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Technology Assessment at SickKids (TASK)

FULL REPORT

A COST-UTILITY ANALYSIS OF BIOSIMILAR INFLIXIMAB COMPARED TO REFERENCE INFLIXIMAB IN ADULT SWITCH PATIENTS WITH CROHN'S DISEASE: A CANADIAN ANALYSIS

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TASK Technology Assessment at SickKids

Executive Summary

Cost-Utility Analysis of Biosimilar Infliximab Compared to Reference Infliximab in Adult Switch Patients with Crohn's Disease: A Canadian Analysis

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BACKGROUND: Biologics, such as infliximab, are an important treatment option for patients with moderate-to-severe Crohn's Disease (CD), but their costs are often high. The introduction of lower-cost biosimilars offers a unique opportunity to address affordability concerns. Due to the complexity of these products, stakeholders have identified a need for evidence regarding the cost-effectiveness of switching patients from reference biologics to biosimilars.

PURPOSE to assess the incremental cost of maintenance treatment for adults with CD who have been switched from reference infliximab to biosimilar infliximab compared with those who have been maintained on reference infliximab per quality adjusted life year (QALY) gained from the healthcare system perspective.

METHODS: A probabilistic cohort Markov decision model with eight-week cycle lengths was constructed to estimate the incremental costs and effects of switching to biosimilar infliximab over a five-year time horizon. Clinical inputs were obtained from NOR-SWITCH and other published pivotal trials. Costs were obtained from Canadian sources. A total of 10,000 simulations were run. Sensitivity analysis was used to test the robustness of the results to variations in uncertain parameters.

RESULTS: In the reference case, total costs for switching to biosimilar infliximab were $50,191 (standard deviation [SD]: $4,771) and 3.06 (SD: 0.38) QALYs. Costs for maintaining treatment with reference infliximab were $96,385 (SD: $6,834) and 3.19 (SD: 0.35) QALYs. The intervention was associated with incremental costs of -$46,194 (95% Confidence Interval [CI]: -$42,420 to -$50,455) and a loss in quality adjusted life-years of -0.13 (95% CI: -0.16 to -0.07). Eighty-three percent of the simulations were in the south-west quadrant with incremental cost savings and an incremental loss of effectiveness.

CONCLUSIONS: Biosimilar infliximab is associated with incremental savings when CD patients on maintenance therapy are switched from reference infliximab. However, decision makers must also account for an incremental loss of effectiveness with biosimilars in accordance with the NOR-SWITCH subgroup analysis. Further evidence regarding switching to biosimilar treatments for CD patients will be integral as jurisdictions work to develop effective reimbursement policies for biosimilars.

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Table of Contents

Executive Summary……..2

Acknowledgments.....4

Table of Contents.....5

List of Tables 9

List of Figures.....11

List of Appendices 12

List of Abbreviations 13

Chapter 1 Background 14

1.1 Introduction.....14

1.2 Biologics 14

1.2.1 Development Process 14

1.2.2 Regulatory Approval 15

1.2.3 Healthcare Cost, Utilization Trends and Patents.....16

1.3 Biosimilars 18

1.3.1 Development of Biosimilars.....18

1.3.2 Regulatory Approval & Reimbursement Pathway.....19

1.3.3 Canadian Biosimilar Policy, Costs & Utilization.....22

1.4 Disease State: Crohn's Disease.....26

1.4.1 Background 26

1.4.2 Prevalence & Incidence in Canada.....26

1.4.3 Symptoms & Complications 27

1.4.4 Diagnosis.....28

1.4.5 Treatment Options.....28

1.4.6 Treatment Care Pathway & Guidelines.....31

1.5 Infliximab in the Treatment of Crohn's Disease.....36

1.5.1 Reference Infliximab 36
1.5.2 Biosimilar Infliximab 38
1.6 Economic Evidence in the Treatment of CD with Biologics 43
1.6.1 Burden of Illness & Healthcare Expenditure 43
1.6.2 Cost-Effectiveness of Infliximab in Crohn's Disease 45
1.6.3 Cost-Effectiveness of Biosimilar Infliximab 51
1.7 Knowledge Gap & Research Question 59
1.7.1 Research Question 61
Chapter 2 Methods 62
2.1 Decision Problem 63
2.2 Type of Evaluation 63
2.3 Perspective & Population of Interest 63
2.4 Intervention & Comparator 64
2.4.1 Dosing of Infliximab 65
2.5 Outcomes 66
2.6 Model Framework 66
2.6.1 Time Horizon, Cycle Length & Discounting 67
2.6.2 Model Design, Structure & Key Assumptions 68
2.6.3 Model Inputs 70
2.6.4 Probabilities 71
2.6.5 Utilities and Quality of Life Inputs 73
2.6.6 Resource Use & Costs 75
2.6.7 Societal Perspective 83
2.6.8 Summary of Inputs 84
2.7 Analysis & Incremental Cost-Effectiveness 90
2.8 Uncertainty Analyses 91

Chapter 3 Results 97
3.1 Reference Case Results 97
3.1.1 Societal Perspective 100
3.2 Uncertainty Analyses 101
3.2.1 Threshold Analysis 101
3.2.2 Parameter Sensitivity Analyses 102
3.2.3 Structural Uncertainty Analyses 108
3.2.4 Decision Uncertainty 110
3.3 Summary of Results 110
Chapter 4 Discussion 112
4.1 Cost-Utility Analysis of Biosimilar Infliximab 112
4.1.1 Societal Perspective 113
4.1.2 Uncertainty Analyses – Costs 114
4.1.3 Uncertainty Analyses – Effects 116
4.1.4 Decision Making in the South-West Quadrant 118
4.2 Strengths & Limitations 120
4.3 Implications for Canadian Stakeholders & Policy Options 128
4.3.1 Canadian Economic Evidence of Biosimilar Infliximab 128
4.3.2 Implications 130
4.3.2.1 Implications for Patients & Physicians 131
4.3.2.2 Implications for Healthcare & Drug Plan Decision Makers 133
4.3.3 Policy Options 135
4.4 Future Research 140
4.4.1 Clinical Effectiveness 140
4.4.2 Cost Effectiveness & Budget Impact 143
4.4.3 Preference Research 145
4.4.4 Pediatric Research 146

Chapter 5 Conclusion.....148

References.....150

Appendices.....168

List of Tables

Table 1 - Health Canada Biosimilar Requirements 20

Table 2 - Health Canada Policy Positions on Biosimilar Approval and Market Use 21

Table 3 - Biosimilar Reimbursement Policy Across Canada 23

Table 4 - Canadian Reimbursement of Inflectra® for Crohn's Disease (as of May 2018) 25

Table 5 - Treatment Categories 29

Table 6 - Biologic Induction Therapy 32

Table 7 - Biologic Maintenance Therapy 33

Table 8 - Economic Evaluations of Infliximab 55

Table 9 - Economic Evidence of Biosimilar Infliximab 57

Table 10 - Model Overview 62

Table 11 - Initiation & Maintenance Dosing of Infliximab 65

Table 12 - Dosage 66

Table 13 - Infusion Related Reactions 73

Table 14 - Model Utility Inputs 74

Table 15 - Biologic & Biosimilar Drug Costs 76

Table 16 - Biologic Dispensing Fees 76

Table 17 - Administration Costs 77

Table 18 – Immunosuppressive & Steroid Treatment Cost 78

Table 19 - ICD-10 Codes for Crohn's Disease Costs (OCCI 2015/16) 78

Table 20 - Average Surgical Cost Resection & Length of Stay 79

Table 21 - Average Surgical Length of Stay 79

Table 22 - Surgical Procedure Fee 79

Table 23 - Surgical Consultations 80

Table 24 - Post Surgical General Surgery Fees 80

Table 25- Ontario Schedule of Benefits: Surgical and Physician Visit Costs 80

Table 26 - Physician Visits 81

Table 27 - Cost per Infusion Reaction 82

Table 28 - Loss of Productivity 83

Table 29 - Parameter Table 84

Table 30 – Parameter Sensitivity Analyses 95

Table 31 – Structural Sensitivity Analyses 96

Table 32 – Probabilistic Reference Case: Cost Results 97

Table 33 - Probabilistic Reference Case: Effectiveness Results 98

Table 34 - Societal Results 101

Table 35 – One-Way Probabilistic Analysis: Patient Weight 103

Table 36 - Sensitivity Analysis Relapse Rates & Differences 105

Table 37 – Parameter Sensitivity Analyses Results 106

Table 38 - Structural Analyses: Time Horizon & Discount Rate 109

List of Figures

Figure 1- Step-Up Therapy 30

Figure 2 - Step Down Therapy..... 31

Figure 3 - Intervention (Biosimilar Infliximab) and Comparator (Reference infliximab) 65

Figure 4 - Model Structure..... 70

Figure 5 - Incremental Cost-Effectiveness Plane..... 91

Figure 6 - Reference Case Results (1,000 of 10,000 iterations with 95% Confidence Ellipse) ... 98

Figure 7 - Cost Effectiveness Scatterplot..... 99

Figure 8- Proportion in Remission & Response States..... 100

Figure 9 - Societal Perspective Results (1,000 of 10,000 iterations with 95% Confidence Ellipse) 101

Figure 10 Cost Effectiveness Acceptability Curve..... 110

List of Appendices

Appendix I – Biosimilar Observational Studies 168

Appendix II – Drug Price Distributions 171

Appendix III – Physician Fee Distributions 172

List of Abbreviations

5-ASA – 5-Aminosalicylates

6-MP – 6-mercaptopurine

ADA – Anti-Drug Antibodies

BIA – Budget Impact Analysis

CADTH – Canadian Agency for Drugs and Technologies in Health

CAG – Canadian Association of Gastroenterology

CBA – Cost-Benefit Analysis

CD – Crohn's Disease

CDAI – Crohn's Disease Activity Index

CDEC – Canadian Drug Expert Committee

CEA – Cost-Effectiveness Analysis

CI – Confidence Interval

CMA – Cost Minimization Analysis

CUA – Cost-utility analysis

ECCO – European Crohn's Colitis Organization

HBI – Harvey Bradshaw Index

IBD – Inflammatory Bowel Disease

ICER – Incremental Cost-Effectiveness Ratio

NOC – Notice of Compliance

pCPA – pan-Canadian Pharmaceutical Alliance

PD – Pharmacodynamic

PK – Pharmacokinetic

PMPRB – Patented Medicines Price Review Board

rDNA – Recombinant DNA

QALY – Quality Adjusted Life Year

SD – Standard Deviation

SF-36 – Short Form 36

SMR – Standardized Mortality Ratio

UC – Ulcerative Colitis

WTP – Willingness to pay

Chapter 1
Background

1.1 Introduction

This chapter will provide an overview of the key background information that was utilized to provide the rationale for an economic evaluation of a switch to biosimilar infliximab in an adult population treated for moderate-to-severe Crohn's Disease (CD) from the Canadian perspective. Biosimilar data in the pediatric CD population is currently sparse therefore, this analysis will focus on the adult population and "patient" will hereby refer to an individual older than age 18. CD is frequently diagnosed in young people; therefore, it is important to acknowledge that independent evidence will need to be developed for these patients.

This chapter will include a brief review of biologics and biosimilars, as well as, an overview of the CD therapeutic space. Subsequently, the clinical evidence for the use of both reference and biosimilar infliximab will be presented in addition to a brief review of the economic evidence of infliximab. The chapter will conclude with a summary of the knowledge gap that the thesis research will address.

1.2 Biologics

Biologic drugs are produced using living cells using various biotechnologies. As such, they are generally larger, more complex and more sensitive to variation in manufacturing conditions than chemically produced small molecule drugs (Health Canada, 2016b). Many biologic therapies are a life changing treatment option for patients because of substantial gains in both efficacy and safety (Lybecker, July 2016). These drugs are valuable for patients, physicians and the healthcare system overall however, they also bring unique considerations related to their development and cost. The following section will present some of these characteristics to provide context on the biologic landscape in Canada.

1.2.1 Development Process

In the 1970s, the "biologics revolution" demonstrated that genes from one organism could be isolated and cloned into vectors for expression in unrelated organisms (Kinch, 2015). Biologics are proteins produced by genetically engineering living cells, rather than the chemical synthesis, used to produce traditional small molecule products (Lybecker, July 2016). Most biologics are

produced through the use of recombinant DNA (rDNA) technology (Kinch, 2015; Lybecker, July 2016).

Due to their size, complexity and reliance on living organisms, biologics are naturally variable (European Medicines Agency & European Commission, 2017). A biologic can have minor variability within or between batches, but it must fall within an acceptable range to ensure consistent safety and efficacy (European Medicines Agency & European Commission, 2017). Variants of a given biologic always have the same amino acid sequence, but can differ in three-dimensional structure because of post-translation modification (CARE, January 13, 2017). Therefore, the manufacturing processes and environment are significant determinants of this variability.

These variations can affect both efficacy and immunogenicity of the drug (Kinch, 2015). Immunogenicity is an important safety concern for biologics and occurs when the host immune system recognizes the protein as foreign and produces neutralizing antibodies (Kinch, 2015). Biologics usually cause no or a limited immune response, and adverse reactions of an immune nature are normally not severe (Danese, Bonovas, & Peyrin-Biroulet, 2017). However, in some cases antibodies directed against the biologic, also referred to as anti-drug antibodies (ADA), can neutralize their activity, reduce efficacy or cause serious immune reactions (Lybecker, July 2016). This can increase the risk of drug hypersensitivity reactions (Pichler, 2007). Given this, variability and potential for immunogenicity, each biologic must be closely evaluated and monitored to ensure sustained patient safety and efficacy (Health Canada - Health Products and Food Branch, 2016).

1.2.2 Regulatory Approval

Health Canada is the regulatory body responsible for the approval and monitoring of medications. Its approval process for biologics is notably distinct from that for small molecule drugs, due to the concerns discussed above. With a new drug submission for a reference biologic, the sponsor must independently demonstrate the quality, safety and efficacy (Ridgway, March 2017). Furthermore, a biologic must also go through an on-site evaluation and lab analysis, due to the fact that the manufacturing process is integral in maintaining safety and efficacy (Lybecker, July 2016; Ridgway, March 2017).

A few of the primary requirements that a biologic sponsor must submit to Health Canada include:

- A full package of chemistry and manufacturing studies;
- A full data package of non-clinical studies;
- Pharmacokinetic (PK) and pharmacodynamic (PD) studies;
- Proof of clinical efficacy for all requested indications with superiority, non-inferiority or equivalent clinical trials with clinical outcomes or validated surrogates as the study endpoint;
- Established evidence of efficacy and safety with an acceptable risk and benefit profile;
- An acceptable immunogenicity profile; and
- A risk management plan for post-market.

All of these factors are important for Health Canada reviewers to determine if a biologic demonstrates an acceptable benefit/risk profile as it pertains to efficacy and safety in the requested indications. Once this has been established a biologic may be approved for use in Canada, enter the reimbursement channels and become accessible to patients.

1.2.3 Healthcare Cost, Utilization Trends and Patents

1.2.3.1 The Cost of Biologics in Canada

Due to their clinical value and complex development and manufacturing processes, biologics tend to be high-cost drugs. Spending on the top biologics accounted for 15.9% of all of Canada's pharmaceutical sales in 2016, with sales growing from $0.8 billion in 2006 to $3.6 billion in 2016 (National Prescription Drug Utilization Information System, April 27, 2017). Furthermore, the market is highly concentrated with five top selling biologics (infliximab, adalimumab, ranibizumab, etanercept and insulin glargine) accounting for 11.4% of total pharmaceutical sales (National Prescription Drug Utilization Information System, April 27, 2017). These drugs have become important treatment options for patients in a variety of disease states and both public and private drug plans have substantial levels of expenditure on these products.

With regards to the public drug plans, anti-TNFs drugs accounted for the highest proportion of spending at 8.7% in 2016, and cost approximately $10,000 per beneficiary(Canadian Institute for Health Information, 2017). Furthermore, they were the top two contributors to spending growth

among public plans (Canadian Institute for Health Information, 2017; QuintilesIMS, 2017). It is evident that biologics are a substantial contributor to drug expenditure, particularly the anti-TNF class including infliximab.

Similarly, in the private market, biologics – specifically those for the treatment of rheumatoid arthritis, inflammatory bowel disease (IBD) and plaque psoriasis- represented 10% of private drug plan costs in 2012 (IMS Brogan, November, 2013). By 2015, infliximab alone represented 4.5% of overall private drug costs and was the top selling drug (National Prescription Drug Utilization Information System, 2016). It is also worth noting that these high-cost drugs can impact patients since patient copayments can be substantial even with coverage. In conclusion, biologics are a critical treatment option for patients, and have the potential to reduce costs elsewhere in the healthcare system. However, the direct costs to public and private drug plans are substantial and growing.

1.2.3.2 Utilization: Canadian Case Study

Using an administrative database from Saskatchewan Yao et al. (2016) found that the number of patients receiving at least one dispensation of a biologic agent increased from 133 in 2001 to 2,402 in 2013 (Yao et al., 2016). This was associated with an increase in total spending from $0.5 million in 2001 to $51.8 million in 2013, with the majority being paid by the provincial government (Yao et al., 2016). Infliximab accounted for the majority of all biologic spending and individuals initiated on infliximab had the highest average costs during follow-up (Yao et al., 2016). Overall, total spending was primarily influenced by number of recipients and the growth in average cost of biologics in the first year of treatment (Yao et al., 2016).

Although, this analysis did not adjust for factors such as population growth there are still a number of key take-aways. Firstly, utilization of these agents in Canada has increased since the introduction of biologics in 2001 due to an increased number of biologics available on the market and more patients being treated for a variety of indications. Second, these agents have high costs which can create sustainability challenges for Canadian drug plans (Yao et al., 2016).

1.2.3.3 Intellectual Property

Biologics typically require a patent for both the chemical structure and the processing of the molecule (Lybecker, July 2016). Patents for small molecules are in place for a twenty year term

however, biologics are challenging to comprehensively protect so the term can vary (Lybecker, July 2016). While biologics are increasingly dominating in market share, a record number of patent expiries are approaching (Industry Canada, February 2014). The patent “cliff” as it is sometimes called, is the loss of revenues to branded products due to genericization (Industry Canada, February 2014). However, the complexity of biologic production means that competitors often do not enter the market immediately when a patent expires and the potential for savings differs from those generated by small molecule generics (Ridgway, March 2017) .

1.3 Biosimilars

Once a patent on a biologic has expired the market is open to competition from a biosimilar. A biosimilar, is a drug demonstrated to be highly similar to a biologic that was previously authorized for sale (referred to as a reference biologic) (Health Canada, 2016b). However, biosimilars are not the same as generic drugs. Due to their size, complexity and variability, biosimilars can be shown to be similar, but not identical to the reference (Health Canada, 2016b). Biosimilars tend to be lower cost than their reference biologics, entering the Canadian market at price discounts ranging from 15 to 47% of the reference and offering the potential for cost savings in the high expenditure biologics market (CARE, January 13, 2017). However, due to their complex nature and relatively recent market introduction, several regulatory, health technology assessment and reimbursement policy questions have been raised. The following section will provide an overview of biosimilars, with a focus on the Canadian context.

1.3.1 Development of Biosimilars

The biosimilar development process is similar to that of innovator biologics (see Section 1.2). Due to the nature of their production, biosimilars are not pharmaceutically equivalent to their reference biologics, unlike generic small molecules (Health Canada, 2016b; Ridgway, March 2017). Biologics may be subject to post-translational modifications that can alter their molecular structure (European Medicines Agency & European Commission, 2017). It is this inherent variability and potential for modification that distinguishes the development of biosimilars from that of traditional generics.

When developing a biosimilar product it must have the same amino acid sequence and highly similar 3-dimensional structure (folding of the protein) as the reference since these determine biological activity (European Medicines Agency & European Commission, 2017). The finished

biosimilar must also have the same posology and route of administration (European Medicines Agency & European Commission, 2017). However, just as batches of a reference biologic can vary as discussed in Section 1.2.1, there can be minor differences between a biologic and their biosimilars in associated sugar moieties (European Medicines Agency & European Commission, 2017).

1.3.2 Regulatory Approval & Reimbursement Pathway

1.3.2.1 Regulatory Approval

Health Canada is responsible for determining whether a biosimilar manufacturer has adequately demonstrated similarity to the reference (Health Canada, 2016b). Similarity is demonstrated with extensive structural, functional and human clinical studies showing no clinically meaningful differences in safety and efficacy between the reference and the biosimilar (Health Canada, 2016b; Ridgway, March 2017). If these requirements are met a biosimilar may be authorized for sale in Canada.

Biosimilars are regulated as new biologic drugs in Canada, however, since a biosimilar submission can rely in part on relevant publicly available information about the reference product, they can submit a reduced data package (Health Canada - Health Products and Food Branch, 2016; Ridgway, March 2017).

The primary difference between the review for biosimilars and that for biologics, is that the biosimilar sponsor must independently demonstrate quality and also develop a side-by-side structural and functional comparison (Ridgway, March 2017). This can include physicochemical characterization, biological activity, immunochemical properties, purity, impurities, contaminants and quantity (Health Canada - Health Products and Food Branch, 2016; Ridgway, March 2017). The biosimilar should have the same dosage form, strength, and route of administration as the selected reference product and the reference should also have accumulated adequate safety, efficacy and effectiveness data in the post-market setting (Health Canada - Health Products and Food Branch, 2016). Once the appropriate reference has been determined the biosimilar sponsor must follow the sequential step-by step development program to evaluate residual uncertainty at each step prior to gaining market approval (Wang, 2017).

If a sponsor successfully demonstrates similarity it implies that any differences in quality attributes should have no adverse impact upon safety or efficacy of the biosimilar and that non-clinical and clinical data previously generated for the reference biologic are applicable to the biosimilar (Health Canada - Health Products and Food Branch, 2016). However, the sponsor is still required to develop a risk management plan and comply with post-market adverse drug reaction and periodic reporting (Health Canada - Health Products and Food Branch, 2016). The risk management plan should include monitoring impurity and immunogenicity (Health Canada - Health Products and Food Branch, 2016).The complete data package of quality, non-clinical and clinical studies described in Table 1 will be utilized to determine if the product can be deemed similar and be approved for the Canadian market.

Table 1 - Health Canada Biosimilar Requirements

Regulatory Requirement	Description
Quality Information	Extensive data package demonstrating similarity (side-by-side format) Quality Attributes include: physicochemical and biological characterization data, relevant samples during the manufacturing process, stability data, bioactivity, folding, amino acid sequence and modifications, and data on variability.
Non-Clinical Information	In-vitro studies: extensive receptor binding studies and cell-based assays. In vivo studies: animal PK/PD studies when feasible, at least one repeat dose toxicity study.
Clinical Information	Objective of studies: to show that there are no clinically meaningful differences between the biosimilar and reference with regards to efficacy, safety and/or immunogenicity in a sensitive population. Requires comparative PK & PD studies. Equivalence trials are preferred to non-inferiority.

(Ridgway, March 2017; Wang, 2017)

Given the unique regulatory framework for biosimilars Health Canada has also released policy statements surrounding authorization of indications (also referred to as extrapolation), interchangeability and switching (Ridgway, March 2017; Wang, 2017). These positions have been summarized in Table 2.

Table 2 - Health Canada Policy Positions on Biosimilar Approval and Market Use

	Description
Authorization of Indication	Biosimilars are similar in structure and function to a reference biologic and therefore, clinical studies do not need to be repeated for each indication. Biosimilars can therefore be authorized in some or all of the Health Canada approved indications of the reference biologic. Health Canada makes the decision to authorize in the requested indications depending on the totality of evidence provided and scientific justification
Interchangeability	Interchangeability refers to the ability to change from one drug to an equivalent by a pharmacist without the involvement of the prescribing physician. Health Canada's authorization of a biosimilar is **not** a declaration of equivalence. The authority to declare two products interchangeable rests with the provinces and territories.
Switching	Switching refers to a one-time change from the reference to a biosimilar in consultation with the prescribing physician. Health Canada considers well-controlled switches from reference to biosimilar in an approved indication to be acceptable.

(Health Canada - Health Products and Food Branch, 2016; Parker, March 20, 2017; Wang, 2017)

1.3.2.2 Reimbursement Pathway

After receiving approval from Health Canada, a biosimilar must go through the traditional Canadian reimbursement pathway, however as stakeholders adjust to the introduction of these drugs tailored requirements are being established.

The Canadian Agency for Drugs and Technologies in Health (CADTH) conducts evaluations of the clinical, economic and patient evidence on drugs. They then use this evaluation to provide reimbursement recommendations to public drug plans, with the exception of Quebec, which has their own health technology assessment agency (CADTH, 2017).

In comparison to a standard CADTH review, a biosimilar manufacturer must submit as much or more data, but there are reduced requirements for economic, clinical and non-clinical data (CADTH Common Drug Review, February 2018; Sehgal, 2014). The data supplied to CADTH must be the same evidence which was used as the basis for demonstrating similarity to Health Canada (CADTH Common Drug Review, February 2018). With regards to economic evidence, the biosimilar requirements are drastically reduced. Similar to the Ontario drug review requirements for a multi-source drug, the sponsor must submit a basic cost comparison table which includes the price, cost differential, recommended dose and average drug cost (CADTH

Common Drug Review, February 2018; Ontario Public Drug Programs Ministry of Health and Long-Term Care, September, 2016). A complete pharmacoeconomic model is not required.

Once the review is completed CADTH will release a biosimilar summary document for the public drug plans detailing the results of their review and any recommended conditions for reimbursement(CADTH Common Drug Review, February 2018). This is then referenced by the pan-Canadian Pharmaceutical Alliance (pCPA), an alliance of all thirteen provinces and territories, and federal drug plans which works to achieve greater value for brand name and generic drugs (Canada's Premiers, 2017). The pCPA conducts joint price negotiations on behalf of the drug plans to achieve greater value and have also released specific guidelines that pertain to the negotiations of biosimilars entitled the *First Principles for Subsequent Entry Biologics* (Canada's Premiers, 2017; The pan-Canadian Pharmaceutical Alliance, 2016). Once the pCPA process is complete, whereby the negotiation has either been closed or an agreement has been reached, the public drug plans can decide to list the drug with their respective listing criteria for the populations they cover.

It is important to note that since policy governing biosimilars is evolving, both the pCPA processes for these products are being re-evaluated. In 2017, the pCPA held consultations regarding updates to their processes and how best to improve value as it relates to biosimilar reimbursement.

1.3.3 Canadian Biosimilar Policy, Costs & Utilization

1.3.3.1 Biosimilar Policy

To date, the provinces have utilized a variety of policy approaches with regards to reimbursement of biosimilars. Policy development presents specific challenges since payers wish to develop the biosimilar market to derive savings and encourage uptake, while also respecting the perspectives of patients and physicians, and utilizing available evidence (Institute of Health Economics, October 6, 2016). The primary strategies are summarized in Table 3.

Table 3 - Biosimilar Reimbursement Policy Across Canada

	Description
Preferential Listing	The biosimilar is listed preferentially compared to the reference product (e.g. as a limited use product rather than exceptional access, which requires authorization for use by the drug plan).
Naïve Patients Only	Mandating the use of the biosimilar for patients who are naïve to the molecule but continue to cover those patients who are currently using the reference product.
New Course Starts	Requires use in naïve patients as above, but patients who are currently on the reference will only receive coverage until the Special Authority expiry date (a specialized drug program for the coverage of outpatient drugs used in the treatment of specific conditions which requires a request form and approval from the public drug program) (BC Pharmacare, 2017; Ontario Ministry of Health and Long Term Care, 2013).
Best Lowest Price	The payer will only cover up to the biosimilar price and patients would need to pay the difference to continue to obtain the reference.
Parity Listing	The biosimilar is listed at parity with the reference in terms of reimbursement criteria with no specialized policy.
Change in treatment protocol	Phased approach to coverage where all patients currently treated with the reference are switched at their next cycle and then switch any remaining patients at next dispense.

Biosimilars are a reimbursement challenge for decision makers as evidenced by the substantial variety in their reimbursement processes. It is these policies which have in part influenced the expenditure and uptake of biosimilars to date. The coverage that has been enacted for Inflectra® (infliximab) will next be reviewed as a case study of costs and uptake associated with biosimilars thus far.

1.3.3.2 Inflectra® (infliximab) in Canada: Case Study

Inflectra® received its first notice of compliance (NOC) from Health Canada in 2014 for inflammatory conditions including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis (Health Canada, 2014). In 2016 the manufacturer also completed a supplemental submission to seek authorization for IBD indications of Crohn's Disease (CD) and ulcerative colitis (UC). (Health Canada, 2016a) Health Canada had previously identified concerns with regards to the physicochemical and biological aspects of the biosimilar in CD and UC. However, in considering previously submitted clinical studies and newly submitted physicochemical and biological data, Health Canada found that CD and UC indications could be authorized (formerly known as indication extrapolation) (Health Canada, 2016a).

Due to separate approvals for specific indications, Inflectra® completed two assessments through CADTH's process. The first review was completed in December 2014 and the Canadian Drug Expert Committee (CDEC) recommended the provincial drug plans list Inflectra® with certain conditions (CADTH Canadian Drug Expert Committee, December 19, 2014). These conditions were; use in patients for whom infliximab is considered to be the most appropriate treatment option and listing in a manner similar to Remicade® (CADTH Canadian Drug Expert Committee, December 19, 2014). This recommendation was based on similar efficacy, safety and PK profiles, and similar pathophysiology allowing extrapolation to PSA and PSO (CADTH Canadian Drug Expert Committee, December 19, 2014) . From a price perspective, the price of $650 per 100mg vial Inflectra® was lower than that of Remicade®, but still more costly than other treatment options for these conditions (CADTH Canadian Drug Expert Committee, December 19, 2014).

The second review was conducted in 2016 for the indications of CD and UC. The CDEC recommended that the provinces reimburse Inflectra® with clinical criteria and/or conditions (CADTH Canadian Drug Expert Review Committee, October 25, 2016). The clinical criterion was use in patients for whom infliximab is considered to be the most appropriate treatment option. In comparison to the first review there were two conditions: reimburse in a manner similar to Remicade® and that the cost of treatment with Inflectra® should provide a significant cost savings for jurisdictions (CADTH Canadian Drug Expert Review Committee, October 25, 2016) .

After completing the reviews, the manufacturer also had to complete negotiations with the pCPA. These negotiations resulted in a reduced transparent price of $525.00 per 100mg vial which is a 47% discount from the Remicade® price (Ontario Drug Benefit Formulary, 2017). After the pCPA negotiation was completed and the price discount determined each province established their independent reimbursement criteria.

Table 4 shows the benefit type and price for Inflectra® compared to Remicade® where publicly available as of May 2018. The coverage of these products for the CD indication also typically involve approval criteria for patients which can include failures or contraindications to other therapies or specific clinical scores, e.g. Harvey Bradshaw Index (HBI) (Vermeire, Schreiber, Sandborn, Dubois, & Rutgeerts, 2010).

Table 4 - Canadian Reimbursement of Inflectra® for Crohn's Disease (as of May 2018)

	Inflectra®		Remicade®		Criteria for Coverage
	Benefit Type	Price	Benefit Type	Price	
British Columbia	Special Authority	$551.25	Special Authority	$1,036.94	Corticosteroid trial and either dependent, resistant, or intolerant Current HBI ≥ 8
Alberta	Special Authorization	$525.00	Special Authorization	$962.68	5-ASA Glucocorticoids Immunosuppressants HBI ≥ 7
Saskatchewan	Exception Drug Status	$650.00	Exception Drug Status	$977.00	5-ASA Glucocorticoids Immunosuppressants
Manitoba	Part 3		Part 3		5-ASA corticosteroids Immunosuppressants
Ontario	Limited Use	$525.00	Exceptional Access Program	$987.56	Glucocorticoids tried at least 2 weeks at maximum dose AND immunosuppressants tried for at least 3 months HBI ≥ 7 (HBI < 7 considered on a case by case basis)
Quebec	Regular Benefit	$525.00	List of Exceptional Medicines	$940.00	Corticosteroids immunosuppressants
Nova Scotia	Exception Drug	$525.00	Exception Drug	$987.56	5-ASA Corticosteroids immunosuppressants
New Brunswick	Special Authorization		Special Authorization		5-ASA Corticosteroids immunosuppressants
Prince Edward Island	Special Authorization		Special Authorization		5-ASA Corticosteroids immunosuppressants HBI ≥ 7
Newfoundland	Special Authorization	$569.63	Special Authorization	$1,071.50	Corticosteroids Immunosuppressants

Some provinces, such as Saskatchewan, listed Inflectra® at parity with Remicade® with regards to their approval criteria (Government of Saskatchewan - Drug Plan and Extended Benefits Branch, 2017). However, the majority of provinces have listed Inflectra® as the first infliximab product considered for naïve patients and as such there are no longer new starts on the reference product (CARE, January 13, 2017; Gastrointestinal Society, 2017). Some provinces, such as Ontario, have employed multiple strategies for reimbursing Inflectra® which included preferential listing for naïve patient starts (Ontario Drug Benefit Formulary, 2017). The landscape for Inflectra® is very complex as funding and reimbursement approaches vary across the country.

1.4 Disease State: Crohn's Disease

Biologics, and now biosimilars such as infliximab, are a key part of the IBD treatment pathway. IBD is used to refer to a group of disorders characterized by chronic inflammation of the digestive tract (Crohn's and Colitis Foundation of Canada, 2012). The forms of IBD include CD, UC and indeterminate colitis (Crohn's and Colitis Foundation of Canada, 2012; Tremaine, 2011). While all forms of IBD are characterized by an inappropriate response of the immune system there are marked differences between them, and the following analysis will focus on CD.

1.4.1 Background

In CD, inflammation can occur either continuously or in isolated areas of the GI tract from mouth to the perianal area however, it commonly affects the distal small intestine (terminal ileum) (Al Hashash & Regueiro, 2018; Crohn's and Colitis Foundation of Canada, 2012; Gastrointestinal Society - Canadian Society of Intestinal Research, 2017). It can affect the full thickness of the bowel wall with edema, ulceration and fibrosis (Gastrointestinal Society - Canadian Society of Intestinal Research, 2017). Due to its transmural nature and variability of disease location, CD can have heterogenous clinical presentations (Al Hashash & Regueiro, 2018; Crohn's and Colitis Foundation of Canada, 2012).

Two instruments are used commonly to assess the severity of CD; the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw Index (HBI), which is simpler to assess (Al Hashash & Regueiro, 2018; Vermeire et al., 2010). The CDAI classifies activity and severity from asymptomatic remission (CDAI < 150) to severe-fulminant disease (CDAI > 450) (Al Hashash & Regueiro, 2018).

1.4.2 Prevalence & Incidence in Canada

The Crohn's and Colitis Foundation of Canada estimated that in 2012 there were 129,000 Canadians with CD (Crohn's and Colitis Foundation of Canada, 2012). It is unsurprising that Ontario, Quebec and Alberta, as more populous provinces, have the highest numbers of affected individuals (Crohn's and Colitis Foundation of Canada, 2012). The average incidence was estimated at 16.3 new cases of CD for every 100,000 Canadians. Therefore, based on these estimates, every year there are 5,700 individuals diagnosed with CD (Crohn's and Colitis Foundation of Canada, 2012). Provincially, British Columbia had the lowest incidence and the

highest was in Nova Scotia and Quebec (Crohn's and Colitis Foundation of Canada, 2012). From an international perspective, Canada has among the highest reported prevalence and incidence of IBD in the world (Crohn's and Colitis Foundation of Canada, 2012). Furthermore, an Ontario study demonstrated that the incidence of IBD is increasing particularly in children and adults, with stable rates in elderly people (Benchimol et al., 2014). This demonstrates that there is a growing burden of CD in Canada and the age distribution is disproportionately shifting towards younger individuals.

The causes and pathogenesis of CD have not been determined (Crohn's and Colitis Foundation of Canada, 2012). However, there is a growing evidence base suggesting environmental factors such as diet, antibiotic use, lifestyle, intestinal microorganisms, immune dysregulation and genetic predisposition may all play a role (Crohn's and Colitis Foundation of Canada, 2012; Gastrointestinal Society - Canadian Society of Intestinal Research, 2017). One of the primary indicators of environmental factors is the geographical distribution of the disease. CD is predominately a disease centered in the developed world and as migrants enter a developed country their offspring tend to take on the frequency of CD of the new country (Crohn's and Colitis Foundation of Canada, 2012). Environmental factors that have been linked to CD include high levels of hygiene which may reduce exposure to bacteria, antibiotics in the first year of life, smoking, certain pollutant exposure in children, and high intake of total fat, polyunsaturated fatty acids, omega 6 fatty acids and red meat (Crohn's and Colitis Foundation of Canada, 2012). All of these factors may in part explain the high incidence and prevalence of CD in the Canadian environment.

1.4.3 Symptoms & Complications

CD can lead to a number of symptoms and complications which affect both the intestinal tract and other parts of the body since it is a systemic disease (Gastrointestinal Society - Canadian Society of Intestinal Research, 2017). Furthermore, the symptoms may vary over time for an individual. CD is chronic but fluctuating, meaning that patients will go through periods of disease flares where symptoms are active, but other times of remission (Crohn's and Colitis Foundation of Canada, 2012).

Common symptoms that a patient with CD may experience include: diarrhea, constipation, abdominal pain, fever, rectal bleeding, loss of appetite and weight loss (Crohn's and Colitis

Foundation of Canada, 2012). Another severe complication which affects approximately 30% of CD patients are fissures or fistulas. A fissure is a tear in the lining of the anus or rectum which can lead to fever or pain particularly during bowel movements (Crohn's and Colitis Foundation of Canada, 2012; Gastrointestinal Society - Canadian Society of Intestinal Research, 2017). A fistula is an abnormal tunnel which connects from one loop of intestine to another or even to the bladder, vagina or skin (Crohn's and Colitis Foundation of Canada, 2012). These are a serious complication of CD and these patients must be managed differently from those with luminal CD, on which this analysis will focus.

1.4.4 Diagnosis

Phenotypic heterogeneity, variable activity and symptom overlap with other digestive disorders can make the diagnosis of CD challenging (Hanauer, Sandborn, & The Practice Parameters Committee of the American College of Gastroenterology, 2001). There are however several tests that can be conducted to confirm a CD diagnosis. These can include: blood tests, stool sample analysis, ultrasounds, computed tomography scans, magnetic resonance imaging or endoscopy (Gastrointestinal Society - Canadian Society of Intestinal Research, 2017). All of these techniques will be utilized to diagnosis CD and classify a patient’s disease activity and severity, which will facilitate the development of a treatment plan for that individual.

1.4.5 Treatment Options

As there is no cure for CD the goals of treatment are three-fold; to reduce or control symptoms, to suppress the inflammatory response through mucosal healing and to maintain remission (Crohn's and Colitis Foundation of Canada, 2012; Gastrointestinal Society - Canadian Society of Intestinal Research, 2017; Lichtenstein, Hanauer, Sandborn, & The Practice Parameters Committee of the American College of Gastroenterology, 2009). The following therapeutic options are utilized to achieve these objectives and to improve quality of life (Lichtenstein et al., 2009). There are five primary categories of pharmaceuticals that are used to treat CD in Canada which are summarized in Table 5.

Table 5 - Treatment Categories

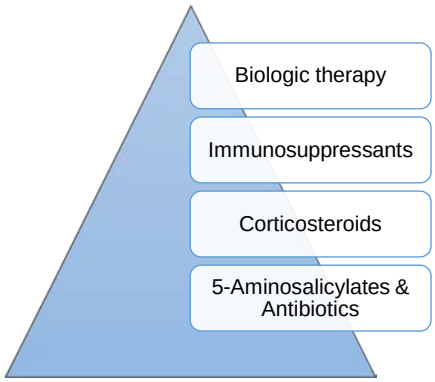
Category	Drugs	Used to Treat	Effectiveness
Antibiotics	Metronidazole, ciprofloxacin	Fistula treatment Bacterial infections or abscesses	Effective in treating the complications of CD Controlled trials have not consistently demonstrated efficacy in the treatment of the primary processes
5-Aminosalicylates (5-ASA)	Sulfasalazine, mesalamine	Mild to moderate CD Acute flares	Mesalamine tends to be better tolerated than sulfasalazine Efficacy for both induction and maintenance of remission has been questioned in systematic literature reviews.
Corticosteroids	Prednisone, budesonide	Suppress the immune system Used in moderate to severe CD or flares	Overall very potent and fast acting, but due to the associated short and long-term side effects they should not be utilized as maintenance medication Patients in remission who cannot taper their dose are generally considered steroid-dependent and are not in full clinical remission
Immunosuppressants	Azathioprine, 6-mercaptopurine (6-MP), methotrexate and cyclosporine	Decrease corticosteroid dependency Maintain remission	Immunosuppressants can induce response and remission Capable of inducing mucosal healing in some patients Effective for long-term control, for reducing the risk of CD recurrence and steroid sparing
Biologics	Infliximab, adalimumab, certolizumab, ustekinumab, vedolizumab	Block the specific targets in the immune system to reduce inflammation Induce and maintain remission	Effective in symptom control, inducing clinical remission and maintaining remission

(Akobeng, Zhang, Gordon, & MacDonald, 2016; Al Hashash & Regueiro, 2018; Bonis & MacDermott, 2017; Canadian Digestive Health Foundation, November, 2013; Cheifetz & Cullen, 2015; Crohn's and Colitis Foundation of Canada, 2012; Gastrointestinal Society - Canadian Society of Intestinal Research, 2017; Lichtenstein et al., 2009; Sartor, 2017)

In conventional “step up” therapy, patients who have tried steroids and immunosuppressants with maximum doses and still display symptoms or become intolerant will be considered for biologic therapy (Crohn's and Colitis Foundation of Canada, 2012). However, there has been debate as to whether this approach best optimizes use of biologics.

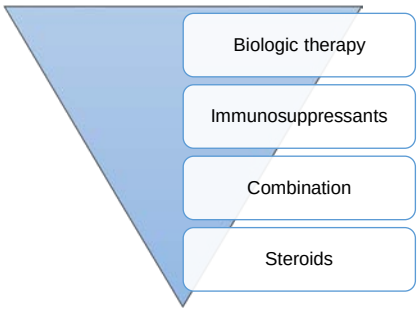
Step-up therapy is defined by sequentially shifting patients “up” the therapeutic ladder according to severity and failure of treatment, see Figure 1 (Lin, Blonski, & Lichtenstein, 2014). It starts with therapies that are less costly and/or with more preferable routes of administration, but potentially less effective. It escalates to the therapies which are more effective, but also more costly and with intravenous or subcutaneous administration (Lin et al., 2014). If a patient fails one level of therapy or becomes intolerant they are moved up to the next strategy (Lin et al., 2014). However, using this method also means that effective therapy may be delayed, with a risk of disease progression and disability (Lin et al., 2014).

Figure 1- Step-Up Therapy



In comparison, step down therapy is defined by the early use of biologic therapy, see Figure 2. Therefore, it is the reverse of step up and follows the order; biologic therapy, immunosuppressants, combination therapy and steroids. The rational for this being that since biologic therapy can induce mucosal healing and reduce complications and the need for surgical intervention it should be given to patients first (Lin et al., 2014). While the evidence has demonstrated significant mucosal healing in patients treated earlier compared with conventional therapies there are safety issues associated with this approach (Lin et al., 2014). For example, there is a potential for increased risk of TB, infections and lymphoma (Lin et al., 2014). Further, it may over treat patients with mild CD. Accordingly, careful patient selection is essential for this approach (CARE Gastroenterology Faculty, 2017; Lin et al., 2014). Even with these extensive treatment options surgical intervention will still be required in one in two patients either to manage complications or refractory symptoms (Fleshner, 2016).

Figure 2 - Step Down Therapy



1.4.5.1 Operative Management

Surgery is a necessary treatment for some variants of medically refractory disease, if complications such as fistulas, abscesses, scarring or narrowing of the bowel arise, or if dysplasia or cancer of the colon is detected (Crohn's and Colitis Foundation of Canada, 2012). There are a number of procedures available to treat CD patients depending on the indication for operative intervention and location of disease (Fleshner, 2016). Surgical resection is used to remove diseased segment of bowel, abscesses or address a perforated bowel (Crohn's and Colitis Foundation of Canada, 2012; Fleshner, 2016). Patients may also be managed endoscopically for certain complications such as hemorrhage or stricture (Fleshner, 2016). The overall goal of surgery in CD patients is to conserve bowel and return the patient to the best possible quality of life (Crohn's and Colitis Foundation of Canada, 2012).

1.4.6 Treatment Care Pathway & Guidelines

Building upon the therapeutic options discussed above, the Canadian guidance documents released by the Canadian Association of Gastroenterology (CAG) relating to these treatments will be summarized to provide clinical perspective on the use of biologics and the treatment pathway.

1.4.6.1 Canada: The Use of Tumour Necrosis Factor-alpha Antagonist Therapy in CD

The 2004 Canadian guidelines on the use of infliximab were updated in 2009 to account for new anti-TNFα therapies including adalimumab and certolizumab (which is currently not available in Canada) (Panaccione et al., August, 2004; D. C. Sadowski et al., 2009). This document has three primary themes including: induction therapy, maintenance therapy and safety (D. C. Sadowski et

al., 2009). An updated CAG clinical practice guideline for treatment of CD is currently in development.

Firstly, the CAG defined the following key concepts which will be important for determining treatment pathways and drug responsiveness for patients:

- Clinical Response: reduction of 70 points or more in the CDAI
- Clinical Remission: CDAI of less than 150 points
- Disease Relapse/ Loss of Response: increase in the CDAI of at least 70 points
- Moderate-to-Severe CD: CDAI scores between 220 and 400 points
- Corticosteroid dependent: a patient who will experiences relapse or flare if their steroid dose is tapered

The following summary of the guidelines will focus on recommendations specific to luminal CD as fistulizing CD has independent recommendations for treatment. The primary recommendation for the use of anti-TNFα therapy is in patients who demonstrate continuing CD despite conventional therapy. Infliximab, adalimumab or certolizumab are clinically effective for the induction of remission of luminal CD patients who continue to demonstrate active CD (D. C. Sadowski et al., 2009). For luminal CD the induction regimens are described in the table below.

Table 6 - Biologic Induction Therapy

Drug	Administration	Dosage
Infliximab	Intravenously	5mg/kg at weeks 0, 2 and 6
Adalimumab	Subcutaneously	Week 0 – 160 mg Week 2 – 80 mg
Certolizumab	Subcutaneously	400mg at weeks 0, 2 and 4

If a patient remains unresponsive to one of the above regimens it is recommended that they not receive additional doses, but that increased treatment doses or switches to other TNF antagonists be considered on a case-by-case basis (D. C. Sadowski et al., 2009). However, given this is a complicated and evolving area an update to these guidelines is warranted. More recent American Gastroenterological Association guidelines recommend the use of treatment intensification after failure in certain cases (Feuerstein et al., 2017).

It is recommended that patients who successfully respond to an induction regimen receive maintenance therapy to maintain remission (D. C. Sadowski et al., 2009). Select patients may be successfully maintained with an immunosuppressive alone, however there was a higher-grade

recommendation that patients continue with their respective anti-TNF therapy at the following dose:

Table 7 - Biologic Maintenance Therapy

Drug	Administration	Dosage
Infliximab	Intravenously	5mg/kg every 8 weeks
Adalimumab	Subcutaneously	40 mg every 2 weeks
Certolizumab	Subcutaneously	400mg every 4 weeks

During this phase if a diminished or suboptimal response occurs with any of the three anti-TNF treatments it can be managed by either shortening the interval between dosing, increasing the dose or providing a supplemental dose (D. C. Sadowski et al., 2009). This maintenance therapy can help reduce sensitization to TNF antagonists and therefore reduce the formation of ADAs, infusion reactions and likelihood of loss of clinical response (D. C. Sadowski et al., 2009). The use of concomitant immunosuppressive therapy with azathioprine, 6-mercaptopurine or methotrexate may also reduce the incidence of these events (D. C. Sadowski et al., 2009). The final recommendation for patients on maintenance therapy is that for those who respond favorably to 52 weeks of therapy the benefits of continuing therapy outweigh the risks of discontinuation (D. C. Sadowski et al., 2009).

Serious adverse events associated with TNF-antagonist therapy are rare however, there are recommendations to improve safety and prevent these events (D. C. Sadowski et al., 2009). Firstly, TNF antagonist treatment is contraindicated in patients with clinically significant bacterial infection and patients with moderate-to-severe congestive heart failure (D. C. Sadowski et al., 2009). Furthermore, anti-TNF therapy should be administered with caution in the following patients:

- Patients with pre-existing demyelinating disorders;
- Patients with a suspected abscess or in patients with a suspected intestinal obstruction;
- Patients with a history of recurrent bacterial or viral infections;
- Patients with HIV infection, hepatitis B and C or organ transplant recipients on multiple immunosuppressives.

Any individual who experiences a severe hypersensitivity reaction to a TNF antagonist should not be retreated with the same agent. Switching agents after such an occurrence is possible, but should be approached with caution (D. C. Sadowski et al., 2009). Ultimately, with these guidelines the CAG acknowledged that infliximab, adalimumab and certolizumab are an

accepted treatment option in the mainstream treatment pathway and represent an important advancement in the management of patients with CD.

1.4.6.2 Canada: Subsequent Entry Biologics for the Management of IBD

In 2013, the CAG also released a position statement on subsequent entry biologics. The objective of this document was to provide a primer on subsequent entry biologics (now referred to as biosimilars in Canada), the data available to date, opportunities for use, and the CAG's position statements (Devlin et al., 2013). While not explicitly a clinical treatment guideline, this document is the first and only document currently available which acknowledges the opinion statement of Canadian gastroenterologists on the use of biosimilars for CD patients.

The CAG acknowledged that there is potential for the use of biosimilars in the Canadian market as high-cost biologics such as infliximab are being used more frequently and earlier in the treatment pathway. Since biosimilars enter the market at a reduced price there is potential to reduce costs to patients and payers which can expand access to these treatments (Devlin et al., 2013). However, the CAG also emphasized that this is contingent on the available clinical data showing comparability to the reference product. A number of questions were raised regarding the data that was available at the time, particularly regarding how clinical trials in patients with IBD would be conducted and issues with immunogenicity. The CAG was against extrapolation for biosimilars and indicated that their previous experience found that this can be problematic and generate unanticipated results (Devlin et al., 2013).

The following position statements were issued by the CAG with regards to biosimilars in the market (Devlin et al., 2013) :

1. *Subsequent entry biologics represent a potentially effective and cost saving option for the management of IBD that may serve to enhance access to biologic therapy.*
2. *Subsequent entry biologics should be regarded as stand-alone products and should be supported by well-designed nonclinical and clinical studies in a population relevant to Canadian patients.*
3. *Subsequent entry biologics cannot be regarded as interchangeable with the reference biologic.*
4. *Prescriptions for the reference biologic should not be automatically substituted for less expensive subsequent entry biologics by dispensing pharmacies.*
5. *Subsequent entry biologics should be supported by long-term pharmacovigilance data in a fashion similar to the reference biologic.*

6. *Companies bringing SEBs to the Canadian market should be committed to improving patient care by acquiring new scientific data beyond that which is required as a minimum to satisfy regulatory authorities and their commercial imperatives.*

These statements are primarily in line with the caution that was raised by the European Crohn's Colitis Organization (ECCO) and several European IBD societies regarding the use of biosimilars in their original 2013 position statement (Danese, Gomollon, & ECCO, 2013). While biosimilars have been available in the European market for almost ten years, those for IBD were only recently introduced. Since the release of the initial ECCO statement more data from IBD specific studies has been released. As such, ECCO has revised their position to be in line with the change in perception of IBD experts (Danese, Fiorino, et al., 2017). ECCO has released 8 new consensus statements, several of which notably differ from the CAG (Danese, Fiorino, et al., 2017);

1. *Clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation. Therefore, data for the usage of biosimilars in IBD can be extrapolated from another sensitive indication.*
2. *Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients.*

ECCO supports the use of extrapolation to IBD indications, as well as, switching from a reference biologic to a biosimilar which is in stark contrast to the position statements of the CAG. This in part reflects the rapidly changing nature of the biosimilar space. As more evidence becomes available it is likely that these positions and the perceptions of IBD experts will continue to evolve.

In conclusion, the management of adult patients with CD is a complex process with a primary objective to restore the patient to well-being through clinical response and remission and ultimately improve their quality of life. However, the guidelines demonstrate that there are a number of treatment options available and the best route for individual patients may vary which emphasizes the importance of developing a variety of cost-effective treatment options for this disease state.

1.5 Infliximab in the Treatment of Crohn's Disease

The following section will review clinical evidence of infliximab to provide an overview of the risks and benefits of this treatment. This section will also include a summary of the evidence used to demonstrate similarity and switching between the reference and biosimilar infliximab.

1.5.1 Reference Infliximab

Remicade® (reference infliximab) received the first NOC from Health Canada in 2001 and received an additional indication in CD in 2004 (Health Canada, 2017b). Infliximab is a chimeric IgG1κ monoclonal antibody and it binds specifically to tumour necrosis factor (TNF) alpha and neutralizes its biologic activity (MacDermott & Lichtenstein, 2017). The mechanism of action likely involves the destruction of activated effector cells through apoptosis in order to provide symptom relief and induce/maintain remission (MacDermott & Lichtenstein, 2017). However, as with any pharmaceutical, there is also the risk of adverse drug reactions associated with the use of the treatment. The most common reactions associated with Remicade® include infections, allergic reactions and infusion-related reactions (Janssen Inc., April 26, 2016). Another potential issue associated with the use of Remicade® is immunogenicity – the development of antibodies to infliximab. Patients who become antibody positive are more likely to experience reduced efficacy and infusion reactions (Janssen Inc., April 26, 2016). Therefore, it is important to consider effectiveness, safety and immunogenicity when treating patients with infliximab. The pivotal clinical studies which assess these risks and benefits in the treatment of CD are summarized below.

In their 1997 study Targan et al randomly assigned 108 patients with moderate-to-severe CD to either a single dose of placebo or infliximab infusion with either 5 mg/kg, 10mg/kg or 20mg/kg (Targan et al., 1997). At two weeks, 61% of infliximab patients had a clinical response compared with 17% in the placebo group, and after four weeks 33% of the infliximab treated group were in remission as compared with 4% of the placebo group. The differences in rates of clinical response remained significant through 12 weeks of study however, the difference in the percentage of patients who were in remission was not significant. With regards to safety, the percentages of patients with adverse events were similar in the treatment and placebo groups (Targan et al., 1997). Overall, the study suggested infliximab is an effective short-term treatment for patients with moderate-to-severe CD that was resistant to treatment (Targan et al., 1997).

This was an important study to inform decision makers and economic researchers on the short-term effects of treatment with infliximab.

ACCENT I was a randomized control trial of 573 patients to assess the benefit of maintenance therapy with infliximab in patients who responded to a single infusion (Hanauer et al., 2002). Eligible patients were given a 5mg/kg infusion at week 0 and reassessed at week 2 for response. Patients who responded were then randomly assigned subsequent infusions or placebo thereafter until week 46 (Hanauer et al., 2002).At week 30 the proportion of week 2 responders in remission was higher in the maintenance therapy groups than in the placebo group and these results were sustained thereafter. The study concluded that maintenance therapy offers better long-term efficacy for patients with CD and as they were more likely to maintain clinical response, remission and to discontinue corticosteroids (Hanauer et al., 2002). This study was imperative for demonstrating the benefit of infliximab as maintenance therapy for the treatment of CD and supported the approval of reference infliximab in this indication.

In the SONIC study by Colombel et al in 2010 infliximab and azathioprine therapy alone or in combination for inducing and maintaining corticosteroid-free clinical remission in patients with CD was evaluated (Jean Frederic Colombel et al., 2010). 508 patients with moderate-to-severe CD were randomly assigned to receive either intravenous infusions of infliximab at 5mg/kg plus an oral placebo, oral azathioprine capsules, or combination therapy with infliximab and azathioprine (Jean Frederic Colombel et al., 2010). At week 26, 56.8% of patients receiving combination therapy, 44.4% receiving infliximab and 30.0% receiving azathioprine were in corticosteroid free clinical remission. With regards to safety, the incidence of adverse events was similar among the groups and antibodies to infliximab at week 30 were detected in 0.9% of the combination group and 14.6% of those receiving infliximab (Jean Frederic Colombel et al., 2010).Based on these results, the authors concluded that infliximab monotherapy and combination therapy with azathioprine as compared with azathioprine alone resulted in higher rates of corticosteroid-free clinical remission. Combination therapy was the most effective, which may have been due to the suppression of immunogenicity or the additive effects (Jean Frederic Colombel et al., 2010).

Infliximab has become a powerful treatment option for these patients in Canada in both the induction and maintenance of clinical remission. Additional trials not discussed here have further

demonstrated that infliximab is associated with an induction of remission, improvement in quality of life and maintenance of remission (MacDermott & Lichtenstein, 2017; Sands et al., 2004; Sands, Blank, Diamond, Barrett, & Van Deventer, 2006).

1.5.2 Biosimilar Infliximab

In the following section, an overview of the clinical evidence of biosimilar infliximab will be presented, including an in-depth summary of NOR-SWITCH, the first double-blind randomized trial comparing switching to biosimilar and reference in all indications.

1.5.2.1 Overview - Clinical Studies of Biosimilar Infliximab

The PLANET clinical program was the pivotal clinical evidence that was referenced in the approval process for biosimilar infliximab (CT-P13) in Canada.

Firstly, PLANETAS, was a phase I randomized double-blind study conducted in 250 ankylosing spondylitis patients. They found that PK profiles of biosimilar infliximab and the reference were equivalent in patients and that the biosimilar was well tolerated with comparable safety up to week 30 (W. Park et al., 2013). PLANETRA, was a double-blind multi-center parallel group study in 606 rheumatoid arthritis patients with inadequate response to methotrexate treatment to compare the efficacy and safety of reference infliximab and biosimilar infliximab (Braun & Kudrin, 2016; Dae Hyun Yoo, Hrycaj, Miranda, & Ramiterre, 2013). This study found that biosimilar infliximab demonstrated equivalent efficacy to the reference at week 30 where American College of Rheumatology 20% response were 60.9% for biosimilar infliximab and 58.6% for the reference. The treatments were deemed equivalent if the 95% confidence interval (CI) for the treatment difference was within +/- 15% (Dae Hyun Yoo et al., 2013). Furthermore, it was demonstrated that biosimilar infliximab was well-tolerated with a safety profile comparable to that of the reference, as well as, comparable PK profiles and immunogenicity (Braun & Kudrin, 2016; Dae Hyun Yoo et al., 2013). Both the PLANETRA and PLANETAS were pivotal in demonstrating the comparability of the biosimilar to the reference, however they only studied ankylosing spondylitis and rheumatoid arthritis.

Investigators also conducted an extension study of PLANETRA to assess the efficacy and safety of switching from the reference to biosimilar or continuing the biosimilar for an additional six infusions from weeks 62 to 102 (D. H. Yoo et al., 2017). This open label study measured

efficacy, immunogenicity and safety in patients who completed the PLANETRA trial and who were either switched from the reference or continued treatment with the biosimilar. (D. H. Yoo et al., 2017) The study found that comparable efficacy and tolerability were observed in patients who switched from the reference to biosimilar for an additional year, and in those who had continued treatment (Dae Hyun Yoo et al., 2013). Overall, these results suggest that clinical efficacy and safety of the biosimilar are comparable for switch patients in the rheumatoid arthritis disease space and that efficacy is maintained for an additional year of treatment on the biosimilar.

1.5.2.2 Observational Studies

The clinical experience with biosimilar infliximab in both IBD indications is still limited. However, several observational studies were conducted and are summarized in Appendix I. There was a wide array of efficacy endpoints utilized including: remission rates, response rates, treatment persistency, biochemical response, mucosal healing, efficacy maintenance, surgery or readmission rates, laboratory results, use of steroids and disease activity.

In studies of non-switch infliximab patients, it was found that biosimilar infliximab was efficacious and comparable to reference infliximab (Argüelles-Arias et al., 2017; Farkas et al., 2015; Fiorino et al., 2017; Gecse et al., 2016; Hlavaty et al., 2016; Jahnsen, Detlie, Vatn, & Ricanek, 2015; Jung et al., 2015; Kang, Moon, Lee, Lim, & Kang, 2015; Keil et al., 2016; Kolar et al., 2017; S. H. Park et al., 2015). One notable exception was the descriptive study of induction patients on biosimilar infliximab conducted by Murphy et al. (2015). In this study a cohort of patients started on biosimilar infliximab were compared against a cohort of induction patients on reference infliximab who started therapy two years prior. The study found that 29% of the biosimilar group required surgery vs. 0% in the reference infliximab group (Murphy, Sugrue, Mohamad, McCarthy, & Buckley, 2015).

The literature also demonstrated that patients who switched from reference infliximab to biosimilar infliximab had comparable efficacy to the reference and the switch did not result in significant changes in efficacy outcomes, such as disease activity scores (Argüelles-Arias et al., 2017; Buer et al., 2017; Farkas et al., 2015; Fiorino et al., 2017; Hlavaty et al., 2016; Jung et al., 2015; Kang et al., 2015; Kolar et al., 2017; S. H. Park et al., 2015; Sieczkowska et al., 2016; Smits et al., 2016; Soret et al., 2017).

Biosimilar infliximab was well tolerated in patients with CD or UC for both naïve and switch patients. Most of the adverse events were mild or moderate, and the studies did not report significant differences between the reference and biosimilar with regards to adverse events or immunogenicity (Radin, Sciascia, Roccatello, & Cuadrado, 2017).

A recently conducted systematic review and meta-analysis included eleven of the studies considered in Appendix I (Komaki et al., 2017). Using the pooled results in CD, the biosimilar had high rates of clinical response of 0.79 (95% Confidence Interval: 0.65 to 0.88) at 8 to 14 weeks and 0.77 (0.63 to 0.86) at 24 to 30 weeks (Komaki et al., 2017). Similarly, the pooled results for clinical remission for CD were 0.66 (0.53 to 0.77) at weeks 8 to 14 and 0.6 (0.49 to 0.7) for weeks 24 to 30 (Komaki et al., 2017). With regards to safety the pooled rate of overall adverse events was 0.08 (0.02 to 0.26) (Komaki et al., 2017).

In the eleven studies, there were six which included 277 IBD patients who switched from reference to biosimilar infliximab. For the CD patients, sustained clinical response was demonstrated at 30 to 32 weeks (0.85, 0.71 to 0.93) and at weeks 48 to 63 (0.75, 0.44 to 0.92) however, this latter data only included two studies. The pooled rates for sustained clinical remission were 0.74 (0.55 to 0.87) at week 16 and 0.92(0.38 to 0.99) at week 51 however, each only included a small number of studies. The overall adverse event in this population was 0.1 (0.02 to 0.31).

Overall, this meta-analysis of the observational clinical studies for the use of biosimilar infliximab in CD populations showed high rates of clinical response and remission that persisted. Patients who switched demonstrated durable response with similar risk of adverse events to the reference (Komaki et al., 2017).

1.5.2.3 Randomized Controlled Trials of Switching to Biosimilar Infliximab

1.5.2.3.1 NOR-SWITCH

The NOR-SWITCH study was the first randomized, non-inferiority, double-blind, phase 4 trial with 52 weeks of follow-up with the objective of examining switching from reference infliximab to a biosimilar (Jørgensen et al., 2017). The study included adult patients on stable treatment with reference infliximab treated in a hospital setting for at least six months in the following indications; ankylosing spondylitis, rheumatoid arthritis, Crohn’s Disease, ulcerative colitis,

psoriatic and plaque psoriasis. Hospital setting herby refers to participating Norwegian hospital centers which provided infliximab infusions for the mentioned diagnoses, and does not reflect an in-patient setting (Jørgensen et al., 2017). However, the study was not powered to show non-inferiority in the individual disease groups (Jørgensen et al., 2017).

Patients were randomized in a 1:1 ratio to either continue reference infliximab or switch to biosimilar infliximab and were given the same dose and infusion levels as prior to randomization. The primary outcome was disease worsening during follow-up according to a disease specific composite measure which was HBI for CD with a change from baseline of 4 points or more and a score of 7 points or greater (Jørgensen et al., 2017).

Secondary endpoints included time to disease worsening, study drug discontinuation, overall remission status based on the main composite measure, and patient global assessments. NOR-SWITCH also included patient reported outcomes with the RAND 36-item Short Form Health Survey, the EQ-5D and the Work Productivity and Activity Impairment Questionnaire. To analyze safety, the study measured clinical and laboratory adverse events. Immunogenicity was assessed with trough serum concentrations and ADAs with inhibition assays. The non-inferiority margin for the 52 weeks was 15%, implying that biosimilar infliximab would be inferior if the proportion of patients with disease worsening was greater than the 15% margin (Jørgensen et al., 2017). This margin was determined based on clinical discussions within the study group, the PLANETRA study which employed the same margin and discussions with the Norwegian Medicines Agency (Jørgensen et al., 2017).

A total of 482 patients were randomized into the trial with 241 continuing treatment and 241 switching to biosimilar. Within the full analysis set, 32% had Crohn's Disease, 19% had ulcerative colitis, 19% had ankylosing spondylitis, 16% had rheumatoid arthritis, 6% had psoriatic arthritis and 7% had plaque psoriasis. The primary efficacy endpoint was assessed in the per-protocol set, which only included eligible randomized patients with no protocol deviations affecting treatment efficacy. This included 202 patients and 206 patients in the reference and biosimilar groups respectively. Disease worsening occurred in 26% (53) of the reference group and 30% (61) of the biosimilar group. The adjusted risk difference of -4.4% (95% confidence interval: -12.7% to 3.9%) was within the pre-specified margin implying biosimilar infliximab was not inferior to reference infliximab across all therapeutic areas.

In the CD cohort, the per-protocol set included 66 patients and 63 patients in the reference and biosimilar group respectively. For CD, disease worsening occurred in 21.2% (14) of the reference group and 36.5% (23) of the biosimilar infliximab group in the per-protocol set. This gave a risk difference of -14.3% (-29.3% to 0.7%) which while a larger separation than other sub-groups was within the 15% clinical margin (Jørgensen et al., 2017).

With regards to the secondary endpoints; remission occurred in 61% (123) patients in the reference group and 61% (126) in the biosimilar group, an adjusted rate difference of 0.6% (-7.5% to 8.8%). Disease specific composite measures such as Harvey Bradshaw Index (HBI), HBI Remission and Inflammatory Bowel Disease Questionnaire total score, from baseline to end of follow-up were generally similar between groups (Jørgensen et al., 2017).

With regards to safety, 70% of the reference group and 68% in the biosimilar infliximab group had at least one adverse event. The most frequently reported events were infections. The rate of serious events also did not differ between groups (10% reference vs. 9% biosimilar) (Jørgensen et al., 2017). Regarding immunogenicity, it was found that the trough drug concentration levels were similar in the two groups. The incidence of ADAs detected during the study (not including those with detectable ADAs at baseline) was 7% (17) for the reference group and 8% (19) for the biosimilar group (Jørgensen et al., 2017).

These results support earlier observational studies in suggesting that switching is not associated with safety concerns (Jørgensen et al., 2017). However, the sample particularly in some diseases, was small, therefore the study was not powered to show non-inferiority in CD or other individual diseases. Rather, it was powered to study differences in outcomes across all disease states (Jørgensen et al., 2017). Furthermore, the 15% clinical margin may be too wide (Jørgensen et al., 2017). Some specialists, particularly within gastroenterology, have expressed concerns with a 15% margin, and would have preferred a narrower margin (Community Academic Research Education (CARE), 2017). Understanding this concern, one of the most controversial results is the subset analysis for CD which was 14.3% in favor of the reference (Community Academic Research Education (CARE), 2017).

Considering these limitations, Canadian gastroenterologists have expressed caution with the results of NOR-SWITCH particularly regarding interchangeability. Gastroenterologists have encountered difficulties with immunogenicity and sensitizing patients in the past and have

expressed a need for further research as the Canadian biosimilar environment continues to evolve (Community Academic Research Education (CARE), 2017; Pichler, 2007).

1.5.2.3.2 NCT02096861 – Phase III

One year maintenance and switching results of a Phase III randomized controlled trial to compare biosimilar infliximab with reference infliximab in patients with active CD were recently released as an abstract in late 2017 (Y. Kim et al., 2017). The objectives of this study were two-fold. Firstly, to investigate the efficacy and safety throughout the 1-year treatment period and secondly, to assess switching from reference to biosimilar at week 30.

Patients with moderate-to-severe CD were assigned to one of four groups: maintenance group on either biosimilar or reference and switch groups biosimilar to reference and vice versa (Y. Kim et al., 2017). 180 patients completed the week 30 visit and 166 completed the entire study. At week 54 clinical remission and response (defined by the CDAI 70 response) were similar among all four groups (Y. Kim et al., 2017). 53.7 percent of patients maintained on reference for the study period and 60 percent of patients who switched from reference to biosimilar, were in clinical remission at the end of the study period. Similarly 70.4 percent and 76.4 percent demonstrated CDAI-70 response for the reference and switch groups respectively (Y. Kim et al., 2017).

This study was conducted specifically in the CD population, unlike NOR-SWITCH, which examined all therapeutic areas for which infliximab is indicated. It is important to acknowledge that the time frame of this study is comparably shorter than that of NOR-SWITCH which examined a switch over a full 54-week period whereas this analysis compared the switch from week 30 to 54 (Jørgensen et al., 2017; Y. Kim et al., 2017). The results for this study indicated that the switch group from reference to biosimilar was comparable to the maintenance groups in terms of both efficacy and safety (Y. Kim et al., 2017).

1.6 Economic Evidence in the Treatment of CD with Biologics

1.6.1 Burden of Illness & Healthcare Expenditure

The economic burden of an illness for patients and society includes direct, indirect and intangible costs. Direct costs refer to healthcare expenditure to improve and prevent the deterioration of health status (Public Health Agency of Canada, 2014). Indirect costs in comparison refer to the dollar value of lost production due to illness, injury or premature death (Public Health Agency of

Canada, 2014). Finally, intangible or psychosocial costs refer to pain and suffering for example, and these costs can in some ways be captured by estimates of quality of life.

There is a substantial burden of illness associated with CD in Canada due to its chronic nature, its debilitating symptoms, and the absence of a cure. Direct medical costs for IBD were estimated at $1.2 billion in Canada in 2012 (Crohn's and Colitis Foundation of Canada, 2012). These resources include prescription drugs, hospitalizations, surgeries, emergency department visits, physician services, allied health care professional visits, laboratory tests, social services and long-term care. It was prescription medications ($521M) and hospital in-patient costs ($395M) that made up the majority of the direct medical costs in Canada. Indirect costs in comparison are borne by people and by society. Recent estimates of indirect costs were higher than direct medical costs for IBD in Canada at $1.6 billion in 2012, $868 million of which was for CD (Crohn's and Colitis Foundation of Canada, 2012). The 2012 IBD impact report estimated that long term work loss ($979M), out-of-pocket expenses ($300M) and short-term work loss ($181M) made up the majority of indirect costs.

Work and productivity losses, two of the largest contributors to indirect costs in Canada, are analyzed in both the short and long term. The short term analyzes the effect that IBD has upon employed individuals, i.e., how much work is missed due to medical appointments, illness or hospitalization (Crohn's and Colitis Foundation of Canada, 2012). On average, 43% of employed individuals with IBD took time off work every year with each person being absent 7.2 days on average due to IBD (Rocchi et al., 2012). Long-term work losses in comparison, refer to long absences from employment, reduction in hours of work, and premature retirement and mortality (Crohn's and Colitis Foundation of Canada, 2012). A meta-analysis of several studies of long term work losses estimated that IBD was associated with a 13% reduction in the probability of employment (Crohn's and Colitis Foundation of Canada, 2012).

The burden of illness of IBD from an economic lens is clearly substantial, however beyond these financial costs, there are significant quality of life burdens. An Australian study estimated the cost of the decreased quality of life associated with IBD at $2.2 billion dollars in 2005, this included estimating the years of life lost due to premature death, years of healthy life lost due to disability and the net value of healthy life lost (Access Economics for the Australian Crohns and Colitis Association, June 2007). Converting their estimate to Canadian prevalence rates results in

a quality of life cost in Canada of $4 billion dollars (Crohn's and Colitis Foundation of Canada, 2012). The burden of illness in Canada is significant and this emphasizes the importance of high value treatment pathways with cost-effective therapies to improve patients' quality of life while reducing both indirect and direct costs (Crohn's and Colitis Foundation of Canada, 2012; Floyd, Langham, Séverac, & Levesque, 2015).

1.6.2 Cost-Effectiveness of Infliximab in Crohn's Disease

Infliximab is widely used in the clinical treatment of CD and as such there have been numerous economic evaluations of this treatment. These evaluations quantify the trade-off between resources used and outcomes gained in order to determine the relative efficiency of a treatment (Hoch & Dewa, 2008). Cost-effectiveness analysis is frequently used as a broad term to refer to the field of economic evaluation however, there are a variety of different types of evaluations which assess the costs and benefits of a health technology. In order to be a cost-effectiveness analysis the evaluation must necessarily involve a comparison of one or more alternatives (Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015). Furthermore, while all economic evaluations consider the costs and resources associated with an intervention and comparator, the evaluations will differ based on how and if clinical outcomes are assessed (CADTH, March, 2017; Drummond et al., 2015).

For example, in a basic cost analysis one simply considers the valuation of costs in monetary units and the analysis does not identify or measure consequences of benefits in any form (Drummond et al., 2015). Similarly, in a cost minimization analysis (CMA) the interventions being compared are considered equivalent in terms of their outcomes and the analysis only evaluates costs associated with the intervention and comparator (CADTH, March, 2017). Therefore, the lowest-cost intervention is preferred (CADTH, March, 2017). For the purposes of this research outcomes associated with switching patients to biosimilar infliximab are also of interest and therefore, neither of these forms of evaluation will be appropriate.

There are three primary types of evaluation which identify and measure consequences and benefits of a new health technology; cost-effectiveness analysis (CEA), cost-benefit analysis (CBA) and cost-utility analysis (CUA). In a CEA outcomes are measured in natural health units which are common to both the intervention and the comparator, but which are achieved to different degrees (CADTH, March, 2017; Drummond et al., 2015). A natural health unit can

refer to life years gained, lives saved or clinical event avoided or achieved for example (CADTH, March, 2017; Drummond et al., 2015). A main disadvantage of this type of analysis is the inability to compare across disease states or between evaluations which utilize a different natural health unit (CADTH, March, 2017). This can create challenges for decision makers who must make funding decisions across a breadth of technologies and disease spaces.

A CBA can solve this issue as all outcomes are valued in monetary terms (Drummond et al., 2015). Therefore, the natural health outcomes that are considered for the comparator and the intervention do not need to be the same as they will be converted to a monetary value (Drummond et al., 2015). Values are typically obtained using a willingness-to-pay approach, such as contingent valuation, however this requires value judgments which can be controversial particularly in a healthcare setting (Detsky & Naglie, 1990). Therefore, CBAs are not typically the preferred type of analysis for assessing health technologies (CADTH, March, 2017; Detsky & Naglie, 1990).

The preferred method of economic analysis by Canadian reimbursement agencies is the CUA (CADTH, March, 2017). In a CUA clinical consequences and benefits are identified and measured by accounting for the utility associated with the effectiveness of the intervention so that the final outcome is expressed as a quality adjusted life year (QALY) (CADTH, March, 2017; Drummond et al., 2015). The use of a generic measure such as a QALY allows decision makers to make broad comparisons across disease states and interventions when considering resource allocation in the healthcare sector (Drummond et al., 2015). While there are disadvantages in the use of CUAs, primarily due to debates surrounding eliciting preferences and utilities for different health states, it is still the recommended reference case approach (CADTH, March, 2017; Neumann, Goldie, & Weinstein, 2000).

Through assessing the incremental gains in QALYs and incremental costs associated with a new intervention when compared to another treatment option, one can derive an incremental cost-effectiveness ratio (ICER) (Drummond et al., 2015). An ICER represents the incremental cost of one additional QALY when comparing a new intervention with the standard of care for example (Hoch & Dewa, 2008). Because QALYs are a universal metric, decision makers who allocate budget can use the QALYs or ICERs to make comparisons across patient groups and can set willingness-to-pay (WTP) thresholds for funding decisions. These thresholds determine the

maximum one is willing to pay for one additional QALY or unit of benefit, and therefore, determines if an intervention is cost-effective (Marseille, Larson, Kazi, Kahn, & Rosen, 2015). For example, if the WTP threshold was $50,000 per QALY then any intervention with an ICER below $50,000 would be considered cost-effective from the perspective of that decision maker.

In comparison the purpose of a budget impact analysis (BIA) is to "estimate the financial consequences of adoption and diffusion of a new health-care intervention within a specific health-care setting or system given inevitable resource constraints"(Mauskopf et al., 2007). BIAs consider how a change in the mix of drugs will impact spending for one or more budgets on a given health condition, and evaluate the affordability of a technology for a public or private health plan (Mauskopf et al., 2007).

In the following section, CUAs which have been conducted to assess the cost-effectiveness of reference infliximab will be reviewed followed by a summaryof the economic analyses and BIAs that have considered biosimilar infliximab. It is important to acknowledge that there have been a number of these analyses and the following is not a systematic literature review.

1.6.2.1 Review Articles

There are a variety of modelling decisions and parameter assumptions that must be made when conducting a CUA which can create methodological, structural and parameter uncertainty. There may be variability in treatment protocols (i.e. initiation, maintenance, episodic infusions), in comparators (i.e. surgery, conventional care or adalimumab) and perspective (i.e. third-party payer or societal). Ultimately, these factors can drive significant differences in the model structure, the results and conclusions.

Tang et al. (2013) emphasized this in a recently conducted systematic review of economic evaluations on biological agents used to treat CD. They found a variety of results depending on the treatment pathway, timeframe, and comparators used in the model (Tang, Harrington, Lee, Lin, & Armstrong, 2013). It was found that infliximab is cost-effective in certain scenarios; for example when compared against standard care in luminal CD with induction and episodic therapy over a 5 year plus time frame (Tang et al., 2013). However, there was mixed evidence in a number of other cases including analyzing infliximab vs. standard care for luminal CD with induction and maintenance therapy over 1 year. Using conventional WTP thresholds, 2 U.K.

based studies found infliximab was cost-effective in this scenario (Tang et al., 2013). However, 2 other U.K. studies and 2 Canadian studies found it was not (Tang et al., 2013). This type of conflicting evidence can create challenges in drawing conclusions related to the cost-effectiveness of a given therapy and emphasizes the importance of setting the context and analyzing uncertainty.

Another review conducted by Marchetti & Liberato similarly found that the cost-effectiveness profile of infliximab was highly dependent on the comparator, perspective and time frame of the analysis (Marchetti & Liberato, 2014) . Infliximab was shown to be cost-effective when compared with standard care in a number of studies, and in some cases was the dominant strategy (Marchetti & Liberato, 2014). When an intervention is dominant it implies it is both less costly and more effective than the comparator (CADTH, March, 2017). However, there were conflicting results when infliximab maintenance therapy was compared with adalimumab maintenance over a one to five year time horizon (Marchetti & Liberato, 2014).

Despite mixed evidence, review articles assessing the cost-effectiveness of infliximab for the treatment of CD have generally suggested infliximab may be cost-effective in certain cases (Smart & Selinger, 2014; Tang et al., 2013). The cost-effectiveness of biologic treatment for CD may be optimized in certain contexts by tailoring maintenance therapy to certain populations such as severe luminal disease or pediatric patients, adopting a long term time horizon, considering societal costs and determining which patients should switch to standard therapy or other biologics after failure (Tang et al., 2013).

1.6.2.2 Cost-Effectiveness Analyses

A summary of the analyses which have been reviewed can be found in Table 8. These evaluations show that there is substantial variability in the ICERs associated with infliximab. Some results were below conventional thresholds, implying infliximab was cost-effective, for example when infliximab was compared with other biologics in the U.S. setting or when infliximab maintenance therapy was compared with standard care in the UK (Lindsay, Punekar, Morris, & Chung-Faye, 2008; Tang, Armstrong, & Lee, 2012). However, in other treatment settings infliximab was associated with ICERs that greatly surpassed these thresholds (i.e. not cost-effective) (Blackhouse et al., 2012; J. Marshall et al., March 2002). Considering the Canadian context specifically this review focused on models conducted by Blackhouse et al

(2012) and Marshall et al (2002). Both of the analyses considered initiation and maintenance with infliximab therapy, however Blackhouse et al. included adalimumab and standard therapy and Marshall et al. assessed a variety of dosing regimens and standard care (Blackhouse et al., 2012; J. Marshall et al., March 2002). The results of these models emphasized that the ICER spread is substantial depending on choice of comparator and time horizon. Both suggested that the cost-effectiveness ratio for infliximab was above traditional thresholds (Blackhouse et al., 2012; J. Marshall et al., March 2002). In Blackhouse et al (2012) the ICER ranged from $222,955 when compared with usual care up to $451,165 when compared with adalimumab. Similarly, depending on the dosing strategy the results of Marshall et al (2002) showed the ICER could range from $181,201 up to $696,078. Some of the model structures and assumptions which influence this range of ICERs, for both Canadian and international analyses, will be presented first and secondly, some of the common parameters which the models were particularly sensitive to will be discussed.

The primary model structural factors which influence the cost-effectiveness of infliximab include: disease type, intervention, comparators, time horizon and perspective. Disease type refers to luminal vs. fistulizing CD and severity of disease activity. Most models considered luminal disease in patients that were refractory to conventional medications, however incorporating fistulizing disease will necessarily alter the results due to the varied treatment pathway.

The evolution of the dosing for infliximab has led to changes on both the effectiveness and cost side of the evaluation for the intervention. Incorporating solely a single dose, versus multiple doses, episodic doses for relapse, complete maintenance therapy or dose intensification will drastically impact the effectiveness and the costs associated with infliximab treatment. Therefore, some of the earlier models which include single doses greatly differ from those which include long term maintenance treatment. Given current Canadian treatment guidelines these early models do not necessarily reflect current practice and therefore, their relevance is limited (D. C. Sadowski et al., 2009). Similarly, the choice of comparator is imperative when considering cost-effectiveness. Comparing against traditional therapy, surgery or other biologics will all result in drastically varied results due to the substantial cost and effectiveness differences associated with these options.

With regards to time horizon the evaluation must make assumptions regarding the length of time that a patient is treated and the time period that the analysis will cover. A short time-frame of a year or less may not fully capture the benefit of infliximab and therefore, may make the intervention appear less cost-effective. While longer time horizons, particularly lifetime time horizons, are preferred, there tends to be a lack of long term data which necessitates numerous assumptions which may create uncertainty in the results. Finally, perspective will also play a significant role in determining the cost-effectiveness of infliximab particularly in the CD population. Since CD occurs at a young age in a highly productive population, including societal costs will significantly impact the ratio. However, the majority of these studies focused on the perspective of the third-party payer and time losses are frequently challenging to collect. These structural assumptions of the model are important factors in determining the cost-effectiveness of infliximab. However, sensitivity analysis permits evaluation of influential parameters.

The goal of sensitivity analysis is to assess the impact of uncertainty on the estimated costs and outcomes for each intervention (CADTH, March, 2017). Through a review of the analyses included in Table 8, several parameters which were frequently identified as a primary driver of the results of the model have been identified.

With regards to effectiveness and outcomes; the utilities played a substantial role in determining cost-effectiveness in several analyses. Utility scores for remission, non-remission and fistulas significantly affected the model outputs, and were among the most influential parameters (Arseneau, Cohn, Cominelli, & Connors, 2001; Blackhouse et al., 2012; Jaisson-Hot, Flourié, Descos, & Colin, 2004; Lindsay et al., 2008; Saito et al., 2013; Tang et al., 2012). Differences in utilities between analyses may occur for a number of reasons including elicitation method for example so if the utilities were elicited using a standard gamble approach or the EQ-5D (Gregor et al., 1997). Preferences for health states (utilities) are an essential determinant of the effectiveness of infliximab when outcomes are measured in QALYs, however, parameters which affect the cost side of the comparison also have substantial impact.

One primary example of a parameter affecting the cost side of the analysis is patient weight. Since infliximab is given as an intravenous injection with a weight-based dose, patient weight is an important factor in determining how many vials are required per patient which in turn determines overall treatment cost (Blackhouse et al., 2012; Janssen Inc., April 26, 2016; Lindsay

et al., 2008). For example, in the Canadian context, treatment cost can range from $2,962.68 per maintenance dose for a 60 kg patient to $4,938 per maintenance dose for a 90 kg patient. Similarly, another factor which is highly influential on the cost side of the comparison is the unit drug cost for both infliximab and comparators (Arseneau et al., 2001; Blackhouse et al., 2012; Tang et al., 2012). The importance of the cost of infliximab as a determinant of cost-effectiveness speaks to the potential of biosimilar infliximab to improve the cost-effectiveness of biologic therapy for CD and emphasizes the value of assessing the cost-effectiveness of these products.

Within the selected analyses alone the ICERs ranged from a low of approximately $30,000 per QALY to upwards of $400,000 per QALY depending on the factors discussed above. This warrants the production of evidence that includes the new biosimilar options to further inform the cost-effectiveness of infliximab.

1.6.3 Cost-Effectiveness of Biosimilar Infliximab

As biosimilars are a relatively novel pharmaceutical the cost-effectiveness evidence to date is limited. The following section will briefly review the available evidence on the cost-effectiveness of biosimilar infliximab including budget impact analyses (BIA) as well as economic evaluations. Due to the limited evidence base the following summary includes non-IBD indications.

The manufacturer of Inflectra® (biosimilar infliximab) completed two submissions to CADTH; one for the indications of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis and a second approximately a year later for the two IBD indications. The review team highlighted that Inflectra® will most likely be used exclusively in naïve patients and that patient support programs and infusion clinics currently covered by the manufacturer of Remicade® will similarly be covered by the biosimilar manufacturer and therefore, this is not expected to result in additional costs to the public system (CADTH Canadian Drug Expert Review Committee, October 25, 2016). The findings of both CDEC reviews showed that Inflectra® will likely result in cost savings to the Canadian system, however these are strictly cost comparison results. In the report for the initial recommendation it was found that the cost of Inflectra® of $650 per 100 mg vial was 34.2% less costly than Remicade® (using the Ontario price) (CADTH Canadian Drug Expert Committee, December 19, 2014) . In comparison, at the

time of the CD and UC report the reviewers noted that the reduced manufacturer submitted price of Inflectra® ($525.00 per 100mg vial) is 47% less than that of Remicade® (using the Ontario price) (CADTH Canadian Drug Expert Review Committee, October 25, 2016) . Given these are strictly cost comparison results it remains imperative to produce cost-effectiveness evidence and consider the switch population specifically since costs and outcomes will differ between naïve and switch patients.

A rapid review report of clinical effectiveness and cost-effectiveness of switching from reference to biosimilar infliximab was conducted by CADTH in early 2017. With regards to the cost-effectiveness of switching, CADTH identified one systematic review which included six BIAs and two additional BIAs all of which focused on European jurisdictions (Li et al., 2015). The CADTH review concluded that cost savings would be substantial with switching, however, the amount of savings is dependent on factors such as the rate of interchangeability, patient numbers, price reductions of the biosimilar and prescribing behavior (i.e. whether physicians will prescribe biosimilars) (Canadian Agency for Drugs and Technologies in Health, January 18, 2017). CADTH outlined several limitations of their review including: the budget impact results were European and cannot be extrapolated to the Canadian system, cost-effectiveness was not examined in any study, and all studies considered introduction and not switching to biosimilar (Canadian Agency for Drugs and Technologies in Health, January 18, 2017).

A summary of economic analyses of biosimilar infliximab can be found in Table 9, and they are divided into two sections. Firstly, there were six BIAs which examined the introduction of biosimilar infliximab into a variety of European markets and in several of the indicated disease areas, however none considered the Canadian perspective.

Of the six BIAs reviewed, four were published as full articles and two were abstracts only (Brodszky, Baji, Balogh, & Péntek, 2014; Brodszky et al., 2016; Jha, Upton, Dunlop, & Akehurst, 2015; J. Kim, Hong, & Kudrin, 2014; McCarthy G, Bitoun CE, & H., 2013; Severs et al., 2017). They focused on several disease areas: three considered rheumatoid arthritis exclusively, one solely considered CD, one examined both IBD indications and one utilized all inflammatory diseases. Furthermore, while all took a third-party payer perspective they focused on a variety of European countries over time horizons ranging from 1 to 5 years. All analyses made a variety of assumptions surrounding comparator products, uptake, prevalence, price

discounts and switching. Ultimately, these short time horizons and perspective imply that these results are less relevant to the Canadian setting as the European experience cannot be extrapolated to the larger and varied Canadian population. However, these analyses provide context on the potential of biosimilars to provide cost-savings to a variety of markets.

The Jha et al. study used a 1 year time horizon and demonstrated cumulative savings ranging from €25.79 million ($39.16 million CAD 2017) to € 77.37 million ($117.52 million CAD 2017) across five countries and six indications (Jha et al., 2015). In comparison, the two Brodszky et al. studies that considered CD and rheumatoid arthritis independently used a three-year time horizon and demonstrated savings that ranged from €8 million ($12.15 CAD 2017) (CD with no switching) to €20.8 million ($31.59 million CAD 2017) (rheumatoid arthritis with switching) (Brodszky et al., 2014; Brodszky et al., 2016). Finally, the three BIAs with 5-year time horizons had drastically different cost savings estimates ranging from €5 million ($7.59 million CAD 2017) (rheumatoid arthritis only, Ireland) to €493 million ($748.67 million CAD 2017) (IBD, Netherlands) (J. Kim et al., 2014; McCarthy G et al., 2013; Severs et al., 2017). These analyses suggest that while the results differ across countries and indications, biosimilar infliximab is likely a more affordable option for healthcare systems.

The analyses that were published as peer-reviewed journal articles included details on one-way sensitivity analyses and several assumptions were identified as being influential on the amount of savings. These included: the cost of biosimilar infliximab, the size of the initial population eligible for treatment, if switching takes place and if so, the extent that occurs (Brodszky et al., 2014; Brodszky et al., 2016; Jha et al., 2015; Severs et al., 2017). While the BIAs speak to the cost-savings that healthcare systems may derive from the introduction of biosimilars, they do not speak to the efficacy or provide an estimate of the incremental cost-effectiveness of this treatment compared to reference products. There were two cost-effectiveness analyses of biosimilar infliximab compared with the reference infliximab in the Canadian context, one focusing upon initiation therapy and the other was a switch analysis.

The first cost-effectiveness analysis a study conducted by Beilman et al. with an objective to provide an economic analysis comparing the cost-effectiveness of infliximab to the biosimilar for the management of CD (Beilman, McCabe, Fedorak, & Halloran, 2017). When using the conventional $50,000 per QALY WTP threshold the biosimilar had a 91% chance of being cost-

effective in this population (Beilman et al., 2017).This limited evidence suggests that biosimilar infliximab is cost-effective, however this was an analysis specific to treatment initiation.

In comparison, Husereau et al (2018) recently analyzed the incremental cost-effectiveness of reference versus biosimilar infliximab in patients with CD based on the NOR-SWITCH trial. This cost-utility analysis modelled a one-time switch to biosimilar infliximab using a 10 year time horizon and a Canadian third party payer perspective (Husereau, Feagan, & Selya-Hammer, 2018). The Markov Model showed that reference infliximab was associated with costs of $168,210 and 6.02 QALYs whereas the biosimilar was associated with costs of $120,753 and 5.76 QALYs (Husereau et al., 2018). This gave an ICER in the southwest quadrant of $176,695 implying the switch to biosimilar was less costly, but also less effective (Husereau et al., 2018). The results of the probabilistic analysis similarly suggest that most replications lie in the southwest quadrant with some in the southeast quadrant (less costly and more effective) (Husereau et al., 2018). Ultimately this analysis suggests that there are no clear or universal pathways for decision makers with regards to biosimilar reimbursement and uptake. The authors also emphasized the need for further evidence that will benefit payers and health technology asssessment bodies as they move forward with developing biosimilar policies (Husereau et al., 2018).

Table 8 - Economic Evaluations of Infliximab

First Author	Dosing	Intervention	Comparator	Disease Status	Type of Model	Time Horizon	Perspective	Results
(Arseneau et al., 2001)	Initiation & Episodic	IFX 1) 3 infusions at 0, 2 and 6 weeks with combination 6MP/metronidazole for failures 2) Same as Strategy 1, but with episodic reinfusions for failures 3) first line combination 6MP/metronidazole with failures crossing over to strategy 2	Combination of metronidazole & 6MP	Adult CD with symptomatic perianal fistulae	Markov Model Cost-Utility	1 year	Third party payer	Among CD Patients: 1) First line IFX with 6MP/metronidazole for treatment failures: $355,450/QALY 2) First line IFX with episodic reinfusion: $360,900/QALY 3) First-line 6MP/metronidazole and second line IFX with episodic reinfusion: $377,000/QALY
(Blackhouse et al., 2012)	Initiation & Maintenance	1) IFX induction and maintenance (weeks 0, 2 and 6 and every 8 weeks thereafter) 2) ADA induction and maintenance	UC (corticosteroids & immunosuppressants)	Adult CD refractory to conventional non-anti TNF therapy with CDAI >= 200	Markov Model Cost-Utility	5 years	Publicly funded health care system	ADA vs. UC: $193, 305/QALY IFX vs. ADA: $451,165/QALY IFX vs. UC: $222,955
(Bodger, Kikuchi, & Hughes, 2009)	Initiation & Maintenance	1) IFX at weeks 0, 2, 6 then 8 weekly for maintenance of remission 2) ADA induction and maintenance	UC Medical management Surgery	Severely active CD	Markov Model Cost-Utility	Lifetime (60 years)	UK National Health Service	IFX 1) 1 year - £19,050/QALY 2) 2 years - £21,300/QALY ADA 1) 1 year- £7,190 2) 2 years - £10,310
(Assasi et al., 2009)	Initiation & Maintenance	IFX induction weeks 0, 2 and 6 and maintenance every 8 weeks ADA induction and maintenance therapy	UC (corticosteroids & immunosuppressants)	Refractory CD	Markov Model Cost-Utility	5 years	Publicly funded health care system	IFX ICUR vs. UC: $193,305 ADA ICUR vs. UC: $222, 955
(Jaisson-Hot et al., 2004)	Initiation & Maintenance	IFX 1) one infusion with retreatment when patients relapse or do not respond 2) maintenance infusions every 8 weeks	Surgery	CD resistant to conventional therapy	Markov Model Cost-Utility	Lifetime	Third party payer	Option 1) £63,701 vs. strategy 2 Option 2) £ 784,057.49 vs. strategy 2
(Lindsay et al., 2008)	Maintenance	IFX maintenance	UC	Adult CD patients with luminal active OR fistulizing	Markov Model Cost-Utility	5 years	NHS - UK	Luminal: 26,128 pounds/QALY Fistulizing: 29,752 pounds/QALY

(J. Marshall et al., March 2002)	Initiation, Episodic & Maintenance	Strategy B: Single dose IFX week 0. Relapse patients receive usual care. Strategy C: IFX dose week 0. Relapse patients are retreated with a single infusion of IFX. Strategy D: IFX at week 0. Patients who respond receive maintenance infusions of every 8 weeks. Patients who do not respond or subsequently relapse on maintenance receive usual care	UC	CD resistant to conventional therapy	Markov Model Cost-Utility	1 year	Canadian provincial ministry of health	Incremental cost utility ratios: Strategy B vs. A: $181,201 Strategy C vs. B: $480,111 Strategy D vs. C: $696,078
(Saito et al., 2013)	Initiation & Maintenance	IFX plus AZA oral AZA capsules 2.5mg/kg daily in addition to equivalent IFX therapy	IFX monotherapy at weeks 0, 2, 6 and every 8 weeks thereafter	Refractory Crohn's Disease	Decision Tree Cost-utility	1 year	UK National Health Service	24,917 GBP/QALY Lower than the 30,000 GBP/QALY limit
(Tang et al., 2012)	Initiation & Maintenance	IFX	ADA CPG NAT	Patients with moderate to severe CD who are treatment naïve to biologics	Decision Tree Cost-utility	1 year	US Payer Perspective	IFX was most cost-effective in 95.2% of scenarios when comparisons were made among IFX, ADA, CPG and NAT

CD – Crohn's disease, IFX – infliximab, ADA – adalimumab, CPG – certolizumab pegol, NAT- natalizumab, QALY- quality adjusted life year, UC – usual care, AZA - azathioprine

Table 9 - Economic Evidence of Biosimilar Infliximab

First Author (Year)	Title	Indication	County	Perspective	Intervention & Comparators	Time Horizon	Main Assumptions	Results	Sensitivity Analyses (Main Drivers)
Budget Impact Analyses									
(Brodszky et al., 2016)	A budget impact model for biosimilar infliximab in Crohn's disease in Bulgaria, the Czech Republic, Hungary, Poland, Romania, and Slovakia	CD	Bulgaria Czech Republic Hungary Poland Romania Slovakia	Third party payer	Biosimilar IFX Reference IFX ADA	3 years	• Prevalence based model with real patient numbers treated with biologics as initial population • 75% discount • 75% of patients eligible for reference and 25% of patients eligible for ADA • 0-80% range of switching	• Scenario 1 with no switching • Total savings: € 8 million • Scenario 2 with switching • Total savings: € 16.9 million	• Drug acquisition • Costs of biosimilar IFX • Size of the initial population
(Brodszky et al., 2014)	Budget impact analysis of biosimilar infliximab (CT-P13) for the treatment of rheumatoid arthritis in six Central and Eastern European countries	RA	Bulgaria Czech Republic Hungary Poland Romania Slovakia	Third party payer	Biosimilar IFX Reference IFX	3 years	• Scenario 1 no switching • Scenario 2: switching 6 months after treatment start in 80% of patients • 75% discount from list price • 65% of eligible patients for reference IFX receive the biosimilar and 25% of non-IFX patients	• Scenario 1 total savings: € 15 million • Scenario 2 total savings: € 20.8 million	• The number of the initial population treated with biologics • The acquisition cost of the biosimilar
(Severs et al., 2017)	The Economic Impact of the Introduction of Biosimilars in Inflammatory Bowel Disease	IBD	Netherlands	Third party payer	Biosimilar IFX Reference IFX ADA	5 years	• Prevalence based model • ADA used in 20% of patients, IFX in 80% (80% of those on biosimilar) • Gradual exponential decreases in prices of all drugs • Switching dependent on % price reduction	• CD: € 9,850 in savings/patient • UC: € 2,250 in savings/patient • Total savings: € 493 million	• Price reduction of anti-TNF therapy • Threshold price reduction at which physician's switch patients • Extent of switching
(Jha et al., 2015)	The Budget Impact of Biosimilar Infliximab (Remsima) for the	RA, CD, UC, PSO, PSA	Germany UK Italy	Third party payer	Biosimilar IFX Reference IFX	1 year	• Uptake of biosimilar was assumed to be 25% in	• Cumulative drug cost savings were projected to range from € 25.79	• The percentage of patients treated with Remicade®

	Treatment of Autoimmune Diseases in Five European Countries		Netherlands Belgium				switch population and 50% in naïve • Prevalence based • Price discount of 10-30% range	million to € 77.37 million	(i.e. total number of patients in the model)
(J. Kim et al., 2014)	5 Year Budget Impact Analysis of Biosimilar Infliximab for the Treatment of Rheumatoid Arthritis in UK, Italy, France and Germany [abstract]	RA	UK Italy France Germany	Third party payer	Biosimilar IFX Reference IFX	5 Years	• Eligible patients based on total population, growth rate and prevalence • Varied price discounts • Varied market uptake growths	• Total budget savings ranged from € 96 million to € 433 million	• N/A
(McCarthy G et al., 2013)	Introduction of an infliximab biosimilar (CT-P13): a five-year budget impact analysis for the treatment of rheumatoid arthritis in Ireland [abstract]	RA	Ireland	Third party payer	Biosimilar IFX Reference IFX	5 Years	• Eligible patients based on total population, prevalence and incidence, proportion eligible for a biologic, and proportion receiving a biologic	• Cost savings up to € 5,313,184 equivalent to treating an extra 337 new patients with a biosimilar for one year	• N/A
Cost-Effectiveness Analyses									
(Beilman et al., 2017)	Cost-Effectiveness of Infliximab's Biosimilar CT-P13 Compared to Innovator Infliximab for the Management of Crohn's Disease [abstract]	CD	Canada	Payer	Biosimilar IFX Reference IFX	5 years	• Compare the cost-effectiveness of IFX to its biosimilar for the management of CD • Markov model	• Reference IFX: 3.91 QALYs and costs $167,388 • Biosimilar IFX: 3.61 QALYs and costs $111,981 • At a WTP of 50,000 per QALY IFX biosimilar had a 91% chance of being cost-effective	• Details not provided
(Husereau et al., 2018)	Policy Options for Infliximab Biosimilars in Inflammatory Bowel Disease Given Emerging Evidence for Switching	CD	Canada	Third party payer	Biosimilar IFX Reference IFX	10 years	• Modelled a one-time switch to biosimilar infliximab using NOR-SWITCH data • Markov model	• Reference: $168,210 and 6.02 QALTs • Biosimilar Switch: $120,753 and 5.76 QALYs • ICER in the southwest quadrant $176,69	• Details not provided

RA – rheumatoid arthritis, CD – Crohn's Disease, UC – ulcerative colitis, PSO – psoriasis, PSA– psoriatic arthritis, IBD – inflammatory bowel disease, IFX – infliximab, ADA – adalimumab, CPG – certolizumab pegol, NAT- natalizumab, QALY- quality adjusted life year, AZA - azathioprine

1.7 Knowledge Gap & Research Question

Biologics are an important treatment option for many Canadian patients with serious diseases such as cancer or IBD, however they are complex molecules produced using living cells. This creates variability and therefore, requires different manufacturing, regulatory and evaluative practices compared with small molecule drugs. Due to these unique characteristics and their value to patients, biologics also tend to be high-cost drugs. Many studies have shown that Canadian expenditures on these products, both public and private, have grown dramatically over time which can create sustainability concerns for health care payers (Canadian Institute for Health Information, 2017; IMS Brogan, November, 2013).

High-cost biologics offer immense value in treating complex disease states such as CD; a fluctuating and chronic disease which greatly affects an individual's quality of life. Treatment with infliximab has been shown to induce and maintain remission, reduce symptom flares, and slow progression in some cases (Hanauer et al., 2002; Targan et al., 1997). The introduction of biosimilar infliximab to the Canadian market represents another treatment option for these patients at a lower cost than the reference biologic. A biosimilar is a drug demonstrated to be highly similar to a biologic that was previously authorized for sale (referred to as a reference biologic) and that tends to enter the market at a price discount from the reference (Health Canada, 2016b). However, biosimilars are not the same as generic drugs as they cannot be shown to be identical to the reference drug (Ridgway, March 2017). Biosimilars offer a unique opportunity to derive cost-savings for the healthcare system, but have raised a number of questions amongst all stakeholders including patients, physicians, and policy makers.

Biosimilars are complex for a number of reasons which has led to these issues for stakeholders. Their clinical development is more complicated than that of a small molecule drug and there may be variability between the biosimilar and the reference product whereas a small molecule drug will be an identical copy (European Medicines Agency & European Commission, 2017). The pivotal trials and observational clinical evidence suggest that there are no clinically meaningful differences between the reference and biosimilar infliximab, however, stakeholders have maintained concerns regarding their use, particularly as it relates to effectiveness and have identified a need for further evidence (Canadian Arthritis Patient Alliance, Canadian Psoriasis Network, Crohn's and Colitis Canada, Gastrointestinal Society, & The Arthritis Society, March,

2017; CARE, January 13, 2017; Community Academic Research Education (CARE), 2017; Institute of Health Economics, October 6, 2016).

From the economic perspective specifically, the evidence base for the cost-effectiveness of biosimilar infliximab is limited. Budget impact analyses have suggested that cost-savings with biosimilar infliximab may be substantial depending on a number of factors including uptake or switching, however, this does not speak to the incremental cost-effectiveness of biosimilar infliximab and assumes there is no effectiveness difference (Canadian Agency for Drugs and Technologies in Health, January 18, 2017). CADTH emphasized this in their rapid response report particularly for switch patient populations and identified that existing evidence does not adequately address concerns regarding switching from reference infliximab to biosimilar in terms of the economic impact (Canadian Agency for Drugs and Technologies in Health, January 18, 2017) . This review was prior to the release of the cost-effectiveness analysis comparing reference to biosimilar infliximab in patients with CD conducted by Husereau et al. (2018), however the development of further evidence is still warranted.

The Institute of Health Economics from Alberta, Canada, has expressed a similar need for further evidence in their report summarizing next steps to address reimbursement of biosimilars in Canada (Institute of Health Economics, October 6, 2016). One primary step was to: “identify the clinical efficacy, safety, and economic questions we wish to answer over time that will demonstrate where biosimilars can play a useful role, and where they should be avoided” (Institute of Health Economics, October 6, 2016).

One salient question that will be important for policy makers to consider is the cost-effectiveness of switching, whereby a patient that is currently maintained on the reference biologic is switched to treatment with the biosimilar with the same dosing (Jørgensen et al., 2017). This clinical question was in part addressed for infliximab and its indications with regard to effectiveness in the adult population by the NOR-SWTICH trial (Jørgensen et al., 2017). The objective of this thesis research will be to utilize the NOR-SWITCH trial and published findings to inform an economic evaluation and address the knowledge gap identified by both the Institute of Health Economics and CADTH surrounding the economic value of switching from the reference infliximab to the biosimilar in the CD population in Canada.

1.7.1 Research Question

The objective of this thesis research is therefore to assess the incremental cost of maintenance treatment for patients with CD who have been switched from reference infliximab to biosimilar infliximab compared with those who have been continued on reference infliximab per QALY gained from the healthcare system (public & private payer) perspective.

Chapter 2 Methods

The following chapter will detail the methodology for a cost-utility analysis of biosimilar infliximab in the adult CD population from the Canadian healthcare system perspective. A brief summary of the model structure and key parameters can be found in Table 10.

Table 10 - Model Overview

Overview of Model	
Decision Problem	Assess the incremental cost of maintenance therapy for adult patients with Crohn's disease who were switched from reference infliximab to biosimilar infliximab with those who were maintained on reference infliximab per QALY gained
Type of Evaluation	Cost-Utility Analysis
Target Population	Adult patients with moderate-to-severe Crohn's Disease (CDAI 220 – 400) Currently maintained on reference infliximab for > 6 months and concomitant therapy is allowed (immunosuppressives or prednisone)
Comparators	Intervention: Biosimilar Infliximab Comparator: Reference Infliximab
Perspective	Canadian Healthcare System (Public & Private) & Societal
Time Horizon	5 years
Discounting	1.5%
Model Structure	Markov Model
Effectiveness	Primary Effectiveness Study: NOR-SWITCH (Jørgensen et al., 2017) Additional literature including: (Blackhouse et al., 2012) (J. F. Colombel et al., 2007) (Silverstein et al., 1999) (Feagan et al., 2008) (Singh et al., 2015) (Onali et al., 2016) (Bitton, Vutcovici, Sewitch, Suissa, & Brassard, 2016) (Statistics Canada, 2017) (Sandborn et al., 2007)
Measurement and Valuation of Health	Clinical Outcome Measured As: Quality Adjusted Life Years Health State Utilities (Greenberg et al., 2015)
Resource Use and Costs	Drug Costs Surgical Costs Physician Visits
Analysis	Outcome of the model: Incremental Costs, Incremental Effects and Incremental Cost-Effectiveness Ratio (ICER) where appropriate Probabilistic (10,000 Monte Carlo Simulations)
Uncertainty	Assessed with: One-Way Probabilistic Analyses Structural Analyses Cost-Effectiveness Acceptability Curves

2.1 Decision Problem

The objective of this economic evaluation was to assess the incremental cost of maintenance doses for adult patients with moderate-to-severe CD who have been switched from reference infliximab to biosimilar infliximab with those who continued reference infliximab per incremental QALY gained from the healthcare system perspective over a five-year time horizon. The target audience is Canadian healthcare decision makers, in order to provide essential information on the question of the cost-effectiveness of switching within this population.

2.2 Type of Evaluation

In considering the advantages of this type of analysis, and in keeping with the CADTH guidelines, the economic evaluation of biosimilar infliximab was conducted as a CUA. Therefore, the effectiveness outcome for both the intervention and the comparator was measured in QALYs and the ultimate point estimate of the analysis was the incremental cost associated with one additional QALY gained summarized as an ICER (where appropriate).

2.3 Perspective & Population of Interest

This analysis adopted the healthcare system perspective and costs were those incurred by the provincial health care system and private payers. The societal perspective was also examined. When this broader perspective is taken the impact of the intervention on time lost by patients is also accounted for (CADTH, March, 2017).

The analysis was conducted in adult patients with moderate-to-severe CD. The Health Canada indication for Remicade® (reference infliximab) and Inflectra® (biosimilar infliximab) in CD is: "Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing and reduction of corticosteroid use in adult patients with moderately-to-severely active Crohn's disease who have had an inadequate response to a corticosteroid and/or aminosalicylate. Infliximab can be used alone or in combination with conventional therapy" (Celltrion Healthcare Co Ltd, 2016; Janssen Inc., April 26, 2016).

Moderate-to-severe Crohn's disease is defined by the CAG as a patient with Crohn's Disease and a CDAI score of between 220 and 400 points (Daniel C. Sadowski et al., 2009). It is assumed the reference patient is 38 years old with a previous diagnosis of moderate-to-severe CD (CDAI: 220 – 400 points) and weighs 75 kg (Blackhouse et al., 2012; Jørgensen et al., 2017). Patient weight

was determined based on a subgroup analysis of the Manitoba IBD Cohort, which is the largest population based registry of IBD in North America (Leslie, Miller, Rogala, & Bernstein, 2009). In a study of body mass and composition it was found that the mean patient weight of the CD subgroup was 75.6 kg (Leslie et al., 2009). It is also assumed that the reference patient does not have any major co-morbidities and has not had a functional colostomy, ileostomy or extensive colonic resection with less than 25 cm of the colon left in situ (Jørgensen et al., 2017).

With regards to treatment, it is assumed that the patient has been maintained on stable treatment with reference infliximab for a minimum of six months for the treatment of moderate-to-severe CD and may also be taking concomitant immunosuppressives or prednisone (Jørgensen et al., 2017). In accordance with the characteristics of the patient population of NOR-SWITCH, the breakdown of concomitant therapy is assumed to be as follows:

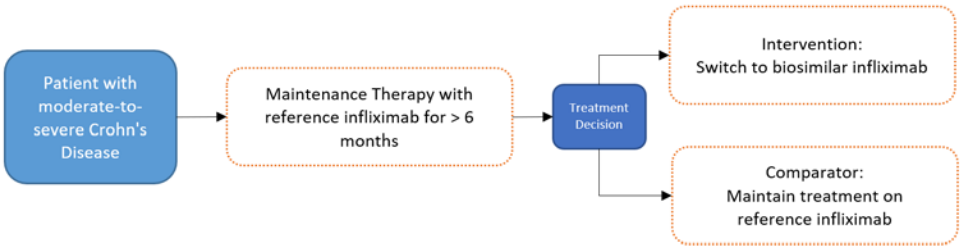
- Patients maintained on reference infliximab: 3% on prednisone and 38% on concomitant immunosuppressives;
- Patients switched to biosimilar infliximab: 0% on prednisone and 47% on concomitant immunosuppressives (Jørgensen et al., 2017).

These proportions are comparable to those employed in Blackhouse et al. which was based on Canadian expert opinion (0.4 on immunosuppressives and 0.04-0.07 on steroid therapies) (Blackhouse et al., 2012). It is assumed that concomitant immunosuppressive therapy will include azathioprine, 6-mercaptopurine and methotrexate with a 50:20:30 proportional split according to expert opinion. Finally, it is also assumed that a patient who is taking concomitant immunosuppressives or steroids is compliant with their dosage regimens as required.

2.4 Intervention & Comparator

The intervention of interest is biosimilar infliximab, also known by the brand name Inflectra®. This pharmaceutical was approved for an adult CD indication and is a biosimilar of the reference biologic Remicade® for the same indication. This model evaluated an intervention of a one-time switch from the reference to the biosimilar infliximab with identical dosing and administration. Therefore, the comparator of interest is continued maintenance treatment on the reference biologic which will also be referred to as the “reference infliximab” group (Figure 3).

Figure 3 - Intervention (Biosimilar Infliximab) and Comparator (Reference infliximab)



2.4.1 Dosing of Infliximab

It is assumed that the population of interest has been on stable treatment with reference infliximab for at least six months. Therefore, it is assumed that the patient successfully completed the induction regimen and is receiving standard maintenance therapy on the reference drug, both of which are described in Table 11.

Table 11 - Initiation & Maintenance Dosing of Infliximab

Initiation	Maintenance
5mg/kg given as an induction regimen at: • Week 0 • Week 2 • Week 6	5mg/kg every 8 weeks thereafter for a maintenance regimen For example, in the first-year post initiation treatment: • Week 14 • Week 22 • Week 30 • Week 38 • Week 46 • Week 54

Sources: (Celltrion Healthcare Co Ltd, 2016; Janssen Inc., April 26, 2016; Jørgensen et al., 2017)

Both the biosimilar and reference infliximab are available as a 100 mg vial injection (Celltrion Healthcare Co Ltd, 2016; Janssen Inc., April 26, 2016). Therefore, there are cases where a patient requires a fraction of a vial to meet their required dose. To account for this, it is assumed that there is vial wastage, meaning that the usage is rounded up to the next whole vial. For example, a patient that required 375 mg would require 3.75 vials and it is assumed they utilize 4 vials of infliximab. The reference case dosing for the biosimilar and the reference infliximab was as follows:

Table 12 - Dosage

	Maintenance Dose	Patient Weight	mg per Maintenance Dose	Vials Needed	Rounded up to nearest vial (assumes wastage)
Reference Infliximab	5mg/kg	75 kg	375	3.75	4
Biosimilar Infliximab	5mg/kg	75 kg	375	3.75	4

Furthermore, it is assumed that the patient is compliant with this dosing regimen and is infused with the appropriate amount of infliximab at the correct time.

2.5 Outcomes

Effectiveness outcomes were measured with quality-adjusted life years. Since the model incorporated mortality, life years were measured by accounting for any time spent in a health state that is not the absorbing death state. Utilities were assigned based on patient health state; therefore, effectiveness was ultimately measured by accounting for the time a patient spends in each health state for the extent of the time horizon. Therefore, a strategy is more effective if a patient is maintained in a health state with a higher utility.

2.6 Model Framework

The model was built utilizing a health-state transition (Markov) framework. A Markov model is of particular use for clinical problems with ongoing risk. This includes chronic diseases such as CD where there is a risk that a patient will transition between a number of health states over the course of the time horizon of the analysis and transition back and forth between states (Blackhouse et al., 2012; Sonnenberg & Beck, 1993). The time horizon of the analysis was divided into Markov cycles; equal increments of time over which a patient may experience transitional costs/disutilities and transition from one state to another (Sonnenberg & Beck, 1993). It was assumed that a patient is always in one of the defined health states and each state was assigned a utility and associated cost (Sonnenberg & Beck, 1993). For the Markov process to end there must be an absorbing state in the model, meaning that once a patient entered the state they could not transition out, and in many health economic models this state is death. Evaluating the Markov process yielded the average amount of time spent in each health state, and through applying an appropriate cost and utility to each state an average cost and benefit of an intervention over the established time period was derived (Sonnenberg & Beck, 1993). This

process was repeated for both the intervention and the comparator included in the model so that the costs and outcomes could be compared.

It is important to acknowledge the primary restriction of a Markov analysis; it is memoryless. The Markov property "specifies that the behavior of the process subsequent to any cycle depends only on its description in that cycle" (Sonnenberg & Beck, 1993). Therefore, the transition probabilities in a given state did not depend on how much time a patient may have spent in an earlier state (Sonnenberg & Beck, 1993). This may be an issue in CD as patients' treatment options may vary depending on how long they are in a given health state therefore, this limitation was accounted for in the model design.

2.6.1 Time Horizon, Cycle Length & Discounting

The Markov model was used to simulate disease progression and to assess costs and effects associated with infliximab treatment over a 5-year time horizon. For an economic evaluation the selected time horizon should be the period over which the costs and/or effects of the options being compared might be expected to differ in order to capture any relevant differences (Drummond et al., 2015). Given the available data, a 5-year time horizon was utilized to most accurately assess the decision problem.

Given that CD is a chronic disease where costs and effect implications are experienced over the entire lifetime of the patient, a longer time horizon (10 years) was also tested in a sensitivity analysis. While a longer time horizon will capture these differences it also necessitates numerous long-term assumptions due to uncertainty, therefore for the purposes of the reference case a 5-year time horizon was applied.

Within a state transition model one must also determine the cycle length, which is an important feature of the model's structure as it determines when the transitions will occur (Sculpher, Fenwick, & Claxton, 2000). The choice of cycle length for a Markov model should be dictated by the underlying disease state and capture the minimum interval over which the patient may transition between states (Sculpher et al., 2000).In keeping with the maintenance dose schedule of infliximab, which requires an infusion every 8 weeks, the cycles for the Markov analysis was 8 weeks in length (Celltrion Healthcare Co Ltd, 2016; Janssen Inc., April 26, 2016). A half-cycle correction was also applied to account for the fact that transitions occur throughout the cycle in

reality, not only at the beginning of a time period (Sonnenberg & Beck, 1993). Assuming that state transitions occur on average half-way through each cycle balances any overestimations that may occur if state membership was only counted at the beginning of a cycle and more accurately reflects continuous transitions (Sonnenberg & Beck, 1993).

Finally, future costs and benefits after one year were discounted to a present value at a rate of 1.5% in keeping with current CADTH guidelines (CADTH, March, 2017).

2.6.2 Model Design, Structure & Key Assumptions

The structure of the model is summarized in a simplified diagram in Figure 4. It is assumed that the patient enters the model and the treatment decision either requires the patient to continue maintenance therapy with reference infliximab or switch to treatment with biosimilar infliximab with identical dosing and administration, as previously summarized in Figure 3.

Patients then enter the Markov model and were distributed into one of two states: clinical remission or clinical response. These states are defined as follows:

- Clinical Remission: Patient maintains a Harvey-Bradshaw Index (HBI) ≤ 4 points or CDAI of ≤ 150 and is being maintained on stable treatment with infliximab. (See Section 1.4.1 for a description of CDAI & HBI)

- Clinical Response: Patient demonstrates a response to treatment defined by a reduction in HBI (of at least four points) or CDAI (of at least 70 points) since initiating treatment but have not achieved clinical remission as defined above. They are maintained on stable treatment with infliximab.

It is assumed that since the patient has been maintained on stable treatment with infliximab for a minimum of six months they will not be in a drug refractory state in the initial cycle after the treatment decision. From the remission or response state it is assumed that a patient can either stay in this state or they can relapse. Relapsing is defined as disease worsening where a patient experiences an increase in HBI of 4 points or more and a score of 7 or greater points (Jørgensen et al., 2017). Therefore, it is assumed if a patient relapses in either the clinical remission or response state they will enter a drug refractory state in the next cycle. A patient in a drug

refractory state has persistent acute symptomatic disease despite anti-inflammatory therapy and has an HBI ≥ 7 or a CDAI ≥ 220 (Jørgensen et al., 2017; D. C. Sadowski et al., 2009).

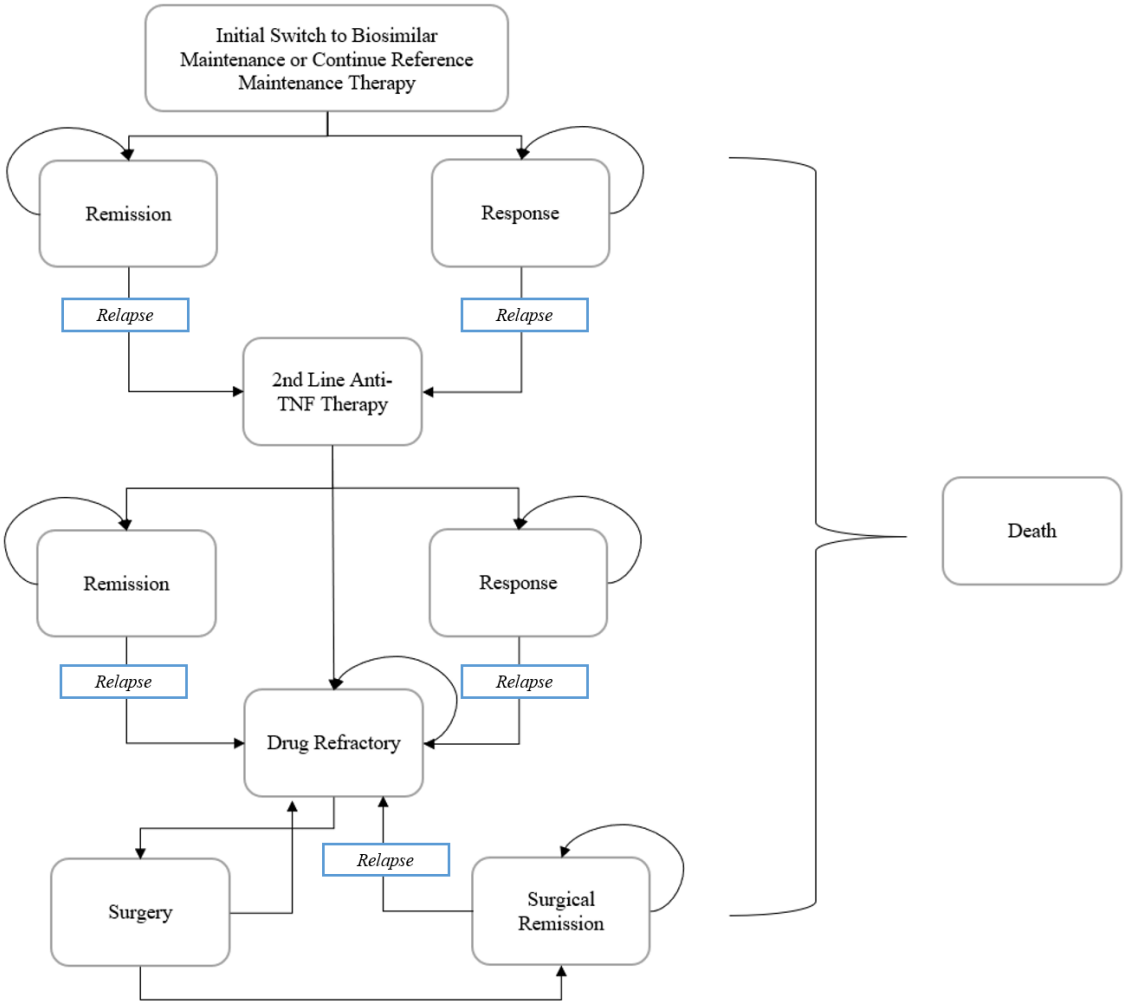
The CAG practice guidelines stipulate that CD patients with diminished response or who become intolerant to a particular anti-TNF treatment may be switched to a different TNF antagonist to maintain response (D. C. Sadowski et al., 2009). Therefore, it is assumed that in the event that a patient relapsed while maintaining remission or response on infliximab treatment they were switched to a 2nd line anti-TNF therapy (Blackhouse et al., 2012; D. C. Sadowski et al., 2009). It is further assumed that 2nd line treatment is adalimumab per the Canadian guidelines and available treatments. If the patient responded to adalimumab initiation therapy, then they either entered a remission or response state (similarly defined as above except the patient received maintenance therapy with adalimumab). Alternatively, if a patient failed on adalimumab, either during the initial induction phase or on maintenance therapy, then they entered a drug refractory state. In the initiation phase of treatment with adalimumab, failure implies that a patient did not achieve a decrease in CDAI score of 100 or more points (Sandborn et al., 2007), whereas on maintenance therapy it is assumed a patient relapsed if they did not maintain clinical remission (CDAI < 150) or response (J. F. Colombel et al., 2007). Finally, it is also assumed that a patient on an initiation or maintenance cycle with adalimumab was adherent with the dosing regimen.

A portion of the patients in the drug refractory state received a surgical intervention to treat their active disease and therefore, entered the surgical state. If the surgery was successful, the patient transitioned to a surgical remission state. However, if it was unsuccessful or if a patient in surgical remission relapsed it is assumed that the patient re-entered a drug refractory state for the remainder of the time horizon of the model and could not receive a second surgery.

Finally, a patient could enter the absorbing death state from any health state in the Markov model over the course of the time horizon.

Patients were also subject to infusion-related adverse events during the infliximab treatment phase of the model. Therefore, a proportion of patients in the infliximab clinical remission or clinical response states experienced a transitional adverse event.

Figure 4 - Model Structure



2.6.3 Model Inputs

Since the analysis is probabilistic in nature it required a probability distribution be assigned to each input parameter for which there is uncertainty, this included transition probabilities, costs and utilities. These distributions were determined based on the mean values and standard deviations where available in the literature source. Beta distributions were applied to both utilities and transition probabilities as they are bound by 0 and 1. However, since cost inputs tend to be skewed right a gamma distribution was applied in most cases.

2.6.4 Probabilities

The clinical inputs of the model were primarily informed by the NOR-SWITCH study, particularly the CD cohort in the per protocol set of the analysis (see Section 1.5.2.3) (Jørgensen et al., 2017). The NOR-SWITCH trial showed that 41 patients in the reference group and 43 in the biosimilar group were in clinical remission as defined by HBI ($\leq$ 4 points) at the baseline of the trial (Jørgensen et al., 2017). It is assumed that all patients must be in clinical remission or response in the first cycle subsequent to the switch. Therefore, this analysis employed the proportion of patients in remission from NOR-SWITCH as the initial distribution of patients in the clinical remission health state. It is further assumed that any patients not in remission were in a clinical response state in the first cycle of the model.

The rate of disease worsening, defined as a consensus between investigator and patient leading to major change in treatment or a change from baseline in HBI of 4 points or more and a score of 7 points or greater, was applied as a probability of relapse to patients in the clinical remission and response states (Jørgensen et al., 2017). HBI has been shown to correlate with the CDAI and a 3-point change in change in the HBI corresponds to a 100-point change in the CDAI (Regueiro & Al Hashash 2018; Vermeire et al., 2010).

These probabilities, and all other clinical inputs where applicable, were converted into a rate, multiplied by a constant hazard and converted back into a probability for the cycle (Briggs, Claxton, & Sculpher, 2006). This was conducted to account for the fact that the probability derived from the literature may be derived from an annual period for example. As this model has 8-week cycles, probability parameters needed to be appropriately adjusted for the cycle length.

Once a patient relapsed it was assumed they received 2nd line anti-TNF therapy with adalimumab. The transition probabilities for this portion of the model were based on the methodology described in Blackhouse et al. (2012) and the clinical trials referenced for initiation and maintenance therapy.

The initial response and remission rates for 2nd line adalimumab therapy were derived from the GAIN trial [Gauging Adalimumab Efficacy in Infliximab non-responders] (Blackhouse et al., 2012; Sandborn et al., 2007). The results of the GAIN study informed the patient distribution between clinical remission, response and drug refractory states related to 2nd line treatment with

adalimumab after failure on treatment with infliximab (Sandborn et al., 2007). It was assumed that the results of the four-week GAIN study will be applicable to the eight-week cycle length.

For patients who are in remission or response following the initiation therapy with adalimumab there was a risk of relapse which was informed by the results of the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) trial (J. F. Colombel et al., 2007). The rate of relapse was derived by assuming that any patient who did not remain a responder or in remission after 52 weeks of maintenance therapy had relapsed.

The probability that a patient received a surgical intervention after entering the drug refractory state was derived from the CHARM trial as well, specifically a study on the effects of adalimumab therapy on incidence of surgery (Feagan et al., 2008). The one-year rate of surgery reported by Feagan et al. for the placebo branch was 0.038 (Feagan et al., 2008). The probability of achieving surgical remission was derived from a Markov cohort model in CD (Silverstein et al., 1999). That study defined disease states by medical and surgical treatment and determined the maximum likelihood estimate of 2-month probabilities of transition between disease states (Silverstein et al., 1999). The maximum likelihood of transition from surgery to post surgery remission (0.52022) was employed as the probability of achieving surgical remission. (Silverstein et al., 1999).

Finally, the results of a prospective study of post-operative recurrence of CD at 5 years was used to derive a relapse rate from surgical remission to the drug refractory state (Onali et al., 2016). Within 5 years 40% of patients had relapsed after surgery and the annual rates of relapse are described in Table 29.

For all states other than surgery, the probability of death was determined using annual probabilities of death from the Statistics Canada Life Table from the years 2012-2014 as well as a standardized mortality ratio (SMR) for CD. The SMR of 1.45 derived from a Quebec study of CD mortality, was applied to the annual probabilities of death from Statistics Canada to account for the higher all-cause mortality associated with CD (Bitton et al., 2016). In comparison, mortality in the surgical state was derived from a meta-analysis of population-based studies of postoperative mortality among patients with IBD, which was 0.6% (95% CI: 0.2% to 1.7%) for elective procedures for patients with CD (Singh et al., 2015).

The probability of an adverse event occurring in the infliximab clinical remission or clinical response states was based on the NOR-SWITCH results for treatment emergent adverse events in the safety population (Jørgensen et al., 2017). The safety population consisted of eligible randomized patients who received at least one infusion of infliximab after randomization (Jørgensen et al., 2017). CD only data on adverse events was not available, however given that CD represented the majority of the safety patient population it is assumed that the adverse event rate was appropriate. Furthermore, this analysis only considered infusion related reactions as they are among the most frequently reported treatment emergent adverse events (Jørgensen et al., 2017).

Specific infusion-related reactions and their corresponding rates were not reported by the trial. Therefore, reaction rates were informed by a costing study conducted on infusion therapy for rheumatoid arthritis in a hospital-based infusion center setting in the United States (Schmier et al., 2017). It was assumed that the rates and types of infusion reactions for infliximab will be comparable to the CD population of this model and that a patient could only experience one reaction per infusion. Therefore, the rates applied from the NOR-SWITCH will be broken down as follows.

Table 13 - Infusion Related Reactions

Grade	Reaction	Rate
Grade 1	Dizziness	7%
	Flushing	9%
	Headache	12%
	Skin Reactions	9%
Grade 2	Dyspnea	9%
	Hypertension	14%
	Hypotension	14%
	Nausea	12%
	Urticaria	14%

For a summary of all probability inputs for the model see Table 29.

2.6.5 Utilities and Quality of Life Inputs

Health-related quality of life represents the effect of an illness and its treatment upon a patient, as perceived by the patient (van der Have et al., 2014). A utility is a numeric weight that reflects a patient's preference for a health state in terms of quality of life (CADTH, March, 2017). Utilities are generally measured on a scale of 0 to 1 where 0 indicates death and a utility of 1 represents

perfect health, therefore the higher the utility the more preferable the state and the higher the quality of life (CADTH, March, 2017) Utilities allow analysts to quantify the quality of life of a given state and compare between alternatives (Gregor et al., 1997).

The utilities from a study by Greenberg et al. (2015) were employed in this model, this study was conducted in an adult population (age 18 years or older) with a confirmed CD diagnosis. While it was conducted in an Israeli population it was assumed this would be comparable to a Canadian population, and it was completed more recently than the Gregor et al study (Greenberg et al., 2015; Gregor et al., 1997). However, given that the Gregor et al study was conducted specifically in Canadian populations these values were also tested in a sensitivity analysis (Gregor et al., 1997; J. Marshall et al., March 2002). The utilities that were applied to the Markov health states in the reference case are shown in Table 14.

Table 14 - Model Utility Inputs

Markov Health State	Utility Value (Standard Deviation)
Remission (IFX, 2nd Line & Surgical)	0.75 (+/- 0.12)
Response (IFX & 2nd Line)	0.63 (+/- 0.10)
2nd Line Anti-TNF, Drug Refractory & Surgery	0.51 (+/- 0.12)

IFX – maintenance therapy with infliximab (reference or biosimilar)

It was assumed that remission utilities are equivalent regardless of treatment with infliximab, 2nd line anti-TNF (adalimumab) or surgery. A similar assumption was employed for those with response to therapy in either the infliximab or 2nd line anti-TNF states. It is further assumed that those in a clinical response state will have mild disease and therefore, 0.63, the utility for mild disease, was applied to patients in a clinical response state. Similar to the methods applied in Blackhouse et al. (2012), it is assumed that those in a surgical or drug refractory state are currently experiencing severe CD and a utility of 0.51 was employed for those patients.

Finally, as informed by the results of the NOR-SWITCH and observational studies, it was assumed that there was no difference in utilities between the reference and biosimilar (Jørgensen et al., 2017). Therefore, differences in QALYs were driven by state distribution differences between the biosimilar and reference.

2.6.6 Resource Use & Costs

Resource use and costs in the model were determined based on the given strategy and health state of the model. Costs in the model were considered from the public and private payer perspective and as such included costs related to maintenance infliximab treatment, concomitant immunosuppressive and steroid therapy, 2nd line anti-TNF-α therapy (adalimumab), physician services and surgery.

In Ontario, the unit cost for reference infliximab was $987.56 per 100mg/10ml vial based on the price listed in the Ontario Exceptional Access Program Formulary (Ontario Ministry of Health and Long Term Care, 2018b). The unit cost for biosimilar infliximab was based on the Ontario Drug Benefit Formulary at a price of $525.00 per 100mg/10ml vial (Ontario Ministry of Health and Long Term Care, 2018c). The cost of adalimumab was $769.97 per 40mg/0.8ml vial per the Ontario Drug Benefit Formulary and costs were calculated based on the dosage regimen detailed in the product monograph (AbbVie Corporation, March 26, 2018; Ontario Ministry of Health and Long Term Care, 2018c).

Normal distributions for biologic costs were established based on real world Canadian prices. Therefore, an average price for reference infliximab was established based on Canadian formularies which included a publicly available price. A standard deviation was then derived based on these prices. A similar methodology was employed to establish a mean value and distribution for adalimumab prices. The distribution for biosimilar infliximab was derived based on the Ontario price as the mean value and the same standard deviation as reference infliximab was applied. A summary of these Canadian prices, the calculated means and standard deviations can be found in Appendix II – Drug Price Distributions. The costs and dosage regimes for the anti-TNF-α therapies can be found in Table 15.

Table 15 - Biologic & Biosimilar Drug Costs

Biologic Costs Sources: Canadian Public Drug Plan Formularies, Product Monographs for dosing						
Drug	**Price (SD)**	**Dose**	**Total mg per cycle**	**Vials per Cycle**	**Total Vials Per Cycle ***	**Total Cost Per Cycle**
Infliximab Maintenance Cycle						
Reference Infliximab	$994.75 (44.94) per 100mg/10ml	5mg/kg Patient Weight: 75kg	375 mg	3.75	4	$3,979.00
Biosimilar Infliximab	$525.00 (44.94) per 100mg/vial	5mg/kg Patient Weight: 75kg	375 mg	3.75	4	$2,100.00
Adalimumab Initiation Cycle						
Adalimumab	$916.86 (334.06) per 40mg/0.8ml	Week 0: 160 mg Week 2: 80mg Week 4, 6, 8: 40mg	360mg	Week 0: 4 vials Week 2: 2 vials Week 4, 6, 8: 1 vial	9	$8,251.74
Adalimumab Maintenance Cycle						
Adalimumab	$916.86 (334.06) per 40mg/0.8ml	Week 2, 4, 6, 8 of Cycle: 40mg	160mg	Week 2, 4, 6, 8: 1 vial	4	$3,667.44

** assuming wastage*

The dispensing fee in Ontario is $8.83 and there is a maximum of two dispensing fees per medication per recipient per calendar month (Ontario Ministry of Health and Long Term Care, 2014, 2018a). Therefore, it is assumed one dispensing fee will be applied per cycle for both reference and biosimilar infliximab since it is only administered once in an eight-week cycle. However, it is assumed a maximum of four fees will be applied for the adalimumab initiation and maintenance cycles since this drug is administered between four to five times in an eight-week cycle.

Table 16 - Biologic Dispensing Fees

Drug	**Dispensing Fee**	**Number of Fees**	**Total Dispensing Fee per Cycle**
Reference Infliximab	$8.83	1	$8.83
Biosimilar Infliximab		1	$8.83
Adalimumab Initiation		4	$35.32
Adalimumab Maintenance		4	$35.32

Adalimumab is a subcutaneous injection typically given at home (AbbVie Corporation, March 26, 2018). Infliximab by comparison is usually provided to patients through intravenous

administration in an infusion clinic setting therefore, this analysis also included administration costs (Benefits Canada, 2017). Infusions are delivered over two to three hours and require the supervision of a nurse (J. Marshall et al., March 2002). The infusion costs approximated in Marshall et al (2002) were employed and inflated to 2017 Canadian dollars using the Consumer Price Index for Health and Personal Care in Canada (Statistics Canada, 2018). However, for the gastroenterology partial assessment the updated Ontario cost for code A418 – Partial Assessment (Gastroenterology) was applied and an updated Nursing Supervision salary based on the Ontario Nurses Association full-time hourly rate was employed (Ontario Ministry of Health and Long Term Care, 2015; Ontario Nurses Association, April 1, 2016). These costs are summarized in Table 17.

Table 17 - Administration Costs

Item	Total Cost ($CAN 2017)
Nursing supervision (2.5 hours @ $35.16/hour)	$87.90
Gastroenterologist partial assessment	$38.05
250 mL saline bag	$1.27
Alaris IV infusion set	$4.13
Alaris IV secondary set	$2.10
0.22 micron filter	$2.82
Needle lock device	$0.85
20-inch extension tubing	$1.18
#22 1” In-Syte	$1.19
Tegaderm	$0.20
Alcohol swab	$0.01
Chlorhexidine swab	$0.06
2x2” gauze	$0.04
Total	**$139.80**

Drugs used in the drug refractory state or as concomitant therapy included prednisone, 6-mercaptorurine, methotrexate and azathioprine. The dosage regimen was based on expert opinion and on that employed by Blackhouse et al. (Blackhouse et al., 2012; Ontario Ministry of Health and Long Term Care, 2018c). Normal distributions for these prices were determined using a range of publicly available Canadian prices, see Appendix II – Drug Price Distributions. The mean prices and standard deviations are summarized in Table 18.

These costs also included an ODB dispensing fee of $8.83 (Ontario Ministry of Health and Long Term Care, 2014) . For all chronic immunosuppressive and steroid treatments it is assumed that a 100-day supply is dispensed at a time therefore, half of the dispensing fee is applied for each 8 week cycle (Ontario Public Drug Programs Ministry of Health and Long-Term Care, 2015).

Table 18 – Immunosuppressive & Steroid Treatment Cost

Concomitant Therapy Costs Sources: Publicly Available Canadian Formularies & Blackhouse et al. (2012) for Dosing					
Drug	**Price (SD)**	**Dispensing Fee for 100 day Supply**	**Dose**	**Daily Cost**	**Cost Per 8 Week Cycle**
Prednisone 5mg Tab	$0.0480 (0.0269) per tab	$8.83	20 mg per day 4 tabs	$0.19	$15.17
Azathioprine 50mg tab	$0.2140 (0.0836) per tab	$8.83	150 mg per day 3 tabs	$0.64	$40.37
6 Mercaptopurine 50mg Tab	$2.9378 (0.1202) per tab	$8.83	75 mg per day 1.5 tabs	$4.41	$251.19
Methotrexate 2.5 mg Tab	$0.6474 (0.0255) per tab	$8.83	25 mg per day 10 tabs	$6.47	$366.96

The costs for surgery were derived from the Ontario Case Costing Initiative (OCCI) for the 2015/16 year (Ontario Ministry of Health and Long Term Care, 2016). An age restriction of 18-69 was applied to account for the appropriate patient population and all costs were inflated to 2017 Canadian dollars using the Consumer Price Index for Health and Personal Care in Canada (Statistics Canada, 2018).

Firstly, costs were derived for the 18-69-year-old age group in all institutions with the following ICD-10 codes; K500 (Crohn's Disease of Small Intestine) and K501 (Crohn's Disease of Large Intestine). A summary of these costs inflated to 2017 Canadian dollars including the average for treating a given case, the standard deviation, minimum and maximum costs can be found in Table 19.

Table 19 - ICD-10 Codes for Crohn's Disease Costs (OCCI 2015/16)

Code	Name	Cases	Average	Standard Deviation	Min	Max
ICD-10 K500	CD of small intestine	336	$7,443.39	$8,208.81	$251.37	$79,297.54
ICD-10 K501	CD of large intestine	231	$8,814.64	$8,116.67	$777.74	$54,128.34

These costs were then subsequently broken down by Case Mix Group (CMG) in order to derive the costs for specific procedures in patients with a CD diagnosis according to the ICD-10 code.

It was assumed that an ileocolic surgical resection was conducted during the surgical state therefore, the two CMG that were utilized are CMG222 (Open Large Intestine/Rectum Resection without Colostomy, Unplanned) and CMG223 (Open Large Intestine/Rectum Resection without Colostomy, Planned). A weighted average of these codes (by number of cases) was derived for a cost for resection for patients with a CD diagnosis (K500 or K501) and in the age group of 18-69

in Ontario. A summary of the average cost, standard deviations, minimums and maximums, and length of stay are described below.

Table 20 - Average Surgical Cost Resection & Length of Stay

Code	Name	Cases	Average	Standard Deviation	Min	Max
222	Open Large Intestine/Rectum Resection without Colostomy, Unplanned	8	$16,986	$9,624	$8,858	$37,739
223	Open Large Intestine/Rectum Resection without Colostomy, Planned	26	$10,647	$4,531	$5,638	$24,978
Weighted Average			**$12,138**	**$5,729**	**$6,395**	**$27,981**

Table 21 - Average Surgical Length of Stay

Code	Name	Cases	Average	Standard Deviation	Min	Max
222	Open Large Intestine/Rectum Resection without Colostomy, Unplanned	8	12.0	6.0	5	24
223	Open Large Intestine/Rectum Resection without Colostomy, Planned	26	6.8	2.7	3	14
Weighted Average			**8.03**	**3.51**	**3.47**	**16.35**

This average resection cost was applied for any patient that entered the surgical state of the model.

Billing for this procedure was based upon expert opinion, the Ontario Schedule of Benefits and the methodologies described in the systematic review and cost-utility analysis of infliximab conducted by the Canadian Coordinating Office for Health Technology Assessment in 2002 (J. Marshall et al., March 2002; Ontario Ministry of Health and Long Term Care, 2015). The fees for the surgical procedure included code S166 – Resection with anastomosis, as well as the appropriate fees for anesthesia and assists per the Ontario Schedule of Benefits, see Table 22.

Table 22 - Surgical Procedure Fee

Code	Name	Amount	Anesthesia Units	Anesthesia Cost	Assist Units	Assist Cost	Total Cost
S166	Resection with anastomosis - Small and large intestine terminal ileum, cecum and ascending colon (right hemicolectomy)	$799.55	7	$15.01	7	$12.04	$988.90

It was assumed that a surgical admission included the following prior to the procedure; a general surgeon's fee for consultation and a gastroenterologist's consultation fee for one in-patient hospital visit (Ontario Ministry of Health and Long Term Care, 2015). Fees for physician services were based on the Ontario codes detailed below. Comparable fees for other Canadian

provinces were then utilized to derive a mean and standard deviation which were applied as a normal distribution in the analysis (see Appendix III – Physician Fee Distributions).

Table 23 - Surgical Consultations

Code	Name	Amount
C415	Gastroenterology Consultation	$157.00
C035	General Surgery Consultation	$90.30

It was assumed for in-patient days in hospital following the procedure, determined by the length of stay from OCCI, that the following fees were applied, with a general surgeon as the most responsible physician for the care of the patient following the resection.

Table 24 - Post Surgical General Surgery Fees

Code	Name	Amount
C122	Day following the hospital admission assessment	$58.80
C123	Second day following the hospital assessment	$58.80
C124	Day of discharge	$58.80

Physician services utilization for all other health states included assessment fees for physician visits, see Table 25 (Ontario Ministry of Health and Long Term Care, 2015) .

Table 25- Ontario Schedule of Benefits: Surgical and Physician Visit Costs

Code	Name	Amount
A413	Gastroenterology – Medical Specific Assessment	$79.85
A005	Family Physician & General – General Assessment	$77.20
A033	General Surgery - Specific Assessment	$44.40

It was assumed that since the patient is maintained on infliximab prior to the treatment decision and start of the model, they received repeat assessments rather than consultations for the duration of the time horizon. As described above, comparable fees for other Canadian provinces were then utilized to derive a mean and standard deviation which were applied as a normal distribution in the analysis (see Appendix III – Physician Fee Distributions).

The number of physician visits was estimated based on a profile of resource utilization for CD patients developed by consensus of a three-member expert panel of clinical gastroenterologists (J. Marshall et al., March 2002). It was assumed that the visit rates for clinical remission and response states were equivalent regardless of whether a patient was maintained on infliximab or

adalimumab. Furthermore, it was assumed that physician visits for the drug refractory state would be applicable for this model's drug refractory and 2nd line anti-TNF health states.

Table 26 - Physician Visits

Health State	Family Physician per 8 weeks	Gastroenterologist per 8 weeks	General Surgeon per 8 weeks
Clinical Remission (IFX or ADA)	0	0.15	0
Clinical Response (IFX or ADA)	1	2	0
Drug Refractory or 2nd line anti-TNF	1	2	0.15
Surgical Remission	1	0.5	1
Surgery	1	1	0.23

IFX – maintenance therapy with infliximab, ADA – maintenance therapy with adalimumab

Treatment costs for infusion-related reactions were based on nursing supervision time for treating the reaction as well as any required medications. Choice of treatment and dosing was informed by Schmier et al. (2017) which utilized a guideline of the management and preparedness for infusion and hypersensitivity reactions to inform their model (Schmier et al., 2017). Prices for medication treatment were taken from the ODB formulary, and when unavailable were sourced from the Alberta Drug Benefit List as an alternative (Alberta Health, April 1, 2018; Ontario Ministry of Health and Long Term Care, 2018c). It was assumed that Grade 1 reactions were less severe and required 10 minutes of nursing supervision and Grade 2 reactions required 15 minutes of supervision. Table 27 summarizes these medication and nursing costs per infusion reaction event.

Table 27 - Cost per Infusion Reaction

Grade	Reaction	Medication Dose	Cost (Source)	Total Cost of Medication per Event	Nursing Time (in Hours)	Nursing Wage	Total Nursing Cost Per Event	Total Cost Per Event
1	Dizziness	N/A	N/A	N/A	0.17	$35.16	$5.86	$5.86
	Flushing	N/A	N/A	N/A				$5.86
	Headache	acetaminophen 1000mg PO	$0.0285 per 500mg (ODB Formulary)	$0.06				$5.92
	Skin Reactions	N/A	N/A	N/A				$5.86
2	Dyspnea	epinephrine 0.5 mg	$22.30 per 30mg/30ml (ODB Formulary)	$22.30	0.25	$35.16	$8.79	$31.09
	Hypertension	captopril 25 mg PO	$0.3 per 25 mg (ODB Formulary)	$0.60				$9.39
	Hypotension	epinephrine 0.5 mg	$22.30 per 30mg/30ml (ODB Formulary)	$22.30				$31.09
	Nausea	diphenhydramine 50mg	$4.04 per 50mg/ml (Alberta Drug Formulary)	$4.04				$12.83
	Urticaria	diphenhydramine 50mg	$4.04 per 50mg/ml (Alberta Drug Formulary)	$4.04				$12.83

2.6.7 Societal Perspective

Finally, employing the model described above, a societal perspective was also tested. When this broader perspective was taken the impact of the intervention on time lost by patients is also accounted for (CADTH, March, 2017). As it is assumed that the patient is an adult of working age (38 years) an average hourly wage for the Canadian population aged 25 to 54 years of $28.33 per hour was applied to account for lost productivity time (Statistics Canada, April 6, 2018). Lost time was accounted for in the event of an in-patient hospital stay for surgical intervention, a physician visit and infusion visit as shown in Table 28 (Bashir, 2018). Time losses therefore were only included for health services and none were applied for time lost to sickness and this may represent an underestimate of productivity loss for this adult CD population.

Table 28 - Loss of Productivity

Procedure	Time assumed for CD Procedure (hours/day)	Average Length of stay (days)	Standard Deviation of Length of Stay (days)	Source
Physician Visit	4	0.50	Fixed	Assumption
Infusion Visit	4	0.50	Fixed	Assumption
Resection Hospital Stay	8	8.03	3.51	OCCI 2015/16 Weighted Average

2.6.8 Summary of Inputs

The following table summarizes all parameters which were applied in the model including the sources, standard deviations, alpha values, beta values and distributions where applicable.

Table 29 - Parameter Table

Clinical Inputs				
Initial Distribution				
Health State	**Reference (alpha, beta)**	**Biosimilar (alpha, beta)**	**Distribution**	**Source**
Clinical Remission	0.62 (41,25)	0.68 (43,20)	Beta	Jorgensen et al (2017)
Clinical Response	0.38 (25,41)	0.32 (20,43)	Beta	Jorgensen et al (2017)
Mortality				
Health State	**Reference (alpha, beta)**	**Biosimilar (alpha, beta)**	**Distribution**	**Source**
Surgery	0.6% (15, 2733)		Beta	Singh et al (2015)
All other Markov Health States	Standardized Mortality Ratio: 1.45 Mortality calculated as SMR*Statistics Canada Probability of Mortality Depending on Age		N/A	Bitton et al. (2016) Statistics Canada (2017)
Transition Probabilities				
	Reference (alpha, beta)	**Biosimilar (alpha, beta)**	**Distribution**	**Source**
Clinical Remission/Clinical Response				
Relapse	0.212 (14,52)	0.365 (23,40)	Beta	Jorgensen et al (2017)

2nd Line Anti-TNF Therapy			
Respond to initial therapy	0.38 (61,98)	Beta	Sandborn et al. (2007)
Remission (after response)	0.21 (34, 27)	Beta	Sandborn et al. (2007)
2nd Line Remission			
Maintain Remission	0.36 (62, 110)	Beta	Colombel et al. (2007)
2nd Line Response			
Maintain Response	0.413 (71, 101)	Beta	Colombel et al. (2007)
Drug Refractory			
Surgery	0.038 (10, 251)	Beta	Feagan et al. (2008)
Surgery			
Successful Surgery	0.52022 (52.022, 47.978)	Beta	Silverstein et al. (1999)
Surgical Remission			
Relapse	Year 1: 0.05 (2, 38) Year 2: 0.211 (8, 30) Year 3: 0.143 (3, 21) Year 4: 0.111 (2, 18) Year 5: 0.06 (1, 15)	Beta	Onali et al. (2016)
Adverse Events			

Health State	Reference (alpha, beta)	Biosimilar (alpha, beta)	Distribution	Source
IFX Clinical Remission or Response	0.04 (10,231)	0.02 (4,236)	Beta	Jorgensen et al (2017
Utilities				
Markov Health State	**Reference (SD)**	**Biosimilar (SD)**	**Distribution**	**Source**
Remission (IFX, 2nd Line & Surgical)	0.75 (0.12)	0.75 (0.12)	Beta	Greenberg et al. (2015)
Response (IFX & 2nd Line)	0.63 (0.1)	0.63 (0.1)	Beta	Greenberg et al. (2015)
2nd Line Anti-TNF, Drug Refractory & Surgery	0.51 (0.12)	0.51 (0.12)	Beta	Greenberg et al. (2015)
Costs				
Markov Health State	**Reference (SD)**	**Biosimilar (SD)**	**Distribution**	**Source**
Clinical Remission (IFX)	Biologic Cost Per Cycle ($994.75 (44.94)): $3,979 Biologic Dispensing Fees: $8.83 Concomitant Therapy Cost per Cycle: Prednisone: $0.46 Immunosuppressives: $51.78 Physician Services Per Cycle: $9.68	Biologic Cost Per Cycle ($525 (44.94)): $2,108.83 Biologic Dispensing Fees: $8.83 Concomitant Therapy Cost per Cycle: Immunosuppressives: $64.05 Physician Services Per Cycle: $9.68	Drug Prices: Normal Distribution Physician Services: Normal Distribution	Canadian Public Drug Formularies Blackhouse et al. (2012) Nugent et al (2010) Canadian Public Schedule of Benefits
Clinical Response (IFX)	Biologic Cost Per Cycle ($994.75 (44.94)): $3,979 Biologic Dispensing Fees: $8.83 Concomitant Therapy Cost per Cycle: Prednisone: $0.46 Immunosuppressives: $51.78	Biologic Cost Per Cycle ($525 (44.94)): $2,108.83 Biologic Dispensing Fees: $8.83 Concomitant Therapy Cost per Cycle: Immunosuppressives: $64.05	Drug Prices: Normal Distribution Physician Services: Normal Distribution	Canadian Public Drug Formularies Blackhouse et al. (2012) Nugent et al (2010) Canadian Public Schedule of Benefits

	Physician Services Per Cycle: $172.61	Physician Services Per Cycle: $172.61		
Drug Refractory	Concomitant Therapy Cost per Cycle: Prednisone: $0.46 Immunosuppressives: $51.78 Physician Services Per Cycle: $179.10	Concomitant Therapy Cost per Cycle: Immunosuppressives: $64.05 Physician Services Per Cycle: $179.10	Drug Prices: Normal Distribution Physician Services: Normal Distribution	Canadian Public Drug Formularies Blackhouse et al. (2012) Nugent et al (2010) Canadian Public Schedule of Benefits
2nd Line- Anti-TNF (ADA)	Biologic Cost Per Cycle ($916.86 (334.06)): $8,251.74 Biologic Dispensing Fees: $35.32 Concomitant Therapy Cost per Cycle: Prednisone: $0.46 Immunosuppressives: $51.78 Physician Services Per Cycle: $179.10	Biologic Cost Per Cycle ($916.86 (334.06)): $8,251.74 Biologic Dispensing Fees: $35.32 Concomitant Therapy Cost per Cycle: Immunosuppressives: $64.05 Physician Services Per Cycle: $179.10	Drug Prices: Normal Distribution Physician Services: Normal Distribution	Canadian Public Drug Formularies Blackhouse et al. (2012) Nugent et al (2010) Canadian Public Schedule of Benefits
Clinical Remission (ADA)	Biologic Cost Per Cycle ($916.86 (334.06)): $3,667.44 Biologic Dispensing Fees: $35.32 Concomitant Therapy Cost per Cycle: Prednisone: $0.46 Immunosuppressives: $51.78	Biologic Cost Per Cycle ($916.86 (334.06)): $3,097.54 Biologic Dispensing Fees: $35.32 Concomitant Therapy Cost per Cycle: Immunosuppressives: $64.05	Drug Prices: Normal Distribution Physician Services: Normal Distribution	Canadian Public Drug Formularies Blackhouse et al. (2012) Nugent et al (2010) Canadian Public Schedule of Benefits

	Physician Services Per Cycle: $9.68	Physician Services Per Cycle: $9.68		
Clinical Response (ADA)	Biologic Cost Per Cycle ($916.86 (334.06)): $3,667.44 Biologic Dispensing Fees: $35.32 Concomitant Therapy Cost per Cycle: Prednisone: $0.46 Immunosuppressives: $51.78 Physician Services Per Cycle: $172.61	Biologic Cost Per Cycle ($916.86 (334.06)): $3,667.44 Biologic Dispensing Fees: $35.32 Concomitant Therapy Cost per Cycle: Immunosuppressives: $64.05 Physician Services Per Cycle: $172.61	Drug Prices: Normal Distribution Physician Services: Normal	Canadian Public Drug Formularies Blackhouse et al. (2012) Nugent et al (2010) Canadian Public Schedule of Benefits
Surgery	Physician/Assist/Anesthesia Procedure Cost: $988.90 Surgical Cost: $12,138 ($5,729) Pre-Surgery Consultation Fees: $219.75 Post-Surgery Assessments (Total Length of Stay 8 days): $411.60 Physician Assessment Services Per Cycle: $118.06	Physician/Assist/Anesthesia Procedure Cost: $988.90 Surgical Cost: $12,138 ($5,729) Pre-Surgery Consultation Fees: $219.75 Post-Surgery Assessments (Total Length of Stay 8 days): $411.60 Physician Assessment Services Per Cycle: $118.06	Procedure Cost was not varied Surgical Cost: Gamma Distribution (per OCCI) Physician Fees post were not varied Length of Stay: Normal Distribution Consults & Assessments: Normal	Canadian Public Schedule of Benefits OCCI 2015/2016 Marshall et al (March 2002)
Surgical Remission	Physician Services Per Cycle:	Physician Services Per Cycle:	Normal	Blackhouse et al (2012) Nugent et al (2010)

	$119.10	$119.10		Canadian Public Schedule of Benefits
Adverse Events				
Health State	**Reference (alpha, beta)**	**Biosimilar (alpha, beta)**	**Distribution**	**Source**
IFX Clinical Remission or Response Per Event	$13.95	$13.95	Not varied	Schmier (2017) ODB Formulary Ontario Nurses Association Alberta Drug Benefit List

Abbreviations:

ADA – maintenance therapy with adalimumab, IFX – maintenance therapy with infliximab, OCCI – Ontario Case Costing Initiative, ODB – Ontario Drug Benefit, SMR – Standardized Mortality Ratio,

2.7 Analysis & Incremental Cost-Effectiveness

The inputs and framework described above were utilized to inform the reference case analysis. For the purposes of this work, "reference case" refers to the results of the model when the inputs described above were employed. This is distinct from "reference infliximab" group which refers to the comparator in the evaluation.

Treeage Pro 2018 software was utilized to run a cohort simulation to evaluate the reference case, whereby hypothetical cohorts of the reference patient were run through the model in the intervention and the comparator branches and compared. Patients were cycled through the various states given the transition probabilities until 5 years of the model were completed.

Results were reported as an average total cost per patient, an average outcome for each comparator, incremental costs, and incremental outcomes with 95% confidence intervals. Given that the reference case analysis was probabilistic in nature, the incremental costs and outcomes were derived through taking the mean of the 10,000 Monte Carlo iterations. Each simulation ran a random value from each of the input parameters according to the specified distributions (Table 29). This process subsequently yielded a distribution of costs and outcomes for the 10,000 iterations. This allowed the calculation of confidence intervals of the expected costs and outcomes for each strategy. Outcomes were reported as QALYs. These costs and outcomes were then utilized to derive the ICER for results where appropriate, calculated as follows:

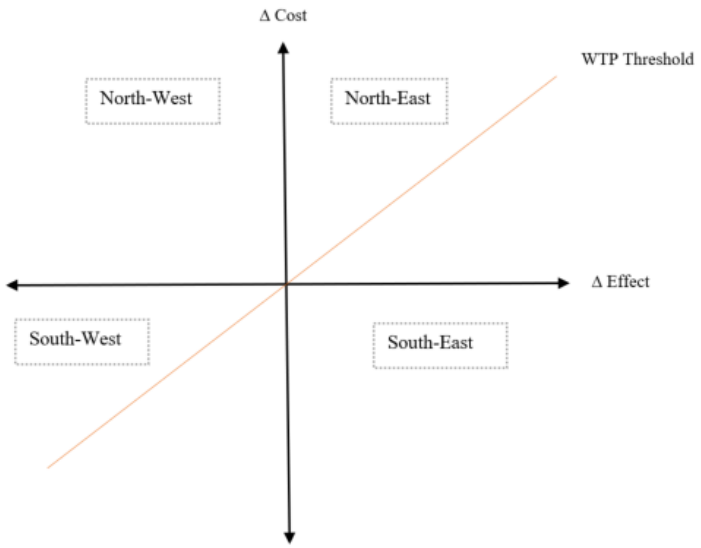
$$ICER = \frac{Cost_{Biosimilar} - Cost_{Reference}}{Effect_{Biosimilar} - Effect_{Reference}}$$

If applicable, the ICER provided an estimate of the incremental cost per QALY gained associated with the biosimilar. In the event that the biosimilar was associated with greater effectiveness and less cost, this implied a dominant and preferred strategy (South-East quadrant of the ICER plane). In comparison, if the biosimilar was associated with more cost and less effectiveness then it was dominated by the reference drug, implying that the reference drug was the preferred strategy (North-West quadrant of the plane).

If the ICER is positive, a decision-maker's WTP threshold determined if the intervention was cost-effective and worthy of budget allocation. A WTP threshold represents a maximum the

decision maker is willing to pay for one additional unit of outcome (Marseille et al., 2015). When an ICER is positive it must lie below the WTP threshold for the intervention to be considered a cost-effective option. This is shown on an incremental cost-effectiveness plane in Figure 5.

Figure 5 - Incremental Cost-Effectiveness Plane



The final results were estimated through a probabilistic analysis which incorporates uncertainty associated with each parameter (CADTH, March, 2017). The CADTH economic guidelines recommend a minimum of 5,000 replications therefore 10,000 were used to ensure stability (CADTH, March, 2017) . The results of these 10,000 replications were presented as a scatter plot on an incremental cost-effectiveness plane, including a 95% confidence ellipsis. These were presented for both the health care system and societal perspectives.

Using a probabilistic analysis as the reference case addressed uncertainty in part surrounding the input parameters. However, to further assess the impact of uncertainty of specific inputs several sensitivity analyses were conducted.

2.8 Uncertainty Analyses

The results of this economic evaluation are intended to inform decision makers regarding the cost-effectiveness of biosimilar infliximab and therefore, uncertainty was also characterized and

assessed to provide a robust analysis of the expected costs and outcomes. This included a threshold analysis as well as assessment of parameter, structural and decision uncertainty.

A threshold analysis was conducted on two key variables; probability of relapse in the biosimilar group and the price of reference infliximab. This type of analysis assessed the variables values which altered the conclusions of the analysis, for example shifting from a south-western quadrant to a south east quadrant. For example, when assessing the probability of relapse, the assessment identified the per cycle transition probability where the average QALYs associated with the biosimilar infliximab treatment group surpassed that of the reference infliximab group. Similarly, when testing the price of reference infliximab, the threshold analysis identified the price where the costs over the five-year time horizon for the reference group would be less than that of the biosimilar switch group. This type of analysis allows for the assessment of uncertainty surrounding the conclusions of the model by identifying these values and determining if these may reasonably occur in a real-world setting.

Parameter uncertainty was in part addressed using probabilistic analysis in the reference case since this approach accounted for the likelihood that an input takes on a given value when sampled from a distribution within a specified plausible range over 10,000 simulations. However, influential variables were identified to assess their effects on the results. One-way probabilistic analyses were run on patient weights, infliximab drug costs, health state utilities and the relapse rate from clinical remission or response states after being switched to biosimilar infliximab. Patient weight was the sole variable which was fixed in the reference case, all other variables in the sensitivity analyses were sampled from a distribution established based on the literature or available public drug prices. A one-way probabilistic analysis was conducted by altering the point estimate and distribution, where applicable, for the variable of interest and running the probabilistic analysis with 10,000 simulations.

As infliximab dosing is weight-based, this parameter is a significant determinant of drug cost and was therefore identified as a key variable to test in sensitivity analysis. A range of weights from 40kg up to 90kg were tested in a series of one-way probabilistic analyses with the reference case being a 75 kg patient who required four vials of infliximab per maintenance dose. This range was informed by consultation with CD experts and by economic evaluations of infliximab, such as

Blackhouse et al (2012) and Lindsay et al (2008), which similarly tested a range of patient weights in sensitivity analyses.

Second, since this model focuses on infliximab, it was important to test the costs of reference and biosimilar infliximab in a sensitivity analysis. The distributions were assumed to be the same as those employed in the reference case which were determined by evaluating Canadian publicly available drug prices for reference infliximab. Based on the experience described in Norway, where the biosimilar manufacturer offered a substantial discount on the reference price due to their tendering system, a biosimilar price which reflects a 72% discount from the Canadian reference infliximab drug price was tested as an estimate in the probabilistic analysis (Generics and Biosimilar Initiative, 2015). In the reference case of the present analysis, the biosimilar price of $525.00 represents an approximately 47% discount from the Canadian average price of $994.75 for reference infliximab. Therefore, the sensitivity analysis was run with a biosimilar price of $279.07 which represents a 72% discount was applied.

It has also been demonstrated that reference drug manufacturers are willing to offer price discounts, including volume-price discounts and bundling arrangements, to certain payers to maintain market share (Davio, September 5, 2017; SunLife Financial, 2015). These discounts and arrangements are confidential and not publicly available. However, results from an analysis of the cost per year for biologics in Norway showed that the cost for treatment with Remicade® decreased approximately 20% from its highest cost in 2010 after the introduction of biosimilars (Madsen, 2018). Therefore, a 20% reduction from the current Canadian reference infliximab price, $795.95 per vial, was tested as an approximation to assess the impact that these confidential arrangements may have upon the results of the model.

Given the importance of utility weights in determining quality adjusted life years, an alternative set of utility weights was tested in a sensitivity analysis. The values and distributions derived by Gregor et al (1997) are specific to a Canadian CD population and have been employed in several economic evaluations of infliximab (Blackhouse et al., 2012; J. Marshall et al., March 2002). This study was conducted in 1997 and therefore, these values were not employed in the reference case analysis. However, given that these results were specific to a Canadian population it was deemed appropriate to test these values in a sensitivity analysis.

Finally, an alternative source was employed in a sensitivity analysis of the relapse rate from clinical remission or response after being switched to treatment with biosimilar infliximab. Given the uncertainty surrounding the performance of the biosimilar and the relative difference in relapsing between the maintain treatment with reference infliximab and switch to biosimilar groups it was decided that only the relapse rate from biosimilar would be varied. The CD subset of the NOR-SWITCH study had the most substantial difference between groups with 14.3% in favor of the reference, which was an outlier relative to the other disease states and overall results of the trial which showed only a 4.4% difference in favor of the reference (Jørgensen et al., 2017). Therefore, for the purposes of this sensitivity analysis a reduced difference between the groups was tested to assess the influence on the results of the model.

It is important to acknowledge that there is a dearth of literature and clinical trials surrounding switching to biosimilar infliximab particularly in the CD therapeutic area, therefore the available estimates were limited. Komaki et al (2017) conducted a meta-analysis of studies regarding this question and found that the biosimilar demonstrated high rates of sustained clinical response at weeks 48-63 of 0.75 (95% CI: 0.44 to 0.92) and rates of clinical remission of 0.92 (95% CI: 0.38 to 0.99) at week 51. It was assumed that if a patient did not maintain remission or response that they had relapsed. That meta-analysis was utilized to inform a point estimate and distribution for the rate of relapse for the switch group. Their meta-analysis was limited in scope as the response rate only included two studies and the remission rate only included one study (Komaki et al., 2017). Furthermore, for the purposes of the present sensitivity analysis the relapse rate of the reference treatment group was not changed from the reference case, and therefore remains based on the NOR-SWITCH trial.

Table 30 includes a summary of all tested variables and their corresponding distributions where appropriate.

Table 30 – Parameter Sensitivity Analyses

Parameter	Reference Case Value	Distribution (If Applicable)	Sensitivity Analysis Value	Sensitivity Analysis Distribution (If Applicable)
Drug Cost				
Infliximab Drug Cost	Reference Infliximab: $994.75	Beta SD: 44.936	Reference Infliximab: $795.95	Beta SD: 44.936
	Biosimilar Infliximab: $525.00	Beta SD: 44.936	Biosimilar Infliximab: $279.07	Beta SD: 44.936
Utility Values				
Health State Utilities	Remission (IFX, 2nd Line & Surgical): 0.75	Beta Distribution SD: 0.12	Remission (IFX, ADA & Surgical): 0.82	Beta Distribution alpha: 0.82, beta: 0.18
	Response (IFX & 2nd Line): 0.63	Beta Distribution SD: 0.1	Response (IFX & 2nd Line): 0.73	Beta Distribution alpha: 0.73, beta:0.27
	2nd Line, Drug Refractory & Surgery: 0.51	Beta Distribution SD: 0.12	2nd Line, Drug Refractory & Surgery: 0.54	Beta Distribution alpha: 0.54, beta: 0.46
Patient Weight				
Patient Weight	75 kg	Not Applicable Fixed Variable	40 kg 50 kg 60 kg 70 kg 80 kg 90 kg	Not Applicable Fixed Variable
Relapse Rates				
Relapse Rate for Switch to Biosimilar Treatment Group	Clinical Remission: 0.365	Beta Distribution alpha: 23, beta: 40	Clinical Remission: 0.08	Beta Distribution SD: 0.08
	Clinical Response: 0.365	Beta Distribution alpha: 23, beta: 40	Clinical Response: 0.25	Beta Distribution SD: 0.3

IFX – maintenance therapy with infliximab, ADA- maintenance therapy with adalimumab

Structural uncertainty was evaluated through varying a number of key assumptions of the model. This included a sensitivity analysis conducted on the discount rate, which was varied from 0% to 5%. This was informed by the CADTH guidelines for economic evaluations of health technologies. The current 4th edition of the guidelines, recommend testing 0% and 3% in uncertainty analysis and the 3rd edition recommended employing a reference case discount rate of 5% (CADTH, 2006, March, 2017). Therefore, this analysis tested a range from 0% to 5% to assess the influence of this rate.

The time horizon of the model was also tested in sensitivity analysis from a relatively short time horizon (one year) up to a ten-year time horizon in order to assess when costs and outcomes were accrued in the model.

In order to assess the model over a ten-year time horizon the number of cycles run in the model was doubled to sixty-six eight-week cycles. Mortality data from StatsCan lifetables were extended by an additional five years to account for the change in mortality (Statistics Canada, 2017). For the remaining transition probabilities, the same parameter inputs and distributions were applied in all additional cycles of the model. However, in cases where the rate varied by year, such as surgical relapse rate, the rate from year five of the model was applied.

A summary of the structural sensitivity analyses that were conducted can be found in Table 31**.**

Table 31 – Structural Sensitivity Analyses

	Reference Case	Tested Value
Discount Rate		
Discount	1.50%	0% 1% 3% 5%
Model Duration		
Time Horizon	5 years	1 year 10 years

IFX – maintenance therapy with infliximab, ADA- maintenance therapy with adalimumab

Finally, decision uncertainty was assessed with a cost-effectiveness acceptability curve (CEAC). A CEAC presents a summary of the impact of uncertainty on the final ICER result of the model in relation to values of the WTP threshold (York, 2016). This graph plots a range of WTP thresholds against the probability that the intervention will be cost-effective at that threshold, using the results from the 10,000 Monte Carlo replications (York, 2016). This type of summary provides the decision maker with an estimate of the probability that the ICER for the biosimilar intervention as compared to reference infliximab falls below a maximum acceptable ratio and serves as a characterization of decision maker uncertainty (Fenwick & Byford, 2005).

Chapter 3 Results

The following section presents the results of the cost-utility analysis of a one-time switch to maintenance therapy with biosimilar infliximab compared with maintaining treatment with reference infliximab in adult patients with CD. Firstly, the reference case results of the probabilistic model will be presented, including the incremental costs and effects associated with the intervention. Subsequently, the results from several uncertainty analyses will be presented.

3.1 Reference Case Results

The primary analysis was run as a probabilistic model with distributions applied to key probability, utility and cost variables where appropriate. Therefore, the results of the analysis are also presented with corresponding standard deviations and 95% confidence intervals of the estimates.

Using 10,000 Monte Carlo simulations, a five-year time horizon and 1.5% global discounting the results were as follows. The average total costs were $96,385 (Standard Deviation [SD]: $6,834) and $50,191 (SD: $4,770.72) for the maintain treatment on reference infliximab and switch to biosimilar strategy respectively. Total incremental costs were -$46,194 (95% CI: -$42,420 to -$50,455) over the five-year time horizon.

Table 32 – Probabilistic Reference Case: Cost Results

	Cost	Standard Deviation	95% Confidence Interval	Incremental Cost (95% CI)
Maintain Treatment with Reference Infliximab	$96,385.25	$6,833.75	($83,213 to $109,976)	-$46,194.08 (-$42,420 to -$50,455)
Switch to Maintenance Treatment with Biosimilar Infliximab	$50,191.17	$4,770.72	($40,792 to $59,521)	

With regards to effectiveness, measured in QALYs, maintenance treatment with reference infliximab was associated with 3.187 QALYs (SD: 0.3503). In comparison, the switching to biosimilar strategy was associated with 3.061 QALYs (SD: 0.3775) resulting in an incremental loss of 0.1266 QALYs (95% CI: -0.1604 to – 0.0729) (or 6.5 quality adjusted weeks) over the five-year time horizon.

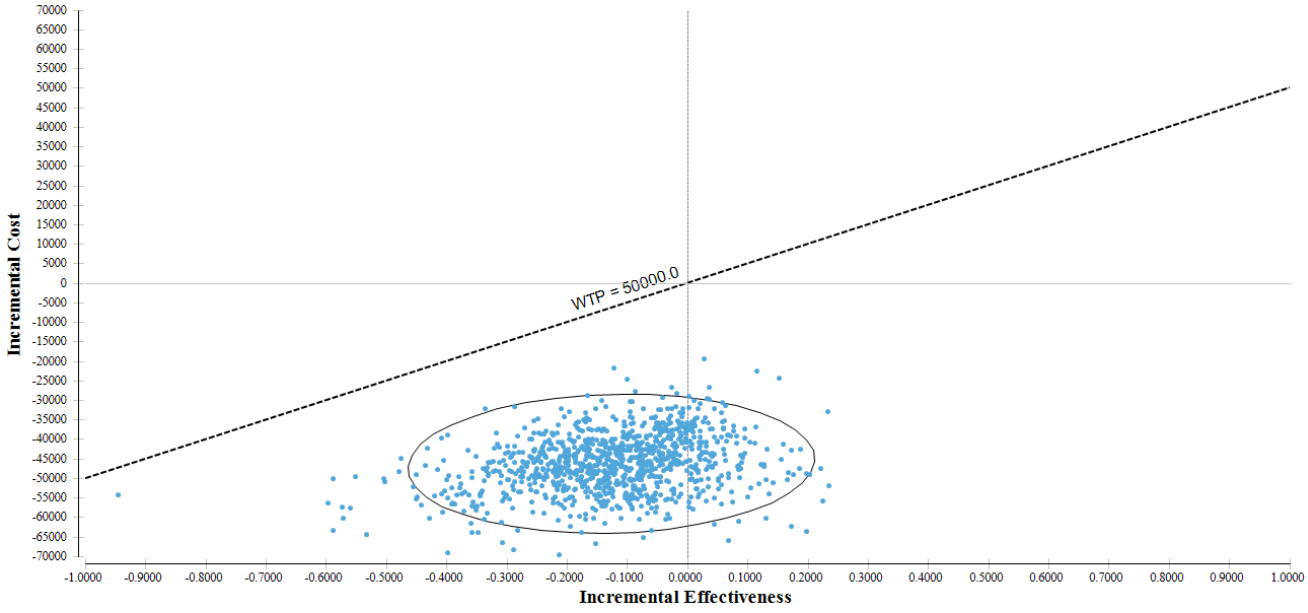
Table 33 - Probabilistic Reference Case: Effectiveness Results

	Effectiveness per patient	Standard Deviation	95% Confidence Interval	Incremental Effect (95% CI)
Maintain Treatment with Reference Infliximab	3.187	0.3503	(2.47 to 3.83)	-0.1266 (-0.1604 to -0.0729)
Switch to Maintenance Treatment with Biosimilar Infliximab	3.061	0.3775	(2.31 to 3.76)	

Therefore, the results of the reference case probabilistic analysis indicate that switching to maintenance treatment with biosimilar infliximab as compared to maintaining treatment with reference infliximab is associated with incremental savings, but an incremental reduction in QALYs over a five-year time horizon. These results lie in the south-west quadrant of the cost-effectiveness plane and an ICER will therefore, not be presented.

As shown in Figure 6 83.67% of the iterations lie in the southwest quadrant (less costly and less effective) and 16.33% lie in the south-east quadrant (less costly and more effective). Those simulations that lie in the south-east quadrant imply that switching to biosimilar infliximab is a dominant strategy as it results in incremental cost-savings and an incremental gain in QALYs.

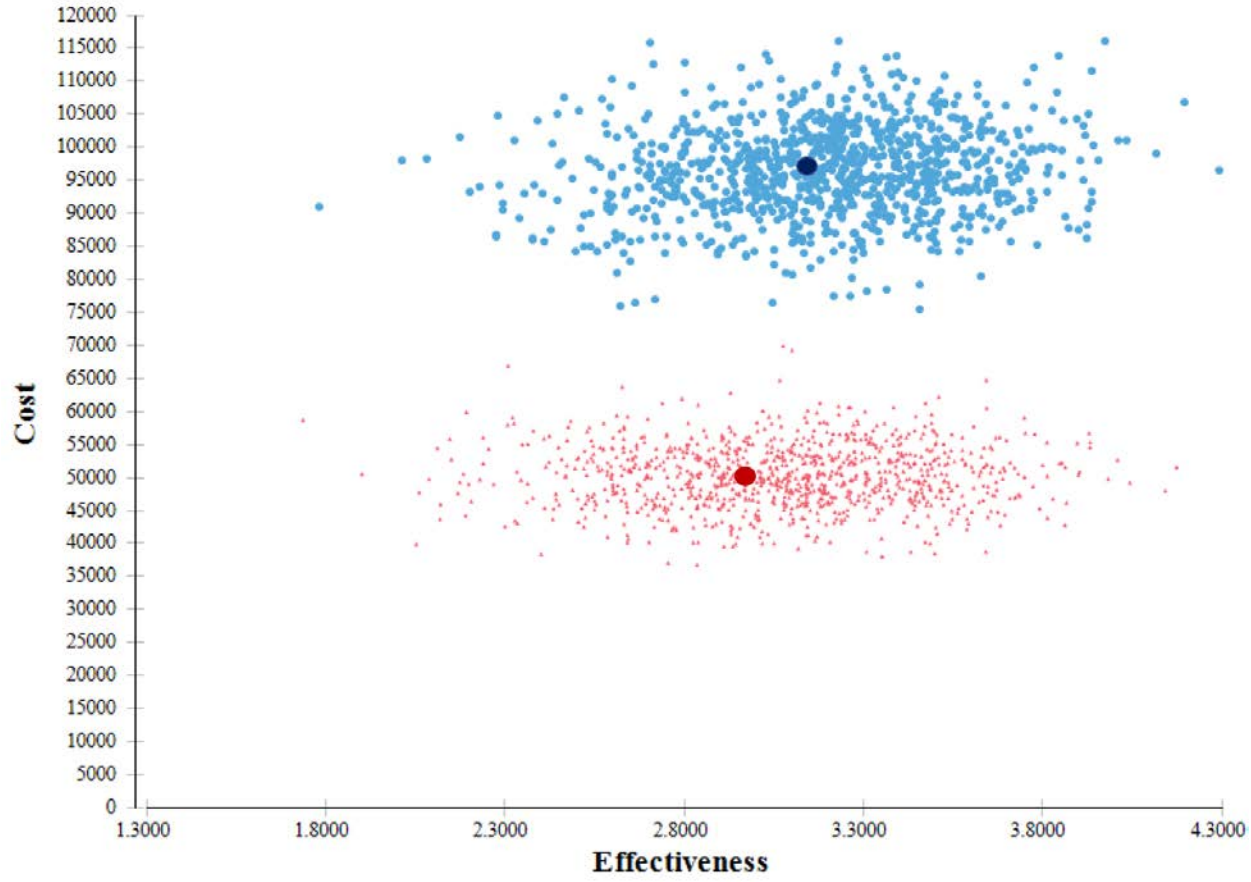
Figure 6 - Reference Case Results (1,000 of 10,000 iterations with 95% Confidence Ellipse)



The cost-effectiveness scatter plot shown in Figure 7 similarly demonstrate that switching to biosimilar infliximab is on average associated with less cost and fewer QALYs over the five-year time horizon, however the effectiveness difference is minimal. The average costs per patient for the maintaining reference infliximab treatment group ranges from a minimum of $67,571 to a maximum of $124,718 whereas switching to biosimilar infliximab ranges from $34,334 to $71,811.

With regards to effectiveness, maintenance treatment with reference infliximab ranges from a minimum of 1.78 QALYs to 4.35 QALYs per patient. In comparison, the switching to biosimilar infliximab treatment group ranges from a minimum of 1.64 QALYs to a maximum of 4.41 QALYs pet patient.

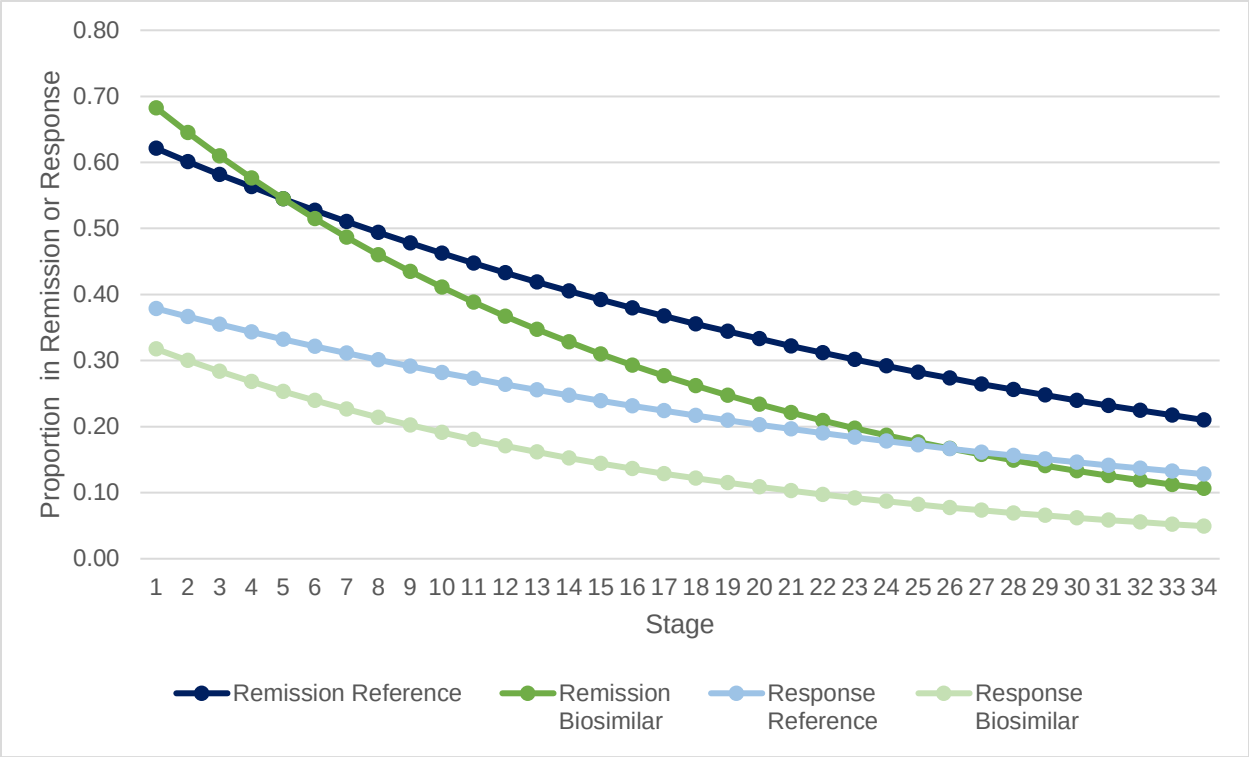
Figure 7 - Cost Effectiveness Scatterplot



Blue – Maintenance with Reference, Red – Switch to Biosimilar, Larger dots represent reference case results

Finally, the results of the Markov analysis also demonstrated how the proportion of patients in clinical remission or response while being treated with infliximab changed over the five-year time horizon of the model. Assuming a constant rate of relapse based on the NOR-SWITCH study and a rate of death based on StatsCan and a CD standardized mortality ratio resulted in the following state probability over the course of the analysis. The proportion of patients in the biosimilar treatment group in clinical remission or response at the end of the time horizon was 0.156 and the proportion in the reference infliximab group in remission or response was 0.338.

Figure 8- Proportion in Remission & Response States



Stages are cycles of 8 weeks in length for a total time horizon of five years.

3.1.1 Societal Perspective

Finally, the model was run as a probabilistic analysis from the societal perspective and lost time due to healthcare service utilization was accounted for. With this perspective, costs in both groups increased and cost savings moderately decreased compared to the healthcare system perspective (see Table 34). When the societal perspective is taken, costs in the maintain treatment on reference infliximab group were $105,063 (95% CI: $83,213 to $109,976) and the switch group costs were $59, 998 (95% CI: $40,792 to $59,521) for incremental costs over the

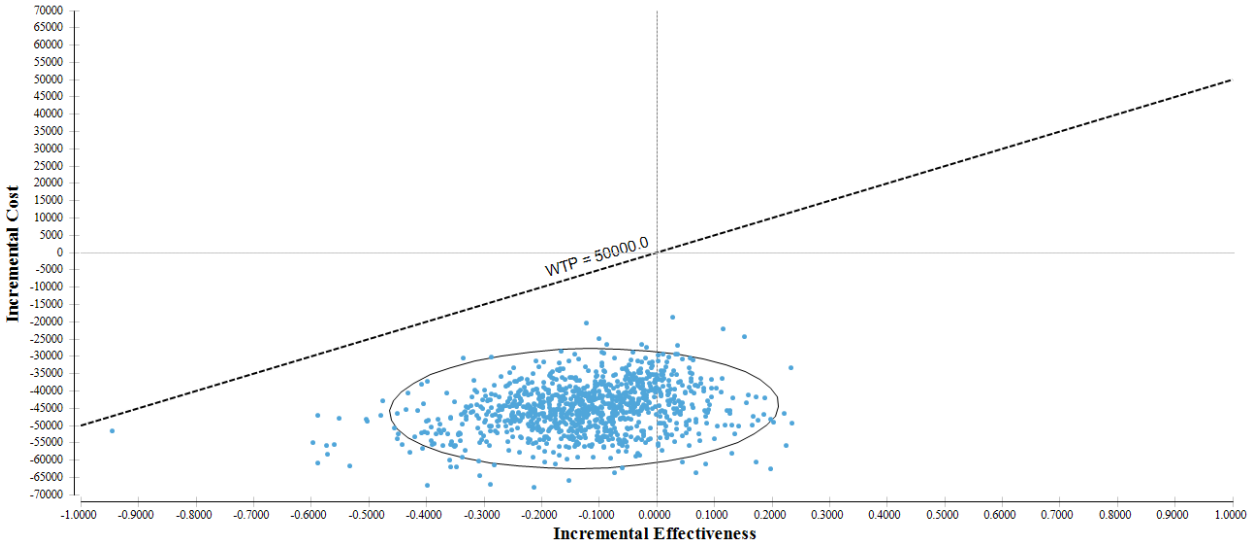
five years of -$45,066 (95% CI: -$41,520 to -$49,046). While the costs are higher for both branches there are moderately less savings associated with switching in this case.

Table 34 - Societal Results

	Cost (95% CI)	Incremental Cost (95% CI)	Effect (95% CI)	Incremental Effect (95% CI)
Maintain	$105,064 ($92,213 to $118,295)	-$45,066 (-$41,520 to -$49,046)	3.1873 (2.47 to 3.83)	-0.1266 (-0.1604 to -0.0729)
Switch	$59,998 ($50,693 to $69,248)		3.0607 (2.31 to 3.76)	

Figure 9 demonstrates that the iterations of the societal perspective are comparable to the healthcare system perspective. The Monte Carlo simulations show that 83.67% of iterations lay in the southwest quadrant, with incremental cost savings and an incremental loss in effectiveness.

Figure 9 - Societal Perspective Results (1,000 of 10,000 iterations with 95% Confidence Ellipse)



3.2 Uncertainty Analyses

3.2.1 Threshold Analysis

Threshold analyses were run on key parameters to assess the variables values which may alter the conclusions from the analysis, for example shifting from a south-western quadrant to a south east quadrant. Firstly, if the probability of relapsing from a clinical remission state after being switched to biosimilar infliximab is less than 0.0327 per eight-week cycle then the expected

QALYs for the biosimilar treatment group will be greater than that of the reference infliximab group resulting in a dominant strategy (SE quadrant). In the reference case the rate of relapse is 0.05461, therefore a 40% reduction in relapse rate per 8-week cycle would be required.

The other key parameter with a relevant threshold value was infliximab drug cost. If the reference infliximab drug cost is less than $426.77 per vial, then the average costs of the reference infliximab group over the five-year time horizon would be less than that of the biosimilar group and the reference treatment would be dominant. This would represent a 57% discount from the average Canadian price of $994.75 for reference infliximab, however this does not account for any confidential price discount arrangements which already may exist in the market.

3.2.2 Parameter Sensitivity Analyses

Several one-way probabilistic analyses were conducted to assess the influence of certain parameters on the costs and outcomes of the model. Firstly, given that infliximab dosing is weight-based this assumption is an important determinant of the number of required vials and thus overall drug cost, which is one of the primary drivers of the model. Vial re-use was not applied in the reference case or structural analysis as experts in the CD field identified that this was not standard practice in the Canadian environment.

In the reference case patient weight was fixed and assumed to be 75kg, meaning four vials of infliximab were required per maintenance dose. A range of patient weights were tested from 40kg to 90kg in a series of probabilistic analyses. The results showed that as patient weight increased the potential for cost savings over the five-year time horizon increased as well. For example, a 40kg patient required 2 vials of infliximab per dose and the incremental costs were -$21,791 (95% CI: -$21,251 to -$22,340) whereas a 90kg patient requiring 5 vials of infliximab per dose resulted in incremental costs of -$58,396 (95% CI: -$52,841 to -$64,401).

Table 35 – One-Way Probabilistic Analysis: Patient Weight

Reference Case Value Weight (kg)	Sensitivity Analysis Weight (kg)	Total mg per cycle	Vials per Cycle	Accounting for Wastage	Treatment Group	Cost (95% CI)	Incremental Cost (95% CI)	Effect (95% CI)	Incremental Effect (95% CI)
75	40	200	2	2	Maintain	$55,923 ($48,186 to $63,442)	-$21,791 (-$21,251 to -$22,340)	3.1873 (2.47 to 3.83)	-0.1266 (-0.1604 to -0.0729)
					Switch	$34,132 ($26,935 to $41,102)		3.0607 (2.31 to 3.76)	
	50-60	250	2.5	3	Maintain	$76,154 ($65,765 to $86,528)	-$33,992 (-$31,769 to -$36,357)	3.1873 (2.47 to 3.83)	-0.1266 (-0.1604 to -0.0729)
					Switch	$42,162 ($33,996 to $50,171)		3.0607 (2.31 to 3.76)	
	70-80	350	3.5	4	Maintain	$96,385 ($83,213 to $109,976)	-$46,194 (-$42,420 to -$50,455)	3.1873 (2.47 to 3.83)	-0.1266 (-0.1604 to -0.0729)
					Switch	$50,191 ($40,792 to $59,521)		3.0607 (2.31 to 3.76)	
	90	450	4.5	5	Maintain	$116,617 ($100,351 to $133,422)	-$58,396 (-$52,841 to -$64,401)	3.1873 (2.47 to 3.83)	-0.1266 (-0.1604 to -0.0729)
					Switch	$58,221 ($47,510 to $69,021)		3.0607 (2.31 to 3.76)	

Infliximab drug costs were also individually varied in a one-way probabilistic analysis. The biosimilar price was set at a 72% discount from the reference as in the Norwegian tendering system and in a separate analysis the reference price was reduced by 20% to reflect potential price reductions. The probabilistic model was then run to assess the impact of these variations in prices on the outcomes of the model. The incremental savings increased to $61,245 (95% CI: $56,624 to $66,335) when the biosimilar price was reduced to $279.07 per vial. Therefore, if the biosimilar price was reduced to levels similar to that of the Norway tendering system Canadian payers could increase incremental savings. In the event that a reference manufacturer lowers their price to compete with the biosimilar, by 20% in this analysis, the cost savings were reduced to $30,011 (95% CI: $27,639 to32,653). This reduced the savings associated with switching patients to biosimilars and may make this type of policy less appealing.

The probabilistic model was also run using the utility weights derived by Gregor et al (1997). Employing beta distributions and a utility of 0.82 (reference case: 0.75, SD: 0.12) for remission states, a utility of 0.73 (reference case: 0.63, SD: 0.10) for response states and utility of 0.54 (reference case: 0.51, SD: 0.12) for severe states resulted in an increase to the average QALYs gained for each treatment group. The reference infliximab group was associated with 3.51 (95% CI: 1.5 to 4.95) QALYs compared to 3.19 (95% CI: 2.47 to 3.83) in the reference case model. The biosimilar group was associated with 3.33 (95% CI: 1.04 to 4.95) QALYs compared to 3.06 (95% CI: 2.31 to 3.76). However, this also increased the decrement in QALYs from -0.1266 to -0.17 when the two strategies were compared making the biosimilar less attractive.

Finally, when alternative relapse rates from clinical remission and response states for the switch to biosimilar treatment group were tested both costs and outcomes of the model differed from the reference case analysis. The relapse rates in the biosimilar group were lower when the rates produced by the meta-analysis of Komaki et al (2017) were employed as a transition probability rather than those derived from NOR-SWITCH (Jørgensen et al., 2017; Komaki et al., 2017). The mean relapse rates derived from the Komaki et al study, the lower and upper bounds calculated based on the distributions and 10,000 Monte Carlo simulations, and finally the difference between the reference and biosimilar rates are presented below.

Table 36 - Sensitivity Analysis Relapse Rates & Differences

	Reference Case	Sensitivity Analysis Remission			Sensitivity Analysis Response		
	Risk Difference from NOR-SWITCH	Reference Infliximab Relapse Rate	Biosimilar Infliximab Relapse Rate	Difference	Reference Infliximab Relapse Rate	Biosimilar Infliximab Relapse Rate	Difference
Mean	-14.30%	21%	8%	13%	21%	25%	-4%
Lower Bound	-29.3	12%	0%	12%	12%	0%	12%
Upper Bound	0.7	32%	30%	2%	32%	96%	-64%

Therefore, when employing these rates, costs associated with the biosimilar increased to $67,502 (95% CI: $50,158 to $83,679) which reduced the incremental costs to -$28,924 (95% CI: -$26,280 to -$33,213). Importantly, with this lower relapse rate the outcomes for the biosimilar group increased to 3.40 QALYs (95% CI: 2.53 to 4.13) which surpassed that of the reference infliximab group at 3.19 QALYs. This resulted in an incremental gain in effect of 0.21 QALYs (95% CI: 0.06 to 0.3) which implied that a one-time switch to biosimilar infliximab was a dominant strategy. Using these relapse rates biosimilar infliximab was associated with incremental savings and an incremental gain in effect. While the savings associated with the intervention decreased from the reference case, this analysis highlights the importance of these rates in determining the cost-effectiveness of a one-time switch. If the relapse rates associated with switching are lower than those derived by NOR-SWITCH, then there is the potential for the biosimilar strategy to be dominant.

A summary of all one-way probabilistic analyses can be found in Table 37.

Table 37 – Parameter Sensitivity Analyses Results

Parameter Sensitivity Analysis	Reference Case Value (Distribution)	Sensitivity Analysis Value (Distribution)	Treatment Group	Cost	Incremental Cost (95% Confidence Interval)	Effectiveness (95% Confidence Interval)	Incremental Effect (95% Confidence Interval)
Reference Case	N/A	N/A	Maintain	$96,385 ($83,213 to $109,976)	-$46,194 (-$42,420 to -$50,455)	3.1873 (2.47 to 3.83)	-0.1266 (-0.1604 to -0.0729)
			Switch	$50,191 ($40,792 to $59,521)		3.0607 (2.31 to 3.76)	
Drug Costs							
Reference Infliximab Price 20% Price Reduction in Reference Infliximab Price	$994.75 SD:44.936	$795.95 SD:44.936	Maintain	$80,203 ($68,432 to $92,173)	-$30,011 (-$27,639 to -$32,653)	3.1873 (2.47 to 3.83)	-0.1266 (-0.1604 to -0.0729)
			Switch	$50,191 ($40,792 to $59,521)		3.0607 (2.31 to 3.76)	
Biosimilar Price Biosimilar Price set at 72% Discount from Reference Infliximab Price	$525.00 SD:44.936	$279.07 SD:44.936	Maintain	$96,385 ($83,213 to $109,976)	-$61,245 (-$56,624 to -$66,335)	3.1873 (2.47 to 3.83)	-0.1266 (-0.1604 to -0.0729)
			Switch	$35,140 ($26,588 to $43,641)		3.0607 (2.31 to 3.76)	
Health State Utilities							
Utility Employed Gregor et al (1997) Utilities Increased Utilities for All States	Remission 0.75 (SD: 0.12) Response 0.63 (SD: 0.1) Severe 0.51 (SD: 0.12)	Remission (alpha: 0.82, beta: 0.18) Response (alpha: 0.73, beta: 0.27) Severe (alpha: 0.54, beta: 0.46)	Maintain	$96,385 ($83,213 to $109,976)	- $46,194 (-$42,420 to -$50,455)	3.5008 (1.487 to 4.9537)	-0.1633 (-0.2386 to -0.0054)
			Switch	$50,191 ($40,792 to $59,521)		3.3375 (1.2484 to 4.9483)	

Switch to Biosimilar Relapse Rate							
Biosimilar Relapse Rate Lowered to Komaki et al (2017) Relapse Rates	Clinical Remission 0.365 (alpha: 23, beta: 40) Clinical Response 0.365 (alpha: 23, beta: 40)	Clinical Remission 0.08 (SD:0.08) Clinical Response 0.25 (SD: 0.3)	Maintain	$96,426 ($83,370 to $109,959)	-$28,924 (-$26,280 to -$33,213)	3.1873 (2.47 to 3.83)	0.21 (0.06 to 0.30)
			Switch	$67,502 ($50,158 to $83,679)		3.3973 (2.53 to 4.13)	

3.2.3 Structural Uncertainty Analyses

Structural uncertainty analyses were employed to assess the influence of key methodological assumptions in the model. The first primary assumption that was tested was the discount rate. In the reference case a 1.5% rate was applied and a range of 0% to 5% was tested in the structural analyses (CADTH, March, 2017).

A change in the discount rate was associated with minimal influence on the results. The incremental costs were reduced to -$42,798 (95% CI: -$39,526 to $46,477) with a 5% discount rate and increased to -$47,807 (95% CI: -$43,846 to -$52,339) with a 0% discount rate. With regards to effects, the loss in QALYs was moderately reduced to -0.1139 (95% CI: -0.1393 to -0.0671) with a 5% rate and increased to -0.1327 (95% CI: -0.1697 to -0.0764) with a 0% rate over the five-year time horizon.

In the reference case, a five-year time horizon was employed to compare the two treatment groups. However, in the structural uncertainty analyses, a relatively short one-year time horizon was tested, as this was the length of time of the NOR-SWITCH study. A longer time horizon of ten years was also tested however, certain assumptions had to be extended for the ten-year period which increased uncertainty.

The results of these assessments demonstrated that with a shorter time horizon, the increment in costs associated with switching to biosimilar infliximab was reduced to -$13,106 (95% CI: -$13,481 to - $12,778) however, the difference in incremental effect was also smaller at -0.0068 (95% CI: -0.0052 to – 0.0097). When the time horizon was extended to ten years the increment in costs increased to -$67,212 (95% CI: -$55,688 to -$81,392) as did the incremental loss in QALYs to -0.2326 (95% CI-0.365 to - 0.0378).

The results for the time horizon and discount rate sensitivity analyses are summarized in Table 38.

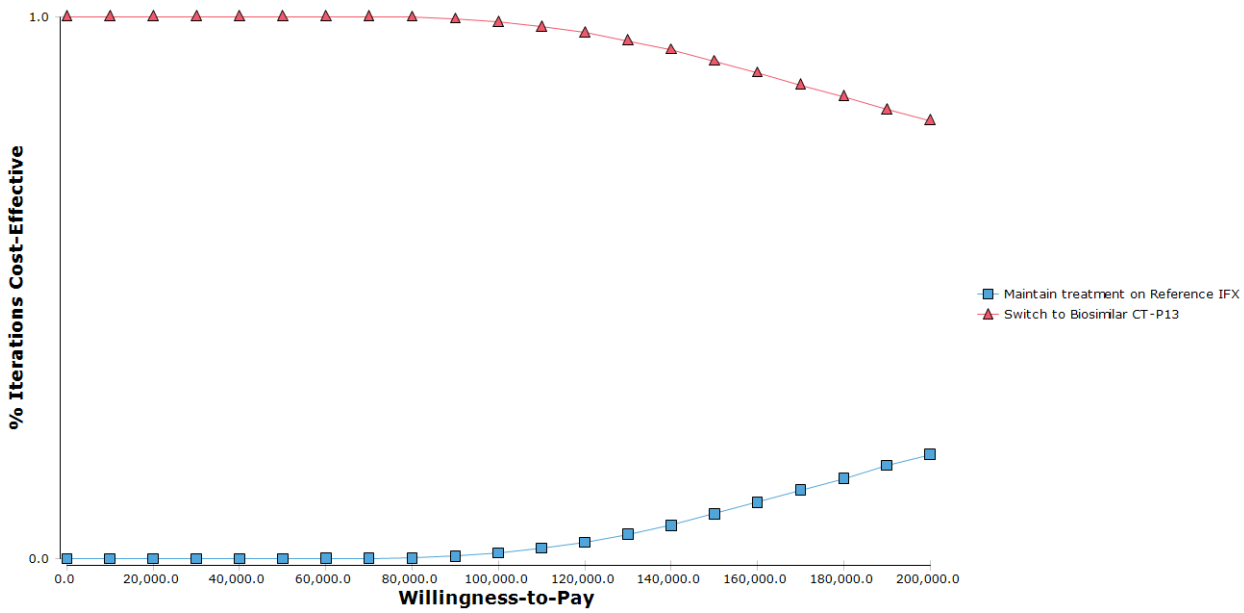
Table 38 - Structural Analyses: Time Horizon & Discount Rate

Reference Case Value	Structural Analysis Value	Treatment Group	Cost (95% CI)	Incremental Cost (95% CI)	Effect (95% CI)	Incremental Effect (95% CI)
Reference Case	N/A	Maintain	$96,385 ($83,213 - $109,976)	-$46,194 (-$42,420 to -$50,455)	3.1873 (2.47 - 3.83)	-0.1266 (-0.1604 to -0.0729)
		Switch	$50,191 ($40,792 - $59,521)		3.0607 (2.31 - 3.76)	
Time Horizon						
5 years	1 year	Maintain	$32,334 ($29,403 - $35,264)	-$13,106 (-$13,481 to - $12,778)	0.8366 (0.6372 - 0.9988)	-0.00680 (-0.0052 to -0.0097)
		Switch	$19,228 ($15,922 - $22,486)		0.8298 (0.6275 - 0.9891)	
	10 years	Maintain	$132,420 ($107,873 - $159,986)	-$67,212 (-$55,688 to -$81,392)	5.7176 (4.2724 - 7.0729)	-0.2326 (-0.365 to - 0.0378)
		Switch	$65,207 ($52,185 - $78,594)		5.485 (3.9074 - 7.0351)	
Discount Rate						
1.5 percent	0 percent	Maintain	$99,466 ($85,787 to $113,634)	-$47,807 (-$43,846 to -$52,339)	3.3050 (2.555 to 3.9771)	-0.1327 (-0.1697 to -0.0764)
		Switch	$51,659 ($41,941 to $61,295)		3.1723 (2.3853 to 3.9007)	
	1 percent	Maintain	$97,391 ($84,073 to $111,162)	-$46,721 (-$42,925 to -$51,061)	3.2257 (2.495 to 3.8812)	-0.1286 (-0.1639 to -0.0754)
		Switch	$50,671 ($41,148 to $60,101)		3.0971 (2.3311 to 3.8058)	
	3 percent	Maintain	$93,487 ($80,792 to $106,522)	-$44,679 (-$41,120 to -$48,669)	3.077 (2.3794 to 3.6989)	-0.1209 (-0.149 to - 0.0714)
		Switch	$48,808 ($39,672 to $57,853)		2.9561 (2.2304 to 3.6275)	
	5 percent	Maintain	$89,881 ($77,820 to $102,245)	-$42,798 (-$39,526 to $46,477)	2.9403 (2.2737 to 3.5324)	-0.1139 (-0.1393 to - 0.0671)
		Switch	$47,083 ($38,294 to $55,768)		2.8264 (2.1344 to 3.4653)	

3.2.4 Decision Uncertainty

A CEAC was derived to assess decision uncertainty in the analysis. The acceptability curve shows that at lower willingness-to-pay thresholds all iterations of the model showed that switching to biosimilar was cost-effective (see Figure 10). At a threshold of $100,000/QALY switching to biosimilar is cost-effective in 98.9% of iterations. However, as the threshold increases the percentage of iterations that are cost-effective decreases, since the results of the analysis primarily lie in the south-west quadrant of the ICER plane. For example, at a threshold of $200,000/QALY only 80.8% of iterations are cost-effective and the reference strategy appears increasingly attractive. At higher willingness-to-pay thresholds decision makers are less willing to accept an incremental loss in effect with biosimilars to gain additional cost savings.

Figure 10 Cost Effectiveness Acceptability Curve



3.3 Summary of Results

Ultimately, the results of the cost-utility analysis of switching to biosimilar infliximab compared with maintaining treatment on reference infliximab in adult patients with CD from the healthcare system perspective suggest that this intervention is associated with incremental cost savings and an incremental loss in QALYs over a five-year time horizon.

The reference infliximab treatment group was associated with average total costs of $96,385 and 3.1873 QALYs. In comparison, the switch biosimilar infliximab group was associated with average total costs of $50,191 and 3.0607 QALYs. This resulted in incremental costs of -$46,194 and an incremental decrement in QALYs of -0.1266. The majority of the 10,000 simulations (83%) were in the south-west quadrant with incremental savings and an incremental loss in effect associated with switching to biosimilar infliximab.

The results of the sensitivity and structural analyses suggested the model was sensitive to utilities, the probability of relapse, the cost of reference and biosimilar infliximab, and the time horizon of the analysis.

Chapter 4 Discussion

Given that biosimilars are a relatively new therapeutic option in Canada, stakeholders such as physicians, patients, and drug policy makers identified a need for further evidence – particularly with regards to switching from a reference biologic to a biosimilar product (Canadian Agency for Drugs and Technologies in Health, January 18, 2017; Institute of Health Economics, October 6, 2016) . As more biosimilars enter the Canadian market it is important to evaluate these technologies from both economic and clinical perspectives in order to develop effective reimbursement policies.

This chapter discusses the results of a CUA of a one-time switch to biosimilar infliximab compared with continuing treatment with reference infliximab in adult patients with CD. The strengths and limitations of this work are presented and the results are compared with currently available evidence. This chapter also discusses the implications these results may have for physicians, patients and healthcare decision makers. Finally, it shall conclude with recommendations for future research and evidence development in the biosimilar space.

4.1 Cost-Utility Analysis of Biosimilar Infliximab

The purpose of this thesis research was to assess the incremental cost of maintenance treatment for adults with CD who have been switched from reference infliximab to biosimilar infliximab compared with those who have continued on reference infliximab per QALY gained from the healthcare system perspective. The probabilistic reference case showed that average total costs and effects for switching to biosimilar infliximab were $50,191 (SD: $4,771) and 3.06 (SD: 0.38) QALYs over the five-year time horizon. In comparison, average total costs and effects for maintaining treatment with reference infliximab were $96,385 (SD: $6,834) and 3.19 (SD: 0.35) QALYs. While the intervention was associated with incremental costs of -$46,194 (95% CI: -$42,420 to -$50,455) it was also associated with a small loss in QALYs of -0.13 (95% CI: -0.16 to -0.07).

Results of the 10,000 Monte Carlo iterations indicated that approximately 84% of results were in the south-west quadrant of the incremental cost effectiveness plot, where an intervention is both less costly and less effective. This implies that biosimilar infliximab is likely associated with incremental savings over a five-year time horizon. This is an important finding with regards to

sustainability, particularly as patients with CD require lifetime treatment. However, decision makers must also account for an incremental loss of effectiveness. The analysis indicates that the average incremental loss over the five-year time horizon was approximately 6.5 quality adjusted life-weeks.

While these results suggest that a one-time switch to biosimilar infliximab is cost-effective based on a WTP threshold of 50,000/QALY, it is ultimately dependent on the willingness of drug plan decision makers to fund interventions in the south-west quadrant – which requires weighing a loss in effect against cost savings. It is important to note that all iterations of the evaluation lay under the conventional 50,000 WTP threshold. This suggests, based on this threshold, that the minimal loss in effectiveness is acceptable to healthcare decision makers in order to derive the incremental savings associated with switching to biosimilar infliximab.

4.1.1 Societal Perspective

When the analysis was conducted from the societal perspective, the differences compared to the healthcare system perspective were minimal. The costs in each treatment group increased as time spent in hospital, at physician visits and at infusion appointments were accounted for. However, the incremental cost savings associated with switching to the biosimilar were comparable to the reference case. Systematic reviews of the cost-effectiveness of biologics in the treatment of IBD have suggested that studies including both direct and indirect costs produce more favorable ICERs than those that exclusively consider the healthcare system perspective (Huoponen & Blom, 2015). However, the present analysis did not find a substantial impact when a societal perspective was employed.

The indirect costs of CD in Canada are substantial – in fact, indirect costs make up an estimated 56% of total annual IBD costs. However, the ability to capture these effects is limited (Crohn's and Colitis Foundation of Canada, 2012). There was a lack of direct biosimilar data, such as patient diaries or surveys, available to accurately model losses due to absenteeism, unemployment, caregiver time, loss of education, or delayed entry to the workforce, all of which would have substantial impact on the societal perspective of this analysis. It is therefore likely that this model is underestimating the benefit of reference infliximab in the societal perspective. Based on the NOR-SWITCH data, the relapse rate is lower for those who maintain treatment on the reference (Jørgensen et al., 2017). Due to this lower rate, those in the reference infliximab

treatment group would similarly likely benefit from lower absenteeism and unemployment rates. By not including these factors, the overall benefit for the reference group is therefore, likely being underestimated in the present societal analysis.

It is also important to acknowledge that the magnitude of these effects would likely be more substantial for young adults of working age as well as pediatric patients, particularly regarding costs associated with caregiver time and delayed entry to the workforce. There is a rising incidence of IBD in children in Canada; given that the results of the present analysis cannot be generalized to these populations it will be imperative to consider future research in this space, such as economic analyses which account for indirect costs for these patients (Crohn's and Colitis Foundation of Canada, 2012).

4.1.2 Uncertainty Analyses – Costs

On the cost side of the analysis the results showed the following variables were influential to outcomes of the model, including: the cost of the reference infliximab, the cost of biosimilar infliximab, and the number of vials required for a maintenance dose of infliximab. Firstly, the lower the per unit cost of biosimilar infliximab the higher the savings potential. This emphasized the importance of negotiating a substantial price discount for payers. If drug plan decision makers are able to negotiate a steeper price discount, this will improve the cost-effectiveness of switching to biosimilar infliximab and make the intervention more attractive from a policy perspective. Furthermore, if payers and physicians are willing to switch patients this may encourage biosimilar manufacturers to offer lower prices as there will be a higher volume of available patients.

However, sensitivity analysis also showed that a lower infliximab reference cost reduces the incremental savings associated with switching to biosimilars. This is an important finding as it suggests that a healthcare payer’s current formulary listing agreements for the reference infliximab product and any new confidential offers from the reference manufacturer may influence the amount of incremental savings they derive – which in turn affects the attractiveness of switching to biosimilar for all stakeholders. Consequently, this could influence the willingness of the drug plan decision makers and physicians to support a one-time switch to biosimilar infliximab. The cost effectiveness and incremental savings for each drug plan will vary based not

only on the price discount they are able to negotiate, but also on their individual arrangements with the reference manufacturer.

Some plans may be more, or less, willing to develop policies supporting a one-time switch dependent on this factor. For example, Manulife, a private plan in Canada, and the government of Prince Edward Island, a public payer, have each developed arrangements with the reference manufacturer whereby reference infliximab is less costly or equivalent in price to the biosimilar (Janssen, March 27, 2018; Manulife, 2016). Therefore, they may be less likely to develop biosimilar policies that support switching as the attractiveness of the intervention from a cost saving perspective is reduced. In contrast, Greenshield, another private payer in Canada, is developing a program which supports switching and has not acknowledged any arrangement with the reference drug manufacturer (Green Shield Canada, March 8, 2018). The uncertainty analysis in the present study underscores that drug plan managers will need to consider their individual arrangements with manufacturers when assessing the cost-effectiveness of a switch to biosimilar for their populations as these prices significantly influenced the conclusions of the model.

The threshold analysis found that in order for the costs of maintaining treatment with reference infliximab to be less than that of the switch group the price of reference infliximab would need to be less than $426.77 per vial. This is an 18% discount on the Ontario biosimilar infliximab price of $525.00 per vial and a total discount of 57% on the current Ontario reference infliximab price of $987.56 per vial. It is likely that reference infliximab would need to have a lower price than biosimilar infliximab to account for the fact that more patients stay on high cost maintenance treatment for the duration of the analysis due to the lower relapse rate. Treatment with reference infliximab was more effective according to NOR-SWITCH, and therefore the lower relapse rate allows those on reference treatment to avoid further downstream costs such as 2nd line anti-TNF therapy and surgery. However, avoiding these downstream costs does not appear to outweigh the higher costs of maintenance therapy with reference infliximab as evidenced by this threshold analysis which suggests that the reference would need to be priced lower than the biosimilar to be comparable.

It is unlikely that in the current Canadian policy environment the price of reference infliximab, even with confidential discounting, would be low enough to surpass this threshold for all payers.

Domestically, the pCPA, a collective of the Canadian public drug plans, was only able to negotiate a 47% discount for biosimilar infliximab and the reference manufacturer did not transparently match this price (Ontario Drug Benefit Formulary, 2017; Ontario Ministry of Health and Long Term Care, 2018b). Similarly in Norway, which employs an aggressive winner-take-all strategy with a national tender agreement process, the reference manufacturer did not offer a lower price than either of the biosimilar manufacturers (Mack, 2015). However, in Hungary, which employs a centralized tender for infliximab for 12 – 24 months, the reference manufacturer recently won the bid in 2017 (Medicines for Europe, September, 2017; Nemzeti Egészségbiztosítási Alapkezelő (National Health Insurance Fund), November 20, 2017). For drug plan decision makers this is a key consideration. Their ability to negotiate a price for reference infliximab will greatly influence the attractiveness of employing switching to biosimilar as a drug policy strategy. To date the collective bargaining power of the pCPA has not negotiated a lower transparent price for reference infliximab, however the international experience in Norway and Hungary suggests that with more competition through aggressive tendering processes and higher patient volumes, lower prices for both biosimilar and reference infliximab may be feasible. However, the competitiveness of the biosimilar market must also be considered when implementing any agreements with the reference manufacturers, as limiting biosimilar potential will reduce the attractiveness of the Canadian market to these producers.

Finally, uncertainty analyses also demonstrated that the more vials required per dose, the more savings can be derived from switching to biosimilar infliximab. This was demonstrated in a structural analysis comparing patient weights, that found that incremental costs for a 90 kg patient were higher at approximately -$58,000 over the five-year time horizon. Therefore, value in terms of incremental savings is in part dependent on the population using the therapy. Regional decision makers and physicians who manage CD populations in a higher weight range therefore, may be more likely to deem switching an attractive strategy.

4.1.3 Uncertainty Analyses – Effects

On the effectiveness side, probabilistic sensitivity analyses indicated that the results were sensitive to utility weights for the given health states and variations in the probability of relapse derived from the NOR-SWITCH trial. By increasing the utility weights for all states, the outcomes of the analysis increased for both treatment groups, however the incremental loss in effectiveness also moderately increased. Therefore, while influential to the overall effectiveness

of each treatment group the sensitivity analysis indicated that employing higher utility weights did not significantly alter the conclusions of the model.

In comparison, it was the probability of relapse from the biosimilar switch group that was particularly influential to the conclusions of the model. If the probability of relapse from clinical remission per cycle was lower for the biosimilar switch group, the incremental loss in effect associated with switching to biosimilar infliximab was reduced. The threshold analysis indicated that if the per cycle relapse rate for the biosimilar group was less than 0.0327, then the expected QALYs for the biosimilar group were higher than the reference infliximab group, which would imply that switching to biosimilar would be a dominant strategy. NOR SWITCH trial data, which was employed in the reference case, indicated that the per cycle relapse rate from remission for the biosimilar group was 0.0546. The threshold value of 0.0327 for the biosimilar relapse rate, is similar to the per cycle relapse rate for those who maintain treatment with reference infliximab in the NOR-SWITCH study of 0.0321 (Jørgensen et al., 2017). Given the results of other randomized and observational studies, which showed safety and efficacy between biosimilar and reference groups were not significantly different, it is feasible that the biosimilar switch group may achieve a more comparable rate of relapse to the reference infliximab group (Argüelles-Arias et al., 2017; Buer et al., 2017; Y. Kim et al., 2017; Soret et al., 2017). For example, in a randomized study of switching to biosimilar conducted in IBD, Kim et al, (2017) found that the percentage of patients who relapsed after one year was lower in the switch group (40%) than in the continue treatment with reference infliximab group (66.3%). In the case that a more comparable relapse rate occurs between the two groups then it is likely that the biosimilar switch group would not be associated with an incremental loss in effectiveness and could potentially be a dominant strategy.

Ultimately, this uncertainty analysis raised several questions surrounding the NOR-SWITCH data for the CD population. The primary analysis of NOR-SWITCH focused on all available indications and suggested that switching to biosimilar was non-inferior as the overall risk difference was -4.4% (95% CI: -12.7 to 13.2) in favor of reference infliximab which was within the established non-inferiority margin (Jørgensen et al., 2017). However, the CD specific results had a risk difference of -14.3% (95% CI: -29.3 to 0.7) in favor of reference infliximab (Jørgensen et al., 2017). No other disease states had a risk difference that was as strongly in favor of reference infliximab or that was as substantial in magnitude, which raises the question of

whether or not this controversial result for CD was an anomaly (Community Academic Research Education (CARE), 2017; Jørgensen et al., 2017).

Using the rates from the meta-analysis conducted by Komaki et al. (2017) allowed for the analysis of the model while employing relapse rates with a less substantial difference between the reference and the biosimilar infliximab groups. This uncertainty analysis tested a difference of 13% in favor of the biosimilar from the remission state and 4% in favor of reference infliximab from the response state. Due to the small number of available studies, these rates were highly variable. However, the results of this uncertainty analysis suggested that switching to biosimilar infliximab was associated with an incremental gain in QALYs. Overall, this sensitivity analysis suggests that if the NOR-SWITCH data is in fact an anomaly and the difference between the maintain and switch groups is less substantial or even in favor of the biosimilar as suggested by the meta-analysis then the incremental loss in effect is minimized or eliminated entirely (Komaki et al., 2017).

Finally, the structural uncertainty analyses also demonstrated that time horizon is an important consideration for both clinical and drug plan decision makers. The reference case analysis was five years in length; however, when a long-term time horizon of ten years was employed, both the incremental cost savings and the incremental loss in QALYs increased. Given that CD is a life-long disease a one-time switch to maintenance treatment with a biosimilar represents an opportunity to derive savings on a substantial portion of the drug budget over the long term. However, for patients and physicians this is weighed against a loss in QALYs which increases if they are maintained on the treatment for a longer time period. Therefore, the cost-effectiveness again depends on the willingness to accept this loss in exchange for incremental savings particularly in the long term.

4.1.4 Decision Making in the South-West Quadrant

Ultimately, the sensitivity analyses suggest that the results are robust in demonstrating that the intervention is likely cost-effective and associated with incremental cost-savings and a minimal incremental loss in effect. However, the fact that the majority of the probabilistic simulations lie in the south-west quadrant of the ICER plane which raises an interesting challenge for decision makers.

Frequently, health care decision makers must evaluate interventions that fall in the north-east quadrant, where a new intervention is associated with an incremental gain in effect, but at an incrementally higher cost. In this case, if an intervention has an ICER below the willingness-to-pay threshold then it is considered cost-effective (Drummond et al., 2015). However, the same decision rule is not consistently applied to the south-west quadrant and this creates reimbursement challenges for interventions which are associated with incremental cost-savings and an incremental loss in effect (Dowie, Kaltoft, Nielsen, & Salkeld, 2015). This can occur when there is conscious effort by healthcare decision makers to reduce expenditures by replacing or delisting expensive technologies with less costly ones – albeit with an acceptable loss in effectiveness.

While such interventions can technically be cost-effective, as was the case in this analysis where all 10,000 simulations lay under the WTP threshold of $50,000/QALY (see Figure 6), they are frequently excluded from consideration by decision makers due to the incremental loss in effect (Dowie, 2004). The basis for this argument tends to be ethical in nature, as it is important for society and decision makers to consider ethical values in addition to cost savings and effectiveness.

Dowie et al. (2015) identified that one of the primary arguments against SW interventions is that treating a SW intervention the same as a NE intervention involves “taking away” QALYs from those who are currently endowed with the treatment (Dowie et al., 2015). However, drug plan managers and physicians who are evaluating interventions from a wider healthcare perspective must make policy choices which account both for patients who are currently affected by the disease as well as patients who will be affected in the future. In the case of biosimilars, if the savings are reinvested and result in more QALYs gained than if those same funds were utilized for reference infliximab, then there may be additional value in switching for society as whole. For example, with those savings there may be potential to fund biologic treatment for more CD patients or provide treatment to a broader spectrum of future patients. By not considering an intervention which lies in the SW quadrant there are opportunity costs and potential downstream effects for future patients and society as whole (Dowie, 2004).

The case for adopting an intervention with an incremental loss in effect is stronger when the incremental savings increase since the overall health benefits for society, which may be

generated elsewhere by reinvestment also increase (Dowie et al., 2015). For example, the results of this analysis suggest that the incremental savings generated from switching one adult CD patient to biosimilar infliximab could provide maintenance therapy with biosimilar infliximab for approximately 4 additional patients for one year. Therefore, while it is important for drug plan managers and physicians to weigh social and ethical considerations of the current patient population they must also consider the opportunity costs for future patients.

This analysis ultimately suggests that switching to biosimilar infliximab is cost-effective for the Canadian environment when employing a willingness-to-pay threshold of $50,000/QALY. However, it is important to acknowledge that any economic evaluation is associated with inherent uncertainty and limitations.

4.2 Strengths & Limitations

This cost-utility analysis is one of the first economic evaluations of biosimilar infliximab in the Canadian environment which focused on adult CD patients who have been switched from reference to biosimilar infliximab. This is an important question for physicians, patients and drug policy decision makers as they establish reimbursement policies for these interventions; this analysis sought to add to the currently available evidence base. While biosimilar policy is steadily being developed for naïve patient populations, the safety and cost-effectiveness of switching from reference to biosimilar are still prominent questions for stakeholders (Canadian Agency for Drugs and Technologies in Health, January 18, 2017; Institute of Health Economics, October 6, 2016).

A primary strength of this analysis is the focus on a relevant policy question specific for the Canadian context. CD is a chronic disease with high prevalence and incidence in Canada. In 2012 it was estimated 129,000 Canadians had CD with an average of 16.3 new cases of CD per 100,000 people per year (Crohn's and Colitis Foundation of Canada, 2012). Biosimilars are still a relatively novel therapy in Canada and offer an opportunity to expand access to high value treatments for CD patients and improve Canadian outcomes.

The model framework was built in consultation with experts in CD and in keeping with other Canadian economic evaluations of infliximab (Blackhouse et al., 2012; J. K. Marshall et al., 2002). This framework accounted for differences between clinical remission and response states

and also modeled subsequent treatment options post-relapse on infliximab, including 2nd-line anti-TNF therapy and surgery. However, as with any disease state, there are limitations to modelling a complex disease and treatment pathway.

For example, CD is a relapsing and remitting disease, however this model did not allow patients to cycle between response and remission states when on a given therapeutic treatment. Another limitation relates to the structure of the model for treatment after loss of response to infliximab. Treatment guidelines recommend that the physician consider dose escalation as well as a switch to a 2nd line-anti TNF therapy (D. C. Sadowski et al., 2009). For the purposes of this analysis, only a switch to 2nd line treatment was modelled after relapsing on treatment with infliximab. Therefore, this does not account for patients in the Canadian context who may otherwise receive dose escalation to maintain response. These additional costs for infliximab and benefits from reestablishing remission or response are therefore not included in this model.

Furthermore, if a patient entered a drug refractory state after surgery it was assumed they could not exit this state and no second surgery or alternative treatment pathways were modeled after this point. The proportion of patients receiving surgery within the five years was small and was not found to be an important determinant of the results of the model. Therefore, modeling a second surgery would not have had a substantial impact on the results within a five-year time frame.

The model framework also included a death state, which is a strength as it provides a more complete analysis of the Canadian CD population. However, controversy exists on whether mortality due to CD differs from the general population (Bitton et al., 2016). These mortality rates, particularly for all-cause mortality are low, since this analysis focused on a relatively young population. Despite the controversy, this analysis also included an adjustment for the moderately higher mortality which is associated with having a CD diagnosis. This was accounted for by employing a standardized mortality ratio derived by Bitton et al (2016) based on a Quebec administrative database. Since this ratio was based on the Quebec public drug plan population of CD patients it may not be entirely representative of other Canadian CD populations. However, given that this ratio is comparable to others derived in the U.S. and Europe and as it was one of the only Canadian sources available, it was deemed appropriate for use in this analysis (Bitton et al., 2016; Hutfless, Weng, Liu, Allison, & Herrinton, 2007; Jess et al., 2007).

It is important to note that the model framework did not account for immunogenicity and the presence or development of anti-drug antibodies. The incidence of ADAs detected during the NOR-SWITCH trial were comparable between groups; excluding patients with detectable ADAs at baseline, there were 17 patients (7%) with ADAs in the reference group and 19 patients (8%) in the biosimilar group (Jørgensen et al., 2017). Given Canadian gastroenterologists and patient concerns regarding immunogenicity, it is a limitation that this model did not evaluate ADA development and the potential impact it may have upon outcomes or relapse (Community Academic Research Education (CARE), 2017). It has been shown that immunogenicity is a major cause of loss of response with infliximab (Komaki et al., 2017). Furthermore, a systematic review of infliximab biosimilars in the treatment of IBD found that efficacy could vary for patients who were switched to the biosimilar who had already developed ADAs against the reference molecule compared with those who had not developed these ADAs (Radin et al., 2017). This factor could therefore influence the outcomes associated with switching and could also assist in identifying those subgroups of patients who may be more likely to benefit from the biosimilar. Therefore, this represents a limitation of this model as the influence of this clinical factor and the potential for additional benefit in a specific subset of the CD patient population could not be identified.

The model framework did account for adverse events in the infliximab treatment states and considered infusion-related reactions. Serious adverse events were not accounted for in this model, however results from clinical studies suggested that safety outcomes do not differ between biosimilar and reference infliximab (Jørgensen et al., 2017; W. Park et al., 2017; Dae Hyun Yoo et al., 2013). Furthermore, adverse events of any type have frequently been excluded from other published economic models of reference infliximab due to their relatively small impact on costs or were assumed to be included as part of the administration or hospitalization costs (Blackhouse et al., 2012; Lindsay et al., 2008). By incorporating infusion reactions into the present model, the most commonly occurring adverse event for infliximab use, a reasonably complete picture of the costs and health effects of infliximab were included.

Finally, given that the model was a Markov analysis, it is important to acknowledge the primary limitation of this design; it is memoryless. The framework attempted to account for this property by including a second line therapy, accounting for changing mortality rates with age, alerting the surgical relapse rate by year and restricting patients to one surgical intervention in a five-year

period. However, given that the transition probabilities in a given state did not depend on how much time a patient may have spent in an earlier state or what adverse events they may have experienced this memoryless property may still represent a limitation in this regard (Sonnenberg & Beck, 1993). For example, the relapse rate was constant and did not account for how long a patient had been in remission, nor were any probabilities altered if a patient experienced an adverse event. Given that patients with ADA development are more likely to develop acute infusion reactions and to relapse from a treatment it represents a limitation that this history was not accounted for in the model (Moss, 2015).

Ultimately, these are simplifications of the CD care pathway and the framework of the model may not accurately represent the clinical progress of all CD patients. However, upon consultation with CD experts it was deemed appropriate to incorporate the assumptions previously described, particularly given the five-year time horizon of the reference case analysis.

On the cost side of this analysis, administration costs were included which is a strength in the sense that it accounts for infusion clinics representing a healthcare cost even if they are paid for by the manufacturer (Benefits Canada, 2017). A drug manufacturer paying for these services directly does not fit the typical Canadian model of publicly or privately funded health care. By taking a wider public-private healthcare system perspective this analysis provides a robust picture of the costs associated with administering and providing infliximab to Canadian patients. However, these drug administration costs may in some ways be reflected in the price of the drug as manufacturers do not provide these services for free, therefore there may be potential double counting, and this may represent a limitation in this regard.

The present analysis did not find that administration costs were influential with regards to the cost-effectiveness of switching to biosimilar. However, administration costs and the provision of patient support programs (which are provided by the manufacturer in Canada), were assumed to be equivalent between the reference and biosimilar infliximab groups. If biosimilar manufacturers are unable to offer the same level of service provision as reference manufacturers then this could be a potential limitation of the model, given that these programs can affect adherence and uptake by physicians and patients (Ganguli, Clewell, & Shillington, 2016). This model assumed one hundred percent compliance with infliximab, adalimumab and concomitant immunosuppressive treatments. If, however patients are less likely to be compliant when

switched to treatment with the biosimilar, due to the patient support program for example, this could impact the results of the model. Specifically, nonadherence to infliximab dosing has been associated with increased likelihood of antidrug antibody development and disease relapse (Ma et al., 2015). If adherence between the two treatment arms is not equivalent, it is possible that the model is overestimating the effectiveness of the treatment in a real-world cohort. Therefore, assuming one hundred percent compliance potentially represents a limitation of the model given the influence of adherence on outcomes of infliximab treatment.

CADTH recommendations have specified explicitly that the biosimilar manufacturer must provide similar patient support programs (CADTH Canadian Drug Expert Committee, October 25, 2016). Ensuring these programs are equivalent will thereby likely factor into negotiations with both private and public payers. Therefore, in order to receive reimbursement, biosimilar manufacturers will likely need to provide comparable programs; it was reasonable to assume that these service offerings and their influence upon costs and effects would be equivalent in this analysis. However, given that other factors may impact treatment adherence it is still a potential limitation that the influence of this variable was not accounted for in this model.

There were also limitations to costs associated with the societal perspective as it is particularly challenging to capture all indirect costs related to productivity. The present analysis did not include estimates for loss of caregiver time, absences from work due to illness, losses due to delayed entry to the workforce or unemployment. There was a dearth of literature available regarding estimates for these costs and this represents a substantial limitation of economic evaluation in the CD disease space. Therefore, this analysis solely included time lost due to healthcare services utilization which likely undervalues the additional societal costs associated with switching to biosimilar.

There were also strengths and limitations associated with the primary data sources that were utilized to inform the model, particularly the NOR-SWITCH study (Jørgensen et al., 2017). NOR-SWITCH was not powered to show non-inferiority in individual diseases. The study was powered to test the null hypothesis that biosimilar infliximab would be inferior to reference infliximab with regard to disease worsening during 52 weeks of treatment by 15% across six indicated disease states, including Crohn’s Disease, ulcerative colitis, ankylosing spondylitis, rheumatoid arthritis, chronic plaque psoriasis and psoriatic arthritis (Jørgensen et al., 2017).

Therefore, while the CD specific outcomes were utilized to inform the model the study itself was not powered to test whether there was non-inferiority between the reference and biosimilar infliximab treatment groups within this individual disease. The non-inferiority nature of the trial and the 15% margin, particularly as it relates to the CD group, has been highly criticized, particularly by Canadian gastroenterologists (Community Academic Research Education (CARE), 2017).

In a non-inferiority study the analysis is attempting to prove that a new treatment is not clinically inferior to standard therapy, and therefore the researcher must determine what is clinically meaningless in order to set the margin (Community Academic Research Education (CARE), 2017; Hahn, 2012). Herein lies the limitation with non-inferiority trials, as determining what is "clinically meaningless" can differ amongst experts. Canadian gastroenterologists have expressed concern with the 15% margin, stating that a narrower margin of 7.5% would be preferred (Community Academic Research Education (CARE), 2017). In some Canadian centers the relapse rate for patients on reference infliximab is close to 4% per annum (Walters, 2017). Therefore, Canadian gastroenterologists have expressed concern with applying results from NOR-SWITCH to their populations since the study was powered assuming that 30% of patients would relapse on infliximab treatment (Walters, 2017).

Furthermore, the point estimate for CD in NOR-SWITCH was 14.3% in favor of the reference. This was an outlier in the trial compared to the treatment effects for other disease areas, which were within a range of 8.7% in favor of the reference for psoriatic arthritis to 6.3% in favor of the biosimilar for ankylosing spondylitis (Jørgensen et al., 2017). This raised the issue of whether these two treatments were truly similar for CD and whether this difference was clinically meaningful (Community Academic Research Education (CARE), 2017; Jørgensen et al., 2017; Walters, 2017). The NOR-SWITCH study ultimately concluded that switching to biosimilar infliximab was non-inferior across all tested disease states. However due to the nature of the study Canadian gastroenterologists have cautioned against altering policy based on these results (Community Academic Research Education (CARE), 2017; Jørgensen et al., 2017).

Applying these results to a Canadian economic analysis therefore may not be directly applicable to Canadian centers, especially given the concerns raised by physicians. The NOR-SWITCH data may not be entirely generalizable to the Canadian CD patient population. For example, patients

in NOR-SWITCH had been maintained on Remicade® for a minimum of six months; however, at baseline only 60 – 70% were in remission. This may not be reflective of Canadian CD populations who are maintained on reference infliximab, where standards for maintaining or achieving remission while on treatment may be different (Walters, 2017) . For example; in Ontario, to receive renewal for coverage, a patient must demonstrate a minimum of a 50% reduction in HBI from pre-treatment, improvement in symptoms, and that they are no longer using steroids (Ontario Ministry of Health and Long Term Care, 2017). Therefore, the NOR-SWITCH data may not be entirely generalizable to Canadian populations maintained on reference infliximab who may have lower relapse rates or are more likely to be in a remission state.

Furthermore, NOR-SWITCH and consequently, the present analysis solely focused on adult patients. Therefore, a limitation of this is analysis is that these results cannot be extrapolated to child health. This is an important consideration given that CD is becoming increasingly prevalent in young populations (Crohn's and Colitis Foundation of Canada, 2012). Additionally, the trial and this analysis do not differentiate patients based on whether they are at a high or low risk for relapse. Therefore, the results of this analysis cannot be considered for specific age ranges or risk populations. There may be specific populations for which a switch to biosimilar may be more likely to lie in the south-east quadrant (incremental gain in effect and incremental cost savings), however these subgroups were not identified by this analysis. Rather it attempted to capture an average adult CD patient.

Ultimately, all of these limitations associated with NOR-SWITCH and the effectiveness data emphasized that the primary limitation of this analysis was the lack of literature available on the efficacy of switching patients from maintenance on the reference to the biosimilar. This not only limited the reference case analysis, but also limited the ability to inform separate uncertainty analyses around key parameter estimates of highly influential variables such as the relapse rates. While the data had its weaknesses, ultimately due to the lack of available literature NOR-SWITCH was the best available evidence to inform relapse rates for an economic model of switching to biosimilar infliximab as it was the first randomized controlled trial to examine this research question.

It is also worth noting that while randomized controlled trials such as NOR-SWITCH are the gold standard in evaluating treatments their study design can influence the generalizability of the results to a wider more diverse population (Gartlehner, Hansen, Nissman, Lohr, & Carey, 2006). Efficacy studies determine whether an intervention produces a given outcome in an ideal circumstance however, an effectiveness study measures whether the outcomes occurs in a real world setting (Gartlehner et al., 2006). Given that NOR-SWITCH was the best available randomized controlled trial, it was appropriate to employ this data to inform the analysis, however it is possible that these outcomes will differ in the real-world setting with a more heterogeneous CD population. Observational data, focused in the real world setting of CD, have generally shown that patients switched to maintenance treatment with biosimilar infliximab do not have significantly different safety or efficacy outcomes compared with patients who continued treatment with the reference biologic (Argüelles-Arias et al., 2017; Jung et al., 2015; Kang et al., 2015; Smits et al., 2016; Soret et al., 2017). However, these are small studies in terms of sample size and the variability suggests confounding, therefore these observational studies, while perhaps more reflective of a diverse population, were not utilized to inform the model (Walters, 2017).

Finally, NOR-SWITCH was conducted over a one-year period and therefore this model employed the same relapse rates for all five years of the time horizon. There is currently no other long-term data for relapse rates associated with switching to biosimilar infliximab. Due to this lack of data, this analysis assumed these rates were consistent in the long term, unlike the analysis conducted by Husereau et al (2018) which utilized a network meta-analysis to inform the long-term. This network meta-analysis was conducted as an indirect treatment comparison to compare one-year efficacy of biologics in CD (Mesana, Pacou, Naessens, Sloan, & Gauthier, 2017). It is advantageous to inform the long term with a calibration to real world evidence as studies have shown that maintenance of response can vary over longer time periods (Teshima, Dhanoa, Dieleman, & Fedorak, 2009). However, given that the mathematical model and input parameters of the model conducted by Husereau et al (2018) are privately owned an assumption surrounding long term relapse rates was made in the present analysis. While this is a potential limitation, the structural uncertainty analysis employing a ten-year time horizon suggested the outcomes between the Husereau et al analysis and this evaluation were comparable.

4.3 Implications for Canadian Stakeholders & Policy Options

The results of this analysis have implications for numerous Canadian stakeholders, including physicians, patients and provincial and private payers who are in the process of establishing reimbursement policies in an evolving marketplace. First, this section will compare this analysis with currently available Canadian evidence followed by a discussion of the implications for Canadian stakeholders, and potential policy directions with regards to switching.

4.3.1 Canadian Economic Evidence of Biosimilar Infliximab

To date, two economic evaluations of biosimilar infliximab have been conducted from the Canadian perspective. The first evaluated an induction and maintenance cohort and the other was similar in design to this study and focused on a population which was switched from maintenance therapy with the reference infliximab to biosimilar infliximab (Beilman et al., 2017; Husereau et al., 2018).

The study conducted by Beilman et al (2017) aimed to compare the cost-effectiveness of reference infliximab to the biosimilar infliximab for the management of CD. They utilized a five-year time horizon and probabilities and loss of response rates were extracted from published trial data and observational studies (Beilman et al., 2017). Costs were derived from the perspective of the Alberta public payer and the study ultimately found that biosimilar infliximab was associated with incremental cost savings and an incremental loss in QALYs (Beilman et al., 2017). Costs for the five-year time horizon in the study conducted by Beilman et al were higher for both treatment groups than those derived by the present analysis. Beilman et al found that average total costs were $167,388 for the reference group and $111,981 for the biosimilar group. This may be in part because their evaluation included initiation cycles, whereas the present study focused solely on patients on maintenance therapy who were subsequently switched. The effects over the five-year time horizon were however comparable between both evaluations. Ultimately, Beilman et al (2017) found that at a WTP of $50,000 per QALY biosimilar infliximab had a 91% probability of being cost-effective and suggested that biosimilar infliximab may help reduce the economic burden associated with CD.

This evidence is informative for private and public drug plan decision makers as they formulate reimbursement policies for infliximab naïve patients. To date numerous drug plans, such as the Ontario public drug plan, have established that naïve patients must start on biosimilar infliximab

therefore, it is promising that evidence from Beilman et al suggests this intervention is cost-effective (Ontario Drug Benefit Formulary, 2017). However, there is a population of CD patients in each drug plan who are already maintained on reference infliximab and therefore, switching these patients to biosimilar is a different policy and research question.

Husereau et al (2018) conducted an economic evaluation of switching Canadian CD patients to biosimilar infliximab as a part of their research examining policy options for infliximab biosimilar in inflammatory bowel disease. Their evaluation modelled a one-time switch to biosimilar infliximab based on the NOR-SWITCH study. The major differences between the present analysis and the Husereau et al evaluation are threefold. Husereau et al (2018) utilized a ten-year time horizon, accounted for dose escalation and relapse rates after year one of the evaluation were based on a network meta-analysis and calibration exercise. In comparison, the present analysis utilized a five-year time horizon, did not include escalation and relapse rates were assumed to remain constant over the course of the model.

This evaluation utilized one-year relapse rates for the maintain and switch groups from NOR-SWITCH adjusted to an eight-week cycle length which was subsequently applied to each cycle for the entire five-year time horizon. Husereau et al (2018) similarly employed NOR-SWITCH data to inform relapse rates in year one of their analysis. Since NOR-SWITCH was only conducted for a one-year period Husereau et al (2018) informed relapse rates post one year of clinical trial data with alternative sources. Their model estimated treatment effects for the remaining years of the analysis based on a network meta-analysis and calibration to real-world evidence (Husereau et al., 2018). This network meta-analysis was conducted as an indirect treatment comparison to compare one year efficacy of biologics in CD, including infliximab, adalimumab, vedolizumab and ustekinumab, and Bayesian probabilities for remission or response were derived (Mesana et al., 2017). Despite these differences, the results and conclusions of the Husereau et al analysis and the present evaluation are similar.

Husereau et al found that switching to biosimilar infliximab was associated with an incremental reduction in costs and with an incremental loss in benefits. The majority of the probabilistic iterations were similarly in the southwest quadrant of the ICER plane. Their ten-year costs associated with reference infliximab and biosimilar infliximab were CDN $168, 210 and $120, 753 respectively (Husereau et al., 2018). The results of the ten-year structural uncertainty

analysis of the present mode, were lower with CDN $132,420 and $65,207 total average costs for reference and biosimilar infliximab, respectively. The incremental savings associated with biosimilar infliximab were therefore, slightly higher than the evaluation conducted by Husereau et al (2018). This may in part be due to the differences associated with post one-year relapse rates.

Additionally, the differences in assumed relapse rates may have influenced the observed differences in effectiveness outcomes between the two evaluations. Husereau et al (2018) found that reference infliximab was associated with 6.02 QALYs while biosimilar infliximab was associated with 5.76 QALYs, an incremental loss of 0.27. In comparison the results of the present model in a ten-year structural uncertainty analysis suggested reference infliximab was associated with 5.72 QALYs and biosimilar infliximab was associated with 5.49 QALYs -- an incremental loss of 0.23.

Ultimately, while there were differences between these evaluations the results consistently suggest that switching to biosimilar infliximab is associated with incremental cost savings and an incremental loss in benefits.

4.3.2 Implications

As identified by CADTH, key elements which should be considered when evaluating whether a new technology should be reimbursed includes: patient input, clinical and economic evidence, existing treatment options, submitted prices and comparator prices, requested reimbursement criteria and jurisdictional implementation considerations (CADTH - pCODR, March, 2016). Therefore, this section will consider current position statements released by Canadian physicians and patients and the implications of this research for these stakeholders. The implications of this research for healthcare and drug plan decision makers will then be presented.

It is important to acknowledge that the results of this analysis speak to a one-time switch from reference infliximab to biosimilar infliximab. For the purposes of the implications of this research switching does not refer to multi-switches, i.e. where a patient may switch between biosimilar and reference multiple times or between biosimilars, nor does it refer to interchangeability. Switching will require a one-time change for the patient in consultation with a physician, whereas interchangeability implies the molecules are equivalent and can be changed at the pharmacy level without the involvement of a physician (Parker, March 20, 2017). While

these policies can be considered, the results of this analysis speak to a one-time switch and therefore, issues of multi-switches and interchangeability must be considered independently.

4.3.2.1 Implications for Patients & Physicians

A number of Canadian studies have utilized surveys to garner an understanding of patient concerns and to gauge their knowledge of biosimilars(Attara, Bailey, Marshall, Panaccione, & Aumais, 2016; Canadian Arthritis Patient Alliance et al., March, 2017; Gastrointestinal Society, 2017). These results speak to the challenges that biosimilars face upon market entry related to patients' values and serve as an important source of information for policy makers. In a biosimilar focus group conducted by several patient associations, the majority of patients living with one of the six inflammatory diseases which are treated by infliximab, were not confident in their knowledge of biosimilars, and there were concerns associated with them including; safety, switching stable patients, adverse events, and loss of patient support programs or coverage (Canadian Arthritis Patient Alliance et al., March, 2017). Generally, patients reported wanting more clinical studies on biosimilars and expressed anxiety surrounding switching for stable patients, particularly for non-medical reasons (Canadian Arthritis Patient Alliance et al., March, 2017) . Patients have expressed a need for further evidence on these topics and drug plan policy makers will need to exercise careful consideration of these concerns prior to implementing biosimilar switching policies. Physicians will similarly need to account for patients concerns if they implement a switch in order to ensure compliance and patient confidence in their treatment plan.

As another key stakeholder group, physicians have expressed similar concerns to their patients. It has been recognized that biosimilars represent a cost saving option which offer the potential of expanding coverage and access to more patients (CARE, January 13, 2017). However, there are still potential concerns regarding data extrapolation, immunogenicity and non-medical switching (CARE Gastroenterology Faculty, 2017). Furthermore, Canadian gastroenterologists have cautioned against the use of NOR-SWITCH results to justify non-medical switching due to the wide non-inferiority margin of 15% and the CD point estimate difference which was a 14.3% in favor of the reference (Community Academic Research Education (CARE), 2017). Physicians have emphasized the need for further evidence and post-marketing studies to support switching (Community Academic Research Education (CARE), 2017). Ultimately, the present analysis

sought to address this knowledge gap identified by patients and physicians from an economic perspective.

For patients, the results of this analysis show that switching to biosimilar infliximab may result in a minimal incremental loss of effectiveness for some patients and potentially an equivalent or even incremental minor gain in effect for others. While the average incremental loss is minimal, -0.13 QALYs over a five-year time horizon, it raises the question of what level of loss, if any, is a patient willing to accept? For while this analysis shows that the loss is acceptable to a decision maker with a 50,000/QALY threshold, a patient who is already endowed these QALYs may not share the same willingness to accept. As evidenced by the Crohn's and Colitis Canada's "No Forced Switch" campaign patients may not be willing to accept the risk of a minimal incremental loss in effectiveness even if some iterations of the model show that the treatments are equivalent or even minimally incrementally better (British Columbia Ministry of Health, December 2, 2016; Crohn's and Colitis Canada, 2016). Patient associations have expressed that stable patients should not be forced to switch therefore, this research may contribute to the patient associations' resistance to accept switching policies in some regards. Given the importance of political will in developing new policies if the patient associations are not supportive of a switching policy this may create challenges for physicians and drug plan decision makers in Canada.

However, the analysis also demonstrated that incremental cost savings were associated with switching to the biosimilar which is an important consideration for patients as well. If these savings are reinvested into the health system and utilized to increase access to biologic treatment for future patients with CD earlier in their care pathway for example this could lead to an overall improvement in outcomes for Canadian patients with CD. Similarly, with more room in the healthcare budget this may improve opportunities for current patients as it may extend access to new biologic treatments or to other 2nd line therapies for those patients who do lose response. Therefore, there is potential to improve the lives of current and future patients with CD if these savings are appropriately reinvested. Ultimately, this thesis research demonstrated that while patient concerns regarding loss of effect may be valid the incremental loss is minimal and switching to biosimilar is a cost-effective strategy in Canada. There is potential to improve the lives of more patients by expanding access to biologic treatment earlier in the care pathway with the savings derived through employing a switching strategy.

Similarly, this research contributes to the evidence base required by physicians to support the use of biosimilars in their patient populations. This analysis demonstrates that if physicians employ a one-time switch to biosimilar infliximab in their populations it may lessen the economic burden associated with the treatment of CD in Canada. While physicians are cautious regarding the NOR-SWITCH data given the 14.3% difference in relapse rates between reference and biosimilar infliximab this analysis showed that the incremental loss in effect over a five-year time horizon when employing these rates in an economic model were minimal (Jørgensen et al., 2017). For physicians this ultimately implies that switching may be a valid strategy to employ particularly if future research can distinguish which subgroups of patients may be more likely to benefit from treatment on the biosimilar.

Ultimately this research can improve physicians' confidence in using these products particularly as it relates to the cost-effectiveness of these treatments. As evidenced by the experience in Europe, where biosimilars entered the market earlier than in Canada, it took time, evidence and experience for physicians to build confidence in biosimilar usage. For example, the ECCO while initially cautious about the use of switching, recently updated their position statement and determined that an increasing number of publications have shown that there are no safety or efficacy concerns about switching (Danese, Fiorino, et al., 2017; Danese et al., 2013). However, they do express caution surrounding switching within six months of starting treatment in order to avoid the development of ADAs (Danese, Fiorino, et al., 2017). Therefore, while the Canadian system differs from that of Europe, Canadian physicians can utilize the growing evidence base, including this research, to inform their practice and similar to the European experience, build confidence in employing switching in certain patient populations.

4.3.2.2 Implications for Healthcare & Drug Plan Decision Makers

To date Canada has seen relatively low uptake of biosimilars (Health Canada, 2017a). Inflectra® initially had a small impact on public drug plan budgets with $0.6 million in sales in its first year, compared with Remicade's® $912 million in Canada in 2015 (QuintilesIMS, 2017). Since then sales have increased; growing to $3.8 million in 2016, and an estimated $5.7 million for 2017, however there was no corresponding decrease in the sales of Remicade® (QuintilesIMS, 2017).

This is likely due to the evolving reimbursement policy implemented by public payers, particularly for naïve patient starts. For example, provinces such as Ontario removed

administrative barriers to access by making Inflectra® a limited use product rather than exceptional access only, and by mandating usage of Inflectra® in naïve patient starts (CARE, January 13, 2017; Ontario Ministry of Health and Long Term Care, April 10, 2016). In another study conducted by the Patented Medicines Price Review Board (PMPRB), it was found that if the use of biosimilar infliximab in Canada mirrored the median Organization for Economic Co-operation and Development use in 2015 it would have translated into a $41.7 million reduction in drug expenditures(National Prescription Drug Utilization Information System, April 27, 2017). Therefore there is the potential for substantial savings with higher uptake (National Prescription Drug Utilization Information System, 2017). For private and public drug plan decision makers the policy question remains of how to benefit from these savings by encouraging uptake where it is appropriate.

The present analysis suggests that it is cost-effective to encourage switching in the adult CD patient population currently maintained on reference infliximab assuming drug plan decision makers are willing to fund interventions in the south-west quadrant. The results demonstrate that switching patients from reference infliximab to biosimilar infliximab is associated with incremental cost-savings. However, it also highlights the concerns of patients and physicians in that it was also associated with an incremental loss in effectiveness over the course of the 5-year time horizon. If drug plan decision makers are willing to accept a minimal reduction in benefit then this intervention is cost-effective, and they should consider establishing policies which support switching to biosimilar. However, the current policy landscape, for biosimilars and all pharmaceutical products in Canada is challenging.

Drug plan decision makers are in the midst of many changes in the Canadian market which has greatly increased uncertainty for payers, both public and private, and manufacturers. Drug prices and the rising costs of healthcare are under heavy scrutiny as evidenced by the Canadian Health Minister’s focus on lowering Canadian drug prices and the increase in federal funds to the PMPRB, which serves as a consumer protection agency in the pricing of patented medicines (Government of Canada, December 2, 2017; Sawa & Ellenwood, January 13, 2017). The PMPRB has also recently released regulations amendments which would expand their scope in lowering patented prices (Government of Canada, December 2, 2017). The amendments include a requirement that manufacturers report confidential rebates to the PMPRB which may affect the discounts that payers are able to derive through these non-transparent measures (Government of

Canada, December 2, 2017). Should these regulations come into effect there would be substantial changes to how drug prices are regulated in Canada which increases uncertainty for manufacturers and payers as the reimbursement and pricing environment in the coming years is unclear.

These potential changes are coupled with a growing interest in national pharmacare, which is another policy that is being evaluated to reduce healthcare costs and improve outcomes but it could be a costly endeavor for Canadian governments (Adhopia, Feb 26, 2018). It is estimated that a universal pharamacare program would save Canadians $4.2 billion a year, however that does not include the cost to government of extending insurance coverage (Adhopia, Feb 26, 2018). A federal government advisory council is currently examining the creation of a national pharmacare plan and is consulting with a wide range of stakeholders regarding how this policy would be designed and implemented (Adhopia, Feb 26, 2018). It is evident based on these changes that there is substantial focus on lowering drug prices and deriving cost savings for the Canadian healthcare system. Drug plan managers are therefore dealing with numerous levels of uncertainty in their policy landscape based on these changes and are under substantial pressure to lower prices and address sustainability.

The results of this thesis research are therefore, particularly relevant for drug plan managers and policy makers. Biosimilars represent a unique opportunity for drug plan decision makers to derive cost savings on a substantial portion of their drug budgets due to the high costs of biologic treatment (Canadian Institute for Health Information, 2017). By considering a switch to biosimilar infliximab for CD populations on maintenance therapy with the reference, drug plan managers could achieve incremental cost savings in their budgets, which is a primary objective of the current Canadian policy environment. In a landscape of uncertainty and long-term policy options, such as national pharmacare or pricing reform, biosimilar switching policy is an option that drug plan managers can implement in the current environment and at the provincial or private level to achieve savings with a cost-effective intervention.

4.3.3 Policy Options

Several policy options which address switching have been identified by international drug plans, domestic private payers and the literature. Certain policies are more aggressive in terms of driving switching to biosimilar whereas others attempt to address uncertainty through further

evidence requirements or incentive schemes. Evidence based policy options which support switching will be briefly discussed below, but it is important to acknowledge that this is not a systematic analysis of options and regional policy makers will need to consider the characteristics of their patient populations and their individual evidence needs.

First, one example of a policy option which is strongly supportive of switching to biosimilar is the tendering strategy. For this policy, the public payers or private group purchasing organization releases a tender for a molecule (either reference or biosimilar) where the winning bidder supplies the product of choice for a given period of time (Mack, 2015). Norway for example, employs this strategy with infliximab amongst other biologics (Mack, 2015). The Norwegian Drug Procurement Cooperation negotiates a tender with the winning manufacturer, typically the one with the lowest offered price, and subsequently funds and recommends the winning drug, either biosimilar or reference, for their populations over a one-year time horizon (Mack, 2015). It is however possible for physicians to use another drug based on a specific patient's needs and the public payer will cover the cost after a request has been submitted (Mack, 2015). This is an aggressive strategy and as such Norway has realized almost a 72% discount from the Remicade® list price (Mack, 2015). With these savings, hospitals in Norway were able to treat a patient for three years with the biosimilar for the same price as one year with the reference (Generics and Biosimilar Initiative, 2015). While this policy option would likely encourage substantial savings to a drug plan payer, this type of strategy would not address the concerns of Canadian physicians and patients regarding autonomy of choice. Furthermore, if the winning bidder of the tender changed year over year which has occurred in the Norway system it could potentially create switches between multiple agents which this analysis did not assess.

Drug plan managers could also consider the use of outcome-based agreements in the reimbursement of biosimilars (Husereau et al., 2018). These schemes, also known as managed entry agreements, "are an arrangement between a manufacturer and payer that… uses a variety of mechanisms to address uncertainty about the performance of technologies" (Vitry & Roughead, 2014). To accomplish this objective, these arrangements can involve outcome guarantees or coverage with evidence development (Roughead, 2017; Vitry & Roughead, 2014). With an outcome guarantee a manufacturer may be required to rebate or reimburse the payer if certain patient level outcomes are not met (Vitry & Roughead, 2014). With coverage with evidence development, the reimbursement status of the product and/or the price are dependent on

data that the manufacturer must develop and later submit to the payer (Vitry & Roughead, 2014). While these agreements have not been prominent in Canada to date, six agreements have been identified by the literature (Toumi, Zard, Duvillard, & Jommi, 2013). For example, Merck-Frost established a payment for performance agreement for finasteride where the manufacturer offered full cost reimbursement to provincial payers if a patient required surgical treatment after one full year of drug treatment (Toumi et al., 2013). Therefore, drug plan policy makers could develop outcome-based agreements with biosimilar manufacturers to ensure that patients who are switched perform equally as well on the biosimilar as the reference product. Similar to the agreement established with Merck-Frost biosimilar manufacturers could for example offer rebates for patients that relapse on maintenance treatment or those which require surgical intervention.

This option is beneficial in that it addresses uncertainty surrounding effectiveness and also necessitates the development of post-marketing data which was identified as a need by Canadian gastroenterologists (Community Academic Research Education (CARE), 2017). However, there are challenges associated with the execution of these agreements (Montilva, Degun, & Xue, 2016).

While there is support present for the use of these arrangements it can be logistically challenging to set up this type of agreement when the Canadian system is designed as a patchwork of many public and private drug plans (Montilva et al., 2016). Furthermore, there is the administrative challenge of how and who will collect the required clinical endpoint data (Montilva et al., 2016; Wonder, Backhouse, & Sullivan, 2012). If biosimilar manufacturers must set up data registries in order to ensure their product is reimbursed in switch populations it may no longer be competitively viable to offer a substantial price discount (Wonder et al., 2012). This could potentially limit the competitiveness of the biosimilar market in Canada. Finally, drug plans must also consider that this likely will not address patient concerns related to switching since these arrangements will involve a rebate to the payer should outcomes not be met, and it will be the patient that experiences the incremental loss in benefit.

Another policy option is for Canadian agencies, such as CADTH and drug plan payers, to mandate the development of switching evidence in order to support switching designations. This policy would encourage evidence development to inform physicians and patients. However,

again these types of requirements may discourage the development of a viable market for biosimilar manufacturers and could limit the number of biosimilars that come to the Canadian market (Husereau et al., 2018). Ultimately, regulators and drug plans will need to weigh whether the loss of value due to lack of information is outweighed by the potential loss of biosimilar development should this requirement be mandated.

One final approach that policy makers could consider would be one which encourages a one-time switch from the reference to the biosimilar through incentive schemes. Payers could provide support for a one-time switch informed by physician and patient choice which would allow payers to derive the incremental cost savings that the present analysis demonstrated (Husereau et al., 2018). Canadian payers, both public and private, have allowed for switching with their current reimbursement criteria for biosimilar infliximab thus far however, uptake has been low (QuintilesIMS, 2017). Therefore, while a hands-off approach respects patient and physician autonomy it likely will not encourage high switch rates or generate cost savings. Implementing an incentive based initiative may be more likely to drive uptake in eligible patient populations (Husereau et al., 2018)

With an incentive-based policy, public and private drug plans could encourage switching by offering payment incentives for example. Payers can incent a switch by fully funding the biosimilar product if a patient chooses to switch and charging a top up fee to patients who choose to maintain treatment with the reference (Husereau et al., 2018). Green Shield Canada is in the process of rolling out this policy, referred to as the Biosimilar Transition Program for infliximab, but only for rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis indications (Green Shield Canada, March 8, 2018). Green Shield will provide a team of care-coordinator nurses to assist those patients who choose to switch and those members who do not transition will pay the difference in cost between the two products (Green Shield Canada, March 8, 2018). This strategy actively encourages uptake of the biosimilar product through an incentive-based program while still permitting autonomy of patient choice.

Should public drug plans choose to implement reimbursement policies which support switching the results of this analysis can be utilized to further inform price negotiations at the pCPA level. Both biosimilar infliximab and reference infliximab have completed negotiations with the pCPA however, should the drug plans collectively consider implementing switching, as suggested by

this analysis, they could potentially re-negotiate agreements for these populations (Canada's Premiers, 2017). The pCPA First Principles which details negotiations for biosimilars also allows for reference manufacturers to negotiate, however both manufacturers must be willing to offer a transparent price reduction which could therefore also benefit private plans (The pan-Canadian Pharmaceutical Alliance, 2016). It is also worth noting that while there must be a transparent price available according to the principles this does not exclude the use of additional confidential discounts. Manufacturers may be willing to offer more substantial confidential discounts for switch patient populations to access these markets. The results of this analysis imply that switching to biosimilar is a cost-effective strategy, and also includes thresholds that the reference manufacturer would need to meet to dominate the savings derived from the biosimilar. Therefore, evidence such as this economic evaluation could be leveraged to inform a collective negotiation and derive the highest potential price discount from either biosimilar or reference manufacturers where appropriate.

However, it is important to acknowledge that while there are benefits to negotiating as a collective through the pCPA there are also challenges due to the fact that Canada’s health care system is designed as a patchwork. Provinces may vary in their willingness to implement switching policies and need to account for their individual patient populations, political landscapes and financial arrangements. Therefore, it may be challenging to collectively agree on one policy and move forward with a collective negotiation. Some drug plans may be more willing than others to implement a switching policy. Ongoing discussions in British Columbia suggest that their pharmacare program is under significant budget pressure and are therefore, considering switching to biosimilar infliximab in order to derive cost savings which can allow funds to be used for other health priorities (British Columbia Ministry of Health, December 2, 2016). In comparison, other provinces have not expressed the same interest in switching policy and given their own needs have turned to alternative arrangements. For example, the government of Prince Edward Island recently signed an agreement in March, 2018 with the reference manufacturer of infliximab which set the cost of Remicade® at the same level of other treatment options including biosimilars (Janssen Inc., April 26, 2016). Therefore, this shows that some public payers may be may be willing to pursue non-transparent individual arrangements with reference manufacturers despite the principles outlined by the pCPA (The pan-Canadian Pharmaceutical Alliance, 2016). Overall this highlights that a national approach in this regard

may not be possible as some payers may be more open to switching than others and each will adjust to their independent jurisdictional needs.

Ultimately, it is evident that these policy options each have relative strengths and weaknesses which must be considered by decision makers when moving forward in the biosimilar pricing and reimbursement environment. The present analysis contributes to the growing evidence base regarding the cost effectiveness of a one-time switch to biosimilar infliximab. It demonstrated that biosimilar infliximab is associated with incremental cost-savings however, it must be weighed against an incremental loss in benefits. Therefore, policy makers should take this evidence into account when negotiating prices and developing policies which must also account for physician and patient preferences and autonomy regarding treatment choices.

4.4 Future Research

While this analysis contributed to the growing evidence base surrounding biosimilars it also highlighted that there are knowledge gaps that remain. There is therefore, value in conducting future research in clinical, economic and budgetary analyses of biosimilar infliximab in the treatment of CD.

4.4.1 Clinical Effectiveness

Given the importance of the rate of relapse from treatment with infliximab, it would be valuable to conduct further clinical research into these rates over the long term and in studies focused solely on IBD indications. Health Canada has stated a preference for equivalence trials when testing the clinical efficacy of biosimilars (Health Canada - Health Products and Food Branch, 2016). Therefore, equivalence studies focusing on switching in CD could provide evidence to address uncertainty expressed by physicians and patients regarding biosimilar usage.

In the United States, to support switching manufacturers must successfully demonstrate that the proposed product can be expected to produce the same clinical result as the reference (U.S. Department of Health and Human Services, January 2017). Similar studies could be beneficial in the Canadian context to support switching. As noted above Health Canada expressed an equivalence design is preferred where the study is conducted using a “sensitive endpoint to show that there are no clinically meaningful differences and where the acceptable margin should take into account the smallest effect size that the reference biologic would reliably be expected to

have based on publicly available historical data" (Health Canada - Health Products and Food Branch, 2016). Since one cannot show that treatments have equal efficacy, an equivalence trial requires a margin be established in which two treatments can be considered not to differ "too much"(Lesaffre, 2008). This varies from a non-inferiority trial where one only defines an upper bound to establish that the intervention is non-inferior to the standard (Lesaffre, 2008).

In this case researchers could design double blind and randomized equivalency trials comparing patients maintained on reference infliximab and those who were switched to biosimilar specifically in CD populations. The study should be designed whereby CD patients who are safely maintained on reference infliximab according to Canadian standards either continue treatment or are switched to biosimilar with the same dosing and administration in a controlled clinical trial setting. Relapse rates, and other key outcome measures such as ADA development, adverse events and quality of life can then be evaluated over the course of the trial. The acceptable margin to show that the treatments do not differ "too much" however, should be carefully considered with Canadian gastroenterologists in order to establish results which would be generalizable to Canadian practice. Furthermore, this study should attempt to identify factors, such as presence of ADAs or age groups, which influence the relapse rate. This may assist physicians in identifying patients who may be more likely to perform equally as well or better upon switch to biosimilar. Overall, further clinical trials assessing switching would address the uncertainty expressed by physicians regarding the NOR-SWITCH data and could provide further evidence to patients regarding any differences in relapse rates.

Given that NOR-SWITCH was only conducted over a one-year time period it would also be beneficial to conduct long term extension trials of any switching studies of biosimilar infliximab. This would assist in addressing one of the limitations identified by this analysis in that relapse rates after a one-year period were unavailable and therefore, the long-term outcomes associated with maintenance therapy with infliximab are unclear. Typically, an extension study follows a double blind randomized controlled trial and at the end of the time period a patient is invited to enroll in an extension study (Taylor & Wainwright, 2005). All participants are given the intervention of interest and the objective is to gather information about safety and efficacy in the long term (Taylor & Wainwright, 2005). Therefore, after the completion of an equivalence trial it would be informative to allow patients to continue maintenance therapy on the biosimilar in order to assess how relapse rates may vary for these patients who were switched in the long term.

Furthermore, patients who were maintained on reference infliximab for the duration of the equivalence may also be offered the biosimilar at this point. In this way it may be possible to evaluate the effects of a one-time switch in a setting which is less rigid than that of a clinical trial (Taylor & Wainwright, 2005). Ultimately, this type of extension study would answer important questions for physicians and patients on how these drugs perform in the long term which is a key consideration due to the chronic nature of CD.

There is also uncertainty surrounding the fact that multiple infliximab biosimilars are coming to the Canadian market (CADTH, April, 2018). Therefore, it may also be beneficial to assess multi-switches in a clinical trial setting. Again, an equivalence trial would provide important data on the clinical endpoints associated with switching however, in these designs the switching branch should involve two separate exposure periods to both the biosimilar and reference infliximab (or an alternative biosimilar) (U.S. Department of Health and Human Services, January 2017). This type of clinical study would inform stakeholders on the clinical outcomes associated with multiple switches between reference and several biosimilars. Therefore, this would provide essential information to patients who have expressed concern about switching between various biologic treatments and would also support policy design. While this analysis only assessed a one-time switch, physicians and drug plan policy makers will need to consider how to address multiple biosimilar products as they enter the market and will require further evidence regarding any difference in relapse rates and clinical outcomes.

Finally, from a clinical perspective, physicians will also likely require updated treatment guidelines and position statements regarding biosimilars as they become more prominent in the Canadian market and the evidence base expands. The Canadian treatment guidelines for CD do not currently include biosimilars; for either initiation or switching (D. C. Sadowski et al., 2009). According to expert opinion new guidelines for CD are expected in the coming year, and it will be important to address the inclusion of biosimilars in the care pathway. Furthermore, as experience with biosimilars in Canada increases and the evidence base grows an updated CAG position statement regarding the use of biosimilars may also be required. The current position statement was produced in 2013 and the environment has evolved rapidly since that time (Devlin et al., 2013). This type of clinical research and guidance will be imperative to inform practice for Canadian gastroenterologists and guide the treatment pathway of Canadian patients with CD.

4.4.2 Cost Effectiveness & Budget Impact

The clinical research discussed above will be imperative to inform Canadian stakeholders on the evolving biosimilar environment, however it is also important to address the economic and budget perspectives. The intervention in this model was associated with an incremental loss in benefits therefore, further economic evidence, perhaps informed by the clinical research described above, would be useful in developing a more thorough understanding of the cost-effectiveness of a one-time switch.

Given that relapse rates were influential to the results of the model and there was a lack of literature surrounding outcomes after a switch, further clinical evidence which can inform on these inputs will be imperative in developing future cost-effectiveness analyses of biosimilar infliximab. This may reduce uncertainty surrounding the incremental effect associated with switching to biosimilar infliximab. Furthermore, if factors which may influence the relapse rate, such as the development of ADAs, are identified this may allow for sub-group analysis from the economic perspective. This may facilitate an understanding of which patients may be less likely to experience an incremental loss in effect and for whom switching to biosimilar may be a dominant strategy. Ultimately, by conducting more economic models of biosimilar infliximab researchers could reduce the uncertainty surrounding the effectiveness of a switch and identify those subgroups in which this intervention may be more likely to be a dominant strategy.

It would also be informative to an economic model of switching to biosimilar infliximab to conduct a meta-analysis of relapse rates from clinical remission and response states after switching, similar to the study conducted by (Komaki et al., 2017). Since the release of this meta-analysis further clinical evidence has been published which could be informative of these rates. For example, it would be valuable to include rates from all studies referenced in Appendix I, as not all were considered by Komaki et al, as well as recently published observational data which shows there is no difference in remission or response rates between those who maintain treatment on reference infliximab and those who switch to biosimilar infliximab (Høivik et al., 2018; Ratnakumaran et al., 2018). It would also be beneficial to incorporate rates derived from a phase III randomized controlled trial conducted by Kim et al (2017). This trial, which was discussed previously in this work and demonstrated that clinical remission and response rates were maintained and similar even after switching(Y. Kim et al., 2017). Ultimately, conducting a

meta-analysis incorporating further data would reduce the variability of these estimates and be informative for future economic models of biosimilar infliximab.

Similarly, a limitation of the present study was utilizing a constant rate of relapse for the entire five-year time horizon of the model. Therefore, incorporating rates from long term studies such as the extension trial of NOR-SWITCH would be useful to inform the model and improve the generalizability of the results(Jørgensen et al., 2018). This was a 26 week open label extension trial which demonstrated the disease worsening rate for the Crohn's Disease subgroup was 20.6% in the reference infliximab group and 13.1% in the switch to biosimilar group which gave a risk difference of 7.9% (95% CI: -5.2 to 21)(Jørgensen et al., 2018). Given these rates are in favor of the biosimilar, future research may find that the incremental loss in effectiveness associated with switching is less than the results suggested by this analysis.

Furthermore, the present model did not address multiple switches between the reference and biosimilar infliximab (Inflectra®), nor did it consider switches to a different biosimilar infliximab. As more biosimilars enter the market researchers should consider developing economic models which account for switches to multiple alternative products to inform on the cost-effectiveness of multiple biosimilars.

When considering multiple biosimilars it will also be necessary to consider the impact this may have upon costs and effects. Drug prices were one of the primary drivers of this cost-effectiveness analysis, therefore if multiple infliximab biosimilars enter the Canadian market and increase competition this could affect costs through more substantial price discounts. Furthermore, the second line treatment included in this analysis, adalimumab, will also go off patent in the coming years and biosimilars of this product are forecasted to arrive in Canada between 2019 – 2021(National Prescription Drug Utilization Information System, April 27, 2017). Future research should consider incorporating adalimumab biosimilars in economic evaluations of infliximab as the effectiveness and costs related to the 2nd-line therapy included in this model will vary with the introduction of these products. This will provide a more robust picture of the evolving Canadian environment and allow drug plan decision makers and physicians to have an economic understanding of how these new products may fit into the treatment care pathway.

Finally, public and private payers may be more likely to consider an intervention which lies in the south-west quadrant of the cost-effectiveness plane when they are associated with substantial incremental cost-savings. Therefore, conducting budget impact analyses of switching from reference to biosimilar infliximab for patients with CD may also be of value. Conducting budget impact analyses for the public drug plans which can be adjusted for the given provinces' current CD population and any confidential arrangements which may exist in the public sphere would allow decision makers to assess the true level of savings they may derive from switching policies. Similarly, private drug plans fund a substantial portion of biologic spending and creating a BIA with cost per plan member estimates would allow them to adjust based on individual plan populations and support their decision making. Ultimately, these assessments would assist public and private payers in developing reimbursement policy, particularly to incorporate the effects of any confidential arrangements they may already have in place.

4.4.3 Preference Research

Uncertainty analysis of the present economic model identified that utility weights for the health states associates with CD were influential to the effectiveness results of the model. This model assumed that utilities for patients being treated with reference or biosimilar infliximab were equivalent. However, given the importance of these weights and the concerns expressed by patients regarding the efficacy of these treatments there would be value in conducting further research into health state preference utilities in the CD disease space.

Measuring health state preferences can be challenging as it attempts to measure the way in which individuals perceive and make judgements regarding subjective health states (Froberg & Kane, 1989). Due to these challenges researchers have designed multiple methods which vary based on their reliability, validity and feasibility including; standard gamble, time trade-off, rating scales and willingness-to-pay methods (Froberg & Kane, 1989). While more complex to administer the standard gamble and time trade methods are valid and reliable methods to derive utilities which provide a single cardinal measure of health-related quality of life (Torrance, 1987).

Therefore, it would be valuable to conduct a standard gamble or time trade-off analysis for Canadian patients with CD, particularly of those who may be switched to the biosimilar treatment. This would inform economic evaluations of these technologies while also assessing whether these two treatments are equivalent in terms of utility weights for health states. Patients

have expressed anxiety surrounding potential switches so it would be valuable to assess if this in turn has any impact upon patient quality of life (Canadian Arthritis Patient Alliance et al., March, 2017).

4.4.4 Pediatric Research

Finally, it is important to acknowledge that the present analysis and the future research discussed above solely addressed adult patients with CD and therefore, these results cannot be generalized to pediatric patients. Given the growing incidence and prevalence of CD in young Canadian patients it will be imperative to assess the clinical and economic effects of biosimilar infliximab for these populations (Crohn's and Colitis Foundation of Canada, 2012).

Biosimilar infliximab is not currently indicated in pediatric populations for the treatment of CD in Canada as the safety and efficacy has not been established (Celltrion Healthcare Co Ltd, 2016). While small scale studies have been conducted in pediatrics and have suggested the treatments are not significantly different with regards to safety and efficacy, a complete clinical data package will need to be developed (Jahnsen, 2016; Sieczkowska et al., 2016). It will first be necessary to assess the clinical effectiveness and safety of biosimilars as a potential treatment option for pediatric patients. Therefore researchers will need to conduct pharmacokinetic, pharmacodynamic and clinical trials to demonstrate that the biosimilar and reference are similar in the treatment of pediatric patients with CD as required by Health Canada (Health Canada - Health Products and Food Branch, 2016; Ridgway, March 2017).

Once clinical effectiveness and safety of the product has been established for naïve pediatric patient populations switching will also need to be assessed. Switching from reference to biosimilar infliximab is an independent research question. Therefore, it will need to be assessed separately preferably with a clinical trial designed as an equivalence study (Health Canada - Health Products and Food Branch, 2016).

Finally, cost-utility analyses for initiation and maintenance therapy as well as switching will be an important consideration in the health technology assessment of biosimilar infliximab for pediatric patients. In order to inform these analyses researchers should also consider preference research specific to pediatric patients as well as patient surveys to assess caregiver time and delayed entry to the workforce as these will have a significant impact on the costs associated with the societal perspective. While the societal perspective did not significantly impact the

results in the present analysis, there will likely be significant costs impacts if these factors can be incorporated into a model in the pediatric space. Economic evaluations in this space will be imperative to address questions of value and cost-effectiveness of the use of these products specifically in the pediatric space.

Ultimately, evidence will need to be produced for the entire spectrum of clinical and economic questions surrounding the use of biosimilar infliximab in pediatric patients to inform key stakeholders such as patients, families, physicians and healthcare decision makers. The results from adult studies cannot be extrapolated for use in these populations therefore, stakeholders will require evidence which focuses specifically on pediatrics in order to incorporate these products into their treatment pathway where appropriate.

Chapter 5 Conclusion

Biologics are an important treatment option for adult patients with Crohn's Disease however, they represent a substantial cost for both public and private plans. In this regard, biosimilars represent an important treatment option to derive cost savings particularly if patients currently receiving long-term maintenance therapy on reference infliximab are switched to treatment with biosimilar infliximab. However, physicians, patients and policy makers have raised a number of questions related to the clinical and cost-effectiveness of switching to biosimilar infliximab in these populations.

This thesis work is one of the first economic evaluations of switching to biosimilar infliximab compared with continuing treatment on reference infliximab. It confirms the results of Husereau et al (2018), which examined a similar research question from the Canadian perspective. The results indicate that a one-time switch to biosimilar infliximab is associated with incremental savings for patients with CD compared with maintaining treatment on reference infliximab. However, decision makers must also account for an incremental loss of effectiveness with biosimilars in accordance with the NOR-SWITCH subgroup analysis.

This research ultimately suggests that a switch from reference infliximab to biosimilar infliximab in adult patients with CD is cost-effective. However, key stakeholders, such as drug plan managers, physicians and patients, must establish if the minimal incremental loss of effectiveness is acceptable to derive cost savings. The incremental savings derived from policies which encourage a one-time switch to biosimilar infliximab may allow for expanded access to high value biologic treatments for Canadian patients with CD. However, given the incremental loss in effectiveness demonstrated by this analysis and other evidence, it is clear that there is still uncertainty present.

Further evidence regarding switching will be integral as jurisdictions work to develop effective reimbursement policies for biosimilars. In addition, given that switching to biosimilar infliximab in an adult CD population may be more desirable if more savings can be derived, drug plan managers may also benefit from further research into the budget impact of biosimilar infliximab in the Canadian context.

In conclusion, biosimilars represent an important addition to the treatment options available to Canadian adult patients with CD. This chronic disease can have serious impacts on patients' quality of life and expanding access to high-value treatments is integral to improve patient outcomes. This cost-utility analysis provides valuable information to decision makers regarding the cost-effectiveness of a switch to biosimilar infliximab and emphasizes that making reimbursement decisions is challenging and therefore, further research will be important to develop policies which meet the needs of society.

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Appendices

Appendix I – Biosimilar Observational Studies

First Author	Study Type	Objective	Indications & Populations	Study Type	Endpoints	Results
(Argüelles-Arias et al., 2017)	Biosimilar Naïve & Switch	Assess the effectiveness and safety of biosimilar infliximab in IBD patients in real clinical practice	Moderate to severe CD UC	Prospective observational study in a single centre	• Remission Rates • Adverse Events	• 83.9% of switched CD patients continued in remission • 50% of the naïve patients reached remission. • In UC 91.3% of switched patients continued in remission • Naïve patients 66.7% achieved remission
(Buer et al., 2017)	Biosimilar Switch	Prospectively investigate the feasibility, safety and immunogenicity of switching	Adult patients with IBD who were treated with reference infliximab at Oslo University Hospital	Prospective, open label study from a single centre	• Proportion of patients remaining on medication 6 months after switching • Adverse events • Development of ADAs	• 97% of the patients continued on the biosimilar with few adverse events and infusion reactions • Switching did not result in a significant change in disease activity scores
(Farkas et al., 2015)	Biosimilar Naïve & Switch	Assess the efficacy of CT-P13 induction therapy in patients with CD and UC	CD and UC patients	Prospective single centre	• Disease activity at the start and end of the induction therapy	• CD clinical response and remission was achieved in 37.5% and 50% of the patients at week 8 • UC clinical response and remission was achieved in 20% and 66.7% patients at week 8
(Fiorino et al., 2017)	Biosimilar Naïve & Switch	Evaluate the efficacy, safety and immunogenicity of biosimilar infliximab in patients with IBD in induction and maintenance of remission either in naïve patients, previously exposed or switched	CD and UC patients	Prospective, nationwide, observational study	• Serious Adverse Events • Clinical remission/response • Treatment persistency • Immunogenicity and loss of response	• Rate and characteristics of SAEs are in line with previous experience with IFX • Occurrence of infusion reactions and drug withdrawal were similar • Induction and/or maintenance of remission/response was high • Rate of primary failure and loss of response was in line with previous experience with infliximab • Switch patients had a comparable efficacy and incidence of SAEs
(Gecse et al., 2016)	Biosimilar Naïve	Examine the efficacy, safety and immunogenicity of infliximab biosimilar in induction and maintenance of remission in CD and UC	Moderate to severe CD patients (luminal or fistulizing) UC patients	Prospective, nationwide, multicentre, observational study	• Clinical remission, response and biochemical response (week 14) • Steroid free clinical remission (week 30)	• Biosimilar infliximab is safe and effective in the induction of clinical remission and response in both CD and UC

						• Patients with previous IFX exposure had: decreased response rates and were more likely to develop allergic reactions
(Hlavaty et al., 2016)	Biosimilar Naïve & Switch	Retrospectively assess biosimilar infliximab's efficacy and safety in IBD patients	Patients with CD or UC who were treated in the IBD centre	Retrospective single centre cohort study	• Clinical remission and sustained clinical response	• 100% of switch patients showed a sustained clinical response at week 24 and 75% at week 48
(Jahnsen et al., 2015).	Biosimilar Naïve	Assess the efficacy, tolerability and safety of CT-P13	Patients with CD or UC	Single center prospective observational study	• Remission • Levels of Inflammatory Markers • Adverse Events	• 79% of CD patients and 56% of UC patients achieved remission at week 14
(Jung et al., 2015)	Biosimilar Naïve & Switch	Assess the efficacy and safety of CT-P13 in IBD patients	Patients with CD or UC	One-year retrospective multicenter study	• Clinical response and remission • Mucosal healing • Efficacy maintenance • Adverse events	• Comparable efficacy, safety and interchangeability with its reference in the treatment of IBD
(Kang et al., 2015)	Biosimilar Naïve & Switch	Describe the experience of CT-P13 in IBD at tertiary center	17 patients diagnosed with CD or UC	Retrospective single center study	• Response and Remission Rates • Disease flare up • Adverse reactions	• Clinical response and remission at 8 weeks were achieved in seven patients • Nine patients in maintenance with the reference were switched • One patient was discontinued and one lost response
(Keil et al., 2016)	Biosimilar Naïve	Monitor responses to induction treatment with biosimilar infliximab in patients with CD or UC in centres across the Czech Republic	Patients with CD or UC	Multi-centre prospective observational study	• Effectiveness • Serum C-reactive protein levels • Adverse events	• Remission was achieved in 50% of CD cases and partial response in the other 50%. • Remission was achieved in 40.9% of UC cases, response in 54.5% and no response in 4.5%
(Kolar et al., 2017)	Biosimilar Naïve & Switch	Generate evidence on the efficacy and safety of biosimilar infliximab in patients with IBD	IBD patients	Prospective cohort who were switched Retrospective cohort of naïve patients	• Standard clinical indices • C-reactive protein and fecal calprotectin • Trough levels and antidrug antibodies	• Disease activity remained stable in the majority of switched patients • 92% of CD and 83% of UC patients responded to induction therapy at week 14 • No increased immunogenicity was found in switched patients
(Murphy et al., 2015)	Biosimilar Naïve	Description of the use of biosimilars in an IBD population	IBD patients	Descriptive study of 14 consecutive patients from Jan to July 2014 vs. 22 consecutive patients commenced on Remicade® from Dec 2011 to Dec 2013	• Surgery rates • Readmission rates • Use of steroids • Disease activity • CRP trends	• Biosimilars may not be as efficacious as the reference • 29% of biosimilar group required surgery versus 0% in the infliximab group • 80% required hospital readmission vs. 5%.

(S. H. Park et al., 2015)	Biosimilar Naïve & Switch	Evaluate the safety and efficacy of biosimilar infliximab in patients with IBD in South Korea	Patients with active moderate to severe CD, fistulizing CD or moderate to severe UC	post-marketing clinical study	• Adverse events • Clinical response and remission	• No unexpected adverse events were observed • Positive outcomes for response/remission were reported regardless of whether a patient had received prior infliximab
(Sieczkowska et al., 2016)	Biosimilar Switch	Preliminary study of switching patients	Paediatric patients diagnosed with CD or UC	Preliminary prospective switching study	• Disease Severity • Laboratory Parameters • Adverse Events	• Switching from infliximab reference to its biosimilar seems to be a safe option in children with CD • After the switch, the biosimilar was just as effective as the reference.
(Smits et al., 2016)	Biosimilar Switch	Investigate long-term efficacy, safety, PK profile and immunogenicity of patients after switching	IBD patients treated with Remicade® switched to biosimilar infliximab	Single center prospective observational cohort study	• Change in disease activity scores at week 52 • Infliximab trough levels • Anti-drug antibodies	• Disease activity scores and inflammatory markers remained unchanged • No serious adverse events occurred
(Soret et al., 2017)	Biosimilar Switch	Assess the efficacy and safety of switching from reference infliximab to biosimilar infliximab	Remicade® patients who were currently on maintenance therapy with stable treatment	Prospective observational study	• Rate of patients still treated with biosimilar infliximab • Clinical activity • infliximab trough levels • anti-infliximab antibodies changes	• The switch does not change IBD evolution. • 95.2% patients remained on biosimilar • No changes in clinical activity, infliximab doses and ITL were observed

Appendix II – Drug Price Distributions

	Reference Inflixmab	Adalimumab	Prednisone 5mg	Azathioprine 50 mg	6 Mercaptopurine 50 mg	Methotrexate 2.5 mg	Source
	Price	Price	Price	Price	Price	Price	
BC	$1,036.94	$800.70	$0.04	$0.03	$3.06	$0.68	BC Pharmacare Formulary
AB	$962.68	$762.57	$0.04	$0.24		$0.63	Alberta Drug Benefit List
SK	$977.00	$762.57	$0.04	$0.24	$2.86	$0.63	Saskatchewan Drug Plan Formulary
ON	$987.56	$769.97	$0.02	$0.24	$2.86	$0.63	ODB Formulary
QB	$940.00	$714.24	$0.11	$0.24	$2.86	$0.63	Quebec List of Medications
NS	$987.56	$953.21	$0.04	$0.24	$2.86	$0.63	Nova Scotia Formulary
NL	$1,071.50	$1,654.78	$0.04	$0.27	$3.12	$0.69	NLPDP Drug Product Database
Mean	**$994.75**	**$916.86**	**$0.05**	**$0.21**	**$2.94**	**$0.65**	
SD	**$44.94**	**$334.06**	**$0.03**	**$0.08**	**$0.12**	**$0.03**	

Sources: (Alberta Health, April 1, 2018; British Columbia Ministry of Health, 2018; Government of Nova Scotia, 2018; Government of Saskatchewan Drug Plan and Extended Benefits Branch, 2018; Nova Scotia Pharmacare, 2018; Ontario Ministry of Health and Long Term Care, 2018c; Regie de l'assurance maladie Quebec, April 18, 2018)

Appendix III – Physician Fee Distributions

Province	Code	Name	Amount	Source
Ontario	**A413**	**Gastroenterology – Medical Specific Assessment**	**$79.85**	**Ontario Schedule of Benefits**
British Columbia	33306	Gastroenterology - continuing care by consultant Directive care	$46.19	BC Ministry of Health Medical Services Commission Payment Schedule December 31, 2017
Alberta	03.03A	Diagnostic interview and evaluation described as limited	$25.09	Alberta Health Care Insurance Plan - Medical Procedure List as of April 1, 2017
Saskatchewan	5D	Internal Medicine - Partial assessment or subsequent visit	$69.00	Saskatchewan Payment Schedule For Insured Services Provided by a Physician
Manitoba	8403	Internal Medicine - Regional History and Examination or Subsequent Visit	$56.75	Manitoba Physician's Manual April 1, 2018
Nova Scotia	3.07	Medicine - Repeat Consultation	$27.40	Nova Scotia Medical Services Insurance Physician's Manual
New Brunswick	6.1 Code 8765	General Internal Medicine - Repeat Consultation	$110.00	New Brunswick Physicians' Manual
Prince Edward Island	562	Internal Medicine - Repeat Consultation	$71.68	Prince Edward Island Master Agreement April 1, 2017
Newfoundland and Labrador	113	Internal Medicine - specific assessment	$79.85	Newfoundland and Labrador Medical Payment Schedule
Quebec	9127	Gastroenterology Visit	$79.20	Quebec Manuel des Medecins Specialistes Remuneration a l'Acte
Mean			**$64.50**	
Standard Deviation			**$26.15**	

Province	Code	Name	Amount	Source
Ontario	**A005**	**Family Physician & General – General Assessment**	**$77.20**	**Ontario Schedule of Benefits**
British Columbia	100	General Practice - Visit in office for any condition(s) requiring partial or regional examination and history - includes both initial and subsequent examination for same or related condition(s)	$30.92	BC Ministry of Health Medical Services Commission Payment Schedule December 31, 2017
Alberta	03.03A	Diagnostic interview and evaluation described as limited	$25.09	Alberta Health Care Insurance Plan - Medical Procedure List as of April 1, 2017
Saskatchewan	5b	General Practice - partial assessment or subsequent visit	$35.00	Saskatchewan Payment Schedule For Insured Services Provided by a Physician
Manitoba	8529	General Practice - Regional Intermediate Visit - Regional or Subsequent Visit	$37.40	Manitoba Physician's Manual April 1, 2018
Nova Scotia	3.07	Family Practice - Repeat Consultation	$31.00	Nova Scotia Medical Services Insurance Physician's Manual
New Brunswick	1.1 Code 12	General Practice - Repeat Consultation	$31.00	New Brunswick Physicians' Manual
Prince Edward Island	162	General Practice - Repeat Consultation	$40.96	Prince Edward Island Master Agreement April 1, 2017
Newfoundland and Labrador	112	General Practice - General assessment	$80.51	Newfoundland and Labrador Medical Payment Schedule
Quebec	15803	Visite de suivi (500 patients ou plus)	$47.00	Quebec Manuel des Medecins Omnipracticiens Remuneration a l'Acte
Mean			**$43.61**	
Standard Deviation			**$19.56**	

Province	Code	Name	Amount	Source
Ontario	**A033**	**General Surgery - Specific assessment**	**$44.40**	**Ontario Schedule of Benefits**
British Columbia	7010	General Surgery – continuing care by consultant subsequent office visit	$24.57	BC Ministry of Health Medical Services Commission Payment Schedule December 31, 2017
Alberta	03.03A	Diagnostic interview and evaluation described as limited	$25.09	Alberta Health Care Insurance Plan - Medical Procedure List as of April 1, 2017
Saskatchewan	7L	General Surgery - follow up assessment	$35.70	Saskatchewan Payment Schedule For Insured Services Provided by a Physician
Manitoba	8403	General surgery - Regional History and Examination or Subsequent Visit	$31.80	Manitoba Physician's Manual April 1, 2018
Nova Scotia	3.07	Surgery - Repeat Consultation	$27.00	Nova Scotia Medical Services Insurance Physician's Manual
New Brunswick	5.1 Code 33	General Surgery Repeat Consultation	$66.00	New Brunswick Physicians' Manual
Prince Edward Island	460	General Surgery Repeat Consultation	$52.74	Prince Edward Island Master Agreement April 1, 2017
Newfoundland and Labrador	113	General Surgery - specific assessment	$56.12	Newfoundland and Labrador Medical Payment Schedule
Quebec	9127	General Surgery Visit	$69.00	Quebec Manuel des Medecins Specialistes Remuneration a l'Acte
Mean			**$43.24**	
Standard Deviation			**$16.89**	

Province	Code	Name	Amount	Source
Ontario	C415	Gastroenterology - Consultation	$157.00	Ontario Schedule of Benefits
Alberta	03.04A	Comprehensive assessment of a patient's condition requiring a complete history, a complete physical examination appropriate to the physician's specialty, an appropriate record and advice to the patient	$40.14	Alberta Health Care Insurance Plan - Medical Procedure List as of April 1, 2017
British Columbia	33310	Gastroenterology - Consultation	$161.07	BC Ministry of Health Medical Services Commission Payment Schedule December 31, 2017
Saskatchewan	9D	Internal Medicine - Consultation	$146.20	Saskatchewan Payment Schedule For Insured Services Provided by a Physician
Manitoba	8403	Internal Medicine - Hospital Care Extended Complete History and Physical Examination minimum of forty-five minutes of patient/physician contact time	$119.95	Manitoba Physician's Manual April 1, 2018
Nova Scotia	3.08	Medicine - Comprehensive consultation	$62.00	Nova Scotia Medical Services Insurance Physician's Manual
New Brunswick	6.1 Code 8764	General Internal Medicine - Consultation	$141.00	New Brunswick Physicians' Manual
Prince Edward Island	560	Internal Medicine - Consultation	$194.56	Prince Edward Island Master Agreement April 1, 2017
Newfoundland and Labrador	101	Internal Medicine - Consultation	$150.78	Newfoundland and Labrador Medical Payment Schedule
Quebec	9165	Gastroenterology Consultation	$121.59	Quebec Manuel des Medecins Specialistes Remuneration a l'Acte
Mean			**$129.43**	
Standard Deviation			**$46.60**	

Province	Code	Name	Amount	Source
Ontario	**C035**	**General Surgery – Consultation**	**$90.30**	**Ontario Schedule of Benefits**
Alberta	03.04R	General Surgery - Pre-surgical planning and patient navigation visit	$78.46	Alberta Health Care Insurance Plan - Medical Procedure List as of April 1, 2017
British Columbia	7010	General Surgery – Consultation	$101.47	BC Ministry of Health Medical Services Commission Payment Schedule December 31, 2017
Saskatchewan	9L	General Surgery - General, thoracic and vascular surgery consultation	$115.00	Saskatchewan Payment Schedule For Insured Services Provided by a Physician
Manitoba	8403	General surgery - Hospital care Complete history and physical examination	$56.90	Manitoba Physician's Manual April 1, 2018
Nova Scotia	3.08	Surgery - Comprehensive consultation	$39.40	Nova Scotia Medical Services Insurance Physician's Manual
New Brunswick	5.1 Code 31	General Surgery Consultation	$85.00	New Brunswick Physicians' Manual
Prince Edward Island	460	General Surgery Consultation	$105.47	Prince Edward Island Master Agreement April 1, 2017
Newfoundland and Labrador	101	General Surgery Consultation	$91.78	Newfoundland and Labrador Medical Payment Schedule
Quebec	9165	General Surgery Consultation	$139.45	Quebec Manuel des Medecins Specialistes Remuneration a l'Acte
Mean			**$90.32**	
Standard Deviation			**$28.40**	

Sources: (British Columbia Ministry of Health, 2017; Government of Alberta, 2017; Government of New Brunswick, May 18, 2017; Government of Saskatchewan, April 1, 2018; Manitoba Ministry of Health, 2018; Newfoundland and Labrador Department of Health and Community Services, 2013; Nova Scotia Medical Services Insurance, 2014; Ontario Ministry of Health and Long Term Care, 2015; Regie de l'assurance maladie, April 18, 2018a, April 18, 2018b)