Cost-Effectiveness of Anti-TNF Therapy for the Management of Inflammatory Bowel Disease

by

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Abstract

Anti-TNF therapy is effective for the induction and maintenance of remission in patients with inflammatory bowel disease (IBD). The benefits of anti-TNF therapy include improved quality of life, steroid discontinuation, and reduced hospitalization and surgery rates. Due to their high costs and potential serious adverse side effects, anti-TNF agents are generally prescribed once patients have failed to respond to less aggressive medical therapies, such as 5-ASAs, steroids, and immunosuppressants. Recently, it has been suggested that early initiation of anti-TNF therapy reduces rates of surgery and loss of response by minimizing irreversible, structural changes to the bowel. However, the costly nature of these medications gives rise to concerns regarding their usage. Also, the introduction of anti-TNF biosimilars has resulted in a need to assess how the economic burden of IBD will be affected by these agents.

The aim of this study was to determine the cost-effectiveness of anti-TNF therapy for patients with moderate to severe IBD in several novel areas. First, we aimed to determine if adalimumab is cost-effective for the management of ulcerative colitis (UC), compared to patients who choose to remain on chronic steroids, opposed to undergoing surgery. Secondly, we wanted to determine when anti-TNF therapy initiation is most cost-effective for the management of Crohn's disease (CD) comparing early (≤2 years after diagnosis) versus late (>2 years after diagnosis) initiation. Lastly, we aimed to determine the impact of the lower price of biosimilars on CD treatment cost efficacy, while making necessary assumptions regarding their efficacy, cost, and safety.

In all three studies, a Markov model was constructed that simulated the progression of a hypothetical cohort of patients with moderate to severe IBD upon initiation of either infliximab or adalimumab. Transition probabilities were obtained from randomized

controlled trials and real-life rates published by expert IBD centres. Costs and utility values were obtained using a variety of sources, including literature searches, cost estimators, and provincial databases. Sensitivity analysis was conducted to characterize uncertainty related to outputs.

The first study revealed an incremental cost-effectiveness ratio (ICER) of $59,000 per quality-adjusted life year (QALY) for adalimumab therapy compared to ongoing steroid therapy, at a 10-year time horizon for patients with moderate to severe UC. For patients needing to be dose escalated, we calculated an ICER of $102,000 per QALY, above currently accepted willingness-to-pay (WTP) thresholds.

The second study revealed that early initiation of infliximab (≤2 years of diagnosis) resulted in a lifetime savings of $18,054 and a gain of 1.02 QALYs compared to late initiation of anti-TNF therapy for patients with CD. Similarly, early initiation of adalimumab resulted in a savings of $18,526 and an increase of 0.74 QALYs. Sensitivity analysis revealed that early initiation of both infliximab and adalimumab had a 68% chance of being cost-effective at a WTP threshold of $50,000 per QALY.

Our final study found that an infliximab biosimilar would result in a lifetime savings of $120,889 to $241,800 for patients with CD compared to the originator biologic. Similarly, an adalimumab biosimilar would result in a cost savings of $277,260 to $344,565 over a patient's lifetime.

In conclusion, anti-TNF therapy is very expensive and represents a large proportion of the financial burden of IBD. We concluded that anti-TNF therapy, particularly its early usage, is cost-effective for the management of IBD, however, adalimumab use in UC becomes costly in patients requiring escalated dosing. Anti-TNF biosimilars represent a

promising way to reduce costs associated with IBD, although further research is needed to assess the true efficacy and cost of these agents.

Preface

This thesis is an original work by Candace Beilman. No part of this thesis has been previously published, however Chapter 3 has been submitted for publication pending review.

For Chapter 3, I was responsible for data analysis, obtaining input parameters, study design, manuscript drafting and editing. Victoria Ung contributed to model development and manuscript editing. Nguyen Xuan Thanh, Arto Ohinmaa, and Phil Jacobs contributed to economic analysis and manuscript editing. Chris Ma contributed to data collection, data analysis and manuscript editing. Karen Kroeker, Karen Wong, Thomas Lee, Haili Wang, and Brendan Halloran contributed to manuscript editing. Richard N. Fedorak contributed to study design, data analysis, and manuscript editing.

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ACCENT – A Crohn's disease clinical trial evaluating infliximab in a new long-term treatment regimen

ACT – Active ulcerative colitis trials

ADA – Adalimumab

ASA – aminosalicylic acid

CADTH – Canadian agency for drugs and technologies in health

CBA – Cost-benefit analysis

CD – Crohn's disease

CE – Cost-effectiveness

CEA – Cost-effectiveness analysis

CHARM – Crohn's trial of the fully human antibody adalimumab for remission maintenance

CI – Confidence interval

CLASSIC – Clinical assessment of adalimumab safety and efficacy studied as induction therapy in Crohn's disease

CMA – Cost-minimization analysis

CUA – Cost-utility analysis

GI – Gastrointestinal

HRQL – Health-related quality of life

IBD – Inflammatory bowel disease

ICER – Incremental cost-effectiveness ratio

IFX – Infliximab

INMB – Incremental net monetary benefit

IPAA – Ileal pouch-anal anastomosis

NHB – Net health benefit

NMB – Net monetary benefit

PSA – Probabilistic sensitivity analysis

QALY – Quality-adjusted life year

TNF – Tumor necrosis factor

ULTRA – Ulcerative colitis long-term remission and maintenance with adalimumab treatment

VOI – Value of information

WHO – World health organization

WTP – Willingness-to-pay

α – alpha

< – less than

> – greater than

≥ – greater than or equal to

≤ – less than or equal to

1 Introduction

1.1 Inflammatory Bowel Disease

Ulcerative colitis (UC) and Crohn's disease (CD), collectively known as inflammatory bowel disease (IBD), are chronic conditions characterized by a relapsing and remitting course of intestinal inflammation**.** The manifestation of disease often occurs in young adulthood and continues throughout a patient's lifespan. In periods of disease activity, patients frequently experience diarrhea, weight loss, abdominal pain, and fatigue.[1] Given that there is no curative treatment, patients often require lifelong treatment in an attempt to induce and maintain remission, improve quality of life, and prevent surgery.[2]

CD and UC are generally considered together because of their multiple similarities including gastrointestinal inflammation, related signs and symptoms, and unknown etiology.[3] However, these two disorders are clearly separated by distinct patterns of inflammation, different locations within the gastrointestinal tract, and disease-specific complications.[4] Furthermore, it has recently been proposed that these conditions likely represent a spectrum of diseases, with clearly defined UC and CD at opposite ends, rather than two distinct diseases. This hypothesis is supported by the fact that approximately 10% of patients have indeterminate features that cannot be clearly categorized as either disease.[5]

1.1.1 Ulcerative Colitis

UC is characterized by relapsing mucosal inflammation that is restricted to areas of the colon. UC is typically classified as either proctitis (involvement limited to the rectum), left-side colitis (involving the sigmoid colon with or without involvement of the descending

colon), or pancolitis (involving the entire colon).[6] UC may present with a gradual onset of symptoms or with an acute first attack. Generally, UC is diagnosed based on clinical findings, followed by confirmation using either flexible sigmoidoscopy or colonoscopy.[7]

Several risk factors have been associated with the development of UC, including consumption of a "Western diet" and depression. Breastfeeding, appendectomy, and smoking have shown to be associated with a reduced risk of UC.[7]

1.1.2 Crohn's Disease

CD involves transmural inflammation that can affect any portion of the digestive tract from mouth to anus, predominantly seen in the terminal ileum and/or colon. CD results in asymmetrical inflammation and ulceration that occurs with healthy tissue interspersed and often extends deeply into the intestinal wall.[8] Complications that can arise during the progression of disease include strictures, abscesses or fistulas.[6]

Risk factors for CD include smoking, appendectomy, use of oral contraceptives, nonsteroidal anti-inflammatory drugs, and antibiotics.[8]

1.1.3 Epidemiology of IBD

The incidence and prevalence of IBD is strongly associated with industrialization, giving North American and Europe the highest rates. As industrialization progresses, rates are beginning to rise in low-incidence areas such as southern Europe, Asia and other developing countries.[9] Canada has one of the highest rates of IBD in the world, with approximately 129,000 and 104,000 Canadians living with CD and UC, respectively, in 2012.[1]

The average age of onset for IBD is between 15 and 30 years old, with approximately 10% of individuals being diagnosed under the age of 18 years old.[5] In terms of gender,

UC is slightly more prevalent in males, whereas CD has a small female predominance. Higher rates of IBD occur in people of Caucasian and Ashkenazic Jewish origin, compared to other ethnicities.[10]

1.2 Treatment of IBD

Due to its chronic and relapsing nature, the management of IBD is often complex and requires ongoing medical therapy. The goal of therapy for patients with IBD is to induce and maintain clinical and endoscopic remission, while attempting to avoid further complications. Several factors need to be considered when choosing an appropriate management strategy, including disease type and severity, patient demographics, medical comorbidity, the presence of extra-intestinal manifestations, and the efficacy and side effects of each medication.[11]

1.2.1 Non-Biologic Therapy

Non-biologic therapies for IBD include 5-aminosalycylyc acids (5-ASA), systematic and topical corticosteroids, and immunosuppressants.

5-ASAs are currently recommended as the first line of therapy for mild to moderate UC, and can be administered either orally or rectally.[12] 5-ASA use for CD has been a longstanding and controversial debate, as multiple studies have found conflicting results in terms of their effectiveness to induce and maintain remission.[13] Until recently, they were still prescribed in the majority of CD patients at some point in the course of their disease despite the lack of evidence.[14]

Corticosteroids are used as an effective method to treat acute flare-ups of IBD as an induction therapy, although their use as a maintenance therapy is limited due to their numerous serious side effects and lack of efficacy as a maintenance agent.[15] Therefore,

an important goal of therapy for patients with IBD is to reduce the use of corticosteroids as much as possible while attempting to maintain remission.

When 5-ASAs and steroids have failed to maintain remission, immunosuppressants are used in an attempt to suppress the overly active immune system that is seen in patients with IBD. The main immunosuppressants used in IBD include thiopurines (azathioprine and 6-mercaptopurine), and methotrexate. The goal of these medications is to help patients who are steroid-dependent maintain remission following steroid treatment.[16]

1.2.2 Surgery

Although medical therapy for IBD is expanding and becoming more effective, there still exists a need for operative management in cases of severe or long standing disease. Currently, it is estimated that 70% to 90% of CD patients will need surgical intervention at some point in their lifetime[17] Although less common, surgery is needed for approximately 25 to 35% of UC patients either due to a complication or inadequate control of symptoms.[18]

Indications for surgery for patients with CD include fibrotic strictures, partial or complete bowel obstruction, fistulas, and abdominal abscess.[6] Surgical resection is the most commonly performed surgical procedure for CD, and a need for multiple resections is common due to recurrence of disease.[19]

Surgery is needed in severe cases of UC when a patient fails to respond to medical therapy. In an emergent setting, a total or subtotal colectomy and end ileostomy is performed in order to remove the inflamed bowel while minimizing morbidity.[20] Currently, the most frequent elective surgery performed for UC is a restorative protocolectomy with ileal pouch-anal anastomosis (IPAA) due to its ability to eliminate disease and improve quality of life. Although this procedure is effective, it can be associated with significant

morbidity and requires substantial lifestyle changes post-surgery, often resulting in patient resistance to undergo surgery.[21,22]

1.2.3 Biologic Therapy

Recently acquired knowledge regarding the pathogenesis and biology of IBD has led to the emergence of biologic therapies that target specific inflammatory pathways. Several mediators of inflammation in IBD have been proposed, including the pro-inflammatory cytokine tumor necrosis factor-alpha (TNFα), which is found elevated in the stool, mucosa, and blood of patients with IBD.[23–25] Infliximab, adalimumab, certolizumab pegol and golimumab are anti-TNF agents that work by inhibiting this pathway, thereby reducing the amount of intestinal inflammation in patients with IBD. Several other biologic therapies targeting inflammatory pathways have been recently introduced for the treatment of IBD, including vedolizumab and natalizumab. For the purpose of this thesis, we have focused on the two most commonly used anti-TNF agents for IBD: infliximab and adalimumab.

1.2.3.1 Infliximab

Infliximab, a chimeric mouse-human monoclonal antibody targeting TNFα, is effective for the induction and maintenance of clinical and endoscopic remission, steroid-sparing, and mucosal healing in patients with moderate to severe IBD who have failed conventional therapies.[26,27] Infliximab is given as a 5 mg/kg infusion, administered at week 0, 2 and 6 as an induction regimen, and then every 8 weeks as a maintenance regimen. Dose escalation is common due to secondary loss of response, where the dose is increased to either 10 mg/kg per infusion, or the dosing interval is reduced to 4 weeks between infusions.[28]

The first study to examine the efficacy of infliximab in the treatment of CD involved patients with moderate to severe, medically-refractory disease that received a single infusion of varying doses.[29] At week 4, 33% of all infliximab patients compared to 4% of placebo achieved remission after the single infusion (p=0.005). Although patients who received infliximab had higher remission rates, 37% of the patients relapsed by week 12, therefore suggesting that a single dose was insufficient.

More recently, scheduled maintenance therapies of infliximab have been proposed in order to optimize treatment. Scheduled infliximab maintenance therapy was associated with improvements in mucosal ulceration, and fewer CD related hospitalizations.[30] Also, infliximab is effective for the treatment of fistulizing CD. The ACCENT II trial showed that most patients with draining fistulas experienced improvement or cessation of draining within 8 weeks of starting infliximab.[31]

The active ulcerative colitis trial (ACT) 1 and ACT 2 trial have supported the use of infliximab in patients with moderate to severe UC, demonstrating a 67% response rate and a 36% remission rate after 8 weeks.[27] Furthermore, several meta-analyses have shown infliximab to be superior to placebo in patients with active UC who have failed to respond or were dependent on corticosteroids.[32–34]

Despite its effectiveness, the safety of infliximab remains a concern due to its risk of side effects, such as infusion reactions, opportunistic infections including tuberculosis, non-Hodgkin's lymphoma, and other malignancies.[35] In a large cohort study, infliximab-related infections were seen in 8% of patients, half of which were serious.[36] Based on these results, it has been concluded that short- and long-term infliximab therapy is generally well tolerated, however clinicians must remain vigilant in detecting the occurrence of these rare but serious events.

1.2.3.2 Adalimumab

Adalimumab is a fully human, immunoglobulin G1 monoclonal antibody that binds with high affinity and specificity to human TNFα.[37] The benefits of adalimumab for patients with IBD include increased quality of life, steroid discontinuation, and reduced hospitalization and surgery rates.[38,39] Adalimumab is often used when a patient either fails to respond or loses response to non-biologic therapy, or as a second line therapy in patients who have lost response to infliximab due to the development of antibodies, consequently leading to infusion reactions, loss of efficacy and delayed hypersensitivity reactions.[37] Adalimumab is administered subcutaneously with an induction dose of 160 mg at week 0 and 80 mg at week 2, followed by a maintenance regimen of 40 mg every 2 weeks. Dose escalation involves either doubling the dose to 80 mg every 2 weeks or halving the infusion intervals to every week.

The first placebo-controlled trial to study the use of adalimumab for the treatment of CD was the CLASSIC I trial, which examined patients with moderate to severe disease who were naïve to anti-TNF therapy. This study revealed that subcutaneous injections of adalimumab was significantly more effective than placebo in inducing remission (36% vs 12%, p=0.001) after 4 weeks.[40] Furthermore, a follow-up to this trial (CLASSIC II) found that adalimumab was superior to placebo in maintaining remission over a 56-week period for patients who responded to adalimumab induction therapy.[41] These findings were further supported by the CHARM trial that found remission rates to be significantly greater with adalimumab compared to placebo at week 26 and 56 in patients with moderate to severe CD.[37]

The ULTRA I trial was the first randomized controlled trial to demonstrate the ability of adalimumab to induce clinical remission in patients with moderate to severe UC. After 8

weeks, 18.5% of patients receiving adalimumab therapy were in remission compared to 9.2% in the placebo group, demonstrating that adalimumab is effective for inducing remission once patients with UC have failed corticosteroids and/or immunosuppressants.[42] A follow-up study (ULTRA II) found that adalimumab was also effective in maintaining clinical remission after 52 weeks compared to placebo (17.3% vs 8.5%, p=0.004) in patients with UC.[38] Similarly to infliximab, adalimumab has been shown to be well tolerated and safe, although serious adverse events such as injection reactions and opportunistic infections do occur infrequently.[42]

1.2.3.3 Loss of Response to Anti-TNF Therapy

Despite the effectiveness of anti-TNF agents, a significant number of patients either do not respond or lose response over time. Primary non-response to anti-TNF therapy occurs in a significant portion of IBD patients,[26,27,38,40] where lack of response can be attributed to immunoinflammatory mechanisms, stage of disease, disease activity level, and individual differences.[43]

A proportion of patients who initially respond to anti-TNF therapy will eventually lose clinical response, resulting in recurrence of disease. The main contributor to this secondary loss of response is an individual's immunogenicity against a specific biologic.[44] Immunogenicity is associated with anti-drug antibodies, which may decrease the drug bioavailability by preventing the drug from entering circulation and reaching the inflammation site, enhancing clearance of the drug, and preventing complete absorption.[45] Furthermore, antibodies may increase the risk of infusion reactions, which may consequently result in decreased drug levels and shorter duration of response.[46,47] There are several factors that could potentially influence the formation of anti-drug antibodies, including dosing quantities and intervals, scheduled versus episodic

treatment regimens, and concomitant use of other medications namely immunomodulators: thiopurines and methotrexate .[47,48]

Patients who lose response to anti-TNF therapy have several options for continued therapy, including dose escalation, addition of an immunomodulator, a change to another anti-TNF agent, or a change of drug class.[49] In a significant portion of patients, dosing and interval adjustments can restore response, particularly when drug concentration levels are sub-therapeutic and there is no evidence of drug antibody formation.[50,51] The addition of an immunomodulator may also be an effective strategy to increase response to anti-TNF therapy and lead to better clinical outcomes.[52] Although these mentioned strategies work to restore response in the majority of patients, there remains a significant portion of patients who will ultimately fail anti-TNF therapy, either requiring a change in therapy or surgical intervention.

1.2.4 Step-up vs. Top-down Strategy

Traditionally, clinicians have adopted a "step-up" approach for patients with IBD where treatment is progressed from topical therapy to more aggressive therapies once patients become unresponsive to previous treatments.[53] This approach generally involves the initiation of 5-ASAs, followed by corticosteroids, immunosupressants, biologic therapy, and if failing all medical therapy, surgery.[54] The main goal of this strategy is to treat active disease, while avoiding over-treating or exposing patients to potential adverse events associated with more aggressive treatment options.[55]

Recently, a "top-down" approach has been introduced for CD, in which certain patients are subjected to a more aggressive approach earlier in the disease course.[54] This strategy involves initiating anti-TNF therapy and immunosuppressants earlier in an effort to delay the progression of disease. A randomized controlled trial of patients with newly

diagnosed CD who were naïve to all therapies found that after 104 weeks, the rate of mucosal healing was significantly higher (71% vs 30%) in the group that had been treated with early infliximab, compared to patients treated in a step-up manner.[56] Mucosal healing after 2 years proved to be a strong surrogate predictor of steroid-free remission, absence of subsequent flares, and need for further anti-TNF therapy. This suggests that aggressive therapy early on in the disease course has the potential to result in long-term benefits. Furthermore, a study conducted at our centre found that initiating infliximab or adalimumab within the first two years of diagnosis reduces rates of surgery and secondary loss of response requiring dose escalation.[57]

The benefits of "top-down" therapy for UC are not as pronounced as in CD, and unpublished data from our center did not show a reduction in hospitalizations or surgeries for patients treated with anti-TNF therapy within three years of diagnosis. This may be due to the fact that UC does not cause transmural inflammation with permanent structural changes to the bowel as CD does, or that patients with UC, unlike CD, will have a strong response to 5-ASA therapies in many cases.

1.3 Costs of Inflammatory Bowel Disease

IBD is associated with a high economic burden due to its early onset and chronic nature, in addition to the high morbidity accompanying the disease. In 2012, the direct medical costs of IBD were estimated at $1.2 billion in Canada, as well as indirect costs totaling approximately $1.6 billion.[1] The main factor that predicts costs of disease is severity due to the increased need for medications, hospitalizations, and surgeries during periods of severe disease activity.[58,59] Overall, the economic impact of IBD is significantly increasing due it's high incidence in Canada combined with its high per-patient costs.[60]

The majority of direct health costs for patients with IBD include prescription drugs, hospitalizations, surgeries, and the services of physicians and other healthcare providers.[61]

1.3.1 Prescription Medications

The majority of patients with IBD require regular medications to control their disease. In periods of disease flares, most patients will require additional medications or increased doses in an attempt to induce remission and prevent further complications. The cost of prescription drugs for IBD has increased dramatically in the past 10 years, mainly due to the introduction of high-cost biologics.[62] In 2012, approximately $521 million was spent on IBD medications in Canada, with approximately 84% of these costs coming from biologic therapies.[1] Furthermore, it has been demonstrated that other medications including 5-ASAs, corticosteroids and immunomodulators account for a significant portion (16%) of resource use in the first year of follow-up in patients with IBD.[63]

1.3.2 Hospitalizations and Surgeries

CD and UC are diseases associated with high hospitalization and surgery rates, which significantly contributes to their economic burden. In 2004, Bassi *et al* found that inpatient services for IBD accounted for 49% of total care costs.[58] However, a more recent study has found that hospitalization and surgery together accounted for 20% and 24% of healthcare costs in CD and UC, respectively.[64] The shift in spending is likely a result of the introduction of biologic therapies, which have been shown to decrease hospitalization and surgery rates.[39]

A study examining the direct costs associated with hospitalization of patients with IBD found a mean cost of admission to be $3,149 for CD and $3,726 for UC.[65] Predictors of high hospitalization costs include length of stay (OR=1.29, $p<0.001$), poor prognosis

(OR=6.78, p<0.001), surgery (OR=3.16, p<0.001), and endoscopy (OR=2.44, p<0.001).[66] Furthermore, it has been reported that a small minority of patients (7%) accounted for a disproportionate amount of hospital bed days (69%).[67]

1.3.3 Healthcare Provider Services

Services from physicians, IBD nurses, dieticians, and social workers account for a significant portion of direct healthcare costs for patients with IBD.[61] It has been estimated that IBD patients visit physicians and outpatient clinics twice as often as the general population, resulting in an increased expenditure of approximately $132 million in Canada.[1,68]

1.3.4 Indirect costs

In 2012, indirect costs associated with IBD such as short- and long-term disability, out-of-pocket expenses, and premature retirements were estimated at $868 million for CD and $693 million for UC in Canada.[1] Employment and education can be severely affected by IBD due to productivity losses. Productivity losses include missed work or school due to medical appointments, illness or hospitalization, as well as long-term absences from employment due to disability, reduction in work hours, or premature retirement. It is important to note that loss of productivity often affects the patient's caregivers as well, who may take time off work to provide assistance to patients with IBD.

Out-of-pocket expenses, such as home aids and modifications, formal care (housekeeping and daycare), travel for medical appointments, and alternative medicines contribute significantly to the economic burden of IBD. A Canadian study found that approximately 50% of patients with IBD had used or currently use complementary or alternative medicines, with an average spending of $568 per patient per year.[69] Other

out-of-pocket expenses such as travel, household support, and patient activities related to IBD have been estimated to cost $268 million per year in Canada.[1]

1.4 Cost of Anti-TNF Therapy

The introduction of anti-TNF therapy has not only revolutionized the way in which IBD is treated, but has also led to a shift in resource utilization.[70] Prior to the introduction of anti-TNF therapy to treat IBD, patient medical costs were attributed to high rates of surgeries and hospitalizations.[71] Recently, the traditional cost profile of IBD has changed to be driven by pharmaceutical costs, particularly anti-TNF therapy.[64] It has been hypothesized that the costs of anti-TNF therapy are being offset by a reduction in surgeries and hospitalizations, however there is conflicting evidence as to whether this reduction in inpatient services counterbalances the significant costs of these medications.

In 2006, a US study estimated total medical expenditures for 1 year to be $US18,963 for CD patients, and $US15,020 for UC, approximately 3 to 3.5 times the expenditure of matched controls.[72] In the same study, approximately 50% of costs were attributed to inpatient admissions, 30% to outpatient visits, and 10-15% to medications. In 2008, a similar study found that 31% of costs of CD could be associated with hospitalizations, 33% with outpatient expenses, and 35% with medications. For UC, 38% of direct costs were attributed to hospitalization, 35% to outpatient, and 27% to pharmaceuticals.[70]

The COIN study in 2014 found that anti-TNF use was the main cost driver in IBD, accounting for 64% and 31% of total costs in CD and UC, respectively.[64] This study further demonstrated the decreased costs of hospitalization and surgery rates due to the initiation of anti-TNF therapy, accounting for approximately 20% and 1% of CD and UC costs, respectively. Ultimately, this study did not show any overall cost savings due to anti-TNF therapy.

A prospective study determined that the mean total CD cost reduction, 12 months after infliximab therapy, was £2,750 per patient.[73] Although numbers of hospitalizations decreased after the initiation of anti-TNF therapy, the reductions were not sufficient to cover the cost of treatment. These results were replicated in a systematic review looking at published articles between 1995 and 2012, where costs associated with maintenance treatment of anti-TNF therapy exceeded the additional healthcare benefits provided and resources saved.[74]

Not only has the introduction of anti-TNF resulted in decreased expenditure on inpatient services, but there has also been a reported decline in prevalence of prolonged steroid exposure for patients with CD.[75] Furthermore, the use of infliximab has resulted in a decrease in annual incidence of outpatient services, such as endoscopies, emergency room visits, outpatient GI visits, and radiologic examinations.[76]

Several cost-utility analyses have been carried out in order to determine if anti-TNF therapy is cost-effective compared to conventional medical therapies for patients with IBD. In 2009, Bodger *et al* conducted an analysis that examined the cost-effectiveness of standard care versus infliximab and adalimumab in patients with CD.[77] The study calculated an incremental cost-effectiveness ratio (ICER) of £7,190/quality-adjusted life year (QALY) for adalimumab compared to standard care, and an ICER of £19,050/QALY when comparing infliximab to standard care. This study concluded that both infliximab and adalimumab may be cost-effective for limited durations (up to 4 years), however lifelong therapy of either agent does not appear to be cost-effective.

Many studies have attempted to determine if infliximab is cost-effective in the management of UC. A Canadian study determined that infliximab is a cost-effective strategy for moderate to severe UC at a willingness-to-pay (WTP) threshold of $80,000

per QALY.[78] A British studied reiterated these findings, calculating an ICER of £27,424 per QALY for infliximab compared to standard care for the management of UC.[79]

Loftus *et al* attempted to compare adalimumab to non-biologic therapy for patients with CD over a 1-year time horizon.[80] This study concluded that adalimumab therapy was cost-effective versus current standard care for the maintenance of remission in patients with active CD, particularly for those with severe disease. In contrast, a cost-utility analysis comparing standard care to adalimumab therapy determined that it may not be cost-effective, with a calculated ICER of $193,305.[81] Currently, there are no studies that examine the cost-effectiveness of adalimumab for the treatment of UC.

Several studies have attempted to determine which anti-TNF therapy is most cost-effective for patients with IBD. A study assessing the costs of infliximab versus adalimumab determined adalimumab to be a dominant strategy over infliximab therapy for patients with moderate to severe CD.[82] On the contrary, Tang *et al* determined that infliximab was the preferential biologic agent for patients with moderate to severe CD, compared to adalimumab, certolizumab pegol, and natalizumab.[83] Different methods used in cost-utility analyses makes general conclusions difficult, and should therefore only be applied to the patient population being studied.

2 Economic Evaluations

2.1 Definition of Economic Evaluations

In a society with increasing budgetary restraints, difficult decisions must be made to identify health interventions and technologies that are worth providing versus those that are not. Economic evaluations are useful in providing information to help make decisions about the allocation of limited healthcare resources. By evaluating both the costs and consequences of new interventions, we are able to compare them to previously used interventions, therefore providing the most cost-effective intervention going forward.

Economic evaluations are primarily designed for policy makers who are responsible for decisions regarding how to allocate funding to new health technologies and interventions. These policy makers include health advisors, as well as those working in jurisdictional drug plans, regional health authorities, hospitals and other healthcare facilities. A secondary audience includes academics, healthcare providers, specialist groups, patients, patient advocacy groups, manufacturers, media and the general public.[84]

The main goal of economic evaluations is to inform the aforementioned audiences about the value for money by identifying, measuring and comparing the costs and consequences of alternative technologies or interventions. In this setting, consequences are most often defined as the health outcomes associated with the alternatives being compared.[84] Economic evaluations do not provide a definitive answer regarding how to allocate limited resources, however they do serve as a method to predict the consequences of allocating resources in different ways.[85]

It is important to note that not all costs studies are considered economic evaluations. Several cost studies examine the cost of disease, however in order to be an economic evaluation, alternatives must be compared. Furthermore, a full economic evaluation would not only consider the costs of alternatives, but it would also consider the consequences of the alternatives to help guide decision making.[86]

2.1.1 Cost-Effectiveness Analysis (CEA)

The goal of CEA is to identify strategies that can achieve more health benefit at the same cost or achieve the same health benefit at a lower cost.[85] CEA is most useful in situations where the decision maker must decide between alternatives while operating with a restricted budget.[86] Based on the costs and consequences of each alternative, we can calculate the ICER, which is the difference in cost needed for an incremental gain in benefit between two interventions.[87]

An advantage of CEA is that it is relatively simply to carry out, and that it is generally easy for the general public to understand clinical measures. Disadvantages include that it often has a narrow scope, interventions with different objectives cannot be compared, and the relationship between outcome and health is often unclear.[85]

2.1.2 Cost-Utility Analysis (CUA)

A CUA is a type of economic evaluation that takes into account patient preference by measuring effectiveness in terms of “health years”. Healthy years are generally determined using a utility-based measurement which combines both quantity and quality of life. The most common unit of measure is the quality-adjust life year (QALY).[85]

A utility value aims to measure a preference or value that a person places on being in a particular health state.[85] An important assumption regarding utility assessment is that the value of being in a health state does not depend on the length of time in that health

state, or on the health states preceding or following it.[88] Generally, utilities can be determined by comparing each health state to a value of 1 for perfect health and a value of 0 for dead. When a health state is considered worse than dead, the utility values take on negative values.[85] Several methods are used to determine appropriate health utilities, including the visual analogue scale, the time trade-off method, and the standard gamble method. Also, a range of generic preference-based questionnaires can be used to determine the value placed on each health state.[89]

A benefit of CUA compared to CEA is that there is a standard measure (the QALY) which can be compared between different healthcare programs that may have different natural units for the outcome. Furthermore, unlike CEA, CUA incorporates quality of life and patient preferences when examining outcomes associated with each health state. A disadvantage associated with CUA is that it is limited to health benefits and that there are often challenges finding appropriate utility values.[85]

2.1.3 Cost-Benefit Analysis (CBA)

CBA is a technique that values both costs and outcomes in monetary terms.[84] The CBA is based on the idea that social welfare exists, and helps make decisions regarding how much of society's resources should be spent on a particular goal.[85] The use of CBA in healthcare decision making has been limited due to methodological difficulties and ethical issues regarding assigning monetary values to health outcomes.[84]

2.1.4 Cost-Minimization Analysis (CMA)

CMA works on the principle that the effectiveness and outcomes of alternatives are equal, therefore making the alternative with the lowest cost more cost-effective. Although simple, an issue that arises with CMA is whether there is evidence that proves both alternatives are indeed equivalent in terms of patient outcomes.

2.1.5 Incremental Cost Effectiveness Ratios (ICERs)

ICERs are important measures both in CEA and CUA, where two interventions are compared in terms of cost and effectiveness. The ICER is calculated by dividing the difference in costs between the two alternatives by the difference in effectiveness between the two alternatives:

$$ICER = \frac{C_2 - C_1}{E_2 - E_1}$$

where *C*=cost, *E*=effectiveness

2.1.6 Simple and Extended Dominance

Simple dominance refers to situations where one strategy is more effective and costs less than the strategy being compared. In this case, we say that this strategy dominates, and would therefore be implemented.[85] Simple dominance results in negative ICERs.

When more than two alternatives are being considered, we also need to determine if a combination of two or more options is less costly and more effective. This concept refers to extended dominance. If extended dominance is not noticed and subsequently adjusted for, misleading statements and invalid conclusions can occur that may lead to incorrect decision making.[90]

2.1.7 Net Benefit

In situations of dominance where negative ICERs result, the net benefit approach can be used to determine which strategy is most cost-effective. The net benefit approach involves converting either the costs into the same units as effectiveness, or effectiveness into the same units as costs.[91] In this sense, we can reformulate the ICER into either net health benefit (NHB) or net monetary benefit (NMB) using the following formulas:

$$NMB = (\lambda * \Delta E) - \Delta C$$

$$NHB = \frac{NMB}{\lambda}$$

Where *E* = effectiveness, *C* = cost, λ=willingness-to-pay threshold

In all cases, the intervention with the highest net benefit will be the most cost-effective option. The net benefit approach can be advantageous to calculating the ICER due to the ambiguity of negative ICERs, and because it does not require us to check for simple or extended dominance.[92]

2.2 Markov Modeling

Markov modelling is a tool used in health economics to represent a stochastic process, where random processes are occurring as time passes.[93] Markov models are most appropriately used for chronic illnesses due to the long term health effects that repeat over time.[85] One of the main advantages of using Markov models is their ability to handle both costs and outcomes simultaneously while systematically dealing with parameter uncertainty.[93] An important limitation of Markov models that must be considered is their "memoryless" feature, which states that one's current health state is independent of their previous health states and how long they've been in the current health state.[94]

While constructing a Markov model, the disease being studied is divided into mutually exclusive and complete states depending on clinically important events in the disease process. Each state is assigned transition probabilities for moving between health states over a pre-defined cycle length. Each health state is associated with costs and health outcomes, and the model is run over a large number of cycles depending on the time horizon used.[93]

2.2.1 Effectiveness Parameters

Effectiveness parameters refer to health outcomes associated with each health state, and can be represented by transition probabilities. Depending on the data we have to analyze effectiveness, we may use different methods to determine the health outcomes of each health state. In an ideal situation, we would be able to directly observe health outcomes from the desired patient population, and we would use this data in our analysis. Most commonly, we have to rely on other methods to obtain appropriate data, including published clinical trials, systematic reviews and meta-analyses. Published literature may obtain summary information about parameters, relative risks, or survival analysis which can be used to estimate effectiveness and fit an appropriate probability distribution to model uncertainty.[85]

In terms of obtaining data from literature, there are advantages and disadvantages to using various sources. Randomized controlled trials are experimental studies where the effect of an intervention is assessed by comparing randomized groups either receiving a particular intervention or a control group who does not.[95] The advantages of randomized controlled trials are that they generally produce the strongest empirical evidence of a treatment's effectiveness, and they minimize any bias between groups by randomization. Disadvantages of these studies include the high dropout rates due to undesirable side-effects, and that they generally study a very specific group of patients that may not be entirely generalizable to the population of interest. On the contrary, observational studies provide access to patients in real life situations and are more generalizable to the patient population being studied, although bias can occur as randomization is not used.

2.2.2 Cost Parameters

Cost parameters are essential in modelling, however they are often associated with

large uncertainty.[85] The perspective of the analysis determines which costs and resources will be included in the analysis, and should be relevant to the decision maker. A limitation related to appropriate cost parameters is the lack of economic literature examining the indirect and non-medical costs associated with specific illnesses. These types of costs can be included in the sensitivity analysis if data is available and if it is thought to make a difference on the results. Also, it is important to obtain costs not only relevant to that patient population, but also the country and healthcare system where the study is taking place. Cost and resource use data can be obtained using many different sources, including cost studies, clinical trials, government databases, or expert opinion.[84]

2.2.3 Utility Parameters

Utility parameters are determined by examining patient preferences for each health state associated with the disease. Utilities are generally derived from measures of health-related quality of life (HRQL) and are used to determine QALYs gained from interventions. As with other parameters, utility values often present with uncertainty, highlighting the importance of choosing an appropriate probability distribution. Utility values can be obtained using measures of quality of life, and at times can be found in published literature.[84]

2.2.4 Uncertainty

Parameter uncertainty in Markov modelling occurs when the true value of a parameter is unknown. Although natural variation exists for each parameter, uncertainty in economic modeling has the potential to result in making an incorrect decision regarding the value of an intervention or technology. Uncertainty can also relate to model design features, such as model structure, analytical methods, and generalizability.[84] While conducting economic evaluations, data is often obtained from sample information, which has a risk

of not being truly representative of the population of interest. Furthermore, many healthcare parameters have long-term effects that often need to be accounted for by extrapolation, resulting in uncertainty related to how these parameters change over time.[85]

Uncertainty related to model structure is due to the model representing a simplification of the disease process compared to reality. It is important to account for all necessary processes in the disease pathway, however it's important that the model is also economical and feasible to use. Finally, methodological uncertainty can occur due to the process of obtaining parameter evidence and the choice of modelling methods.[85]

Deterministic or probabilistic sensitivity analyses are used to account for parameter uncertainty in a model. Deterministic sensitivity analysis involves changing one or more parameter and examining how the outputs change in response to that change.[85] A deterministic sensitivity analysis is useful for determining which parameters have the strongest influence on the results, and therefore which parameters are most important to the decision maker. The main limitation of a deterministic sensitivity analysis is that while changing one parameter, all other values remain constant, therefore assuming that uncertainty exists only in that particular parameter. Assuming that there is no relationship between the parameter that is changed and the remaining parameters, results in an oversimplification that limits its use as a way to analyze uncertainty.

To overcome this limitation, a probabilistic sensitivity analysis (PSA) can be used to model the uncertainty related to all parameters. For all uncertain parameters, a representative probability distribution is fit to the parameter of interest. PSA can be done through Monte Carlo simulation, which takes random draws of the uncertain parameters from their distribution, and running the model for each simulated set of parameters to

obtain outputs.[96]

2.2.5 Discounting

Discounting in health economics is based on the principle that the opportunity cost or benefit of an intervention is dependent on the point in time when costs or benefits are incurred. Conventionally, future costs and benefits are represented in terms of their present value, resulting in a need to discount these to reflect the true cost and benefit when they are actually experienced. Much debate exists regarding appropriate discount rates, as well as if costs and benefits should be discounted at the same rate.[97]

2.3 Willingness-to-Pay (WTP) Thresholds

A WTP or cost-effectiveness (CE) threshold refers to a monetary value indicating how much the decision maker is willing to pay for one QALY. The WTP threshold is used in many countries to determine if an intervention is cost-effective, and is generally estimated using expert opinion, human capital, and World Health Organization (WHO) recommendations.[98] Despite these methods to determine an appropriate WTP threshold, the appropriate cut-offs for each healthcare system remains inconclusive.

Threshold values are appealing due to their simplicity, however their ambiguity remains a key limitation to their use. The first WTP threshold established was $US50,000 per QALY by Kaplan and Bush in 1982.[99] Using the US Consume Price Index, this is equivalent to $US123,000 in 2016, although the original $US50,000 value is still commonly cited in cost-effectiveness studies. Furthermore, Grosse argued that the $50,000 per QALY threshold is an arbitrary decision rule that lacks theoretical and empirical justification and is outdated due to the failure to adjust the value for inflation and changing levels of income or healthcare budgets since its introduction.[100]A tiered system has also been suggested, with “strong” evidence being interventions with ICERs

lower than $20,000 per QALY, “moderate” evidence for interventions with ICERs ranging from $20,000-$100,000 per QALY, and “weak” evidence for interventions with ICER’s greater than $100,000 per QALY.[101] Another method used by the WHO estimated the WTP threshold on the basis of plausible assumptions about people’s values attitudes toward risk, and suggested a threshold of two to three times the per capita annual income, which is equivalent to a US threshold of $110,000 to $160,000 per QALY in 2014.[102]

In Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) recommends using a WTP threshold of $CAN50,000 per QALY. The Canadian Drug Expert Committee between 2003 and 2007 has accepted therapies up to $CAN80,000 per QALY; further demonstrating the ambiguity in the determination of an appropriate WTP threshold.[103] Due to different approaches, each with their own assumptions, inferences, and contexts; further research is required to determine a WTP threshold that will result in appropriate decisions regarding the allocation of resources.[102]

2.4 Value of Information (VOI)

Economic evaluations are accompanied with a great deal of uncertainty due to the sometimes limited evidence regarding parameter values. In these situations, further research may be warranted in an attempt to reduce uncertainty in the analysis. Although this is ideal, research is expensive and subjects patients to the risk of experimentation. VOI analysis is a tool used to quantify decision uncertainty and helps to estimate the potential benefit of conducting further research. Furthermore, VOI analysis helps prioritize which research projects should be undertaken, as well as where the research should focus on within that specific project.[85] By knowing how much and what type of evidence is required to reduce uncertainty, there is an increased likelihood that decision

makers will make correct decisions regarding the cost-effectiveness of new interventions or therapies.

2.5 Advantages of Economic Evaluations

The healthcare sector is required to make important decisions regarding the adoption of new interventions and technologies in the face of limited resources. Economic evaluations act as a tool in order to help decision makers make appropriate decisions regarding the allocation of resources, as well as prevent them from adopting interventions that have poor value. While costs and resource studies give us information regarding how much a particular disease or treatment costs, they fail to take into consideration the consequences of choosing a particular treatment over another. Economic evaluations provide a framework where direct comparisons can be made in order to aid in the decision-making process by identifying the consequences when resources are allocated in certain ways.[85]

2.6 Disadvantages of Economic Evaluations

Although economic evaluations provide key information to decision-makers regarding the cost-effectiveness of new interventions or technologies, methodological flaws exist that must be considered. Despite the attempt of models to take into account resource use and benefits, it is impossible to consider all costs and benefits that could affect the decision. Furthermore, the range of parameters that is considered important depends on the perspective or viewpoint chosen in the analysis.[104] For example, economic analyses with a public healthcare system viewpoint generally omit indirect costs associated with the intervention, including loss of productivity and out-of-pocket expenses.

Flaws in data collection and analysis can also contribute to uncertainty regarding outputs. In some situations, an economic model may obtain all of their data from one

clinical trial, although this is rare. In most circumstances, models rely on obtaining information from multiple sources. This may result in indirect comparisons being made between interventions, as well as incomplete information in some cases.[105] Also, models often need to use extrapolation beyond the observed period of clinical studies. Extrapolation results in uncertainty regarding the long-term benefits and side effects of the intervention, and the method used to extrapolate can significantly affect the results of the analysis.[104]

Finally, flaws exist in the methods of interpretation and reporting of results. The generalizability of the results can be difficult, as data is often obtained from a very specific population. Also, analysts must consider how they are reporting their results to ensure that emphasis is not being placed too heavily or not enough on certain findings.[104] Although flaws exist, they can generally be controlled for by providing transparent methodology, conducting sensitivity analysis, and acknowledging any limitations of the evaluation while reporting results

3 Cost-Effectiveness of Adalimumab in the Management of Ulcerative Colitis

3.1 Introduction

Ulcerative colitis (UC) is a relapsing and remitting chronic disease that results in mucosal inflammation of the colon. Treatment for UC is focused on the induction and maintenance of clinical remission and endoscopic mucosal healing. Maintaining remission requires continuous medical therapy and ongoing monitoring of disease activity. Conventional medical therapies, including mesalamine, corticosteroids and oral immunosuppressants (azathioprine, 6-mercaptopurine) may be inadequate to maintain disease remission in some patients.[42]

For patients who fail to maintain remission with the above therapy, the options for treatment are limited to repeated corticosteroid use, colectomy, or biologic therapy. The chronic use of corticosteroids is associated with significant adverse effects and can leave the patient in a chronically unwell state.[106] While colectomy with a permanent ileostomy or an ileoanal pouch procedure can result in improved quality of life, it may be associated with significant morbidity and can lead to concerns with body image.[21,22] In this regard, patients often delay the colectomy and elect to remain in a chronically unwell state, often on repeated courses of corticosteroids.

The use of the anti-tumor-necrosis factor-alpha (TNFα), adalimumab, has been shown to be well tolerated and effective in inducing and maintaining remission in patients with moderate to severe active UC. [38,42,107,108] The benefits of adalimumab for patients with UC include increased quality of life, steroid discontinuation, and reduced hospitalization and surgery rates.[38] However, the cost of adalimumab is significant, varying from

$18,000 to $33,000 per patient per year, and therefore must be taken into consideration when deciding an appropriate treatment option for patients with UC.[109]

In this analysis, the costs and benefits of patients receiving readily available adalimumab treatment for UC was compared to that where adalimumab was not readily available and thus the patient preference for a chronically unwell state, with or without corticosteroids, rather than immediate colectomy dominated.[110–112]

3.2 Methods

3.2.1 Type of Study and Outcome

A cost-utility analysis was conducted to compare the cost-effectiveness of adalimumab versus chronic steroid therapy for the management of moderate to severe UC. Our study replicated a previously validated Markov model in UC that was conducted by our centre for another anti-TNF agent, infliximab, that calculates the difference in costs divided by the differences in effectiveness between the study option and alternative intervention; the result being the incremental cost-effectiveness ratio (ICER).[78] In the current study, this validated anti-TNF Markov model was replicated for the use of adalimumab treatment of UC. The perspective of this analysis was from the publicly funded healthcare system, with only direct costs included in the analysis,

3.2.2 Target Population

A base-case analysis was used that consisted of a theoretical cohort of patients with moderate to severe active UC who are corticosteroid dependent and either failed and/or are intolerant to immunosuppressive therapies. Approximately 60% were male, with an average age of 40 years old.

3.2.3 Markov Model Structure

A previous established Markov model was used to determine the ICER of two management strategies: (1) No adalimumab, which includes scenarios where adalimumab was not available and patients therefore remained in a chronically unwell state in order to avoid colectomy, and (2) Adalimumab therapy, where adalimumab was readily available to induce and maintain clinical response. Patients in this group were modeled as being treated initially with 160 mg, 80 mg at week 2, followed by 40 mg every other week.

The different health states used in the model were defined and verified by a panel of gastroenterologists and gastrointestinal surgeons with expertise and experience in the treatment of inflammatory bowel disease (Table 3-1). Based on their treatment strategy, patients were assigned to an initial health state of 3 months and were evaluated every 3 months over a 10 year time horizon. At the end of every 3-month cycle, patients were assigned probabilities of moving on to ensuing health states.

The probabilities of moving on to subsequent health states were as follows: patients who received adalimumab therapy either experienced an induction response or became “non-responders”. The patients who responded to adalimumab may continue to respond to treatment over time or they may experience a secondary loss of response. The patients who did not respond to the initial adalimumab treatment or who lost response to treatment returned to ongoing steroid therapy, where a portion of patients eventually underwent colectomy. Patients who experienced an adverse effect due to adalimumab therapy could sometimes be successfully treated for the complication. If they could not be treated for the complication, they were either taken off adalimumab and returned to ongoing steroid therapy or offered a colectomy. Patients who received a colectomy could

develop complications associated with the surgery or could remain in a response state. The possibility of patient mortality was considered for each health state.

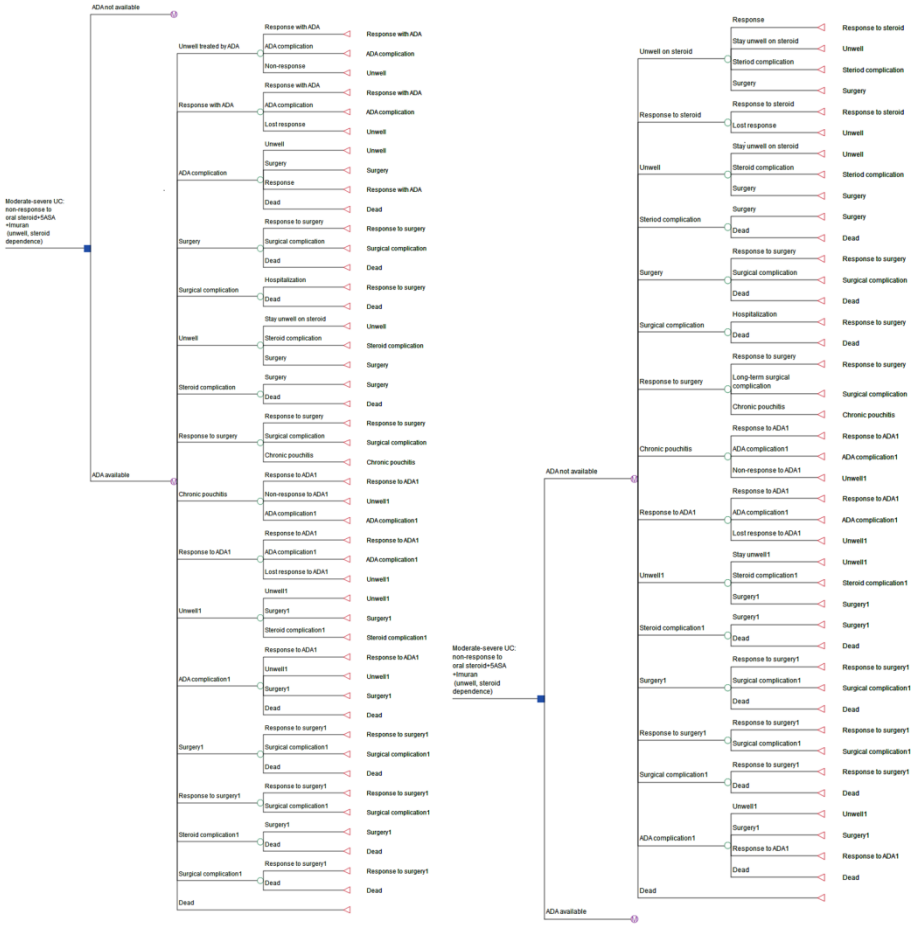

Figure 3-1 Model structure diagram.

Table 3-1 Health state definitions

Health State	Definition
Response to medical treatment (steroid/ADA)	Reduction/resolution of symptoms due to patients' respective treatment regimens. Patients in this cohort would have a UC Disease Activity Index (DAI) score of 0-2 (out of 12) or a partial Mayo score of 0-1 (out of 9).

Unwell	Patients are experiencing recurrent disease activity despite being treated with medical therapy (steroids, 5-ASA, azathioprine, or biologics). Patients in this cohort would have a UC DAI score of 3-8 (out of 12) or a partial Mayo score of 2-6 (out of 9). Symptoms often include 5-8 bowel movements per day, some rectal bleeding, and chronic fecal urgency.
Chronic pouchitis	A common long-term complication after restorative protocolectomy with ileal pouch-anal anastomosis for patients with UC. Chronic pouchitis is characterized by inflammation of the ileal pouch after surgery, presenting with symptoms of increased stool frequency, urgency, incontinence, and dehydration.
Steroid/ADA complication	Any complication that occurred as a result of the medical treatment (steroid or ADA) that required a change in treatment or health state.
Non-/loss response (ADA)	Non-response refers to patients who never responded to ADA, whereas loss of response refers to patients who experienced an initial response but lost response in subsequent cycles.
Surgery	Proctocolectomy with ileal pouch-anal anastomosis for those patients who did not respond to medical treatment. Typically patients with severe UC undergo surgery in order to manage their disease.
Surgical Complication	Any complication that occurred as a result of surgery that requires patient to be hospitalized or to undergo further surgery to correct the complication.

3.2.4 Model Inputs

Our analysis follows the 2006 economic evaluation guidelines as set out by the Canadian Agency for Drugs and Health Technologies.[84]

3.2.4.1 Transition Probabilities

The probabilities of patients moving between health states were derived from a review of the literature from both randomized controlled trials and real-life observational studies. Study results were weighted based on sample size. Loss of response to adalimumab was obtained from our centre data in an attempt to replicate real-life clinical response. The weighted probabilities were then reviewed by the panel of gastroenterologists for face validity. Tables 3-2 and 3-3 show the transition probabilities associated with each health state.

3.2.4.2 Costs

A literature search was administered to assess the costs of each health state per 3-month cycle. To estimate resource use, we included physician, hospital and outpatient drug costs. Physicians' fees were obtained from the Alberta Schedule of Medical Benefits price list.[113] Hospital costs for all hospitalization episodes came from the Ontario Case Costing Initiative.[114] The costs of drugs were obtained from the Alberta Health and Wellness Drug Benefit List.[109] The costs of corticosteroids, adalimumab, or surgical-complication health states were estimated by averaging the cost of complication weighted by the likelihood of occurrence. Cost-of-death was counted once and equal to the cost of the health state that led to the death. Tables 3-2 and 3-3 outline the costs of each health state per 3-month cycle.

3.2.4.3 Utilities

In order to calculate quality-adjusted life years (QALY) for each treatment regimen, utilities for each health state were determined through a review of the literature and access to expert opinion. When determining the utility score for a response-to-adalimumab, we obtained 2 different score values that represents the utility of patients in remission. Using 2 different estimation methods, the utility scores for patients with steroid-refractory ulcerative colitis were: 0.79 by time trade-off and 0.82 by visual rating scale.[115] The utility value assigned to each health state is outlined in Tables 3-2 and 3-3.

Table 3-2 Markov model input parameters for ulcerative colitis

		Transition probabilities (%) per cycle	**Costs (CA$) per cycle**[109,113,114]	**Utility Scores per year**[115]
A. Ongoing Steroids[27,116]			**917 (±25%)**	**0.32 (±0.31)**
	1. Response	33.92 (28.09-40.33)		
	2. Unwell	57.11 (50.50-63.27)		
	3. Complication	2.80 (0.56-7.63)		
	4. Surgery	#		
B. Response to Steroids[116]			**0**	**0.79 (±0.21)**
	1. Response	53.30 (46.81-59.67)		
	2. Loss of Response	#		
C. Unwell on Steroids[27,116]			**917 (±25%)**	**0.32 (±0.31)**
	1. Unwell	#		
	2. Complication	2.80 (0.56-7.63)		
	3. Surgery	10.00 (6.40-14.28)		

D. Steroid Complication[106,116]			**23,919 (±25%)**	**0.16 (±0.16)**
	1. Surgery	98.00 (93.70-99.78)		
	2. Death	#		
E. Surgery[117,118]			**37,159 (±25%)**	**0.16 (±0.16)**
	1.Early Response	#		
	2. Complication	12.80 (8.76-17.91)		
	3. Death	2.50 (0.98-5.69)		
F. Response to Surgery[117,119]			**0**	**0.58 (±0.15)**
	1. Response to surgery	85.80		
	2. Surgical complication	#		
	3. Chronic pouchitis (CP)	11.70		
G. Chronic Pouchitis[22]			**8,144 (±25%)**	**0.32 (±0.31)**
	1. Response to ADA (CP)	See Table 3-4		
	2. Non-response (unwell-CP)	#		
	3. ADA complication (CP)	4.20		
H. Surgical Complication[117]			**17,586 (±25%)**	**0.49 (±0.32)**
	1. Hospitalization	99.50 (97.22-99.99)		
	2. Death	#		

I. Adalimumab (ADA)			**8,144 (±25%)**	**0.32 (±0.31)**
	1. Response to ADA	86.80 (75.74-97.86)		
	2. ADA Complication	3.04		
	3. Non-Response (unwell)	#		
J. Response to ADA			**4,442 (±25%)**	**0.79 - 0.82**
	1. Response to ADA	See Table 3-4		
	2. ADA Complication	7.88		
	3. Loss of Response (unwell)	#		
K. Adalimumab Complications			**12,059 (±25%)**	**0.16 (±0.16)**
	1. Response to ADA	70.00		
	2. Unwell on Steroids	14.00		
	3. Surgery	14.00		
	4. Death	#		
L. Death		1	**Equal to cost of corresponding health state**	**0**

#=complement probability

Table 3-3 Markov model input parameters for chronic pouchitis

Health states	**Transition probabilities (%) per cycle**	**Costs (CA$) per cycle**[109,113,114]	**Utility Scores per year**[115]

M. Response to ADA1			**4,442 (±25%)**	**0.58 (±0.15)**
	1. Response to ADA1	See Table 3-4		
	2. Lost-response (unwell1)	#		
	3. ADA complication1	4.20		
N. Unwell1			**917 (±25%)**	**0.32 (±0.31)**
	1. Unwell1	#		
	2. Surgery1	10.00		
	3. Steroid complication1	2.80		
O1. ADA complication1 in the ADA not available arm			**12,059 (±25%)**	**0.16 (±0.16)**
	1. Response to ADA1	60.00		
	2. Unwell1	19.00		
	3. Surgery1	19.00		
	4. Death	#		
O2. ADA complication1 in the ADA available arm			**12,059 (±25%)**	**0.16 (±0.16)**
	1. Response to ADA1	51.00		
	2. Unwell1	23.50		
	3. Surgery1	23.50		

	4. Death	#		
P. Surgery1 (Permanent ileostomy)			**37,159 (±25%)**	**0.16 (±0.16)**
	1. Response1	#		
	2. Surgery Complication1	12.80		
	3. Death	2.50		
Q. Steroid Complication1			**23,919 (±25%)**	**0.16 (±0.16)**
	1. Surgery1	98.00		
	2. Death	#		
R. Response to Surgery1			**0**	**0.44 (±0.11)**
	1. Response to surgery1	#		
	2. Surgical Complication1	2.50		
S. Surgical Complication1			**17,586 (±25%)**	**0.37 (±0.24)**
	1. Response to surgery	#		
	2. Death	0.50		

#=complement probability

3.2.4.4 Probabilities of Response

Patients on adalimumab tend to lose response over time,[120,121] and loss of response generally requires additional interventions such as dose escalation, rescue steroids or surgical intervention. The average loss of response rates to adalimumab for each 3-month cycle (Table 3-4) were collected from data obtained by Ma *et al* at the University

of Alberta Inflammatory Bowel Disease Consultation and Research Clinic, Edmonton, Alberta, Canada.[120]

In a retrospective cohort study from our expert IBD center, it was determined that dose escalation was required in 50% of UC patients after a mean time span of 59.3 (±70.5) weeks.[120] Dose escalation of adalimumab typically consists of increasing the dose to 80 mg or increasing to weekly injections of 40 mg. Currently, there is a lack of research that examines the response rates of dose escalation in UC patients. Thus, it was agreed by collaboration with a gastroenterology expert panel that loss of response rates in UC after dose escalation would be fixed to that seen for Crohn's disease; therefore our expert IBD center Crohn's disease outpatient data was used to estimate loss of response to dose escalation at each 3 month cycle (Table 3-4).

Table 3-4 Maintenance probabilities of patients on adalimumab over time

Cycle #	Rate of Response of UC Patients[120]	Chronic Pouchitis patients (ADA not available arm)[122]	Chronic Pouchitis patients (ADA available arm)*	Rate of response of patient's dose escalated[50] **
0	86.8	62.6	53.2	93.8
1	73.3	61.2	52.0	80.5
2	66.5	59.9	50.9	73.7
3	62.0	58.6	49.8	69.1
4	58.7	57.3	48.7	65.8
5	56.2	56.1	47.7	63.2
6	54.1	54.9	46.7	61.1
7	52.4	53.7	45.6	59.4

8	50.9	52.5	44.6	57.8
9	49.6	51.4	43.7	56.5
10	48.5	50.3	42.8	55.3
11	47.5	49.2	41.8	54.3
12	46.5	48.1	40.9	53.3
13	45.7	47.0	40.0	52.5
14	45.0	46.0	39.1	51.7
15	44.3	45.0	38.3	51.0
16	43.6	44.0	37.4	50.3
17	43.0	43.1	36.6	49.7
18	42.4	42.1	35.8	49.1
19	41.9	41.2	35.0	48.5
≥20	41.4	40.2	34.2	48.0

*To calculate the response probability for patients with chronic pouchitis who had been previously exposed to and failed adalimumab, a 15% discount was taken from the probability of response of patients with chronic pouchitis who had never been exposed to ADA

**These maintenance probabilities are based on Crohn's disease patient information

3.2.5 Deterministic Sensitivity Analysis

One-way sensitivity analyses were conducted on all key parameters for 6 scenarios with a time horizon of 5, 10, or 15 years, and a utility score of the response-to-adalimumab health state of 0.79 or 0.82. The probabilities and utility scores were varied between the lower and upper ends of 95% confidence intervals, and the costs of each health state were varied by 25%, as shown in Tables 3-2 and 3-3.

3.2.6 Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis for costs and utility scores was performed. A log normal distribution was used for costs and a beta distribution for utility scores that are far from 0; utility scores close to 0 were transformed to utility decrement (=1-U), and a gamma distribution was used.

3.2.7 Discounting

Costs and outcomes were discounted annually at the rate of 5%.

3.3 Results

3.3.1 Costs and Quality-Adjusted Life Years

With a utility score of 0.79, repeated steroid therapy costs $97,000 and yielded 3.154 QALYs over a 10-year period. Adalimumab therapy costs $107,000 and resulted in 3.321 QALYs over a 10-year period. The incremental cost associated with adalimumab therapy compared to chronic steroid therapy is $10,000 and the incremental effectiveness is 0.167 QALYs.

3.3.2 Incremental Cost-Effectiveness Ratio

The ICER at 10 years, when comparing readily available adalimumab treatment to ongoing steroid therapy, was $59,000 per QALY when using a utility score of 0.79 measured by time trade-off, and $53,000 per QALY when using a utility score of 0.82 measured by visual–analog-scale.

3.3.3 Deterministic Sensitivity Analysis

Sensitivity analysis of probabilities, costs and utility scores showed that the ICER varied from $37,000 to $81,000 (utility score of 0.79) or from $33,000 to $72,000 (utility score of 0.82) at the 10-year horizon (Table 3-5). The most sensitive variables were the cost of

response to adalimumab and the utility of an unwell state, whereas the least sensitive variables were the probability of surgical complication and the probability of hospitalization among surgical complications.

Sensitivity analyses were also performed with varying time horizons. The ICER of adalimumab therapy versus no adalimumab therapy ranged from $25,000 to $65,000 (utility score of 0.79) and from $22,000 to $58,000 (utility score of 0.82) at a 5-year horizon. At a 15-year horizon, the ICER ranged from $45,000 to $91,000 (utility score of 0.79) and from $40,000 to $81,000 (utility score of 0.82).

Table 3-5 Incremental cost-effectiveness ratios between adalimumab treatment and chronic steroid treatment

Time Horizon	Utility score of response with ADA measured by time trade-off **(u=0.79)***	Utility score of response with ADA measured by visual rating scale **(u=0.82)***
5 years	$45,000 ($25,000 - $65,000)	$40,000 ($22,000 - $58,000)
10 years	$59,000 ($37,000 - $81,000)	$53,000 ($33,000 - $72,000)
15 years	$68,000 ($45,000 - $91,000)	$60,000 ($40,000 - $81,000)

*u = utility score for the response-to-adalimumab health state

3.3.3.1 ICERs Associated with Adalimumab Dose Escalation

Upon analyzing dose escalation response rates using Crohn's disease data, we estimated dose escalation ICERs to be $85,000 at 5 years, $102,000 at 10 years, and $113,000 at 15 years when using a utility score of 0.79. Analysis of dose escalation with a utility score of 0.82 revealed ICERs of $77,000, $92,000, and $102,000 at 5, 10, and 15 years, respectively.

3.3.4 Probabilistic Sensitivity Analysis

3.3.4.1 Cost-Effectiveness Acceptability

Cost-effectiveness acceptability curves are presented in Figure 3-2 to 3-7. Given a time horizon of 10-years and a utility score of 0.79 for a response to adalimumab, the graph shows a 45% chance that adalimumab treatment will be cost-effective if the willingness-to-pay (WTP) for an extra QALY is $50,000. The probability of adalimumab treatment being cost-effective if the WTP is $100,000 and $150,000 is 56% and 60%, respectively.

Using the same time horizon (10 years) with a utility score of a response to adalimumab health state to be equal to 0.82, the probability of adalimumab treatment being cost-effective is 46%, 57%, and 61% at a willingness-to-pay of $50,000, $100,000, and $150,000, respectively.

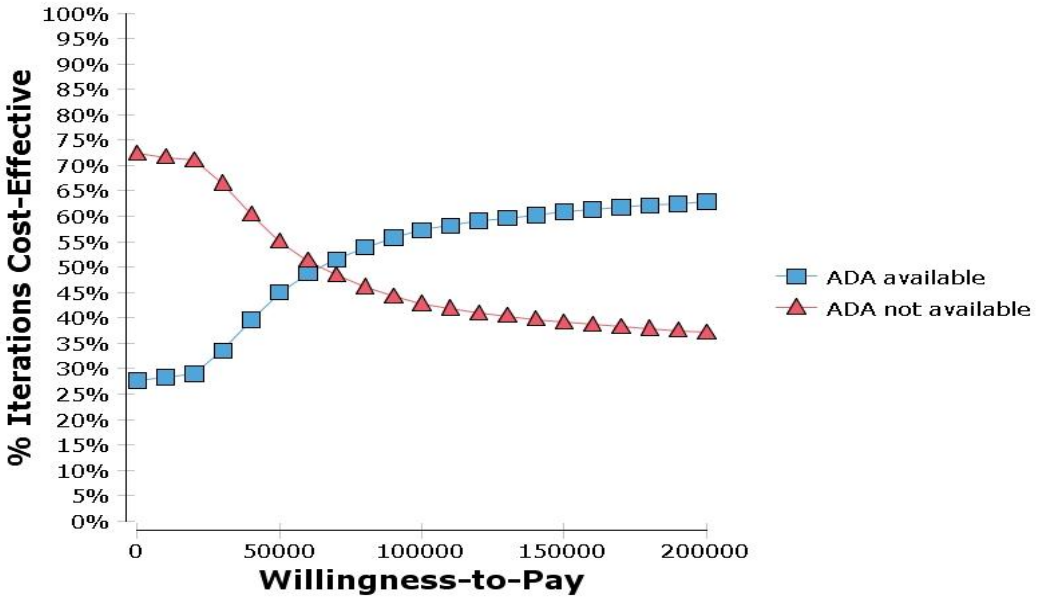

Figure 3-2 Cost-effectiveness acceptability curve at a time horizon of 5 years and a utility value of 0.79 for the response-to-adalimumab health state.

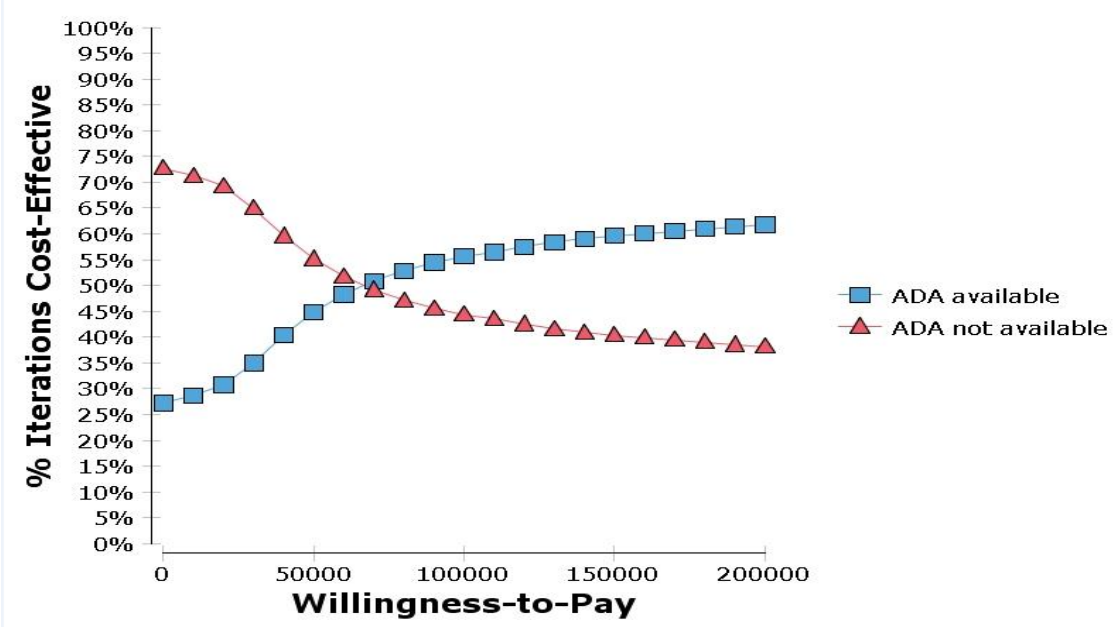

Figure 3-3 Cost-effectiveness acceptability curve at a time horizon of 10 years and a utility value of 0.79 for the response-to-adalimumab health state.

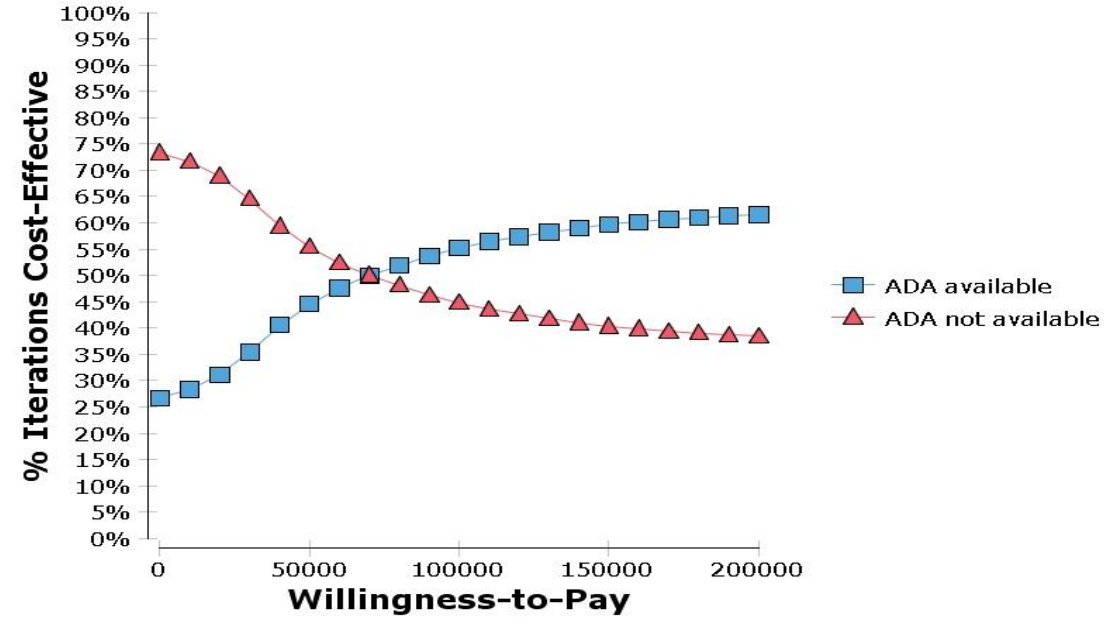

Figure 3-4 Cost-effectiveness acceptability curve at a time horizon of 15 years and a utility value of 0.79 for the response-to-adalimumab health state.

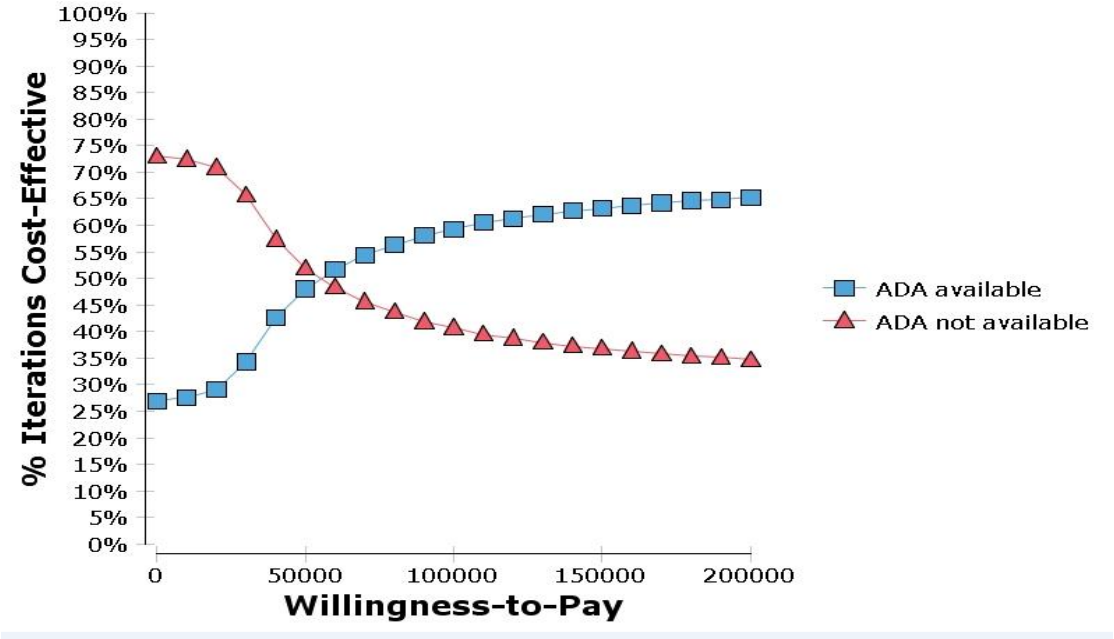

Figure 3-5 Cost-effectiveness acceptability curve at a time horizon of 5 years and a utility value of 0.82 for the response-to-adalimumab health state.

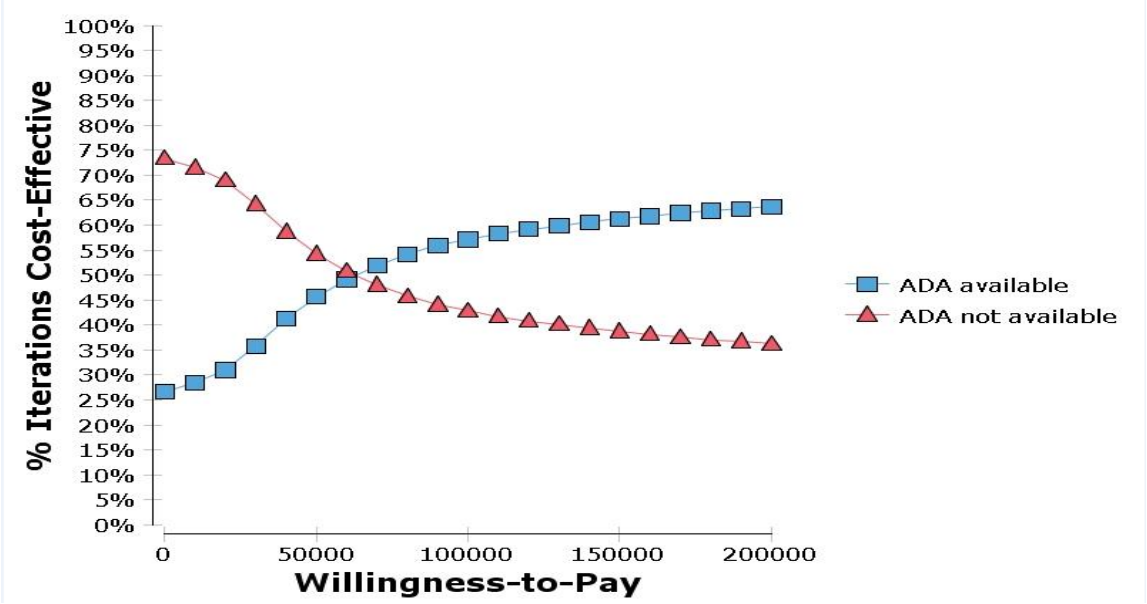

Figure 3-6 Cost-effectiveness acceptability curve at a time horizon of 10 years and a utility value of 0.82 for the response-to-adalimumab health state.

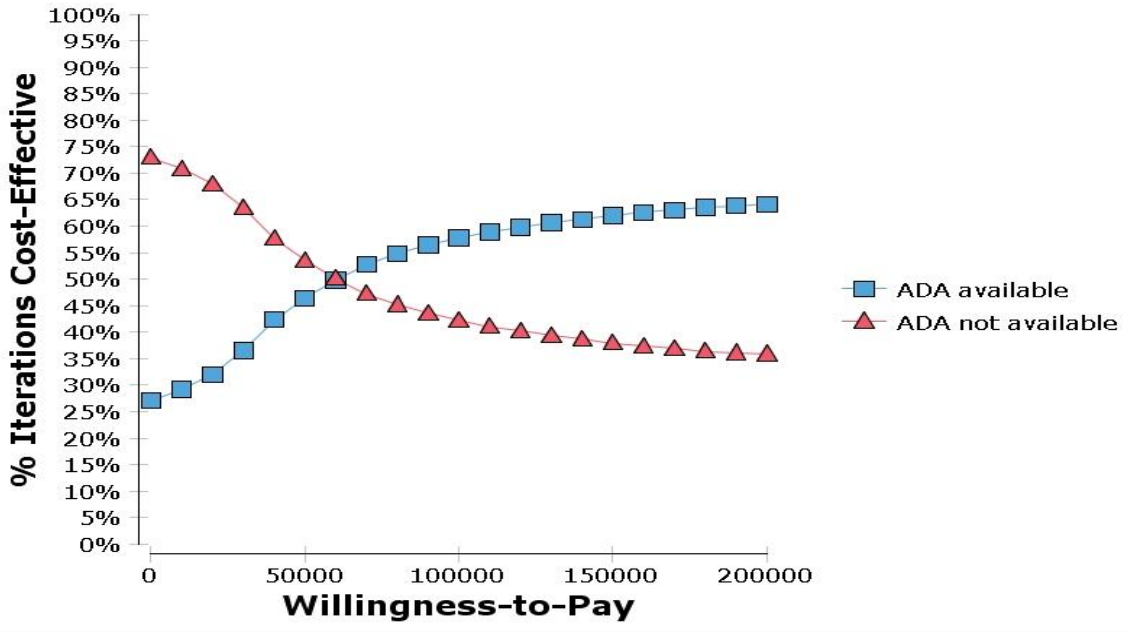

Figure 3-7 Cost-effectiveness acceptability curve at a time horizon of 15 years and a utility value of 0.82 for the response-to-adalimumab health state.

3.4 Discussion

Multicenter, randomized, placebo-controlled trials have shown adalimumab to be well-tolerated and effective in inducing and maintaining remission in patients with moderate to severe UC,[38,42] in addition to an abundance of open-label studies that further support these findings.[107,121,123–126] The emergence of adalimumab and other biologic agents has given UC patients an additional treatment option to consider once they have become corticosteroid-dependent. While considering any treatment strategy, the costs of therapy must be taken into consideration regardless of outcome. In order to determine if a strategy is worthwhile, a WTP threshold must be set.

To date, there is no WTP threshold that is accepted universally throughout healthcare systems. A threshold value of $50,000 per QALY has been widely used in many studies and countries as a reference threshold since the 1970s, although its use is often

debated as being too low. Grosse argued that the $50,000 per QALY threshold is an arbitrary decision rule that lacks theoretical and empirical justification and is outdated due to the failure to adjust the value for inflation or changing levels of income or healthcare budgets since its introduction.[100] Also, it should be noted that different medical conditions can have different WTP thresholds, depending on the severity of the disease.[127] The Canadian Drug Expert Committee between 2003 and 2007 has accepted therapies up to $80,000 per QALY; further demonstrating the ambiguity in the determination of an appropriate WTP threshold.[103] Due to the long-lasting and debilitating nature of UC, we assume that a threshold of $80,000 per QALY is appropriate to consider the cost-effectiveness of adalimumab in the treatment of UC.

Based on the $50,000 per QALY WTP threshold, it appears that adalimumab therapy is cost-effective compared to repeated steroid use at a 5-year time horizon. Although the ICERs for 10-year and 15-year time horizons surpass this threshold, they are all considered to be cost-effective according to a WTP threshold of $80,000 per QALY gained as per Rocchi *et al*.[103] These results demonstrate that although the cost of adalimumab is significant, it may present as a worthwhile treatment option in patients with moderate to severe active UC.

By using the previously establishedMarkov model validated for infliximab[78] as the model for this current study, we are able to compare the cost-effectiveness of the two main biologic agents currently in use for the management of UC: infliximab and adalimumab. Our original infliximab analysis demonstrated infliximab to have an ICER of $US64,000 and $US79,000 at 5 and 10 years, respectively, therefore being cost-effective at a WTP threshold of $US80,000. The current study demonstrated adalimumab to have an ICER of $US44,000 and $US58,000 at 5 and 10 years, respectively, when converted to $US using the conversion rate implemented in the infliximab study. Given these results, it

appears that adalimumab, at the cost available in Canada ($740.36/40mg), may be similar or numerically more cost-effective for the management of moderate to severe active UC than infliximab.

The lower ICER for adalimumab compared to infliximab is likely due to the lower cost of adalimumab in Canada compared to infliximab. In addition, this difference may be larger than expected due to the lack of the infliximab model taking into consideration the indirect costs of infliximab administration. Infliximab administration requires patients to receive intravenous injections at an outpatient health center, opposed to adalimumab which can be administered by the patients subcutaneously.

An exploratory analysis of ICERs associated with dose escalation was conducted due to the high rate of patients who require dose escalation as a result of secondary loss of response. The average ICER associated with dose escalation was $85,000, $102,000, and $113,000 at 5, 10 and 15 years, respectively. This data clearly demonstrates that a need for dose escalation in patients who experience a loss of response to adalimumab results in additional costs, thus increasing the ICER above frequently used WTP thresholds.

In conclusion, this study demonstrates that using response rates from real-life centers and real-life patient preference to avoid colectomy, readily available adalimumab treatment of ulcerative colitis is cost-effective according to WTP thresholds of $80,000 per QALY compared with when adalimumab is not available and the patients elect for a chronic unwell state to avoid colectomy. Dose escalation will increase these costs beyond commonly used WTP thresholds.

4 Cost-Effectiveness of Early versus Late Initiation of Anti-TNF Therapy in Crohn's Disease

4.1 Introduction

Crohn's disease (CD) is a relapsing and remitting inflammatory bowel disease (IBD) that is associated with an evident economic burden to the Canadian healthcare system due to its chronic nature and early onset.[128] Anti-TNF therapies, particularly infliximab and adalimumab, are effective for the induction and maintenance of clinical remission in patients with CD, although they are accompanied with a significant cost, ranging from $18,000 to $33,000 per patient per year.[109]

Anti-TNF agents are generally prescribed once patients have failed to respond to conventional, less-costly medical therapies such as 5-ASAs, immunosuppressants, and corticosteroids.[55] The main goal of this "step-up" therapy is to treat symptoms, while attempting to avoid over-treating or exposing patients to side effects associated with more aggressive therapies.

An increasingly used approach to CD management is referred to as a "top-down" approach. This strategy involves subjecting certain patients to more aggressive therapy early in the disease course in an effort to delay the progression of irreversible, structural changes to the bowel.[129] These irreversible processes, such as fibrosis, stenosis, and the formulation of fistula, have shown to be key indications for surgery in patients with CD.[130] The goal of "top-down" therapy is to promote mucosal healing rather than treating symptoms, as symptoms may have a poor correlation with disease activity. "Top-down" therapy has focused on mucosal healing as a primary outcome because of its ability to

serve as a strong predictor of steroid-free remission, absence of subsequent flares, and a decreased need for further anti-TNF therapy.[56]

In a recently published study, early treatment of infliximab or adalimumab within 2 years of diagnosis was associated with a reduced need for surgical resection, as well as a reduced rate of loss of response requiring dose escalation in a cohort of CD patients.[57] This study provides supportive evidence that early, aggressive therapy may be warranted in certain patients, and can potentially change the natural progression of disease.

The emergence of this treatment paradigm results in a need to examine the economic implications of the decision of when to initiate anti-TNF therapy for patients with CD. The aim of this study is to determine the cost-effectiveness of early versus late initiation of infliximab and adalimumab for the management of moderate to severe CD.

4.2 Methods

4.2.1 Type of Study and Outcome

An economic evaluation was conducted to examine the cost-effectiveness of anti-TNF therapy when initiated early in the disease course (≤2 years of diagnosis) compared to later in the disease course (>2 years after diagnosis). A cut-off of 2 years was based on a previously proposed definition to classify early CD.[131] A representative Markov model was constructed to calculate the differences in costs and effectiveness between the two strategies over the lifetime of a cohort of CD patients. A cost-utility analysis was chosen for this analysis in order to incorporate patient preferences by defining health-related quality of life based on health state utility values. The perspective of this analysis was

from the publicly funded healthcare system. Only direct costs to the healthcare system were included.

4.2.2 Target Population

A base-case analysis was used that consisted of a theoretical cohort of patients with moderate to severe active CD. Approximately 50% were female. Drug dosage was modeled for patients weighing an average of 70 kg.

4.2.3 Markov Model Structure

The structure of the Markov model was developed by IBD clinical experts, with clinical expertise and academic record in the treatment of CD. Furthermore, health economists were consulted for support in model development and analysis. Model validation was completed by consulting IBD experts, as well as comparing model traces to previously published literature.

The Markov model contains two branches to compare: early initiation and late initiation of anti-TNF therapy. Based on literature review, as well as the expertise of gastroenterologists with experience in the treatment of IBD, the mutually exclusive health states used in this model were: clinical remission, active disease, surgery, surgical complications, drug complications, and death (defined in Table 4-1). In each health state, patients consume resources and accumulate quality-adjusted life years (QALYs) based on the patient's quality of life in each heath state.

Each patient began in the "Active Disease" state, where the decision to initiate anti-TNF agents would have been made. Patients were evaluated at the end of every 3-month cycle and assigned probabilities of moving onto subsequent health states depending on their current health state. A lifetime time horizon, with an average diagnosis age of 25 years old was used to replicate the chronic nature of CD.

From “Active Disease”, patients are initiated on anti-TNF induction therapy, where they can either respond or remain unwell despite treatment. If patients do not respond, they can either choose to remain in a chronically unwell state or undergo surgery. If the patient responds, they will proceed to “Remission”, where they can either remain responsive or experience a disease flare. If they experience a flare, they return to “Active Disease”. The patients who initially responded may continue to respond to treatment over time or they may experience a secondary loss of response. Drug complications and death are considered for both of these health states.

If the patient decides to undergo surgery, they may respond, remain unwell, experience complications, or die. If they respond, they continue onto “Remission”, where as if they do not, they experience “Active Disease”. In the case of surgical or drug complications, a proportion can be resolved, and the patient will subsequently return to “Remission”. If the complications cannot be resolved, they will remain in the complications health states or die.

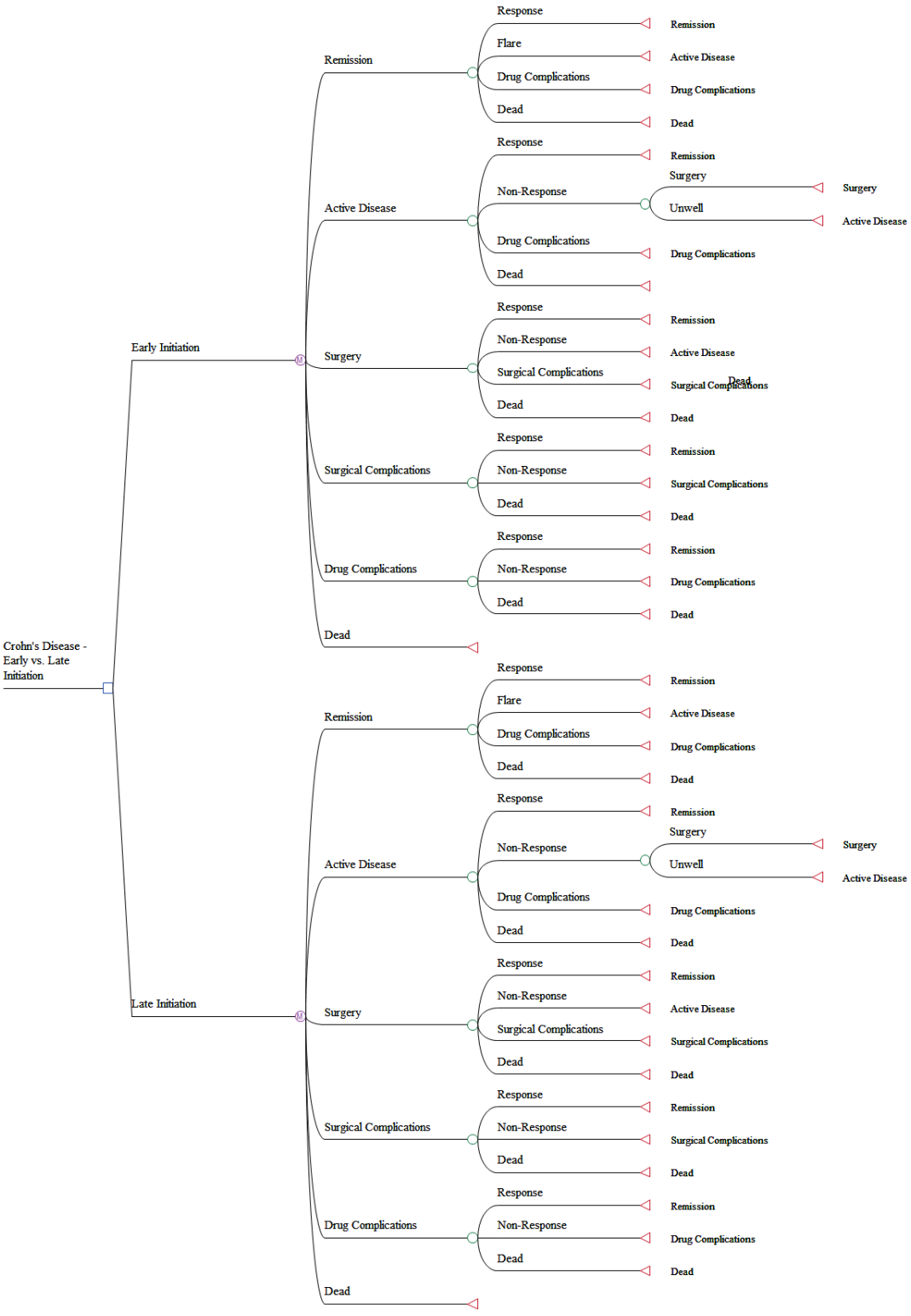

Figure 4-1 Model structure diagram.

Table 4-1 Health state definitions

Health State	Definition
Remission	Achieved response with anti-TNF induction therapy and continues to achieve response with scheduled maintenance therapy
Active Disease	Patients are experiencing recurrent disease activity despite being treated with anti-TNF therapy
Surgery	Resection of the small or large intestine
Drug Complication	Any complication that occurred as a result of anti-TNF treatment that required a change in treatment or health state
Surgical Complication	Any complication that occurred as a result of surgery that requires patient to be hospitalized or to undergo further surgery to correct the complication

4.2.4 Model Inputs

Our analysis follows the 2006 economic evaluation guidelines as set out by the Canadian Agency for Drugs and Health Technologies (CADTH).[84]

4.2.4.1 Transition Probabilities

Relevant articles used to obtain transition probabilities between health states were attained using a literature search. Further sources were obtained by scanning each publication's references for applicable articles. Randomized controlled trials with large sample sizes were given priority, followed by open-label observational studies if needed. Expert opinion from gastroenterologists with experience treating IBD was used where

research was lacking, including response, non-response and mortality rates following a drug or surgical complication.

Loss of response rates to anti-TNF therapy were obtained using previously published data from the Division of Gastroenterology at the University of Alberta.[57] Loss of response rates were used to demonstrate the effectiveness of anti-TNF agents, with non-response defined using clinical disease activity indices, inflammatory markers, and endoscopic and radiographic evidence of disease activity.

Probabilities obtained from the literature were then converted to rates corresponding to a 3-month cycle, and then converted to a 3-month probability using the following formulas:

$r = \ln(1 - p)$

$$p = 1 - e^{-r}$$

where *p* = probability and *r* = rate

Transition Probability Definitions

pFlare: The probability of a flare of active disease when patient is in remission

pResponse: The probability a patient responds to anti-TNF therapy and experiences remission

pDrug_Comp: The probability a patient experiences a complication associated with anti-TNF use while experiencing either active disease or remission

pDead: The probability of death when in remission or active disease

pNonR: The probability of non-response to anti-TNF therapy and patient continues to experience active disease after a flare

pSurgery: The probability of undergoing surgery as a result of active disease

pResp_Comp: The probability of responding to treatment after experiencing a drug or surgical complication

pNonR_Comp: The probability of non-response to treatment after experiencing a drug or surgical complication

pDead_Comp: The probability of death after experiencing a drug or surgical complication

pResponse_Surg: The probability of responding to surgery and inducing remission

pNonR_Surg: The probability a patient does not respond to surgery and continues to experience active disease

pSurg_Comp: The probability a patient experiences a complication associated with surgery

pDead_Surg: The probability of death resulting from surgery

Table 4-2 Model transition probabilities

Probabilities each 3-month cycle	**Infliximab Value**	**Adalimumab Value**
pFlare	#	#
pResponse	See Figure 4-2	See Figure 4-3
pDrug_Comp[26,37]	0.034	0.063
pDead[132]	Age Specific	Age Specific
pNonR	#	#
pSurgery[133]	0.135	0.135
pResp_Comp	0.680	0.680

pNonR_Comp	0.280	0.280
pDead_Comp	0.040	0.040
pNonR_Surg[134]	0.079	0.079
pResponse_Surg[134]	0.760	0.760
pSurg_Comp[135]	0.126	0.126
pDead_Surg[136]	0.035	0.035

- complement probability

4.2.4.2 Costs

To estimate costs for patients diagnosed with CD, a retrospective cohort of 8434 Albertans diagnosed between January 1, 2000 and December 31st, 2014 were identified through the Alberta Disease Registry. From this cohort, Alberta Blue Cross payment records from 2006 to 2014 were searched for individuals with records for infliximab and adalimumab. Surgery records were obtained from inpatient records, and complications were obtained by searching inpatient, ambulatory, and physician claim databases. The costs were adjusted for inflation using the medical component of the Canadian Consumer Price Index and are given in 2014 dollars. Detailed methodology for obtaining costs can be found in Appendix A.

Table 4-3 Costs assigned to each health state

Health State	Infliximab	Adalimumab
Remission	$6,812	$4,534
Active Disease	$12,197	$8,025
Surgery	$17,029	$17,029
Drug Complications	$7,472	$9,600
Surgical Complications	$12,239	$12,239

Dead	$24,522	$24,522

4.2.4.3 Utilities

Utility scores were assigned to each health state based on the patient's health-related quality of life in that state, such that death is represented by 0 and perfect health is represented by 1. Similarly to transition probabilities, utilities were assigned to each health state based on literature search. Literature that utilized the Standard Gamble approach was used in our analysis to directly assess utility for each health state. Utilities were then used to calculate quality-adjusted life years (QALYs) for both the early and late initiation treatment regimens.

Table 4-4 Utility values assigned to each health state

Health States	**Utility value per year**[137]	**Utility value for 3 month cycle**
Remission	0.88	0.22
Active Disease	0.62	0.16
Surgery	0.54	0.14
Drug Complications	0.52	0.13
Surgical Complications	0.52	0.13
Dead	0.00	0.00

4.2.4.4 Probabilities of Response

Similarly to other drugs, patients on anti-TNF agents tend to lose response over time, and loss of response generally requires additional interventions such as dose escalation, rescue steroids or surgical intervention. The average loss of response rates to anti-TNF agents for each 3-month cycle were collected from data obtained by Ma *et al* at the

University of Alberta Inflammatory Bowel Disease Consultation and Research Clinic, Edmonton, Alberta, Canada, and presented in Figures 4-2 and 4-3.[57] Data was extrapolated using an exponential regression.

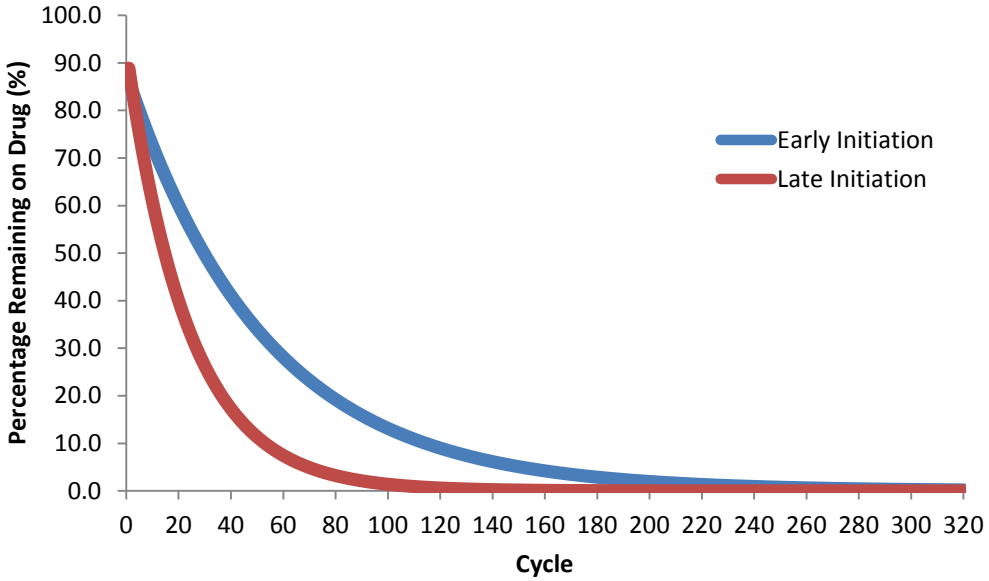

Figure 4-2 Probability of response to infliximab.

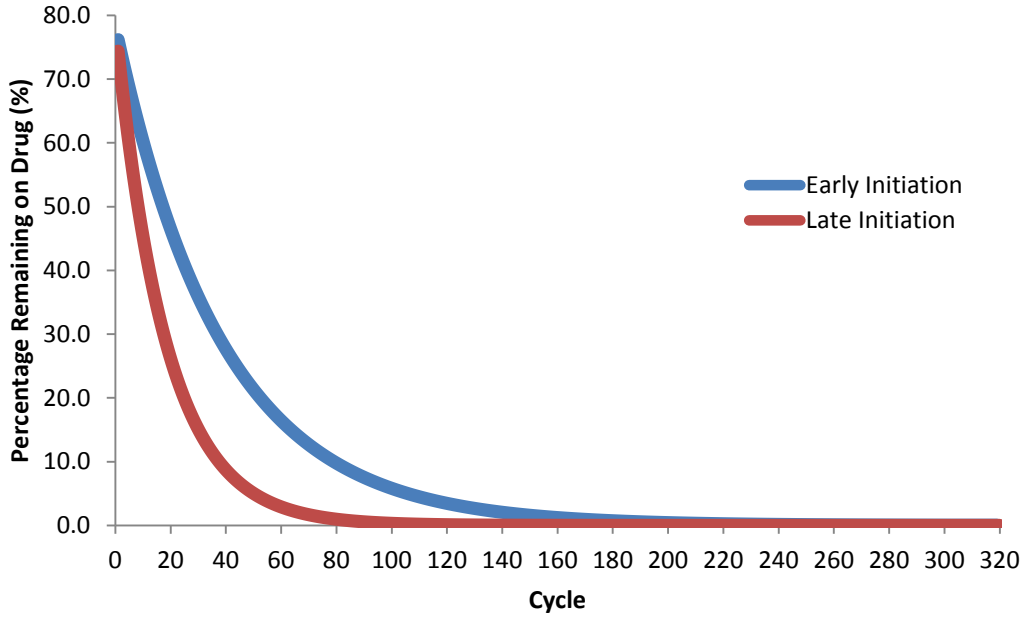

Figure 4-3 Probability of response to adalimumab.

4.2.5 Deterministic Sensitivity Analysis

A one-way sensitivity analysis with tornado diagrams was performed on all key parameters. Transition probabilities, loss of response rates, and utility scores were varied between the lower and upper ends of 95% confidence intervals. Costs were varied ±25% from the mean obtained in Table 4-3. Utility values using the visual-analog-scale (VAS) approach were also analyzed in the sensitivity analysis.

Table 4-5 Lower and upper ends of 95% confidence intervals (CI) for transition probabilities used in one-way sensitivity analysis

Transition Probabilities	Infliximab		Adalimumab	
	Lower End of 95% CI	Upper End of 95% CI	Lower End of 95% CI	Upper End of 95% CI
pDrug_Comp[26,37]	0	0.215	0	0.306
pSurgery[133]	0	0.477	0	0.477
pNonR_Surg[134]	0	0.349	0	0.349
pResponse_Surg[134]	0	1.000	0	1.000
pSurg_Comp[135]	0	0.458	0	0.458
pDead_Surg[136]	0	0.219	0	0.219

Table 4-6 Cost of health states used in one-way sensitivity analysis

Health States	Infliximab		Adalimumab	
	-25% from mean	+25% from mean	-25% from mean	+25% from mean
Remission	$5796	$8056	$2688	$7673

Active Disease	$8853	$16,901	$4129	$15,727
Surgery	$14,008	$20,806	$14,008	$20,806
Drug Complications	$5281	$10,628	$6154	$15,075
Surgical Complications	$9693	$15,562	$9693	$15,562
Dead	$20,214	$29,909	$20,214	$29,909

Table 4-7 Lower and upper ends of 95% confidence intervals for utility values used in one-way sensitivity analysis

Health States	**Lower end of 95% CI for each 3 month cycle**	**Upper end of 95% CI for each 3 month cycle**
Remission	0.14	0.25
Active Disease	0.03	0.23
Surgery	0.01	0.23
Drug Complications	0.01	0.21
Surgical Complications	0.01	0.21
Dead	0.00	0.00

4.2.6 Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis was conducted by Monte Carlo simulation to account for uncertainty related to input parameters. This method allows repeated model simulations which randomly draw from pre-determined statistical distributions in order to provide a distribution of outputs.[85] A gamma distribution was used for costs and disutility (1-U), and transition probabilities were distributed according to a beta distribution. All analyses used 10,000 simulations.

4.2.7 Discounting

Costs and utilities were discounted at a rate of 5% per year. A discount rate of 1.5% was analyzed as part of the deterministic sensitivity analysis.

4.3 Results

4.3.1 Markov Model Trace

A Markov trace consists of a graphical representation that demonstrates the percentage of patients in each health state as time passes.

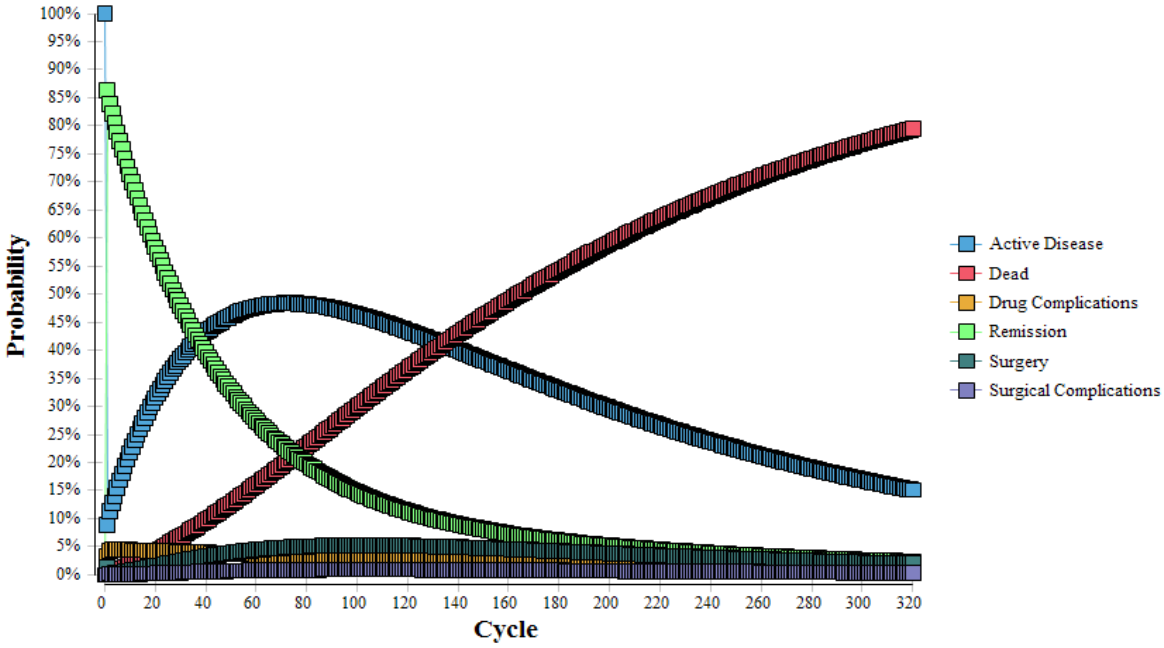

Figure 4-4 Markov trace showing the progression of patients throughout their lifetime when initiating infliximab within the first two years of diagnosis.

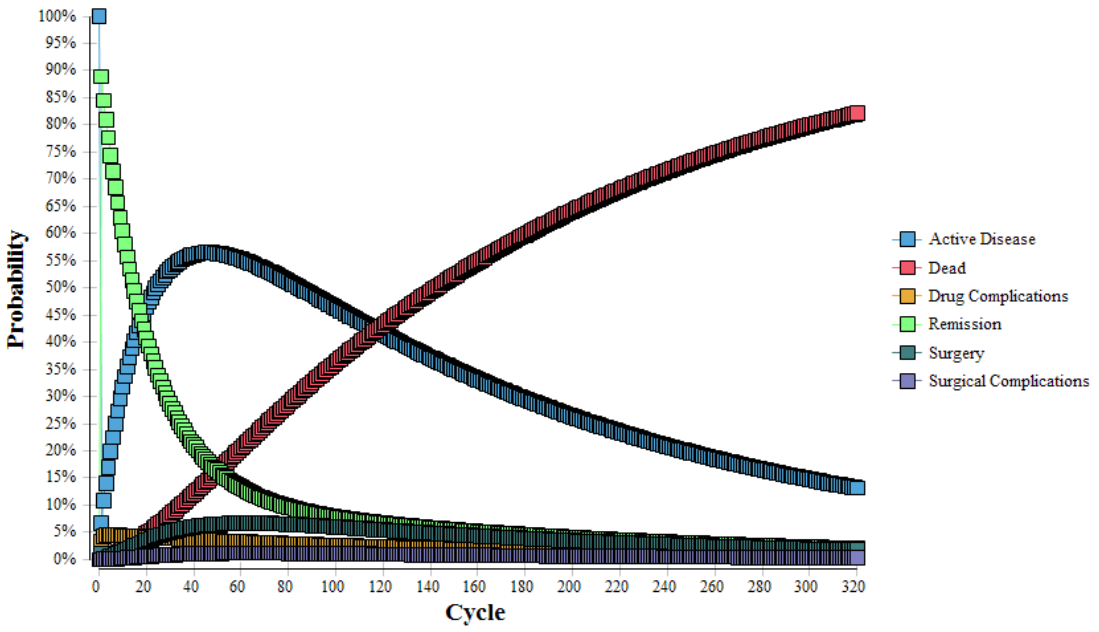

Figure 4-5 Markov trace showing the progression of patients throughout their lifetime when initiating infliximab over two years after diagnosis.

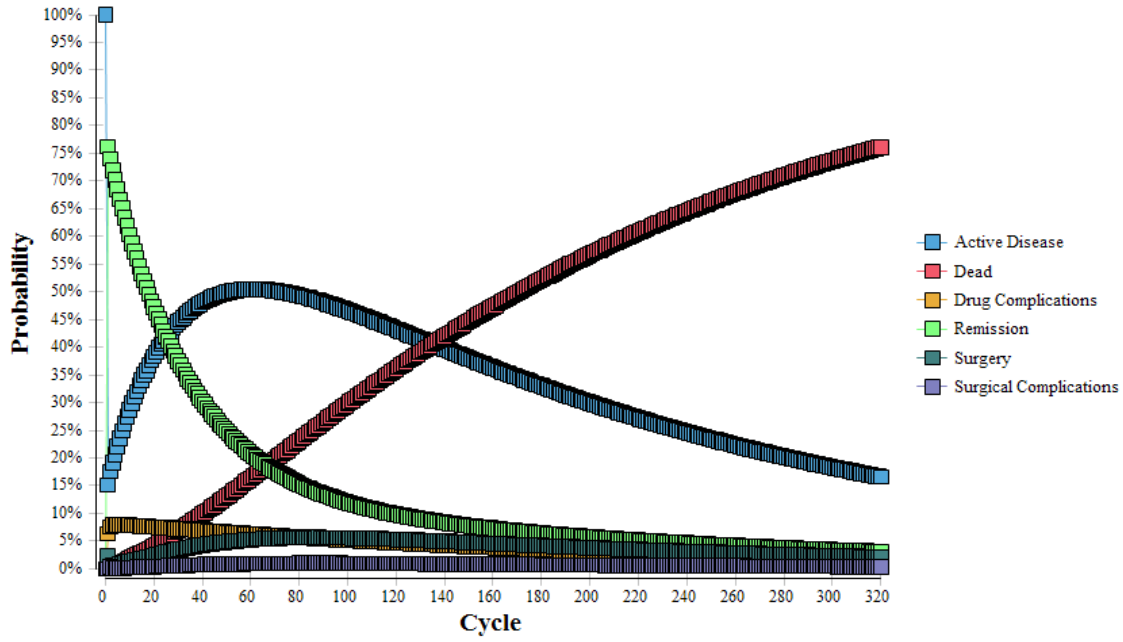

Figure 4-6 Markov trace showing the progression of patients throughout their lifetime when initiating adalimumab within the first two years of diagnosis.

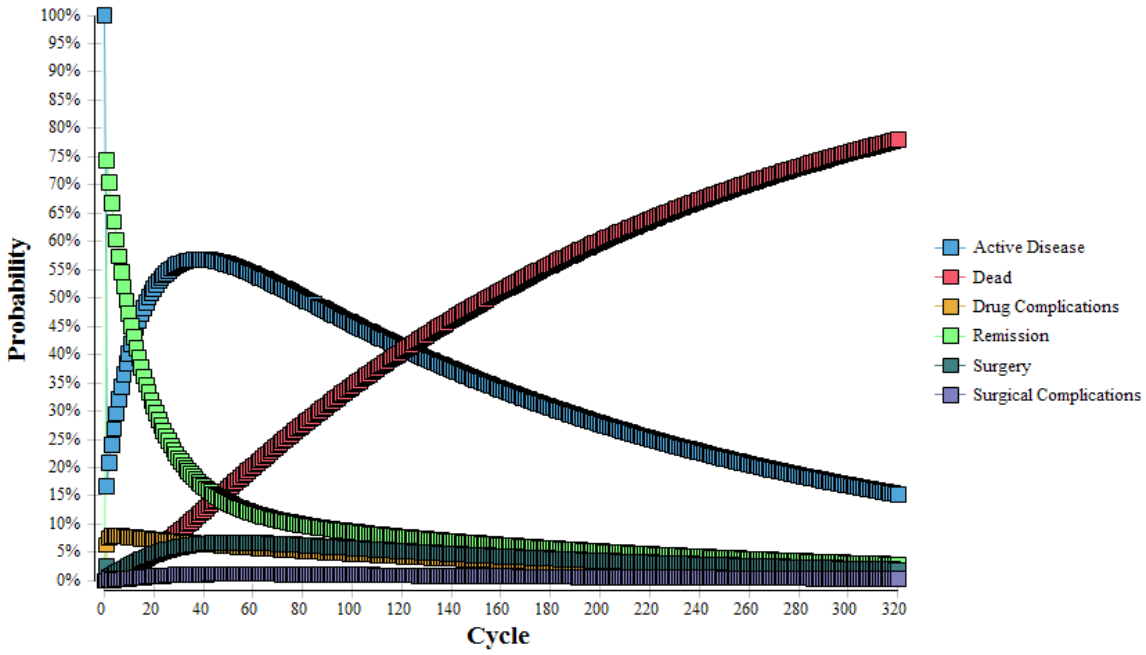

Figure 4-7 Markov trace showing the progression of patients throughout their lifetime when initiating adalimumab over two years after diagnosis.

4.3.2 Costs and Quality-Adjusted Life Years

Infliximab

Early initiation of infliximab costs patients with CD $632,343 for 11.45 QALYs over their lifetime. Late initiation of infliximab costs $650,397 for 10.43 QALYs over a patient's lifetime.

The incremental cost associated with early versus late initiation of infliximab is -$18,054 and the incremental effectiveness is 1.02 QALYs.

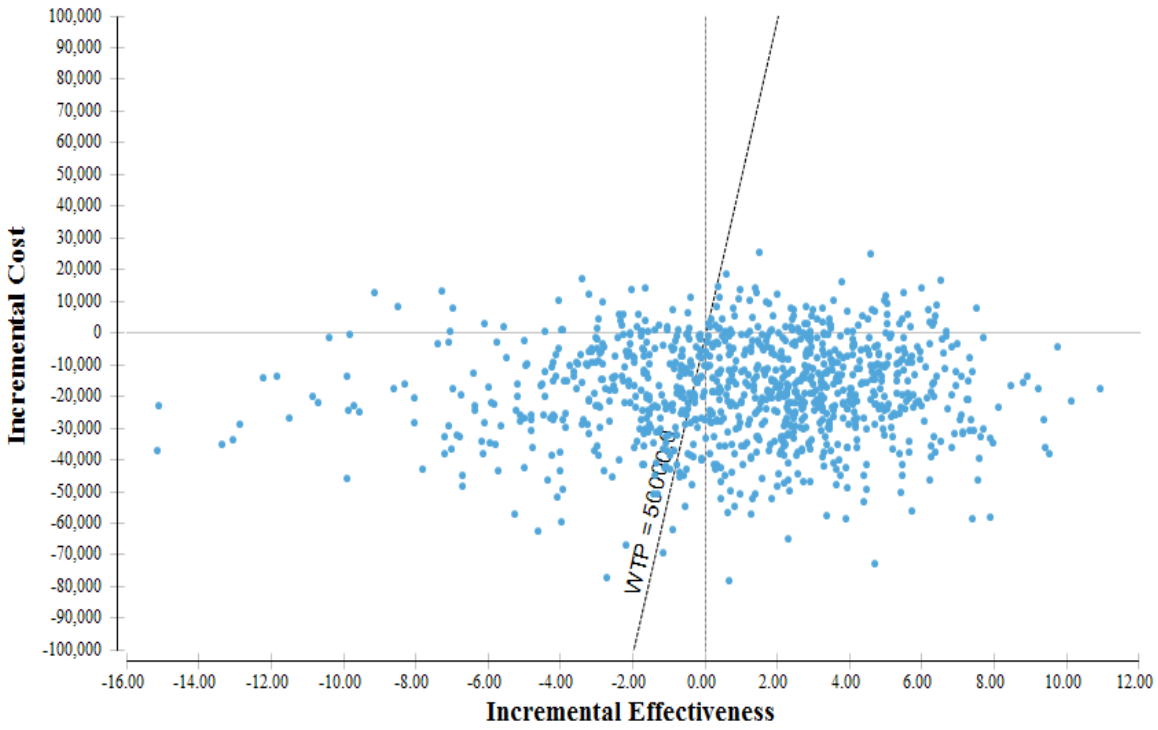

Figure 4-8 Incremental cost-effectiveness plane for early versus late initiation of infliximab. A sample of 10,000 Markov Chain Monte Carlo simulations is plotted. The diagonal line represents a willingness-to-pay (WTP) threshold of $50,000 per QALY. Simulations below the line are considered to be cost-effective at that threshold.

Adalimumab

Early initiation of adalimumab costs patients with CD $491,199 for 11.13 QALYs over their lifetime. Late initiation of adalimumab costs $509,725 for 10.39 QALYs over a patient's lifetime.

The incremental cost associated with early versus late initiation of adalimumab is -$18,526 and the incremental effectiveness is 0.74 QALYs.

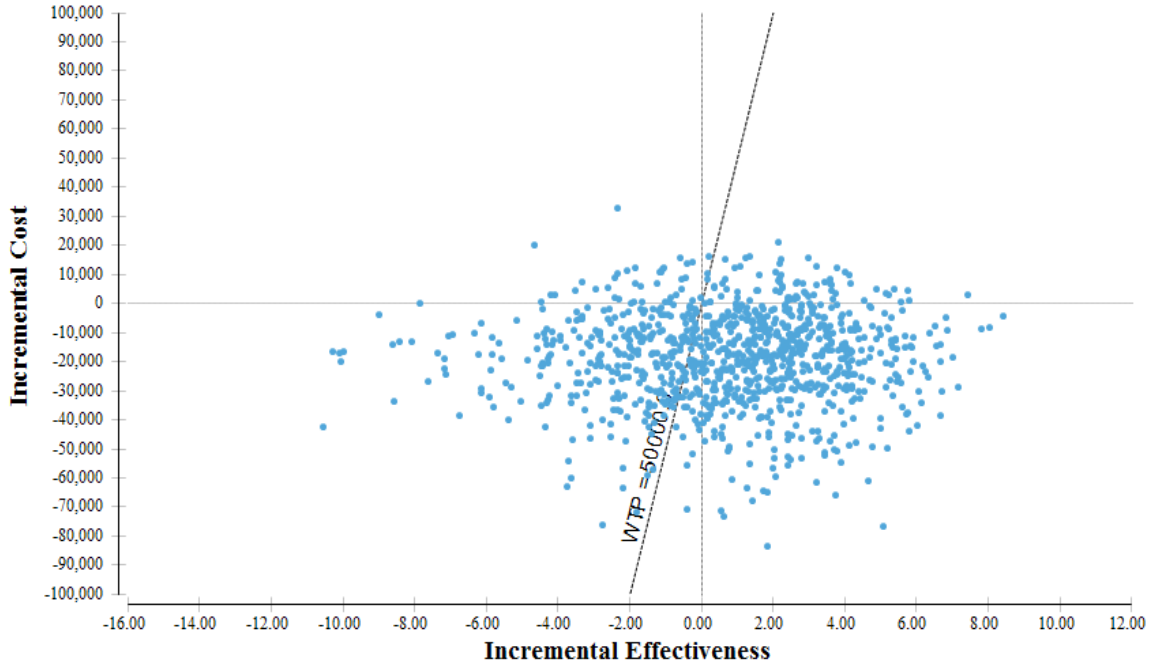

Figure 4-9 Incremental cost-effectiveness plane for early versus late initiation of adalimumab. A sample of 10,000 Markov Chain Monte Carlo simulations is plotted. The diagonal line represents a willingness-to-pay (WTP) threshold of $50,000 per QALY. Simulations below the line are considered to be cost-effective at that threshold.

4.3.3 Net Monetary Benefit

The net monetary benefit (NMB) approach involves converting effectiveness into the same unit as costs using the following formula:

$$NMB = (\lambda * E) - C$$

where *E* = effectiveness and *C* = cost

Infliximab

The net monetary benefit at a WTP threshold of $50,000 per QALY for early initiation of infliximab is -$59,843. The net monetary benefit at the same threshold for late initiation of infliximab is -$128,897. Early initiation has a higher net monetary benefit at a WTP of $50,000 per QALY and is therefore more cost-effective at this threshold.

Adalimumab

The NMB at a WTP threshold of $50,000 per QALY foradalimumab is $65,301 for early initiation, and $9,775 for late initiation. The NMB is higher for early initiation at a WTP of $50,000 per QALY, therefore it is more cost-effective at this threshold.

4.3.4 Deterministic Sensitivity Analysis

4.3.4.1 Tornado Diagrams

Infliximab

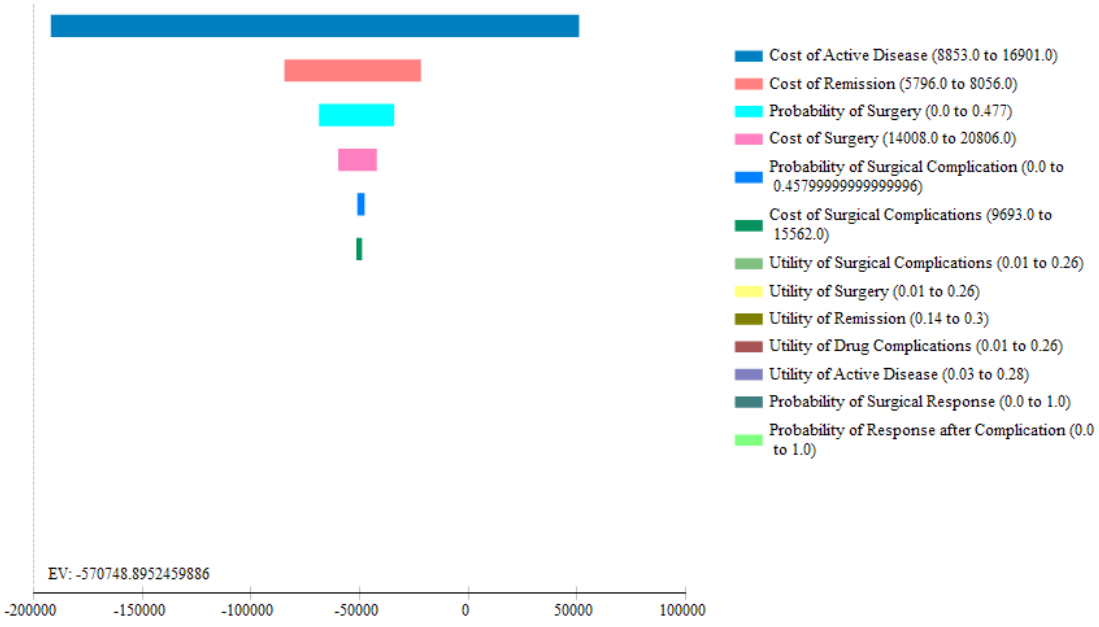

Figure 4-10 Tornado diagrams demonstrating the range of possible values of net monetary benefit for infliximab while parameters are varied between 95% confidence intervals.

The cost of active disease and remission were the most sensitive parameters, whereas the probability of response after complication and the probability of surgical response are the least sensitive parameters.

Adalimumab

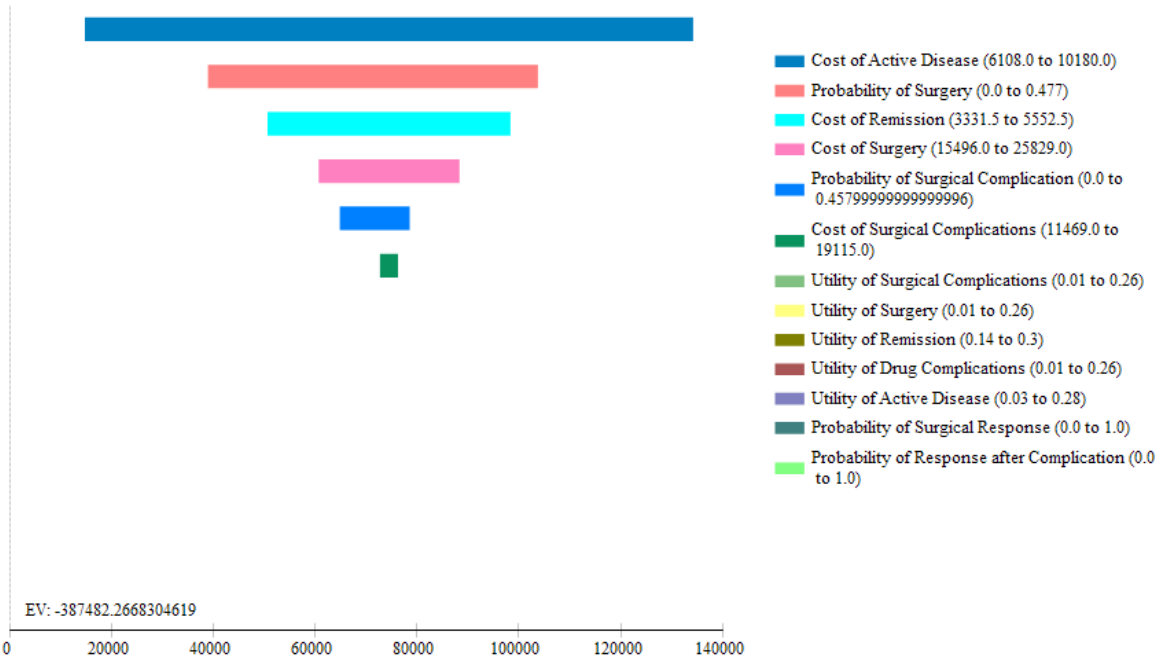

Figure 4-11 Tornado diagrams demonstrating the range of possible values of net monetary benefit for adalimumab while parameters are varied between 95% confidence intervals.

The cost of active disease and the probability of surgery are the most sensitive variables, whereas the probability of surgical response and the probability of response after complication are the least sensitive variables.

4.3.4.2 Utility Values using Visual-Analog-Scale

A one-way sensitivity analysis was performed using utility values by the Visual-Analog-Scale (VOS) method opposed to the Standard Gamble (SG) approach. The following utility values were used for this analysis:

Table 4-8 Utility values assigned to each health state using the Visual-Analog-Scale method

Health States	Utility value per year[137]	Utility value for 3 month cycle
Remission	0.71	0.18
Active Disease	0.44	0.11
Surgery	0.31	0.08
Drug Complications	0.29	0.07
Surgical Complications	0.29	0.07
Dead	0.00	0.00

Infliximab

Using the VOS method, we obtained 11.37 QALYs opposed to 11.45 QALYs when using the SG approach, for patients initiated early on infliximab. For patients with late initiation of infliximab, QALYs gained throughout the patient's lifetime was 10.40 using the VOS approach, opposed to 10.43 QALYs with the SG approach.

Adalimumab

When using the VOS approach, a patient gained 10.88 QALYs when initiating adalimumab early compared to 11.13 QALYs when using the SG method. When patients initiated adalimumab late, QALYs gained were 10.21 when using the VOS method compared to 10.39 when using the SG approach.

4.3.4.3 Discount Rate of 1.5%

Infliximab

When the discount rate was adjusted to 1.5% for both costs and outcomes, the incremental cost associated with early versus late initiation of infliximab was $21,231 and the incremental effectiveness was 2.17 QALYs.

Adalimumab

When the discount rate was adjusted to 1.5% for both costs and outcomes, the incremental cost associated with early versus late initiation of adalimumab was -$4539 and the incremental effectiveness was 1.46 QALYs.

4.3.4.4 Loss of Response Rates

Infliximab

When the loss of response rates were varied between the lower and upper bound of their 95% confidence intervals, the incremental cost ranged from -$32,787 to -$7,026. The incremental effectiveness ranged from 0.59 to 1.51 QALYs when the loss of response rates were varied.

Adalimumab

When the loss of response rates were varied between their 95% confidence intervals, the incremental cost ranged from -$41,231 to -$4,515 and the incremental effectiveness ranged from 0.18 to 1.44 QALYs.

4.3.5 Probabilistic Sensitivity Analysis

4.3.5.1 Net Monetary Benefit

Infliximab

Early initiation of infliximab has a higher NMB at all WTP thresholds from $0 to $100,000 per QALY, as demonstrated in Figure 4-12.

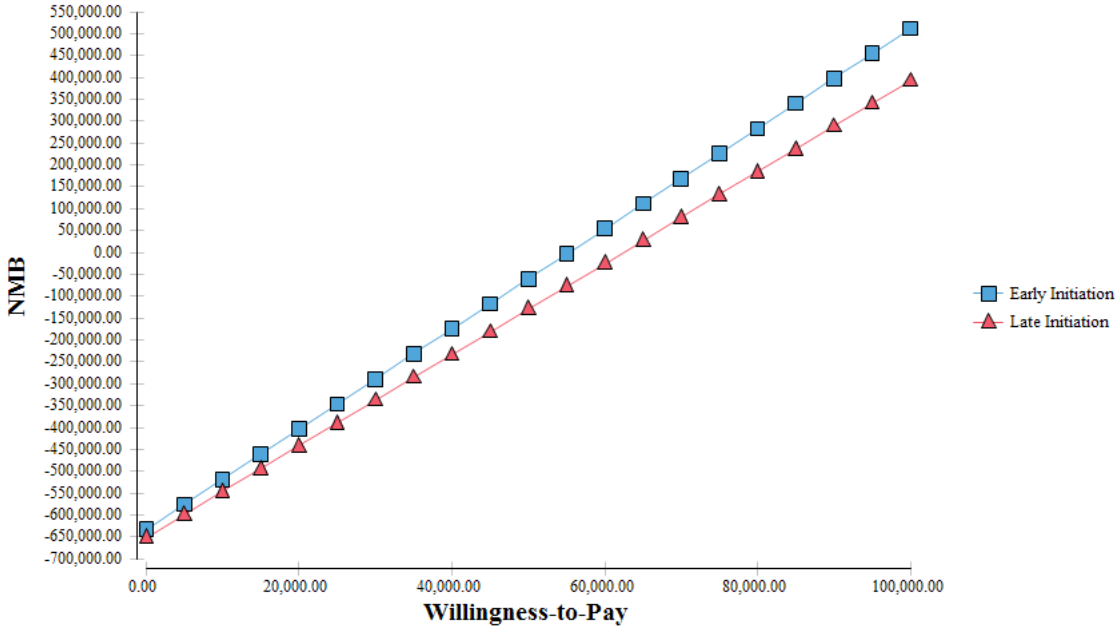

Figure 4-12 Willingness-to-pay versus net monetary benefit (NMB) for early and late initiation of infliximab.

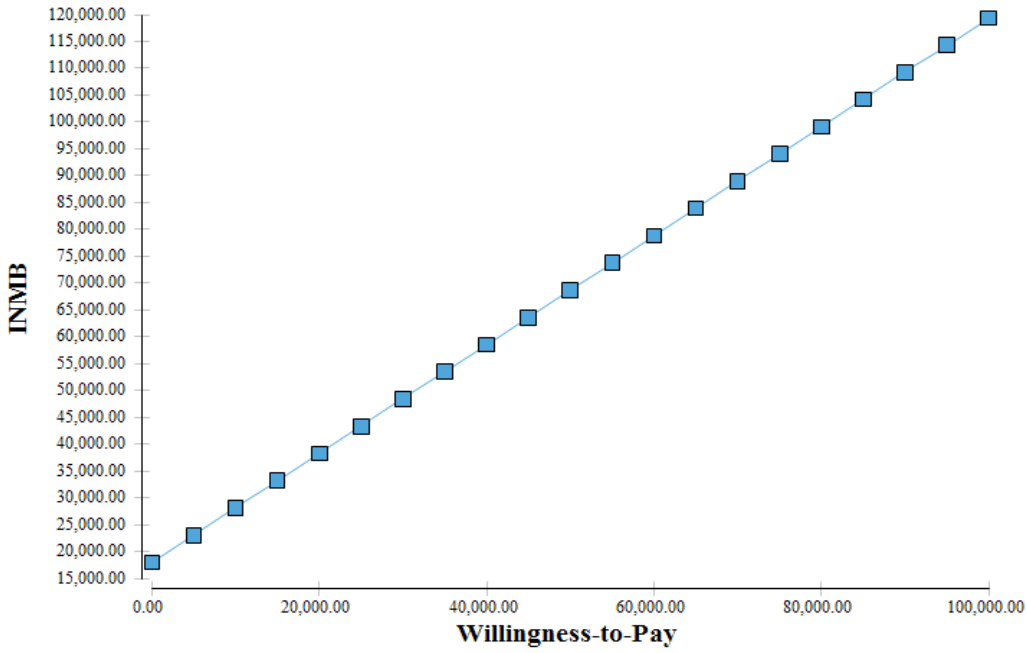

Figure 4-13 Willingness-to-pay versus incremental net monetary benefit (INMB) for early versus late initiation of infliximab.

Adalimumab

Early initiation of adalimumab has a higher NMB at all WTP thresholds from $0 to $100,000 per QALY, as demonstrated in Figure 4-14.

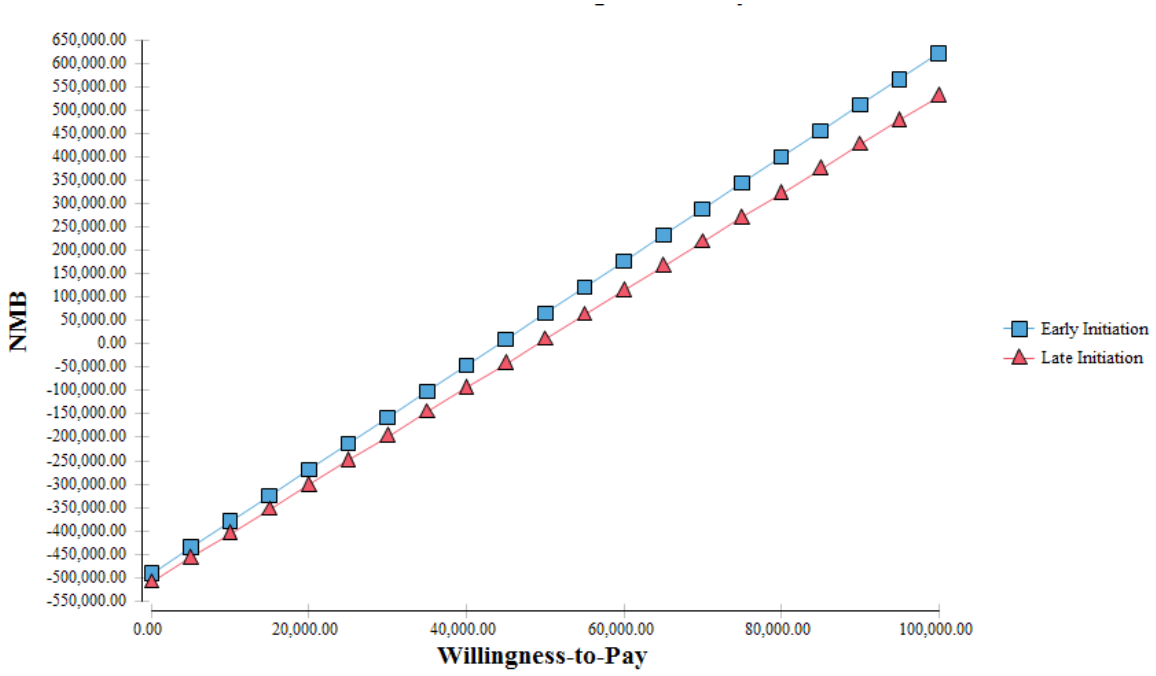

Figure 4-14 Willingness-to-pay versus net monetary benefit (NMB) for early and late initiation of adalimumab.

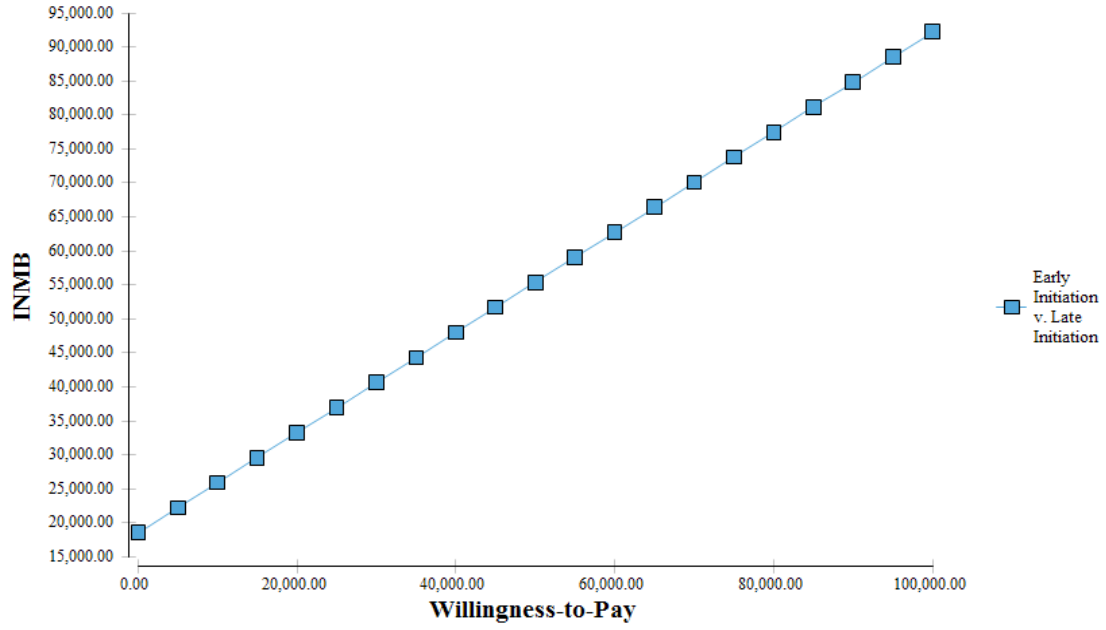

Figure 4-15 Willingness-to-pay versus incremental net monetary benefit (INMB) for early versus late initiation of adalimumab.

4.3.5.2 Cost-Effectiveness Acceptability

Infliximab

Early initiation of infliximab had a 68% chance of being cost-effective at a WTP threshold of $50,000 per QALY.

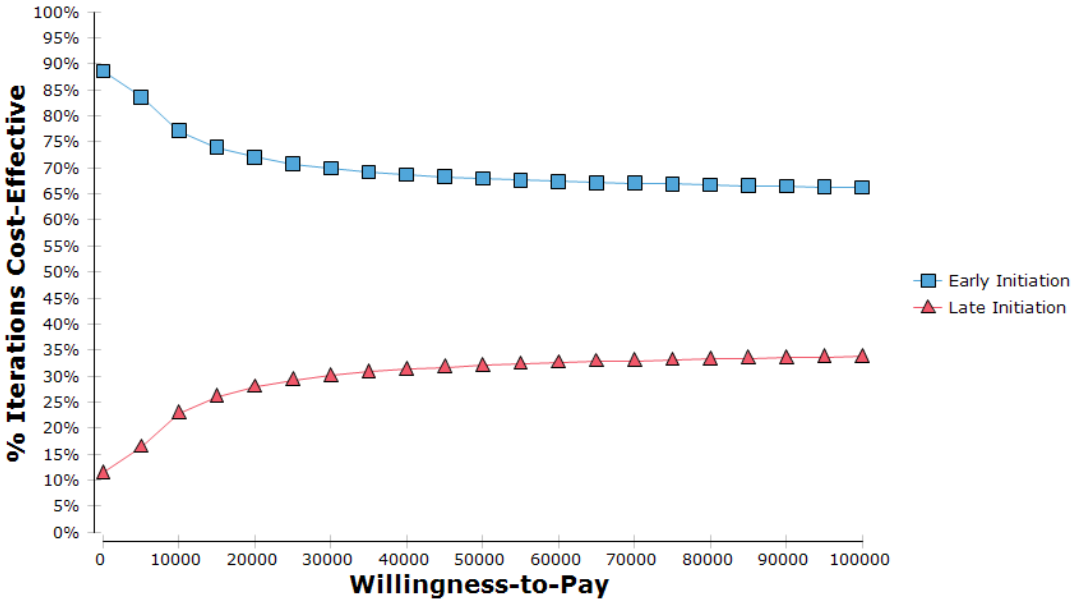

Figure 4-16 Cost-effectiveness acceptability curve for infliximab.

Adalimumab

Early initiation of adalimumab had a 68% chance of being cost-effective at a WTP threshold of $50,000 per QALY.

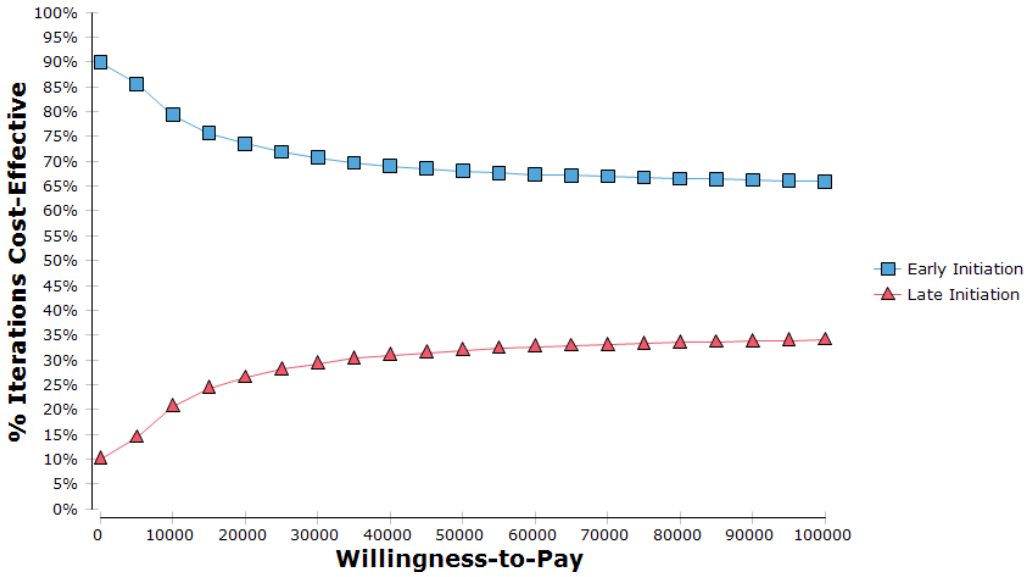

Figure 4-17 Cost-effectiveness acceptability curve for adalimumab.

4.3.5.3 Value of Information

The expected value of perfect information (EVPI) refers to the price that one would be willing to pay in order to gain access to perfect information.

Infliximab

The EVPI for all parameters at a WTP threshold of $50,000 per QALY is $47,714 for infliximab therapy.

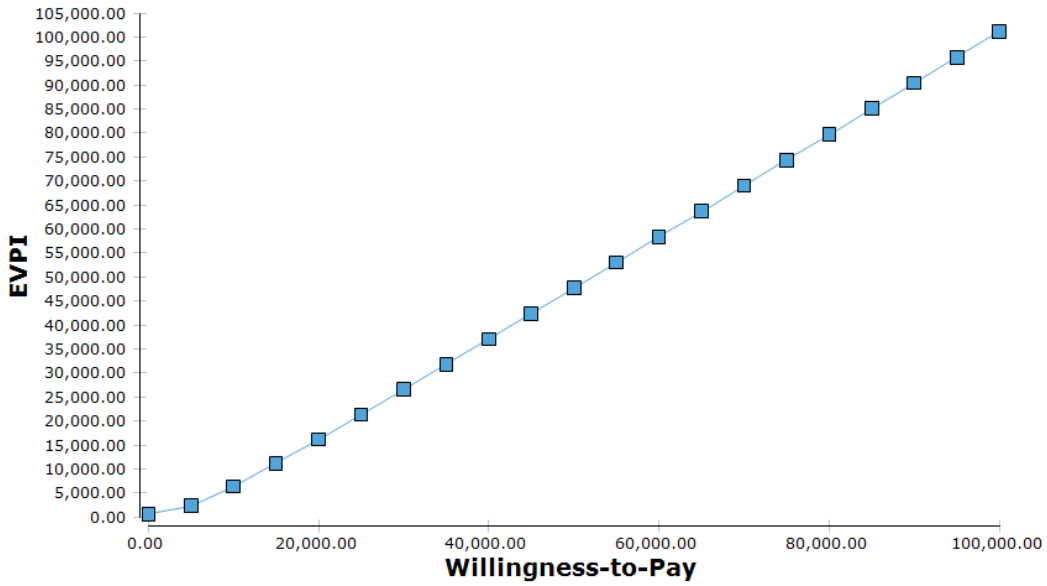

Figure 4-18 The expected value of perfect information (EVPI) calculated for a range of WTP thresholds for infliximab therapy.

Adalimumab

The EVPI for all parameters at a WTP threshold of $50,000 per QALY is $38,168 for adalimumab therapy.

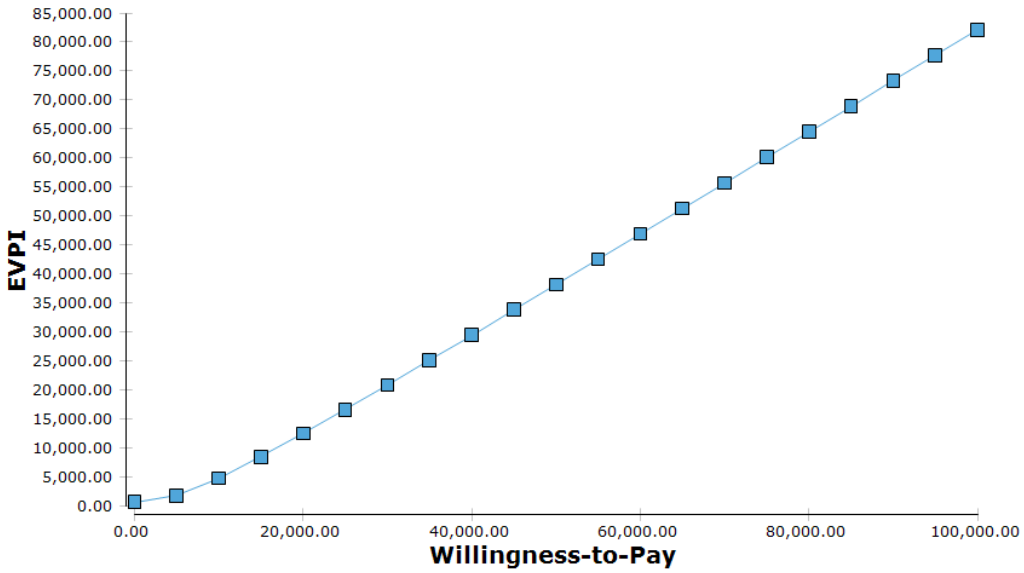

Figure 4-19 The expected value of perfect information (EVPI) calculated for a range of WTP thresholds for adalimumab therapy.

4.4 Discussion

This study suggests that early initiation of anti-TNF therapy appears to be cost-effective compared to late initiation for patients with moderate to severe CD. As with all economic analyses, challenges related to uncertainty in the outcomes results in a need to interpret these findings with caution. Further research is required in order to make a definitive recommendation regarding which treatment strategy to adopt.

The only previous analysis examining the cost-effectiveness of early versus late initiation of anti-TNF therapy is a European transition-state model that compared “step-up” to “top-down” therapy for patients with luminal CD on infliximab.[138] This study used a time-horizon of 5 years, therefore not capturing the long-term effects of the therapy. Furthermore, the model represented a simpler representation of disease, with 3-steps that can be progressed through depending on the treatment strategy chosen. The model may not accurately represent clinical practice, as only induction infliximab therapy was

taken into consideration without examining the effects of maintenance therapy. Despite the differences in methodology, the results obtained from this study were similar to that of our study, with decreased costs and increased QALYs for those patients adopting a "top-down" approach. The baseline analysis revealed an increase in 0.14 QALYs and a saving of €773 over 5-years. This is comparable to the 1.02 QALYs gained and $18,000 saved throughout the patient's lifetime in our analysis. Similarly to our study, the sensitivity analysis revealed that the results were robust.

Since we determined that early initiation is cost-saving and dominates late initiation, calculating the incremental cost-effectiveness ratios (ICERs) would result in a negative value. This is problematic because of our inability to distinguish if the intervention dominates or is dominated by its comparator. To solve this issue, we calculated the NMB by converting the effectiveness into monetary terms. For infliximab therapy, we obtained a NMB of -$59,843 for early initiation and -$128,897 for late initiation, at a WTP threshold of $50,000 per QALY. When analyzing adalimumab at this same threshold, we calculated a NMB of $65,301 for early initiation and $9,775 for late initiation. Both anti-TNF therapies had a higher NMB with early initiation, and therefore the early initiation strategy was more cost-effective at this threshold. When comparing infliximab to adalimumab, adalimumab had a higher NMB at both early and late initiation strategies, allowing us to conclude that it may be the more cost-effective anti-TNF therapy. Although adalimumab has slightly higher loss of response rates, this higher NMB seems to result from the decreased cost of the drug compared to infliximab. Also, the increased cost of infliximab can be attributed to its administration costs, as it requires an intravenous injection at a clinic, rather than at-home subcutaneous injections used for adalimumab.

The deterministic sensitivity analysis aimed to determine how our results changed by altering key parameters based on plausible values as advised by clinical experts. The tornado diagrams reveal that altering the cost of the active disease and remission health states would have the greatest effect on our results when analyzing infliximab use. Similarly, the cost of active disease was a sensitive parameter in the adalimumab analysis, in addition to the probability of surgery.

A one-way sensitivity analysis was performed to determine how our outcomes are affected when we obtain utility values using a different method, in this case the VAS approach. Health utility values are used to represent the strength of an individual's preferences for a specific outcome, and are used to value specific health states.[139] Health utilities are determined through multiple different approaches, each with their own advantages and disadvantages. The method used in the primary analysis was the standard gamble (SG) approach, which involves presenting individuals with a choice between two alternatives: a health state that is certain and a gamble with a better and a worse outcome possible. Individuals are then asked what probability of the better outcome would make them indifferent compared to remaining in the certain state.[139] The SG approach has been shown to be a very reliable measurement of health utility values, although there are some limitations to this method.[140] This is a subjective process and depends on an individual's willingness to take risk. In general, humans are risk aversive, meaning they are more likely to choose the certain outcome rather than the gamble.[139] The VAS method asks respondents to place each health state on a single line such that the distance between the lines represents the perceived differences between each of the health states. Although it is less grounded in economic theory, it is sometimes advantageous due to its simplicity.[139] Gregor *et al* reported both SG and VAS values, and on average, VAS reported lower utilities for each health state.[137] Lower utility values

using the VAS method had little effect on our results, as the amount of QALYs gained with each strategy varied only slightly when using this method, both for the infliximab and adalimumab analyses.

CADTH is a national organization responsible for setting guidelines for economic evaluation of health technologies in Canada. CADTH is responsible for setting a discount rate that is applied to both costs and outcomes. Although most health economists agree regarding the need to discount, there is less consensus regarding how much costs and benefits should be discounted.[141] CADTH currently states that a discount rate of 5% should be used for both costs and benefits, therefore this rate was used in our primary analysis.[84] As part of our deterministic sensitivity analysis, a discount rate of 1.5% was applied to costs and outcomes. This was because a rate of 5% is argued to unjustifiably discriminate against interventions with large up-front costs and/or long-term benefits, such as the early usage of anti-TNF therapy. Adjusting the discount rate to 1.5% had significant effects on our results by increasing the costs and QALYs gained throughout a patient's lifetime. Costs and QALYs associated with early and late initiation were approximately double, and incremental costs and QALYs were also altered. For infliximab, adjusting the discount rate to 1.5% resulted in early initiation costing more than late initiation. This is likely a result of the fact that early and late initiation had the greatest differences in benefit early on. As time passed, response rates became very similar and the benefit of early initiation was dampened; therefore early initiation is favored with a higher discount rate. This trend was also demonstrated when analyzing adalimumab, although early initiation remained less costly than late initiation.

Probabilistic sensitivity analysis was conducted by Monte Carlo simulation to characterize uncertainty related to parameters. Although a WTP threshold of $50,000 per QALY is recommended in Canada, Figure 4-12 and 4-14 aimed to show the NMB

and how it is affected by different WTP thresholds. From $0 to $100,000 per QALY, late initiation has a lower NMB, and we can therefore conclude that early initiation would be more cost-effective at all of these thresholds for both infliximab and adalimumab. Expectantly, Figure 4-13 and 4-15 shows the INMB to increase as the WTP threshold increases.

In order to determine the probability of early and late initiation of anti-TNF therapy being cost-effective at different thresholds, we calculated the proportion of simulations in our Monte Carlo analysis that had an INMB greater than 0. Figure 4-15 and 4-16 show how the probability of the strategy being cost-effective differs depending on the WTP threshold used. From $0 to approximately $25,000 per QALY, late initiation has a low probability of being cost-effective. At WTP thresholds greater than $25,000 per QALY, the probability that early initiation is cost-effective is approximately 70%, and remains similar up to a WTP threshold of $100,000 per QALY.

The VOI analysis revealed an EVPI of approximately $48,000 for infliximab and $38,000 for adalimumab at a WTP threshold of $50,000 per QALY. The EVPI can be interpreted as a measure of the expected cost of uncertainty, since perfect information eliminates any uncertainty that count potentially result in making an incorrect decision.[142] This implies that the EVPI is the maximum amount that would be considered worthwhile to invest in further research. EVPI increases linearly as the WTP thresholds increase.

Our model aims to represent the real-life cost-effectiveness of early versus late initiation of anti-TNF by accounting for the different health states that one can experience throughout their disease. Our model had 6 disease states, as we thought it was an adequate representation of disease progression while ensuring the model was not overly complex to the point where effectiveness parameters were not able to be found in

published literature. Other cost-utility analyses looking at anti-TNF therapy in CD differentiated between drug-induced and surgical remission, and also separated full and partial response into different health states.[77,81,143] We chose not to differentiate between drug-induced and surgical remission because we assumed that they would include the same costs, quality of life, and mortality rates. Furthermore, we did not separate partial and full response since the loss of response rates used in our study did not differentiate between these response states.

A single trial was not available to obtain all transition probabilities needed in our analysis, therefore we were required to obtain data from multiple sources. Loss of response rates were acquired from centre data, however surgical and complication rates required the use of published literature. We used a mixture of randomized controlled trials and real-life studies, therefore our inputs may be biased towards the methods used in the original study. For example, the loss of response data that we used was examined retrospectively, possibly resulting in differences between the early initiation and late initiation group. Also, the loss of response rates obtained from our centre's data only included follow-up periods up to approximately 7 years, resulting in a need for extrapolation. Finally, certain transition probabilities were not reported in the literature and therefore needed to be assigned based on expert opinion by IBD clinicians, such as response, non-response and death experienced after medication or surgical complications.

Although there were limitations in terms of obtaining data, our model aims to represent a real-life cohort of patients with moderate to severe CD, initiating anti-TNF therapy due to active disease. Early initiation of anti-TNF therapy (≤2 years after diagnosis) appears to be cost-saving and dominates late initiation of anti-TNF therapy. Sensitivity analysis

revealed that these results were robust. The results of this study may serve to support early treatment with anti-TNF therapy from both a cost and patient outcome perspective.

5 Cost-Effectiveness of Anti-TNF Biosimilars for the Management of Crohn's Disease

5.1 Introduction

Biologic therapies are drugs derived from a living organism, with an aim to target and block molecules involved in the process of inflammation. Anti-TNF agents, such as infliximab and adalimumab, are a subclass of biologics that work by inhibiting the protein tumor necrosis factor-alpha (TNF-α) and therefore preventing it from causing inflammation.[144] The emergence of anti-TNF therapy has provided an effective way to not only treat symptoms, but also a way to induce and maintain long-term mucosal healing for patients with inflammatory bowel disease (IBD).[145] Currently, the most widely used anti-TNF therapies for Crohn's disease (CD) are infliximab and adalimumab, which are marketed as Remicade and Humira, respectively.

Biosimilars refer to biologic products similar to previously developed and approved biologic agents. Biosimilars are appealing due to their lower costs, similar to the savings associated with generic versions of chemical medicines.[146] However, the similarity of biosimilars to their respective biologic agents has been a contested issue, due to their molecular complexity and their sensitivity to changes in manufacturing.[147] For example, biologic materials have many more molecular ingredients compared to low molecular weight drugs, and generally require more sophisticated tools to evaluate their similarity in terms of effectiveness and safety to the original biologic agent.[148] Due to these challenges, verification of the similarly between biosimilars and their respective drugs remains difficult.

Despite these challenges, biosimilars have many advantages that will likely make them a viable option for patients with CD in the near future. The cost of biologic agents is an important issue in times of increasing restrictions on healthcare budgets and spending. Biosimilars may offer a partial solution to this problem, as they generally being brought to market at approximately 30% less than their respective innovator biologics.[149] Despite these cost reductions, the development of a biosimilar generally costs $100 million to $250 million.[150] Due to these high production costs, the cost-saving impact of biosimilars will likely take many years, due to the extra obstacles for biologics to overcome in the approval and implementation processes compared to small-molecule generics.[151]

Recently, Johnson & Johnson's Remicade patent has expired in the US and is expected to expire in Canada in August 2017, leading to the emergence of a new biosimilar referred to as CT-P13 (marketed as Inflectra or Remsima). Similarly, the patent of Abbvie Inc's drug Humira is expected to expire in February 2017 in Canada, opening the door for pharmaceutical companies to generate new biosimilars that could potentially be used to treat patients with CD. Currently, a biosimilar to adalimumab, referred to as ABP 501, is undergoing approval processes.

Currently, there are limited studies that have examined the similarly of CT-P13 to its innovator infliximab. The PLANETRA study examined patients with active rheumatoid arthritis and found that CT-P13 exhibited equivalent efficacy at week 30 compared to infliximab (60.9% vs 58.6%, 95% CI: -6% to 10%). Also, it's immunogenicity, pharmacokinetic and safety profile were shown to be equivalent to that of infliximab.[152] Similarly, the PLANETAS study found that CT-P13 and infliximab had comparable efficacy and safety profiles up to 30 weeks for patients with ankylosing spondylitis.[153] Recently, the efficacy and safety of CT-P13 compared to infliximab has also been examined in a retrospective multicenter study for patients with IBD.[154] This study

concluded that CT-P13 appears to have comparable efficacy, safely, and interchangeability with infliximab for patients with IBD. These results need to be further studied due to the retrospective nature of the study, as well as short follow-up times compared to infliximab studies. A small case series (n=17) was also done to examine the efficacy and safety of CT-P13 in patients with IBD.[155] The study concluded that CT-P13 may be similar to infliximab, although they acknowledged the limitations of their small sample size and lack of control group.

The first prospective study to evaluate the use of CT-P13 for induction therapy in CD was completed at a tertiary center with extensive experience with its originator drug, infliximab.[156] The study found that clinical response and remission were achieved in 37.5% and 50% of patients with CD after induction therapy, similar to previously published infliximab trials. Although this study examined patients prospectively, the study still had a relatively small sample size, did not have a control group, and only looked at induction therapy. Similar to this study, a prospective Norwegian study found a significant reduction in disease activity at week 14 compared with baseline values. The most recent study looking at the use of CT-P13 for IBD was a prospective, multicenter study using a nationwide cohort from Hungary.[157] The study concluded that CT-P13 is safe and effective for the induction of clinical remission in CD, although they also noted that previous infliximab exposure resulted in decreased response rates and highly rates of allergic reactions. Finally, a randomized, double-blind, phase 3 study is currently underway, attempting to demonstrate noninferiority in efficacy and safety of CT-P13 compared to infliximab in patients with active CD, with an estimated completion date of February 2017.[158]

Two randomized, double-blind, phase 3 studies have been completed examining the clinical effectiveness and safety of ABP 501 for patients with moderate to severe plaque

psoriasis and rheumatoid arthritis.[159,160] Both of these trials are now complete, although results are yet to be published. There are currently no studies examining the similarity of ABP 501 to adalimumab for patients with moderate to severe CD.

Due to the changing economic climate of CD due to the emergence of biosimilars, the economic implications of these drugs must be considered. The aim of this study is to provide a preliminary analysis regarding the cost-effectiveness of biosimilars in the management of CD, with key assumptions regarding their effectiveness, safety, and cost.

5.2 Methods

5.2.1 Type of Study and Outcome

A cost-minimization analysis (CMA) was performed with two key assumptions:

- The effectiveness and safety of anti-TNF biosimilars are equal to their respective innovator biologic (infliximab or adalimumab)
- The cost of biosimilars are 30% less expensive than their respective innovator biologic

These assumptions were necessary due to a lack of trial evidence of new biosimilars, as well as our lack of knowledge on the exact cost of biosimilars once they are on the market. Based on these assumptions, we examined the cost savings of biosimilars over a patient's lifetime compared to their more expensive innovator biologic. The perspective of this analysis is from the publicly funded healthcare system, and only direct costs to the healthcare system are included.

5.2.2 Target Population

The CMA analysis assumed a cohort of patients with moderate to severe active CD, where approximately 50% were male. Drug dosage was based on an average patient weight of 70 kg.

5.2.3 Markov Model Structure

The Markov model structure was replicated from Chapter 4, with 6 mutually exclusive disease states: remission, active disease, surgery, surgical complications, drug complications, and dead (Defined in Table 4.1). In each health state, patients use resources and accumulate quality-adjusted life years (QALYs). A lifetime time horizon was chosen, with an average diagnosis age of 25 years old. Cycle length was 3 months.

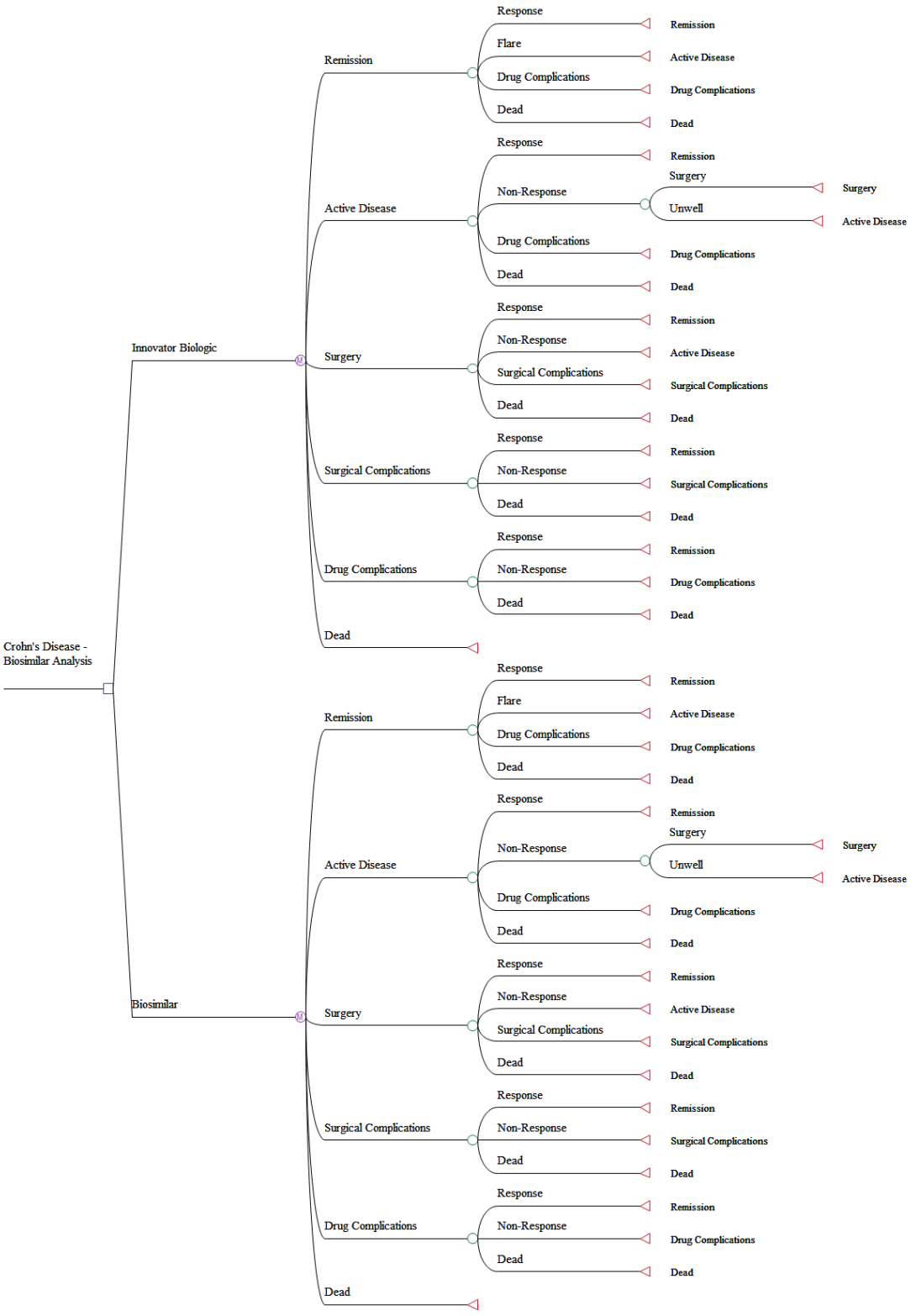

Figure 5-1 Model structure diagram.

5.2.4 Model Inputs

Our analysis follows the 2006 economic evaluation guidelines as set out by the Canadian Agency for Drugs and Health Technologies.[84]

5.2.4.1 Transition Probabilities

Transition probabilities were obtained from the same sources as indicated in Chapter 4.[26,37,132–136] Loss of response rates were obtained from published data from the University of Alberta Inflammatory Bowel Disease Consultation and Research Clinic, Edmonton, Alberta, Canada.[28]

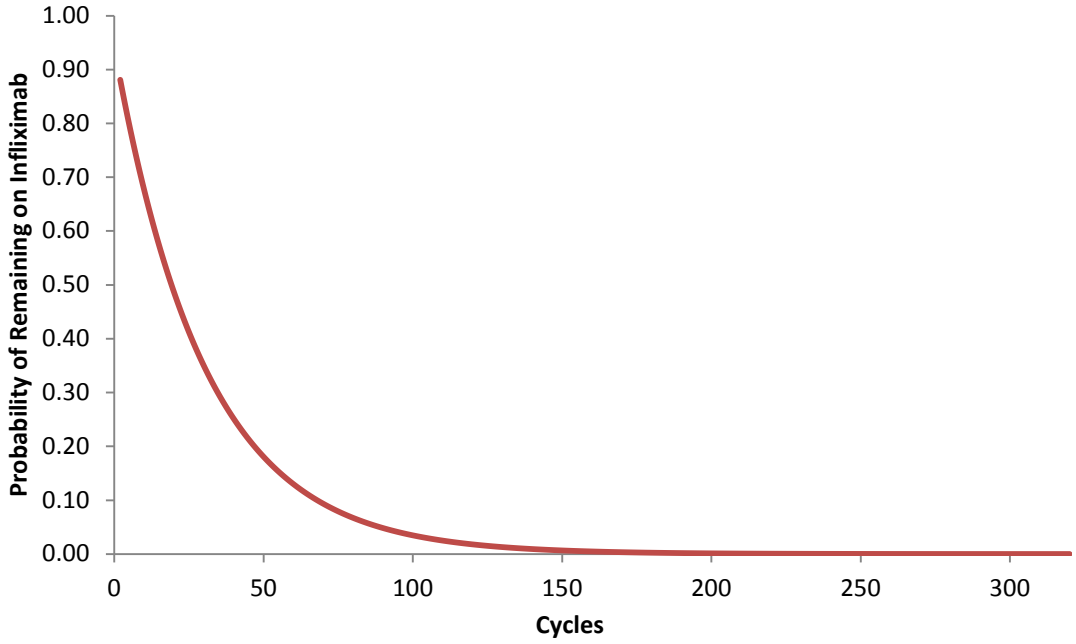

Figure 5-2 Probability of response to infliximab.

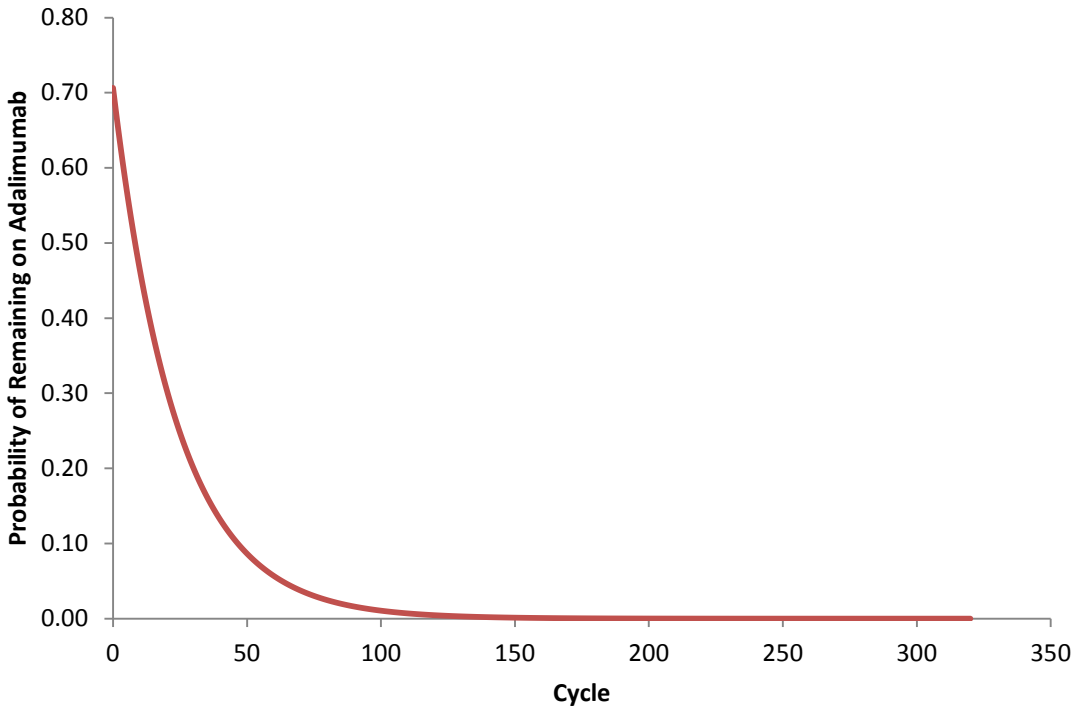

Figure 5-3 Probability of response to adalimumab.

5.2.4.2 Costs

Costs of health states were determined through the CIHI patient cost estimator.[161] The cost of the respective biosimilars were assumed to be 30% less than the price of infliximab and adalimumab, as per the Alberta Health and Wellness Drug Benefit List.[109] The cost of complications were estimated by averaging the cost of complication weighted by the likelihood of occurrence. The cost of death is counted once. Table 5-1 displays the costs of each health state per 3-month cycle.

Table 5-1 Costs assigned to each health state

Health State	Infliximab	Adalimumab	Biosimilar of Infliximab	Biosimilar of Adalimumab
Remission	$7,847	$4,442	$5,493	$3,109
Active Disease	$12,901	$8,144	$9,031	$5,701

Surgery	$20,663	$20,663	$20,663	$20,663
Drug Complications	$8,757	$4,531	$8,757	$4,531
Surgical Complications	$15,292	$15,292	$15,292	$15,292
Dead	$24,522	$24,522	$24,522	$24,522

5.2.4.3 Utilities

Health utility values were obtained from the same sources as indicated in Chapter 4.[137] The Standard Gamble approach was used in our analysis.

5.2.5 Sensitivity Analysis

A one-way sensitivity analysis was performed on the cost of biosimilars to account for the fact that our 30% price reduction from the innovator biologic was an estimate, and that there is not precise information as to how much the prices of biosimilars will change compared to their respective biologics. We performed our analysis with a reduced price of 20% and 40% as well.

5.2.6 Discounting

A discount rate of 5% was applied to both costs and outcomes.

5.3 Results

5.3.1 Costs and Quality-Adjusted Life Years

Infliximab

Throughout a patient's lifetime, infliximab would cost a patient with CD an average of $699,995. Assuming a cost of 30% less than infliximab, its biosimilar would cost a patient with CD an average of $519,650 over their lifetime. The incremental cost associated with infliximab compared with its biosimilar would be $181,345, assuming that infliximab and its biosimilar had equivalent efficacy and safety. Based on this assumption, the QALYs gained throughout a patient's lifetime were the same for infliximab and its biosimilar.

Adalimumab

Throughout a patient's lifetime, adalimumab would cost a patient with CD an average of $655,059. Assuming a cost of 30% less than adalimumab, its biosimilar would cost a patient with CD an average of $344,155 over their lifetime. The incremental cost associated with adalimumab and its biosimilar would be $310,905, assuming that adalimumab and its biosimilar had equivalent efficacy and safety. Based on this assumption, the QALYs gained throughout a patient's lifetime were the same for adalimumab and its biosimilar.

5.3.2 Net Monetary Benefit

The net monetary benefit (NMB) is calculated using the following formula:

$$NMB = (\lambda * E) - C$$

where E = effectiveness, C = cost

Infliximab

At a willingness-to-pay (WTP) threshold of $50,000 per QALY, the NMB of infliximab therapy is $249,505. The NMB of infliximab's biosimilar is $429,850 at a WTP threshold

of $50,000 per QALY. Infliximab's biosimilar has a higher NMB, and is therefore more cost-effective at this threshold.

Adalimumab

The NMB at a WTP threshold of $50,000 per QALY is $298,441 for adalimumab therapy and $642,595 for adalimumab's biosimilar. The NMB is higher for the biosimilar compared to adalimumab therapy, therefore biosimilar therapy appears to be more cost-effective at a WTP threshold of $50,000 per QALY.

5.3.3 Sensitivity Analysis

Infliximab

When a cost reduction of 20% is applied to infliximab's biosimilar, it would cost a patient $579,106 over their lifetime for biosimilar therapy. This would result in an incremental cost of $120,889 compared to innovator infliximab. With an assumed cost reduction of 40%, biosimilar therapy would cost $458,195, resulting in an incremental cost of $241,800 compared to infliximab therapy.

Adalimumab

Assuming a cost reduction of 20% for a biosimilar compared to adalimumab, biosimilar therapy would cost $377,799 over a patient's lifetime, resulting in an incremental cost of $277,260. If a cost reduction of 40% was applied to the biosimilar, it would cost a patient $310,495 over their lifetime, resulting in an incremental cost of $344,565 compared to adalimumab therapy.

5.4 Discussion

Our study concludes that biosimilars of anti-TNF therapy are cost-effective compared to innovator anti-TNF agents, if we assume equivalent effectiveness and safety. We assumed an average price reduction of 30% for biosimilars compared to their respective biologics, although our sensitivity analysis examined the consequences of 20% and 40% price reductions as well. As expected, the QALYs gained from biosimilars and their respective biologics were equal.

A budget impact analysis was the first study to examine the economic implications of biosimilar infliximab (CT-P13) for the treatment of rheumatoid arthritis in six European countries.[162] This study looked at two scenarios: one where switching between infliximab and its biosimilar is disallowed, and a scenario where switching infliximab with its biosimilar is allowed after 6 months from treatment start, and it is interchanged in 80% of patients. In the first scenario, the introduction of infliximab's biosimilar resulted in an estimated savings of €15.3 M in the first 3 years. The second scenario led to a total budget savings of €20.8 M over the first 3 years. The study conducted a sensitivity analysis that found the parameters with the largest impact on the budget were the initial number of patients receiving biologics and the price of infliximab's biosimilar. Due to these savings, the authors estimated that an additional 1205 and 1790 patients with rheumatoid arthritis could be treated with biologic therapy in scenarios 1 and 2, respectively. Similar to our study, the authors did not address any clinical differences between infliximab and its respective biosimilar.

More recently, the budget impact of the introduction of biosimilar infliximab for the treatment of CD has been studied in 6 European countries.[163] This study used the same methodology as the previously mentioned study examining patients with rheumatoid

arthritis, including the use of two scenarios depending on if patients could interchange between infliximab and its biosimilar. The study concluded that over a 3-year time horizon, biosimilar therapy could lead to savings of €8.0 M in the scenario that disallowed interchanging, and €16.9 M in the scenario that allowed interchanging. Based on these budget savings, they estimated that 722 to 1530 additional CD patients could be treated with biosimilar infliximab therapy.

Another study aimed to determine the budget impact of the infliximab biosimilar, Remsima, for the treatment of autoimmune diseases in five European countries.[164] This study found that over a 1-year time horizon, the projected range of cost savings in all six countries due to the introduction of Remsima was €25.79 M to €77.37 M. They concluded that these savings could translate into 250 to 2602 additional patients being treated with biosimilar infliximab. Similar to our study, the exact price of Remsima was not known, and therefore an assumed price reduction of 10% to 30% was applied for biosimilar infliximab compared to innovator infliximab.

The mentioned studies all took place in European countries, likely due to their advancement in terms of approval and access to biosimilars compared to North America. To our knowledge, there are no North American studies examining the budget impacts of biosimilars. Also, there are currently no studies that examine the economic implications of biosimilar adalimumab therapy.

As mentioned previously, our study has some key limitations that prevent us from making robust conclusions. First, we assumed that infliximab and adalimumab, and their respective biosimilars had similar effectiveness and safety. This assumption was made due to the previously mentioned studies that concluded similar efficacy, immunogenicity, and safety profiles of biosimilars to their respective innovator biologic.[152–157] Randomized

controlled trials are still needed to fully prove these findings. Also, we made the assumption that a biosimilar will cost approximately 30% less than its innovator biologic. It is likely that biosimilars will range in cost, depending on their innovator biologic costs, as well as market competition. Despite the fact that we do not yet know their exact cost, our sensitivity analysis reported how sensitive our results were to changes in price reductions of 20% to 40%.

Our model aims to provide a preliminary analysis examining the economic implications of the introduction of biosimilar anti-TNF therapy for the management of CD. Based on key assumptions, we concluded that biosimilars have the potential to result in large price reductions, and could ultimately lead to further cost savings in a society with a restricted healthcare budget. Further data on the effectiveness and safety of biosimilars compared to their innovator biologics is needed to conclude if these findings are robust.

6 Conclusion & Future Directions

6.1 Summary of Findings

Although effective, the high cost of anti-TNF therapy raises concern regarding its usage for patients with IBD. This thesis aimed to answer questions regarding the cost-effectiveness of anti-TNF therapy for patients with moderate to severe IBD that is currently lacking in published literature. The three studies conducted concluded the following:

1. Adalimumab is cost-effective for the management of moderate to severe ulcerative colitis compared to patients remaining in a chronically unwell state, at a willingness-to-pay threshold of $80,000 per QALY. Dose escalation will increase costs beyond this threshold.
2. Early initiation of anti-TNF therapy (≤2 years of diagnosis) is cost-saving and dominates late initiation of anti-TNF therapy (>2 years after diagnosis) for patients with moderate to severe Crohn's disease.
3. Biosimilars of anti-TNF therapy are cost-saving compared to their respective innovator biologics for patients with moderate to severe Crohn's disease, if it is assumed that they have equal efficacy and safety profiles.

6.2 Future Directions

Further studies will be important to continue to examine the cost-effectiveness of these effective, yet expensive therapies. Firstly, it would be beneficial to study the cost-effectiveness of other biologics besides infliximab and adalimumab that are becoming increasingly popular for patients with IBD, including certolizumab pegol, natalizumab, and vedolizumab. This information would be highly useful to clinicians while trying to

make decisions regarding which biologic should be used in patients with IBD once they fail conventional medical therapies. Also, it would be valuable to examine the cost-effectiveness of dose escalating versus switching between different biologics. This would help clinicians and funding agencies decide how to manage the large proportion of patients who ultimately lose response to biologic therapy.

Secondly, determining if there is a specific group of patients that are more likely to respond to anti-TNF therapy would be useful in order to save the wasted resources of therapy costs for those who ultimately do not respond to these therapies. Currently, research has shown that disease length, phenotype, biologic markers, and genetics may be helpful in selectively treating patients who have the highest chance of response.[165] Further research in this field in imperative to limit adverse events associated with these drugs, increase response rates, and ultimately save costs in a society with increased healthcare budget restraints. Also, it would be valuable to determine which patients would be most likely to respond to early initiation versus late initiation of anti-TNF therapy. For this reason, it has been suggested that for future studies, it may be beneficial to evaluate the effect of early initiation of anti-TNF therapy combined with therapeutic drug monitoring in order to further lower the risk of losing response.[57] If we are able to increase response rates by selectively choosing patients more likely to respond to anti-TNF therapy, we would save substantial resources that could ultimately be used to treat more patients with these expensive therapies.

Lastly, the field of biosimilars is still a very new field that requires further research to determine how they will affect the economic burden of IBD. Although they have potential to reduce the costs associated with IBD treatment, further studies and trials are necessary to determine if biosimilars do indeed have equivalent efficacies and safety profiles compared to their innovator biologic. Long-term follow-up will also be necessary

to determine the long-term effects of biosimilars compared to their respective biologics. Also, the cost-effectiveness of these agents will be able to be fully analyzed once they are brought to the market and the actual cost of these agents is known. Currently, there is uncertainty regarding how much the cost of these agents will be reduced compared to their innovator biologic, which is a major factor that will determine if these biosimilars will be routinely adopted and prescribed by physicians. Not only does the effectiveness and cost of biosimilars need to be considered, but it is also necessary to study how these will affect the market competition. It will be important to determine how the introduction of biosimilars will impact the prices of their innovator biologics. In order to compete, it is likely that the innovator biologic will have to adjust its price, potentially resulting in decreased use of the biosimilar. All of these factors will ultimately need to be considered in order to capture an accurate and representative cost-effectiveness analysis for the use of biosimilars for the management of CD.

6.3 Conclusion

Anti-TNF therapy is very expensive, and represents a large proportion of the financial burden of IBD. In order to decide if they are a worthwhile strategy, a cost-effectiveness analysis must be undertaken that considers both the burden and benefits of therapy. We concluded that anti-TNF therapy, particularly its early usage, is cost-effective for the management of IBD. Biosimilars represent a promising area of research that requires further investigation to determine the economic implications of their introduction.

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Appendices

Appendix A. Crohn's Disease Anti-TNF Cost Estimation

Methodology

To estimate the costs of Crohn's patients with two anti-TNF therapies, surgery, and relevant complications, a gamma distributed log link GLS regression model on panel style data was used. Cohort definition, dummy variable generation and cost estimation methodology are outlined in the section below.

Data Structure

The table below outlines the variables included in the regression model and a brief description. More detailed methods are given following the table below.

Variable	**Definition**
COST_A	Quarterly sum of inpatient, ambulatory, physician claims, and Alberta Blue Cross payments. All costs adjusted to 2014 dollars.
STKH_NUM_1	Unique Lifetime Identifier for each patient. Used to control for individual effects.
TIME	Variable to control for time effects, quarterly from 2009 to 2014.
DX	Dummy variable. 1 if individual has already been diagnosed with Crohn's disease in a given quarter, 0 if prior to diagnosis.
DX_Q	Dummy variable. 1 if individual was diagnosed with Crohn's

	disease in a given quarter, 0 otherwise.
DTH_Q	Dummy variable. 1 if an individual dies in a given quarter, 0 otherwise. All quarters following death excluded.
ADA_ACTIVE	Dummy variable. 1 for the quarter an individual is undergoing induction dosing for adalimumab, 0 otherwise.
IFX_ACTIVE	Dummy variable. 1 for the quarter an individual is undergoing induction dosing for infliximab, 0 otherwise.
ADA_REMISSION	Dummy variable. 1 for any quarter and individual receives a dose of adalimumab categorized as 'remission', 0 otherwise.
IFX_REMISSION	Dummy variable. 1 for any quarter and individual receives a dose of infliximab categorized as 'remission', 0 otherwise.
ADA_COMP	Dummy variable. 1 for any quarter and individual experiences a complication related to adalimumab, 0 otherwise.
IFX_COMP	Dummy variable. 1 for any quarter and individual experiences a complication related to infliximab, 0 otherwise.
SURGERY	Dummy variable. 1 for any quarter and individual has a surgery, 0 otherwise.
SURGERY_COMP	Dummy variable. 1 for any quarter and individual experiences a complication related to surgery, 0 otherwise.

While not all parameter estimates from this analysis will be required for the parameterization of the Markov model, such as DX, DX_Q and perhaps DTH_Q (there are an economic arguments for both the inclusion and exclusion of that value in the

Markov model), it is important that they be included to avoid those costs being absorbed into the model intercept.

Model Estimation and Result Interpretation

The cost data is right skewed, (Skewness 13.07, Kurtosis 280.61), therefore a generalized least squares model was selected using a gamma variance and a log-link structure, using the GENMOD procedure in SAS 9.2. This regression is commonly used for health cost data, as it accommodates the skewness and distribution that is characteristic of this data type.

As this regression-log transforms costs as the dependent variable, parameter estimates have to be back-transformed into cost multipliers. The intercept is used to calculate the cost associated with each disease state, and then the back transformed value of the intercept is removed to remove the basic individual cost from the model.

By raising the parameter estimates to Euler's number, the intercept and parameter estimates are transformed into the base cost, and multipliers, respectively. Therefore, to estimate the cost of a patient who had Crohn's and was in remission treatment with IFX, the estimate would be calculated as follows:

e^(Intercept+DX+IFX_REMISSION)=(e^Intercept)(e^DX)(e^IFX_REMISSION)= ~$6812

This estimation method allows the interpretation to separate confounding effects. For example, by separating the cost multipliers for surgery and a surgical complication, the additional cost of the complication is distinct from the surgery. In this way, even if they were incurred in the same 3 month period, the value can be accurately used within this model structure, where an individual cannot be simultaneously in the surgery and surgical complication arms.

Data Methods

Cohort

All Albertans included in the Alberta Disease Registry with a diagnosis for Crohn's Disease.

Case definition: At least two inpatient, or four SESE, or two ambulatory records within two years with ICD09 codes 555*, 556*or ICD10 codes K50*, K51*. If the higher proportion of diagnostic codes are 555* and K50, it is assumed that the individual has Crohn's disease, and not ulcerative colitis.

Biologics Records

Alberta Blue Cross payment records from 2006 to 2014 were searched for individuals in the cohort described above with records including DIN 02244016 for infliximab and 02258595 for adalimumab. Any record that had a zero payment amount was excluded.

Given the desired analysis, cases had to be identified into the following two categories by quarter (standard quarters - Jan-Mar, Apr-Jun, etc.): active disease or remission.

Active Disease:

- Having previously received a dose of Prednisone, DIN 00271373, 00312770, or 00550957.
- Infliximab: Second dose follows first dose between 7 and 21 days, third dose follows second by 21 to 35 days.
- Adalimumab: Second dose follows first dose between 7 and 21 days, second dose is half the quantity of the first dose.

Remission:

For records following the active disease period, only records from 84 days following the first ‘active dose’ were analyzed. These cases were assessed as either in remission or non-responsive. A small number had to be excluded from the analysis as they could not be conclusively categorized between the two groups. There were many challenges in this evaluation because dosing is based on patient weight which is not known. Therefore dosing patterns and distributions were analyzed statistically to determine break points where non-responsive patients and patients in remission could be separated. If they could not be attributed to one category with confidence, they were excluded from the entire analysis.

- Infliximab: both the dose interval and quantity were used to determine if a case was in remission or non-responsive following induction dosing.
    - If the median dose interval was equal to or greater than 8 weeks:
        - Those receiving less than 6 vials per dose were assumed to be in remission
        - Those receiving 8 or more vials per dose were assumed to be non-responsive
    - If the median dose interval was less than 7 weeks, cases were assumed to be non-responsive.
- Adalimumab: the ratio of the median dose to the median dose interval was used to determine if cases were responsive or non-responsive. If the ratio was less than 0.5, cases were assumed to be in remission, otherwise, they were deemed non-responsive.

Biologics Complications

Inpatient, ambulatory, and physician claims databases were searched for records pertaining to individuals in the cohort defined above, which included one or more of the diagnoses provided, as follows:

Physician Claims:

/*infusion rxn */ HLTH_DX_ICD9X_CODE_1 =: '999/*.8*/' or HLTH_DX_ICD9X_CODE_2 =: '999/*.8*/' or

HLTH_DX_ICD9X_CODE_3 =: '999/*.8*/' or

/*serious infections*/HLTH_DX_ICD9X_CODE_1 =: '038/*.9*/' or HLTH_DX_ICD9X_CODE_2 =: '038/*.9*/' or

HLTH_DX_ICD9X_CODE_3 =: '038/*.9*/' or

/*intest stenosis */ HLTH_DX_ICD9X_CODE_1 =: '560/*.8*/' or HLTH_DX_ICD9X_CODE_2 =: '560/*.8*/' or

HLTH_DX_ICD9X_CODE_3 =: '560/*.8*/' or

/*pyrexia*/ HLTH_DX_ICD9X_CODE_1 =: '780/*.6*/' or HLTH_DX_ICD9X_CODE_2 =: '780/*.6*/' or

HLTH_DX_ICD9X_CODE_3 =: '780/*.6*/' or

/*resp tract infrec */ HLTH_DX_ICD9X_CODE_1 =: '465' or HLTH_DX_ICD9X_CODE_2 =: '465' or

HLTH_DX_ICD9X_CODE_3 =: '465' or

HLTH_DX_ICD9X_CODE_1 =: '419' or HLTH_DX_ICD9X_CODE_2 =: '419' or HLTH_DX_ICD9X_CODE_3 =: '419' or

/*nasophar*/ HLTH_DX_ICD9X_CODE_1 =: '460' or HLTH_DX_ICD9X_CODE_2 =: '460' or

HLTH_DX_ICD9X_CODE_3 =: '460' or

/*uti*/ HLTH_DX_ICD9X_CODE_1 =: '599/*.0*/' or HLTH_DX_ICD9X_CODE_2 =: '599/*.0*/' or

HLTH_DX_ICD9X_CODE_3 =: '599/*.0*/' or

/*lymphoma*/HLTH_DX_ICD9X_CODE_1 =: '202/*.8*/' or HLTH_DX_ICD9X_CODE_2 =: '202/*.8*/' or

HLTH_DX_ICD9X_CODE_3 =: '202/*.8*/' or

HLTH_DX_ICD9X_CODE_1 =: '173' or HLTH_DX_ICD9X_CODE_2 =: '173' or HLTH_DX_ICD9X_CODE_3 =: '173' or

/*demyelating disease*/HLTH_DX_ICD9X_CODE_1 =: '341' or HLTH_DX_ICD9X_CODE_2 =: '341' or

HLTH_DX_ICD9X_CODE_3 =: '341' or

/*lupus like synd*/ HLTH_DX_ICD9X_CODE_1 =: '710' or HLTH_DX_ICD9X_CODE_2 =: '710' or

HLTH_DX_ICD9X_CODE_3 =: '710' or

/*tuberculosis*/HLTH_DX_ICD9X_CODE_1 =: '011 ' or HLTH_DX_ICD9X_CODE_2 =: '011' or

HLTH_DX_ICD9X_CODE_3 =: '011' or

/*chf*/ HLTH_DX_ICD9X_CODE_1 =: '428' or HLTH_DX_ICD9X_CODE_2 =: '428' or HLTH_DX_ICD9X_CODE_3 =:

'428' or

/*intest perf*/HLTH_DX_ICD9X_CODE_1 =: '569/*.83*/' or HLTH_DX_ICD9X_CODE_2 =: '569/*.83*/' or

HLTH_DX_ICD9X_CODE_3 =: '569/*.83*/' or

/*psooriasis*/HLTH_DX_ICD9X_CODE_1 =: '696/*.1*/' or HLTH_DX_ICD9X_CODE_2 =: '696/*.1*/' or HLTH_DX_ICD9X_CODE_3 =: '696/*.1*/' or

/*anaphylactic rxn*/ HLTH_DX_ICD9X_CODE_1 =: '955' or HLTH_DX_ICD9X_CODE_2 =: '955' or HLTH_DX_ICD9X_CODE_3 =: '955' or

/*serum sickness*/ HLTH_DX_ICD9X_CODE_1 =: '999/*.5*/' or HLTH_DX_ICD9X_CODE_2 =: '999/*.5*/' or HLTH_DX_ICD9X_CODE_3 =: '999/*.5*/' or

/*shingles*/HLTH_DX_ICD9X_CODE_1 =: '053' or HLTH_DX_ICD9X_CODE_2 =: '053' or HLTH_DX_ICD9X_CODE_3 =: '053' ;

Inpatient and Ambulatory:

'T80','A41','K56','R50','J06','J22','J00','N39','C44','C86','G37','M32','A15','K63','L40','T78','T88','T80','B02'.

These records were compiled by date and individual, and any complication that followed within 84 days of a dose of either infliximab or adalimumab was included as a drug complication.

Surgery

Patients in the cohort described above receiving surgery were identified in the inpatient records by procedures 1NM87, 1NM89, or 1NM91.

Surgical Complications

Inpatient, ambulatory, and physician claims databases were searched for records pertaining to individuals in the cohort defined above, which included one or more of the diagnoses provided, as follows:

Physician Claims:

HLTH_DX_ICD9X_CODE_1 =: '560' or HLTH_DX_ICD9X_CODE_2 =: '560' or HLTH_DX_ICD9X_CODE_3 =: '560' or HLTH_DX_ICD9X_CODE_1 =: '997.49' or HLTH_DX_ICD9X_CODE_2 =: '997.49' or HLTH_DX_ICD9X_CODE_3 =: '997.49' or

HLTH_DX_ICD9X_CODE_1 =: '578' or HLTH_DX_ICD9X_CODE_2 =: '578' or HLTH_DX_ICD9X_CODE_3 =: '578' or HLTH_DX_ICD9X_CODE_1 =: '415.19' or HLTH_DX_ICD9X_CODE_2 =: '415.19' or HLTH_DX_ICD9X_CODE_3 =: '415.19' or
HLTH_DX_ICD9X_CODE_1 =: '999.32' or HLTH_DX_ICD9X_CODE_2 =: '999.32' or HLTH_DX_ICD9X_CODE_3 =: '999.32' or
HLTH_DX_ICD9X_CODE_1 =: '599.0' or HLTH_DX_ICD9X_CODE_2 =: '599.0' or HLTH_DX_ICD9X_CODE_3 =: '599.0';

Inpatient and Ambulatory:

'K56','K91','K92','I26','B99','N39';

These records were compiled by date and individual, and any complication that followed within 84 days of a surgery as defined above was included as a drug complication.

Death

Vital statistics data was used to flag the quarter in which a member of the cohort died, if applicable.

Diagnosis Quarter

A flag was generated to indicate the quarter in which an individual was diagnosed with Crohn's disease. A flag was also generated for each quarter after an individual was diagnosed, as some individuals may not yet have been diagnosed with Crohn's at the beginning of the study period.

Cost Data

Quarterly costs from the Alberta Cost Registry (which includes quarterly estimates for inpatient, ambulatory and physician claims) for each individual in the cohort defined above were extracted, and added to the quarterly sum of Alberta Blue Cross payments.

These costs were adjusted for inflation using the medical component of the Canadian Consumer Price Index and are given in 2014 dollars.

Exclusions

Three groups of persons were removed from the cohort:

- Those who had a record for infliximab or adalimumab in the Pharmacy Information Network Database but not in the Alberta Blue Cross Payments Database
- Those who were identified as having an induction dose of infliximab or adalimumab but could not be subsequently categorized as in remission or non-responsive
- Those who had records for both infliximab or adalimumab