of all factors and outcomes

The multivariable approach investigated factors that influence the time-to-event. In this case, the event was identified as one of the three outcome variables.

A unique feature of time-to-event data is that typically not all patients experience the event by the end of the observation period (e.g., as a result of death), so the actual event times for some patients are unknown. This phenomenon, referred to as censoring, must be accounted for in the analysis to allow for valid inferences. Appropriate analysis of time-to-event data required specific statistical methods that can deal with censored data. As such, the Cox proportional hazards model was selected as the statistical approach for the multivariable analysis.

The Cox proportional-hazards model is a method for examining the covariate effects on the hazard function. The hazard ratio is defined as the ratio of the hazard for those with the risk factor (X = 1) to the hazard without the risk factor (X = 0). The hazard ratio can be interpreted as patients in the exposed

group having an average % higher/lower risk of event than those in the reference group at any point in time during the follow-up period (e.g., diabetics are X% increased risk of developing ocular hypertension in comparison to non-diabetics).

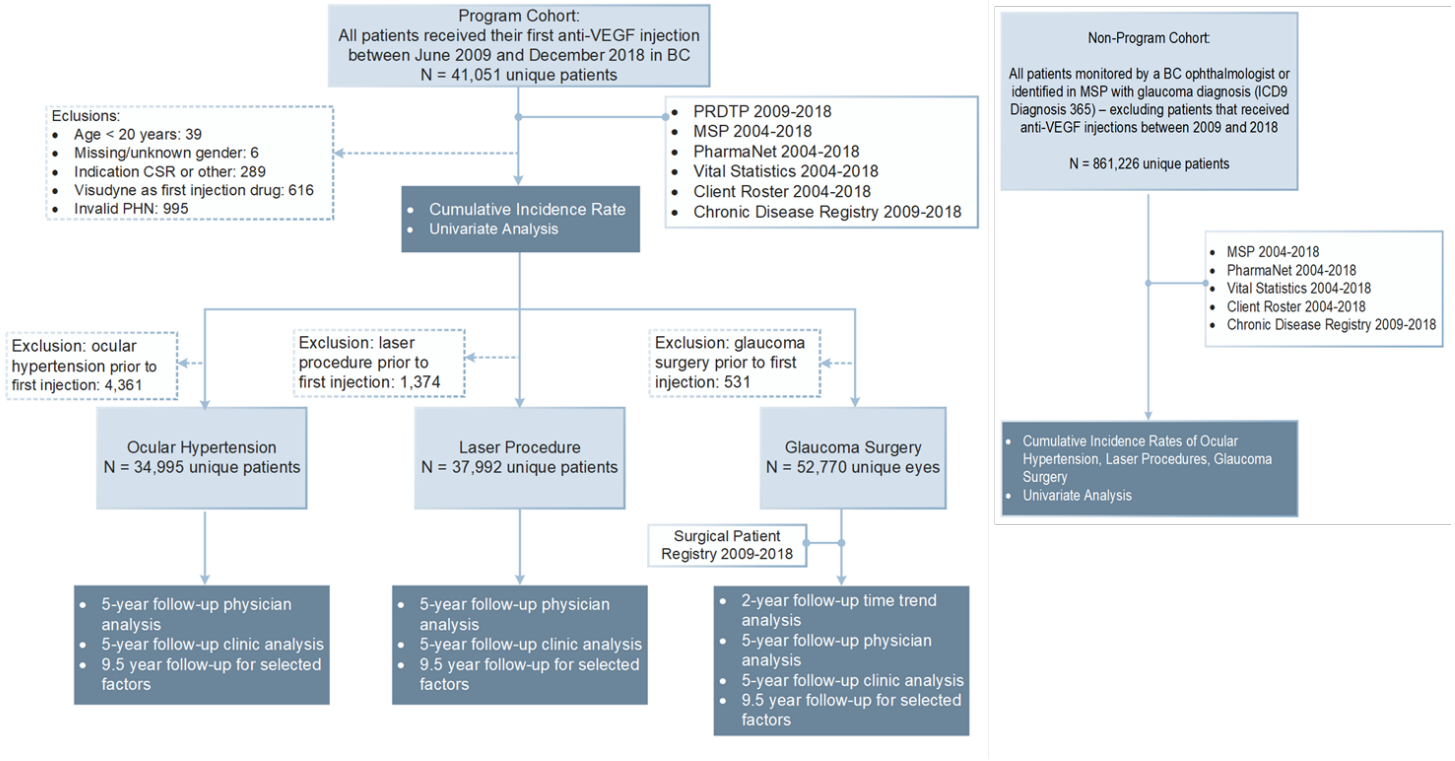
The Fine and Gray sub-distribution hazards model, the method of Fine and Gray (1999) extends the Cox regression to model the cumulative incidence function, was used to estimate the effect of covariates on the cumulative incidence function for the event of interest while taking competing risks into account. In the analysis of glaucoma surgery at the patient eye level, the cause-specific hazards model using clustered robust standard errors was implemented to account for within-cluster homogeneity between eyes in surgery outcomes. Statistical analysis was performed using SAS software (version 9.4, SAS Institute Inc.). For all analysis, a P-value of <0.05 was considered statistically significant.

A summary of the study questions and analysis conducted by outcome event are provided below.

Exhibit 17: Framework for Analysis by Study Question

Study Question	Analysis	Outcome		
		Ocular Hypertension	Laser Procedure	Glaucoma Surgery
1. Is there evidence of an increase in ocular hypertension, laser procedure, or glaucoma surgery rate among patients receiving anti-VEGF injections between 2009 and 2018?	Cumulative Incidence Rate (crude): 9.5 yr follow-up	√	√	√
	Multivariable Model: 2 yr follow-up for time trend analysis			√
2. What is the risk to patients over time from the first anti-VEGF injection to the development of ocular hypertension, laser procedure, or glaucoma surgery?	Cumulative Incidence Rate (crude, stratified by selected factors)	√	√	√
3. What are the factors associated with higher risk of ocular hypertension, laser procedure, glaucoma surgery?	Multivariable Model: 5 yr follow-up for primary physician analysis	√	√	√
	Multivariable Model: 5 yr follow-up for physician practice location analysis	√	√	√
	Multivariable Model: 9.5 yr follow-up for selected factors	√	√	√

Exhibit 18: Study Design Flowchart – Program Cohort and Non-Program Cohort



APPENDIX E: Observed Two-Year Rate BY Outcome and Primary RETINAL SPECIALIST

Observed two-year rate for glaucoma surgery, ocular hypertension and laser procedure by primary retinal physician (2009-2016) are provided below. These rates represent actual events that occurred in patient eyes/patients treated, where two years of follow-up data are available (i.e., a patient that started anti-VEGF treatments in 2017 would not be included as two years of follow-up are not available) and provides information on the distribution of rates across the province. The rates vary substantially by primary retinal physician:

- Glaucoma surgery rates vary from 0.1% to 2.9% (patient eye-level data); provincial average 0.8%.
- Ocular hypertension rates vary from 2.0% to 20.1% (patient level data); provincial average 6.8%.
- Laser procedure rates vary from 0.0% to 6.7% (patient level data); provincial average 1.3%.

It's important to note that these are observed rates and therefore, do not adjust for differences in patient characteristics across retinal specialist practices. For example, we know that patients treated for RVO reported an increased risk of all three outcomes. If one retinal specialist had a higher proportion of RVO patients in comparison to other retinal specialists then the observed rate would be influenced by that difference.

Exhibit 19: Observed Two-Year Rate for Glaucoma Surgery, Ocular Hypertension and Laser Procedure by Primary Retinal Physician by Outcome Measure – Program Cohort (2009-2016)

	Percentage of Cases with:		
Physician Code	Glaucoma Surgery after First Injection (eye level)	Ocular Hypertension after First Injection (patient level)	Laser Procedure after First Injection (patient level)
	%	%	%
2	0.1	2.0	0.0
24	0.1	5.4	0.9
1	0.2	4.1	1.0
3	0.2	5.0	0.7
8	0.3	2.3	1.4
9	0.3	4.5	0.4
30	0.4	8.6	0.5
5	0.4	4.7	0.5
14	0.4	4.7	1.2
17	0.4	2.9	0.3
27	0.4	6.2	0.9
12	0.5	4.1	0.8
21	0.5	11.9	0.9
4	0.6	8.2	0.7
6	0.6	5.7	0.5
7	0.6	4.7	1.3
13	0.6	2.5	0.7
29	0.6	9.3	0.4
15	0.8	3.0	0.8
20	0.8	10.5	0.6
10	0.9	7.0	2.0
11	1.0	5.7	0.6
25	1.0	7.0	1.9
26	1.1	20.1	3.7
23	1.2	9.7	6.7
16	1.6	13.9	2.0
18	2.1	13.7	2.5
28	2.1	3.4	0.8
19	2.6	15.3	4.0
22	2.9	17.8	3.4
Total	**0.8**	**6.8**	**1.3**

Notes:

- Data sorted by lowest to highest Glaucoma Surgery Rate.
- Patients were excluded from the risk analysis if they had the event of interest prior to the first injection date.***- Primary retinal physician:*** The retinal physician primarily responsible for treating AMD, DME or RVO patients with anti-VEGF injections. Where patients are shared, the physician with the highest frequency of injections is assigned.

Data Sources: PRDTP, MSP, SPR, PharmaNet, Vital Statistics (2009-2018).