The Hospital for Sick Children

Technology Assessment at SickKids (TASK)

# 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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## REPORT HIGHLIGHTS

*The Report Highlights consists of a summary of the full report with the same name and should be evaluated in conjunction with the full report. Full documents are available for download at:*

***http://lab.research.sickkids.ca/task/reports-theses/***

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## Introduction

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.[1] In Crohn's Disease (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).[1-3] 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. 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).[4] The introduction of lower-cost biosimilars offers a unique opportunity to address affordability concerns. Clinical evidence suggests 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. [5-8] 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.

## Key Messages

- From a healthcare payer perspective, using 10,000 Monte Carlo simulations, a five-year time horizon and 1.5% global discounting, 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 for switching to the biosimilar strategy. 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.
- 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.
- From a healthcare payer perspective, at a threshold of $100,000/QALY switching to biosimilar is cost-effective in 98.9% of iterations.
- 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).

## Objectives

The objective of this economic evaluation 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 been maintained on reference infliximab per quality adjusted life year (QALY) gained from the healthcare system (public & private payer) perspective and the societal perspective.

## Methods

A probabilistic cohort Markov decision model (Figure 1) 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. The analysis was conducted in adult patients with moderate-to-severe CD. The model evaluated an intervention of a one-time switch from the reference to the biosimilar infliximab with identical dosing and administration. The comparator of interest was continued maintenance treatment on the reference biologic which will also be referred to as the "reference infliximab" group (Figure 2). Effectiveness outcomes were measured with quality-adjusted life years. The utilities from a study by Greenberg et al. (2015) were employed in this model (Table 1).[9] Biologic and biosimilar costs and doses are shown in Table 2. Clinical inputs were obtained from NOR-SWITCH[10] and other published pivotal trials (see Table 3 for model parameters). Once a patient relapsed it was assumed they received 2nd line therapy with adalimumab. Costs such as those for interventions, physician services and hospitalizations were obtained from Canadian sources (Table 3). For the societal perspective, it was 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.[11] A total of 10,000 simulations were run with a 1.5% discounting rate for the reference case. 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. Sensitivity analysis was used to test the robustness of the results to variations in uncertain parameters. A threshold analysis was conducted on two key variables; probability of relapse in the biosimilar group and the price of reference infliximab. One-way probabilistic analyses were run on patient weights, infliximab drug costs, the time horizon, health state utilities[12] and the relapse rate from clinical remission or response states after being switched to biosimilar infliximab. Decision uncertainty was assessed with a cost-effectiveness acceptability curve (CEAC).

# Results

**Cost-effectiveness Analysis**

The primary analysis, from a healthcare payer perspective, was run as a probabilistic model with distributions applied to key probability, utility and cost variables where appropriate. Using 10,000 Monte Carlo simulations, a five-year time horizon and 1.5% global discounting, 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 (Table 4). Total incremental costs were -$46,194 (95% CI: -$42,420 to -$50,455) over the five-year time horizon for switching to biosimilar strategy (Table 4). 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 5). 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. As shown in Figure 3, 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.

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. 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 4).

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) (Table 6).

While the costs are higher for both branches there are moderately less savings associated with switching in this case.

**Threshold Analysis**

Threshold analyses were run on the probability of relapsing from remission after switching to biosimilar infliximab, and the cost of infliximab. 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. 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.

**Parameter Uncertainty**

One-way probabilistic analyses were conducted to assess the influence of patient weight, infliximab drug costs, alternative utility weights and alternative relapse rates on the costs and outcomes of the model. 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 7).

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)[13] were employed as a transition probability rather than those derived from NOR-SWITCH. 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.

**Structural Uncertainty**

In the reference case a 1.5% discount rate was applied and a range of 0% to 5% was tested in the structural analyses[14] (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).

**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 (Figure 5). 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 Incremental Cost-effectiveness 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.

In summary, 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 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.

## Discussion

This cost-utility analysis is one of the first economic evaluations of switching to biosimilar infliximab compared with continuing treatment on reference infliximab. 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). 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. 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. When the analysis was conducted from the societal perspective, the differences compared to the healthcare system perspective were minimal. The work confirms the results of Husereau et al (2018)[15], which examined a similar research question from the Canadian perspective.

A primary strength of this analysis is the focus on a relevant policy question specific for the Canadian context and for CD, a chronic disease with high prevalence and incidence in Canada. The model framework was built in consultation with experts in CD and in keeping with other Canadian economic evaluations of infliximab.[16,17] 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, and only a switch to 2nd line treatment was modelled after relapsing on treatment with infliximab as opposed to the option of dose escalation. Therefore, the additional costs for infliximab and benefits from reestablishing remission or response were 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. It is important to note that the model framework did not account

for immunogenicity and the presence or development of anti-drug antibodies (ADA), but the incidence of ADAs detected during the NOR-SWITCH trial were comparable between groups.[10] The model framework did account for adverse events in the infliximab treatment states and considered infusion-related reactions, but 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. [10,18,19] There were also strengths and limitations associated with the primary data sources that were utilized to inform the model, particularly the NOR-SWITCH study which was not powered to show non-inferiority in individual diseases, but 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.[10] Finally, given that the model was a Markov analysis, it is important to acknowledge the primary limitation of this design; it is memoryless. Given that patients with ADA development are more likely to develop acute infusion reactions and to relapse from treatment it represents a limitation that this history was not accounted for in the model. [20] These simplifications of the CD care pathway and the model framework 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.

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. Patients reported wanting more clinical studies on biosimilars and expressed anxiety surrounding switching for stable patients, particularly for non-medical reasons.[5] Physicians have expressed similar concerns to their patients regarding data extrapolation, immunogenicity and non-medical switching.[21] 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 European Crohn's and Colitis Organisation 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. [22,23] Ultimately, the present analysis sought to address this knowledge gap identified by patients and physicians from an economic perspective.

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. The present analysis contributes to the growing evidence base regarding the cost effectiveness of a one-time switch to biosimilar infliximab. 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. 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.

**Figure 1. Model Structure.**

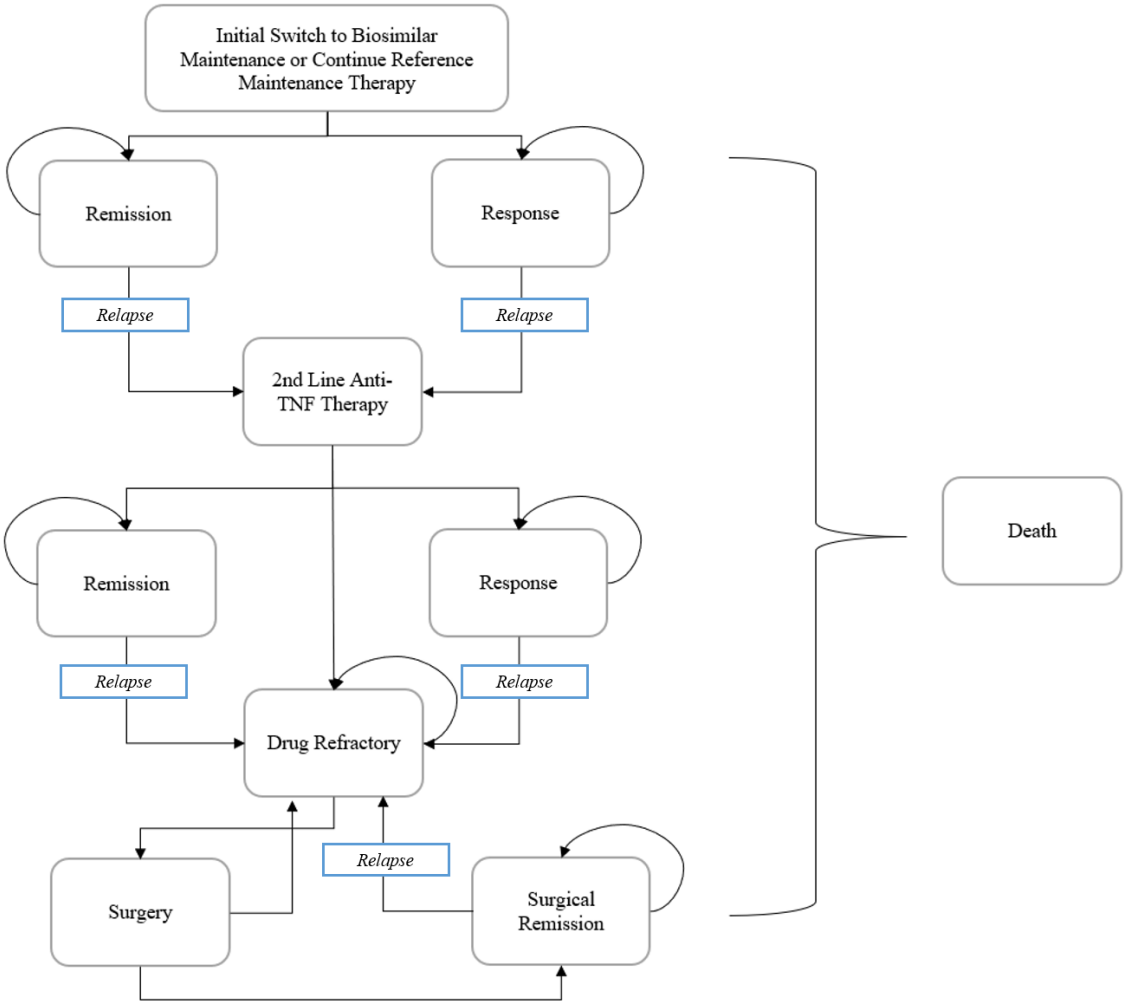



**Figure 2. Intervention (Biosimilar Infliximab) and Comparator (Reference infliximab).**

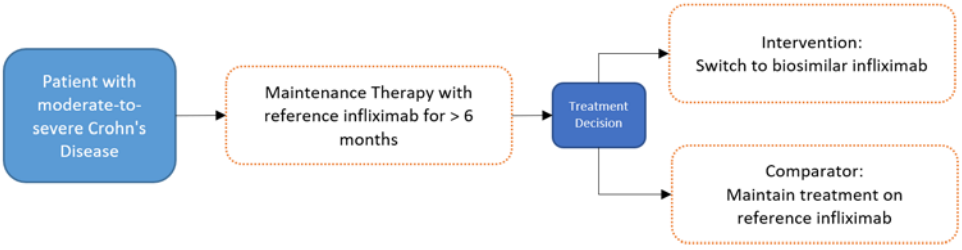


**Table 1. Model Utility Inputs.**

| 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)*

**Table 2. Biologic & Biosimilar Drug Costs.**

| Biologic Costs<br>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<br>Patient Weight: 75kg | 375 mg | 3.75 | 4 | $3,979.00 |
| Biosimilar Infliximab | $525.00 (44.94) per 100mg/vial | 5mg/kg<br>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<br>Week 2: 80mg<br>Week 4, 6, 8: 40mg | 360mg | Week 0: 4 vials<br>Week 2: 2 vials<br>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*

**Table 3 - 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<br><br>Mortality calculated as SMR*Statistics Canada Probability of Mortality Depending on Age | | N/A | Bitton et al. (2016)<br><br>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) |

| Table 3 continued | | | | |
|---|---|---|---|---|
| **Transition Probabilities** | | | | |
| | **Reference (alpha, beta)** | **Biosimilar (alpha, beta)** | **Distribution** | **Source** |
| **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)<br>Year 2: 0.211 (8, 30)<br>Year 3: 0.143 (3, 21)<br>Year 4: 0.111 (2, 18)<br>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) |

| Table 3 continued | | | | |
|---|---|---|---|---|
| **Costs** | | | | |
| **Markov Health State** | **Reference (SD)** | **Biosimilar (SD)** | **Distribution** | **Source** |
| Clinical Remission (IFX) | Biologic Cost Per Cycle ($994.75 (44.94)): $3,979<br>Biologic Dispensing Fees: $8.83<br>Concomitant Therapy Cost per Cycle:<br>Prednisone: $0.46<br>Immunosuppressives: $51.78<br>Physician Services Per Cycle:<br>$9.68 | Biologic Cost Per Cycle ($525 (44.94)): $2,108.83<br>Biologic Dispensing Fees: $8.83<br>Concomitant Therapy Cost per Cycle:<br>Immunosuppressives: $64.05<br>Physician Services Per Cycle:<br>$9.68 | Drug Prices: Normal Distribution<br>Physician Services: Normal Distribution | Canadian Public Drug Formularies<br>Blackhouse et al. (2012)<br>Nugent et al (2010)<br>Canadian Public Schedule of Benefits |
| **Markov Health State** | **Reference (SD)** | **Biosimilar (SD)** | **Distribution** | **Source** |
| Clinical Response (IFX) | Biologic Cost Per Cycle ($994.75 (44.94)): $3,979<br>Biologic Dispensing Fees: $8.83<br>Concomitant Therapy Cost per Cycle:<br>Prednisone: $0.46<br>Immunosuppressives: $51.78<br>Physician Services Per Cycle:<br>$172.61 | Biologic Cost Per Cycle ($525 (44.94)): $2,108.83<br>Biologic Dispensing Fees: $8.83<br>Concomitant Therapy Cost per Cycle:<br>Immunosuppressives: $64.05<br>Physician Services Per Cycle:<br>$172.61 | Drug Prices: Normal Distribution<br>Physician Services: Normal Distribution | Canadian Public Drug Formularies<br>Blackhouse et al. (2012)<br>Nugent et al (2010)<br>Canadian Public Schedule of Benefits |
| Drug Refractory | Concomitant Therapy Cost per Cycle:<br>Prednisone: $0.46<br>Immunosuppressives: $51.78<br>Physician Services Per Cycle:<br>$179.10 | Concomitant Therapy Cost per Cycle:<br>Immunosuppressives: $64.05<br>Physician Services Per Cycle:<br>$179.10 | Drug Prices: Normal Distribution<br>Physician Services: Normal Distribution | Canadian Public Drug Formularies<br>Blackhouse et al. (2012)<br>Nugent et al (2010)<br>Canadian Public Schedule of Benefits |

| Table 3 continued | | | | |
|---|---|---|---|---|
| **Costs** | | | | |
| **Markov Health State** | **Reference (SD)** | **Biosimilar (SD)** | **Distribution** | **Source** |
| 2nd Line- Anti-TNF (ADA) | Biologic Cost Per Cycle ($916.86 (334.06)): $8,251.74<br>Biologic Dispensing Fees: $35.32<br>Concomitant Therapy Cost per Cycle:<br>Prednisone: $0.46<br>Immunosuppressives: $51.78<br>Physician Services Per Cycle: $179.10 | Biologic Cost Per Cycle ($916.86 (334.06)): $8,251.74<br>Biologic Dispensing Fees: $35.32<br>Concomitant Therapy Cost per Cycle:<br>Immunosuppressives: $64.05<br>Physician Services Per Cycle: $179.10 | Drug Prices: Normal Distribution<br>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<br>Biologic Dispensing Fees: $35.32<br>Concomitant Therapy Cost per Cycle:<br>Prednisone: $0.46<br>Immunosuppressives: $51.78<br>Physician Services Per Cycle: $9.68 | Biologic Cost Per Cycle ($916.86 (334.06)): $3,097.54<br>Biologic Dispensing Fees: $35.32<br>Concomitant Therapy Cost per Cycle:<br>Immunosuppressives: $64.05<br>Physician Services Per Cycle: $9.68 | Drug Prices: Normal Distribution<br>Physician Services: Normal Distribution | Canadian Public Drug Formularies Blackhouse et al. (2012) Nugent et al (2010) Canadian Public Schedule of Benefits |
| Clinical Response (ADA) | Biologic Cost Per Cycle ($916.86 (334.06)): $3,667.44<br>Biologic Dispensing Fees: $35.32<br>Concomitant Therapy Cost per Cycle:<br>Prednisone: $0.46<br>Immunosuppressives: $51.78<br>Physician Services Per Cycle: $172.61 | Biologic Cost Per Cycle ($916.86 (334.06)): $3,667.44<br>Biologic Dispensing Fees: $35.32<br>Concomitant Therapy Cost per Cycle:<br>Immunosuppressives: $64.05<br>Physician Services Per Cycle: $172.61 | Drug Prices: Normal Distribution<br>Physician Services: Normal | Canadian Public Drug Formularies Blackhouse et al. (2012) Nugent et al (2010) Canadian Public Schedule of Benefits |

| Table 3 continued | | | | |
|---|---|---|---|---|
| **Costs** | | | | |
| Surgery | Physician/Assist/Anesthesia Procedure Cost:<br>$988.90<br><br>Surgical Cost:<br>$12,138 ($5,729)<br><br>Pre-Surgery Consultation Fees:<br>$219.75<br><br>Post-Surgery Assessments (Total Length of Stay 8 days):<br>$411.60<br><br>Physician Assessment Services Per Cycle:<br><br>$118.06 | Physician/Assist/Anesthesia Procedure Cost:<br>$988.90<br><br>Surgical Cost:<br>$12,138 ($5,729)<br><br>Pre-Surgery Consultation Fees:<br>$219.75<br><br>Post-Surgery Assessments (Total Length of Stay 8 days):<br>$411.60<br><br>Physician Assessment Services Per Cycle:<br><br>$118.06 | Procedure Cost was not varied<br><br>Surgical Cost: Gamma Distribution (per OCCI)<br><br>Physician Fees post were not varied<br><br>Length of Stay: Normal Distribution<br><br>Consults & Assessments: Normal | Canadian Public Schedule of Benefits<br>OCCI 2015/2016<br>Marshall et al (March 2002) |
| Surgical Remission | Physician Services Per Cycle:<br><br>$119.10 | Physician Services Per Cycle:<br><br>$119.10 | Normal | Blackhouse et al (2012)<br>Nugent et al (2010)<br>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)<br>ODB Formulary<br>Ontario Nurses Association<br>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,*

**Table 4 – 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) | |

**Table 5- 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) | |

**Figure 3 - Reference Case Results (1,000 of 10,000 iterations with 95% Confidence Ellipse).**

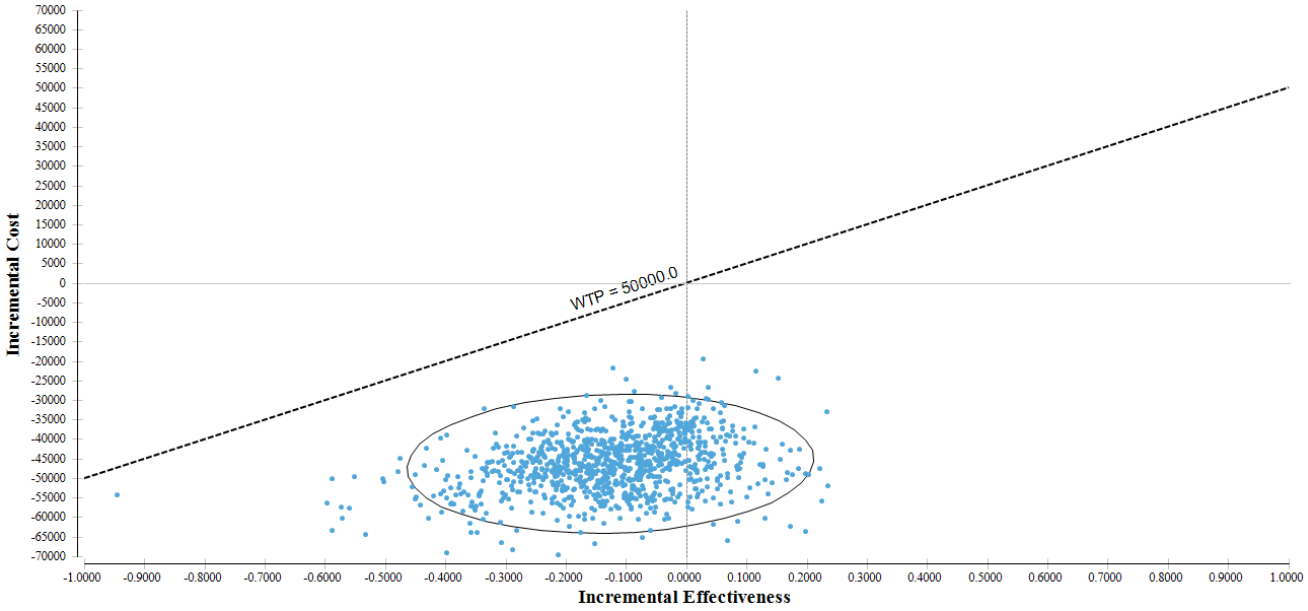
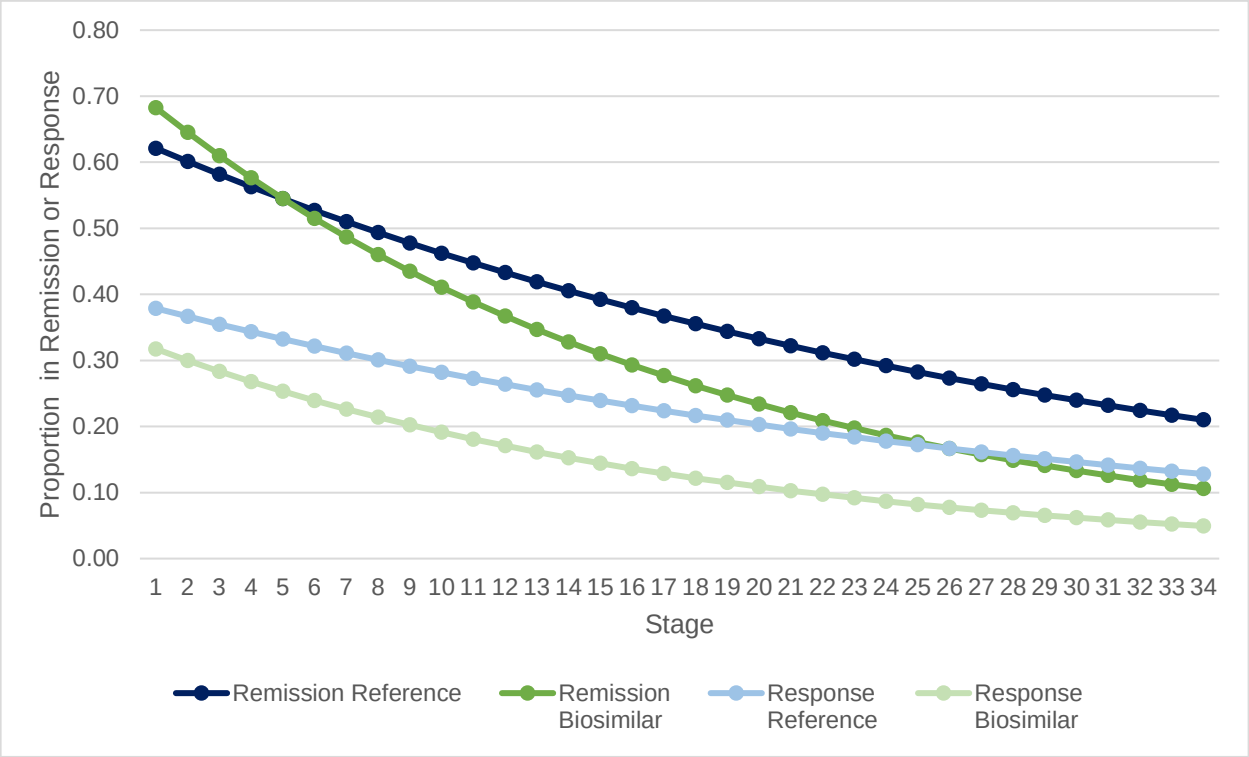


**Figure 4- Proportion in Remission & Response States.**




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

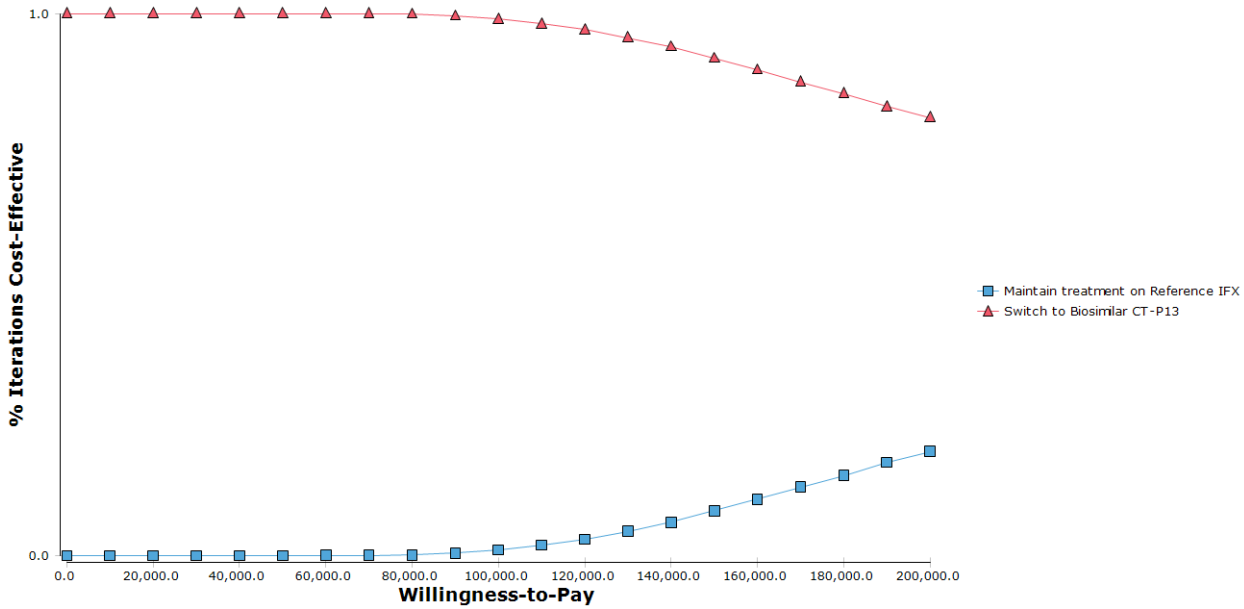
**Table 6 - Societal Results.**

| | 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) | |

**Table 7 – 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) | |

**Figure 5 Cost Effectiveness Acceptability Curve.**



## References


1. Gastrointestinal Society - Canadian Society of Intestinal Research. (2017). Crohn's Disease. Retrieved from https://www.badgut.org/information-centre/a-z-digestive-topics/crohns-disease/

2. Al Hashash, J., & Regueiro, M. (2018). Overview of medical management of high-risk, adult patients with moderate to severe Crohn disease. Retrieved from https://www.uptodate.com/contents/overview-of-medical-management-of-high-risk-adult-patients-with-moderate-to-severe-crohn-disease

3. Crohn's and Colitis Foundation of Canada. (2012). The impact of inflammatory bowel disease in Canada 2012 Final Report and Recommendations. Retrieved from Toronto, Ontario: http://crohnsandcolitis.ca/Crohns_and_Colitis/documents/reports/ccfc-ibd-impact-report-2012.pdf

4. Health Canada. (2016b). Fact Sheet Subsequent Entry Biologics in Canada. Retrieved from http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/fs-fi_seb-pbu_07-2006-eng.php

5. Canadian Arthritis Patient Alliance, Canadian Psoriasis Network, Crohn's and Colitis Canada, Gastrointestinal Society, & The Arthritis Society. (March, 2017). Biosimilar Focus Group Project Report. Retrieved from http://www.arthritispatient.ca/files/3614/9202/9357/TAS_FocusGroupReport_Final_ENG_V5.pdf

6. CARE. (January 13, 2017). CARE Congress on Biosimilars - Congress Report. Retrieved from Toronto, Ontario: https://static1.squarespace.com/static/52f8f139e4b0bae912c96d0d/t/58d15b1fc534a5e7b8465aca/1490115365791/Congress+Report+2017_Interactive.pdf

7. Community Academic Research Education (CARE). (2017). CARE Perspectives: NOR-SWITCH Trial A Discussion between Dr. John Marshall and Dr. Brian Feagan. Retrieved from https://static1.squarespace.com/static/52f8f139e4b0bae912c96d0d/t/589b561ef7e0abd29379675f/1486575149908/CARE+Perspectives+on+NOR-SWITCH+v2.pdf

8. Institute of Health Economics. (October 6, 2016). Towards an Alberta approach for biosimilar reimbursement - Summary report of the IHE Biosimilars Forum. Retrieved from Edmonton, Alberta, Canada: https://www.ihe.ca/publications/towards-an-alberta-approach-for-biosimilar-reimbursement

9. Greenberg, D., Schwartz, D., Vardi, H., Friger, M., Sarid, O., Slonim-Nevo, V., . . . [IIRN], I. I. R. N. (2015). Health-Related Utility Weights in a Cohort of Real-World Crohn's Disease Patients. J Crohns Colitis, 9(12), 1138-1145. doi:10.1093/ecco-jcc/jjv167

10. Jørgensen, K., Olsen, I. C., Goll, G. L., Lorentzen, M., Bolstad, N., Haavardsholm, E., . . . Kvien, T. K. (2017). Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. The Lancet, 1-13. doi:10.1016/ S0140-6736(17)31258-8

11. Statistics Canada. (April 6, 2018). Average hourly wages of employees by selected characteristics and occupation, unadjusted data, by province (monthly) Retrieved from http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labr69a-eng.htm

12. Gregor, J. C., McDonald, J. W. D., Klar, N., Wall, R., Atkinson, K., Lamba, B., & Feagan, B. G. (1997). An Evaluation of Utility Measurement in Crohn's Disease. Inflammatory Bowel Diseases, 3(4), 265-276.

13. Komaki, Y., Yamada, A., Komaki, F., Micic, D., Ido, A., & Sakuraba, A. (2017). Systematic review with meta-analysis: the efficacy and safety of CT-P13, a biosimilar of anti-tumour necrosis factor-α agent (infliximab), in inflammatory bowel diseases. Aliment Pharmacol Ther, 45(8), 1043-1057. doi:10.1111/apt.13990

14. CADTH. (March, 2017). CADTH Methods and Guidelines - Guidelines for the Economic Evaluation of Health Technologies: Canada 4th Edition. In. Ottawa, Ontario.

15. Husereau, D., Feagan, B., & Selya-Hammer, C. (2018). Policy Options for Infliximab Biosimilars in Inflammatory Bowel Disease Given Emerging Evidence for Switching. Appl Health Econ Health Policy. doi:10.1007/s40258-018-0371-0.

16. Blackhouse, G., Assasi, N., Xie, F., Marshall, J., Irvine, E. J., Gaebel, K., . . . Goeree, R. (2012). Canadian cost-utility analysis of initiation and maintenance treatment with anti-TNF-α drugs for refractory Crohn's disease. J Crohns Colitis, 6(1), 77-85. doi:10.1016/j.crohns.2011.07.007.

17. Marshall, J. K., Blackhouse, G., Goeree, R., Brazier, N., Irvine, E. J., & O'Brien, B. J. (2002). Clinical and Economic Assessment: Infliximab for the Treatment of Crohn's Disease. Retrieved from Ottawa:

18. Park, W., Yoo, D. H., Miranda, P., Brzosko, M., Wiland, P., Gutierrez-Ureña, S., . . . Braun, J. (2017). Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis, 76(2), 346-354. doi:10.1136/annrheumdis-2015-208783

19. Yoo, D. H., Hrycaj, P., Miranda, P., & Ramiterre, E. (2013). A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis, 1613-1620.

20. Moss, A. C. (2015). Optimizing the use of biological therapy in patients with inflammatory bowel disease. Gastroenterol Rep (Oxf), 3(1), 63-68. doi:10.1093/gastro/gou087

21. CARE Gastroenterology Faculty. (2017). GASTRO-TIMES: The Changing Landscape of Inflammatory Bowel Disease. Retrieved from http://www.careeducation.ca/gastro-publications-blog/gastro-times

22. Danese, S., Fiorino, G., Raine, T., Ferrante, M., Kemp, K., Kierkus, J., . . . Peyrin-Biroulet, L. (2017). ECCO Position Statement on the Use of Biosimilars for Inflammatory Bowel Disease-An Update. J Crohns Colitis, 11(1), 26-34. doi:10.1093/ecco-jcc/jjw198

23. Danese, S., Gomollon, F., & ECCO, G. B. a. O. B. o. (2013). ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). J Crohns Colitis, 7(7), 586-589. doi:10.1016/j.crohns.2013.03.011