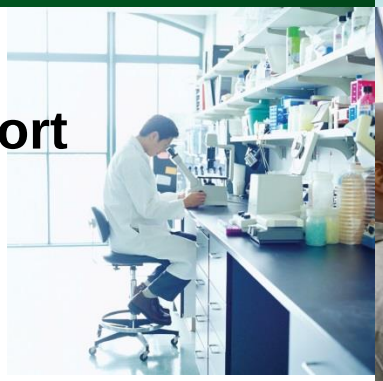
# Provincial Retinal Diseases Treatment Program



## Phase IV: Quality Review Report

March 2020

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# Chapter 1: Introduction



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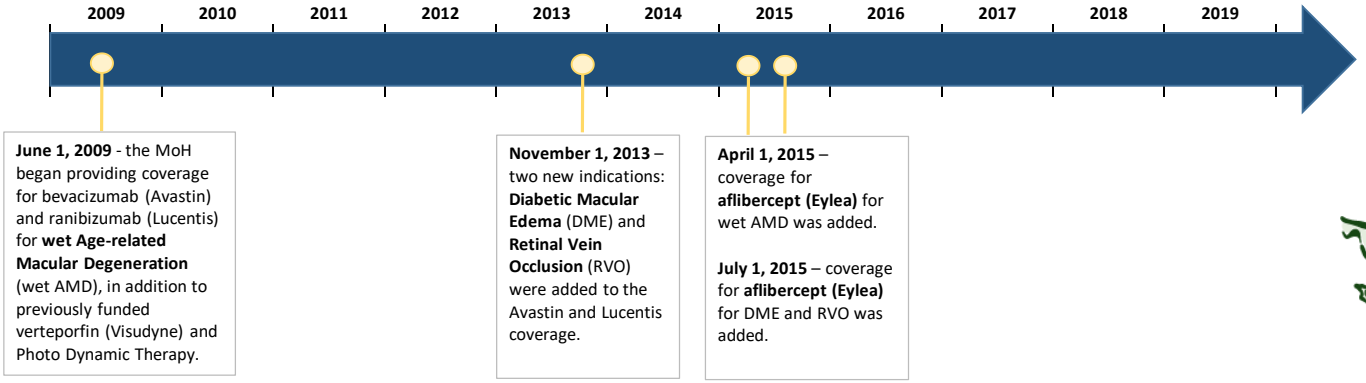
# 1.1 Overview of the Provincial Retinal Diseases Treatment Program (PRDTP)

- PRDTP provides drug treatment therapy for B.C. patients diagnosed with one of three approved indications:
  - wet age-related macular degeneration (wAMD)
  - diabetic macular edema (DME)
  - retinal vein occlusion (RVO).
- Started in 2009, the program provides 100% coverage for drugs for the treatment of retinal diseases when the drugs are prescribed and administered by 29 participating retinal specialists. Provincial Health Services Authority (PHSA) manages the provincial program on behalf of the Ministry of Health (MoH) including monitoring regional access to care; optimizing drug utilization appropriateness and cost control; minimizing drug wastage; and, facilitating data collection, monitoring, measuring, and reporting.
- The standard of care for the treatment of retinal diseases is anti-vascular endothelial growth factor (anti-VEGF) drugs. These medications have been shown to help prevent vision loss and/or blindness, particularly in seniors. B.C. patients who have been diagnosed with one of three approved indications have access to:
  - bevacizumab (Avastin®)
  - ranibizumab (Lucentis®)
  - aflibercept (Eylea®)*.

  Coverage for verteporfin (Visudyne) with photodynamic therapy for wAMD is also provided.
- Dates of MoH approval are summarized below:

* The approved anti-VEGF drugs are identified as Avastin, Lucentis and Eylea throughout the remaining of the report.

*Exhibit 1: PRDTP Indication and Drug Approval Dates*

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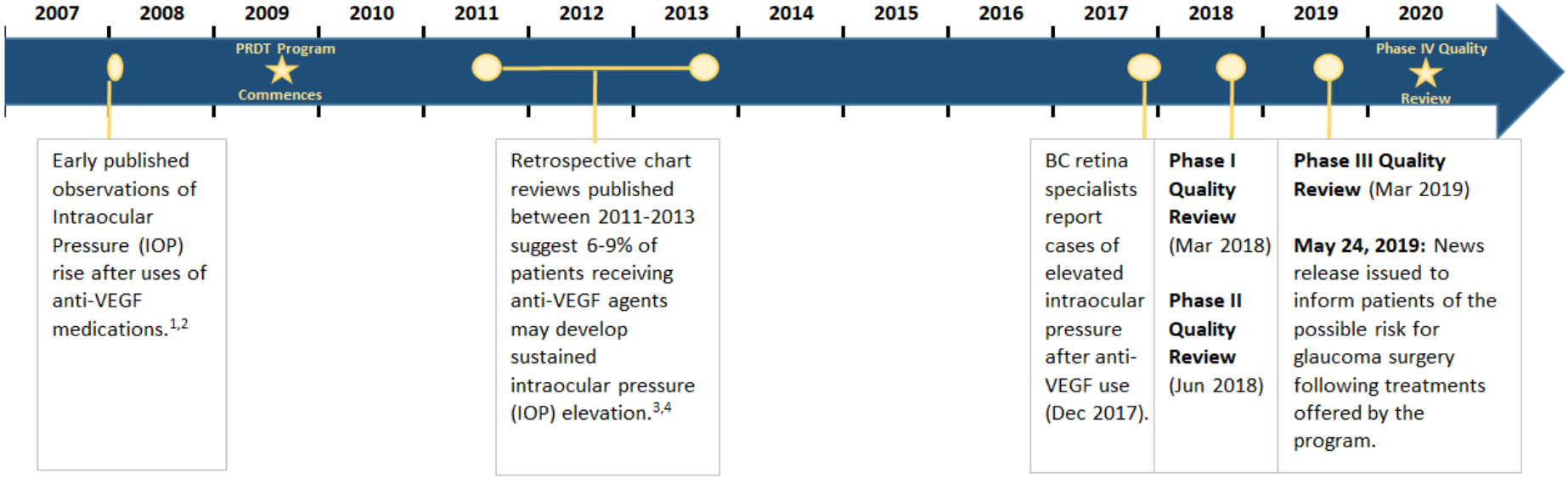
# 1.2 PRDTP Quality Reviews: Phase I-III

## *Timeline of Events*

*Exhibit 2: PRDTP Quality Review Dates*





References:

1. Kahook MY, Kimura AE, Wong LJ, et al. Sustained elevation in intraocular pressure associated with intravitreal bevacizumab injections. Ophthalmic Surg Lasers Imaging. 2009;40:293-295.

2. Loukianou E, Dimitrios Brouzas D, Apostolopoulos E. Sustained ocular hypertension following intravitreal injections of 0.5 mg/0.05 ml ranibizumab. Int Ophthalmol. 2011;31:211–213

3. Good TJ, Kimura AE, Mandava N, Kahook MY. Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents. Br J Ophthalmol. 2011;95:1111–1114.

4. Mathalone N, Arodi-Golan A, Sar S, et al. Sustained elevation of intraocular pressure after intravitreal injections of bevacizumab in eyes with neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2012;250:1435-1440.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# 1.2 PRDTP Quality Reviews: Phase I-III

## *Summary of Quality Reviews*

*Exhibit 3: Summary of PRDTP Quality Reviews: Phase I-III (2018-2019)*

| Phase | Project Timing | Study Focus | Findings | Limitations | Data Linkage | Data Frame |
|---|---|---|---|---|---|---|
| I | Mar-18 | Determine the overall rate of PRDTP patients requiring glaucoma surgery | • The overall rate of PRDTP patients requiring glaucoma surgery, in the four years investigated, is 1% across all approved indications. | • Accuracy of SPR coding<br>• Follow-up interval was variable therefore, could not accurately calculate incidence of glaucoma surgery<br>• Patients with pre-existing glaucoma could not be excluded, only prior glaucoma surgery | PRDTP and SPR | 2014-2017 |
| II | Ju-18 | Determine glaucoma surgery rates controlling for risk factors over a two-year follow-up period | • Indicated a two-year rate of 2.1% for a composite endpoint of first event of either glaucoma laser or surgery in PRDTP patients.<br>• Higher risk was associated with Retinal Vein Occlusion (RVO), male sex, patients with prior glaucoma, but not age. Risk increased with the number of injections received. There was no increased risk related to which pharmacy supplied drug. There did not appear to be a link between which drug was used for treatment and glaucoma surgery. | • MSP data does not include eye-level data rather it is summarized by patient<br>• Limitations to glaucoma definition (based on MSP data only)<br>• Diabetic Macular Edema (DME) and RVO patients included where risk of glaucoma is higher<br>• No information on deaths<br>• Follow-up time limited to 2-years | PRDTP, MSP, PharmaNet | 2011-2015 |
| III | Mar-19 | Determine glaucoma surgery rates in patients (with no pre-existing glaucoma or eye disease that can cause glaucoma) in AMD only patients over a two-year follow-up period | • Indicated a two-year glaucoma surgery rate of 0.5% in wAMD patients.<br>• Found higher number of injections per year was associated with an increased risk of two-year glaucoma surgery rate. For the 11% of patients receiving 10-13 injections per year in one eye only, the two-year rate was 2.4%. | • No information on deaths<br>• Follow-up time limited to 2-years<br>• Large # of exclusions (7,833 or 41% of the cohort included in final cohort)<br>• Analysis based on small number of surgery cases (42), hence analysis restricted and difficult to draw meaningful conclusions | PRDTP, SPR, MSP, PharmaNet | 2011-2015 |

# 1.3 PRDTP Quality Review: Phase IV

## *Overview*

**Purpose:** to further examine the relationship between glaucoma incidence and anti-VEGF treatments with a more robust dataset.

**Study Questions:**

- 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 (i.e., is there evidence of an increase over time)?
- 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?
- What are the factors associated with higher risk of ocular hypertension, laser procedure, glaucoma surgery?

**Project Study Team:**

- The Quality Working Group includes a diverse membership of retinal specialists, ophthalmologists, epidemiologists, statisticians and senior administrators.
  - Additional expertise of out-of-province experts from Kingston, Ontario and London, Ontario are also included in the membership.
- Analytics Sub-Group formed to undertake analyses between the Quality Working Group meetings.
  - The subgroup includes additional biostatistics and epidemiology expertise with some members serving on both groups.

# 1.3 PRDTP Quality Review: Phase IV
## *Project Study Team*

*Exhibit 4: 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

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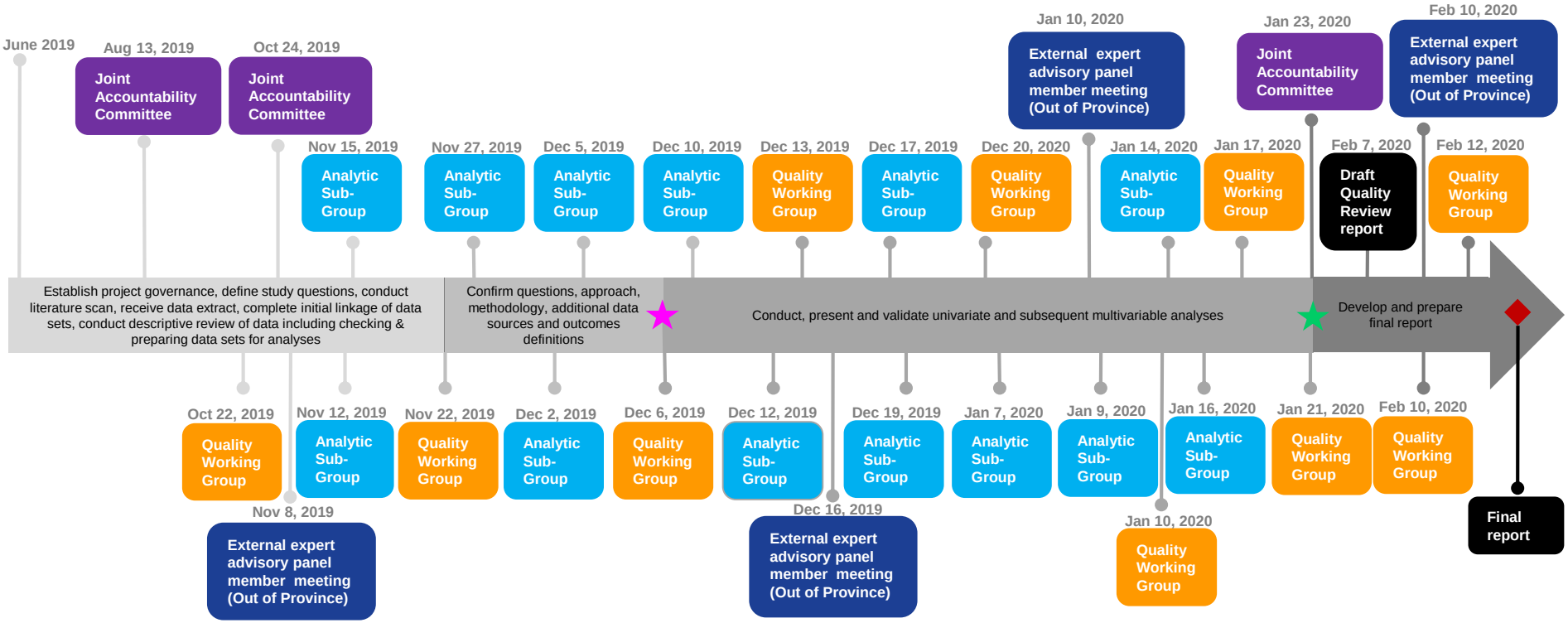
# 1.3 PRDTP Quality Review: Phase IV
## *Project Meetings*

*Exhibit 5: 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

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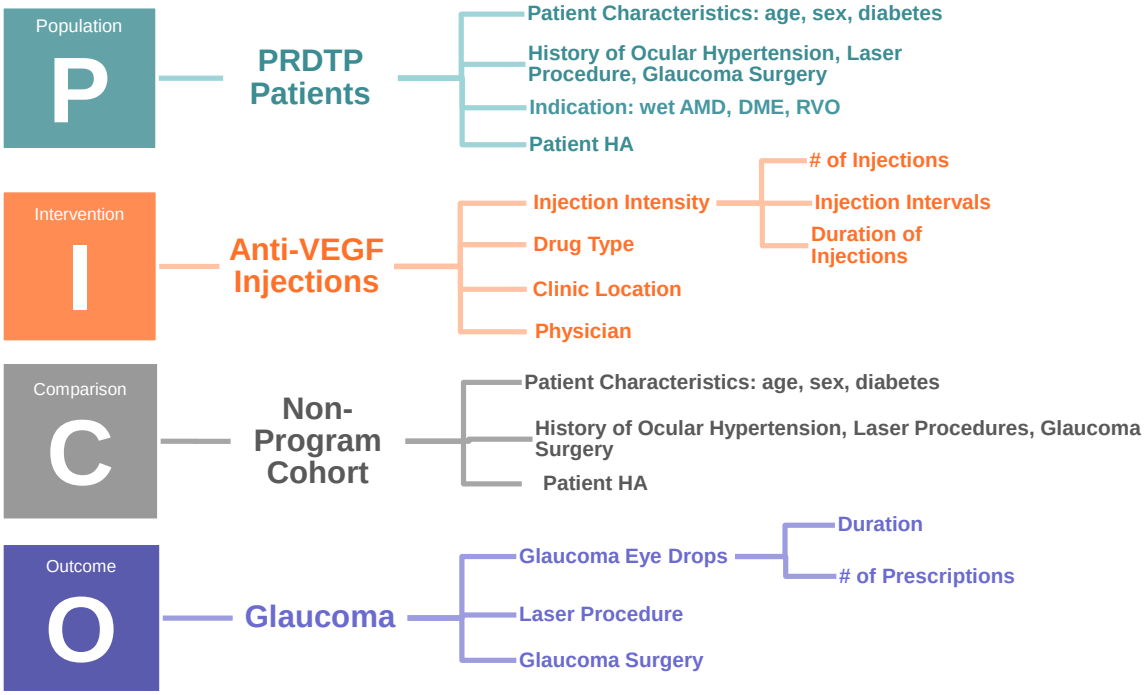
# Chapter 2: Key Study Questions

The three Study Questions for the Phase IV Quality Review include:

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, glaucoma surgery?

*Exhibit 6: Framing of Study Questions in PICO (Population, Intervention, Comparison, Outcome) Format*

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# Chapter 3: Methodology



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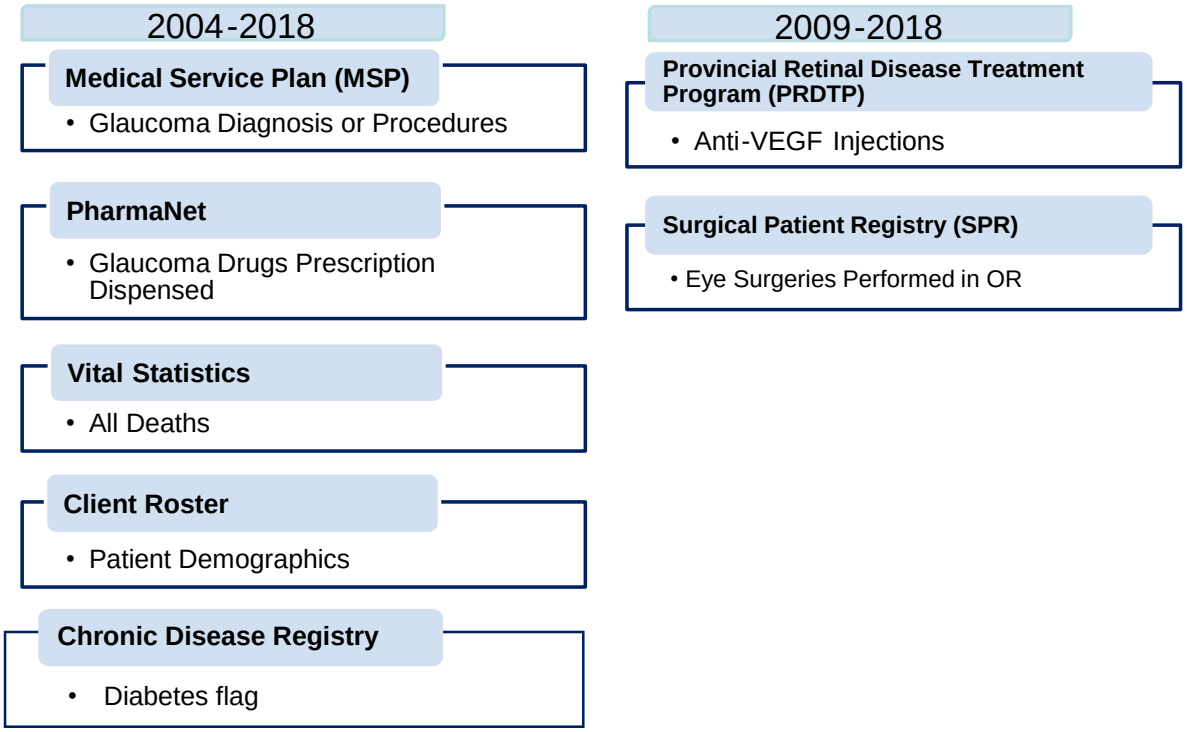
# 3.1 Data Sources

*Exhibit 7: Phase IV Quality Review – Data Sources*




* Note: Data linked using Patient Health Number (PHN)

Details on the data elements within each of the data sources is provided in Appendix A.

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# 3.2 Outcome Definitions

Measuring “glaucoma” as a disease from mild to severe is ideal as an outcome; however, this diagnosis is a broad categorical term with a range of diagnostic features. In addition, no specific diagnostic codes are consistently used to enable the use of this term. Therefore, after thorough review, three primary outcome measures, which together serve as a reasonably close proxy for “glaucoma” are defined as:

- **Ocular Hypertension:** occurs when the pressure inside the eye, called intraocular pressure (IOP), is higher than normal. Higher than normal eye pressure can cause glaucoma. For the purposes of this study, ocular hypertension is 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 is an appropriate definition. The list of medications included are provided in Appendix B. Measured by patient as data does not permit measuring by patient eye.
- **Laser Procedure:** a procedure performed to lower eye pressure in patients with glaucoma. Glaucoma laser procedure is defined as MSP fee item code 22114 - laser trabeculoplasty. Measured by patient as data does not permit measuring by patient eye.
- **Glaucoma Surgery:** several types of variations/combinations of surgeries can facilitate the lowering of IOP.Glaucoma surgery is defined as MSP fee item codes:
    - 2177 - Glaucoma – peripheral iredectomy (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
    - Measured by patient and patient eye. Patient eye comparisons are possible when MSP data are linked with SPR data and surgery is performed in an operating room.

While all three measures are referred as outcome measures, they all reflect an intervention (e.g., medication, procedure, surgery).

* Notes:
Drugs included are those drugs prescribed to treat elevated intraocular pressure due to glaucoma or ocular hypertension. Detailed list provided in Appendix B.

# 3.3 Other Variable Definitions: *Study Cohorts*

*Exhibit 8: Definition of Study Cohorts*

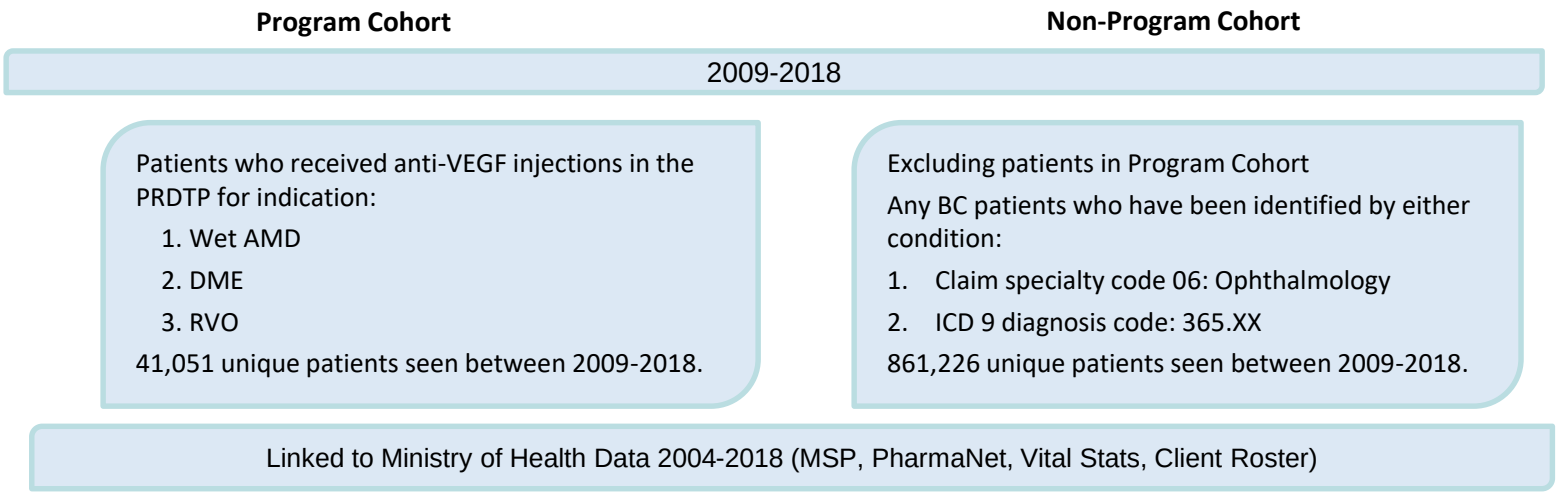


*Exhibit 9: New and Total Patients Seen per Year by Study Cohort*

| | Program Cohort | | Non-Program Cohort | |
|---|---|---|---|---|
| | New (Unique) Patients | Total Patients Seen per Year | New (Unique) Patients | Total Patients Seen per Year |
| 2009 | 4,284 | 4,284 | 95,968 | 379,722 |
| 2010 | 3,150 | 6,416 | 90,349 | 382,710 |
| 2011 | 2,949 | 7,549 | 87,256 | 389,599 |
| 2012 | 2,989 | 8,619 | 85,211 | 399,391 |
| 2013 | 3,693 | 11,041 | 84,390 | 409,814 |
| 2014 | 4,640 | 14,467 | 82,859 | 416,327 |
| 2015 | 4,667 | 16,169 | 83,959 | 430,977 |
| 2016 | 5,040 | 18,126 | 85,314 | 446,091 |
| 2017 | 4,940 | 19,551 | 82,924 | 455,017 |
| 2018 | 4,699 | 20,694 | 82,996 | 464,445 |
| Total | 41,051 | | 861,226 | |

Data Sources: PRDTP and MSP data (2009-2018).

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# 3.3 Other Variable Definitions: *Crude Cumulative Incidence Rate*

*Exhibit 10: Definition of Crude (Unadjusted) Cumulative Incidence Rate*

| Crude Cumulative Incidence Rate | Program Cohort | Non-Program Cohort |
|---|---|---|
| Numerator | Total patients who had the outcome event after their first anti-VEGF injection in a given follow-up timeframe | Total patients who had the outcome event after their initial visit to a BC ophthalmologist in a given follow-up timeframe |
| Denominator | Total patients enrolled in the PRDTP in given follow-up timeframe | Total patients that had an initial visit with a BC ophthalmologist in a given follow-up timeframe |

- Incidence measures the occurrence of new cases during a span of time. Cumulative incidence is a related measure. A useful way to think about cumulative incidence is that it is the probability of developing a condition over a stated period of time; as such, it is an estimate of risk. Cumulative incidence must specify a time period. For example, the glaucoma surgery two-year cumulative incidence for the Program Cohort in 2010 measures, of all the patients who received their first anti-VEGF injection in 2010, the number of patients who had glaucoma surgery within two years of follow-up of their first injection date (e.g., injection on January 1, 2010 is followed until January 1, 2012).
- Cumulative incidence, estimates the cumulative risk from the first anti-VEGF injection to the outcome event and addresses the study questions. Important considerations in calculating crude (unadjusted) cumulative incidence include:
  - Time to event analysis considering death as a competing risk
  - Excluding patients with prior outcome (e.g., glaucoma surgery risk excludes patients with prior glaucoma surgery)
  - Rates stratified by selected factors (e.g., age, indication, physician).

# 3.4 General Approach: *Overview*

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
    - Primary retinal physician/practice location
4. Based on univariate analysis, conduct multi-variable 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

# 3.4 General Approach: *Multivariable Approach*

- The multivariable approach investigates factors that influence the time-to-event. In this case, the event is identified as one of the three outcome variables (defined on slide 13).
- 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 requires specific statistical methods that can deal with censored data. As such, the Cox proportional hazards model was selected as the statistical approach for the multi-variable 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% higher 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 analyses, a P-value of <0.05 was considered statistically significant.

# 3.4 General Approach: *Framework for Analysis*

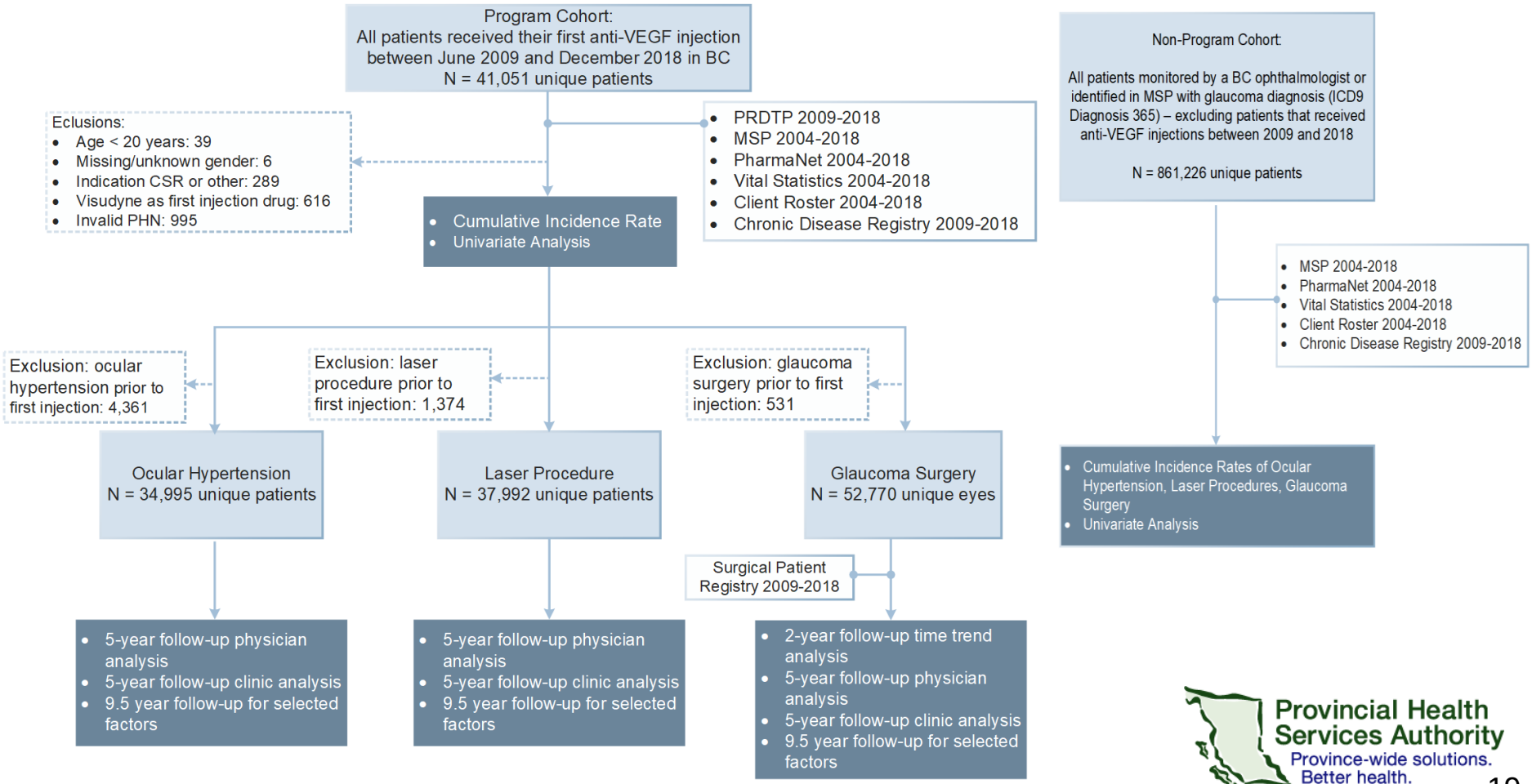
- A summary of the study questions and analysis conducted by outcome event are provided below.

*Exhibit 11: 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 rates 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 retinal physician analysis | √ | √ | √ |
| | Multivariable Model: 5 yr follow-up for physician practice location analysis | √ | √ | √ |
| | Multivariable Model: 9.5 yr follow-up for selected factors | √ | √ | √ |

# 3.4 General Approach: *Study Design Flowchart*

*Exhibit 12: Study Design Flowchart – Program Cohort and Non-Program Cohort*

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# Chapter 4: Results



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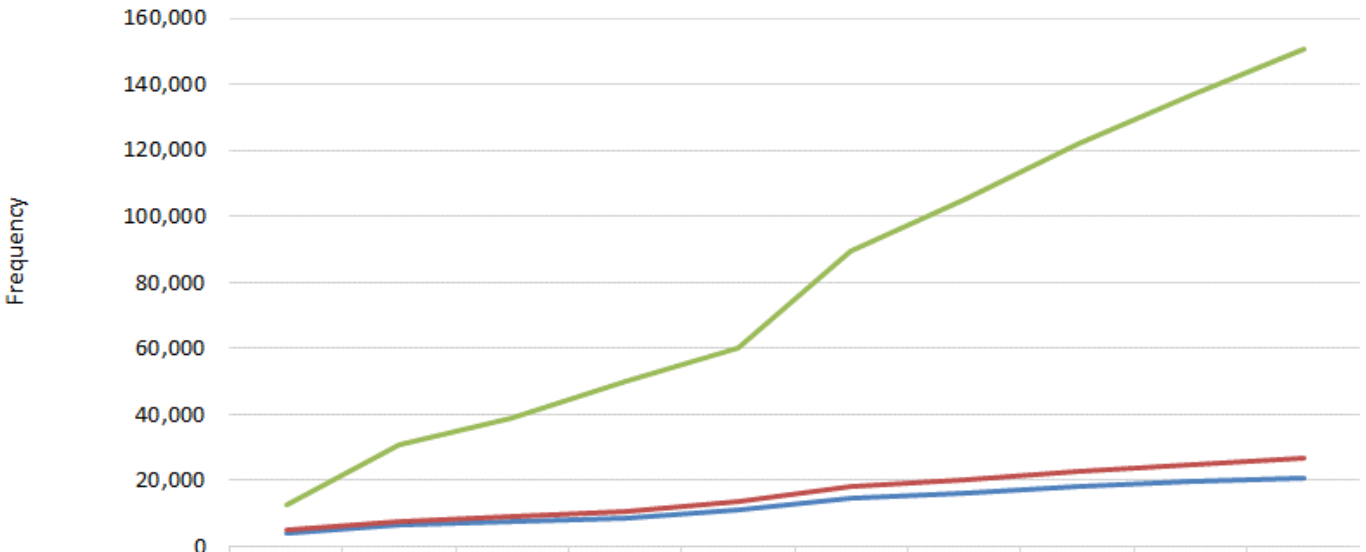
# 4.1 Descriptive Analysis: Program Cohort

## *Number of PRDTP Patients, Patient Eyes & Injections*

*Exhibit 13: 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 |

- PRDTP grew substantially over the last nine years with the number of unique patients increasing from 4,284 in 2009 to 20,694 in 2018 (i.e., a 383% increase in the program participants over 2009). The number of eyes treated is greater than the number of patients as some people have both eyes treated.

Data Source: PRDTP data (2009-2018).
Note: that the PRDTP program commenced mid-way through 2009 in June with approval for treatment of wAMD indication. RVO and DME indications were subsequently approved in November 2013.

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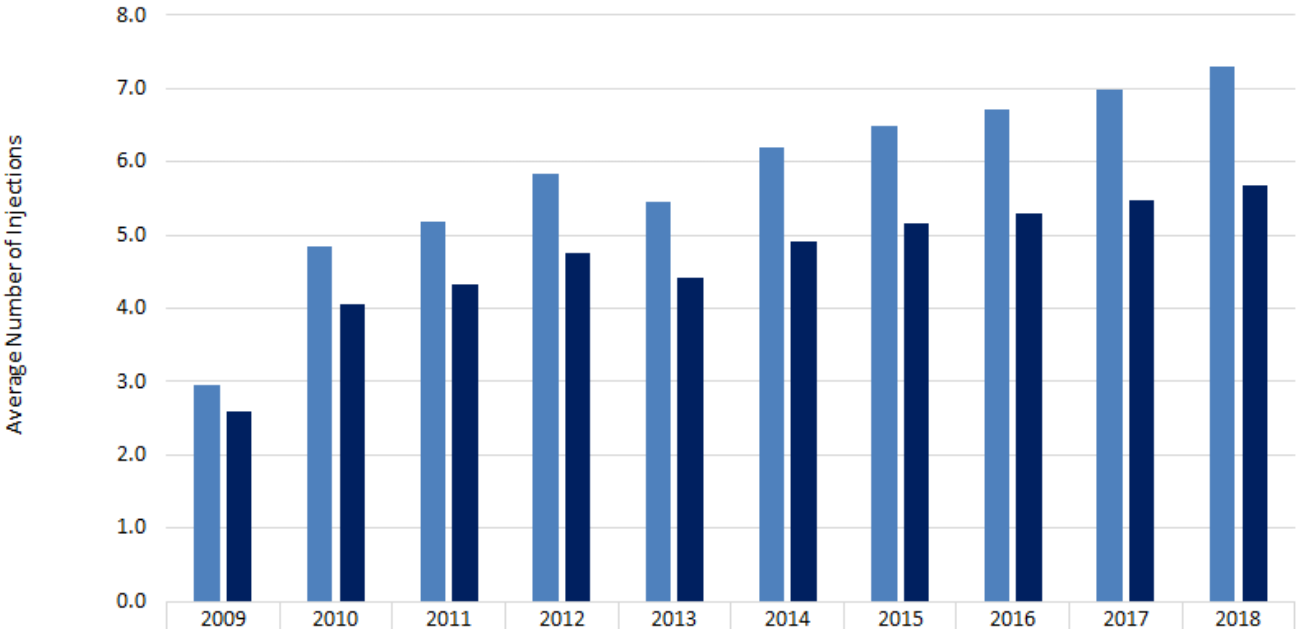
# 4.1 Descriptive Analysis: Program Cohort

## *Average Number of anti-VEGF Injections per Patient/Patient Eye per Year*

*Exhibit 14: Average Number of anti-VEGF Injections per Patient and Patient Eye per Year (2009-2018)*




| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|---|---|---|---|---|
| Average per patient | 3.0 | 4.8 | 5.2 | 5.8 | 5.5 | 6.2 | 6.5 | 6.7 | 7.0 | 7.3 |
| Average per eye | 2.6 | 4.1 | 4.3 | 4.7 | 4.4 | 4.9 | 5.2 | 5.3 | 5.5 | 5.7 |

- The frequency of injections per patient and per eye increased over the period. 2010 represents the first full year of data and indicates an average of 4.8 injections per patient and 4.1 injections per eye. This increased to 7.3 injections per patient and 5.7 injections per eye in 2018.

Data Source: PRDTP data (2009-2018).

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# 4.1 Descriptive Analysis: Program Cohort

## *Percentage of anti-VEGF Injections by Indication and Injected Drug Type*

*Exhibit 15: Percentage of anti-VEGF Injections by Indication by Year (2009-2018)*

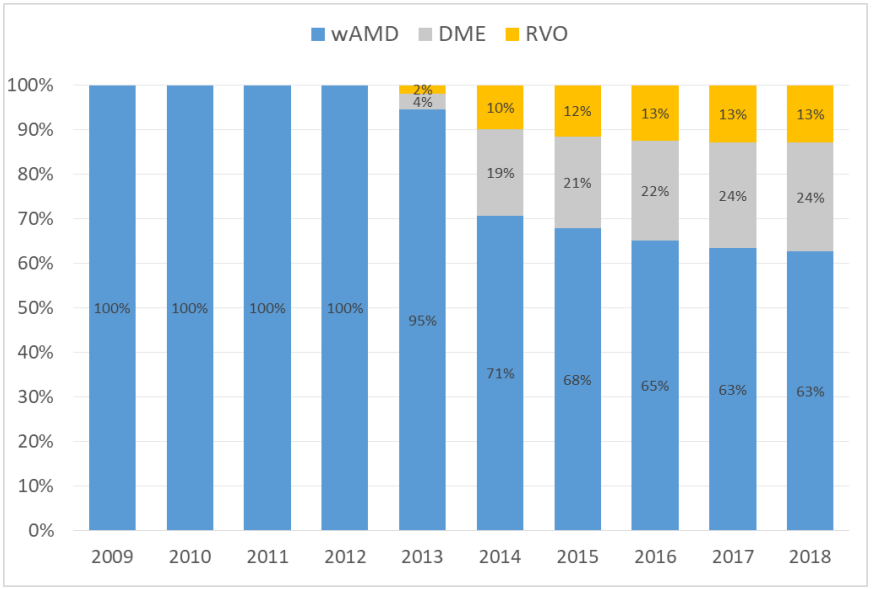
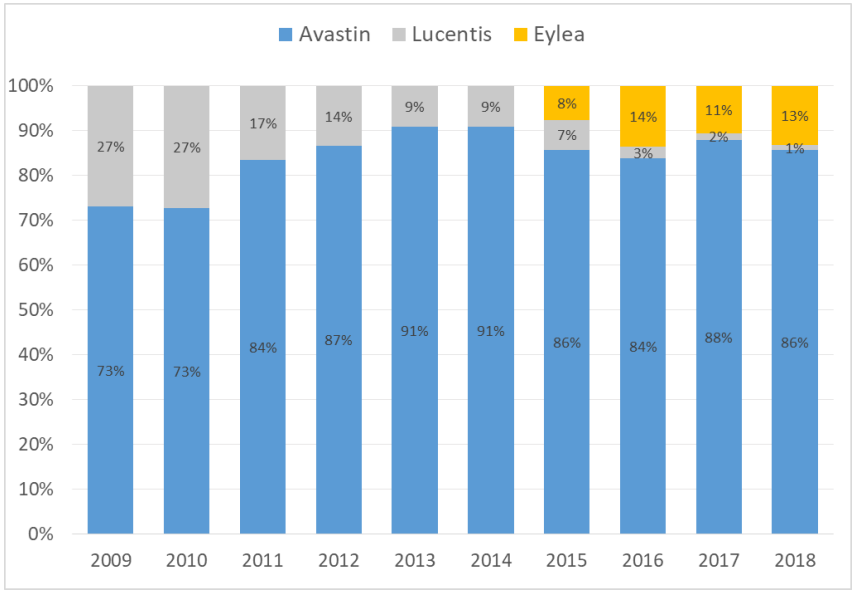



*Exhibit 16: Percentage of anti-VEGF Injections by Injected Drug Type by Year (2009-2018)*




- MoH approvals for DME and RVO indications were provided in November 2013. Prior to that time, virtually all injections were provided for wAMD only. By 2018, 63% of anti-VEGF injections were provided for treatment of wAMD, 24% for DME and 13% for RVO.
- In addition, MoH approved Eylea for wAMD in April 2015 and for DME and RVO in July 2015. This resulted in market share shifting from roughly ¾ Avastin and ¼ Lucentis in 2009 to 86% Avastin, 13% Eylea and 1% Lucentis in 2018.

Data Source: PRDTP data (2009-2018).

Note: The denominator reflects the total number of injections.

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# 4.1 Descriptive Analysis: Program Cohort

## *Summary of Data by Indication and Injected Drug Type*

*Exhibit 17: Total Injections by Indication and Injected Drug Type (2009-2018)*

| | All | Injection Drug Type | | | | | |
|---|---|---|---|---|---|---|---|
| | | Avastin | | Eylea | | Lucentis | |
| | N | n | % | n | % | n | % |
| wAMD | 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 |

- Overall, utilization of Avastin is 85.8% across all indications with greater utilization for wAMD in comparison to DME and RVO.
  - Eylea is utilized in a greater proportion of DME patients.
  - Lucentis is utilized in a greater proportion of AMD patients.
- An analysis of indication and injected drug type indicates a statistically significant correlation ($p<.001$).

Data Source: PRDTP data (2009-2018).

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# 4.1 Descriptive Analysis: Program Cohort

## *Notable PRDTP Policy Changes*

- One dispensing pharmacy held the majority of the market share in the province up to 2016. A new pharmacy joined the PRDTP program in April 2017 and in 2018, this pharmacy held 64% of the market share.

*Exhibit 18: anti-VEGF Pharmacy Market Share (2009-2018)*

| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|---|---|---|---|---|
| Pharmacy A | | | | | | | | | **30%** | **64%** |
| Pharmacy B | 71% | 67% | 71% | 64% | 68% | 78% | 80% | **80%** | **51%** | **21%** |
| Pharmacy C | 22% | 22% | 20% | 17% | 9% | | | | | |
| Pharmacy D | 3% | 5% | 5% | 6% | 6% | 7% | 6% | 6% | 8% | 5% |
| Pharmacy E | | | | 6% | 12% | 11% | 12% | 12% | 10% | 8% |
| Pharmacy F | 4% | 6% | 4% | 7% | 6% | 4% | 3% | 3% | 2% | 1% |
| Total Injections | 12,690 | 31,048 | 39,189 | 50,212 | 60,232 | 89,742 | 104,987 | 121,679 | 136,452 | 150,883 |

- In July 2017, a small subset of these retinal specialists in the PRDTP switched syringes for one week to the Excel syringe. The retinal specialists determined after this short trial to discontinue using the Excel syringe. Given that a minimal number of cases would be impacted by the Excel syringe, the change in syringes is not expected to impact the review. Retinal specialists utilized the same syringe across the study period with the exception of this one small change.

Data Source: PRDTP data (2009-2018).

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# 4.1 Descriptive Analysis: Program Cohort

## *(New) Patient Characteristics by Year of Enrollment*

*Exhibit 19: (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% |

- The average age of the patient population decreased between 2009 and 2014 and stable thereafter. More than ½ the population are females.
- On average, 11.1% of the population had pre-existing ocular hypertension.

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

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# 4.1 Descriptive Analysis: Program Cohort
## *Analytic Summary*

***Analytic Summary:***

The PRDTP program has 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 have 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 in 2013. In 2018, 63% of injections were wAMD, 24% DME and 13% RVO. As well in 2018, 86% of injections were injected with Avastin, 13% Eylea and 1% Lucentis.

This baseline descriptive analysis of PRDTP data informed the subsequent analyses, including:

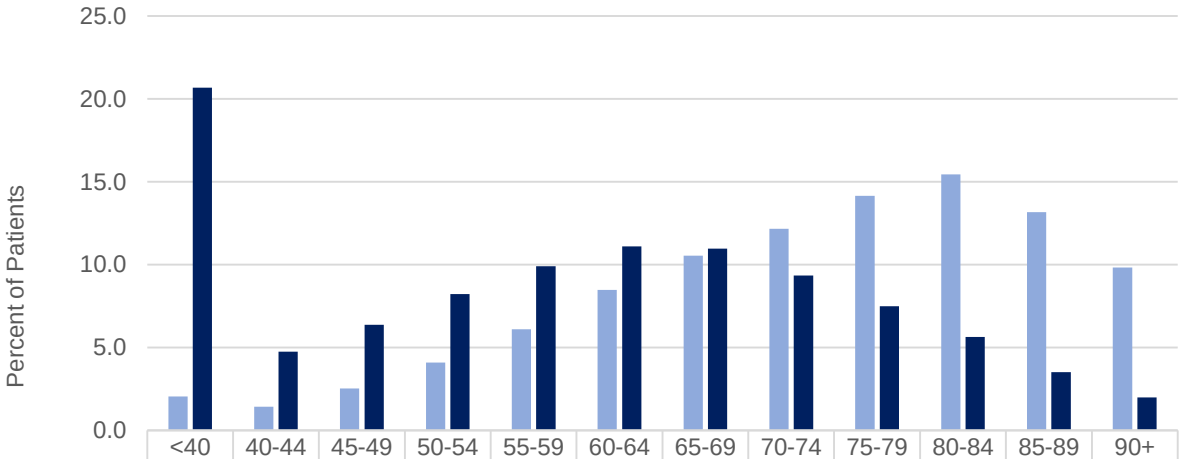
- MoH approval of RVO, DME indications and Eylea drug type mid-way through the study period impacts analysis of year-over-year trends.
- Analyzing data by indication (wAMD, RVO, DME) is important given differences in the underlying patient populations.
- Conclusions by drug type injected (Avastin, Lucentis, Eylea, switchers) 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 will be an important factor for consideration.
- The number of injections per patient eye increased over the study period and should be analyzed.

# 4.2 Select Patient Characteristics: Program/Non-Program Cohort

## *Percentage of Patients by Age Grouping*

- Descriptive statistics comparing the Program Cohort to the Non-Program Cohort is important to compare the patient characteristics of the cohorts. This section compares the age distribution, the prevalence of diabetes, and the prevalence of pre-existing ocular hypertension between the Program Cohort and Non-Program Cohort.

*Exhibit 20: Number of Patients by Age Category – Program Cohort vs. Non-Program Cohort (2009-2018)*




| | <40 | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | 70-74 | 75-79 | 80-84 | 85-89 | 90+ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Program Cohort | 2.1 | 1.4 | 2.5 | 4.1 | 6.1 | 8.5 | 10.5 | 12.2 | 14.2 | 15.5 | 13.2 | 9.8 |
| Non-Program Cohort | 20.7 | 4.8 | 6.4 | 8.2 | 9.9 | 11.1 | 11.0 | 9.4 | 7.5 | 5.6 | 3.5 | 2.0 |

Years of Age

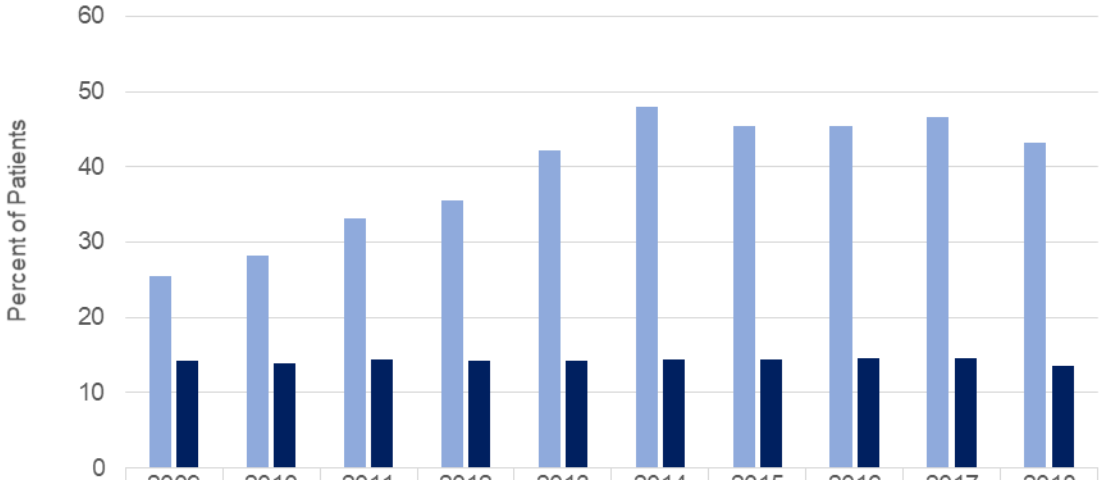
- Almost 1/3 of the Non-Program cohort is less than 50 years of age compared to 6% of the Program cohort. The two cohorts differ substantially with respect to the age distribution of the cohorts.
- The Program cohort represents an older population largely influenced by the wAMD indication. The younger population within the Program cohort represents a population with existing comorbidities (e.g., DME and RVO indication).
- Analysis by year shows that by 2018, 32% of the Program cohort is greater than 85 years of age compared to 8% of the Non-Program cohort.
- When comparing Program cohort to the Non-Program cohort, it is important to take into consideration age as well as comorbid conditions.

Data Sources: PRDTP and MSP data (2009-2018).

# 4.2 Select Patient Characteristics: Program/Non-Program Cohort

## *Prevalence of Pre-existing Diabetes Diagnosis*

*Exhibit 21: Percentage of Patients with a Pre-existing Diagnosis of Diabetes by Year of Enrollment– Program Cohort vs. Non-Program Cohort (2009-2018)**




| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|---|---|---|---|---|
| Program Cohort | 25.4 | 28.3 | 33.2 | 35.6 | 42.1 | 47.9 | 45.4 | 45.4 | 46.6 | 43.2 |
| Non-Program Cohort | 14.3 | 13.9 | 14.4 | 14.3 | 14.3 | 14.4 | 14.5 | 14.6 | 14.5 | 13.5 |

- By year of enrollment, there is a higher percentage of patients with a confirmed diagnosis of diabetes in the Program Cohort (40.2% across all years) as compared to the Non-Program Cohort (14.3% across all years). The two cohorts differ substantially with respect to prevalence of pre-existing diabetes diagnosis.

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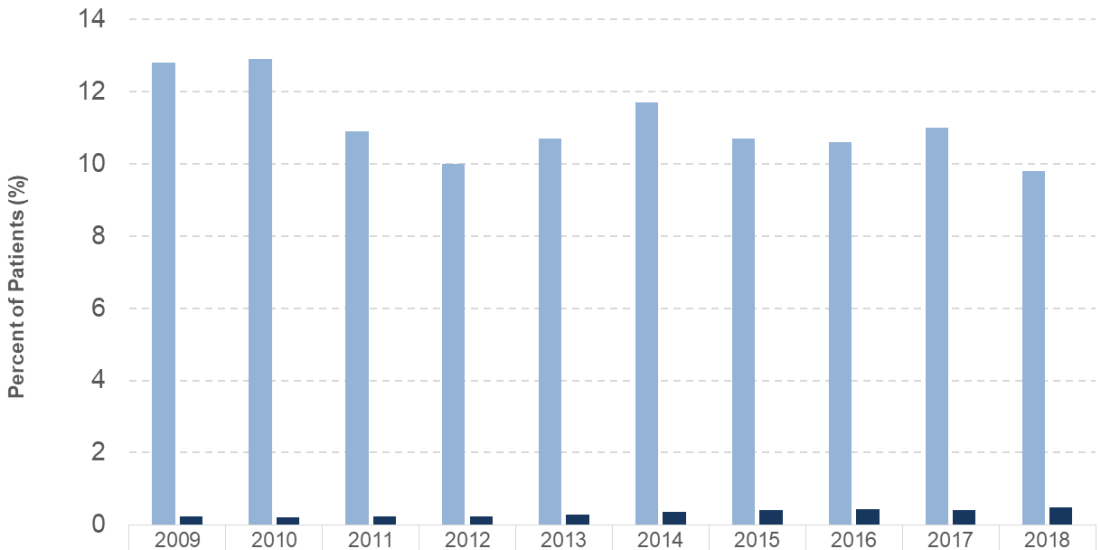
* Pre-existing diagnosis defined as prior to first injection for Program cohort and prior to first ophthalmologist visit for Non-Program cohort.

Data Sources: PRDTP, MSP and CDR data (2009-2018).

# 4.2 Select Patient Characteristics: Program/Non-Program Cohort

## *Prevalence of Pre-existing Ocular Hypertension*

*Exhibit 22: Percentage of Patients with a Pre-existing Ocular Hypertension by Year of Enrollment– Program Cohort vs. Non-Program Cohort (2009-2018)*




| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|---|---|---|---|---|
| Program Cohort | 12.8 | 12.9 | 10.9 | 10.0 | 10.7 | 11.7 | 10.7 | 10.6 | 11.0 | 9.8 |
| Non-Program Cohort | 0.2 | 0.2 | 0.2 | 0.2 | 0.3 | 0.4 | 0.4 | 0.4 | 0.4 | 0.5 |

- Overall, 11.1% of the Program Cohort reported pre-existing ocular hypertension in comparison to the Non-Program Cohort where 0.3% reported pre-existing ocular hypertension. Comparison of crude incidence rates between the two groups will be confounded by pre-existing ocular hypertension in the Program Cohort group.

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* Pre-existing ocular hypertension defined as prior to first injection for Program cohort and prior to first ophthalmologist visit for Non-Program cohort.

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

# 4.2 Select Patient Characteristics: Program/Non-Program Cohort
## *Analytic Summary*

***Analytic Summary:***

A comparison of the Program Cohort to the Non-Program Cohort indicates that the two cohorts differ substantially, including:

- Almost 33% of the Non-Program Cohort is less than 50 years of age compared to only 6% of the Program Cohort. The Program Cohort represents an older population largely influenced by the wAMD indication. The younger population within the Program Cohort represents a population with existing comorbidities (e.g., DME and RVO indication).
- The Program Cohort is an older cohort with higher rates of pre-existing diabetes in comparison to the Non-Program cohort.
- Age and confirmed diabetes diagnosis are included as factors in the multivariable modeling. Both covariates are also identified in the literature as potential risk factors of glaucoma.
- The Program Cohort also reported higher rates of pre-existing ocular hypertension in comparison to the Non-Program Cohort.
- Analysis that compares crude cumulative incidence rates between the two groups are confounded by differences in the age distribution as well as pre-existing diagnoses in the Program Cohort group.
- The Program Cohort are frequently monitored by retinal specialists and therefore, detection of glaucoma may be more likely among the Program Cohort.

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.

# 4.3 Study Question 1: Examination of Time Trends across Outcomes

*Exhibit 23: Framework for Analysis: Study Question 1*

| 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 | | | √ |

- Study Question 1 investigates trends in outcome rates over time. Two analyses are conducted to address this question:
  - Crude (unadjusted) cumulative incidence rates over time are presented for the Program Cohort and Non-Program Cohort for all three outcomes (i.e., ocular hypertension, laser procedure and glaucoma surgery). The rates are expected to be different between the two cohorts given differences in patient baseline characteristics. For example, higher rates of pre-existing ocular hypertension are found in the Program Cohort (11.1%) in comparison to the Non-Program Cohort (0.3%). Differences in the rates between the two groups are confounded by differences in patient characteristics and therefore, the absolute rates are not comparable.
  - Multivariable modelling attempts to adjust for patient baseline characteristics to examine the time trend in two-year glaucoma surgery rates. This analysis is limited to investigating two-year glaucoma surgery rates over time to ensure a consistent follow-up time across patients. For example, a patient that receives their first injection in 2010 is followed for two years (i.e., 2012). The cause-specific hazards model is applied (Section 3.4 provides additional details on the approach).
- Cumulative incidence data comparing the Program Cohort to Non-Program Cohort are presented first for all three outcomes followed by the multivariable modelling of two-year glaucoma surgery rates over time.

# 4.3 Study Question 1: Examination of Time Trends across Outcomes

## *Glaucoma Surgery Crude Cumulative Incidence Rate: Program vs. Non-Program Cohort*

- The next slide shows glaucoma surgery crude incidence by patient as well as by patient eye.
  - Data presented by patient may overestimate the risk of surgery as the surgery could be related to the untreated eye (i.e., the eye without anti-VEGF injections). Data presented at the patient eye level corrects for this issue however, only limited data through a linkage with the SPR data allows for analysis at the patient eye level.
  - Multivariable analyses at the eye-level is an improved approach as it allows for examinations of the association between eye-specific risk factors and the outcome. Eye-level analysis however, may suffer from reduced statistical power given that over 25% of MSP surgeries cannot be identified in SPR (which is used to identify the eye the procedure was performed in). Sensitivity analysis was conducted on the results by patient and by patient-eye and comparable results were found across all factors studied. The eye-level estimate utilizes a more accurate approach to estimating incidence over patient-level data however, it may suffer from reduced statistical power.
  - As a conservative estimate a range of crude incidence is provided using the eye-level and patient-level data.
  - The Non-Program Cohort data, generally representing all non-PRDTP ophthalmology contacts in BC, is calculated at the patient level (as data at the eye level are not available) and rates remain constant over time.
- The incidence of glaucoma surgery is higher in the Program Cohort in comparison to the Non-Program Cohort. This is expected given differences in patient baseline characteristics.
- Glaucoma surgery rates increase year-over-year in the Program Cohort in comparison to the Non-Program Cohort where rates remain relatively constant.
- Crude incidence rates for ocular hypertension and laser procedure are provided following glaucoma surgery data. The increased trend over time in the Program Cohort persists across all three outcomes.

# 4.3 Study Question 1: Examination of Time Trends across Outcomes

## *Glaucoma Surgery Crude Cumulative Incidence Rate - Program vs. Non-Program Cohort*

- Additional summary notes on this analysis are provided on the previous slide. Data are presented at the patient eye-level (for the Program Cohort), followed by data at the patient level (Program Cohort and Non-Program Cohort). A range of estimates (i.e., patient eye-level to patient) are provided as comparators for the Program Cohort.
- The Non-Program Cohort two-year follow-up glaucoma surgery rate remained constant at 0.1% between 2009-2017 (orange table).
- The Program Cohort two-year follow-up glaucoma surgery rate increased over the same time period -- from a range of 0.4 to 0.7% (circled in green) in 2009 increasing to 1.2 to 2.1% in 2017 (circled in purple). Overall, the incidence of glaucoma surgery increased over time in the Program Cohort but, stayed relatively constant in the Non-Program Cohort.

*Exhibit 24: 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 | . | . | . | . | . | . | . | . | . |

*Exhibit 25: Glaucoma Surgery Crude Cumulative Incidence per 100 Patients by Follow-up Year – Program vs. Non-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 | 0.3 | 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 | . | . | . | . | . | . | . | . | . |

| 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 | . | . | . | . | . | . | . | . | . |

Note: Patients that previously had glaucoma surgery are excluded. Data Sources: PRDTP, MSP, SPR, Vital Statistics (2009-2018).

# 4.3 Study Question 1: Examination of Time Trends across Outcomes

## *Ocular Hypertension and Laser Procedure Crude Cumulative Incidence Rate - Program vs. Non-Program Cohort*

- The Non-Program Cohort two-year follow-up ocular hypertension rate remained relatively constant around 2% between 2009-2017. Similarly, the Non-Program Cohort two-year follow-up laser procedure rate remained relatively constant around 0.8%.
- The Program Cohort two-year follow-up ocular hypertension rate increased over the same time period from 3.7% in 2009 to 8.2% in 2017. Similarly, the Program Cohort two-year follow-up laser procedure rate increased from 0.8% in 2009 to 2.3% in 2017.

*Exhibit 26: Ocular Hypertension Cumulative Incidence per 100 Patients by Follow-up Year – Program vs. Non-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 | 2.0 | 1.8 | 2.4 | 2.7 | 3.4 | 3.9 | 4.1 | 5.0 | 5.3 | 4.3 |
| 2 years | 3.7 | 3.6 | 5.7 | 6.4 | 6.9 | 7.7 | 7.9 | 10.2 | 8.2 | . |
| 3 years | 5.5 | 5.7 | 8.0 | 9.1 | 9.9 | 10.3 | 11.3 | 12.8 | . | . |
| 4 years | 7.9 | 7.6 | 10.4 | 11.4 | 12.3 | 13.0 | 13.1 | . | . | . |
| 5 years | 9.9 | 9.3 | 12.3 | 13.0 | 14.1 | 14.6 | . | . | . | . |
| 6 years | 11.7 | 10.8 | 14.0 | 15.2 | 15.9 | . | . | . | . | . |
| 7 years | 12.9 | 12.1 | 15.6 | 16.4 | . | . | . | . | . | . |
| 8 years | 14.0 | 13.1 | 16.9 | . | . | . | . | . | . | . |
| 9 years | 15.2 | 14.3 | . | . | . | . | . | . | . | . |
| 10 years | 15.7 | . | . | . | . | . | . | . | . | . |

| Number of Follow-up Years | Year of First Visit to Ophthalmologist | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
| 1 year | 1.5 | 1.5 | 1.5 | 1.4 | 1.4 | 1.4 | 1.3 | 1.4 | 1.4 | 1.1 |
| 2 years | 2.0 | 1.9 | 2.0 | 1.9 | 1.9 | 1.8 | 1.7 | 1.8 | 1.8 | . |
| 3 years | 2.3 | 2.2 | 2.3 | 2.2 | 2.2 | 2.2 | 2.0 | 2.1 | . | . |
| 4 years | 2.6 | 2.5 | 2.6 | 2.5 | 2.4 | 2.5 | 2.2 | . | . | . |
| 5 years | 2.9 | 2.8 | 2.9 | 2.8 | 2.7 | 2.7 | . | . | . | . |
| 6 years | 3.1 | 3.1 | 3.1 | 3.0 | 2.9 | . | . | . | . | . |
| 7 years | 3.4 | 3.4 | 3.4 | 3.2 | . | . | . | . | . | . |
| 8 years | 3.7 | 3.7 | 3.6 | . | . | . | . | . | . | . |
| 9 years | 3.9 | 3.9 | . | . | . | . | . | . | . | . |
| 10 years | 4.1 | . | . | . | . | . | . | . | . | . |

*Exhibit 27: Laser Procedure Crude Cumulative Incidence per 100 Patients by Follow-up Year – Program vs. Non-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 | 0.4 | 0.2 | 0.4 | 0.2 | 0.3 | 0.5 | 0.7 | 0.8 | 1.1 | 1.3 |
| 2 years | 0.8 | 0.9 | 1.1 | 0.9 | 1.2 | 1.3 | 1.7 | 1.9 | 2.3 | . |
| 3 years | 1.5 | 1.3 | 1.6 | 1.4 | 2.0 | 2.4 | 2.8 | 2.7 | . | . |
| 4 years | 2.1 | 1.9 | 2.2 | 2.1 | 2.8 | 3.2 | 3.6 | . | . | . |
| 5 years | 2.8 | 2.5 | 2.9 | 3.0 | 3.3 | 3.9 | . | . | . | . |
| 6 years | 3.4 | 2.9 | 3.7 | 3.5 | 4.4 | . | . | . | . | . |
| 7 years | 3.8 | 3.4 | 4.2 | 3.6 | . | . | . | . | . | . |
| 8 years | 4.3 | 3.9 | 4.5 | . | . | . | . | . | . | . |
| 9 years | 4.7 | 4.1 | . | . | . | . | . | . | . | . |
| 10 years | 4.8 | . | . | . | . | . | . | . | . | . |

| Number of Follow-up Years | Year of First Visit to Ophthalmologist | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
| 1 year | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.6 | 0.7 | 0.7 | 0.6 |
| 2 years | 0.7 | 0.7 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.9 | 0.9 | . |
| 3 years | 1.0 | 0.9 | 1.0 | 1.0 | 0.9 | 1.0 | 1.0 | 1.1 | . | . |
| 4 years | 1.1 | 1.1 | 1.2 | 1.1 | 1.2 | 1.2 | 1.2 | . | . | . |
| 5 years | 1.3 | 1.3 | 1.4 | 1.3 | 1.3 | 1.4 | . | . | . | . |
| 6 years | 1.4 | 1.5 | 1.5 | 1.5 | 1.5 | . | . | . | . | . |
| 7 years | 1.6 | 1.6 | 1.7 | 1.7 | . | . | . | . | . | . |
| 8 years | 1.8 | 1.8 | 1.9 | . | . | . | . | . | . | . |
| 9 years | 1.9 | 1.9 | . | . | . | . | . | . | . | . |
| 10 years | 2.1 | . | . | . | . | . | . | . | . | . |

Note: Patients previously identified with ocular hypertension are excluded from the ocular hypertension estimates; patients that previously had laser procedure are excluded from the laser procedure estimates. Data Sources: PRDTP, MSP, SPR, Vital Statistics (2009-2018).

# 4.3 Study Question 1: Examination of Time Trends across Outcomes

## *Multivariable Analysis of Time Trend in Two-Year Glaucoma Surgery Cumulative Incidence Rates (Program Cohort)*

*Exhibit 28: 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** | **Hazard Ratio** | **95% Lower CL** | **95% Upper CL** | **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 |

* Note: Details on the multivariable analysis approach is provided on slide 17.

- To control for baseline characteristics, a multivariable cause-specific hazards model examined the time trend in two-year glaucoma surgery rates. 2010 is used as the baseline year as it is the first full year of PRDTP data.
- The model included all indications and adjusted for baseline patient characteristics including age, sex, indication for injection, prior ocular hypertension and prior laser procedure.
  - Patients who had glaucoma surgery prior to first injection were excluded.
  - Note that 2017 cumulative incidence is under-estimated due to insufficient follow-up.
- The model evaluated the Program Cohort only as no changes over time are noted in the Non-Program incidence rate.
- The results indicated that in comparison to 2010, increased glaucoma surgery risks are statistically significant between 2014 to 2018.



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

# Study Question 1: Examination of Time Trends across Outcomes
## *Analytic Summary*

***Analytic Summary:*** 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?

- Yes, there is evidence of an increase in crude cumulative incidence rates in the Program Cohort over time across all three outcomes between 2010 and 2018. Two-year follow-up crude cumulative incidence rates from 2009-2017 increased for:
  - Glaucoma surgery from 0.4% -0.7% for the Cohort with the first injection in 2009, and 1.2% - 2.1% for the Cohort with the first injection in 2017. A range is provided given limitations in the data both at the lower end (i.e., using eye-level data) and at the upper end (i.e., using patient-level data). Only patient level data are available (i.e., no eye-level data are available) for laser procedure and ocular hypertension outcomes.
  - Laser procedure from 0.8% to 2.3% (patient-level data only)
  - Ocular hypertension two year crude cumulative incidence from 3.7 % to 8.2% (patient-level data only).

  The changing incidence rate over time may be influenced by the introduction of DME and RVO in 2013 as a particular increase was seen around that time.

- To better understand the variation over time, controlling for factors such as indication, a multivariable analysis was conducted. Even after adjusting for patient baseline characteristics – including indication, an increased glaucoma surgery risk remains in the Program Cohort during the period of 2014 to 2017.

- Crude cumulative incidence rates are compared between the Program Cohort and the Non-Program Cohort. The rates indicate that the Program Cohort reports higher incidence rates that are increasing over time. The Non-Program Cohort reports lower incidence rates that are stable over time for all three outcomes. These differences are not surprising given the very important distinctions between the two patient populations, as they are confounded by differences in several important patient characteristics including the relevant difference in pre-existing ocular hypertension where 11.1% of the Program Cohort had ocular hypertension before ever receiving an anti-VEGF injection, compared to 0.3% of the non-program cohort having pre-existing ocular hypertension.

# 4.4 Study Question 2: Examination of Risk and of the Factors Influencing the Risk

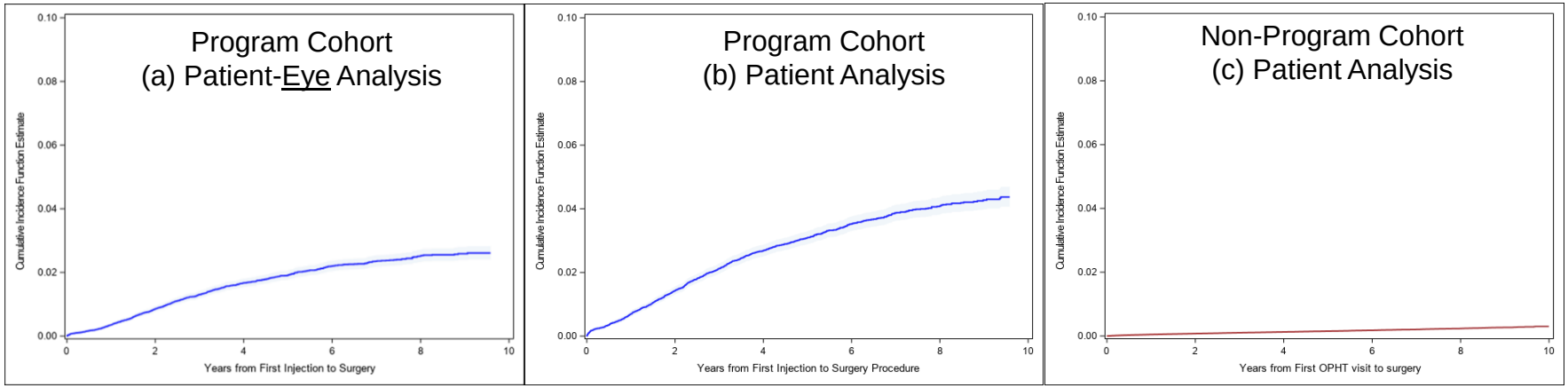
*Exhibit 29: Framework for Analysis: Study Question 2*

| Study Question | Analysis | Outcome | | |
|---|---|---|---|---|
| | | Ocular Hypertension | Laser Procedure | Glaucoma Surgery |
| 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) | √ | √ | √ |

- Study Question 2 investigates the cumulative incidence stratified by potential factors that are associated with increased risk of ocular hypertension, laser procedure and glaucoma surgery. The cumulative incidence provides information on the absolute risk of each outcome and guides the model selection in the multivariable analyses performed for Study Question 3.
- For glaucoma surgery, the cumulative incidence rate is presented by patient and at the eye-level. Given data limitations, the rate is presented by patient for ocular hypertension and laser procedure.
  - As mentioned earlier, patient-level data may represent an overestimate of the risk as the surgery could be related to the untreated eye. Data summarized at the eye-level may provide a better approach to estimating risk; 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.
  - Rates are stratified by selected factors – patient and non-patient factors (see Appendix C for definitions) including:
  - Patient-related factors: age group, sex, indication, cumulative average number of injections per follow-up year
  - Non-patient-related factors: year of enrollment, primary retinal physician.
  - Other factors (e.g., IOP, visual field, optic disc status, eye-related comorbidities) may be relevant to the analysis however, data are not readily available for consideration.
- Results for ocular hypertension and laser procedure are provided in Appendix D.

# 4.4 Study Question 2: Risk as measured by the Crude Cumulative *Glaucoma Surgery* Incidence Rate

*Exhibit 30: Crude Cumulative Glaucoma Surgery Incidence Rate – Program Cohort 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% |

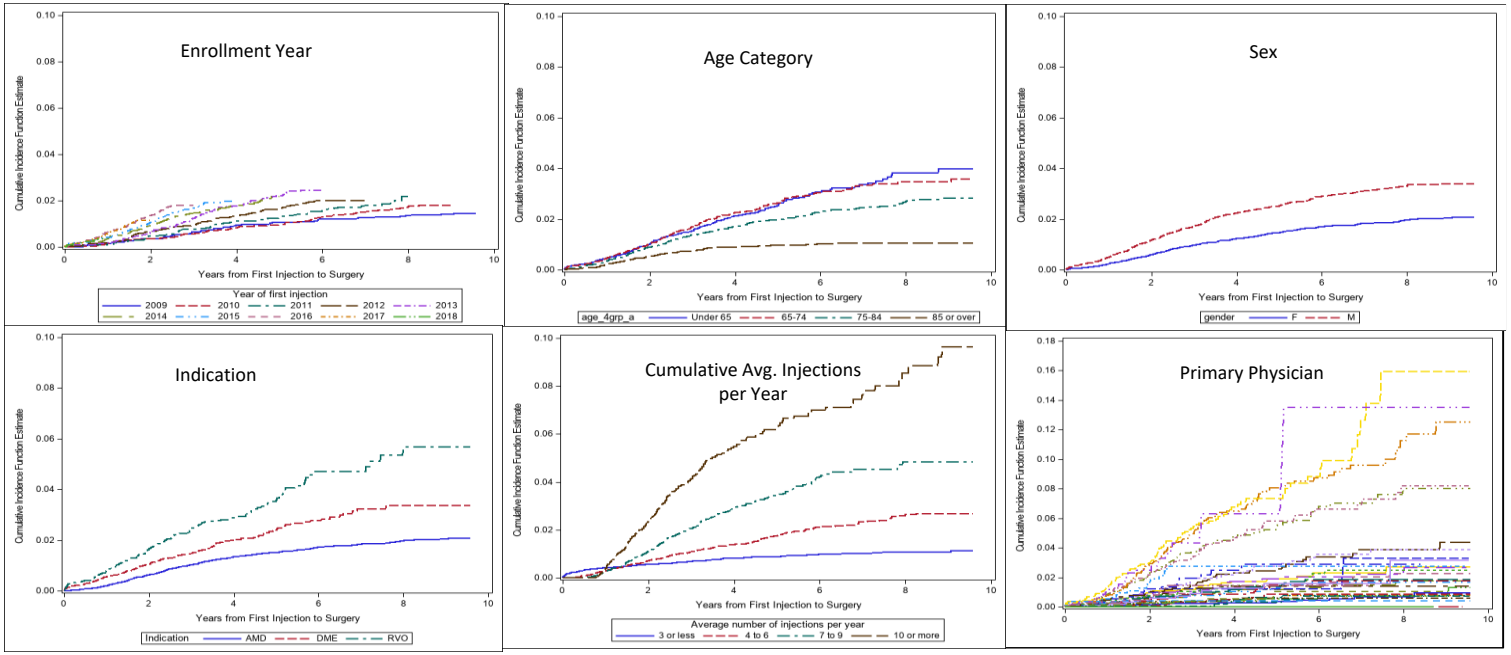
- It is important to note that 11.1 % of the program cohort versus 0.3% of the Non-Program Cohort had pre-existing ocular hypertension before the study period and are included in the Program Cohort. These differences provide some explanation as to why the incidence rates are so different between the Program Cohort and Non-Program Cohort.
- The curves above represent the crude cumulative incidence rate of glaucoma surgery based on Program Cohort (a) patient-eye analysis and (b) patient level analysis. The Non-Program Cohort patient level data are also presented (c). The cumulative incidence rate is plotted against the number of years from the first injection to glaucoma surgery for Program Cohort and from the first visit to an ophthalmologist to glaucoma surgery for Non-Program Cohort, taking into account death or loss to follow-up.
- The curves indicate, for example, that the two-year incidence rate of glaucoma surgery in Program Cohort is between 0.85% and 1.43% (eye-level vs.. patient level estimate), compared with 0.08% in Non-Program Cohort.

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

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

# 4.4 Study Question 2: Examination of Factors Influencing Risk for *Glaucoma Surgery* Univariate Crude Cumulative Incidence Rate – Program Cohort

*Exhibit 31: Crude Cumulative Glaucoma Surgery Incidence Rate – Eye Level – Program Cohort – Selected Factors (2009-2018)*




- Many factors may influence the crude cumulative incidence rate for glaucoma surgery. The selected factors reviewed indicate:
  - **Enrollment year:** There are statistically significant differences by enrollment year with 2009 and 2010 reporting the lowest rates. Incidence rates increase with every 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 is associated with increasing incidence rates ($p$<.001). It is critical to note that this is describing "per year of follow up".
  - **Primary Retinal Physician:** There are statistically significant differences in incidence rates across primary retinal physician ($p$<.001).

* Note: Patients treated with glaucoma surgery prior to their first injection (Program Cohort) or prior to their first visit to ophthalmologist (Non-Program Cohort) and are excluded.
Data Sources: PRDTP, MSP, SPR, Vital Statistics (2009-2018).

# 4.4 Study Question 2: Observed Two-Year Rate by *Primary Retinal Physician* by Outcome Measure

*Exhibit 32: Observed Two-Year Rate by Primary Retinal Physician by Outcome Measure – Program Cohort (2009-2018)*

| Physician Code | Percentage of Cases with: 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** |

- Crude rates with two-year follow-up 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%.

Notes:

- Data sorted by lowest to highest Glaucoma Surgery Rate.
- Patients were excluded from the 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).

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# Study Question 2: Examination of Risk and of the Factors Influencing the Risk

## *Analytic Summary*

***Analytic Summary:*** 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 was calculated to estimate the incidence 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 the Program cohort, as measured by two-year incidence rate of glaucoma surgery was 0.85% (eye-level data) to 1.43% (patient-level data), meaning approximately 1:100 eyes had surgery within two years after injection. While this incidence rate was lower than what was previously identified in Phase II (which was 2.1% for composite endpoint of glaucoma laser procedure or surgery), 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 outcomes. With these methodological differences, there is greater confidence of the findings from Phase IV compared to Phase II.
- While the data linkages with other data sets in Phase IV allows for a broader set of factors to be included, the data allow for only a small set of factors to be analyzed. Of the factors reviewed for the univariate analysis, the following are shown to be predictors of a higher risk for ocular hypertension, laser procedure, or glaucoma surgery over time:
  - Patient-related factors:
    - Age <75 years of age
    - Males
    - RVO or DME indications
    - Higher average number of injections per follow-up year
  - Non patient-related factors:
    - Year of enrollment in PRDTP after 2013
    - Specific clinic location/primary retinal physician.
- These factors are further examined in the multivariable analysis to evaluate associations between risk factors and outcomes.

# 4.5 Study Question 3: Examination of Factors Associated with Higher Risk across Outcomes of interest

*Exhibit 33: Framework for Analysis: Study Question 3*

| Study Question | Analysis | Outcome | | |
|---|---|---|---|---|
| | | Ocular Hypertension | Laser Procedure | Glaucoma Surgery |
| 3. What are the factors associated with higher risk of ocular hypertension, laser procedure, glaucoma surgery? | Multivariable Model: 9.5 yr follow-up for selected factors | √ | √ | √ |
| | Multivariable Model: 5 yr follow-up for physician practice location analysis | √ | √ | √ |
| | Multivariable Model: 5 yr follow-up for primary retinal physician analysis | √ | √ | √ |

- Before moving into multivariable modelling, univariate analysis of selected factors by outcome is first conducted using a Cox regression model.
- To address Study Question 3, controlling for baseline characteristics (i.e., age, sex, indication, previous history), multivariable hazards models examine 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.
  - **Up to five year follow-up:** From the univariate analysis primary retinal physician was identified as a factor associated with increased risk of the outcomes; therefore, the association of variation among physicians and physician location on the risk of outcomes is also examined. A five year time frame is used for the primary retinal physician and physician practice location analysis to decrease the number lost to follow-up and improve the robustness of the estimate.
- After controlling for baseline characteristics, the association of the additional factors is examined on the outcomes:
  - Patient-related factors: interaction of cumulative average injections per follow-up year and, injected drug type.
  - Non patient-related factors: physician practice location, primary retinal physician.

# Study Question 3: Examination of Factors Associated with Increased Risk across Outcomes

## *Univariate Analysis of Selected Factors by Outcome*

*Exhibit 34: 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 increase of age)*** | 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 (used more than one drug over treatment course) | 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 |

* Note: Age factor – e.g., there is a 15% decrease in the risk of glaucoma surgery for every 10 year increase in age.
Data Sources: PRDTP, MSP, SPR, Client Roster, PharmaNet, Vital Statistics, Chronic Disease Registry (2009-2018).

# Study Question 3: Examination of Factors Associated with Increased Risk across Outcomes

## *Univariate Analysis of Selected Factors by Outcome (cont'd)*

- The results of the univariate analysis is consistent across the three outcomes (glaucoma surgery, ocular hypertension, laser procedure).
- Statistically significantly increased risk is identified in the univariate analysis among the following selected factors:
  - Age: Decrease in the risk for every 10 year increase in age
  - Sex: Increased risk among males
  - Diabetes: 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 among 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 >6 injections per year of follow-up.

# Study Question 3: Examination of Factors Associated with Increased Risk across Outcomes

## *Multivariable Analysis of Selected Factors by Outcome*

*Exhibit 35: Multivariable Fine and Gray Sub-Distribution Hazards Model Results by Outcome with up to 9.5 Years of Follow-up (2009-2018)*

| | | Time to Glaucoma Surgery | | | | Time to Ocular Hypertension | | | | Time to Laser Procedure | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Factor** | | **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 |

- The multivariable analysis investigated the effect of baseline patient characteristics, frequency of injections per follow-up year and injected drug type. Similar findings and trends to the univariate analysis are noted in the exhibit above.
- With respect to the specific drug type, data for patients who were treated with Lucentis only or Eylea only were excluded due to a small sample size. Univariate analysis by drug type indicates that switchers (i.e., a switcher used more than one drug over course of treatment) reported increased risk in comparison to Avastin only injections and Lucentis/Eylea 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). The Quality Working Group determined that drawing conclusions from this heterogeneous switcher group is challenging and potentially subject to bias. The analysis above includes only Avastin injections.
- Results indicate that more frequent injections per year of follow-up increases the risk of all three outcomes (i.e., glaucoma surgery, ocular hypertension, laser procedure).

Note: The multivariable analysis results by drug type is not provided on this slide however, was conducted with the full analysis; 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).

# Study Question 3: Examination of Factors Associated with Increased Risk across Outcomes

## *Multivariable Analysis of Primary Retinal Physician by Outcome*

- Building off of the findings presented on the previous slide, the analysis next focuses on studying the variation across primary retinal physicians using up to a five-year follow-up timeframe (Note: primary retinal physician definition in Appendix C).
- To evaluate the effect of primary retinal physician on outcomes, the *initial* multivariable model is adjusted for baseline patient characteristics only (including age, sex and indication for injection, previous history of ocular hypertension and/or laser procedure). Then, to investigate the influence of selected practice differences on primary retinal physician variation, the model adds cumulative average number of injections per follow-up year, followed by injected drug type. Across all three outcome variables and across all models, the results are comparable.
- The following three exhibits summarize the findings by outcome by primary retinal physician.
    - By primary retinal physician (slide 48 and 49):
        - Primary retinal physicians 2, 9 report statistically significantly decreased risk across all three outcomes - ocular hypertension, laser procedure and glaucoma surgery.
        - Primary retinal physicians 19, 22, 26,18,16 report statistically significantly increased risk across all three outcomes - ocular hypertension, laser procedure and glaucoma surgery.
        - The results remain relatively consistent at the physician level even when the analysis excludes patient eyes treated by multiple physicians.

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# Study Question 3: Examination of Factors Associated with Increased Risk across Outcomes

## *Multivariable Analysis of Primary Retinal Physician by Outcome*

*Exhibit 36: Multivariable Cause-specific Hazards Model Results by Outcome with up to 5 Years of Follow-up - Primary Retinal Physician (2009-2018) - Controlling for Baseline Patient Characteristics*

| | 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 |

- Adjusted for patient baseline characteristics including age, sex, indication for injection, prior ocular hypertension (for laser and surgery models), prior laser procedure (for surgery model).

* Notes: Physician names are coded. The data are sorted by lowest Glaucoma Surgery Hazard Ratio to highest Glaucoma Surgery Hazard Ratio. 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).

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# Study Question 3: Examination of Factors Associated with Increased Risk across Outcomes

## *Additional Multivariable Analysis of Primary Retinal Physician by Outcome*

*Exhibit 37: Multivariable Cause-specific Hazards Model Results by Outcome with up to 5 Years of Follow-up - Primary Retinal Physician (2009-2018) – Controlling for Baseline Patient and Non-Patient Characteristics*

| | 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 |

- The previous slide included patient baseline characteristics only as adjustment factors.
- This slide investigates the physician effect after adjusting for patient baseline characteristics AND cumulative average number of injections and drug type
- The results indicate that after adjusting for patient baseline characteristics, statistically significant differences exist at the physician level even after controlling for cumulative average number of injections per follow-up year and injected drug type.

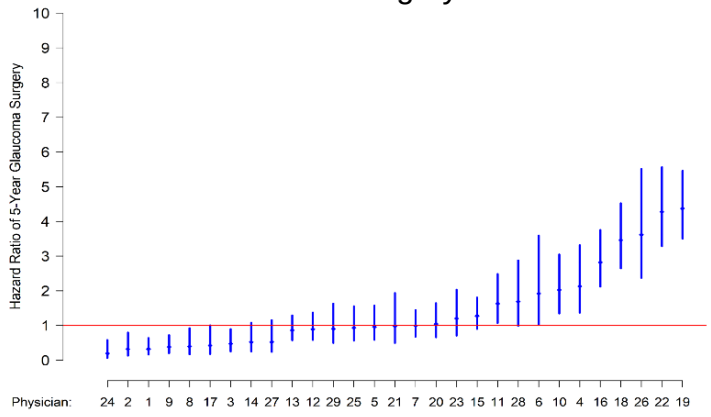
* Notes: Physician name[illegible]d. The data are sorted by lowe[illegible]a Surgery Hazard Ratio to high[illegible]oma Surgery Hazard Ratio. Patients were excluded from the risk analysis if they had the event of interest prior to the first injection date. Red font denotes statistically increased risk; 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).

# Study Question 3: Examination of Factors Associated with Increased Risk across Outcomes

## *Primary Retinal Physician Hazard Ratio Compared to Provincial Average*

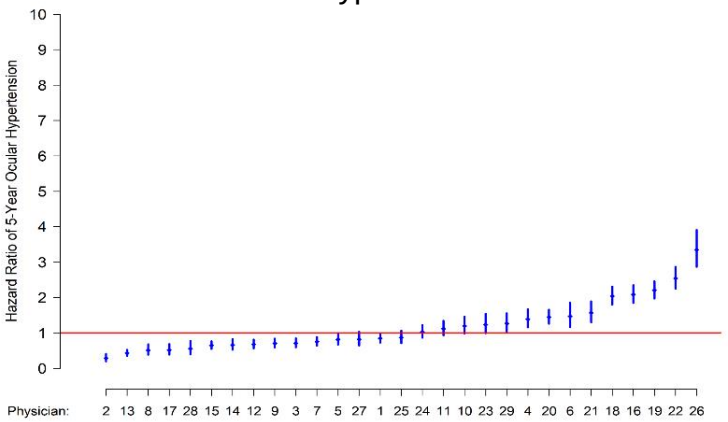
*Exhibit 38: Multivariable Cause-specific Hazards Model Results by Outcome with up to 5 Years of Follow-up - Primary Retinal Physician (2009-2018) - Controlling for Baseline Patient and Non-Patient Characteristics*

Glaucoma Surgery



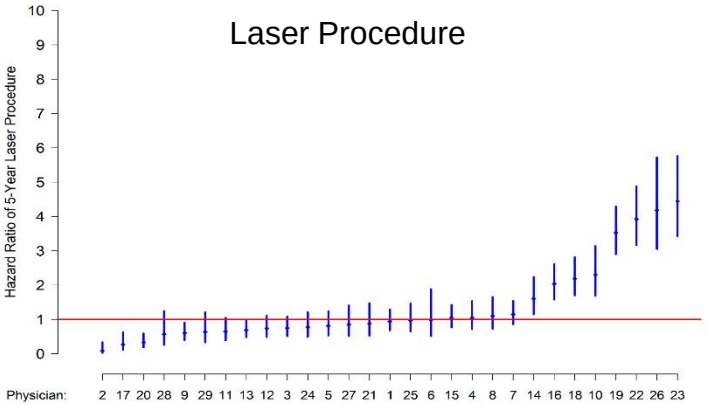

*Note: Adjusted for the average number of injections per year and the injected drug type, in addition to patient baseline characteristics including age, sex, indication for injection, prior ocular hypertension, prior laser procedure.*

Ocular Hypertension




*Note: Adjusted for the average number of injections per year and the injected drug type, in addition to patient baseline age, sex, indication for injection.*

Laser Procedure




*Note: Adjusted for the average number of injections per year and the injected drug type, in addition to patient baseline characteristics including age, sex, indication for injection, prior ocular hypertension, prior glaucoma surgery.*

* Notes: Physician names are coded. The data are sorted by primary retinal physician with the lowest Hazard Ratio to highest Hazard Ratio. 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).

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# Study Question 3: Examination of Factors Associated with Increased Risk across Outcomes

## *Additional Analyses*

- To adjust for the fact that some physicians share patients, a third multivariable model excluded patient eyes treated by multiple physicians
  - Adjusting for patient baseline characteristics including age, sex, indication for injection, prior ocular hypertension, prior laser procedure, cumulative average number of injections per follow-up year, and injected drug type and excluding patient eyes treated by multiple physicians.
  - By primary retinal physician, these results are consistent with the results including all patient eyes.
- Multi-variable analysis is also conducted by retinal physician location.
  - The mapping of physician practice location with primary retinal physician identified examples where physicians with higher hazard ratios are located in the same location as physicians with lower hazard ratios.
  - The one location where all physicians reported higher hazard ratios, 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 be confounded by the physician effect, data are summarized in this report by primary retinal physician only.

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# Study Question 3: Examination of Factors Associated with Increased Risk across Outcomes

## *Analytic Summary*

***Analytic Summary:*** What are the factors associated with increased risk of ocular hypertension, laser procedure, glaucoma surgery after Anti-VEGF treatment?

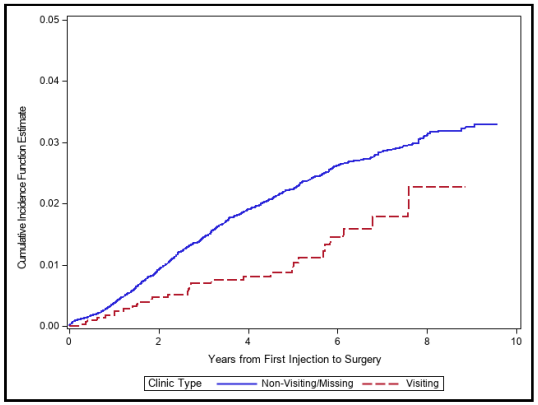
- A multivariable model examined the factors associated with the outcomes using up to 9.5 years of follow-up to examine the association of select factors on the risk of the outcomes. The association of variations among physicians on the risk of the outcomes using up to five years of follow-up is also examined.
- The multivariable analysis reported consistent findings across all outcomes and where similar factors could be tested, results are consistent with Phase II findings. These include:
  - **Age <75 years, male sex, and RVO indication are 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 are more likely to receive glaucoma surgery.**
  - **The data analysis does not support that drug type is associated with increased risk of the three outcomes analyzed.**
    - 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 injections. That is, more patients on Avastin had RVO and also received a higher number of injections. Both RVO and higher anti-VEGF injections 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.**

# 4.6 Additional Subsequent Analyses

Subsequent analyses focused on:

- Association of dispensing pharmacy where the drugs are compounded and syringe and risk of the outcomes
  - In the PRDTP program, one pharmacy held the majority of the market share from 2009 until 2016. Retinal physicians with reported increased glaucoma surgery risk purchase drugs and utilize syringes from the same pharmacy as retinal physicians with reported decreased glaucoma surgery risk. Findings in outcomes cannot be attributed to differences in preparation and storage procedures as the same compounding pharmacy is the provider for multiple physicians some of which report very low risk of outcomes.
  - There is no data findings to support that dispensing pharmacy is associated with the risk of the outcomes analyzed.
  - As the same syringes are used across the pharmacies there are no findings to support the syringe is associated with the risk of outcomes analyzed.
- Visiting clinics (see exhibit below)
  - In rural and smaller urban communities where locum physicians might see patients, a statistically decreased risk of glaucoma surgery was observed ($p$<.001). Visiting clinics represent a small proportion of the total injections at 6.4%.

*Exhibit 40: Cumulative Glaucoma Surgery Incidence Rate by Patient Eye: Visiting Clinics vs.. Others (2009-2018)*




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

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# Chapter 5: Findings



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# 5.1 Findings: *Summary*

**Context:**

- Anti-VEGF agents are the first-line therapy for various eye diseases including wAMD, RVO and DME and are one of the most important treatments for vision stabilization. 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.[1-3] Anti-VEGF injections are generally very 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.
- There is evidence that suggests a risk for glaucoma or sustained ocular hypertension in patients undergoing repeated treatments with anti-VEGF drugs.[4] Therefore, the results of this study are not unique.
- As part of the program quality improvement plan within PRDTP, 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 are complete.
- Based on the data available, Phase II analysis (July 2018) indicated a two-year rate of 2.1% for a composite endpoint of first event of either glaucoma laser procedure or surgery. Increased risk was associated with RVO, male sex, patients with prior glaucoma, but not age. Risk increased with the number of injections received. There was no increased risk related to which pharmacy supplied drug. As well, there did not appear to be a link between which drug was used for treatment and glaucoma surgery. The rates are reported at a patient-level and therefore, may over-estimate the overall risk as the surgery could be related to the untreated eye. Furthermore, the analysis is limited to a two-year follow-up.
- 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.

[1]Solomon SD, Lindsey K, et al. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD005139. DOI: 10.1002/14651858.CD005139.pub4.

[2]Rosenfeld_PJ, Brown_DM, et al. Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2006;355(14):1419-31. [MARINA 2006]

[3]Regillo_CD, Brown_DM, et al. Randomized, double-masked, sham controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 1. American Journal of Ophthalmology 2008;145(2):239-48.

[4]Wingard JB, Delzell DAP, Houlihan NV, Lin J, Gieser JP. Incidence of glaucoma or ocular hypertension after repeated anti-vascular endothelial growth factor injections for macular generation. Clinical Ophthalmology (2019); 13: 2563-2572.

# 5.1 Findings: *Summary (cont'd)*

**The main findings of the report include:**

Program size and description:

- The PRDTP program has 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 have 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 injected with Avastin, 13% with Eylea and 1% with 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 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 syringe for a sub-set of the retinal specialists and filtering of drug across all physicians was instituted after end of the study period).

# 5.1 Findings: *Summary (cont'd)*

**The main findings of the report include (continued from prior slide):**

**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 cumulative incidence rates show that while the absolute rates for this cohort of patients remain relatively low, there is an increase from the time the program started to 2017
  - Glaucoma surgery two year crude cumulative incidence rates are 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. The upper end of each of these ranges represented the incidence when patient level data was used. To be as conservative as possible in these estimates, the range using both eye-level and patient-level results are shown.
  - When the data are examined by year of entry as a whole (i.e., entire follow-up period analyzed), the crude cumulative glaucoma surgery incidence rate at two years ranged from 0.85 % (eye level) to 1.43% (patient level).
  - Laser procedure crude cumulative incidence rates, measured at the patient level identified the two year crude cumulative incidence rate as 0.8% in 2009 and 2.3% in 2017.
  - Ocular hypertension crude cumulative incidence rate, measured at the patient level identified the two year crude cumulative incidence rate as 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.
- 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) also 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.

# 5.1 Findings: *Summary (cont'd)*

**The main findings of the report include (continued from prior slide):**

**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?**

- When the data are analyzed as a whole (across all years), the crude cumulative glaucoma surgery incidence rate at two years is 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 is in the range of 2.59% to 4.27%.
- Consistent results from all the analysis, using different time points and across all three outcomes are reported.

**What are the factors associated with an increased risk of ocular hypertension, laser procedure and glaucoma surgery?**

- Models are primarily used to answer this question based on earlier univariate analyses findings. All three outcomes are examined and indicated consistent results. The analysis indicates that there is increased risk for glaucoma surgery, laser procedure and ocular hypertension among patients with AMD, DME and RVO in comparison to the Non-Program Cohort.
- Within the PRDTP Cohort, there are statistically significant differences with respect to increased risk of all three outcomes with patients whose age is less 75 years, who are of male sex, who are treated for the RVO indication and who have higher injection frequency. Increased glaucoma surgery risk is also associated with patients with pre-existing ocular hypertension or who have 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.
- The analyses did not specifically examine the effect of the syringe as all physicians used the same type of syringe. Differences between physicians' rates cannot 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 are associated with increased risk across all three outcomes and a small number of physicians consistently are associated with decreased risk across all three outcomes. These findings persisted once patients who received treatments from multiple physicians are removed.

# 5.1 Findings: *Summary (cont'd)*

**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.[1]

- 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.

[1] Atchison EA, Wood KM, Mattox CG, et al. The real-world effect of intravitreous anti-vascular endothelial growth factor drugs on intraocular pressure: an analysis using the IRIS registry. Ophthalmology. 2018;125:676-682.

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# Findings: *Phase IV: Study Limitations*

There are some limitations associated with this review.

- It was not possible to compare the PRDTP group to a control group. 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. 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) to 7.8% (DME patients only).[1,2]
  - 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).[2]
- 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 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 investigate other multivariable approaches.

[1] He Y, Ren XJ, Hu BJ, Lam WC, Li XR. A meta-analysis of the effect of a dexamethasone intravitreal implant versus intravitreal anti-vascular endothelial growth factor treatment for diabetic macular edema. BMC Ophthalmol. 2018;18(1):121.
[2] Choi DY, Ortube MC, McCannel CA, et al. Sustained elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab, and pegaptanib. Retina. 2011;31(6):1028-1035.

# Findings: *Phase IV: Study Limitations (cont'd)*

**Study Limitations (continued from previous slide):**

- 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 intra-ocular pressure; however, the outcome measures were based on high quality data and were deemed to represent a reasonable 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 intra-ocular pressure 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.
    - 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.
    - 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 6: *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.

**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, ca review, and learn from BC's program.

# Appendices



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# Appendix A: Phase IV – Data Sources and Data Elements

**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

**Medical Services Plan (MSP) data:** In B.C., public health insurance is called the MSP. It covers the cost of medically-necessary insured doctor services. Under the Medicare Protection Act, enrolment with the MSP is mandatory for all eligible residents and their dependents.
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 ocular hypertension, 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

**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

# Appendix A: Phase IV – Data Sources and Data Elements (cont'd)

**PharmaNet data:** PharmaNet is the province-wide network that links all B.C. pharmacies to a central data system. Every prescription dispensed in community pharmacies in B.C. is entered into PharmaNet.
The data includes Glaucoma drugs identified in Appendix B, 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. Only those glaucoma drugs identified by the study are included. 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

**Vital Statistics data:** The **Vital Statistics Agency** registers all births, marriages, deaths, and changes of name that occur in British Columbia. If a person dies in British Columbia, the death must be registered with the Vital Statistics Agency, which issues death certificates upon request.
The 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

**Client Roster (CR) data**: The Client Roster represents the best available demographic and geographic information for the Ministry's clients and is available by calendar year or fiscal year. 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

**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 an increased risk of developing glaucoma. Data fields include:

- Date of diabetes

# Appendix B: Phase IV – Identified Medications for Treatment of Elevated IOP

The following list of medications (generic drug name) were identified by the MoH Pharmaceutical Division 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 | |

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# Appendix C: Definitions of Factors used in the Multivariable Analysis

- ***Years of follow-up:*** A measure of the maximum number of years of follow-up available following the first anti-VEGF injection in the PRDTP either by patient-eye or by patient
  - Categories: Up to 1 year follow-up; Up to 2 years follow-up; Up to 3 years follow-up; Up to 4 years follow-up; Up to 5 years follow-up; Up to 6 years follow-up; Up to 7 years follow-up; Up to 8 years follow-up; Up to 9 years follow-up
- ***Age group:*** Patient age at the time of the first anti-VEGF injection in the PRDTP grouped into age categories.
  - Categories: Under 65 years of age; Between 65-74 years of age; Between 75-84 years of age; Greater than 85 years of age
- ***Sex:*** Patient sex at the time of the first anti-VEGF injection in the PRDTP
  - Categories: Female; Male
- ***Indication:*** 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. Note: a small number of DME/RVO patients were treated and coded as AMD prior to MoH approval of these indications in 2013. This approach corrects for this data quality issue.
  - Categories: wAMD, RVO, DME
  - Exclusions: Patients with indication as CSR, other, or missing
- ***Cumulative average number of injections per follow-up year****:* This represents the total number of injections received until the end of the follow-up (i.e., death or to the first outcome or to end of study period, whichever occurs first), divided by the total years of follow-up. For example, a patient with 5 years of follow-up with an cumulative average of 10 injections per follow-up year had 50 injections over the follow-up period.
  - Categories: $\leq$ 3 injections per follow-up year; between >3 and $\leq$ 6 injections per follow-up year; between >6 and $\leq$ 9 injections per follow-up year; >9 injections per follow-up year
- ***Primary retinal physician:*** The retinal physician primarily responsible for treating wAMD, DME or RVO patients with anti-VEGF injections. Where patients are shared, the physician with the highest frequency of injections is assigned.

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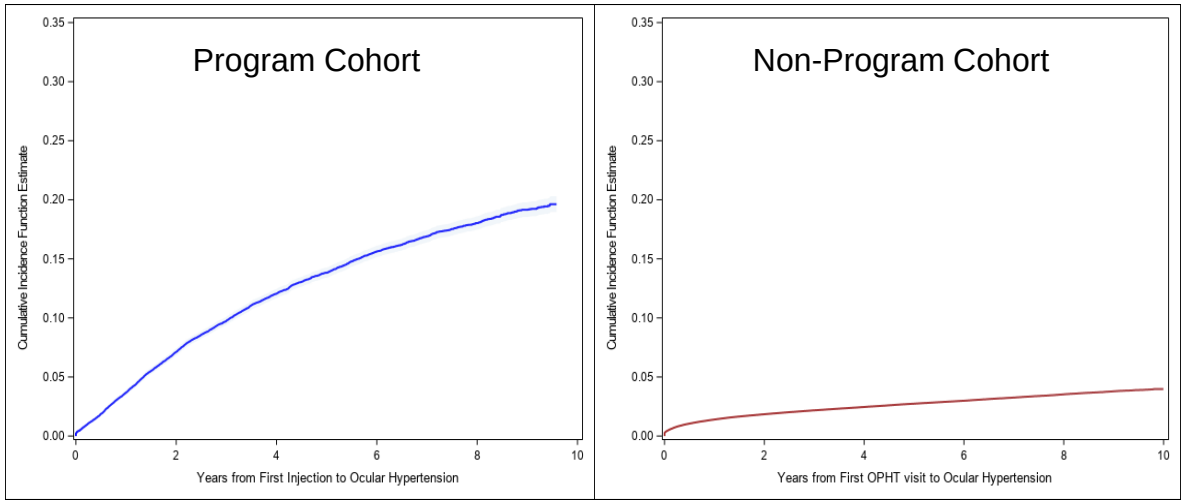
# Appendix C: Definitions of Factors used in the Multivariable Analysis (cont'd)

- ***Clinic location:*** The clinic location is a field reported in the PRDTP database and may represent several physician locations. For example, there are two separate physician office locations in North Vancouver however, the PRDTP database does not differentiate between the two "North Vancouver" locations. The physician practice location defined below attempts to correct for this issue.
- ***Physician practice location:*** To create the physician practice location a review was conducted of all retinal specialists (in the PRDTP program). The review focused on the total number of eyes injected per year by physician by clinic location (as reported in the PRDTP database). The review indicated that there may be more than one physician office location in a clinic location. For example, there are two separate physician office locations in North Vancouver however, the database only identifies "North Vancouver" as a clinic location. In these cases, the physician practice location is denoted as "North Vancouver 1" and "North Vancouver 2". Other notes:
    - Visiting clinic locations are identified separately, noting that some visiting locations became standard locations over time. In the end, a small number of clinic locations are noted as a visiting clinic location.
    - Note that being assigned to a physician practice location with other physicians does not mean that physicians share patients. Sharing a physician practice location with other physicians means that the offices are located in the same physical location. Another field in the analysis identifies at an eye-level, treatments that are shared with other physicians.
    - A small number of eyes overall are treated by locums and/or out-of-province physicians and those injections are assigned to the "other" location. Missing clinic is also assigned to "other" location.

# Appendix D: Crude Cumulative *Ocular Hypertension* Incidence Rate

*Exhibit 41: Crude Cumulative Ocular Hypertension Incidence Rate per Patient – Program Cohort/Non-Program Cohort (2009-2018)*




- The curves above represent the crude cumulative incidence rate of ocular hypertension by patient for the Program Cohort and Non-Program Cohort. The cumulative incidence rate is plotted against the number of years from the first injection to ocular hypertension, taking into account death as a competing risk.
- The cumulative incidence of ocular hypertension estimates the absolute risk of developing ocular hypertension among patients without any prior ocular hypertension as a function of follow-up time from the first injection (Program Cohort) or the first visit to an ophthalmologist (Non-Program Cohort).
- Compared to Non-Program Cohort, Program Cohort has an increased risk of developing ocular hypertension throughout the follow-up period (Program Cohort: 7.0% at the end of 2 years of follow-up, 13.7% at the end of 5 years of follow-up; Non-Program Cohort: 1.9% at the end of 2 years of follow-up, 2.7% at the end of 5 years of follow-up)

* Note: Patients diagnosed with pre-existing ocular hypertension prior to their first injection or first ophthalmologist visit are excluded.

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

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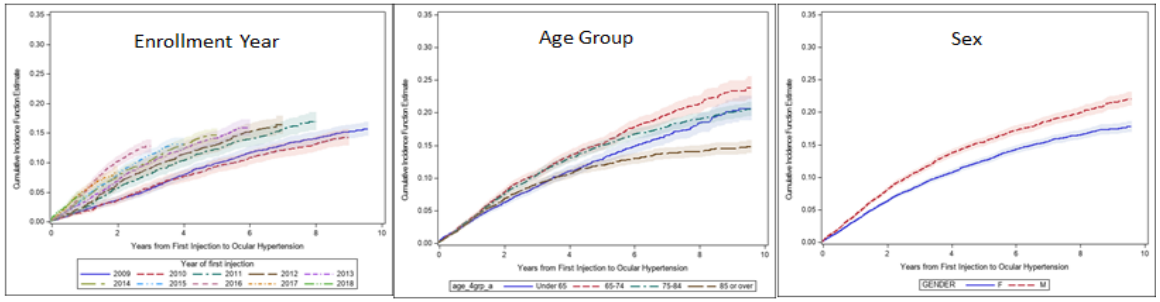
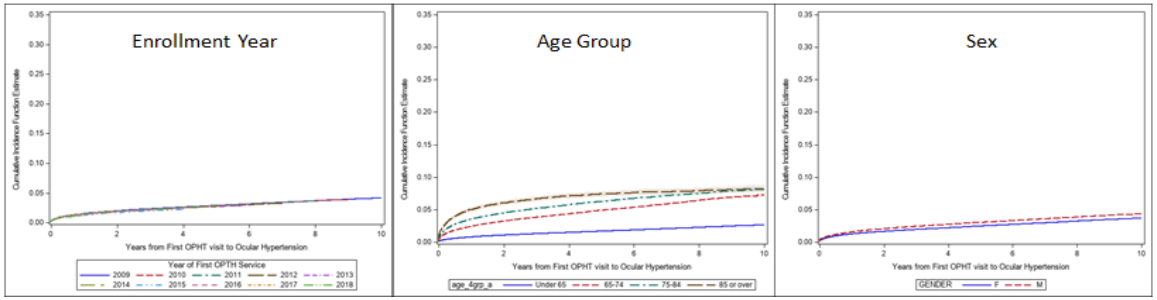
# Appendix D: Examination of Selected Factors Influencing Crude Cumulative *Ocular Hypertension* Incidence Rate

*Exhibit 42: Crude Cumulative Ocular Hypertension Incidence Rate per Patient – Program Cohort/Non-Program Cohort – Selected Factors (2009-2018)*

Program Cohort




Non-Program Cohort

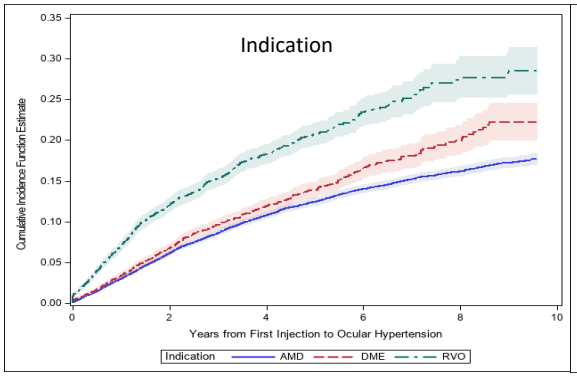


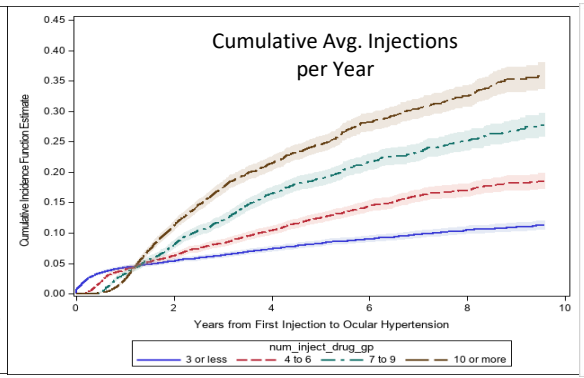

- Many factors influence the crude cumulative incidence rate for ocular hypertension. The factors identified for further analysis indicate the same trends as glaucoma surgery and indicate:
  - **Enrollment year:** There are no differences in incidence by enrollment year in the Non-Program Cohort. In the Program Cohort there are statistically significant differences by enrollment year with 2009 and 2010 reporting the lowest rates. Incidence rates increase with every year of enrollment ($p$<.001).
  - **Age group:** In the Program Cohort those greater than 85 years of age reported the lowest rates and those between 65-74 years of age reported the highest incidence rates ($p$<.001). This compares to the Non-Program Cohort where the older populations reported statistically significantly higher rates as compared to the youngest population ($p$<.001).
  - **Sex:** The Program Cohort and Non-Program Cohort reported higher incidence rates in males compared to females ($p$<.001).

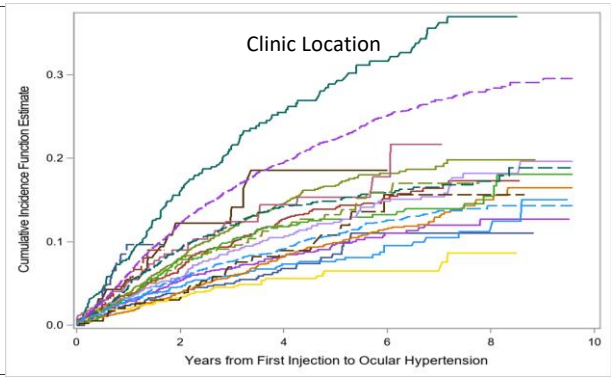
* Note: Patients diagnosed with pre-existing ocular hypertension prior to their first injection or first ophthalmologist visit are excluded.
Data Sources: PRDTP, MSP, PharmaNet, Vital Statistics (2009-2018).

# Appendix D: Examination of Selected Factors Influencing Crude Cumulative *Ocular Hypertension* Incidence Rate

*Exhibit 43: Crude Cumulative Ocular Hypertension Incidence Rate per Patient – Program Cohort – Selected Factors (2009-2018)*




- Additional factors that may influence the Program Cohort crude cumulative incidence rate of ocular hypertension are investigated. The same trends as in the glaucoma surgery analysis are reported including:
  - **Indication:** RVO reported statistically significantly higher incidence rates following DME and wAMD ($p$<.001).
  - **Cumulative average number of injections per year:** Within the first year and half of enrollment, more frequent injections reported lower rates. Thereafter, increasing frequency of injections reported higher incidence rates ($p$<.001).
  - **Clinic location:** There are statistically significant differences in incidence rates across clinic locations ($p$<.001).

- Note: Patients diagnosed with pre-existing ocular hypertension prior to their first injection are excluded.

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

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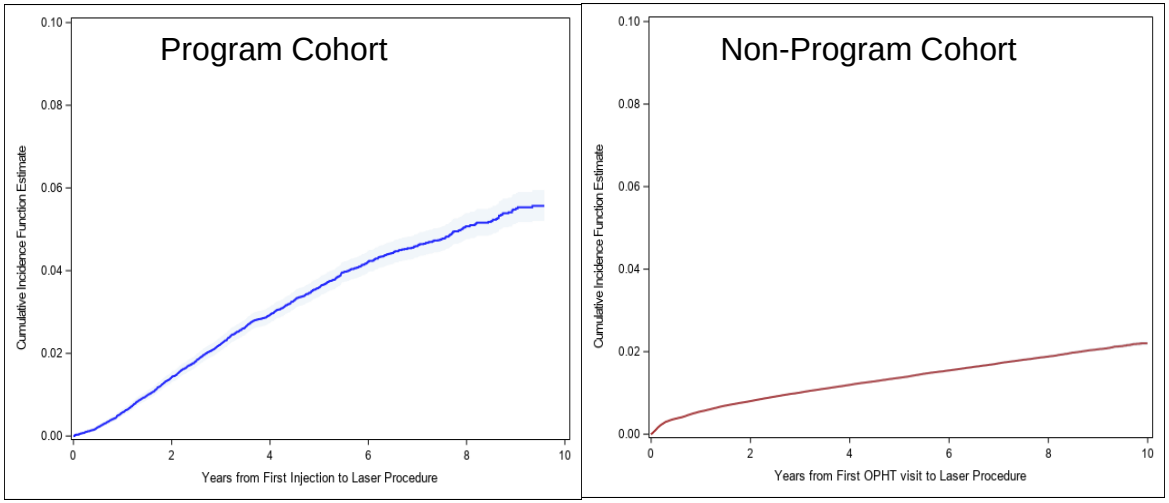
# Appendix D: Crude Cumulative *Laser Procedure* Incidence Rate

*Exhibit 44: Crude Cumulative Laser Procedure Incidence Rate per Patient – Program Cohort/Non-Program Cohort (2009-2018)*




- The curves above represent the crude cumulative incidence rate of laser procedure by patient for the Program Cohort and Non-Program Cohort. The cumulative incidence rate is plotted against the number of years from the first injection to laser procedure, taking into account death as a competing risk.
- The cumulative incidence of laser procedure estimates the absolute risk of requiring a laser procedure among patients without any prior laser procedure as a function of follow-up time from the first injection (Program Cohort) or the first visit to an ophthalmologist (Non-Program Cohort).
- Compared to Non-Program Cohort, Program Cohort has an increased risk of requiring a laser procedure throughout the follow-up period (Program Cohort: 1.4% at the end of 2 years of follow-up, 3.6% at the end of 5 years of follow-up; Non-Program Cohort: 0.8% at the end of 2 years of follow-up, 1.4% at the end of 5 years of follow-up)

* Note: Patients treated with laser procedure prior to their first injection or first ophthalmologist visit are excluded.

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

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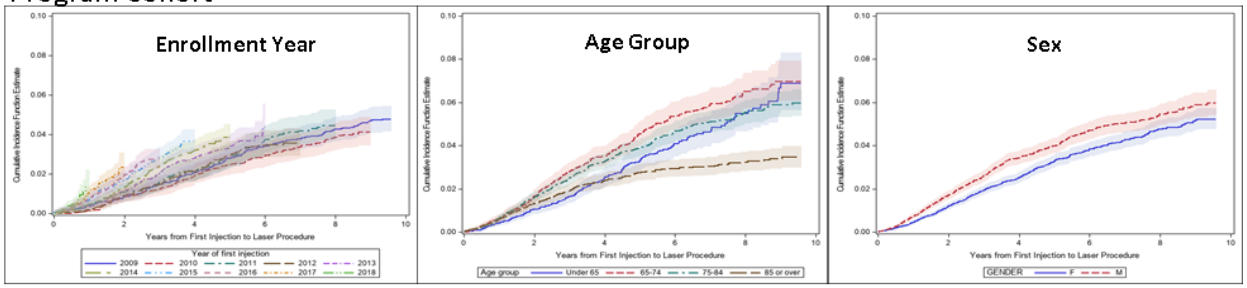
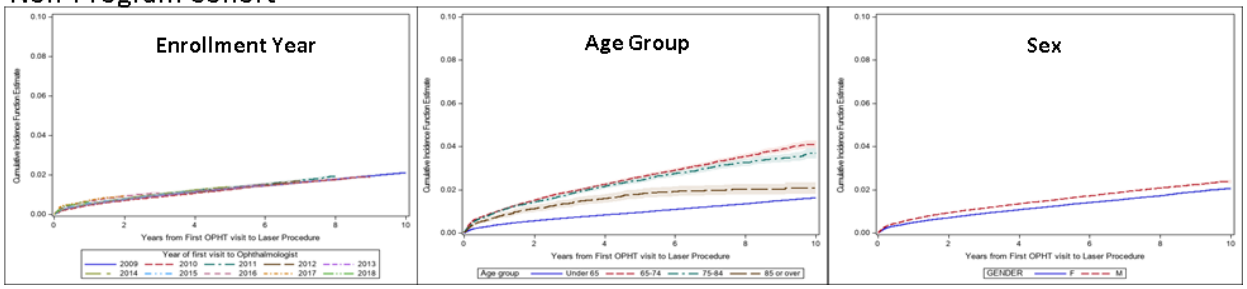
# Appendix D: Examination of Factors Influencing Crude Cumulative *Laser Procedure* Incidence Rate

*Exhibit 45: Crude Cumulative Laser Procedure Incidence Rate per Patient – Program Cohort/Non-Program Cohort – Selected Factors (2009-2018)*

Program Cohort




Non-Program Cohort

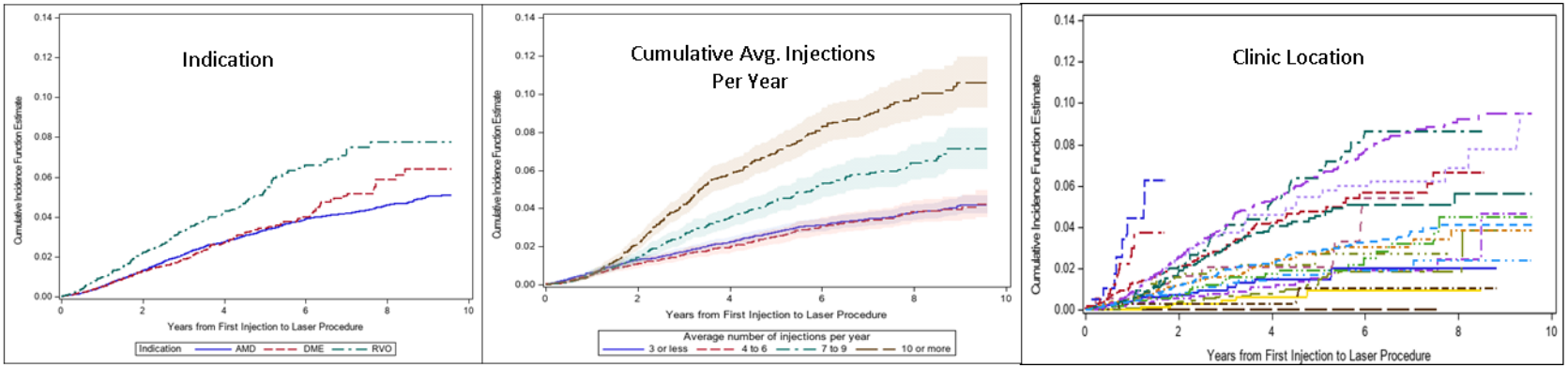



- Many factors influence the crude cumulative incidence rate of laser procedure. The factors identified for further analysis indicate the same trends as glaucoma surgery and indicate:
  - **Enrollment year:** There are no differences in incidence by enrollment year in the Non-Program Cohort. In the Program Cohort there are statistically significant differences by enrollment year with 2009 and 2010 reporting the lowest rates and enrollment years 2015-2018 reporting the highest incidence rates ($p$<.001).
  - **Age group:** In the Program Cohort those greater than 85 years of age reported the lowest rates and those between 65-74 years of age reported the highest incidence rates ($p$<.001). This compares to the Non-Program Cohort where those aged 65-84 years of age reported statistically significantly higher rates as compared to the youngest population ($p$<.001).
  - **Sex:** Both the Program Cohort and the Non-Program Cohort reported higher incidence rates in males compared to females ($p$<.001).

* Note: Patients treated with laser procedure prior to their first injection or first ophthalmologist visit are excluded.
Data Sources: PRDTP, MSP, Vital Statistics (2009-2018).

# Appendix D: Examination of Selected Factors Influencing Crude Cumulative *Laser Procedure* Incidence Rate

*Exhibit 46: Crude Cumulative Laser Procedure Incidence Rate per Patient – Program Cohort – Selected Factors (2009-2018)*




- Additional factors that may influence the Program Cohort crude cumulative incidence rate of laser procedure are investigated. The same trends as in the glaucoma surgery analysis are reported including:
  - **Indication:** RVO reported statistically significantly higher incidence rates following DME and wAMD ($p$<.001).
  - **Cumulative average number of injections per year:** Within the first year and half of enrollment, more frequent injections reported no difference in incidence rate. Thereafter, increasing frequency of injections reported higher incidence rates ($p$<.001).
  - **Clinic location:** There are statistically significant differences in incidence rates across clinic locations ($p$<.001).

* Note: Patients treated with laser procedure prior to their first injection are excluded.

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