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FULL REPORT

THE ECONOMIC EVALUATION OF EARLY INTERVENTION WITH ANTI-TUMOR NECROSIS FACTOR-α TREATMENTS IN PEDIATRIC CROHN'S DISEASE

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List of Abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	Adalimumab
AZA	Azathioprine
CAD	Canadian dollar
CADTH	Canadian Agency for Drugs and Technologies in Health
CD	Crohn's Disease
CDHTA	Crohn's Disease Health Technology Assessment
CEA	Cost-effectiveness analysis
CDN	Canadian
CI	Confidence interval
CIHI	Canadian Institute of Health Information
CMG	Case Mix Group
CS	Corticosteroids
CUA	Cost-utility analysis
EN	Enteral nutrition
HRQoL	Health-related quality of life
g	Gram
HTA	Health technology assessment
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio

IFX	Infliximab
IM	Immunomodulator
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
MOHLTC	Ontario Ministry of Health and Long-Term Care
kcal	Calorie
kg	Kilogram
mg	Milligram
MTA	Material transfer agreement
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence (United Kingdom)
OCCI	Ontario Case Costing Initiative
OR	Odds ratio
PCDAI	Pediatric Crohn's Disease Activity Index
PGA	Physician Global Assessment
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
SD	Standard Deviation
SOC	Standard of Care
TNF	Tumor necrosis factor
UC	Ulcerative colitis
UK	United Kingdom
USA or US	United States of America
wPCDAI	Weighted Pediatric Crohn's Disease Activity Index
WTP	Willingness to pay

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Executive Summary

BACKGROUND: Crohn's disease is a chronic disorder in which sections of the gastrointestinal tract become inflamed and ulcerated through an abnormal immune response. Costly anti-TNF-α treatments are indicated only after other treatments have not worked. However, anti-TNF-α treatments have been proposed as first line therapy due to their effectiveness.

OBJECTIVE: The primary objective was to assess the incremental cost-effectiveness of early intervention with anti-TNF-α treatment vs. conventional step-up strategy at improving the number of steroid-free remission weeks gained from public healthcare payer and societal perspectives.

METHODS: A two-dimensional probabilistic microsimulation Markov model with seven health states was constructed for children with moderate to severe Crohn's disease. Newly-diagnosed children with Crohn's disease aged 4-17 years who received anti-TNF-α treatment and other concomitant treatments, such as steroids and immunomodulators, within the first three months of diagnosis were compared to children with newly-diagnosed Crohn's disease who received standard care of steroids and/or immunomodulators with the possibility of anti-TNF-α treatment only after three months of diagnosis. The outcome measure was weeks in steroid-free remission. The time horizon was three years. A scenario analysis examined variation in costs of anti-TNF-α treatment. A North American multi-centre, observational study of children with Crohn's disease provided input into clinical outcomes and health care resource use. To reduce selection bias, propensity score analysis was used.

RESULT: From a public healthcare payer perspective, early intervention with anti-TNF-α treatment was more costly with an incremental cost of $31,112 (95% CI: 2,939, 91,715) and more effective with 11.3 more weeks in steroid-free remission (95% CI: 10.6, 11.6) compared to standard care, resulting in an incremental cost per steroid-free remission week gained of $2,756. From a societal perspective, the incremental cost per steroid-free remission week gained for early anti-TNF-α treatment was $2,968.

CONCLUSION: While unknown, if a willingness-to-pay threshold was assumed to be $2,500 per week in steroid-free remission, early intervention with anti-TNF-α would not be cost-effective. However, there is considerable uncertainty in the incremental cost-effectiveness ratio and many patients escalate to anti-TNF-α eventually. Therefore, restrictive policies on anti-TNF-α treatment access for pediatric Crohn's patients may want to be re-visited by decision makers.

Key words: cost-effectiveness analysis, pediatric Crohn's disease, anti-TNF-α, infliximab

1 Introduction

1.1 Overview

Crohn's disease (CD) is a chronic gastrointestinal disorder affecting children and adults, in which sections of the gastrointestinal tract become inflamed and ulcerated through an abnormal response of the body's immune system (Crohn's and Colitis Foundation of Canada, 2012). Symptoms and signs of chronic inflammation in CD include abdominal pain, diarrhea, weight loss, vitamin deficiencies and growth retardation (in children) (Crohn's and Colitis Foundation of Canada, 2012). Canada has among the highest prevalence (1:150) and incidence of people with Crohn's Disease (CD) and Ulcerative Colitis (UC), collectively called Inflammatory Bowel Disease (IBD), in the world (Crohn's and Colitis Foundation of Canada, 2012). In Canada, the prevalence of CD is greater than UC for children under the age of 19 and varies from province to province (Crohn's and Colitis Foundation of Canada, 2012). For reasons unknown, the incidence of IBD among children, particularly for those under 10, is on the rise, but there is a lack of studies on treatment for children particularly randomized controlled trials (Benchimol et al., 2017; Benchimol et al., 2009; E I Benchimol et al., 2014; Eric I Benchimol et al., 2014; Crohn's and Colitis Foundation of Canada, 2012). Currently, an estimated 3,900 Canadian children have CD (Benchimol et al., 2017; Benchimol et al., 2009; Crohn's and Colitis Foundation of Canada, 2012). There are approximately 200 new cases of pediatric CD in Ontario per year with an incidence rate of 5.48 per 100,000 children of males and females ranging from 6 months to 17 years of age (Benchimol et al., 2017; Benchimol et al., 2009). The economic burden of IBD overall is estimated at $11,900 per person per year with an estimated annual cost-of-illness in Canada exceeding $70 million (Crohn's and Colitis Foundation of Canada, 2012; Rocchi et al., 2012). These costs include not only health care resource use, but loss of productivity in parents and caregivers. People with CD have approximately 20% higher direct medical costs than those with UC (Crohn's and Colitis Foundation of Canada, 2012). There is a keen interest to introduce effective treatment as early as possible and to maintain remission for as long as possible because of the lifelong burden of disease and its sustained impact on quality-of-life for children and their families.

The traditional treatment of pediatric CD has involved a step-wise approach, or "step-up" strategy, involving several classes of drugs such as corticosteroids, immunomodulators and tumour necrosis factor alpha antagonist (anti-TNF-α) biologics. In Canada and the US, based on clinical practice guidelines, remission is typically induced in newly diagnosed CD pediatric patients using oral corticosteroids or exclusive enteral nutrition (Cincinnati Children's Hospital Medical Center, 2007; Sadowski et al., 2009). For treatment maintenance, immunomodulators (IM), such as the thiopurine-based azathioprine and 6-mercaptopurine, or methotrexate, can then be introduced to maintain a sustained remission and to reduce the need for further steroids which exert deleterious effects on growth. Children who do not respond adequately to IMs or who cannot tolerate them may subsequently be prescribed anti-TNF-α drugs such as infliximab (Remicade®) or adalimumab (Humira®).

There is interest in using anti-TNF-α agents earlier in the care pathway to avoid a prolonged period of exacerbated disease before reaching remission (Jean Frederic Colombel et al., 2010) (Petar Mamula & Kelsen, 2012; Rogler, 2013; Yang, Alex, & Catto-Smith, 2012). A recent observational cohort study by Walters, et al., (2014) showed 85% of children with CD achieved steroid-free clinical remission defined by Pediatric Crohn's Disease Activity Index (PCDAI) at 12 months if they received early treatment with anti-TNFα drugs compared to 60% of children receiving early IM therapy (Walters et al., 2014). Another observational study in pediatric CD showed sustained effectiveness of infliximab in children and adolescents with luminal CD with enhanced linear growth, particularly when therapy is initiated within the first 18 months of diagnosed disease (P. C. Church et al., 2014). While these studies suggest that anti-TNFα drugs are better at achieving remission than traditional therapies, the tradeoff is that they are more than ten times the cost of existing treatment (up to $50,000 per year). An increased risk of neoplasia, particularly lymphomas, has thus far been associated only with thiopurine use alone or in combination with anti-TNF-α, and not with anti-TNF-α monotherapy (Jeffrey S Hyams et al., 2017). Nevertheless, many parents are doubtful that the biologics are without risk (Assasi et al., 2009). Currently the Ontario Ministry of Health and Long Term Care (MOHLTC) covers the treatment of infliximab for approved individuals through the Exceptional Access Program.

Patients are eligible to receive infliximab if they demonstrate an intolerance or unresponsiveness to immunomodulators, or if they have perianal fistulizing disease.

To date, a randomized controlled trial (RCT) examining an anti-TNF-α treatment administered within three months after initial corticosteroid remission (early introduction of anti-TNF-α) compared to a step-up strategy (previously standard care) with the later introduction of anti-TNF-α treatment following immunomodulator treatment has not been completed in newly diagnosed children with CD. However an RCT using infliximab as first-line (top-down) therapy in naïve pediatric CD patients has been started (Cozijnsen, van Pieterson, Samsom, Escher, & de Ridder, 2016). A recent RCT in adult CD patients examining the early intervention with three induction doses of anti-TNF-α followed by thiopurine monotherapy ("top-down" approach) showed a greater proportion of patients (60.0%) in remission at week 26 compared to the standard care ("step-up") group (35.9%) (Geert D'Haens et al., 2008), and, more importantly, greater likelihood of sustained mucosal healing (Baert et al., 2010). Another similar trial in adult CD patients showed similar remission rates among early intervention and step-up comparator groups at 24 months, but a lower adverse event rate in the early anti-TNF-α intervention group (Khanna et al., 2015). A review of predominantly adult studies has concluded that there is insufficient evidence to warrant a change in treatment practices from the traditional "step-up" standard to a "top-down" approach with an early intervention of anti-TNF-α treatments (Spurio, 2012). A more recent review concluded that early combination therapy of biologics and immunomodulators was found to be effective at improving patient outcomes, but early biologics monotherapy did not have a clear benefit over step-up therapy (Tsui & Huynh, 2018). Evidence supporting a top-down approach with biologics in pediatric CD populations was also inconclusive (Tsui & Huynh, 2018). The review also concluded that cost-benefit analyses found that top-down therapy merited further investigation (Tsui & Huynh, 2018). Hence the debate between "top-down" and "step-up" approaches with anti-TNF-α treatments persists. In the absence of pediatric RCT data in newly diagnosed children (as opposed to refractory pediatric patients) with CD, observational data from a large North American registry of pediatric CD patients (the RISK-PROKIIDS observational cohort) may shed light on the effectiveness of the

early introduction of anti-TNF-α treatments in children newly diagnosed with moderate-to-severe CD.

From an economic perspective, a recent systematic review of cost studies, economic evaluations and reviews of economic evaluations comparing the treatment of biological therapies to standard care in moderate to severe CD in adults (and one pediatric study) found that biological treatments were cost-effective and reduced health care resource use compared to standard therapy in certain situations such as for luminal CD when used as induction treatment followed by episodic treatment as opposed to maintenance therapy (Derek H Tang, Amanda R Harrington, Jeannie K Lee, Mark Lin, & Edward P Armstrong, 2013). The only economic evaluation of biological treatments in pediatric CD taking a public payer perspective found that scheduled maintenance therapy with 5 mg/kg of infliximab was cost-effective (assuming a £30,000 per QALY willingness-to-pay threshold) compared to standard care in refractory pediatric CD patients (Punekar, Sunderland, Hawkins, & Lindsay, 2010). More favourable incremental cost-utility ratios (ICURs) or incremental cost-effectiveness ratios (ICERs) may be expected in pediatric CD when a societal perspective is taken. This is because a societal perspective will take into account caregiver costs such as productivity loss. In addition, the pediatric clinical effectiveness of treatments, the pediatric pattern of disease and the pediatric pattern of health care resource use may be different in children than adults (W. J. Ungar, 2010).

To our knowledge there are no economic evaluations comparing the early use of anti-TNF-α treatments to the traditional "step-up" strategy (prior standard care) in pediatric CD. Punekar's et al., economic evaluation examining the use of anti-TNF-α treatments in pediatric CD only looked at infliximab maintenance treatment in non-newly-diagnosed pediatric CD patients (Punekar et al., 2010). While the patient-level cost-of-illness of CD has been studied in adults (Crohn's and Colitis Foundation of Canada, 2012; Rocchi et al., 2012), there have been no studies across the full severity spectrum in children with CD. Current clinical practice guidelines and drug re-imbursement policies are not aligned with an early or first line introduction of anti-TNF-α treatments for moderate-to-severe pediatric CD. Depending on the clinical effectiveness

and economic effectiveness of the early introduction of anti-TNF-α treatments in pediatric CD, policies and clinical practice guidelines may need to be revisited as standard care evolves.

Of particular importance to the pediatric population is the need for access to safe and effective medications for CD including anti-TNFα drugs through drug benefit programs. Currently drug benefit programs vary widely across Canada with respect to eligibility, program characteristics, cost-sharing arrangements, pediatric drugs listed on formularies and the extent of off-label use (Pandolfini & Bonati, 2005; W. J. Ungar & Witkos, 2005). The need to create policies that provide equitable access to necessary medications in a manner that is affordable to families has been voiced as a priority by Crohn's and Colitis Canada (Crohn's and Colitis Foundation of Canada, 2012). Such policies require evidence from high quality economic evaluations. The need for comparative effectiveness studies of treatments for pediatric IBD has also been stated as a research priority in the US and Canada (Denson et al., 2013; Whicher, Chalkidou, Dhalla, Levin, & Tunis, 2009). Research is needed to furnish much needed evidence to inform clinical and policy decision-makers regarding the optimal placement of anti-TNFα drugs in the management of pediatric CD. In children with Crohn's disease, there are limited clinical effectiveness studies of anti-TNF-α treatments in refractory patients and only emerging observational data in newly-diagnosed CD patients (see Table 1.4.1-1). Additional evidence in newly-diagnosed children is emerging and funding decisions pertaining to the use of anti-TNF-α treatments in children with CD may need to be re-evaluated considering emerging data and the lack of economic evaluations in pediatric CD in Canada.

The common thread among reviews examining the cost-effectiveness of anti-TNF-α treatments for CD is that to date cost-effectiveness assessments for biological treatments in CD have limitations and need to consider: a) various payer and other stakeholder perspectives and b) limitations in clinical data (National Institute of Health and Care Excellence, 2010; Odes, 2008; Park & Bass, 2011). Particularly for pediatric disease a societal perspective is important since the loss of productivity and costs to caregivers needs to be taken into account and may affect the cost-effectiveness of a treatment compared to a single payer perspective. This study aims

to perform an economic evaluation of the early anti-TNF-α treatment in pediatric CD by taking provincial and societal perspectives.

1.2 Background Information

1.2.1 Crohn's Disease

The inflammation along the GI tract in CD is increasingly recognized as chronic and progressive, leading to structuring and penetrating complications. The clinical course is, however, variable, influenced in part by the anatomic location within the bowel (Crohn's and Colitis Foundation of Canada, 2012; G. R. Lichtenstein, Hanauer, Sandborn, & Practice Parameters Committee of American College of, 2009). There is no known cure or cause for Crohn's Disease.

Degree of inflammatory activity in pediatric CD is classified by the PCDAI, with a score equal to or greater than 30 points generally signifying activity of at least moderate severity, and a score $\leq$10 as quiescent disease (Sadowski et al., 2009). Children with IBD can differ in their incidence and health care resource depending on their age at diagnosis (Eric I Benchimol et al., 2014). Children in Ontario less than 5 years old at diagnosis had a 6.2% yearly increase in the incidence of Crohn's disease between 1994 and 2009 while children aged 6-9 at diagnosis had a 7.4% yearly increase in incidence and children between 10-17 years had a 1.9% yearly increase in incidence between 1994 and 2009 in Ontario (Eric I Benchimol et al., 2014). The peak age of onset of CD overall is in the second half of the second decade and within the third decade of life. Despite the apparent current greater percentage increases in incidence among very young children, the majority of pediatric CD still occurs in adolescence (Benchimol et al., 2017). For females less than 6 years with CD, there was a lower rate of IBD-specific outpatient visits (OR, 0.70; 95% CI, 0.50 to 0.98) compared to females greater than 6 years of age. This was not present for males less than 6 years with CD for IBD-specific visits (OR, 1.00; 95% CI, 0.81 to 1.24) when compared to males greater than 6 years (Eric I Benchimol et al., 2014). For males and females 6 to 9.9 years, IBD-specific outpatient visits were more frequent in CD patients, but not in UC patients compared to other age groups. In patients with CD, the hazard of hospitalization

was lower for females diagnosed at less than 6 years (HR, 0.56; 95% CI, 0.37 to 0.85; P = .006), but not at 6 to 9.9 years (HR, 0.85; 95% CI, 0.69 to 1.06; P = .15) compared to females greater than 10 years. There was no difference in males diagnosed at less than 6 years (HR, 1.07; 95% CI, 0.81 to 1.41; P = .65) or at 6 to 9.9 years (HR, 1.02; 95% CI, 0.85 to 1.22; P= .86), compared with males diagnosed at 10 years. Within three years of diagnosis there was a 9.6%, 5.1% and 14.7% risk of intestinal resection in those diagnosed with CD between less than 6, 6-9.9, and greater than 10 years of age respectively (Eric I Benchimol et al., 2014). The risk of surgery is known to be associated with location of CD, i.e. most commonly undertaken in the setting of isolated terminal ileitis, a form that is not recognized in the youngest children (Eric I Benchimol et al., 2014). Similarly, there were lower emergency department visits and hospitalizations in younger age groups (Eric I Benchimol et al., 2014). Possible reasons for these variations could be the desire to avoid surgery in younger children, who typically have colonic disease not amenable to resection with re-anastomosis, or the inability for children to verbalize more urgent care needs (Eric I Benchimol et al., 2014).

1.3 Anti-TNF-α Interventions and How They Might Work

The pro-inflammatory TNF-α cytokine plays a major role in regulating the innate immune system and in Th1 and Th17 adaptive immune responses (Peake et al., 2013). Patients with CD have elevated levels of TNF-α in inflamed tissue (Braegger, Nicholls, Murch, MacDonald, & Stephens, 1992). Anti-TNF-α antibodies are thought to neutralize the inflammatory activity of TNF-α. The precise mechanism of action of anti-TNF-α therapies remains unclear but multiple target pathways are postulated such as blocking receptor binding and binding to transmembrane TNF thus restricting activity (Peake et al., 2013). Anti-TNF-α treatments have shown efficacy in inducing and maintaining clinical remission in patients who have failed conventional therapies in several adult randomized controlled trials (Jean–Frédéric Colombel et al., 2007; Feagan et al., 2008; Ford et al., 2011; Hanauer et al., 2002; Hanauer et al., 2006; Peyrin-Biroulet et al., 2008; Present et al., 1999; Rutgeerts et al., 1999; Rutgeerts et al., 2006; Sandborn, Feagan, et al., 2007; Sandborn, Rutgeerts, et al., 2007; Sands et al., 2004; Schreiber et al., 2007; Spurio, 2012; Targan et al., 1997), and have also shown to improve mucosal healing

which can reduce complications and the need for surgical intervention (Feagan et al., 2008; Ford et al., 2011; Gary R Lichtenstein, Yan, Bala, Blank, & Sands, 2005; Rutgeerts et al., 2006). Current anti-TNF-α treatments such as infliximab and adalimumab are given, respectively, by infusion and subcutaneous injection.

1.4 Clinical Efficacy of Anti-TNF-α Treatments in Pediatric Crohn's Disease

A preliminary scoping literature review was conducted to identify any clinical studies using anti-TNF-α treatments introduced early in the treatment paradigm, as first line therapy, in children with CD (see Appendix 1 for details on literature search methods). The clinical studies examining anti-TNF-α use pediatric CD and that are most relevant to this thesis research were reviewed and summarized in Table 1.4.1-1. Based on the search results, there is a great paucity of clinical studies, and particularly randomized controlled trials, examining the induction and maintenance of anti-TNF-α treatments without the use of concomitant therapies. Most papers were retrospective chart reviews. Table 1.4.1-1 also shows that there is a large variation in the sample size and treatment regimen of subjects. The scoping review of the clinical literature identified gaps in the literature identifying the limited number of studies examining the efficacy of anti-TNF-α treatments in children and lack of randomized controlled trials in newly-diagnosed CD children. The scoping review identified that a systematic review of RCTs and a meta-analysis of anti-TNF-α interventions in children with CD is not currently possible due to the lack of studies. The Cochrane Registry of Controlled Trials and ClinTrials.gov have not listed any new prospective trials that examine the first line (top-down) use of anti-TNF-α treatments in children newly diagnosed and non-refractory with Crohn's disease except for a top-down infliximab multicenter pediatric study which is currently recruiting patients (Cozijnsen et al., 2016).

1.4.1 Studies and Reviews of the Clinical Efficacy of Anti-TNF-α Treatments

A Cochrane systematic review by Behm and Bickston (2008), reviewed evidence for the effectiveness of TNF-α blocking agents in the maintenance of remission in adult patients with

Crohn's disease (Behm & Bickston, 2008). They concluded that infliximab 5mg/kg or 10 mg/kg, given every 8 weeks, is effective for the maintenance of remission and maintenance of fistula healing in patients who have responded to infliximab induction therapy. Adalimumab 40 mg weekly or every other week is effective for the maintenance of remission in patients who have responded to adalimumab induction therapy. Certolizumab pegol 400mg every 4 weeks is effective for the maintenance of remission in patients who have responded to certolizumab induction therapy. No comparative trials have evaluated the relative efficacy of these agents and rates and types of adverse events among anti-TNF-α agents were similar compared with placebo (Behm & Bickston, 2008). However the Cochrane reviewers also concluded that the study size and duration generally were insufficient to allow for adequate assessment of serious adverse events associated with long-term use (Behm & Bickston, 2008). As the use of anti-TNF-α treatments is relatively recent compared to corticosteroid and immunomodulator treatments, most patients in these studies who were prescribed anti-TNF-α treatments were refractory to other treatments. The labels for these treatments also state that they are indicated for moderate-to-severe patients who have not responded well to other treatments.

A recent scoping review conducted by other researchers examining a reversal of the current treatment paradigm ("top-down" vs. standard "step-up" treatment) was conducted in 2012 (Spurio, 2012). That review, using predominantly adult studies, concluded that at that time there was insufficient evidence to warrant a change in treatment practices. Since then another review has made similar conclusions (Tsui & Huynh, 2018). While a comparator RCT comparing anti-TNF-α treatments to immunomodulators has not been conducted in newly-diagnosed, naïve pediatric CD patients who have not previously been treated, an open-label RCT in pediatric CD patients of anti-TNF-α therapy (infliximab) and concomitant IM in pediatric CD patients who had been started on immunomodulators and an induction treatment of infliximab showed that a greater percentage of pediatric patients achieved a clinical response and clinical remission at week 54 with a maintenance treatment schedule of 5mg/kg infliximab every 8 weeks compared to a 5 mg/kg infliximab treatment every 12 weeks (J. Hyams et al., 2007). When compared to a similar trial with adults in which adults received 5mg/kg every 8 weeks as

maintenance treatment (Hanauer et al., 2002), it was observed that children had better response rates than adults generally attributed to the much shorter duration of CD prior to infliximab initiation (Spurio, 2012). In all RCTs prior to 2002 reviewed by Hanauer (2002) of anti-TNF therapy in CD, response rates decrease the longer the duration of disease (Hanauer SB, 2002). An open label induction trial of adalimumab followed by dose-ranging maintenance in children with active CD despite conventional therapies showed that 33.5% were in remission at week 26 with a similar safety profile as in adult studies (Jeffrey S Hyams et al., 2012). Most recently, an open-label RCT comparing maintenance infliximab monotherapy to maintenance combination therapy of infliximab and immunomodulators in children with CD previously refractory to non-biologic treatment showed that there was no significance difference in PCDAI scores among groups treated with maintenance monotherapy or combination therapy (Kierkuś et al., 2015). In the absence of pediatric RCT data in newly diagnosed children (as opposed to pediatric patients with unsatisfactory response to prior corticosteroids and immunomodulators) with CD, observational data from a large North American registry of pediatric CD patients (the RISK-PROKIIDS observational cohort) may shed light on the effectiveness of the early introduction of anti-TNF-α treatments in children newly diagnosed with moderate-to-severe CD.

Table 1.4.1-1. Pediatric Crohn's Disease Studies with Infliximab or Adalimumab as Part of the Treatment Scheme.

Reference Study	Experimental Intervention	Results	Age at Diagnosis	Sample Size (n) in Intervention Group	Follow-up Time	Study Design	Location	Early Intervention in Newly Diagnosed/ Naïve to anti-TNF-α
(Walters et al., 2014)	IFX, some ADA monotherapy vs. IM monotherapy vs. no early therapy	85.3% remission at 1 year (IFX)	Median age = 11 years	68	1 year	Retrospective cohort	Multi-centre, (29 sites in USA and Canada)	Yes
(Martin-De-Carpi et al., 2014)	ADA +IM	36/40 in remission at 2 years	Mean =11.3	40	2 years	Retrospective cohort	Multi-centre, (Spain)	Yes
(J. Hyams et al., 2011)	IFX + IM at baseline	50%	Mean= 13.2	60	3 years	Retrospective cohort	Multi-centre (17 sites, North America, Western Europe and Israel)	Not all newly diagnosed
(Yang et al., 2012)	Overview of biologics	Top-down + concomitant IMs is good strategy	children	N/A	N/A	Review (general)	Review	No
(Y. S. Lee et al., 2012)	IFX +IM	76.9% in remission (10/13)	Median=14	13	1 year	Retrospective cohort	Single centre (Korea)	Yes
(Civitelli et al., 2009)	ADA +IM	65.2% in remission at week 48	Median =16.1	23	48 weeks	Prospective cohort	Single centre (Italy)	Not all naïve or newly diagnosed

Reference Study	Experimental Intervention	Results	Age at Diagnosis	Sample Size (n) in Intervention Group	Follow-up Time	Study Design	Location	Early Intervention in Newly Diagnosed/ Naïve to anti-TNF-α
(Assa et al., 2013)	IFX or ADA + concomitant medications	56% in remission at follow-up	Mean= 13.4	101	Median = 15 months	Retrospective	Multi-centre (3 sites in Israel)	Not all newly diagnosed
Navas-Lopez et al, 2013.	ADA + IM/CS	100% in remission at 12 weeks	Mean = 10.6	16	12 weeks	Retrospective Observational	Single centre, (Spain)	Not all newly diagnosed
(Grossi et al., 2014)	IFX + IM or IFX monotherapy	0.4 chance of being on IFX at 5 years with no IM at start	Mean = 11.8	503	Up to 10 years	Retrospective (from registry)	Multi-centre (28 sites in US and Canada)	Not all newly diagnosed
(Gouldthorpe, Catto-Smith, Alex, & Simpson, 2013).	IFX + IM	60% at week 178 (3/5 still on IFX)	65% <16 years	71	178 weeks	Retrospective observational	Single centre (Australia)	Not all newly diagnosed

Abbreviations: IFX=infliximab; ADA= adalimumab; IM=immunomodulator; SOC=standard of care)

1.5 Economic Evaluations and Health Technology Assessments of Anti-TNF-α Treatments in Crohn's Disease

A scoping literature review was also conducted to search for cost-effectiveness, cost-utility or cost-benefit analyses of any anti-TNF-α treatments in children with CD (see Appendix 2 for search methods). The ten most relevant publications are summarized in Table 1.5-1. There were five cost-utility analyses (CUAs), three cost-effectiveness analyses (CEAs), one costing analysis and one health-related quality of life (HRQoL) analysis. None of the studies included exclusively newly diagnosed patients or patients naïve to anti-TNF-α treatments and all the studies listed investigated patients with moderate-to-severe CD. All the studies had different time horizons and none took a multiple payer perspective. The clinical effectiveness outcomes of each economic evaluation were modeled based on the results of one clinical trial. Many studies did not take into account the switching of treatments in the case of adverse events in their models which is common practice in CD management.

Two studies had a Canadian context and two studies considered pediatric health utilities for Quality Adjusted Life Years (QALYs) and assessment of child health-related quality of life. No cost-utility analysis in studies of pediatric subjects used child-specific health utilities as none have been determined for children with CD as yet. In the absence of child utilities, health utilities were derived from one major study or adaptations of this study which established utilities for CD health states in adults using the Standard Gamble and Time Trade Off techniques (Gregor et al., 1997). Utilities for a "non-responder" state in Punekar et al., (2010) were based on expert opinion (Punekar et al., 2010). Punekar et al. (2010) performed the only economic evaluation examining infliximab in pediatric CD. Punekar et al., found that scheduled maintenance therapy with 5 mg/kg of infliximab was cost-effective (assuming a £30,000 per QALY) compared to standard care in refractory pediatric CD patients and that infliximab was cost effective at £14,607 per quality-adjusted life year (QALY) gained with a 0.55 QALY gain in the UK over a 5-year time horizon in patients refractory to conventional treatments, but they

did not include infliximab in the standard care strategy (Punekar et al., 2010). They also ignored the disutility and costs related to adverse event and infection management.

Assasi et al., (2009) and Blackhouse et al., (2012) examined the cost-effectiveness of infliximab or adalimumab compared to non-anti-TNFα usual care in refractory adult CD patients over a five-year time horizon from a Canadian payer perspective (Assasi et al., 2009; Blackhouse et al., 2012a). They found that the cost per QALY gained for infliximab therapy compared with usual care was $222,955 with a 0.166 QALY gain. Marchetti et al., (2013) conducted a cost-effectiveness analysis with a 5-year time horizon comparing the early introduction of infliximab for induction to standard care in newly-diagnosed adult CD patients (Marchetti, Liberato, Di Sabatino, & Corazza, 2013). They incorporated switching of treatments but only included episodic infliximab treatment. They found a 0.14 QALY gain with the early introduction of infliximab and a cost savings of €773 (Marchetti et al., 2013). Their Italian drug costs were also likely to be significantly less than Canadian costs. The variation in cost-effectiveness conclusions in the studies reviewed revealed that model design, anti-TNF-α treatment cost, and frequency of treatment can all impact the results of cost-effectiveness analyses. These results confirm the need for comprehensive economic evaluations in children with Crohn's disease.

Tang et al., conducted a systematic review of cost studies, economic evaluations and reviews of economic evaluations examining the treatment of biological therapies compared to standard care in moderate to severe CD in adults (only one pediatric study) (Derek H Tang et al., 2013). Tang et al., found that biological treatments were cost-effective compared to standard therapy in certain situations such as for luminal CD when used as induction treatment followed by episodic treatment as opposed to maintenance therapy and that biological treatments did reduce health care resource utilization (Derek H Tang et al., 2013).

In 2009, the Canadian Agency for Drugs and Technologies in Health (CADTH) issued a comprehensive report evaluating biological treatments for inflammatory bowel disease in adults (Assasi et al., 2009). The CADTH report made a number of key points. Although infliximab and adalimumab have been shown to provide clinical benefit, the costs associated with these

treatments could be perceived as high. The CADTH report determined, using a five year time horizon, the base case costs of usual care, adalimumab and infliximab to be $17,107, $45,480 and $54,084 and infliximab. Usual care provided 2.555 QALYs while adalimumab provided 2.701 QALYs and infliximab provided 2.721 QALYs. The incremental cost-utility ratio (ICUR) for infliximab compared to usual care was $222,955 and the ICUR for adalimumab compared to usual care was $193,305 (Assasi et al., 2009). Based on incremental cost-utility findings from these primary economic evaluations, the use of adalimumab and infliximab for the treatment of IBD may not be perceived to be a cost-effective use of health care resources. Compared to usual care, anti-TNF-α drugs are unlikely to be cost-effective in adult Crohn's disease unless society is willing to pay more than $208,000 for a healthy year of life (QALY). In adult ulcerative colitis, a treatment strategy based on 5mg/kg of infliximab and adalimumab is unlikely to be cost-effective compared to usual care unless society is willing to pay more than $370,000 for a QALY.

Since the CADTH primary economic analyses adopted a public health care payer perspective, indirect costs, such as loss of productivity, were not considered. If a societal perspective was taken and indirect costs, important to parents and families, were considered, then the cost per QALY of the anti-TNFs may be more favourable. To address the limited perspective pointed out in the CADTH report, this research intends to take a societal perspective as well as a public payer perspective in order to provide a comprehensive examination of indirect costs involved in anti-TNF-α treatment for children. Funding decisions may require more clinical and economic evidence. The CADTH report stated that there are a limited number of long-term randomized controlled trials demonstrating clinical-effectiveness, safety, and cost-effectiveness of anti-TNF-α drugs in adults (Assasi et al., 2009).

Table 1.5-1. Economic Evaluations in Crohn's Disease.

Reference	Analytic technique	Perspective	Time Horizon	Patients	Interventions	Location
(Blackhouse et al., 2012b)	CUA with Markov model	Provincial	5 year	Adults with refractory CD	IFX and ADA and usual care	Canada
	Result: The incremental cost per QALY (ICUR) for adalimumab compared to usual care and for adalimumab compared to infliximab was $193,305 and $451,165, respectively.					
(Jaisson-Hot, Flourie, Descos, & Colin, 2004)	CUA	Third party payer	Lifetime	Adult nonfistulizing resistant CD	IFX vs usual care (surgery & medical management no IFX	France
	Result: The incremental cost per QALYs saved (ICUR) for IFX compared to usual care varied from €63,700.82 (episodic re-infusions) to over €762,245.09 (maintenance therapy).					
(Punekar et al., 2010)	CEA (CUA)	UK NHS payer perspective	5 years	Pediatric CD	IFX maintenance vs. SOC	UK
	Result: ICUR for IFX compared to usual care was £14,607					
(Yu et al., 2009)	CUA	Private payer	56 week	Adult CD	IFX vs ADA for maintenance	USA
	Result: ICUR for ADA compared to IFX was -$4852 per QALY.					
(Choi et al., 2014)	Costs of treatment	UK NHS	12 weeks	Adult CD	First line ADA & IFX	UK
	Result: Costs lower with adalimumab (£6692.95 less per patient)					
(Veereman et al., 2013)	HRQOL via IMPACT III	USA	52 week	Pediatric CD	ADA + IM	Multi-centre (IMAGINE trial)
	Result: Improved HRQOL					
(CADTH) (Assasi et al., 2009)	CEA	Provincial	1 year	Adult CD	ADA & IFX	Canada
	Result: The incremental cost-utility ratio (ICUR) of adalimumab therapy compared with usual care was estimated to be $193,305 per QALY. The ICUR of infliximab therapy compared with adalimumab therapy was estimated to be $451,165.					
(Reinink, Gregory, Kymes, & Dassopoulos, 2011)	CUA	USA	5 year	Adult CD	IFX monotherapy vs AZA monotherapy vs combination	Multi-centre USA
	Result: ICER of $417,955 per QALY for combination treatment compared to AZA monotherapy.					

Reference	Analytic technique	Perspective	Time Horizon	Patients	Interventions	Location
(Lindsay, Punekar, Morris, & Chung-Faye, 2008)	CEA with Markov models	UK NHS (3rd party payer)	5 year	Adult luminal and fistulizing CD	Maintenance IFX	UK
	Result: ICER (ICUR) per QALY for IFX compared to standard care in luminal CD is £26128; and fistulizing CD is £29752					
(Marchetti et al., 2013)	CEA with top-down model	Third Party Payer	5 year	Adult luminal CD	Top-down IFX vs. step-up	Italy
	Result: ICUR for top-down IFX compared to step-up IFX was €12,114 per QALY					

Abbreviations: CUA= cost-utility analysis; CEA= cost-effectiveness analysis; ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life-year; IFX= infliximab; AZA= azathioprine; ADA=adalimumab; ICUR= incremental cost-utility ratio; UK=United Kingdom; NHS=National Health Service; HRQOL=Health-related quality of life.

1.6 Treatment Pathway in Crohn's Disease

The treatment pathway in pediatric CD can be complex due to variations in disease severity and disease localization among patients. Mamula et al., (2017) provide extensive details about managing and diagnosing pediatric inflammatory bowel disease (Petar Mamula, Grossman, Baldassano, Kelsen, & Markowitz, 2017). They indicate that the main outcomes of interest that should be measured in pediatric inflammatory bowel disease are the following:

- Disease activity
- Clinical remission rate
- Interval between relapses
- Complication rates (e.g., fistula)
- Nutritional status
- Growth, final adult height
- Days missed from school
- Emergency department visits
- Hospitalization rate
- Hospital length of stay
- Surgery
- Patient and family satisfaction
- Patient quality of life

The typical treatment algorithm as suggested by the Cincinnati Children's Hospital Medical Center Evidence-based care guideline for management of pediatric moderate-to-severe IBD with infliximab is the following ("Cincinnati Children's Hospital Medical Center. Evidence-based care guideline for management of pediatric moderate/severe inflammatory bowel disease (IBD)," 2007). Canadian practice guidelines are similar (Sadowski et al., 2009). Infliximab or anti-TNF-α treatments are indicated for the induction of remission in children with moderate/severe CD who do not respond to or were intolerant of induction therapy with prednisone and 6MP/AZA, or relapsed during their initial course of steroids and 6-MP / AZA, or have failed immunomodulator therapies 6-MP/AZA and/or MTX, or are steroid dependent/refractory, defined as received more than one course of steroids in one year, or did not achieve remission after one month of prednisone alone, or did not taper off prednisone after three months, or have severe colitis requiring transfusion or severe small bowel disease or draining

enterocutaneous or perianal fistulas. Contraindications include signs of abscess, signs and symptoms of infection, a history of tuberculosis and histoplasmosis. Initial dosing of infliximab is 5mg/kg at initiation, 2, and 6 weeks intravenously. If the initial dosing is successful, maintenance therapy at 5 mg/kg can be given every 8 weeks. If an increase in dose is warranted due to inadequate response then dosing at 10 mg/kg every 8 weeks can be introduced. In the event of continued inadequate response, dosing frequency can be increased to every 6 weeks. Monitoring for acute infusion reactions, infections, and anti-TNF-α associated skin rashes should be undertaken.

Suggested Crohn's disease safety monitoring strategies prior to treatment and during treatment include ensuring appropriate vaccinations, such as varicella and Hepatitis B, have been received, tuberculosis screening has been completed, and vigilance for serious adverse events, opportunistic infections and malignancy (Petar Mamula et al., 2017). Disease activity can be measured using the PCDAI which is used mainly in clinical trials (Jeffrey S Hyams et al., 1991). The PCDAI consists of three domains (laboratory, examination, and history) with several assessments that are converted into a PCDAI score which can range from 0 to 100 points, with a higher score indicating more severe disease activity. Within the "history" domain, a patient's general well-being, abdominal pain and stool description are assessed over the past one week. Within the "laboratory" domain, a patient's hematocrit, erythrocyte sedimentation rate and albumin levels are scored. Within the "examination" domain, weight, height at diagnosis and height at follow-up, abdominal tenderness, perirectal disease, and extra-intestinal manifestations are assessed and scored. Height velocity Z-score (a measure of rate of growth in height) is also assessed. The weighted PCDAI (wPCDAI) is a mathematically weighted and validated version of the PCDAI which does not assess the height velocity Z-score and hematocrit values (Turner et al., 2012). The wPCDAI is described further below.

1.7 Theoretical Framework

The management of chronic diseases such as CD relies on the efficient and integrated coordination of several aspects of health care within the community. The Ontario Ministry of

Health and Long-Term Care (MOHLTC) has developed a policy framework to guide the redesign of health care practices and systems to improve chronic disease prevention and management (Ontario Ministry of Health and Long-Term Care, 2007). This framework has been adapted from frameworks presented by Barr et al., 2003 and emphasizes interconnected and mutually dependent elements such as personal skills and self-management support, delivery system design, healthy public policy, provider decision support, and information systems that are essential to good care and improved chronic care delivery (Barr et al., 2003).

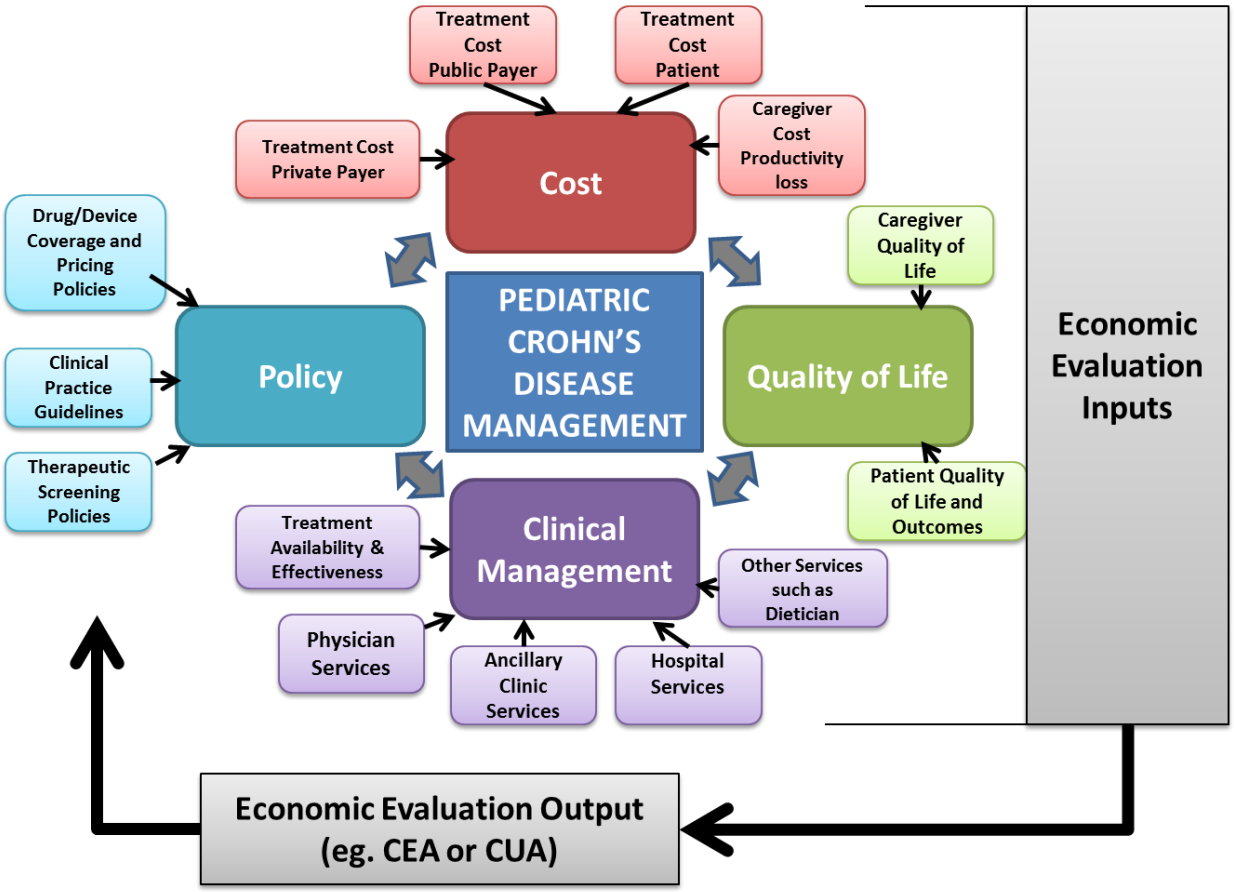
Tugwell et al., (1985), developed a framework for the critical appraisal of need, benefits and costs of health interventions that describes a way of assembling the specific subset of health information that is most likely to tell us how to reduce the burden of both morbidity and mortality (Tugwell, Bennett, Sackett, & Haynes, 1985). The loop depicts how the flow of information such as the burden of illness, disease etiology, community effectiveness of treatments, the efficiency of treatments as they relate to costs and effectiveness, the synthesis, implementation and monitoring of programs and the reassessment of burden of illness feeds into subsequent parts of the loop and is an iterative and continuous process to reduce the burden of illness.

The Crohn's Disease Health Technology Assessment (CDHTA) Framework is developed here to guide the economic evaluation from a societal perspective in this research. The CDHTA framework is a simplification and adaptation of the MOHLTC and Tugwell models as it applies to Crohn's disease management (Figure 1.7-1). The framework merges some of the integrative elements of the MOHLTC framework in chronic disease and the dynamic aspect of Tugwell's details about efficiency and impacts on burden of illness. In the CDHTA framework, four basic domains of pediatric CD management are listed: Cost, Quality of Life, Clinical Management and Policy. Each of these domains can impact each other. For example, health policy elements such as drug coverage policies affect the degree of payers' and patients' costs and may influence the choice of treatment in clinical management. The choice of treatment can in turn affect the quality of life of a patient. Quality of life may be improved through better disease management or diminished as a consequence of increased adverse events. The quality of life domain can

impact clinical management and cost because a lower quality of life can increase the need for more effective and safer clinical management which may in turn affect costs through the procurement of additional health care resources. Each domain in the framework has elements feeding into it as illustrated by the colour-coded bubbles around each domain. Information from each of these bubbles must be taken into account when performing an economic evaluation as it can either influence cost, effectiveness or the probability of reaching a clinical outcome. The Cost, Quality of Life and Clinical Management aspects of the framework inform the inputs of the economic evaluation while the output of the economic evaluation such as a cost-effectiveness analysis or a cost-utility analysis can serve to provide evidence to elicit change in the Policy aspect of the framework.

Figure 1.7-1. The Crohn's Disease Health Technology Assessment (CDHTA) Theoretical Framework.

A framework outlining the interactions among key elements in economic evaluations of pediatric Crohn's disease management.



Abbreviations: CEA= cost-effectiveness analysis; CUA= cost-utility analysis

1.8 The Problem

There is a lack of economic evaluations of the early introduction of anti-TNF-α treatments in children with CD. To effectively manage CD in children, policies to facilitate ready access to the treatments that provide the greatest value in the form of clinical effectiveness and cost-effectiveness need to consider the chronic nature of the disease and its effect on patients and their caregivers. Hence, health technology assessments that consider societal perspectives and caregiver burden as well as single-payer perspectives would be beneficial in informing policies as they related to CD management.

1.9 Primary Objective

The primary objective of this study will be to determine the incremental cost-effectiveness of early intervention with anti-TNF-α treatment with or without concomitant immunomodulators and with or without steroid induction (top-down approach) compared to the conventional step-up strategy consisting of corticosteroid (or enteral nutrition) induction followed by maintenance treatment with immunomodulators and the introduction of anti-TNF-α treatment after 3 months in moderate-to-severe pediatric CD over a three-year time horizon. For the purposes of this model, early introduction of infliximab will be defined as the introduction of infliximab within the first three months of diagnosis with or without the use of concomitant immunomodulators. Clinical outcomes of interest will be the time in steroid-free remission per patient (steroid-free remission weeks), and the time in sustained steroid-free remission. The time in sustained steroid-free remission can be divided into 6-month semester intervals as sustained remission is defined as a minimum of 6 months or greater in remission. Adverse events of special interest (such as severe adverse events or antibody reactions to treatment) within the three year time period of the study will also be considered.

Question 1. The primary research question is, what is the incremental cost of early intervention with anti-TNF-α treatments compared to a step-up strategy of treatment (conventional standard care) per remission week gained over a three-year period than in children with newly-diagnosed moderate-to-severe Crohn's disease?

To further clarify, the treatment comparator groups are:

1. Early intervention (top-down) with anti-TNF-α: An induction phase of anti-TNF-α, and/or corticosteroids, and/or enteral nutrition, with or without concomitant immunomodulators administered within three months of diagnosis followed by a maintenance phase of anti-TNF-α treatment with or without concomitant immunomodulators. Potential dose escalation and switching of medications within a drug class are included.

2. Step up strategy (traditional standard care): An induction phase of enteral nutrition or corticosteroids with or without concomitant immunomodulators administered within three months of diagnosis followed by a maintenance phase with immunomodulators and followed by anti-TNF-α treatment (with or without concomitant immunomodulators) only after three months of diagnosis or later if deemed necessary. Potential dose escalation and switching of medications within a drug class are included.

1.10 Secondary Objective

Randomized controlled studies in pediatric disease are rare and often absent. As such, clinical research in children often relies on observational studies which can use patient-level data. The impact of using patient-level data to inform a cost-effectiveness analysis is understudied. A secondary objective of this study will be to explore methods of propensity score analysis and dataset adjustment prior to propensity analysis, such as imputation of missing data from patient-level data, and examine their effect and feasibility within the context of conducting an economic evaluation. Propensity score analysis is a series of methods to facilitate the comparison of treatment and control groups in an observational study through the reduction of selection bias as would be seen in a randomized controlled trial. Choosing an appropriate method of propensity score analysis is often based on the choice of the researcher and the nature of the study data. Multiple methods of propensity score analysis have not been previously compared in the same set of pediatric CD observational data. Given the lack of RCTs and the more common occurrence of observational studies in child health, determining optimal

methods of propensity scoring for the creation of comparator groups is an important consideration for using observational data in pediatric economic evaluations.

Question 2. The secondary research question is, can methods of propensity score analysis, or the method of dataset adjustment prior to propensity score analysis, affect the feasibility of analysis or the result when conducting a cost-effectiveness analysis undertaken with pediatric patient-level data in moderate-to-severe Crohn's Disease?

1.11 Research Design

To provide background information and establish the status of current research in the clinical effectiveness and cost-effectiveness of anti-TNF-α treatments in pediatric Crohn's disease, the research began with a scoping literature review for clinical studies and economic evaluation studies related to the use of anti-TNF-α treatments in pediatric Crohn's disease.

For the primary objective, a cost-effectiveness analysis (CEA) will assess the economic benefit of early treatment (introduced within the first 3 months of diagnosis) with anti-TNF-α drugs with or without concomitant immunomodulators compared to a step up strategy (prior standard care) consisting of no early therapy with anti-TNF-α agents and where anti-TNF-α treatments are only introduced after three months of diagnosis if needed. The CEA will be conducted from an Ontario healthcare public payer perspective and a societal perspective, and will be conducted using observational patient-level data from the RISK-PROKIIDS study. The RISK-PROKIIDS study, which started in 2008, is a prospective, ongoing multi-centre North American observational cohort study with 1136 children enrolled presenting with untreated, newly diagnosed CD. The data from the RISK-PROKIIDS study will be analyzed retrospectively. As a pragmatic, observational study, children in the RISK-PROKIIDS study were treated according to recommended guidelines at the discretion of the treating physicians, providing high external validity. Comparator groups will be created through propensity score analysis. Optimal methods of propensity score analysis and data compilation for this study will be determined to address the secondary objective of this research. A health state diagram will be created to outline the pathways of Crohn's disease management. The CEA will assess costs and resource use in the

management of pediatric CD. Standard methods for economic evaluation will be followed (Canadian Agency for Drugs and Technologies in Health (CADTH), 2017; Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005) and appropriate ethics review boards have approved this research. The following chapters provide details on the methodology of the cost-effectiveness analysis and related model inputs. The potential impact of the cost-effectiveness analysis results on the policies and practices surrounding anti-TNF-α use for the clinical management of pediatric CD will be discussed.

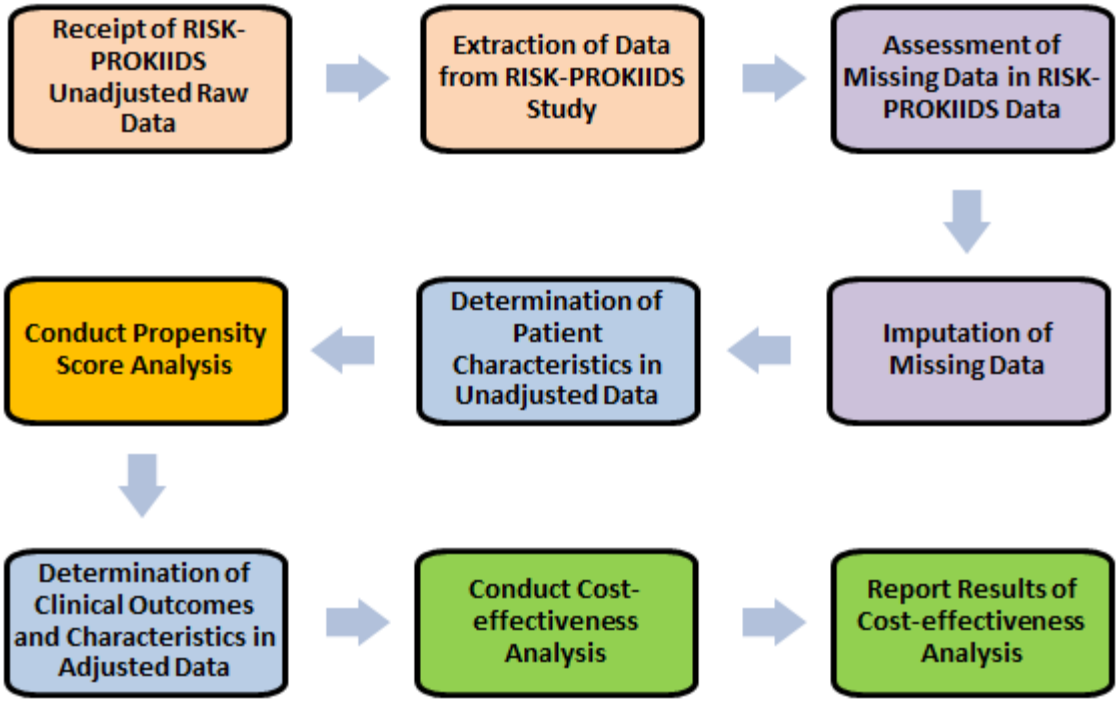
2 Methods

2.1 Overview of Methods and Study Design

With the aim of finding information on clinical studies and health technology assessments conducted with anti-TNF-α treatments in children with Crohn's disease (CD), a scoping literature review for pediatric clinical studies with anti-TNF-α treatments as first line therapy in Crohn's disease, and scoping literature review for health technology assessments of anti-TNF-α treatments in pediatric Crohn's disease were conducted. The methodological approaches for the scoping literature reviews are described in Appendix 1 and Appendix 2. The scoping literature reviews revealed that there were no clinical studies in pediatric Crohn's patients where anti-TNF-α treatments were used as first line therapy, and no health technology assessments where anti-TNF-α used as a first line therapy was compared to standard care in children with CD. Hence, an economic evaluation of early intervention with anti-TNF-α treatment in pediatric CD was undertaken.

The primary goal of this study is a cost-effectiveness analysis of the early intervention with anti-TNF-α in children with moderate-to-severe Crohn's disease. Several steps were required to reach this goal. The steps in determining the incremental cost-effectiveness ratio of early intervention with anti-TNF-α in pediatric Crohn's disease were as follows: 1) assembling a data set of subjects representative of the pediatric Crohn's disease patient population; 2) extracting relevant data from the data set and identifying gaps in the data set; 3) impute missing data; 4) using propensity score analysis to create a data set with two equivalent comparator groups that, similarly to a randomized clinical trial, tries to minimize selection bias between the comparator groups; 5) conduct a cost-effectiveness analysis; and 6) report the results of the cost-effectiveness analysis. A diagram showing the overall process followed in this study is shown in Figure 2.1-1.

Figure 2.1-1. Process flow of data analysis.



The following chapter details the steps leading up to and in conducting the cost-effectiveness analysis. The chapter begins with a description of the RISK-PROKIIDS data set, the representative data set of a multi-site North American cohort of pediatric Crohn's disease patients used to inform the probabilities of transitioning between health states in the cost-effectiveness model. The variables that described pertinent patient characteristics were extracted from the RISK-PROKIIDS data set. The next step described was the identification of any critical missing data. The chapter follows with a description describing the imputation of missing data. Once a complete unadjusted data set was assembled, propensity score analysis was conducted to create two comparable groups of subjects. The next section describes different methods of propensity score analysis that were conducted and compared. Once an optimal method of propensity score analysis was determined, a matched data set was created containing a group of "treated" subjects that received early intervention with anti-TNF-α and a

group of “control” subjects that received standard care. Following the establishment of two matched comparator groups, the methods and details of the cost-effectiveness analysis are described.

2.2 The Pediatric Crohn’s Disease Cohort

This study intends to compare early intervention with anti-TNF-α. Previously, anti-TNF-α has only been used in patients refractory to other treatments, therefore there are no published clinical trials in pediatric Crohn’s patients with an early anti-TNF-α treatment arm. Due to the absence of a randomized clinical trial with children diagnosed with Crohn’s disease and treated with anti-TNF-α without previous treatment with other medications, an observational study of pediatric CD patients, analyzed retrospectively was used to obtain patient-level data on newly diagnosed CD patients. This study was entitled the RISK-PROKIIDS study.

2.2.1 The RISK-PROKIIDS Study Data

The RISK-PROKIIDS study, which started in 2008, is an ongoing, prospective, North American multi-centre observational cohort study with 1136 children enrolled presenting with untreated, newly diagnosed inflammatory CD (https://prokiids.com/RISK_Public.html). Children with structuring or penetrating complications already present at diagnosis were excluded. The children were enrolled at 28 centres across North America, including three Canadian sites (see Appendix 3 for the location of the clinical sites).

The objective of the RISK-PROKIIDS study was to identify significant genetic, immune and microbial factors that accurately predict the risk of disease progression from inflammatory to stricturing and/or penetrating disease. As a pragmatic, observational study, children were treated according to recommended guidelines at the discretion of the treating physicians, providing high external validity. The RISK-PROKIIDS study provided a cohort of newly diagnosed CD pediatric patients with at least a three year follow-up. Patient characteristics such as age, sex, ethnic origin, disease severity, clinical chemistry values, physician assessments of health state and treatments were captured over time. The broad RISK-PROKIIDS study data of Crohn’s disease were used to extract a subset of subjects that met the inclusion criteria required to

inform clinical information for the economic evaluation. The main information required to help populate the cost-effectiveness model was the treatments taken by each patient, and the health state or disease state of each subject over three years. For the purposes of the economic evaluation, health state refers to whether the subject was in a state of active disease (experiencing a disease flare-up), or remission. The health state at diagnosis, and at regular intervals over a three-year period needed to be determined, particularly since CD is characterized by periods of active disease and periods of clinical remission. In parallel to determining the health states of an individual, the medication or treatments and dose that the individual has been prescribed needed to be determined.

Since the RISK-PROKIIDS data, analyzed retrospectively, was being used as the primary data source to inform the transition probabilities in the cost-effectiveness model, a propensity score analysis was conducted to determine the propensity of an individual to be assigned to the "treatment" group or the "standard care" group. The propensity score analysis would result in creating relatively equivalent comparator groups that should minimize any potential selection bias in assigning treatment that may have occurred in the RISK-PROKIIKDS study. To assign a propensity score to an individual, covariates that may influence the tendency to assign an individual to a particular treatment group must be built into the propensity score regression equation. These covariates, such as age, sex, and disease severity, etc., and assessed at the time of diagnosis also needed to be extracted from the RISK-PROKIIDS data. Details about the covariates are outlined below.

2.2.1.1 Inclusion Criteria

The RISK-PROKIIDS data set contained 1136 subjects with Crohn's disease. The criteria listed in Table 2.2.1.1-1 were used to include subjects for the economic evaluation. Based on the inclusion criteria, 573 subjects were included in a data set that was then used to extract patient characteristics at diagnosis, health state information over three years and treatment information.

Table 2.2.1.1-1. Inclusion Criteria for Crohn's Disease Subjects from RISK-PROKIIDS Data Set.

Inclusion Criteria for CD Subjects
• Subjects who had a confirmed CD diagnosis • Subjects who had a minimum three year follow-up from the date of diagnosis • Subjects that had determinable health state information at 6, 12, 18, 24, and 30 or 36 months from the date of diagnosis

Out of the original 1136 RISK-PROKIIDS subjects, subjects that did not meet the inclusion criteria listed in Table 2.2.1.1-1 were excluded from further analysis. Determining whether an individual was in an active disease health state or a remission health state was based on the presence of a Physician Global Assessment (PGA) of health or the availability of parameters to calculate a score on the weighted Pediatric Crohn's Disease Activity Index. The PGA uses the following scores assigned by the physician upon examination to describe disease activity: 1=none, 2=mild, 3=moderate, 4=severe. For the purposes of this study, the score of 1 (none) was considered equivalent to the remission health state while the other scores were considered as having active disease. The weighted Pediatric Crohn's Disease Activity Index (wPCDAI) score is calculated based on a composite assessment of patient functioning, abdominal pain, stool description and frequency, lab albumin and erythrocyte sedimentation rate values, weight, the presence of peri-rectal disease and the presence of extra-intestinal manifestations (Turner et al., 2012). The wPCDAI assessment is described further below. As health state information at various time points was crucial for the cost-effectiveness analysis, if the RISK-PROKIIDS data was missing too much data to assess a subject's health state, the subject was excluded from the analysis. In several instances missing values in one or two variables did not prohibit the assessment of an active disease or remission health state and therefore these subjects were left in the study. The number of subjects that met each inclusion criterion in Table 2.2.1.1-1, are shown in Appendix 4. A total of 573 subjects were isolated from the RISK-PROKIIDS study to

include for further analysis. The data from a small number of subjects still contained a small amount missing data, but imputation of the missing allowed inclusion of those subjects in the analysis. The handling and imputation of missing data are described in sections below.

2.2.2 Data Extraction and Patient Characteristics from the RISK-PROKIIDS Study

The following subsections describe the information extracted from the RISK-PROKIIDS data to compile an unadjusted raw data set of pertinent variables and fitting within certain inclusion parameters that were used to ultimately inform the cost-effectiveness model. The four types of data required to be extracted from the RISK-PROKIIDS study are:

- data to inform when patient information was collected such as patient visits over three years
- data about a subject's health status or health state over time
- data about treatments received over time
- data with respect to patient characteristics at diagnosis to describe the patient population and serve as covariates in the propensity score model

The next subsections describe the data extraction within these categories from the RISK-PROKIIDS study.

2.2.2.1 Assigning Visit Dates

To track disease and treatment course over three years since diagnosis, the dates that patient information was collected needed to be extracted and assigned to comparable time intervals for each patient. As RISK-PROKIIDS was an observational study, visit dates were not at regular intervals. In addition, complete data were not available for each visit and were considered missing at random. Visits ranged from one follow-up visit to twelve follow-up visits over a period of four years. The number of weeks elapsed since diagnosis was used to assign a visit time point to each visit according to Table 2.2.2.1-1. Time points were assigned every 6 months

("semester") until 48 months. The weeks included in each time point were the assigned time point ± 3 months. In instances where there was more than one study visit per 6-month interval, only the data from the visit closest to the actual six month interval was retained. Where two visits were relatively equidistant from the midpoint of the semester, the information from the later visit was kept as representative of that semester's visit.

Table 2.2.2.1-1. Visit Time Point Assignment and Corresponding Weeks in the RISK-PROKIIDS Study.

Range of Weeks Since Diagnosis	Visit Time Point Assignment
13-38	6 months
39-64	12 months
65-90	18 months
91-116	24 months
117-142	30 months
143-168	36 months
169-194	42 months
195-220	48 months

2.2.2.2 Determining Patient Health State

The health state (active disease or remission) for each visit time point was based primarily on the weighted Pediatric Crohn's Disease Activity Index (wPCDAI) score (Turner et al., 2012) . However if wPCDAI parameters were inconclusive to determine whether a subject had active disease, or was in remission, but Physician Global Assessment (PGA) values were available then the PGA could be used as a surrogate for the wPCDAI to make a determination for the health state. Similarly, if PGA values were not available then wPCDAI parameters could be used to make a determination about the health state of the individual. As mentioned above, wPCDAI is a multi-parameter score assessed by the clinician by examining the patient, patient responses and clinical chemistry results. The PGA is a numerical score describing disease activity assigned by the examining physician and based on physical examination. To assess whether the PGA

could be used as surrogate for the wPCDAI in determining health state, a Spearmann's correlation analysis was conducted. The wPCDAI scoring methods and the number of patients which had their health state assessed via the PGA are described below.

2.2.2.2.1 The Weighted Pediatric Crohn's Disease Activity Index and the Physician Global Assessment

The weighted Pediatric Crohn's Disease Activity Index (wPCDAI) score was used to determine the health state of the subjects at each time point where possible (Turner et al., 2012). The scoring system is shown in Table 2.2.2.2.1-1.

Six fields were used to describe perirectal disease: 1) drainage, 2) active fistula, 3) indolent fistula, 4) fissure, 5) inflamed tags, and 6) asymptomatic tags. Where there were missing values in any of these perirectal disease parameters, an assumed perirectal score was assigned according to the convention listed in Appendix 5.

Scores from each individual wPCDAI parameter were added to produce a wPCDAI score. For the purposes of the health state assessment, individuals with scores < 12.5 were considered as in "remission" while subjects with scores >12.5 were considered as having "active" disease.

Several subjects had missing values within each wPCDAI parameter at various time points so a complete wPCDAI score could not be calculated precisely. Appendix 4 lists the number of subjects out of the 573 at each time point with undeterminable health states. However since the classification of "active disease" comprised all subjects not in remission for the purposes of this study, a precise score reflective of disease severity was not necessary and an active disease state could be inferred if a score of 12.5 on the wPCDAI was already achieved without missing values. Where an "active" or "remission" determination could not be made through the wPCDAI at a time point, the Physician Global Assessment (PGA) of health was used to represent the health state.

The PGA uses the following scores to describe disease activity: 1=none, 2=mild, 3=moderate, 4=severe. For the purposes of this study, the score of 1 (none) was considered equivalent to the

remission health state while the other scores were considered as having active disease. Since the wPCDAI is a more comprehensive determination of health, it was chosen as the primary measure of health state. The PGA is based on the physician's determination of a patient's health and may not necessarily take into account lab values or other test results and therefore was used as the "fallback" assessment of health state. Where a determination of health state could not be made at a particular time point, the previous time point was carried over for one semester (see Appendix 4 for the number of subjects where health states were carried over). No subjects had a health state missing for greater than one consecutive semester and therefore a health state only needed to be carried over once. Whether a subject was refractory within the first three months of treatment could not be determined because this state was not captured for the majority of subjects.

Table 2.2.2.2.1-1. The Weighted PCDAI Scoring System.

Parameter	Parameter Description	Parameter Score
Abdominal pain	None (no pain)	0
	Mild, brief, does not interfere with activity	10
	Moderate-to-severe, daily pain, longer lasting, affects activity, nocturnal	20
Patient functioning/ general well-being	No limitation of activity/well	0
	Occasional difficulty maintaining age appropriate activity/subpar	10
	Frequent limitation/very poor	20
Stools (per day)	0 to 1 liquid, no blood	0
	≤2 semi-formed with small blood or 2 to 5 liquid	7.5
	Gross bleeding, ≥6 liquid, or nocturnal diarrhea	15
Erythrocyte Sedimentation Rate ESR (mm/hour)	<20	0
	20–50	7.5
	>50	15
Albumin (g/dL)	≥3.5	0
	3.1–3.4	10
	≤3.0	20
Weight	Gain or voluntary stable/loss=0	0
	Involuntary stable or loss of 1% to 9%	5
	Loss ≥10%	10
Perirectal disease	None/asymptomatic tags=0	0
	1 to 2 indolent fistula/scant drainage, no tenderness	7.5
	Active fistula/drainage/tenderness/abscess	15
Presence of Extra-intestinal manifestations	None (no extra-intestinal manifestations)	0
	≥1 extra-intestinal manifestations (such as fever ≥38.5°C for 3 days in past week, definite arthritis, uveitis, E. nodosum, P. gangrenosum)	10
Total Score: 0 to 125	• <12.5 classified as “remission” • 12.5 to 40 classified as “mild” • >40 classified as “moderate” • >57.5 classified as “severe” **(**A decrease of 17.5 points is taken as evidence of improvement)	

Table 2.2.2.2.1-2. The Number of Subjects at Each Visit Month with Undeterminable Health States.

Visit Month	Number of subjects with health state carried over from previous health state	Number of subjects with undeterminable health state with wPCDAI	Number of subjects with no PGA
0 (at Diagnosis)	Not applicable	16	0
6	0	45	1
12	5	52	5
18	1	49	4
24	47	94	51
30	74	137	80
36	76	146	88

Abbreviations: wPCDAI = weighted Pediatric Crohn's Disease activity index; PGA = Physician Global Assessment

To confirm the use of the PGA as an adequate surrogate for health state determination, the Spearman's correlation between PGA and wPCDAI was determined in the RISK-PROKIIDS CD subjects where both values were obtainable for each patient visit (see Appendix 6). The Spearman's correlation for all visits combined was determined to be 0.702 (where p=< 0.001). Turner et al., 2012 determined a Spearman's correlation between the PGA and wPCDAI to be 0.75 (Turner et al., 2012). The Spearman's correlation determined in this study (0.702) was comparable to the one published by Turner et al., 2012 (0.75) and therefore PGA was used to infer health state when wPCDAI was not available.

2.2.2.3 Treatment Determination

Establishing when and which treatments were taken was needed to determine which subjects were considered as treated with early intervention with anti-TNF-α, which subjects were on corticosteroids, and the cost of treatment. As treatment was at the discretion of the clinician,

each subject could have received a variety of treatments over the course of the study. The start and stop date was recorded in the RISK-PROKIIDS database. The treatments were grouped into the following classes of treatments: biologics, corticosteroids, oral 5-ASA, immunomodulators, antibiotics and enteric nutrition. Concomitant treatments could also have been received. The class of drug received within the first three months of diagnosis was determined for each subject.

In the RISK-PROKIIDS study, while health-related information was recorded based on visits, treatments received were recorded with start and stop dates. Dose was rarely recorded, therefore the RISK-PROKIIDS data was not used as a resource for dose information. Dose information was estimated based on clinical practice guidelines. In the event that a treatment start date was not recorded or indicated that treatment was started before the diagnosis date, it was assumed that the diagnosis date was the start date. In the event that a stop date was not recorded, it was assumed that the treatment continued until the subject's last visit date included in this study and possibly beyond. Each treatment used in the RISK-PROKIIDS study was grouped into its drug class (see Table 2.2.2.3-1). As the primary clinical endpoint in the cost-effectiveness analysis was designated to be time in corticosteroid-free remission, the treatment state of each subject as it related to corticosteroid use and the duration of treatment with corticosteroids were determined for the duration of the study. Specific treatment used and treatment class used per patient were extracted from the RISK-PROKIIDS study.

Table 2.2.2.3-1. Drug Classes and Generic Drug Names That Were Used in the RISK-PROKIIDS Study.

Drug Class	Generic Drug Name
Biologics	Infliximab (anti-TNF-α) Adalimumab (anti-TNF-α) Certolizumab Natalizumab
Oral 5-ASA	Sulfasalazine Mesasalazine Olsalazine
Antibiotics	Metronidazole Ciprofloxacin Rifaxamin
Corticosteroids	MethylPrednisone Hydrocortisone IV Prednisone or Prednisolone Oral Budesonide
Immunomodulators	Azathioprine 6-Mercaptopurine Tacrolimus Cyclosporin Methotrexate (Subcutaneous/Intramuscular) Methotrexate (Oral)
Exclusive Enteral Nutrition	Nutren Junior Vital Junior Pediasure Ensure Modulen Peptamen Enteral Nutrition Other

2.2.2.4 Extracting Patient Characteristics and Covariate Data

Patient characteristics describing the patient population were extracted from the RISK-PROKIIDS study to provide information on the representative pediatric patient population. Patient characteristics at the time of diagnosis were also used to compare the patient characteristics of each treatment arm in an unadjusted and in an adjusted population following propensity score analysis. Some patient characteristics at the time of diagnosis may have influenced the treatment assignment and the tendency to treat a subject with anti-TNF-α as first line therapy. These patient characteristics were considered as covariates in a propensity score model and were also extracted from the RISK-PROKIIDS population. Patient characteristics and covariate variables such as age, sex, etc., that were extracted from the RISK-PROKIIDS study are listed in Table 2.2.2.4-1. Propensity score analysis methods and the covariates used in the propensity score regression model are described in a later section.

The characteristic of height Z score (Htz), or standard deviation score, provides a quantitative measure of how far a child departs from the mean value of height for age, expressed in units of standard deviations (Flegal & Cole, 2013). Change in height Z score, such as in CD patients with diminished growth, may influence treatment selection and was included as a covariate in assessing the propensity to receive early intervention with biologic treatment.

Whether a patient was recruited at a large clinical site or a small clinical site was considered as a possible factor influencing treatment assignment. Twenty-eight clinical sites from across the United States and Canada recruited the subjects in the RISK-PROKIIDS study. The clinical sites and the number of patients recruited per site from the 573 subjects included in this study and as of June 2016 are listed in Appendix 3. Ninety-six out of 573 subjects or 16.8% of subjects came from Canadian sites located in Ottawa, Halifax and Toronto. Since almost all sites claimed to be associated with an academic institution, it was decided to group sites based on the number of patients they enrolled. To simplify the clinical site covariate for the propensity score regression model, a binary variable was created: a site was defined as “large” if 32 or more included subjects were recruited at that site and “small” if otherwise.

Table 2.2.2.4-1. Patient Characteristics Extracted from the RISK-PROKIIDS data.

Patient Characteristic at Diagnosis	Variable Type	Variable used as Covariate in Propensity Score Analysis
Sex	Binary	Yes
Age at Diagnosis	Continuous	Yes
Family History of IBD	Categorical	Yes
Jewish Origin	Categorical	Yes
Hispanic Origin	Categorical	Yes
African Origin	Categorical	Yes
Ethnicity	Categorical	No
Disease Activity at Diagnosis Based on Physician Global Assessment	Categorical	Yes
Disease Location	Categorical	Yes
Presence of Peri-anal disease	Binary	Yes
Height Z score	Continuous	Yes
Albumin Value	Continuous	Yes
Steroid Related Health State at Diagnosis	Categorical	Yes
Recruited at Large Clinical Site (>31 patients)	Binary	Yes

2.2.2.4.1 Summarizing Patient Characteristics

Patient characteristics at diagnosis (listed in Table 2.2.2.4-1) of the 573 RISK-PROKIIDS subjects were compared between unadjusted groups of those who received biologics within the first three months of diagnosis and those that did not. R software v. 3.4.0 (2017-04-21) with the Table One package (v. 0.8.1) was used to create a table of baseline characteristics (Yoshida, Bohn, & Yoshida, 2017). Chi-squared tests, t-tests, and Kruskal-Wallis Rank Sum Test were used for comparisons between groups depending on the nature of the variables (Yoshida et al., 2017).

Once all relevant patient characteristics were extracted from the RISK-PROKIIDS study, an assessment of missing data within these variable fields ensued.

2.3 Handling Missing Data

The RISK-PROKIIDS study contained several fields with missing data. As stated previously, in instances where there was too much missing data for a subject's health state to be ascertained, the subject was excluded. Where missing data prohibited the assessment of health state with the wPCDAI, the PGA acted as a surrogate for health state assessment. Where missing data did not inhibit a health state to be assessed, it was ignored. Where missing data required making assumptions such as in the assignment of peri-rectal scores for calculating the wPCDAI, a scoring scheme was devised to show how judgements were made when scoring was assigned. Where missing data was absent in the RISK-PROKIIDS data such as treatment dose information, clinical practice guidelines were used. A situation where surrogates for missing data could not be used, was if missing values occurred at diagnosis and would be used in further analysis such as propensity score analysis. This situation occurred with missing values for albumin at diagnosis (baseline). The options for handling the missing albumin data were to either exclude these subjects or impute missing values since albumin was a continuous variable and the amount of missing data was small and it appeared that the data was missing at random. Excluding the subjects would have reduced the sample size further. The explanation of the imputation of missing albumin is discussed further below. Loss to follow-up was recorded in the RISK-PROKIIDS study and none of the subjects in the unadjusted data set had any loss to follow-up.

2.3.1 Imputation of Missing Albumin Data

Among the 573 eligible subjects included in the unadjusted data set, 64 subjects had missing values for albumin at diagnosis (baseline, Visit 0). Seven of 131 (5.3%) of subjects with missing baseline albumin values had early intervention with biologics (treated group) and 57/442 (12.9%) did not receive early intervention (control group). Imputation is suggested when missing values are less than ten percent of the total values and that missing values are

considered missing at random (Bennett, 2001). In this case, it was assumed that data were missing at random and therefore imputation of the missing values was conducted. To confirm that albumin data were missing at random, the equality of covariances in groups with identical missing patterns was tested and to determine whether the data were missing completely at random (MissMech R package v.1.0.2), (Jamshidian, Jalal, & Jansen, 2014). The test concluded that normality in the data was rejected at the 0.05 significance level and non-parametric testing concluded that there was not sufficient evidence to reject that the data was missing completely at random at the 0.05 significance level. Hence it was assumed that the data were missing at random.

Multivariate imputation by chained equations (MICE) was conducted using the MICE R package v. 2.25, 2015 (Buuren & Groothuis-Oudshoorn, 2011). MICE imputation operates under the assumption that data are missing at random (Schafer & Graham, 2002). In the MICE procedure a series of regression models were run such that each variable with missing data was modeled according to other variables in the data (Azur, Stuart, Frangakis, & Leaf, 2011) and it is suggested that ten cycles or iterations are sufficient (Buuren & Groothuis-Oudshoorn, 2011; Raghunathan, Solenberger, & Van Hoewyk, 2002). The "mice" function was used to conduct the imputations. The predictive mean matching method was specified as the method for imputation as the data to impute was numerical and it is recommended to be a good overall imputation method (Buuren & Groothuis-Oudshoorn, 2011). Ten iteration cycles were specified and ten imputations were specified to reduce simulation error. The seed was arbitrarily set to 1. Strip plots were prepared to show the distribution of the imputed values among the observed values in each of the ten datasets. A density plot of each imputed dataset was plotted for albumin. The density plots showed the albumin distribution for each dataset plotted against the original dataset with missing values. Each of the ten imputed datasets was extracted using the "complete" function in the MICE R package. Once the datasets were extracted each data set could be used individually or merged in further analysis. The next section describes how the data sets were manipulated so that their data could ultimately be used in the cost-effectiveness analysis.

2.3.2 Handling Imputed Data

The steps leading up to the economic evaluation involved preparing a data set with comparable treatment arms to be used to inform transition probabilities to use in the cost-effectiveness analysis. So far unadjusted data was extracted from the RISK-PROKIIDS data, and missing data was imputed creating ten complete datasets each with a different set of imputed values for albumin at baseline. The next step in preparing the unadjusted data was to create an adjusted matched data set with a "treatment" arm and "control" arm of subjects with comparable characteristics similar to a randomized clinical trial. The method to create the comparable adjusted data set for retrospective observational data was propensity score analysis. Propensity score analysis creates an adjusted data set with subjects of similar characteristics having a similar propensity to be assigned to a treatment group or control group. To move forward with the propensity score analysis and subsequent cost-effectiveness analysis, one adjusted data set needed to be created from the ten imputed data sets. The following section explains the rationale in handling the ten imputed sets and the options for choosing one complete data set representative of the RISK-PROKIIDS population.

Mitra and Reiter suggest that propensity score analysis with imputed datasets can be approached in two ways—the "Within" method and the "Across" methods (Mitra & Reiter, 2016) (Pan & Bai, 2015). The "Within" method calculates propensity scores on each imputed dataset separately (Mitra & Reiter, 2016). The "Across" method averages out the propensity score for each subject from each imputed dataset and then uses that averaged propensity score to create a matched population (Mitra & Reiter, 2016). Mitra and Reiter (2016) ran several simulations of treatment assignment regression models comparing both methods and determined that when treatment assignment depends on both a covariate with missing data and a covariate without missing data that the Across method has a slightly smaller bias than the Within method, but that the variance of the Within method is smaller than the Across method. They also established that each method produced slightly different point estimates and suggested that depending on the data, both methods could work equally well to reduce bias or one method may be dominant over the other (Mitra & Reiter, 2016). While it was suggested

that the Across method could produce a greater reduction in bias, there was not a unequivocal recommendation on which method to choose in proceeding with propensity score analysis. Hence, both the Across and Within methods were tested in the following propensity score analysis.

To create one dataset to represent the Across method, the ten imputed albumin values were averaged for each subject with missing albumin values. Since only the albumin covariate had missing values, averaging the albumin values prior to calculating a propensity score was tantamount to averaging the propensity scores for those subjects. The datasets from the imputation process in the R package were exported into MS Excel using the "write.csv" function to calculate the mean albumin values and the dataset with averaged albumin values was then re-imported into R software (using the "read.csv" function) for propensity score analysis. Owing to the ambiguity around choosing between the Across and Within methods, both methods were used in subsequent propensity score analysis. However, since the Across method produced one data set up front, as opposed to ten, it was chosen as the primary method to inform probabilities in the cost-effectiveness analysis. Any recommendations between the "Across" and "Within" methods for the purposes of a propensity score analysis followed by a cost-effectiveness analysis have not been documented in the literature.

A secondary goal of this research is to examine the different methods of propensity score analysis for the purposes of refining a data set to inform the transition probabilities in a cost-effectiveness model. The next section describes the methods of propensity score analysis.

2.4 Propensity Score Analysis

Propensity score analysis is an approach to reduce selection bias when comparing treatment groups in studies that were not conducted as randomized controlled trials. Since the RISK-PROKIIDS study is an observational study, being analyzed retrospectively in which treatment was up to the clinicians and not according to a set protocol, propensity score analysis was conducted to create comparators for the economic evaluation. The propensity score is the conditional probability of a study participant receiving treatment given observed covariates and

as such is a balancing score representing a vector of covariates (Guo & Fraser, 2014; Rosenbaum & Rubin, 1983). A logistic regression was conducted with the dependent variable being the log odds of receiving treatment. To optimize propensity score analysis, various types of propensity score analysis approaches and subsequent balance diagnostics on the covariates of the propensity score model were conducted in R (v. 3.4.0).

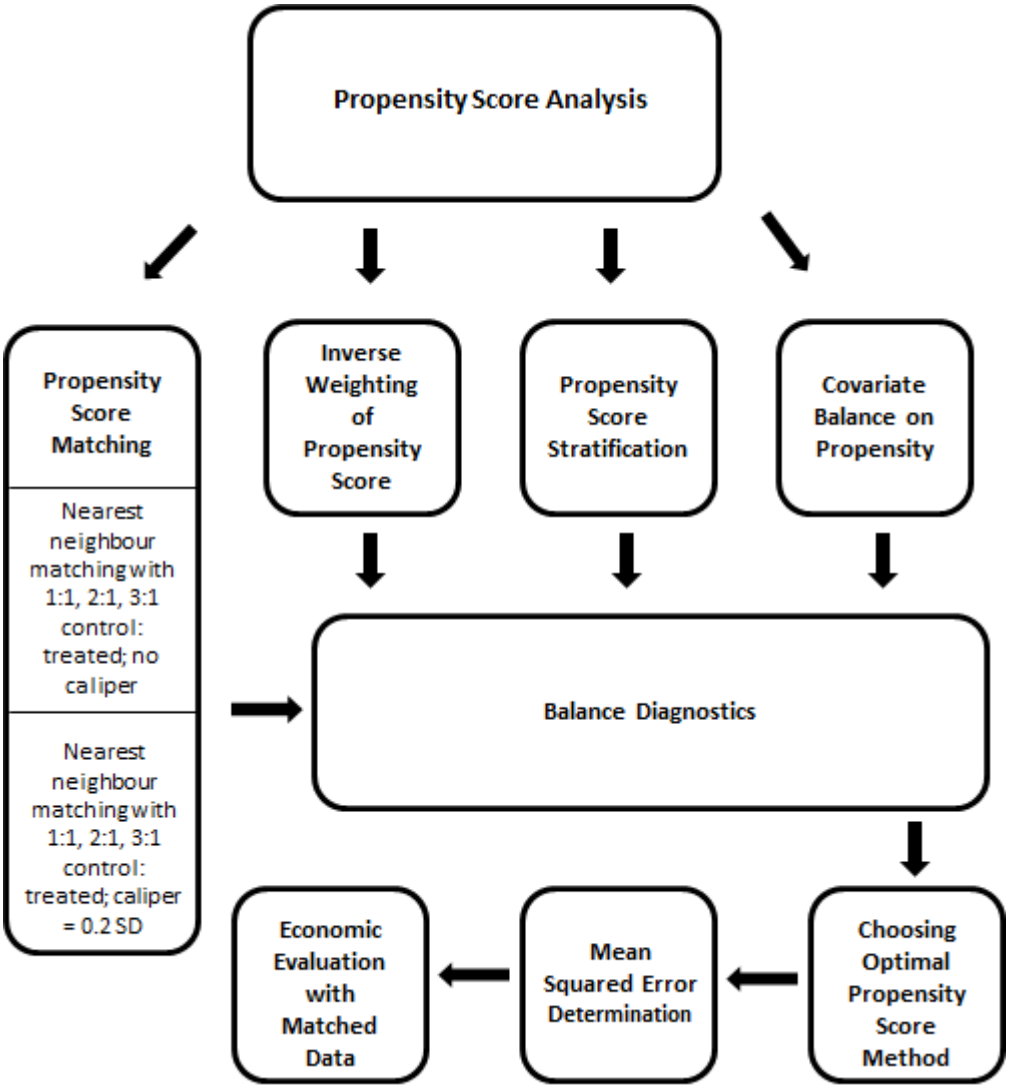
Regardless of approach, the following covariates were considered relevant for the for propensity score regression model as they may have influenced treatment selection: age at diagnosis, sex, disease activity at diagnosis based on PGA, African heritage, disease location, presence of peri-anal disease, height z-score, steroid-related health state at diagnosis, albumin values, and whether the subject was recruited at a large clinical site (>31 patients). The propensity score regression model was as follows where e(x) is the conditional probability of receiving the early anti-TNF-α treatment.

$$e(x)= \beta_{0+} \beta_{age}X_{age} + \beta_{sex} X_{sex}+ \beta_{\text{disease severity at diagnosis(PGA)}} X_{\text{disease severity at diagnosis(PGA)}} + \beta_{\text{African heritage}}X_{\text{African heritage}} + \beta_{\text{disease localization}} X_{\text{disease localization}} + \beta_{\text{presence of peri-anal disease}}X_{\text{presence of peri-anal disease}}+ \beta_{\text{height-zscore}}X_{\text{height-zscore}} + \beta_{\text{Albuminvalues}}X_{\text{Albuminvalues}} + \beta_{\text{steroid-related health state}}X_{\text{steroid-related health state}} + \beta_{\text{clinical site size}}X_{\text{clinical site size}}$$

It was assumed that there were no interactions among the baseline covariates. Four types of propensity score analyses were conducted: propensity score matching, propensity score weighting, stratification (sub-classification), and covariate balance propensity score (CBPS). Each is discussed in greater detail below. Exact matching was also attempted but no exact matches on all covariates could be achieved. Following the propensity score methods, balance diagnostics were used to assess the quality of the propensity score methods in creating balanced data sets. A description of the balance diagnostics follows the descriptions of each propensity score method below.

A summary diagram of the propensity score methods and process is shown in Figure 2.4-1.

Figure 2.4-1. Summary Flow Process of Propensity Score Analysis Methods and Process.



2.4.1 Propensity Score Matching

As stated in the previous section, propensity score analysis was conducted with the single, averaged "Across" dataset, and then with the ten imputed "Within" datasets. Propensity score matching was conducted with each of the ten imputed datasets and with the "Across" averaged dataset of 573 subjects (using the MatchIt R package v. 2.4-22), (Ho, Imai, King, & Stuart, 2011). Each data set had 131 early anti-TNF-α intervention (treated) subjects and 442 step-up (control) subjects. One-to-one exact matching was attempted but the matching failed since the covariates could not be matched exactly to each other. Thus nearest neighbour matching without replacement was used with various control:treatment ratios as specified in Table 2.4.1-1. The propensity score or distance, for all matching methods was calculated using the logit method. In the logit method, the caliper constraint of the matching process specifies the number of standard deviations of the distance measure (propensity score) within which to draw control units. Austin (2009, 2011) determined that matching using a caliper of width of 0.2 of the standard deviation of the logit of the propensity score tended to have superior performance for estimating treatment effects (Austin, 2009, 2011b).

Table 2.4.1-1. Nearest neighbour matching specifications.

Matching Method	Ratio of Control (Step-up strategy) to Treatment (Early intervention with anti-TNFα) subjects	Caliper
Nearest neighbour	1:1	no caliper matching
Nearest neighbour	2:1	no caliper matching
Nearest neighbour	3:1	no caliper matching
Nearest neighbour	1:1	0.2
Nearest neighbour	2:1	0.2
Nearest neighbour	3:1	0.2

2.4.2 Propensity Score Weighting

Propensity score weighting technique was conducted based on the method described by Austin (2011a) using the R Cobalt package version 1.3.1 (Greifer). Propensity score weighting uses the inverse of probability of treatment assignments as a weight in a multivariate outcome analysis (Guo & Fraser, 2014). A logistic regression to generate propensity scores was run within the package. The average treatment effect for the treated was the average effect of treatment on those subjects who ultimately received the treatment (Austin, 2011a). The inverse probability of treatment weights ($w_{i)}$ were defined by:

$w_i = (Z_i/e_i + (1-Z_i/1-e_i)$,

where Z_i was a binary variable indicating whether or not the *i*th subject was treated with early anti-TNF-α, and e_i denotes the propensity score for the *i*th subject.

2.4.3 Propensity Score Analysis with Sub-classification

In this approach, the estimated propensity score was used to stratify subjects into homogenous subclasses, with similar propensity scores. Each subclass consisted of relatively the same number of subjects (Guo & Fraser, 2014). Propensity score analysis with subclassification was conducted with the MatchIt R package v. 2.4-22, 2017-02-22, (Ho et al., 2011) by specifying that four subclasses on the propensity score would be created. Cochran (1968) and later Rosenbaum and Rubin (1983) demonstrated that stratifying on the quintiles of a continuous confounding variable eliminated approximately 90% of the bias due to that variable (Cochran WG, 1968; Rosenbaum & Rubin, 1983). However due to the large number of covariates, four subclasses were chosen to make the calculations less cumbersome computationally.

2.4.4 Covariate Balancing Propensity Score (CBPS) Method

The "CBPS" function in the CBPS R package v. 0.13, 2016-12-27 was used to implement the CBPS method. In this approach the propensity score is estimated such that it maximizes the

resulting covariate balance as well as the prediction of treatment assignment and thus mitigates the potential regression model misspecification (Imai & Ratkovic, 2014) (Fong, Ratkovic, & Imai, 2014).

2.4.5 Balance Diagnostics on the Propensity Score Methods

An appropriate propensity score model achieves balance among the covariates in the control and treated groups. Good balance is achieved when mean standardized differences are below 0.1 and variance ratios are closest to 1 (Austin, 2009). Standardized differences are determined using means and variances from treated and control continuous covariates, and from prevalence for binary covariates (Austin, 2011a). The standardized difference compares the difference in means in units of the pooled standard deviation and as such allows different samples sizes and units to be compared (Austin, 2011a). Covariate balance for each method of propensity score analysis was assessed using the cobalt package v. 1.3.1 in R v. 3.4.0 (Greifer, 2016). A mean standardized difference of 0.1 and a variance ratio of 1.5 were set as thresholds to assess balance for each covariate. The propensity score methods which indicated the greatest degree of balance and included the most covariates with mean standardized differences below 0.1 and variance ratios closest to 1 were chosen as the candidate methods for creating a dataset representative of the RISK-PROKIIDS data set and to inform parameters in the economic evaluation.

2.4.5.1 Propensity Score Analysis Plots

To support the balance determinations and to show balance graphically between covariates in the unadjusted and matched treatment groups, Quantile-quantile plots (Q-Q plots) and jitter plots were created using the MatchIt R package v. 2.4-22, 2017-02-22 (Ho et al., 2011). A Love plot showing balance before and after propensity score analysis was created in the cobalt package v. 1.3.1 in R v. 3.4.0 (Greifer, 2016). Since balance results were similar for the ten imputed databases, the plots were created using an arbitrarily chosen imputed data set (data set 4) as an example.

2.4.6 Choosing an Appropriate Propensity Score Analysis Method and Exporting Matched Datasets

While the CBPS method and the weighting method showed good balance among the covariates, technical limitations with the CBPS R package v. 0.13, 2016-12-27 (Imai & Ratkovic, 2014), and R Cobalt package version 1.3.1 (Greifer) did not facilitate the extraction of the matched data sets.

Both the 2:1 and 3:1 ratio of control to treated subjects nearest neighbour matched data sets with a caliper of (0.2) showed comparable balance among covariates. One to one or two to one control to treated subject ratios are recommended when comparing many to one matching as they tend to reduce mean squared error (MSE) in the treatment effect (Austin, 2010). A 2:1 control to treated ratio nearest neighbour matching method with a caliper of 0.2 was chosen as the preferred propensity score method to create a matched data set to inform the parameters of the economic evaluation.

A common method of determining the treatment effect in a clinical study is to use a regression model with relevant covariates. A reasonably fitted model would have a small mean squared error. To confirm a more predictive model fit, the mean squared error was compared between the 2:1 and 3:1 ratios of control to treated subjects for the nearest neighbour matching method with a caliper of 0.2. The MSE was determined for the treatment effect using the "Across" data sets. The "Across" data set with a 3:1 ratio of control to treated subjects had 293 control subjects and 123 treated subjects. The "Across" data set with a 2:1 ratio of control to treated subjects had 237 control subjects and 123 treated subjects. To determine the MSE on a treatment effect, a logistic regression was performed using the number of steroid-free semesters over three years as the outcome measure when comparing the treatment groups of early intervention with biologics and step-up treatment and relevant covariates. The logistic regression equation was the following:

$$\text{Number of steroid-free semesters} \sim \beta_0 + \beta_{\text{Early biologic intervention}} X_{\text{Early biologic intervention}} + \beta_{\text{age}} X_{\text{age}} + \beta_{\text{sex}} X_{\text{sex}} + \beta_{\text{disease severity at diagnosis(PGA)}} X_{\text{disease severity at diagnosis(PGA)}} + \beta_{\text{African heritage}} X_{\text{African heritage}} + \beta_{\text{disease localization}} X_{\text{disease localization}} + \beta_{\text{presence of peri-anal disease}} X_{\text{presence of peri-anal disease}} +$$

$\beta_{\text{height-zscore}}X_{\text{height-zscore}} + \beta_{\text{Albuminvalues}}X_{\text{Albuminvalues}} + \beta_{\text{steroid-related health state}}X_{\text{steroid-related health state}} + \beta_{\text{clinical site size}}X_{\text{clinical site size}} + \beta_{\text{Immunomodulators within first 3months}}X_{\text{Immunomodulators within first 3months}} + \beta_{\text{5ASA within first 3months}}X_{\text{5ASA within first 3months}} + \beta_{\text{Steroids within first 3months}}X_{\text{Steroids within first 3months}} + \beta_{\text{Antibiotics within first 3months}}X_{\text{Antibiotics within first 3months}} + \beta_{\text{Enteral nutrition within first 3months}}X_{\text{Enteral nutrition within first 3months}}$

The MSE using the matched data set from the 2:1 control to treatment ratio, nearest neighbour matching with a caliper of 0.2 was 2.66. The MSE using the matched data set from the 3:1 control to treatment ratio, nearest neighbour matching with a caliper of 0.2 was 2.77. Therefore, a final data set with a 2:1 control to treatment ratio and a nearest neighbour matching process with a caliper of (0.2) was selected.

The primary goal of this study was to perform an economic evaluation comparing early intervention with anti-TNFα to standard care. Only one data set would be required to inform the parameters for the economic evaluation model. Ten imputed data sets were generated and an eleventh was created using the average of the imputed values. Since the eleventh data set, (the "Across" data set), reflected an average of the ten others, it was used to form the basis of the propensity score analysis and subsequently inform the parameters for the economic evaluation model. Any variations in the economic evaluation that may have arisen as a result of using the other ten imputed datasets (the "Within" approach) were described in a later section as part of a sensitivity analysis examining structural uncertainty. The 2:1 control to treatment ratio nearest neighbour matched data set with a caliper of 0.2 created from the "Across" data set was chosen to inform parameters for the economic evaluation. This matched data set containing 360 total subjects with 237 standard care subjects (control) and 123 early biologic intervention (treatment) subjects was extracted from the R software into an Excel file so that clinical outcomes and transition probabilities between health states could be determined. Prior to data set extraction, baseline patient characteristics and descriptive statistics for this matched data set were determined using the R software v. 3.4.0 (2017-04-21) with the Table One package (v. 0.8.1) (Yoshida et al., 2017). From this point forward, the adjusted, matched data

set of 360 subjects was used as the representative patient population of pediatric Crohn's disease patients. This population of 360 subjects served to inform some health-related transition probabilities in the following cost-effective analysis.

2.5 Cost-effectiveness Analysis

Thus far, all data analysis has served to extract and prepare data so that it, along with information from the scientific literature, can be used to inform inputs in a cost-effectiveness analysis. The primary goal of this research was to perform a cost-effectiveness analysis comparing early intervention with anti-TNF-α in pediatric Crohn's disease patients to standard care. Specifically, the incremental cost per corticosteroid-free weeks in remission for pediatric moderate-to-severe Crohn's disease patients treated with anti-TNF-α within the first three months of diagnosis compared to standard care (which allowed the option of treatment with anti-TNF- α after three months of diagnosis) over three years. The following sections will describe the inputs and parameters for the cost-effectiveness analysis. The target population, comparators, perspectives, clinical outcomes, time horizon, model details, costing details, cost-effectiveness analysis methods and uncertainty analysis will be described in the following sections.

2.5.1 Target Population

The target patient population was newly-diagnosed children, between the ages of 4 to 17 years, with moderate-to-severe Crohn's Disease.

2.5.2 Comparators

The intervention, or investigational treatment group, was defined as receiving anti-TNF-α biologics within the first 3 months of diagnosis (early intervention) with or without other concomitant drugs. The control group was defined as those subjects that did not receive anti-TNF-α biologics within the first 3 months of diagnosis (standard care) but received other classes of treatment. The standard care group could have received biologics after 3 months of diagnosis reflecting a step-up approach to biologic treatment. Currently, there is no standard

definition of “early intervention”, and three months was an arbitrary designation based on the typical time to assess induction of treatment. Alternate definitions of early interventions were not modeled due to a lack of data.

The main anti-TNF-α biologic treatments used in this study are infliximab and adalimumab. The recommended dose of infliximab for pediatric patients (≥ 9 years of age) with moderately to severely active Crohn’s disease is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks (Remicade® product monograph, (Janssen Inc., 2018)). Infliximab is typically indicated for the reduction of signs and symptoms and induction and maintenance of clinical remission in pediatric patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy (corticosteroid and/or aminosalicylate and/or an immunosuppressant). The recommended adalimumab induction dose regimen for pediatric patients with severely active Crohn’s disease and moderately active Crohn’s disease with no response to conventional therapy is 160 mg at Week 0, followed by 80 mg at Week 2 administered by subcutaneous injection. The recommended adalimumab maintenance dose regimen is 20 mg every other week beginning at Week 4 (Humira® product monograph, (Abbvie Corporation, 2018)). The three month time point is approximately the time a response to induction therapy is expected in Crohn’s disease (Siegel, 2010). Other treatments, described previously in the section about treatment determination from the RISK-PROKIIDS study, include corticosteroids, immunomodulators, 5-aminosalicylates, antibiotics, and enteral nutrition which may be used with or without the biologics.

2.5.3 Perspectives

A health care payer and societal payer perspectives were taken for the cost-effectiveness analyses. Specifically, an Ontario public health care system was chosen to represent the health care payer. Due to recent changes in pediatric drug coverage in Ontario, it was assumed that all treatment costs were paid for by the public healthcare payer (Ontario Ministry of Health and Long-Term Care, 2018c). The societal payer perspective includes all public health care sector

costs and caregiver loss of productivity costs. The microsimulation model was run separately for each perspective following adjustment to the appropriate variables.

2.5.4 Clinical Outcomes

Time (measured in weeks) in steroid-free remission was chosen as the primary clinical outcome. The outcome is a composite of two factors—whether the subject was on steroids and their health state. The number of steroid-free remission semesters for each subject during the three years of the study was counted. The greatest number of consecutive steroid-free remission semesters was also assessed for each subject over the 36 months. The number of subjects in steroid-free remission from each intervention arm was assessed at 12, 24 and 36 months. The number of steroid-free remission weeks was determined by the number of weeks in medical remission minus the number of medical remission weeks on steroids.

2.5.5 Time Horizon

While the RISK-PROKIIDS study is an ongoing study that started in 2008 with ongoing follow-up beyond three years, there are a limited number of subjects that had a comprehensive three year follow-up period that received anti-TNF-α treatments. The RISK-PROKIIDS study had only a limited number of subjects that experienced an early anti-TNF-α treatment regime, particularly since it is considered "off-label" use, and each of those subjects had a limited amount of follow-up time to inform the cost-effectiveness analysis. A time horizon longer than three years would have introduced increased uncertainty in the model and would have to be based on studies with non-naïve pediatric and adult CD studies with limited long-term follow-up. Therefore, the time horizon for the cost-effectiveness analysis (CEA) was three years.

2.5.6 The Crohn's Disease Cost-effectiveness Model

Crohn's disease is a chronic disease characterized by recurring periods of active disease flare-ups and relatively asymptomatic times of remission (Crohn's and Colitis Foundation of Canada, 2012). Once diagnosed, patients with moderate-to-severe Crohn's disease are prescribed medication whether they are in a state of active disease or in remission. Treatment regimens

are tailored according to the disease state and are designed to induce a response to treatment and remission when in active phase (the induction phase of treatment), and stave off relapse when in remission and once symptoms have subsided (the maintenance phase of treatment) (F. Ruemmele et al., 2014), (Petar Mamula, Markowitz, Baldassano, Grossman, & Kelsen, 2008). A subject may enter the maintenance phase of drug treatment with active disease if they have completed the treatment course of the induction phase but have some symptoms remaining that still need to be resolved. Some Crohn's disease patients require hospitalization or surgery when experiencing bouts of severe disease and some, on rare occasions can experience serious adverse events during treatment. Hence, an appropriate cost-effectiveness model of Crohn's disease was needed to take into account the various health states, events, outcomes and costs of pediatric CD patients. A health state transition (Markov) model was created to model the possible health states experienced by CD patients and is described below.

2.5.6.1 Health State Transition Model

A health state transition (Markov) model was created to model seven health states experienced by Crohn's disease patients: 1) active disease, 2) active disease experiencing adverse events of special interest, 3) active disease requiring surgery or hospitalization, 4) medical remission, 5) surgical remission, 6) surgical complications and 7) death (see Figure 2.5.6.1-1 for the health state transition diagram). The arrows in the diagram indicate the direction of moving from state to state from one cycle to another. Curved arrows indicate remaining in the same state from one cycle to the next.

The health state of "Active Disease" in moderate-to-severe CD was defined as the state of having active disease flare-up with a wPCDAI score of greater than or equal to 12.5 or a Physician Global Assessment score of greater than 1. It was assumed that people started in the state of Active Disease at the beginning of the microsimulation and entered the induction phase of treatment. Within the Active Disease state, a patient received treatment and relevant treatment costs were assigned while in this state. From the Active Disease state, in the next cycle, a person could remain in active disease, or enter the "Medical Remission" state, enter the "Active disease with adverse events" stage, or enter the "Active disease requiring surgery or

hospitalization" state. Costs associated with treatment and medical visits were assigned to the Active Disease health state. Costs associated with the induction phase and maintenance phase of treatment were assigned to the Active Disease phase if a subject exhibited an active disease state symptomatically.

"Medical Remission" was defined as a state remission state with a wPCDAI of 12.5 or less and a PGA of 1. The time spent in the Medical Remission and whether an individual was on corticosteroids while in medical remission informed the primary effectiveness outcome. As CD required maintenance phase treatment, patients in Medical Remission still incurred treatment drug costs and follow-up physician visits. Once in medical remission, a person could remain in medical remission or relapse back into Active Disease. Maintenance phase costs of treatment were assigned to the medical remission state.

From the state of Active Disease a person could experience an Adverse Event of Special Interest. The state of Adverse Events of Special Interest described a state where treatment could result in possible treatment-related events of particular concern such as serious infection, cancer or an antibody reaction. The type of adverse event experienced was tracked within the model. Once the adverse event of special interest was resolved or addressed, the patient returned to the Active Disease state. Costs related to the treatment of these adverse events were assigned to this health state.

As a result of very severe active disease, a patient may require surgery or hospitalization and enter the state of Active Disease requiring Surgery/Hospitalization. Costs associated with the Active Disease requiring Surgery/Hospitalization included hospitalization costs, and surgery costs. Following surgery, a person entered the state of Surgical Remission or Surgical Complications.

Surgical Remission was defined as remission achieved through surgery and not as a result of drug treatment. The state of Surgical Remission had remission phase drug treatment costs assigned to it similar to medical remission, however, time in surgical remission was not included as time in remission for the purposes of calculating the primary outcome. Patients could remain

in surgical remission or relapse into active disease. If a subject entered into Surgical Remission then relapsed into Active Disease and subsequently went into remission from drug treatment, the subject would enter the Medical Remission state and their time in Medical Remission was counted toward the primary outcome.

Following surgery, a person may have experienced post-surgical complications and entered the state of Surgical Complications. Within this health state the cost of treating the surgical complications were assigned. Sepsis was considered the major surgical complication following surgery (Blackburn et al., 2014; J. F. Colombel et al., 2004). Hospitalization and treatment costs associated with sepsis were assigned to this health state. Patients were limited to remain in the surgical complication health state a maximum of four weeks to reflect average treatment time for this health state.

All states eventually went to the Death state as this was the absorbing state. However since CD does not impact pediatric life expectancy, it was not expected that many individuals would end up in the death state during the time horizon of this model (Bitton, Vutcovici, Sewitch, Suissa, & Brassard, 2016; De Ridder et al., 2014)). It was assumed that no costs were associated with the Death state in this model.

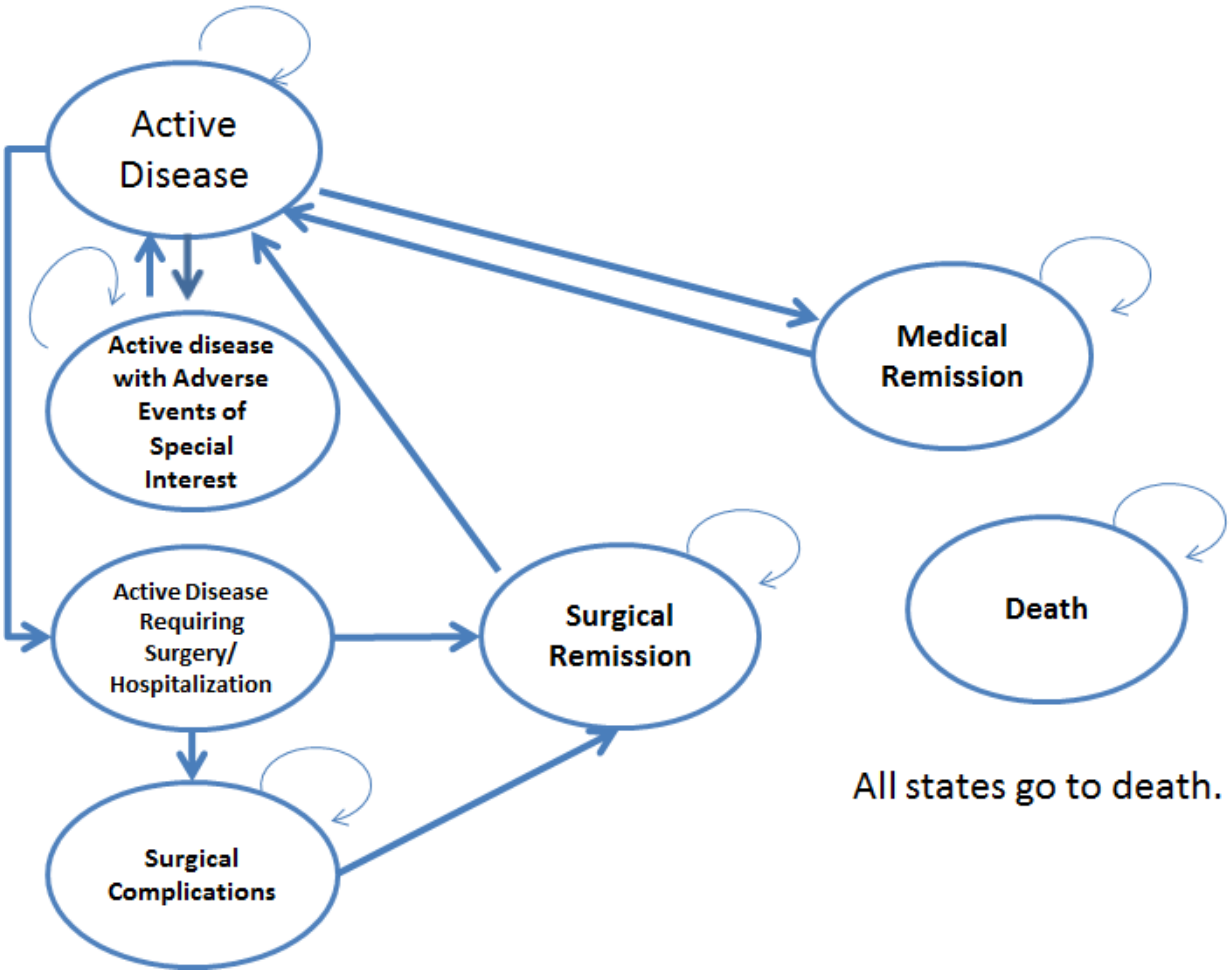
An incremental cost-effectiveness analysis (CEA) was undertaken using individual-level microsimulation in a health state transition (Markov) model. Individual-level microsimulation was chosen to account for the heterogeneity and variation in baseline characteristics and disease progression over time and possible changing risk among the patient population. A model was constructed using TreeAgePro software version 2018 release 1.0 (Williamstown, Massachusetts).

Within the seven health states described above, certain features of Crohn's disease treatment were modelled to provide a comprehensive view of the possible disease pathways experienced by children with CD. A more comprehensive pathway of the Crohn's disease model from one health state to the others (health states are shown at either end) is shown in Figure 2.5.6.1-2. The induction phase of treatment, which has a more aggressive treatment regimen, the

maintenance phase of treatment, which has a lower dose and/or frequency of medication, possible adverse events, and the possible change in treatment or step-up to biologic treatment are all modelled. Where the events lie within the Markov TreeAge Model are shown in Figure 2.5.6.1-2.

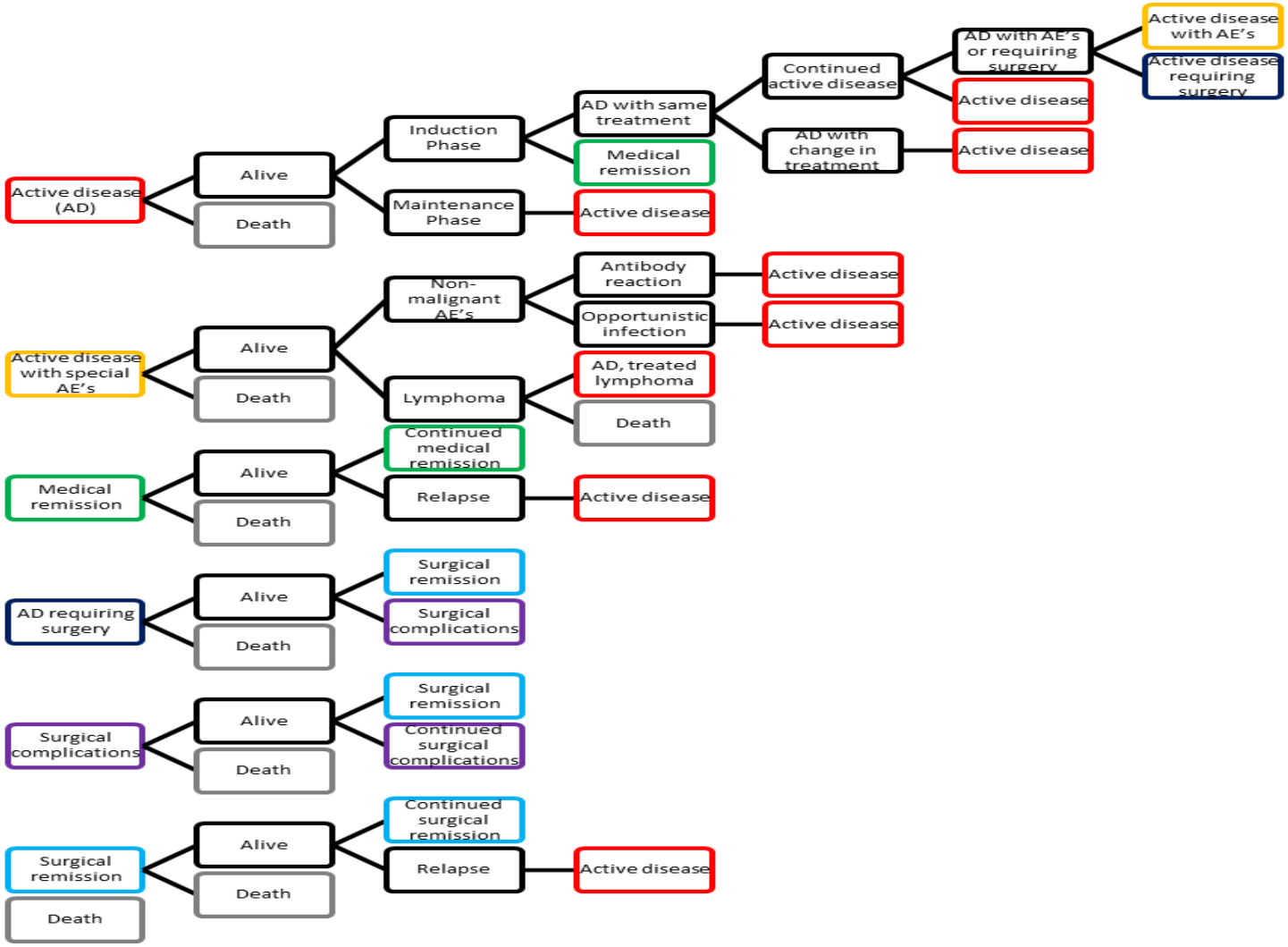
Ten thousand individual-level (one dimensional) Monte Carlo microsimulations were conducted to reflect the increasing incidence and prevalence of the Canadian pediatric CD patient population and to reflect the CADTH guidelines which recommend a minimum of 5000 simulations (Benchimol et al., 2017; Canadian Agency for Drugs and Technologies in Health (CADTH), 2017). A probabilistic analysis was undertaken, whereby all distributions were sampled using a two dimensional (2-D) microsimulation which sampled 50 samples of 10,000 individuals. Fifty samples were chosen as this was the minimum number of samples which showed a consistent incremental cost-effectiveness ratio (ICER). Individual-level microsimulation also allows the use of tracker variables in the TreeAge software to assign treatments in sequence (i.e. create memory). The tracker variables were used to keep track of time in remission, if surgery, death or relapse occurred, and treatment switches. Individuals were run through the model in a serial fashion.

Figure 2.5.6.1-1 The Health State Transition Diagram for Crohn's Disease.



Health states are shown in the ovals. Arrows show the direction of moving from one health state to another. The curved arrows indicate remaining in the same health state from one cycle to the next.

Figure 2.5.6.1-2. Pathways From Each Health State in the Crohn's Disease Cost-Effectiveness Model.



Colours indicate the different health states. Abbreviations: AD= Active disease, AE= active disease with adverse events of special interest

2.5.6.2 Cycle Length

Best practices guidelines suggest that cycle lengths should be short enough that an event occurs at most once per cycle, and short enough to represent the frequency of clinical events and interventions (Siebert et al., 2012). The surgery/hospitalization state averages a few days before transitioning to another health state and thus represents the shortest health state. The transition between active disease and remission may also be short (based on expert opinion discussion with Dr. A. Griffiths and Dr. T. Walters). A one week cycle length was chosen for the cost-effectiveness analysis to reflect the shortest possible time for transitioning between health states. (Siebert et al., 2012) Health states in the RISK-PROKIIDS were only recorded at approximately six month intervals so transition probabilities were adjusted for the one week cycle length (Siebert et al., 2012). The equations used to convert six month probabilities to weekly probabilities are shown in Appendix 7.

2.5.6.3 Transition Probabilities

Transition probabilities were determined using data from the representative propensity matched data set by counting the number of subjects in a comparator group undergoing a particular health transition. Health states were observed at six-month intervals. Transition probabilities were converted to rates and then weekly probabilities to accommodate the chosen one-week cycle length. The following parameters were informed by the representative propensity score matched data set from the RISK-PROKIIDS study:

- the probability of transitioning from active disease to medical remission
- the probability of transitioning from active disease to active disease requiring surgery or hospitalization
- the probability of continued medical remission
- the probability of transitioning from surgical remission to active disease

Complementary probabilities such as the probability of remaining in surgical remission were calculated automatically by the Tree Age 2018 v.1.0 decision modelling software as all branches in the cost-effectiveness model were binary (Figure 2.5.6.1-2). It was assumed that following surgery that an individual automatically transitioned into surgical remission until the possibility of surgical complications or relapse into active disease. It was also assumed that all subjects started in the active disease phase when entering the Markov model. All other transition probabilities were extracted from relevant literature. Adverse event occurrence was not captured in the RISK-PROKIIDS study and therefore the probability of adverse events occurring was derived from the literature. Transition probabilities are listed in Tables 2.5.6.3-1 and Table 2.5.6.3-2. Where standard deviations or standard errors could not be determined, a 20% standard deviation was used for probabilities. The changing probability of switching treatment to an anti-TNF-α treatment from week to week during the course of the three year time horizon was based on the RISK-PROKIIDS study, was assigned a fixed distribution, and is shown in Appendix 8. Distributions for the probability of taking a particular medication or being in a health state were sampled every cycle. The probability of death on anti-TNF-α or other treatments was assumed to be the same as the probability of death from all causes since there was not definite evidence to suggest otherwise for pediatric CD subjects (Bitton et al., 2016; De Ridder et al., 2014).

Table 2.5.6.3-1. Transition Probabilities for Health State Transitions Based on the RISK-PROKIIDS Study.

Event	Comparator	Probability 0-6 months (SE)	Probability 6-12 months (SE)	Probability 12-18 months (SE)	Probability 18-24 months (SE)	Probability 24-30 months (SE)	Probability 30-36 months (SE)	Distribution
Active Disease to Medical Remission	Early anti-TNF-α intervention	0.553	0.396	0.500	0.400	0.355	0.529	Beta
		(0.003)	(0.004)	(0.005)	(0.006)	(0.007)	(0.007)	
	Standard Care (Step-up)	0.515	0.452	0.495	0.526	0.467	0.507	Beta
		(0.001)	(0.002)	(0.002)	(0.003)	(0.003)	(0.004)	
Continued Medical Remission	Early anti-TNF-α intervention	N/A	0.794	0.747	0.899	0.828	0.843	Beta
		N/A	(0.002)	(0.002)	(0.001)	(0.002)	(0.002)	
	Standard Care (Step-up)	N/A	0.680	0.644	0.781	0.835	0.850	Beta
		N/A	(0.002)	(0.002)	(0.001)	(0.001)	(0.001)	

Table 2.5.6.3-2. Transition Probabilities Used in the Cost-Effective Analysis.

Event	Probability	SD	Time	Distribution	Source
Active Disease to Active Disease Requiring Surgery or Hospitalization (Early anti-TNFα)	0.046	1.290E-04	3 years	Beta	RISK-PROKIIDS
Active Disease to Active Disease Requiring Surgery or Hospitalization (Standard Care)	0.030	3.520E-05	3 years	Beta	RISK-PROKIIDS
Surgical Remission to Active Disease (Early anti-TNFα)	5.259E-04	7.543E-04	3 years	Beta	RISK-PROKIIDS
Surgical Remission to Active Disease (Standard Care)	2.987E-04	3.537E-04	3 years	Beta	RISK-PROKIIDS
Serious infection on corticosteroid	0.070	1.408E-02 (20% of mean)	1 year	Beta	(Dulai, Thompson, Blunt, Dubinsky, & Siegel, 2014)
Serious infection on immunomodulator	0.033	6.550E-03 (20% of mean)	1 year	Beta	(Dulai et al., 2014)
Serious infection on anti-TNFα	0.032	6.39551E-03 (20% of mean)	1 year	Beta	(Dulai et al., 2014)
Lymphoma on anti-TNFα	2.100E-04	4.199 E-05 (20% of mean)	1 year	Beta	(Dulai et al., 2014)
Lymphoma on immunomodulator	0.00045	8.998 E-05 (20% of mean)	1 year	Beta	(Dulai et al., 2014)
Antibody reaction on infliximab	3.620E-04	8.114E-04	1 week	Beta	(Jeffrey Hyams et al., 2011)
Surgical complications	0.058	2.444E-03	1 week	Beta	(Leonor, Jacobson, Pinsk, Webber, & Lemberg, 2007)
Death from lymphoma (female)	5.300E-05	1.060E-05 (20% of mean)	1 year	Beta	(Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017)
Death from lymphoma (male)	8.400E-05	1.680E-05 (20% of mean)	1 year	Beta	(Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017)
Death	See Age-specific all-cause mortality table in Appendix 9			Fixed	(Canadian Human Mortality Database. Department of Demography Université de Montréal (Canada), 2014)

2.5.6.4 Discount Rate

A 1.5% base case discount rate was chosen to reflect guidelines released by CADTH (Canadian Agency for Drugs and Technologies in Health (CADTH), 2017).

2.5.7 Costing

The cost-effectiveness analysis assessed costs and resource use in the management of pediatric CD. From a health care public payer perspective, costing measured direct costs and resource use for items associated with two broad categories: (i) treatment costs including medications and medical visits, and (ii) treatment of drug and disease-related adverse events and complications. From a societal perspective, in addition to all costs assigned to the health care public payer perspective, such as treatment costs, costs related to caregiver productivity losses were included. Standard methods for economic evaluation were followed (Canadian Agency for Drugs and Technologies in Health (CADTH), 2017; Drummond et al., 2005). All treatment prices, service fees and procedural costs were based on 2017 prices and costs and if necessary, and unless otherwise specified, costs were adjusted to 2017 Canadian dollars using the Canadian Consumer Price Index for health and personal care (Statistics Canada, 2015). The treatment patterns of the RISK-PROKIIDS population informed the cost of treatment over time for each comparator group and the probability of changing treatments. Due to the chronic nature of CD, patients required treatment and medical services in active and remission phases of disease albeit to different degrees. Hence, CD patients incurred costs in all health states except for Death. Costs associated with the CD health states are outlined in Table 2.5.7-1. Details about the costing of each cost category are specified in the following subsections.

Table 2.5.7-1. Costs Associated with Crohn's Disease Health States.

Cost	Associated Health State(s)
treatment drug costs, medical visits, related caregiver loss of productivity costs	Active Disease, Medical Remission, Surgical remission
surgery, non-surgical hospitalization, hospitalization stays, related caregiver loss of productivity costs	Active Disease requiring Surgery/Hospitalization
treatment drug costs, medical visits, related caregiver loss of productivity costs	Surgical Remission
cost of surgical complications such as sepsis treatment in hospital, related caregiver loss of productivity costs	Surgical Complications
cost of adverse events of special interests such as the treatment of opportunistic infections, treatment of lymphoma, and related caregiver loss of productivity costs	Adverse Events of Special Interest

2.5.7.1 Direct Costs

Direct costs included treatment costs such as drug costs, drug administration services, and costs of medical procedures and services. All direct costs were assigned to the healthcare public payer perspective. Direct costs are specified in the following subsections. The determination of the cost for each treatment drug class, based on 2017 Ontario drug formulary prices, are outlined below. Both comparator groups received the same classes of drugs, but at varying times during the course of the three-year study. The costs of medical procedures and the costs of complications such as serious adverse events and surgery-related complications are also detailed below.

2.5.7.1.1 Costs of Treatments

The RISK-PROKIIDS "Across" data set of 360 subjects was used as a representative pediatric CD population. The RISK-PROKIIDS study treatments were considered as representative of the distribution of clinically relevant drug treatment classes for the cost-effectiveness analysis. These classes included biologic treatments (such as anti-TNF-α treatments), corticosteroids, immunomodulators, 5-aminosalicylates (5-ASA's), antibiotics, and enteral nutrition. Treatments were dynamic and often included concomitant medications, which changed over time for each subject. The start and stop dates of treatments were included in the RISK-PROKIIDS data for the

three-year follow-up period. In instances where a stop date of treatment was not recorded it was assumed that the treatment continued until at least the end of the follow-up period. Within each class of treatment several possible drugs could have been prescribed to an individual. The proportion of subjects on each drug within a class during the course of three years for each comparator group is detailed in Appendix 10. The proportions of subjects in each drug class per week over a three-year period were used to calculate the weighted average utilization per drug class per week for each comparator group. The six month mean of the weighted average utilization per week per drug class was used in the cost-effectiveness model to inform drug treatment costs.

Doses were calculated based on weight or body surface area depending on the drug. Weight fluctuations were not captured throughout the three years for RISK-PROKIIDS subjects so standard growth charts were used to estimate mean sex specific and age-related weights (Kuczmarski et al., 2000). Similarly, body surface area estimates were estimated using the same growth charts. These growth charts were also referenced by the Sick Kids Guidelines for caloric energy requirements for enteral nutrition (Aquilina et al., 2007). Where doses were based on weight, costs were calculated in one kilogram intervals. The proportion of subjects that switched to an anti-TNF-α treatment informed the probability of treatment escalation to a biologic (see Appendix 10). Doses were rarely recorded in the RISK-PROKIIDS dataset, therefore dosing according to standard clinical practice was used in cost estimates (see Table 2.5.7.1.1-1, Table 2.5.7.1.1-2, Table 2.5.7.1.1-3, Table 2.5.7.1.1-4, Table 2.5.7.1.1-5, and Table 2.5.7.1.1-6 for recommended clinical practice dosing references for each drug class). Doses that were recorded in the RISK-PROKIIDS data reflected standard doses. If a dose range was recommended, the largest dose in the range was used to calculate the dose. The number of tablets required to fill that dose were calculated and costed for each weight.

In the CEA model, the probability of drug treatment in each cycle was calculated based on the binary condition of being on particular drug class during each cycle over the course of three years based on the RISK-PROKIIDS study data.

Costs for each medication class were calculated by multiplying the dosage regimen by a unit price. Unit prices were obtained from the Ontario Drug Formulary on a per tablet basis and a per vial basis for intravenous medications. For immunomodulators, corticosteroids, antibiotics, 5-aminosalicylates, and enteral nutrition products, within each class of drug, the price of each class of drug was calculated as the weighted average price of each drug within that class. Details are described in the subsections describing the costs of each drug class.

The total cost of drug treatment per cycle was based on the following formula:

Where CS = corticosteroids, IM = immunomodulators, Anti = antibiotics, 5-ASA = Oral 5-ASA, EN = enteral nutrition, IFX = infliximab, ADA = adalimumab, *p* = probability (0 or 1), *c* = cost

$$\Sigma \text{ drug cost}_{ij} = (p\text{CS} \times c\text{CS})_{ij} + (p\text{IM} \times c\text{IM})_{ij} + (p\text{Anti} \times c\text{Anti})_{ij} + (p\text{5-ASA} \times c\text{5-ASA})_{ij} + (p\text{EN} \times c\text{EN})_{ij} + (p\text{IFX} \times c\text{IFX})_{ij} + (p\text{ADA} \times c\text{ADA})_{ij}$$

For the *i*th patient, *j*th week

The proportions of subjects taking each drug class for each comparator group per cycle are shown in the Appendix 10. All treatment costs were assigned a gamma distribution for the probability sensitivity analysis (Drummond et al., 2005). Pharmacy dispensing costs were assumed to be ten dollars per month and were assigned to the health care system. Treatment costs included infusion clinic costs (where applicable) and were assigned to the public healthcare payer.

Cost of Anti-TNF-α Biologics

The biologics used in the RISK-PROKIIDS data set were infliximab and adalimumab. The costs and dose recommendations are shown in Table 2.5.7.1.1-1. A dose escalation or an increase in treatment frequency for biologics was not recorded in the RISK-PROKIDS data set so dose increases were not modelled. If a treatment switch between biologics occurred, it was modelled as a switch from infliximab to adalimumab to reflect switching in the RISK-PROKIIDS

study. A gamma distribution was assigned to biologic costs for the probability sensitivity analysis (Drummond et al., 2005).

Table 2.5.7.1.1-1. Costs and Doses of Anti-TNF-α Treatments.

Drug Class	Drug Generic Name (Brand name)	Dose or Unit	Price per Unit ($CAD)	Dosing Regimen	Price Reference	Dosing Reference	Distribution for Probabilistic Analysis
Biologics (Anti-TNF-α treatment)	Infliximab (Remicade®)	100 mg vial (one-time use vials)	987.56 per 100 mg vial	5 mg/kg infusion at 0, 2, 6 weeks; 5 mg/kg every 8 weeks thereafter	Ontario MOHLTC Exceptional Access Program (Ontario Ministry of Health and Long-Term Care, 2014a)	(Sadowski et al., 2009)	Gamma
	Adalimumab (Humira®)	40 mg syringe (one-time use syringes)	769.97 per 40mg	160 mg subcutaneous injection at week 0, 80 mg at week 2; 40 mg every 2 weeks thereafter	Ontario Drug Benefit e-formulary (Ontario Ministry of Health and Long-Term Care, 2014b)	(Sadowski et al., 2009)	Gamma

The price of infliximab (Remicade®) was obtained through the Ontario Drug Formulary via the Ontario Exceptional Access Program.

$CAD = Canadian dollars.

Cost of Immunomodulators

The immunomodulators used were azathioprine, oral methotrexate, subcutaneous or intramuscular methotrexate, and 6-mercaptopurine. A folate supplement was included in the cost with methotrexate as described in typical clinical practice (Lahad & Weiss, 2015). The cost of immunomodulators was based on the weighted average of the immunomodulators used in the RISK-PROKIIDS study. The weighted average was based on the proportion of subjects on a particular immunomodulator each week during the course of the three-year time horizon which is shown in Appendix 10. Costs of immunomodulators are shown in Table 2.5.7.1.1-2. The weighted average costs per week per subject weight in each comparator group are shown in Appendix 11. A gamma distribution was assigned to the costs for the probabilistic sensitivity analysis (Drummond et al., 2005).

Table 2.5.7.1.1-2. Costs and Doses of Immunomodulators.

Drug Class	Drug Generic Name	Dose or Unit	Price per Unit ($CAD)	Dosing Regimen	Price Reference	Dosing Reference
Immunomodulator	Azathioprine	50 mg tablet	0.2405/50 mg	2-2.5 mg/kg/day (2.5 mg/kg/day used for costing)	(Ontario Ministry of Health and Long-Term Care, 2014b)	(Lahad & Weiss, 2015)
	Methotrexate oral 15mg/m2	2.5 mg tablet	0.6325/2.5 mg	15 mg/m^2/week max. 25 mg		(Lahad & Weiss, 2015)
	Methotrexate SC or IM 15mg/m2	50 mg	8.92/50 mg	15 mg/m^2/week max 25 mg		(Lahad & Weiss, 2015)
	6-mercaptopurine 1.125 mg/kg	50 mg tablet	2.861/50 mg	1-1.5 mg/kg/day (1.5 mg/kg/day used for costing)		(Lahad & Weiss, 2015)
Supplement (prescribed in conjunction with Methotrexate)	Folate supplement	5 mg tablet	0.0259/ 5 mg	5 mg per week		(Lahad & Weiss, 2015)

Abbreviations: SC= subcutaneous; IM= intramuscular; $CAD = Canadian dollars; mg/m^2= milligram per square meter; mg/kg = milligram per kilogram

Cost of Corticosteroids

The corticosteroids used were methylprednisone, hydrocortisone, prednisone (prednisolone), and budesonide. The cost of corticosteroids (CS) was based on the weighted average of the corticosteroids used in the RISK-PROKIIDS study. The weighted average was based on the proportion of subjects on a particular corticosteroid each week during the course of the three-year period which is shown in Appendix 10. Costs and doses of corticosteroids are shown in Table 2.5.7.1.1-3. The weighted average costs per week per subject weight in each comparator group are shown in Appendix 12. A gamma distribution was assigned to the costs for the probabilistic analysis (Drummond et al., 2005).

Table 2.5.7.1.1-3. Costs and Doses of Corticosteroids.

Drug Class	Drug Generic Name	Dose or Unit	Price per Unit ($CAD)	Dosing Regimen	Price Reference	Dosing Reference	Distribution for Probabilistic Analysis
Corticosteroids	Methylprednisone	4 mg tablet	0.457/ 4 mg	2 mg/kg/day, (max 60 mg/day for 4 weeks)	(Ontario Ministry of Health and Long-Term Care, 2014b)	(Uptodate, 2018c)	Gamma
	Hydrocortisone	10 mg tablet or 20 mg tablet	0.3645/ 20 mg 0.202/10 mg tablet	2 mg/kg/day	(Ontario Ministry of Health and Long-Term Care, 2014b)	(Uptodate, 2018a)	Gamma
	Prednisone/Prednisolone	5 mg tablet	0.022/5 mg	1-2 mg/kg/day, max 60 mg/day for 4 weeks (2 mg/kg/day used in costing)	(Ontario Ministry of Health and Long-Term Care, 2014b)	(Lahad & Weiss, 2015)	Gamma
	Budesonide	3 mg tablet	1.90/3mg	9 mg/ day	(Government of British Columbia, 2018)	(Lahad & Weiss, 2015)	Gamma

$CAD = Canadian dollars; mg = milligram; kg = kilogram

Cost of Antibiotics

The antibiotics used in the RISK-PROKIIDS study were ciprofloxacin, rifaxamin, and metronidazole. The cost of antibiotics did not vary substantially over the course of three years so the mean cost per week for the three years was estimated based on assumed subject weight. The proportion of subjects on antibiotics in a particular week was based on the observed proportion of subjects in the RISK-PROKIIDS study. The cost and dose of antibiotics used in the RISK-PROKIIDS study are listed in Table 2.5.7.1.1-4. Antibiotics are not part of the standard treatment for CD but can be prescribed in conjunction with other treatments (Lahad & Weiss, 2015). Antibiotics were prescribed in the RISK-PROKIIDS study and were thus included in the model. The weighted average cost of antibiotics for each comparator group is shown in Appendix 13. A gamma distribution was assigned to the weekly antibiotic costs for the probability sensitivity analysis (Drummond et al., 2005).

Table 2.5.7.1.1-4. Costs and Doses of Antibiotics.

Drug Class	Drug Generic Name	Dose or Unit	Price per Unit ($CAD)	Dosing Regimen	Price Reference	Dosing Reference	Distribution for Probabilistic Analysis
Antibiotics	Ciprofloxacin	250 mg tablet 500 mg tablet 750 mg tablet	0.6186/ 250 mg 0.6979/500 mg 1.278/750 mg tablet	20 mg/kg/day	(Ontario Ministry of Health and Long-Term Care, 2014b)	(Lahad & Weiss, 2015)	Gamma
	Rifaxamin	550 mg tablet	7.76	10-30 mg/kg/day max. 1200 mg/day	(Ontario Ministry of Health and Long-Term Care, 2014b)	(Uptodate, 2018e)	Gamma
	Metronidazole	250 mg	0.0607	10-20 mg/kg/day	(Ontario Ministry of Health and Long-Term Care, 2014b)	(Uptodate, 2018d)	Gamma

$CAD = Canadian dollars; mg = milligram

Cost of 5-aminosalicylates

The 5-aminosalicylates (5-ASA's) used in the RISK-PROKIIDS study were mesalazine, sulfasalazine, and olsalazine. The cost of oral 5-ASA drugs did not vary substantially over the course of three years so the mean cost per week for the three years was estimated based on assumed subject weight. The weighted average of the 5-ASA's used during the course of the study was estimated based on the proportion of subjects on 5-ASA's in a week was based on the observed proportion of subjects in the RISK-PROKIIDS study. The cost and dose of 5-ASA's used in the RISK-PROKIIDS study are listed in Table 2.5.7.1.1-5. 5-ASA's are not part of the standard treatment for CD but since they were prescribed in the RISK-PROKIIDS study and often still prescribed, they were included in the model. The weighted average cost of 5-ASA's for each comparator group is shown in Appendix 14. A gamma distribution was assigned to the 5-ASA costs for the probability sensitivity analysis (Drummond et al., 2005) .

Table 2.5.7.1.1-5. Costs and Doses of Oral 5-ASA Drugs.

Drug Class	Drug Generic Name	Dose or Unit	Price per Unit ($CAD)	Dosing Regimen	Price Reference	Dosing Reference	Distribution for Probabilistic Analysis
5-ASA	Mesalazine	400 mg tablet or 800 mg tablet	0.3951/ 400 mg tablet 1.1124/800 mg tablet	4-6 g/day	(Ontario Ministry of Health and Long-Term Care, 2014b)	(Uptodate, 2018b)	Gamma
	Sulfasalazine	500 mg tablet	0.2816/ 500 mg tablet	50-75 mg/kg/day (75 mg/kg/day used in costing)	(Ontario Ministry of Health and Long-Term Care, 2014b)	(Uptodate, 2018f)	
	Olsalazine	250 mg tablet	0.533/250 mg tablet	30 mg/kg/day	(Ontario Ministry of Health and Long-Term Care, 2014b)	(Escher, Taminiau, Nieuwenhuis, Buller, & Grand, 2003)	

Abbreviations: $CAD= Canadian dollars; g = grams; kg = kilogram; mg = milligram

Cost of Enteral Nutrition

Enteral nutrition (EN) estimates were based on estimated energy requirements reflective of a child's activity level, sex, weight and age as listed in the Guidelines for the Administration of Enteral and Parenteral Nutrition in Paediatrics, published by the Hospital for Sick Children (Aquilina et al., 2007). For the purposes of this analysis, children were assumed to have an overall sedentary activity level due to their moderate-to-severe CD, and it was assumed that one unit (250 mL) of enteral nutrition contained 1kcal/mL The minimum number of EN units and maximum number of EN units were estimated for each sex and for the age ranges of 4-17 years. Several brands of EN were listed in the RISK-PROKIIDS study with varying price ranges as shown in Table 2.5.7.1.1-6. Using the smallest energy requirement and least expensive brand of EN and the largest energy requirement and the most expensive brand of EN, the minimum and maximum possible prices for an EN supplement were calculated. Since actual brands of EN weren't always specified in the RISK-PROKIIDS study, mean costs per week of EN per age and sex were calculated and are listed in Appendix 15. The cost of one enteral feeding pump and associated apparatus was added and assigned a fixed cost of $1066.58 (The Specialty Food Shop, 2017) which was assigned to the health care payer.

Table 2.5.7.1.1-6. Cost and Dose of Enteral Nutrition Brands.

Supplement Name	Dose or Unit	Price per Unit ($CAD)	Dosing Regimen	Price Reference	Dosing Reference	Distribution for Probabilistic Analysis
Nutren	1kcal/ml in 250 ml unit	2.49	Approximately 1000 kcal per day depending on age and weight as per guidelines	(The Specialty Food Shop, 2017)	(Aquilina et al., 2007)	Gamma
Pediasure	1kcal/ml 250 ml unit	3.10		(The Specialty Food Shop, 2017)		
Ensure	1kcal/ml 250 ml unit	2.39		(Ontario Ministry of Health and Long-Term Care, 2014b)		
Modulen	1kcal/ml 250 ml unit	3.24		(Ontario Ministry of Health and Long-Term Care, 2014b)		
Peptamen	1kcal/ml 250 ml unit	9.99		(The Specialty Food Shop, 2017)		
Osmolite	1kcal/ml 250 ml unit	7.75		Ministry of Health and Long-Term Care, 2014b)		
Vivonex	1kcal/ml	10.99		Ministry of Health and Long-Term Care, 2014b)		
Tolerex	1kcal/ml	6.66		Ministry of Health and Long-Term Care, 2014b)		

Abbreviations: $CAD = Canadian dollars

2.5.7.1.2 Cost of Medical Procedures

It was assumed that all CD subjects, regardless of comparator group or disease activity, underwent one tuberculosis (TB) test, one chest x-ray, one colonoscopy and one gastroscopy upon entry into the model. The cost estimates of these procedures are listed in Table 2.5.7.1.2-1. Since it was assumed that all CD subjects entered the model with active disease, it was assumed that they all received an initial gastroenterologist consultation and a subsequent assessment within a month. If they continued with active disease then they would see the gastroenterologist at three months, six months and twelve months. Subjects in remission would see the gastroenterologist every six months. Physician fees were considered fixed based on the Ontario schedule of benefits.

Hospital inpatient procedures including surgeries were costed using the Ontario Case Costing Initiative based on the K50.0, K50.1, K50.8, K50.9 ICD-10 codes for Crohn's disease (Ontario Case Costing Initiative, 2017; World Health Organization, 2010). Surgical resection was the type of surgery listed in the RISK-PROKIIDS study and its associated costs were estimated based on the appropriate procedure code listed in Table 2.5.7.1.2-1. The rates of use for surgery and hospitalization were based on the rates of use in the RISK-PROKIIDS study. The all ages cost was listed since data for pediatric patients only were unavailable as they were too few to report.

Opportunistic infections, lymphoma and antibody development in response to anti-TNF-α treatment were considered possible adverse events of special interest and their costs were associated with that health state as they are of concern for immunocompromised patients or have been a concern for those taking immunomodulators or anti-TNF-α treatments. Sepsis was considered a possible surgical complication. The probabilities and rates of opportunistic infections, lymphoma, antibody development to anti-TNF-α, and sepsis were based on scientific literature rates (see references listed in Table 2.5.7.1.2-2). The treatment for an antibody reaction to infliximab was assumed to be a change in treatment to adalimumab. The costs of treating lymphoma, opportunistic infections and sepsis were based on estimates from the

Ontario Case Costing Initiative using the appropriate case mix groups (CMG) and procedure codes listed in Table 2.5.7.1.2-2.

The cost of infusion clinics was included in the healthcare public payer perspective. This included nursing time for the infusion (170 minutes per infusion), the infusion supply cost and physician services for the attending physician. Clinic costs are listed in Table 2.5.7.1.2-3, and were assigned a gamma distribution for the probability sensitivity analysis. The mean nursing wage used in the labour cost was $48.06 ± 16. 39 per hour in 2017 dollars which had been converted from the 2013 nursing wage using the consumer price index for health care services (Statistics Canada, 2014) (Statistics Canada, 2015). Non-labour infusion supply costs listed in U.S. dollars were converted to current Canadian dollars using a 1.3 currency conversion rate (Schmier et al., 2017). The cost of one infusion is approximately $150 which is approximately 15% of the cost of one vial of infliximab.

Table 2.5.7.1.2-1. Medical Procedure Costs for CD Patients.

Health Resource	Dose or Unit	Cost ($CAD)	SD	Cost Source	Associated Model Health State(s)	Distribution for Probabilistic Analysis
Gastroenterologist Initial consultation	1 visit	165.50	-	(Ontario Ministry of Health and Long-Term Care, 2013)	Upon model entry	Fixed
Gastroenterologist assessment	1 visit	79.85	-	(Ontario Ministry of Health and Long-Term Care, 2013)	Upon model entry	Fixed
Gastroenterologist subsequent visits active disease (3, 6, 9, 12 month)	1 visit	31.00	-	(Ontario Ministry of Health and Long-Term Care, 2013)	Active disease	Fixed
Gastroenterologist subsequent visits (remission, every 6 months)	1 visit	31.00	-	(Ontario Ministry of Health and Long-Term Care, 2013)	Medical Remission Surgical Remission	Fixed
Lab Tuberculosis test (IGRA blood test)	1 test	90.00	-	(Middlesex-London Health Unit, 2016)	Upon model entry	Fixed
Chest X-ray (screening for tuberculosis in hospital ambulatory care)	1 case	162.00	101.00	(Ontario Case Costing Initiative, 2017)	Upon model entry	Gamma
Surgery (surgical resection)	1 procedure	22,889.00	23,751.00	(Ontario Case Costing Initiative, 2017) (procedure 1NK77R for all ages)	Active disease requiring surgery or hospitalization	Gamma
Non-surgical hospitalization	1 stay	8,172.00	7,506.00	(Ontario Case Costing Initiative, 2017) (Case Mix Group 253, 0-17 years)	Active disease requiring surgery or hospitalization	Gamma
Colonoscopy	1 procedure	1,488.00	824.00	(Ontario Case Costing Initiative, 2017)	Upon model entry	Gamma
Gastroscopy	1 procedure	1,823.00	848.00	(Ontario Case Costing Initiative, 2017)	Upon model entry	Gamma

Abbreviations: CAD= Canadian dollars; SD= standard deviation

Table 2.5.7.1.2-2. Costs for Adverse Events of Special Interest and Surgical Complications.

Adverse Event	Cost ($CAD)	SD ($)	Source	Associated Model Health State(s)	Distribution for Probabilistic Analysis
Lymphoma treatment	51,713.00	85,454.00	(Ontario Case Costing Initiative, 2017) (CMG 628,lymphoma. 0-17 years)	Active disease with adverse events of special interest	Gamma
Opportunistic infection treatment	5,174.00	14,414.00	(Ontario Case Costing Initiative, 2017) (CMG's related to tuberculosis, respiratory infections, urinary tract infection and viral infection. 0-17 years)	Active disease with adverse events of special interest	Gamma
Sepsis treatment	14,168.00	29,050.00	(Ontario Case Costing Initiative, 2017) (CMG 653 related to sepsis, 0-17 years)	Surgical complications	Gamma

Abbreviations: CMG= case mix group; $CAD= Canadian dollars

Table 2.5.7.1.2-3. Infusion Clinic Costs.

Infusion Administration Costs	Cost ($CAD $2017)	SD ($CAD)	Source	Distribution for Probabilistic Analysis
Infusion labour (nursing time) (170 minutes per session)	48.06	16.39	(Tetteh & Morris, 2014)	Gamma
Infusion supplies	47.91	-	(Tetteh & Morris, 2014)	Fixed
Physician services (related to the supervision of intravenous administration of biologic agents)	54.25	-	(Ontario Ministry of Health and Long-Term Care, 2013) (fee code G381)	Fixed

Abbreviations: $CAD= Canadian dollars; SD= standard deviation

2.5.7.2 Indirect Costs

Costs from a societal perspective included all health care payer costs described above and costs associated with caregiver time losses (indirect costs). Each medical procedure and physician visit was assumed to take half a day or four hours of caregiver time for pediatric CD patients. A day in hospital was assumed to take a full day or eight hours of caregiver time. The length of stay and assumed loss of hours for caregivers during their children's hospitalization and medical procedures are shown in Table 2.5.7.2-1. The length of stay was based on the listed length of stay for each medical procedure or possible complication based on the corresponding case mix group listed in Table 2.5.7.1.2-1 and Table 2.5.7.1.2-2. The caregiver labour wage was based on the average Canadian labour wage for people between the ages of 24-54 in January 2018 which was listed as $29.04 based on Statistics Canada (Statistics Canada, 2014).

Table 2.5.7.2-1. Caregiver loss of productivity.

CD Procedure	Caregiver Time Assumed for CD Procedure (Hours/day)	Average Length of Stay (Days)	Standard deviation of Length of Stay (Days)	Source
CD related hospitalization	8	8.7	7.2	(Ontario Case Costing Initiative, 2017)
Lymphoma hospital stay	8	18.8	28.8	(Ontario Case Costing Initiative, 2017)
Sepsis	8	6.5	8.6	(Ontario Case Costing Initiative, 2017)
Infection	8	3.1	4.8	(Ontario Case Costing Initiative, 2017)
Doctor Visit	4	0.5	Fixed	Assumption
Infusion Visit	4	0.5	Fixed	Assumption
Chest x-ray	4	0.5	Fixed	Assumption
Gastroscopy	4	0.5	Fixed	Assumption
Colonoscopy	4	0.5	Fixed	Assumption
Tuberculosis test	4	0.5	Fixed	Assumption

Abbreviation: CD= Crohn's Disease

2.5.7.3 Cost Valuation

A vector of costs per child over the three-year study time horizon was determined by multiplying the modeled volume of health care resource use for each item by a corresponding current Canadian dollar price for items that had a fixed price such as medical visits and medical procedures. For health care resources that were health state dependent, such as treatments for adverse events of special interest, costs were sampled per individual from a distribution and added to the costs per child over the three-year period. Individuals entered the model with a sampled age and sex which determined their weight during the course of three year study period. Medication use was determined per week per child based on the probabilities of being on a particular combination of medications in a particular week over the three-year period and the age-related weight of the child. Corresponding medication costs per week were sampled from a distribution where a weighted average price per drug class was calculated or based on a fixed price for anti-TNF-α treatments. The cost per child for medication use per week based on their sampled treatment regimen was summed for the three-year period. All parent/caregiver costs were assigned to the child as the unit of analysis. The mean cost per child was calculated for each group of 10,000 microsimulations in the two-dimensional microsimulation. Costs were assigned a gamma distribution unless they were fixed (Drummond et al., 2005). Distributions for all costs are listed in the tables in previous sections describing each cost. Costs were assigned to major categories (treatments, and direct health care costs). For the health care public payer perspective, all costs were allocated to the health care payer except for caregiver costs. For the societal perspective, health care payer costs were added to caregiver costs. All costs were adjusted to 2017 Canadian dollars using the Canadian Consumer Price Index for health and personal care (Statistics Canada, 2015).

2.5.8 Model Assumptions

To clarify the experience of subjects within the cost-effectiveness model the following assumptions were made regarding the patient population. Treatment paradigms are constantly evolving for CD patients and treatment choices are often up to the discretion of the physician and the patient. The treatment pathways outlined in this model are representative of common

clinical practice for pediatric CD patients either as recommended by clinical practice guidelines, and as observed by the RISK-PROKIIDS study (F. Ruemmele et al., 2014; Rufo et al., 2012). The list of assumptions is as follows:

- It was assumed that all patients were in complete compliance with treatment regimens.
- Due to a lack of indisputable evidence, it was assumed that CD or taking the prescribed medications did not increase the risk of death in the pediatric patients.
- Within medication classes, costs for steroids, immunomodulators, antibiotics, enteral nutrition and 5-ASA's were determined as a weighted average based on RISK-PROKIIDS use of the drugs. It was assumed that the RISK-PROKIIDS study was representative of the most common drugs prescribed to pediatric CD patients.
- It was assumed that colonic resection was the most common form of surgery and that the probability of surgery did not increase within the three-year time horizon regardless of having a previous surgery as observed in the RISK-PROKIIDS data set.
- It was assumed that immediately following surgery, subjects went into surgical remission unless they suffered surgical complications and remained in surgical remission unless they relapsed into active disease.
- It was assumed that post-surgical complications lasted no more than four weeks.
- It was assumed that treating physicians were gastroenterologists for the purposes of billing fees in Ontario.
- It was assumed that biosimilar anti-TNFα treatments were not used as a substitute for infliximab or adalimumab. The cost difference with the use of biosimilars was explored in scenario analyses.
- Since there were only three Canadian sites among the twenty-eight sites in the RISK-PROKIIDS North American study and differences in practice patterns could not be

assessed among the RISK-PROKIIDS subjects, it was assumed that treatment practices between the United States and Canada did not affect the chance of receiving early anti-TNFα treatments.

- Trough level testing of drug levels and thiopurine methyltransferase (TPMT) testing were not included in the model since they are not yet considered standard practice or entrenched in clinical practice guidelines for pediatric CD treatment.

- Administration costs involved in the filling in paperwork and managing subjects on anti-TNF-alpha treatments were not considered.

- Various private health insurer costs were not included due to the variation in individual plans.

- It was assumed that there were no correlations affecting clinical outcomes.

2.5.9 Model Validation and Calibration

The model was internally calibrated using internal outcomes from the RISK-PROKIIDS study due to a lack of external studies available for calibration. The mean number of steroid-free medical remission weeks in three years, the mean number of medical remissions weeks in three years (steroid-free or on steroids), and the number of surgeries in three years from the RISK-PROKIIDS study were used as calibration targets for the cost-effectiveness model. The model outputs were compared to the actual values observed in the RISK-PROKIIDS study to calibrate the model. The model generated similar results as the RISK-PROKIIDS study and did not require adjustments (see Results section for details). As suggested by ISPOR guidelines, a goodness of fit test comparing the number of surgeries in the cost-effectiveness model and the RISK-PROKIIDS population was performed (Eddy et al., 2012). The number of subjects in medical remission at one year from diagnosis served as an external parameter for model validation. The number of remissions in the cost-effectiveness model were validated against another small pediatric observational study which examined the use of infliximab in pediatric CD (Kim, Lee, Lee, Kim, & Choe, 2011). The number of remissions at one year was also compared to an earlier

published study of a portion of the RISK-PROKIIDS subjects examining early intervention with anti-TNFα treatment (Walters et al., 2014). The percent of pediatric Crohn's disease surgeries among CD patients in Ontario in three years (14.7%) which was based on an epidemiological study also served as an external validation target for the model (Eric I Benchimol et al., 2014). Due the scarcity of studies examining early anti-TNFα treatment in naïve pediatric CD subjects, the model could not be validated more extensively. Model performance comparing the model results to external studies were reported in the Results section.

2.5.10 Incremental Cost-effectiveness Analysis

The cost-effectiveness of early intervention with anti-TNF-α versus standard care was examined by determining the incremental cost-effectiveness ratio (ICER). The ICER was calculated to be the difference in cost (ΔC) of the two treatment strategies divided by the difference in outcome (ΔE) as measured by weeks in steroid-free medical remission between the two strategies. In the reference case, the cost and outcomes for each strategy were averaged for 50 samples of 10,000 individual microsimulations. Multiple sampling from each specified distribution was performed for a probabilistic two-dimensional (2-D) microsimulation for the reference case. A 95% confidence interval for the difference in cost and the difference in steroid-free remission weeks was determined. The ICER was determined using the model inputs from the "Across" data set for the reference case. The results of the 2-D microsimulation were presented as incremental cost effectiveness scatter plots. Cost-effectiveness acceptability curves were also presented.

2.5.11 Uncertainty Analysis

Uncertainty analysis was conducted to assess the robustness in the cost-effectiveness model. Parameter uncertainty was defined by uncertainty introduced in model parameter inputs. Parameter uncertainty was assessed through probabilistic analysis. Structural uncertainty referred to uncertainty introduced in constructing the model and model structure. Structural uncertainty in the model was assessed via scenario analysis. Uncertainty in the estimated costs, outcomes and incremental cost-effectiveness ratio for the early anti-TNF-α intervention and

standard care (step-up) treatment strategies was demonstrated with the cost-effectiveness acceptability curves. Details about the types of uncertainty analyses conducted are described below.

2.5.11.1 Structural Uncertainty

Structural uncertainty was introduced in the model in two ways: through uncertainty in estimating the discount rate, and through the different approaches of compiling the imputed RISK-PROKIIDS datasets to determine health state transition probabilities. In the reference case, the RISK-PROKIIDS propensity matched dataset was compiled using the "Across" method which used an averaged propensity scores from ten imputed datasets. This method resulted in certain health state transition probabilities used as inputs in the cost-effectiveness model. However if the "Within" approach had been used to determined matched RISK-PROKIIDS datasets, different transition probabilities may have resulted from the ten imputed datasets thus introducing structural uncertainty in the model. To examine the structural uncertainty in the ICER as a result of using different approaches of dataset assembly, the incremental cost of early anti-TNF-α treatment per additional week in medical remission week compared to standard care was determined. The results, using transition probabilities obtained with the "Across" method of dataset assembly and subsequent propensity score matching, were compared to the results obtained using transition probabilities from the ten "Within" imputed RISK-PROKIIDS datasets. The probability of transitioning from active disease to medical remission, the probability of transitioning from active disease to active disease requiring surgery or hospitalization, the probability of medical remission to continued medical remission, and the probability of transitioning from surgical remission to active disease were determined depending on the probabilities calculated from each of the ten imputed data sets ("Within" data sets) and the aggregate "Across" data set. Weeks in medical remission, irrespective of steroid use were the outcome determined for this uncertainty analysis to simplify the analysis. Eleven ICERs determined and compared, one using transition probabilities for each of the ten "Within" matched datasets and one for the "Across" matched RISK-PROKIIDS dataset.

Uncertainty in the discount rate was assessed in a one-way sensitivity analysis using discount rates of 0% and 3% (as recommended by CADTH guidelines) in the two-dimensional probabilistic analysis for the three year time horizon (Canadian Agency for Drugs and Technologies in Health (CADTH), 2017). The incremental cost of early anti-TNF-α treatment per additional steroid-free remission week compared to the standard care intervention using discount rates of 0% and 3% from a health care public perspective and a societal perspective were determined.

2.5.11.2 Parameter Uncertainty

Parameter uncertainty was introduced through the variation in the characteristics and treatment patterns of the patient population. While certain model parameters were fixed such as prices for drugs and medical services, individual patient characteristics, disease activity and treatment patterns resulted in a large variation in costs and resource use. For example, drug costs within a drug class were calculated based on patient weights, the weighted average of drug prices within that drug class and the proportion of patients on that drug class at a particular time in each comparator group. Parameter uncertainty was ascertained by conducting a probabilistic analysis via a two-dimensional Monte Carlo microsimulation where all variable distributions were varied simultaneously in the model. The probabilistic analysis was run with 50 samples of 10,000 trials in the reference case and in the scenario analyses. Fifty samples were run as this were the minimum number of samples that demonstrated a consistent ICER. Ten thousand individual-level (one dimensional) Monte Carlo microsimulations were conducted to exceed the minimum 5,000 simulations recommended by CADTH guidelines and be representative of the Ontario pediatric population (Benchimol et al., 2017; Canadian Agency for Drugs and Technologies in Health (CADTH), 2017). As this was a cost-effectiveness analysis, and not a cost-utility analysis, it was difficult to estimate a willingness-to-pay threshold for incremental weeks in steroid-free remission since this is unknown. Hence, the effect of the degree of parameter uncertainty on the ICER could not be ascertained.

Cost-effectiveness acceptability curves (CEACs) illustrated uncertainty in the estimated costs, outcomes and incremental cost-effectiveness ratio for the early anti-TNF-α intervention and

standard care (step-up) treatment strategies from healthcare public payer and societal perspectives.

2.5.11.3 Scenario Analysis

The RISK-PROKIIDS study population was the main source for inputs related to treatment patterns in pediatric CD. However, enrollment in the RISK-PROKIIDS study began ten years ago and the dataset may not necessarily reflect the most recent treatment costs and patterns. Since infliximab (Remicade®) was the primary anti-TNF-α treatment used in the RISK-PROKIIDS study, but other versions of anti-TNF-α treatments, such as biosimilars, with different prices have since entered the market, it was hypothesized that the ICER could be sensitive to the price of infliximab and the rate of switching to infliximab in the standard care group. Therefore, scenario analyses were conducted to examine the sensitivity on the ICER to the price of one vial of infliximab and the rate of switching to anti-TNF-α. The price of one vial of infliximab was fixed at $987.56 in the reference case probabilistic analysis. However, costing of infliximab treatment was complex since the number of vials was based on weight (5mg/kg), the cost of infusion administration was added, and the cost of different dosing regimens depended on whether the patient was in the induction phase ("active") or in the maintenance phase of treatment. A one-way sensitivity analysis was conducted by varying the price of infliximab by a multiplier as this was the simplest way of changing the cost of the anti-TNF-α. The effect of varying the price of one vial by 150%, 87.5%, 75%, 62.5%, 50%, 37.5%, and 25% of the reference case ($987.56) was tested. The range of values were chosen to illustrate the degree of sensitivity to the price of the anti-TNF-α and include a price which may be reflective of a biosimilar such as Inflectra® which is approximately 56% of the cost of Remicade® (brand name infliximab). The one-way sensitivity was restricted to a one-dimensional Monte Carlo analysis with 10,000 trials in the Tree Age 2018 software (version 1.2).

It was also hypothesized that the rate of switching to anti-TNF-α after three months of diagnosis for the standard care group could be an uncertain parameter that may affect the ICER. Therefore, a one-way sensitivity analysis was conducted by varying the probability of switching to a biologic following the first three months of treatment for the standard care

comparator group. Since the RISK-PROKIIDS study represented a unique patient population, and may not reflect current treatment practices and rates of anti-TNF-α uptake, a one-way sensitivity analysis was conducted by varying the rate of escalation to anti-TNF-α treatment after three months post-diagnosis via a multiplier. The probability of switching to an anti TNF-α treatment was varied to quadruple, three-quarters, half, one-quarter the probability of switching to the anti TNF-α treatment in the reference case over the three years. A sensitivity analysis with the probability of not switching to an anti TNF-α in the standard care group was also conducted.

To assess the sensitivity of the ICER to the price of immunomodulator drug treatment, and since drug prices and use may vary across provinces, a one-way sensitivity analysis was conducted comparing the cost of immunomodulators. The cost of immunomodulators was based on the average cost of the drug class per week, and this average cost was multiplied by a factor of 2 or a factor of 0.5 in the sensitivity analysis. All scenario analyses were conducted from the healthcare public payer perspective. A tornado diagram was constructed showing the results of the three one-way sensitivity analyses.

2.6 Data Management

The study has undergone scientific peer review with reviewers from Child Health Evaluative Sciences, at the Hospital for Sick Children. A material transfer agreement was executed between the Hospital for Sick Children and the RISK-PROKIIDS group. The anonymized RISK-PROKIIDS dataset (containing no personal identifying information) maintained by the Crohn's and Colitis Foundation of America Research Network was transferred through secure data transfer from Dr. T. Walters to Ms. N. Bashir. Data are housed securely on the Sick Kids shared hospital server with access limited to the research team. Paper documents were stored in locked cabinets.

The RISK-PROKIIDS data set was transferred in MS Access 2010 and MS Excel 2010 format. The RISK-PROKIIDS data tables were queried within MS Access to create tables to export into MS Excel 2010 for further analysis. MS Excel was used to format and arrange tables for export into

R software v. 3.4.0 for statistical analysis, imputation of missing data, and propensity score analysis. Adjusted data sets were imported into MS Excel 2010 for determining transition probabilities. Probabilities that were obtained from the scientific literature were adjusted to accommodate a one week cycle length in MS Excel. Probabilities were manually entered into Tree Age Software v. 2018 for cost-effectiveness analysis.

2.7 Ethics

All study practices were conducted in accordance with the Tri-Council Policy Statement 2.0 on Research Ethics. The study protocol was reviewed approved by Sick Kids Ethics Review Board (Dec. 2014, REB file #1000047757) and subsequently, the University of Toronto Ethics Review Board (Feb. 2015). Ethics approval has been renewed and maintained. Research Ethics training has been completed by N. Bashir. The dataset was anonymized and de-linked prior to transfer and no personal identifiers were included. Only data where parents of children participating have provided informed consent for participation of their children in the RISK-PROKIIDS study and in RISK ancillary studies were transferred. A waiver for consent was approved by the Sick Kids Ethics Review Board for the economic evaluation using de-identified patient information. All personal identifiers were removed prior to data transfer and participants were identified only by a study ID number. No patients were or will be identified in any reports or publications.

3 Results

3.1 Overview of Results

The following chapter outlines the results from the methodological choices taken in this project and the cost-effectiveness analysis of early intervention with anti-TNF-α treatment in moderate-to-severe pediatric Crohn's disease (CD) compared to standard care. "Early intervention" was defined as treating with anti-TNF-α medications (infliximab or adalimumab) within the first three months of diagnosis with or without the use of other concomitant treatments. "Standard care" was defined as a step-up approach where traditional treatments, such as corticosteroids and immunomodulators were used following diagnosis with the option of escalating to anti-TNF-α treatment after three months from diagnosis. To execute the cost-effectiveness analysis, inputs such as patient characteristics and health state transition probabilities were derived from the retrospectively analyzed, observational cohort RISK-PROKIIDS study of North American newly-diagnosed children with CD.

The following chapter describes:

1) the characteristics of the RISK-PROKIIDS unadjusted representative patient population;

2) the identification of missing data in this population and the results of imputing missing data in this population;

3) the two possible approaches to pool the imputed data as a reference for providing inputs into the cost-effectiveness model;

4) a comparison of different methods of propensity score analysis in creating a matched data set of comparator groups and choosing the most appropriate method to create the matched data set;

5) the cost-effectiveness analysis comparing early anti-TNF-α treatment to standard care in pediatric CD;

6) the uncertainty analysis related to the cost-effectiveness analysis; and

7) the impact on the cost-effectiveness analysis of using two different approaches to pooling imputed data when assembling the representative patient population which informs the cost-effectiveness inputs.

3.2 Characteristics of the Unadjusted Patient Population

The RISK-PROKIIDS study, a North American multi-site, observational study, analyzed retrospectively, of children with inflammatory bowel disease (ulcerative colitis and Crohn's disease) provided a subset of newly diagnosed pediatric patients with confirmed moderate-to-severe CD with at least a three-year follow-up. Included study subjects had determinable health state information at 6, 12, 18, 24, and 30 or 36 months from the date of diagnosis. Five hundred and seventy-three (573) CD patients met the inclusion criteria and were isolated from the RISK-PROKIIDS study. The treatment of each patient was assessed and the 573 subjects were divided into two comparator groups—the early anti-TNF-α intervention group and the standard care (step-up) group. There were 131 patients that received early anti-TNF-α intervention (herein also referred to as the "treated" group), and 442 patients that were assigned to the standard care group (herein also referred to as the "control" group). Among 573 eligible CD subjects isolated from the RISK-PROKIIDS study, 64 subjects had missing lab values for albumin at diagnosis (baseline), a variable needed for the propensity matching. Seven of 131 (5.3%) of subjects with missing baseline Albumin values received early anti-TNF-α intervention (treated group) and 57/442 (12.9%) received standard care (control group).

Patient characteristics at diagnosis of each comparator group in the unadjusted, RISK-PROKIIDS extracted population are shown in Table 3.2-1. In the unadjusted population, the mean at diagnosis in the standard care group was 11.62 years of age and in the early intervention group the mean age was 12.35 years of age, possibly indicating the preference to use biologic treatment in older patients. In the standard care group, 19% of patients were from Canadian sites and in the early anti-TNF-α group, 9.2% of patients were from Canadian sites. Other patient characteristics such as the proportion of males to females, albumin lab values, height Z-

scores, and family history of IBD were similar between the standard care and early anti-TNF-α groups were similar. The ethnic characteristics of each comparator group in the unadjusted RISK-PROKIIDS population are shown in Table 3.2-2. Over 70% of patients in both comparator arms were Caucasian. In the unadjusted population, fewer than 10% of patients in both comparator groups were of Jewish origin, African origin or Hispanic origin. The disease characteristics at diagnosis of each comparator group in the unadjusted RISK-PROKIIDS population are shown in Table 3.2-3. In the early anti-TNF-α group, 38.2% of patients had perianal disease, 60.3% of patients were assessed as having moderate disease, 21.4% of patients were assessed as having severe disease and 55.7% of patients had disease in the ileocolon. Comparatively, in the standard care group, 25.8% of patients had perianal disease, 43.4% of patients were assessed as having moderate disease, 13.8% of patients were assessed as having severe disease, and 58.4% of patients had disease in the ileocolon. In the early anti-TNF-α group, 55% of patients were classified as having active disease but were not on steroids just following diagnosis while 39.6% in the standard care group were classified as having active disease but were steroid-free after diagnosis. The health states and the steroid status (whether or not the patient was taking steroids) at 6, 12, 18, 24, and 36 months post diagnosis were determined for each comparator group in the unadjusted RISK-PROKIIDS population and are shown in Table 3.2-4. In addition, the number of steroid-free remission semesters (6-month periods), the number of consecutive steroid-free remission semesters, and the number of days in hospital and the number of hospitalized patients in 36 months post-diagnosis were determined for each comparator group in the unadjusted RISK-PROKIIDS population and are shown in Table 3.2-4. In the unadjusted population, in the early anti-TNF-α group, 54.2% of patients were in steroid-free remission at 6 months, 61.1% were in steroid-free remission at 1 year, 65.6% were in steroid-free remission at 18 months, 74.8% were in steroid-free remission at two years and 71.0% were in steroid-free remission at three years. In the unadjusted population, in the standard care group, 40.0% of patients were in steroid-free remission at 6 months, 56.3% were in steroid-free remission at 1 year, 57.5% were in steroid-free remission at 18 months, 65.6% were in steroid-free remission at two years and 74.9% were in steroid-free remission at three years. Those in the early anti-TNF-α group, had a mean number of 3.95 days

in hospital over three years while the standard care group had a mean number of 3.35 days in hospital over three years.

Some variables such as age and disease activity at diagnosis did show a statistically significant difference between comparator groups in the unadjusted population. This suggested that the comparator groups are not well matched based on their characteristics, and there may be a possibility of selection bias in treatment allocation given the observational nature of the cohort study design. To alleviate the potential for selection bias in treatment selection and to compare groups with similar characteristics similar to a randomized clinical trial, propensity score analysis was conducted to select comparable groups (described in a later section).

Albumin lab values, age, and height Z-score were the only continuous variables out of all the variables that were assumed to affect treatment assignment. Being continuous variables, their distribution pattern could be determined. The distribution of the continuous variables of "albumin levels", "age" and "height Z-score" at diagnosis for the 573 patients from the RISK-PROKIIDS study are shown in the density plots in Figures 3.2-1, 3.2-2 and 3.2-3 respectively. The plots suggest a normal distribution for these variables.

Table 3.2-1. Patient Characteristics in the Unadjusted RISK-PROKIIDS Comparator Groups.

Unadjusted Population			
Characteristic	**Standard Care n=442**	**Early Intervention with Biologics n=131**	**P value**
Sex = Female (%)	166 (37.6)	44 (33.6)	0.469
Age at diagnosis in years (mean (sd))	11.62 (2.96)	12.35 (2.67)	0.011*
Albumin in g/dL (mean (sd))	3.49 (0.68)	3.44 (0.64)	0.492
Height Z score (mean (sd))	-0.27 (1.08)	-0.41 (1.24)	0.203
At large clinical site (>32 patients) (%)	225 (50.9)	69 (52.7)	0.798
At Canadian site (%)	84 (19.0)	12 (9.2)	0.012*
Family history of IBD: (%)			0.183
No 1st degree relative	355 (80.3)	115 (87.8)	
One 1st degree relative	70 (15.8)	14 (10.7)	
Two 1st degree relatives	7 (1.6)	0 (0.0)	
Unknown	10 (2.3)	2 (1.5)	

Sixty-four missing values were excluded in calculating the mean for albumin. Chi-squared tests, t-tests, and Kruskal-Wallis Rank Sum Test were used for comparisons between groups depending on the nature (continuous or non-continuous) of the variables. * indicates $p<0.05$. Abbreviations: IBD= inflammatory bowel disease; sd= standard deviation; g/dL = grams per deciliter.

Table 3.2-2. The Ethnic Origins of the Unadjusted RISK-PROKIIDS Comparator Groups.

Unadjusted Population			
	Standard Care N=442 n (%)	**Early Intervention with Biologics N=131 n (%)**	**P value**
Ethnicity			0.536
Caucasian	338 (76.5)	94 (71.8)	
African	32 (7.2)	12 (9.2)	
Mixed	24 (5.4)	7 (5.3)	
Other	10 (2.3)	6 (4.6)	
South Asian	7 (1.6)	1 (0.8)	
East South East Asian	5 (1.1)	0 (0.0)	
West Asian or Arab	3 (0.7)	2 (1.5)	
Unknown	28 (5.2)	9 (6.9)	
Known Jewish			0.207
No	391 (86.0)	103 (78.6)	
Jewish	28 (6.3)	13 (9.9)	
Mixed	19 (4.3)	7 (5.3)	
Unknown	15 (3.4)	8 (6.1)	
Known Hispanic			0.173
No	414 (93.7)	115 (87.8)	
Hispanic	8 (1.8)	5 (3.8)	
Mixed	7 (1.6)	4 (3.1)	
Unknown	13 (2.9)	7 (5.3)	
Known African			0.648
No	363 (82.1)	103 (78.6)	
African	32 (7.2)	12 (9.2)	
Unknown	47 (10.6)	16 (12.2)	

Chi-squared tests, t-tests, and Kruskal-Wallis Rank Sum Test were used for comparisons between groups depending on the nature (continuous or non-continuous) of the variables. * indicates $p<0.05$.

Table 3.2-3. Disease Characteristics at Diagnosis in Unadjusted RISK-PROKIIDS Comparator Groups.

Unadjusted Population			
Characteristic	**Standard Care N= 442 n (%)**	**Early Intervention with Biologics N=131 n (%)**	**P value**
Presence of perianal disease (%)			**<0.001***
No	325 (73.5)	75 (57.3)	
Yes	114 (25.8)	50 (38.2)	
Unknown	3 (0.7)	6 (4.6)	
Disease activity at diagnosis (Physician Global Assessment) (%)			**<0.001***
None	14 (3.2)	0 (0.0)	
Mild	175 (39.6)	24 (18.3)	
Moderate	192 (43.4)	79 (60.3)	
Severe	61 (13.8)	28 (21.4)	
Disease location (%)			**0.515**
No L1 to L3 disease	7 (1.6)	1 (0.8)	
L1 (ileum)	64 (14.5)	18 (13.7)	
L2 (colon)	85 (19.2)	25 (19.1)	
L3 (ileocolon)	258 (58.4)	73 (55.7)	
Unknown	28 (6.3)	14 (10.7)	
Number in steroid-free remission at diagnosis (%)	**17 (3.8)**	**1 (0.8)**	**0.136**
Current health state at diagnosis (%)			**0.002***
steroid-free active	175 (39.6)	72 (55.0)	
steroid active	233 (52.7)	58 (44.3)	
steroid-free remission	17 (3.8)	1 (0.8)	
steroid remission	17 (3.8)	0 (0.0)	

The current health state at diagnosis was based on the weighted Pediatric Crohn's Disease Activity Index (wPCDAI) and the steroid state of the patients. Chi-squared tests, t-tests, and Kruskal-Wallis Rank Sum Test were used for comparisons between groups depending on the nature (continuous or non-continuous) of the variables. * $p<0.05$

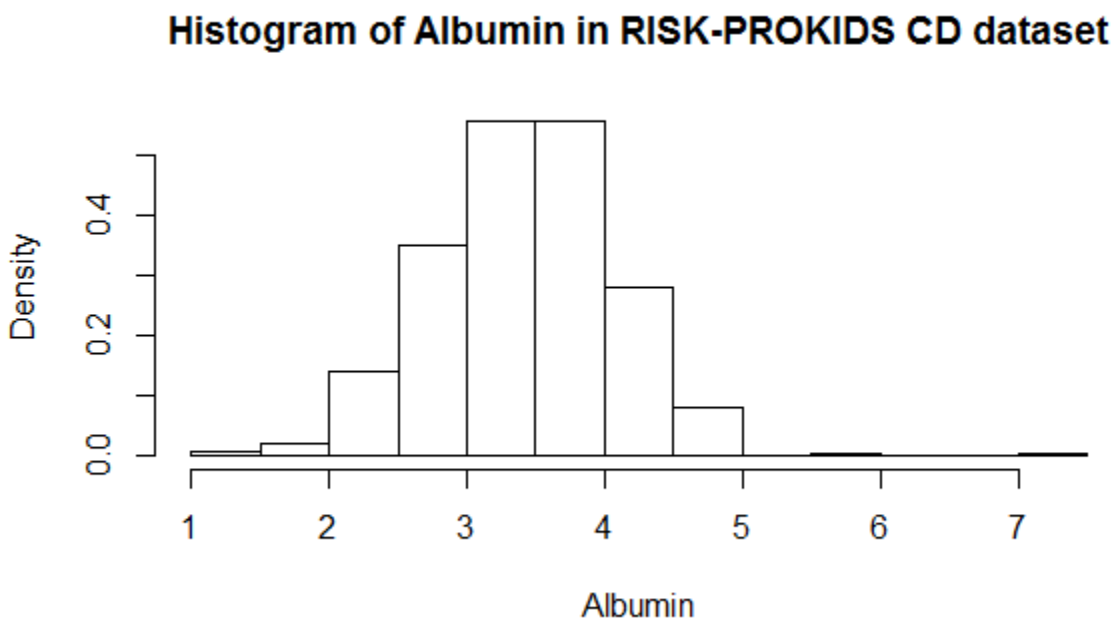
Table 3.2-4. The Steroid-related Health State at 6, 12, 18, 24, 30, and 36 Months Post-diagnosis in the Unadjusted RISK-PROKIIDS Comparator Groups.

	Standard Care n (%)	Early Intervention with Biologics n (%)	P value
Current health state at 6 months (%)			0.003*
steroid-free active	150 (33.9)	45 (34.4)	
steroid-free remission	177 (40.0)	71 (54.2)	
steroid active	62 (14.0)	9 (6.9)	
steroid remission	53 (12.0)	6 (4.6)	
Number in steroid-free remission at 6 months (Yes=1, No =0) (%)	177 (40.0)	71 (54.2)	0.006*
Current health state at 12 months (%)			0.006*
steroid-free active	130 (29.4)	47 (35.9)	
steroid-free remission	249 (56.3)	80 (61.1)	
steroid active	35 (7.9)	2 (1.5)	
steroid remission	28 (6.3)	2 (1.5)	
Number in steroid-free remission at 12 months (Yes=1, No =0) (%)	249 (56.3)	80 (61.1)	0.389
Current health state at 18 months (%)			0.114
steroid-free active	140 (31.7)	39 (29.8)	
steroid-free remission	254 (57.5)	86 (65.6)	
steroid active	31 (7.0)	5 (3.8)	
steroid remission	17 (3.8)	1 (0.8)	
Number in steroid-free remission at 18 months (Yes=1, No =0) (%)	254 (57.5)	86 (65.6)	0.116
Current health state at 24 months (%)			0.052
steroid-free active	121 (27.4)	27 (20.6)	
steroid-free remission	290 (65.6)	98 (74.8)	
steroid active	16 (3.6)	6 (4.6)	
steroid remission	15 (3.4)	0 (0.0)	
Number in steroid-free remission at 24 months (Yes=1, No =0) (%)	290 (65.6)	98 (74.8)	0.061
Current health state at 30 months (%)			0.993
steroid-free active	110 (24.9)	31 (23.7)	
steroid-free remission	308 (69.7)	93 (71.0)	
steroid active	17 (3.8)	5 (3.8)	
steroid remission	7 (1.6)	2 (1.5)	
Number in steroid-free remission at 30 months (Yes=1, No =0) (%)	308 (69.7)	93 (71.0)	0.858
Current health state at 36 months (%)			0.749

	Standard Care n (%)	Early Intervention with Biologics n (%)	P value
steroid-free active	87 (19.7)	30 (22.9)	
steroid-free remission	331 (74.9)	93 (71.0)	
steroid active	15 (3.4)	4 (3.1)	
steroid remission	9 (2.0)	4 (3.1)	
Number in steroid-free remission at 36 months (Yes=1, No =0) (%)	331 (74.9)	93 (71.0)	0.436
Number of steroid-free remission semesters in 36 months (mean (sd))	3.68 (1.7)	3.98 (1.9)	0.075
Number of consecutive steroid-free remission semesters in 36 months (mean (sd))	3.12 (1.8)	3.62 (2.0)	0.006*
Total days in hospital at 36 months (mean (sd))	3.35 (9.4)	3.95 (13.2)	0.556
Hospitalized Yes = 1, No =0 (%)	140 (31.7)	46 (35.1)	0.527

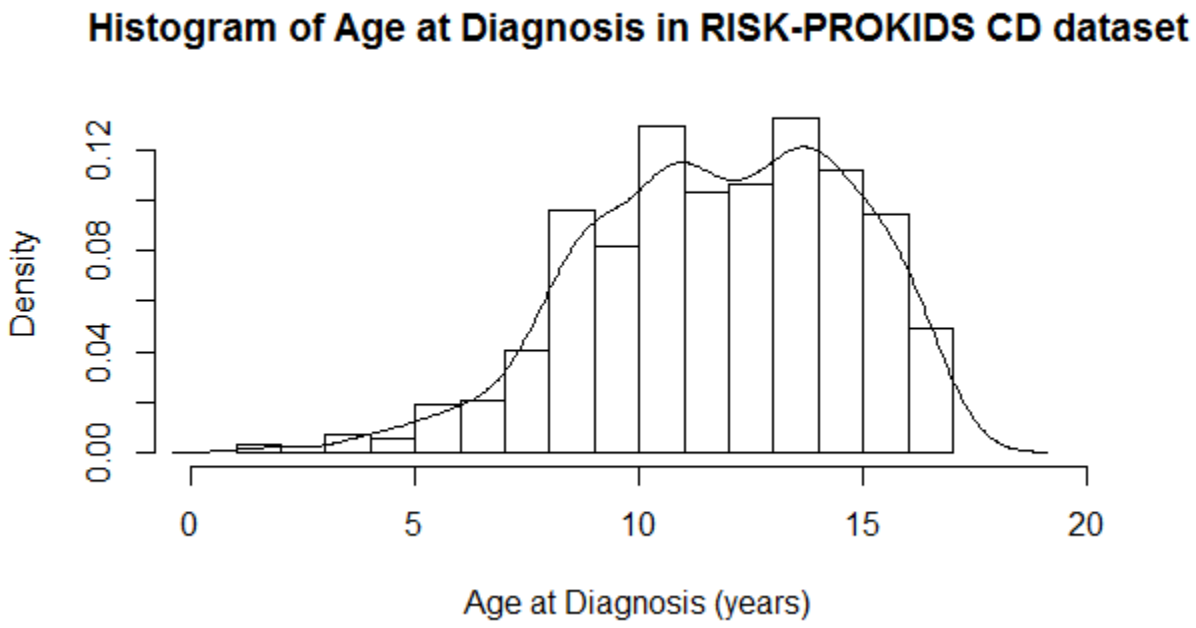
The current health state at diagnosis was based on the weighted Pediatric Crohn's Disease Activity Index (wPCDAI) and the steroid state of the patients. Chi-squared tests, t-tests, and Kruskal-Wallis Rank Sum Test were used for comparisons between groups depending on the nature (continuous or non-continuous) of the variables. * $p<0.05$. Abbreviations: sd=standard deviation.

Figure 3.2-1. Density Plot of Albumin levels (g/dL) at Diagnosis in the Unadjusted RISK-PROKIIDS Crohn's Disease Population.



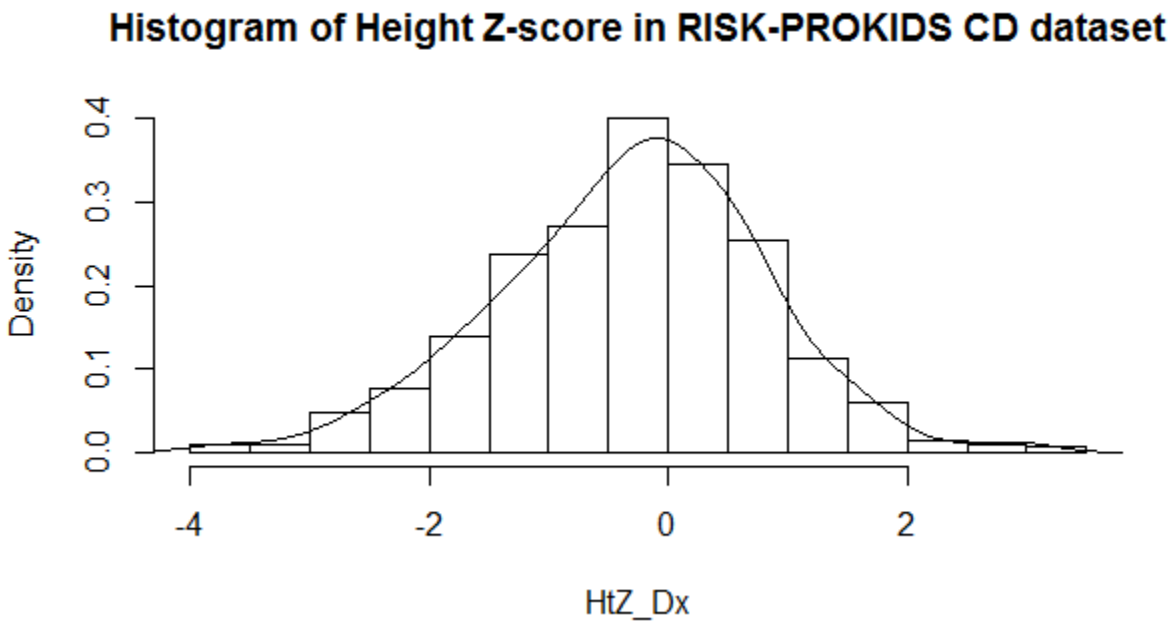
Albumin units in g/dL. Abbreviation: CD= Crohn's disease. g/dL=grams per decilitre

Figure 3.2-2. Density Plots of Age (years) at Diagnosis in the Unadjusted RISK-PROKIIDS Population.



Abbreviation: CD= Crohn's disease.

Figure 3.2-3. Density Plots of Height Z-score (HtDx) at Diagnosis in the Unadjusted RISK-PROKIIDS Crohn's Disease Population.



3.3 Imputation of Missing Data

The imputation of missing data from the RISK-PROKIIDS data was conducted to avoid reducing the potential sample size of the population. Since the missing data was assumed to be missing at random and that the missing data was from a continuous variable (albumin) with a small percentage (11%) of missing values at baseline, it was reasonable to proceed with the imputation of missing data before proceeding with propensity score analysis to create comparator groups. Sixty-four patients had missing lab values for albumin at diagnosis (baseline, Visit 0). It was assumed that data were missing at random, and this was tested using the equality of covariances in groups with identical missing patterns. The test concluded that normality in the data was rejected at the 0.05 significance level ($p=1.33 e-141$) and non-parametric testing concluded that there was not sufficient evidence to reject that the data was missing completely at random at the 0.05 significance level since $p=0.18$. Hence, it was assumed that the data were missing at random. Missing data were therefore imputed. The imputation alleviated having to exclude the 64 patients with the missing data from the original unadjusted population and reducing the sample size for the cost-effectiveness analysis.

Multivariate imputation by chained equations (MICE) using the predictive mean matching method was conducted for ten iterations resulting in ten separate imputed data sets. The distribution patterns of albumin values in the ten imputed data sets are shown in a density plot in Appendix 16, Figure A16-1, and the distribution of the imputed values among original values in each imputed data set is shown in strip plots in Appendix 16, Figure A16-2.

Since ten imputed data sets were created, two options on how to proceed with data sets for the ensuing propensity analysis and cost-effectiveness analysis were considered. One approach, the “Within” approach, calculates propensity scores on each imputed dataset separately and creates ten matched data sets (Mitra & Reiter, 2016). The other approach, the “Across” approach, averages the propensity score for each subject from each imputed dataset and then uses that mean propensity score to create one matched population (Mitra & Reiter, 2016). Since no one approach has been recommended within the context of a cost-effectiveness

analysis, both approaches were used for the propensity score analysis. The “Across” method was the primary approach taken for the determining probability inputs for the cost-effectiveness analysis since the “Across” approach resulted in one data set serving as the resource for the cost-effectiveness model inputs. The “Within” approach was also used but only in a secondary analysis to compare the impact of both approaches on the cost-effectiveness analysis.

The following section describes the comparison of different methods of propensity score analysis performed before choosing an optimal propensity score method to create an adjusted, matched data set of equivalent comparator groups for the cost-effectiveness analysis.

3.4 Propensity Score Analysis

Propensity score analysis was used to reduce selection bias in being assigned a certain treatment in the RISK-PROKIIDS patient population and was used to create comparator groups of patients with similar characteristics. The propensity score for each patient was derived from the propensity score regression model equation which described the conditional probability of receiving the early anti-TNF-α treatment (see section 2.4 for propensity score regression equation). The following variables were considered as covariates in the propensity score regression model since they may have influenced treatment selection:

- age at diagnosis,
- sex,
- disease activity at diagnosis (based on physician global assessment),
- African heritage,
- disease location,
- the presence of peri-anal disease,
- height z-score,
- steroid-related health state at diagnosis,
- albumin values,
- whether the subject was recruited at a large clinical site (>31 patients).

The purpose of the propensity score analysis was to create comparator groups of patients with similarly balanced characteristics. Therefore, it was not necessary to establish whether the covariates actually had an influence on treatment selection but only that covariates were balanced among the two comparator groups. The thresholds used to establish good covariate balance were when covariates achieved mean standardized differences below 0.1 and variance ratios for continuous variables were closest to 1 (Austin, 2009). The imbalance in propensity scores between the early anti-TNF-α intervention group and the standard care group in the unadjusted RISK-PROKIIDS data set is shown graphically in Appendix 17.

Four methods of propensity score analysis were compared to find the optimal method for adjusting the imputed data sets from the RISK-PROKIIDS CD patient population. The four types of propensity score analyses conducted were propensity score matching, propensity score weighting, stratification (sub-classification), and covariate balance propensity score (CBPS). To choose the optimal method of propensity score analysis, balance diagnostics were performed for each approach. Balance diagnostics comprised of graphically showing covariate balance and determining which methods achieved covariate balance through mean standardized differences below 0.1 and variance ratios close to 1 (and below 1.5) for the continuous variables of age at diagnosis, albumin and height z-score. The following sections describe the results from the propensity score analysis methods.

3.4.1 Propensity Score Matching

Nearest neighbour propensity score matching without replacement, using the logit method, was conducted with each of the ten imputed datasets and with the "Across" averaged dataset of 573 subjects. Ratios of 1:1, 2:1 and 3:1, standard step-up care (control): early anti-TNF-α intervention (treatment) patient groups were assembled with and without a caliper constraint of 0.2 the standard deviation of the logit of the propensity score. The 0.2 caliper constraint excluded more patients due to tighter matching parameters. Matching results and covariate balance results for the "Across" data set are shown in Table 3.4.5-1. Matching and covariate balance results for the ten "Within" data sets are shown in Appendix 19. Matched groups with a ratio of 1:1 control:treatment subjects and with a 0.2 caliper constraint had 123 patients in

each group while matched 1:1 groups with no caliper constraint had 131 patients in each group (see Table 3.4.5-1). Matched groups with a ratio of 2:1 control:treatment subjects and with a 0.2 caliper constraint had 237 patients in the control group and 123 patients in the treatment group while matched 2:1 groups with no caliper constraint had 262 patients in the control group and 131 patients in the treatment group (see Table 3.4.5-1). Matched groups with a ratio of 3:1 control: treatment subjects and with a 0.2 caliper constraint had 293 patients in the control group and 123 patients in the treatment group while matched 3:1 groups with no caliper constraint had 393 patients in the control group and 131 patients in the treatment group (see Table 3.4.5-1). The lack of a 0.2 caliper constraint included more patients in the groups, but resulted in more imbalanced covariates with a mean standard difference greater than 0.1. The nearest neighbour matching method with a 2:1 and 3:1 control: treatment ratio and a caliper of 0.2 had zero imbalanced covariates and had variance ratios close to 1, and the nearest neighbour matching method with a caliper of 0.2 and a 1:1 control:treatment ratio had only one imbalanced covariate (see Table 3.4.5-1).

3.4.2 Propensity Score Weighting

The method of propensity score weighting was conducted using the inverse of the probability of treatment assignments as a weight in a multivariate outcome analysis. The weighting method included a matched group of 243 control (standard care) patients and 131 treatment (early anti-TNF-α intervention) patients. There were no imbalanced covariates using the weighting method and variance ratios of “age”, “albumin”, and “height z-score” were close to 1 (see Table 3.4.5-1).

3.4.3 Covariate Balancing Propensity Score (CBPS) Method

The covariate balancing propensity score method of propensity score analysis was conducted such that the propensity score was estimated by simultaneously maximizing covariate balance and prediction of treatment assignment. The CBPS method included a matched group of 232 control (standard care) patients and 131 treatment (early anti-TNF-α intervention) patients.

There were no imbalanced covariates using the CBPS method and variance ratios of “age”, “albumin”, and “height z-score” were close to 1 (see Table 3.4.5-1).

3.4.4 Propensity Score Analysis with Sub-classification

Propensity score analysis with sub-classification was conducted with four subclasses of the propensity score. The number of patients within each treatment group and the number of imbalanced covariates with the subclassification method is shown in Table 3.4.4-1. The first subclass contained 250 control (standard care) patients and 33 treatment (early anti-TNF-α intervention) patients. The second subclass contained 86 control (standard care) patients and 32 treatment (early anti-TNF-α intervention) patients. The third subclass contained 63 control (standard care) patients and 33 treatment (early anti-TNF-α intervention) patients and the fourth subclass contained 43 control (standard care) patients and 33 treatment (early anti-TNF-α intervention) patients. Each subclass had three or more imbalanced covariates. All 442 control subjects and 131 treatment subjects were included in this method with the smallest number of subjects in a subclass having the greatest number of imbalanced covariates (11).

Table 3.4.4-1. The Number of Patients per Treatment Group and the Number of Imbalanced Covariates with the Subclassification Propensity Score Analysis Method.

Subclass	Propensity Score Analysis Method	Control Adjusted	Treated Adjusted	Number of Imbalanced Covariates with Standard Difference >0.1
1	Subclassification	250	33	7
2	Subclassification	86	32	3
3	Subclassification	63	33	8
4	Subclassification	43	33	11

3.4.5 Balance Diagnostics on the Propensity Score Methods

The mean standardized difference, variance ratios of covariates and the resulting number of imbalanced covariates were the criteria for diagnosing balance among the different propensity score methods. A mean standardized difference below 0.1 among covariates of the matched groups and variance ratios close to 1 for the continuous variables of “albumin”, “age at diagnosis” and “height Z score” were used as thresholds to measure covariate balance. Mean standardized differences and variance ratios could only be calculated for continuous variables. Therefore, being the only continuous variables out of all the propensity score covariates, mean standardized differences and variance ratios were determined for “albumin”, “age at diagnosis” and “height Z score”. Covariates that did not meet these thresholds were considered imbalanced. Variance ratios, and mean standardized differences for the nearest neighbour matching method using different ratios of standard care to early intervention patients, with and without a caliper constraint, the propensity score weighting method, and the covariate balance propensity score method are shown in Table 3.4.5-1 for the imputed data set assembled using the “Across” method. The number of imbalanced covariates for the nearest neighbour matching, weighting and covariate balance propensity score methods are shown in Table 3.4.5-1 and the number of imbalanced covariates for the sub-classification propensity method are shown in Table 3.4.4-1 (using the “Across” method of data set assembly).

In addition to assessing covariate balance through mean standardized differences and variance ratios, the efficacy of the propensity score analysis were demonstrated graphically. The distribution of propensity scores in the unmatched and matched treatment groups are shown in a Jitter plot (see Figure 3.4.5-1). Quantile-quantile (Q-Q plots) which show the likelihood that matched covariates from the early anti-TNF-α and standard care populations come from the same distributions, are shown in Appendix 18, Figure A18-1. Covariate balance was shown graphically with a “Love” plot, which plotted mean standardized differences for all covariates before and after propensity score analysis. A “Love” plot for the nearest neighbour matching technique with a 0.2 caliper constraint and a 2:1 ratio of standard care to early anti-TNF-α using the “Across” method of assembling the data sets is shown in Figure 3.4.5-2. While the averaged

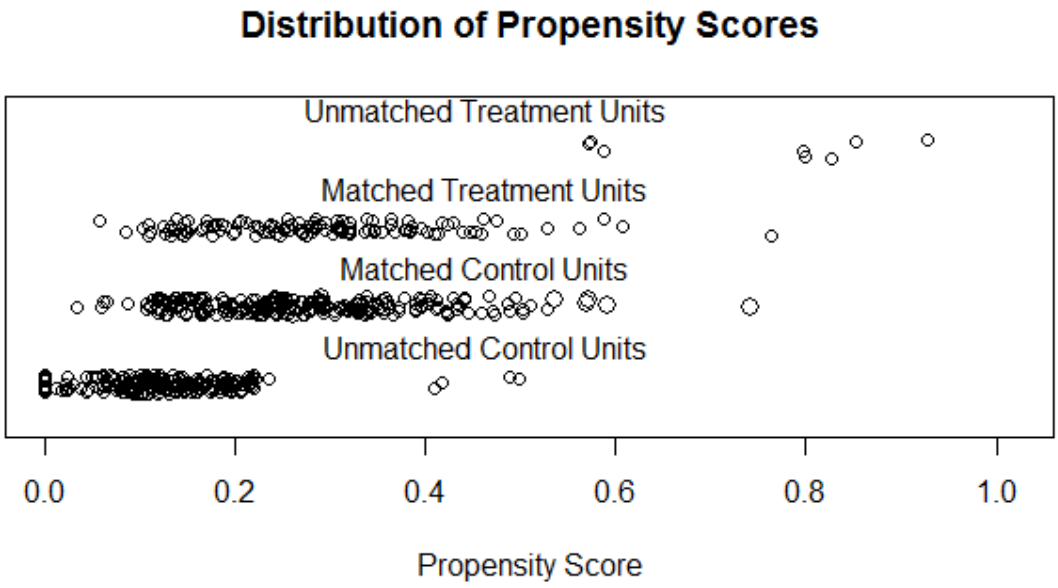
“Across” data set was the primary data set matched here, propensity score balance diagnostics for each of the ten separately imputed RISK-PROKIIDS data sets with the nearest neighbour matching technique, weighting method, CBPS method and subclassification method are shown in Appendix 19.

Table 3.4.5-1. Balance diagnostics with the Nearest Neighbour Matching, Weighting and Covariate Balance Propensity Score Analysis Methods.

Propensity Score Analysis Method (method, control: treatment ratio)	Control Matched	Treated Adjusted	Number of Imbalanced Covariates with Mean Standard Difference >0.1	Covariate with highest Standard Difference	Highest Mean Standard Difference	Age Variance Ratio (<1.5 threshold)	Albumin Variance Ratio (<1.5 threshold)	Height Z Score Variance Ratio (<1.5 threshold)
nearest, 1:1 caliper = 0.2	123	123	1	Albumin	0.105	1.254	1.040	1.246
nearest, 2:1 caliper = 0.2	237	123	0	Disease Activity at Diagnosis (PGA)	0.097	1.035	1.128	1.281
nearest, 3:1 caliper = 0.2	293	123	0	Height Z score	0.087	1.023	1.091	1.252
nearest, 1:1	131	131	6	Perianal Disease	0.188	1.180	1.133	1.048
nearest, 2:1	262	131	2	Perianal Disease	0.188	1.027	1.130	1.249
nearest, 3:1	393	131	6	Disease Activity at Diagnosis	0.403	1.141	1.059	1.330
weighting	243	131	0	Perianal Disease	0.094	1.022	1.017	1.249
Covariate balancing (CBPS)	232	131	0	Perianal Disease	0.064	1.029	1.005	1.254

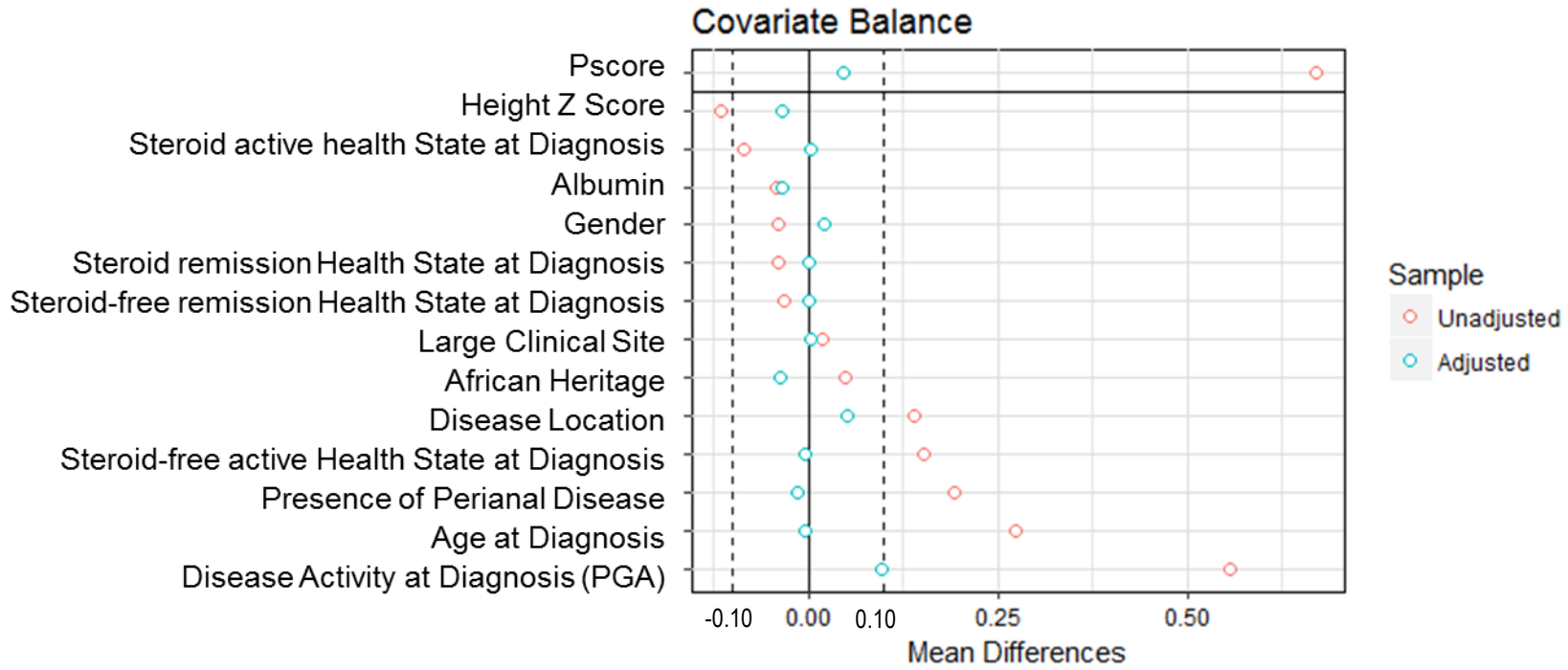
Abbreviations: PGA= Physician Global Assessment; CBPS= covariate balance propensity score.

Figure 3.4.5-1. Jitter Plot Showing the Distribution of the Propensity Score Among Unmatched and Matched Subjects.



Nearest neighbor matching with a 2:1 control:treatment ratio and caliper of 0.2 using the data set assembled with the Across method is shown.

Figure 3.4.5-2. Representative Love Plot Showing Covariate Balance Following Propensity Score Matching.



This plot represents the standard mean differences of covariates in the RISK-PROKIIDS data before matching (red dots) and after a 2:1 control:treatment ratio with nearest neighbor matching with a caliper width of 0.2 (blue dots). Balance is achieved when the standard mean difference <0.1. Note that after matching the standard mean difference approaches 0 for most covariates. The averaged "Across" data set is represented here. Abbreviation: PGA= Physician Global Assessment.

3.4.6 Choosing the Optimal Propensity Score Analysis Method

The results in Tables 3.4.5-1 and Table 3.4.4-1 show that there are differences in covariate balance among the different propensity score methods and suggest that when choosing a propensity score analysis method, that several methods should be considered to find the method that offers the greatest covariate balance for a particular set of data rather than arbitrarily choosing one method. The propensity score methods with the greatest degree of balance included those with the most covariates with mean standardized differences below 0.1 and variance ratios closest to 1. As shown in Table 3.4.5-1, the weighting method, CBPS method and the nearest neighbour matching method using a caliper constraint of 0.2 and using a 2:1 or 3:1 ratio of standard care to early anti-TNF-α intervention patients did not have any imbalanced covariates and had variance ratios close to one. Therefore, all these propensity score analysis methods would be appropriate for creating a dataset representative of the RISK-PROKIIDS population.

The weighting and CBPS methods had technical limitations within their R software packages so that the matched data sets could not simply be extracted into other software programs such as Microsoft Excel for further determination of transition probabilities for the cost-effectiveness analysis model. Therefore, the 2:1 control to treatment ratio nearest neighbour matched data set with a caliper of 0.2 created from the "Across" data set was chosen to inform parameters for the economic evaluation. This matched data set containing 360 total subjects with 237 standard care subjects (control) and 123 early anti-TNF-α intervention (treatment) subjects. When choosing among many-to-one ratios for propensity score analysis, lower ratios are suggested (Austin, 2010) since they tend to reduce mean square error in the treatment effect. Therefore, the 2:1 control to treatment ratio method was chosen over the 3:1 control to treatment ratio technique even though both showed balance in their covariates. To confirm any difference in treatment effect mean square error, the mean square error of the logistic regression equation with the "number of steroid-free remission semesters" as the treatment effect and "early anti-TNF-α intervention" as the treatment variable was examined. Covariates in the regression equation were: "age", "sex", "disease severity at diagnosis", "African

heritage", "disease location", "presence of perianal disease", "height z score", "albumin values", "steroid-related health state at diagnosis", "large clinical site", and "receiving concomitant classes of drugs" (see section 2.4.6 for the regression equation). The mean square error of the regression equation using the matched data set from the 2:1 control to treatment ratio, nearest neighbour matching with a caliper of 0.2 was 2.66. The mean square error using the matched data set from the 3:1 control to treatment ratio, nearest neighbour matching with a caliper of 0.2 was 2.77. Therefore, it was confirmed that the 2:1 standard care to early anti-TNF-α ratio did have a slightly smaller mean square error. Henceforth, using the "Across" method in assembling imputed data, the nearest neighbour matching with a caliper of 0.2 in a 2:1 control (standard care) to treatment (early anti-TNF-α intervention) was chosen as the propensity score method for creating an adjusted dataset representative of the RISK-PROKIIDS patient population and to inform transition probabilities and clinical outcomes in the cost-effectiveness analysis. The characteristics of the adjusted RISK-PROKIIDS CD patient population are described in the next section.

3.5 Characteristics and Clinical Outcomes of the Adjusted RISK-PROKIIDS Patient Population

Propensity score matching was performed on the unadjusted RISK-PROKIIDS CD pediatric patient data to create comparable standard care and early anti-TNF-α comparator groups for the economic evaluation. The characteristics and treatment patterns of the adjusted, matched comparator groups are described in this section. Patient characteristics at diagnosis are listed in Table 3.5-1. The ethnic characteristics of each comparator group in the adjusted RISK-PROKIIDS population are shown in Table 3.5-2. In the adjusted population, the mean at diagnosis in the standard care group was 12.27 years of age and in the early intervention group the mean age was 12.28 years of age. In the standard care group, 24.1 % of patients were from Canadian sites and in the early anti-TNF-α group, 9.8% of patients were from Canadian sites. Other patient characteristics such as the proportion of males to females, albumin lab values, height Z-scores, and family history of IBD were similar between the standard care and early anti-TNF-α groups. Over 70% of patients in both comparator arms were Caucasian. In the

adjusted population, fewer than 10% of patients in both comparator groups were of Jewish origin, African origin or Hispanic origin. The disease characteristics at diagnosis of each comparator group in the adjusted RISK-PROKIIDS population are shown in Table 3.5-3. In the adjusted population, 27.8% of the standard care group had perianal disease at diagnosis and 40.7% of the early anti-TNF- α group had perianal disease. In the early anti-TNF-α group, 60.2% of patients were assessed as having moderate disease, 21.1% of patients were assessed as having severe disease and 56.9% of patients had disease in the ileocolon. Comparatively, in the standard care group, 51.1% of patients were assessed as having moderate disease, 22.8% of patients were assessed as having severe disease, and 57.4% of patients had disease in the ileocolon. In the early anti-TNF-α group, 52% of patients were classified as having active disease but were not on steroids just following diagnosis while 51.1% in the standard care group were classified as having active disease but were steroid-free after diagnosis. The health states and the steroid status (whether or not the patient was taking steroids) at 6, 12, 18, 24, and 36 months post diagnosis were determined for each comparator group in the adjusted RISK-PROKIIDS population and are shown in Table 3.5-4. The number of steroid-free remission semesters (6-month periods), the number of consecutive steroid-free remission semesters, and the number of days in hospital and the number of hospitalized patients in 36 months post-diagnosis were determined for each comparator group in the adjusted RISK-PROKIIDS population and are also shown in Table 3.5-4. In the adjusted early anti-TNF-α group, 52.8% of patients were in steroid-free remission at six months, 61.0% were in steroid-free remission at one year, 74.8% were in steroid-free remission at two years and 71.5% of patients were in steroid-free remission at three years following diagnosis. In the adjusted standard care group, 39.2% of patients were in steroid-free remission at six months, 52.7% were in steroid-free remission at one year, 65.0% were in steroid-free remission at two years and 74.7% of patients were in steroid-free remission at three years following diagnosis. Patients in the early anti-TNF-α group had a mean number of 3.97 days in hospital over three years and patients in the standard care group had a mean number of 3.76 days in hospital over three years. Patients in the early anti-TNF-α group had a mean number of 3.61 consecutive steroid-free remission semesters compared to the patients in the standard care group who had a mean number of

3.01 consecutive steroid-free remission semesters. There were no statistically significant differences between the adjusted comparator groups at diagnosis except for the presence of perianal disease (p=0.048). In the unadjusted population, in the early anti-TNF-α group, 38.2% of patients had perianal disease, and in the standard care group, 25.8% of patients had perianal disease at diagnosis (p<0.001). The propensity score analysis adjusted the population to reduce the differences between the comparator groups to just below the p=0.05 threshold suggesting a statistical difference. Since there was a large proportion of early anti-TNF-α patients with perianal disease compared to the standard care group in the unadjusted group, a small statistical difference may have remained between the groups in the adjusted population.

There were significant differences between the standard care and early anti-TNF-α intervention groups in some clinical outcomes. Time in steroid-free remission was the primary clinical outcome for this study.

Notable clinical outcomes post-diagnosis included:

- 65/123 (52%) of patients that received early anti-TNF-α treatment were in steroid-free remission at 6 months post-diagnosis compared to 93/237 (39.2%) of patients in the standard care group (p<0.05, see Table 3.5-4);

- over the 36-month study period, patients in the early anti-TNF-α treatment group had a mean number of 3.98 (SD = 1.86) steroid-free remission semesters while the standard care group had a mean number of 3.59 (SD=1.61) steroid-free remission semesters (p<0.05, see Table 3.5-4);

- the greatest mean number of consecutive steroid-free remission semesters in the 36 month study period was experienced by patients in the early anti-TNF-α treatment group with a mean of 3.61 (SD=1.97) consecutive steroid-free semesters, while patients in the standard care group experienced a mean of 3.02 (SD=1.66) consecutive steroid-free semesters (p<0.05, see Table 3.5-4).

There were no statistically significant differences between the early anti-TNF-α treatment group and the standard care (step up) group for any other post-diagnostic clinical outcome including the number of hospitalizations or number of patients in steroid-free remission at other time points over the 36-month study period (see Table 3.5-4). The percentage of patients in the early anti-TNF-α treatment group and the standard care (step up) group in steroid-free remission and in remission (in the absence or presence of steroids) at the end of years 1, 2, and 3 is shown in Figure 3.5-1 and appears similar between the groups. The number of steroid-free remission semesters was converted into steroid-free remission weeks for the purposes of the cost-effectiveness Markov model and its one-week cycle length. To provide an accurate representation of the clinical outcomes and costs of patients in each treatment group, in addition to time in steroid-free remission, time in remission and treatment patterns with concomitant medications were also assessed. Treatment patterns of the comparator groups are shown in the following section.

Table 3.5-1. Patient Characteristics in the Adjusted RISK-PROKIIDS Comparator Groups.

Characteristic	Standard Care n=237	Early Intervention with Biologics n=123	P value
Sex = Female (%)	75 (31.6)	41 (33.3)	0.837
Age at diagnosis (years) (mean (sd))	12.27 (2.65)	12.28 (2.70)	0.964
Albumin g/dL (mean (sd))	3.46 (0.59)	3.43 (0.62)	0.717
Height Z score (mean (sd))	-0.38 (1.08)	-0.45 (1.21)	0.577
At large clinical site (>32 patients) = Yes (%)	129 (54.4)	68 (55.3)	0.966
At Canadian site =Yes (%)	57 (24.1)	12 (9.8)	0.002
Family history of IBD (%)			0.164
No 1st degree relative	185 (78.1)	107 (87.0)	
One 1st degree relative	41 (17.3)	14 (11.4)	
Two 1st degree relatives	3 (1.3)	0 (0.0)	
Unknown	8 (3.4)	2 (1.6)	

Chi-squared tests, t-tests, and Kruskal-Wallis Rank Sum Test were used for comparisons between groups depending on the nature (continuous or non-continuous) of the variables.
* indicates $p<0.05$. Abbreviations: IBD= inflammatory bowel disease; sd= standard deviation; g/dL = grams per decilitre

Table 3.5-2. The Ethnic Origins of the Adjusted RISK-PROKIIDS Comparator Groups.

	Standard Care	Early Intervention with Biologics	P value
Ethnicity (%)			0.335
Caucasian	176 (74.3)	88 (71.5)	
African	21 (8.9)	12 (9.8)	
Mixed	18 (7.6)	7(5.7)	
Other	3 (1.3)	6(4.9)	
South Asian	3 (1.3)	1 (0.8)	
East South East Asian	3 (1.3)	0 (0.0)	
West Asian or Arab	1 (0.4)	2 (1.6)	
Unknown	12 (5.1)	7 (5.7)	
Known Jewish (%)			0.106
No	207 (87.3)	96 (78.0)	
Jewish	10 (4.2)	12 (9.8)	
Mixed	10 (4.2)	7 (5.7)	
Unknown	10 (4.2)	8 (6.5)	
Known Hispanic (%)			0.114
No	223 (94.1)	108 (87.8)	
Hispanic	2 (0.8)	5 (4.1)	
Mixed	4 (1.7)	3 (2.4)	
Unknown	8 (3.4)	7 (5.7)	
Known African (%)			0.914
No	186 (78.5)	97 (78.9)	
African	21 (8.9)	12 (9.8)	
Unknown	30 (12.7)	14 (11.4)	

Chi-squared tests, t-tests, and Kruskal-Wallis Rank Sum Test were used for comparisons between groups depending on the nature (continuous or non-continuous) of the variables.
* indicates $p<0.05$.

Table 3.5-3. Disease Characteristics at Diagnosis in Adjusted RISK-PROKIIDS Comparator Groups.

Characteristic	Standard Care n=237	Early Intervention with Biologics n=123	P value
Presence of Perianal Disease (%)			0.048*
No	169 (71.3)	72 (58.5)	
Yes	66 (27.8)	50 (40.7)	
Unknown	2 (0.8)	1 (0.8)	
Disease activity at diagnosis (Physician Global Assessment) (%)			0.235
None	3 (1.3)	0 (0.0)	
Mild	59(24.9)	23 (18.7)	
Moderate	121 (51.1)	74 (60.2)	
Severe	54 (22.8)	26 (21.1)	
Disease location (%)			0.962
No L1 to L3 disease	0 (0.4)	1 (0.8)	
L1	33(13.9)	17 (13.8)	
L2	48 (20.3)	23 (18.7)	
L3	136 (57.4)	70 (56.9)	
Unknown	19 (8.0)	12 (9.8)	
Steroid-free remission at diagnosis (%)	2 (0.8)	1 (0.8)	1
Current health state at diagnosis (%)			0.985
steroid-free active	121 (51.1)	64 (52.0)	
steroid active	114 (48.1)	58(47.2)	
steroid-free remission	2 (0.8)	1 (0.8)	

The current health state at diagnosis was based on the weighted Pediatric Crohn's Disease Activity Index (wPCDAI) and the steroid state of the patients; Chi-squared tests, t-tests, and Kruskal-Wallis Rank Sum Test were used for comparisons between groups depending on the nature (continuous or non-continuous) of the variables. * indicates $p<0.05$.

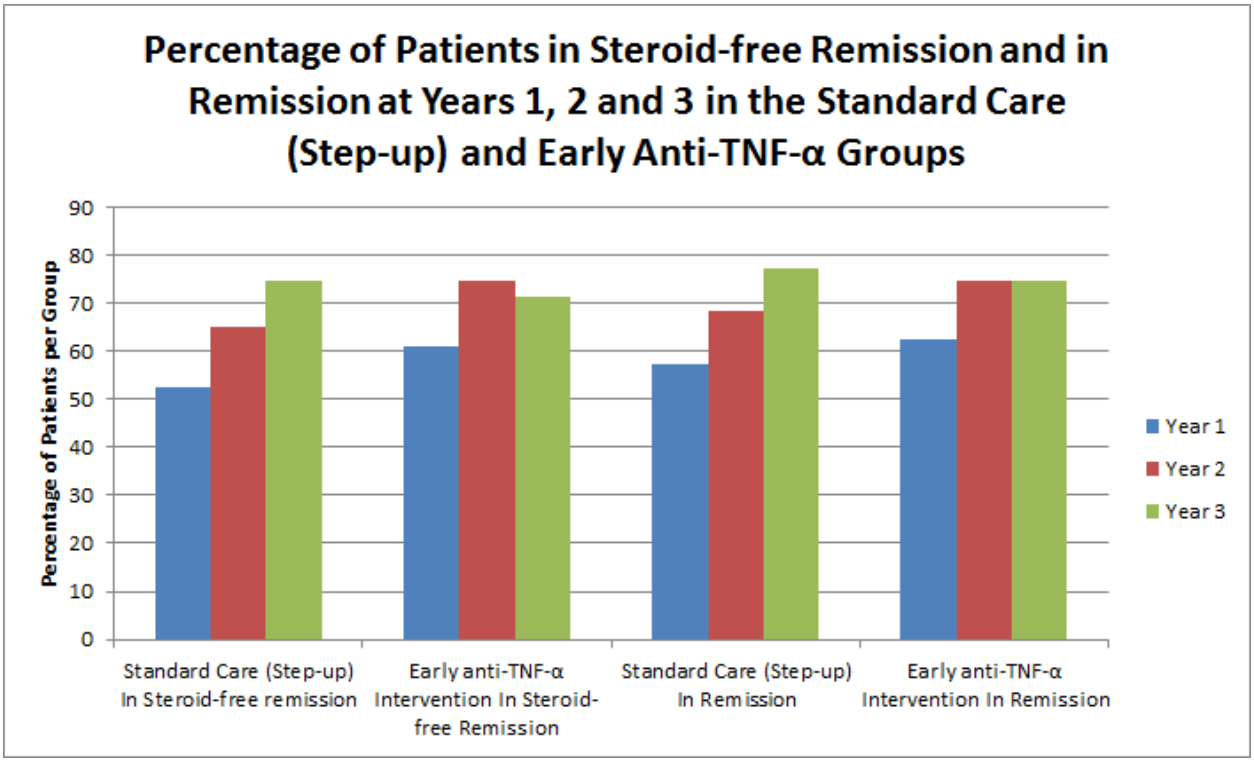
Table 3.5-4. The Steroid-related Health State at 6, 12, 18, 24, 30, and 36 Months Post-diagnosis in the Adjusted RISK-PROKIIDS Comparator Groups.

	Standard Care n= 237	Early Intervention with Biologics n=123	P value
Current health state at 6 months (%)			0.004*
steroid-free active	81 (34.2)	45 (36.6)	
steroid-free remission	93 (39.2)	65 (52.8)	
steroid active	34 (14.3)	8 (6.5)	
steroid remission	29 (12.2)	5 (4.1)	
Number in steroid-free remission at 6 months (Yes=1, No =0) (%)	93 (39.2)	65 (52.8)	0.019*
Current health state at 12 months (%)			0.013*
steroid-free active	78 (32.9)	44 (35.8)	
steroid-free remission	125 (52.7)	75 (61.0)	
steroid active	23 (9.7)	2 (1.6)	
steroid remission	11 (4.6)	2 (1.6)	
Number in steroid-free remission at 12 months (Yes=1, No =0) (%)	125 (52.7)	75 (61.0)	0.168
Current health state at 18 months (%)			0.073
steroid-free active	75 (31.6)	35 (28.5)	
steroid-free remission	132 (55.7)	82 (66.7)	
steroid active	22 (9.3)	5 (4.1)	
steroid remission	8 (3.4)	1 (0.8)	
Number in steroid-free remission at 18 months (yes=1, No =0) (%)	132 (55.7)	82 (66.7)	0.058
Current health state at 24 months (%)			0.092
steroid-free active	61 (25.7)	25 (20.3)	
steroid-free remission	154 (65.0)	92 (74.8)	
steroid active	14 (5.9)	6 (4.9)	
steroid remission	8 (3.4)	0 (0.0)	
Number in steroid-free remission at 24 months (Yes=1, No =0) (%)	154 (65.0)	92 (74.8)	0.075
Current health state at 30 months (%)			0.990
steroid-free active	58 (24.5)	29 (23.6)	
steroid-free remission	167 (70.5)	87 (70.7)	
steroid active	9 (3.8)	5 (4.1)	
steroid remission	3 (1.3)	2 (1.6)	

	Standard Care n= 237	Early Intervention with Biologics n=123	P value
Number in steroid-free remission at 30 months (Yes=1, No =0) (%)	167 (70.5)	87 (70.7)	1.000
Current health state at 36 months (%)			0.819
steroid-free active	44 (18.6)	27 (22.0)	
steroid-free remission	177 (74.7)	88 (71.5)	
steroid active	10 (4.2)	4 (3.3)	
steroid remission	6 (2.5)	4 (3.3)	
Number in steroid-free remission at 36 months (Yes=1, No =0) (%)	177 (74.7)	88 (71.5)	0.607
Number of steroid-free remission semesters in 36 months (mean (sd))	3.59 (1.61)	3.98 (1.86)	0.036*
Greatest number of consecutive steroid-free remission semesters in 36 months (mean (sd))	3.02 (1.66)	3.61 (1.97)	0.003*
Total days in hospital at 36 months (mean (sd))	3.76 (10.51)	3.97 (13.37)	0.872
Hospitalized Yes = 1, No =0 (%)	84 (35.4)	45 (36.6)	0.922

The current health state at diagnosis was based on the weighted Pediatric Crohn's Disease Activity Index (wPCDAI) and the steroid state of the patients; * $p<0.05$; Abbreviations: sd= standard deviation.

Figure 3.5-1. Comparison Between Early anti-TNF-α Intervention and Step-up Groups in the Percentage of People in Remission and Steroid-free Remission at the End of Years 1, 2, and 3.



There were no statistically significant differences between the comparator treatment groups ($p>0.05$) for each year.

3.6 Treatment Patterns in the Adjusted Patient Population

The classes of medications that each patient was taking was assessed for the three years of follow-up of the RISK-PROKIIDS study. While the class and treatment time of medications for each patient was recorded, doses were not. Over the three years of follow-up, patients in the standard care (step-up) group and in the early anti-TNF-α intervention group changed concomitant medications. The treatments with six classes of medications commonly prescribed in the treatment of Crohn's disease were tracked: corticosteroids, immunomodulators, biologics, 5-ASA's, antibiotics and enteral nutrition. The proportion of patients within each comparator group taking each of the six classes of medications over the three-year period are shown in Figure 3.6-1 (for the early anti-TNF-α or biologic intervention group) and Figure 3.6-2 (for the standard care group). As expected, all subjects in the early anti-TNF-α intervention group were taking anti-TNF-α medications (predominantly infliximab, and a few adalimumab) from the point of diagnosis to three months post-diagnosis. Over 90% of patients in the early anti-TNF-α intervention group remained on biologic treatment over three years post-diagnosis (see Figure 3.6-1). In the standard care (step up) group, by definition of the group, there was no use of anti-TNF-α until after three months (see Figure 3.6-2). Three months post-diagnosis anti-TNF-α use began with 11% of patients in the standard care group taking an anti-TNF-α then increasing to 27% of patients by the first year, to 46% of patients taking anti-TNF-α at the end of the second year and 54% of patients taking anti-TNF-α by the end of the third year.

Approximately 56% of patients in the early anti-TNF-α intervention group were on corticosteroids at the beginning of the study but use tapered off to less than 10% of patients after six months and remained low at less than 5% for the rest of the three years. Similar to the early anti-TNF-α group, there was high corticosteroid use within the first month (65% of patients) in the standard care group, which decreased to 14% in the first year, 6% in the second year, and 5% by the third year post-diagnosis.

Nine percent of patients in the early anti-TNF-α intervention group were taking immunomodulators at the beginning of the study and use increased steadily to 30% of subjects

by nine months and 39% by three years. In the standard care group, as expected immunomodulator use was higher than in the early anti-TNF-α group with 59% of patients on immunomodulators at the end of the first year, and decreasing only slightly to 54% of patients taking immunomodulators by the end of the third year after diagnosis.

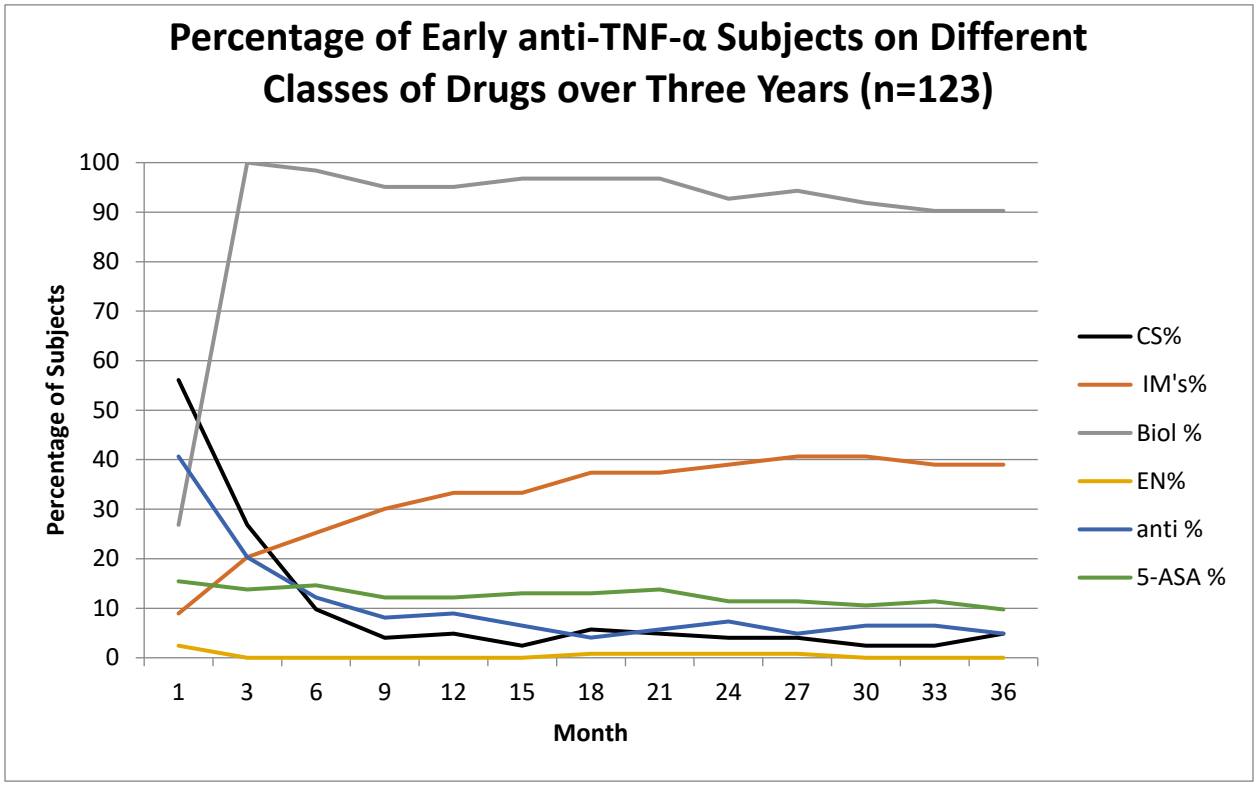
Enteral nutrition use in the early anti-TNF-α intervention group started at 2% of patients at the beginning of the study but by the end of three years, no patients in this group were using enteral nutrition as a form of treatment. Enteral nutrition use started with 7% of patients using enteral nutrition in the first month decreasing to 2% by the end of the third year.

Forty-one percent of patients in the early anti-TNF-α intervention group were taking antibiotics at the beginning of the study and use of antibiotics decreased to 20% by 3 months and to 5% by three years. Antibiotic use in the standard care group started with 27% of patients on antibiotics in the first month after diagnosis and decreased to 14% of patients taking antibiotics by the end of the third year following diagnosis.

The use of 5-ASAs remained fairly constant from 15% of patients in the early anti-TNF-α intervention group to 10% at three years. There was a much greater percentage of patients on 5-ASAs in the standard care group than the early anti-TNF-α group throughout the three years of the study with 34% of patients on 5-ASA in the first month after diagnosis and 27% of patients on 5-ASAs at the end of three years after diagnosis.

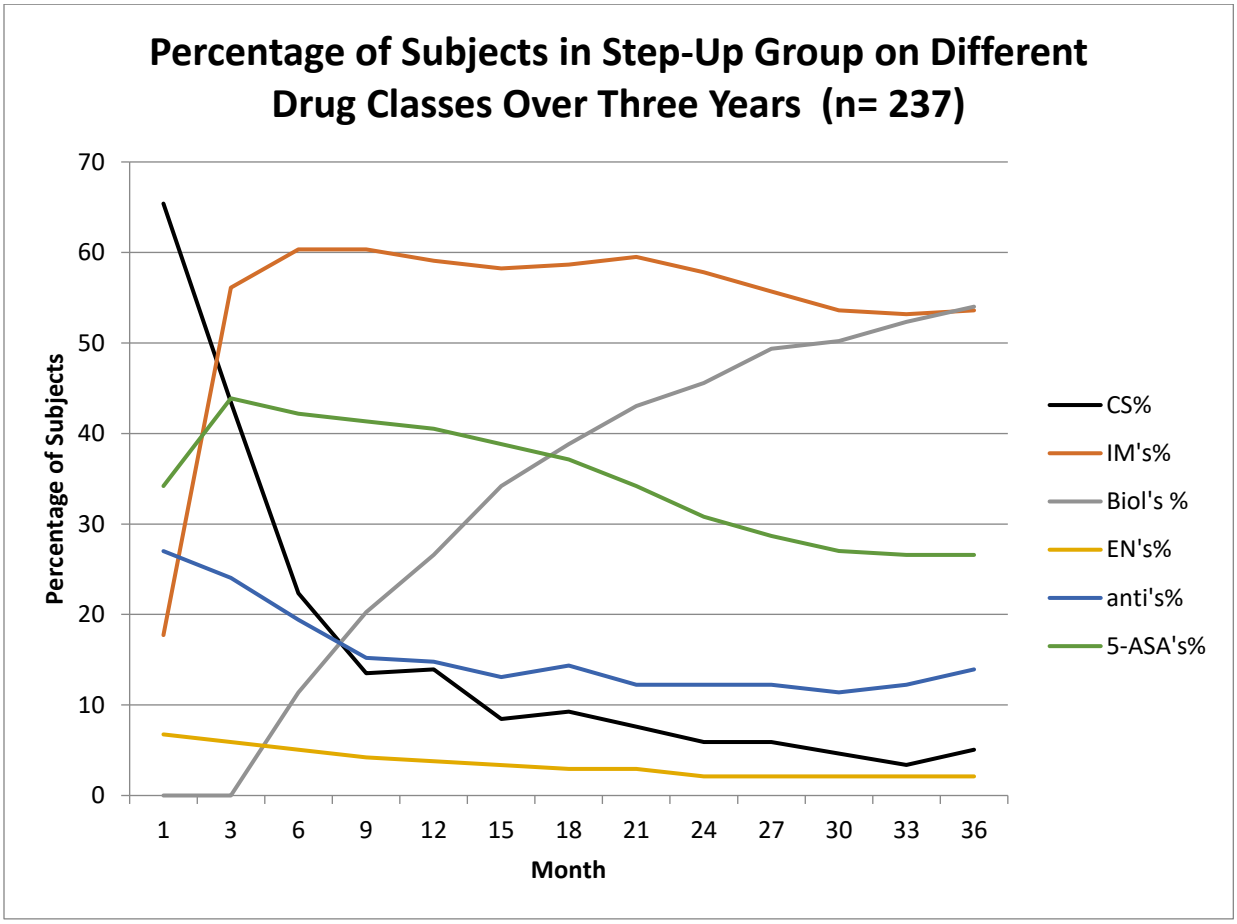
The differences in drug use between the early anti-TNF-α group and the standard care (step up) group was reflected in the difference in drug costs between the two comparator groups in the cost-effectiveness analysis. The proportion of patients on a particular drug class informed the total cost of drugs for each comparator group at a given time.

Figure 3.6-1. The Change in Treatment Over Three Years in the Early anti-TNF-α Intervention Group.



Abbreviations: CS =corticosteroids; IM's= immunomodulators; Biol's = anti-TNF-α biologics, EN's =enteral nutrition; anti's =antibiotics; 5-ASA's = Oral 5-aminosalicylate. The graph does not distinguish between monotherapy and concomitant treatments.

Figure 3.6-2. The Change in Treatment Over Three Years in the Standard Care (step-up) Group.



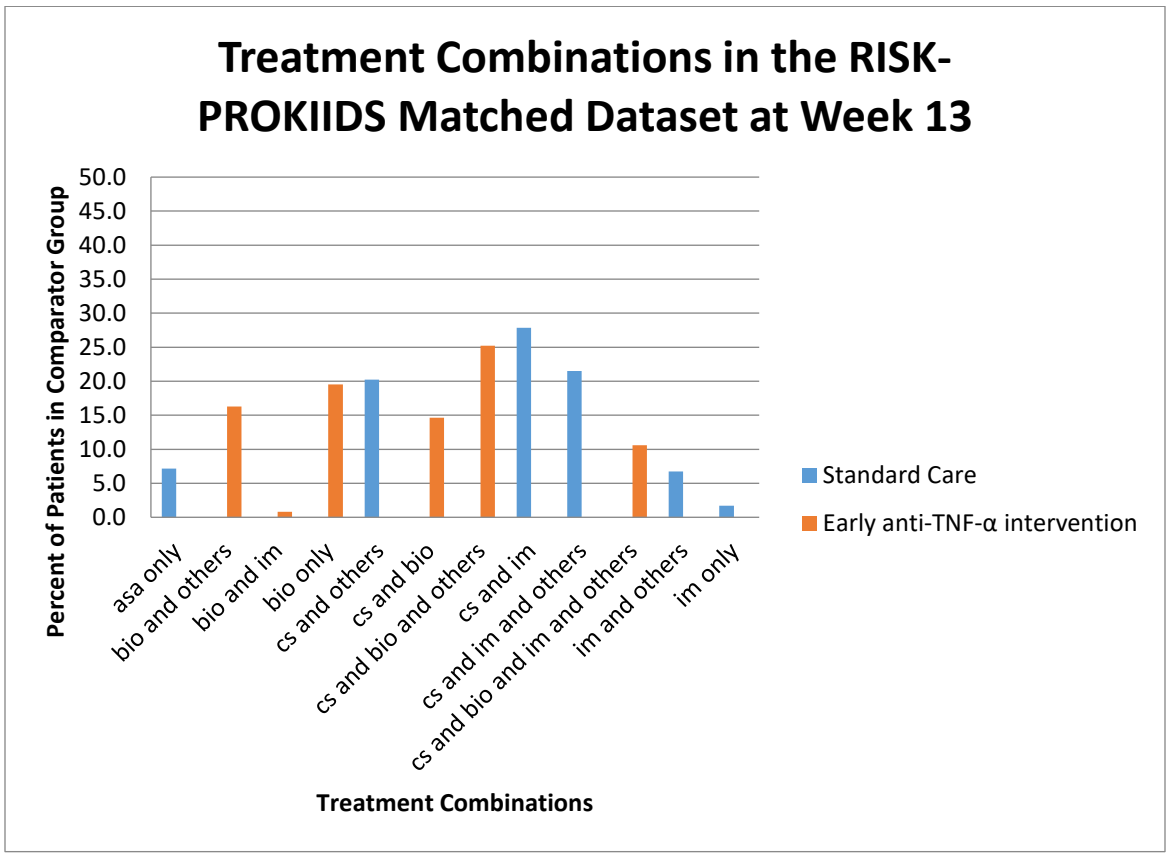
Abbreviations: CS =corticosteroids; IM's= immunomodulators; Biol's =biologics, EN's =enteral nutrition; anti's =antibiotics; 5-ASA's = Oral 5-aminosalicylate. The graph does not distinguish between monotherapy and concomitant treatments.

While not an endpoint of this study, in the course of ascertaining the treatments for the patients in the RISK-PROKIIDS representative comparator groups, concomitant treatments were also obtained for the first 3 months and subsequently at six month intervals. Figures 3.6-3, 3.6-4, 3.6-5, 3.6-6 and 3.6-7 show the proportion of patients in the standard care and early anti-TNF-α groups taking the predominant combinations of drug classes in different weeks over the course of the three year follow-up period. Patients in the RISK-PROKIIDS study received a wide variety of combinations of treatments. All combinations of treatments in the RISK-PROKIIDS study comparator groups are listed in Appendix 20. At week 13 post-diagnosis, the largest proportion of patients in the standard care group (28%) were on a combination of corticosteroids and immunomodulators, and in the early anti-TNF-α group the largest proportion of patients (25%) were on a combination corticosteroids and biologics and either 5-ASAs, enteral nutrition or antibiotics. By week 26, almost half (44%) of patients in the early anti-TNF-α group were on anti-TNF-α monotherapy. By week 26, standard care group patients were split in their treatments with 15% were on corticosteroids and immunomodulators, 14% were on immunomodulator monotherapy, 14% were on 5-ASA monotherapy, and 14% were on corticosteroids with an immunomodulator and either an antibiotic, or 5-ASA, or enteral nutrition. One year post-diagnosis 50% of the early anti-TNF-α group patients were on anti-TNF-α monotherapy, and 20% of the standard care group were on immunomodulator monotherapy. At two years, or 105 weeks post-diagnosis, 49% of the early anti-TNF-α group patients were on anti-TNF-α monotherapy and 27% were on anti-TNF-α and immunomodulators. At two years post-diagnosis, 16% of the standard care patients were on anti-TNF-α monotherapy, 18% were on anti-TNF-α with immunomodulators, 17% were on immunomodulator monotherapy and 16% were on immunomodulator and either 5-ASA's, enteral nutrition or antibiotics. At three years post-diagnosis, 46% of early anti-TNF-α group patients were on anti-TNF-α monotherapy and 26% were on anti-TNF-α with immunomodulators. In the standard care group, at three years, 23% of patients were on anti-TNF-α monotherapy, 19% were on anti-TNF-α with immunomodulators, and 17% were on immunomodulator monotherapy. At three years post-diagnosis, in the standard care group, 6.3% of patients were on corticosteroids with or without other medications, and in the early anti-TNF-α group, 4.9% of patients were on corticosteroids

with or without other medications. This suggests a slightly decreased use of steroids in the early anti-TNF-α intervention group.

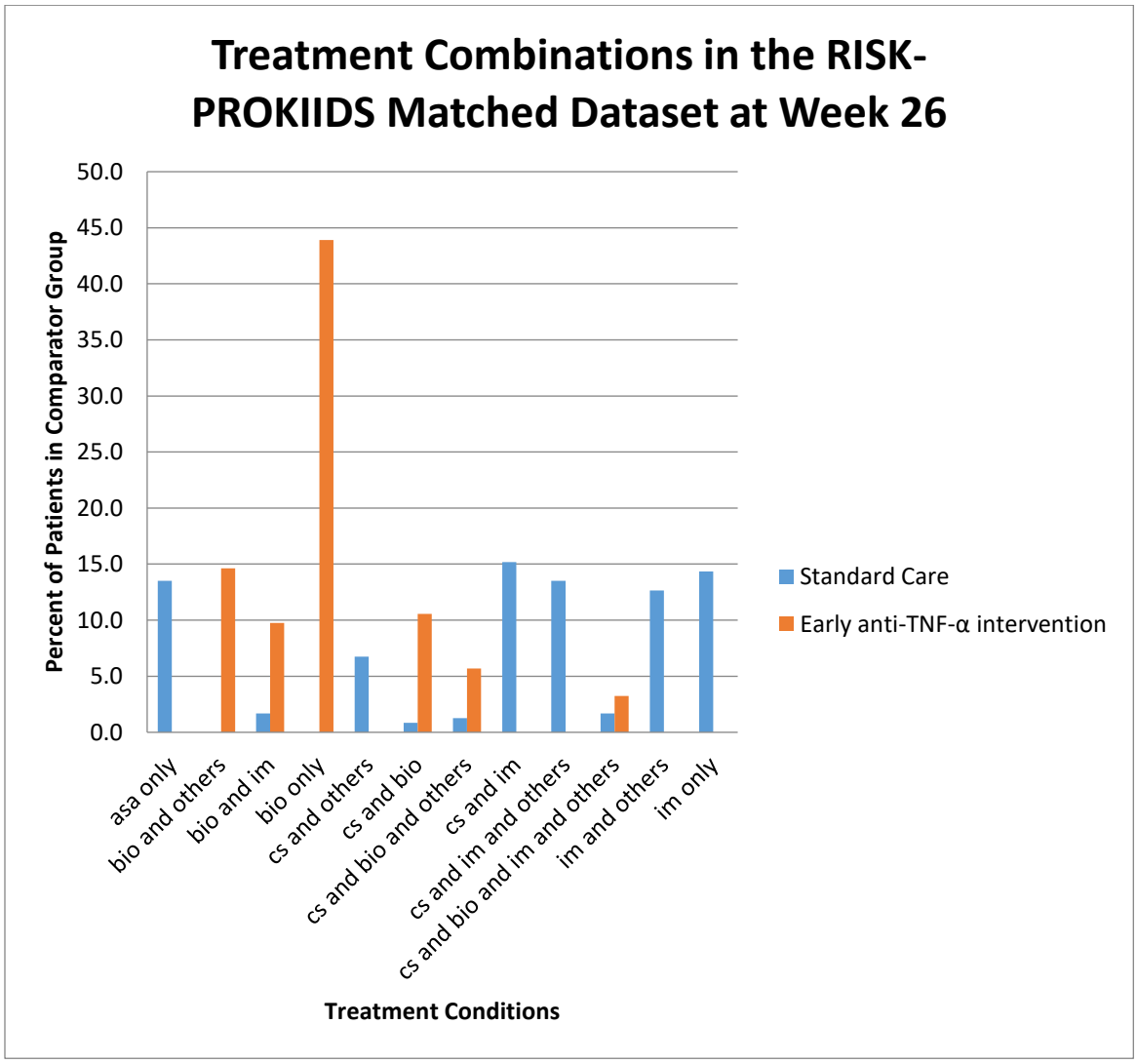
Overall, these results show that anti-TNF-α monotherapy was preferred in the RISK-PROKIIDS patients over anti-TNF-α combination therapy. In the standard care group, immunomodulator monotherapy is slightly preferred over immunomodulator combination therapy. The results also show that treatment among RISK-PROKIIDS patients is quite varied with over twenty combinations of treatments at any given time and as a result, drug costs for each comparator group were also quite varied. Over time, treatment combinations were expected to change to reflect the difference between induction therapy to induce remission and then maintenance therapy to maintain remission. The cost-effectiveness analysis, presented in the next section, accounted for changes in treatments over time.

Figure 3.6-3. Drug Treatment Combinations in the RISK-PROKIIDS Comparator Groups 13 Weeks After Diagnosis.



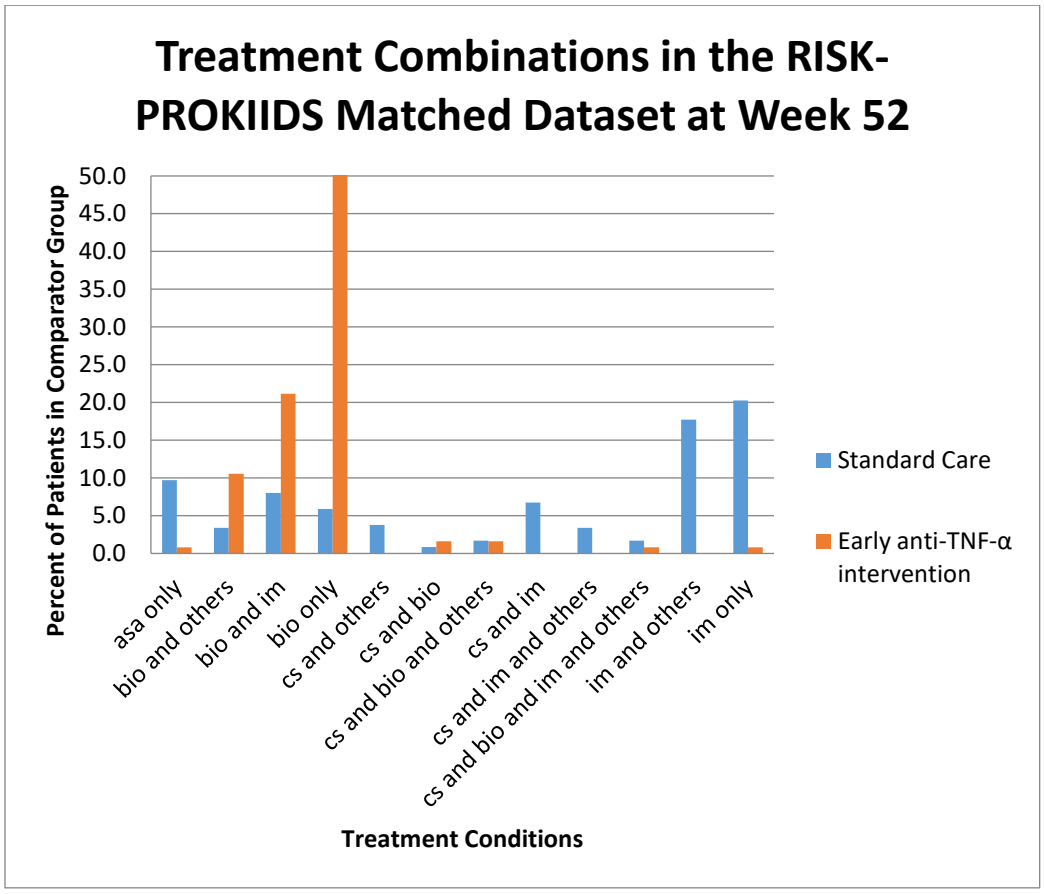
Abbreviations: cs = corticosteroids; im = immunomodulators; bio =biologics, en = enteral nutrition; anti = antibiotics; asa = oral 5-aminosalicylate; others = and/or asa and/or anti and/or en.

Figure 3.6-4. Drug Treatment Combinations in the RISK-PROKIIDS Comparator Groups 26 Weeks After Diagnosis.



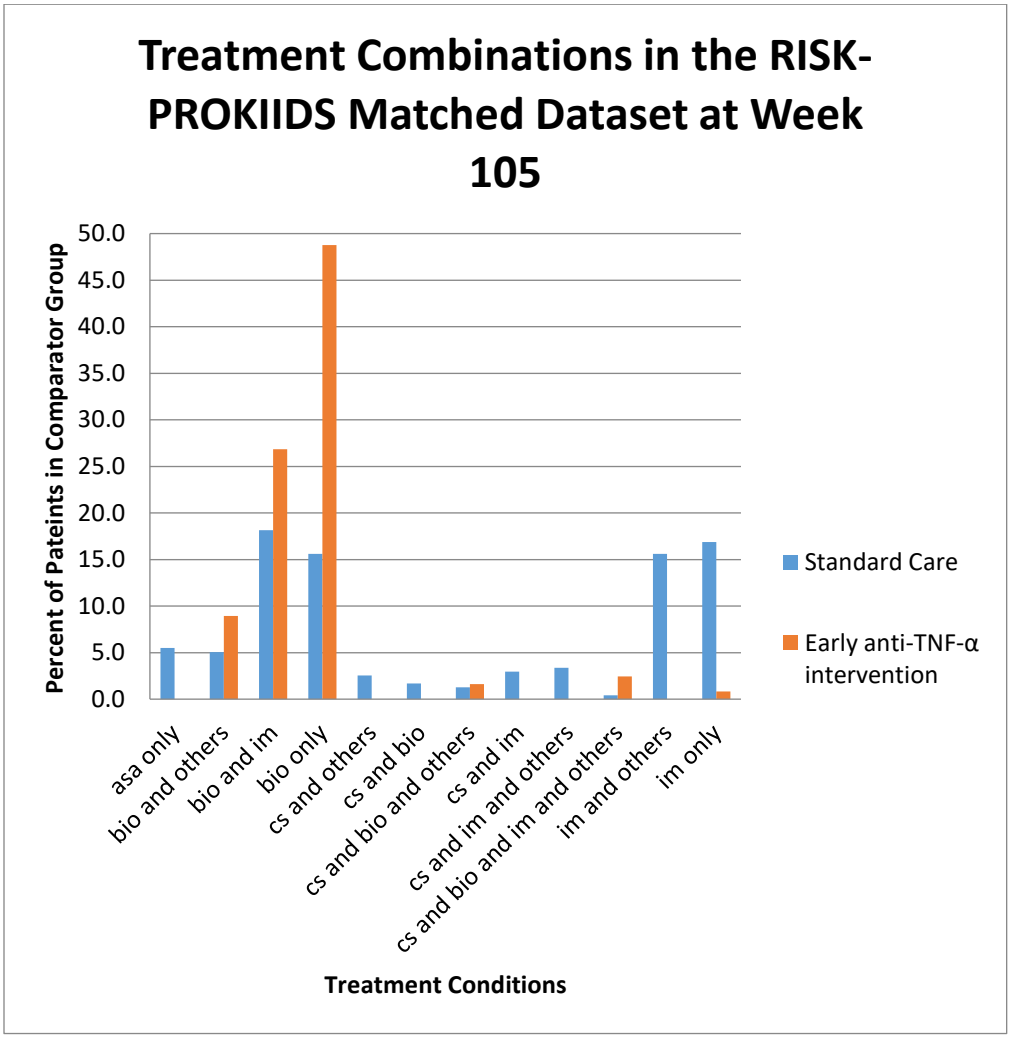
Abbreviations: cs = corticosteroids; im = immunomodulators; bio =biologics, en = enteral nutrition; anti = antibiotics; asa = oral 5-aminosalicylate; others = and/or asa and/or anti and/or en.

Figure 3.6-5. Drug Treatment Combinations in the RISK-PROKIIDS Comparator Groups 52 Weeks After Diagnosis.



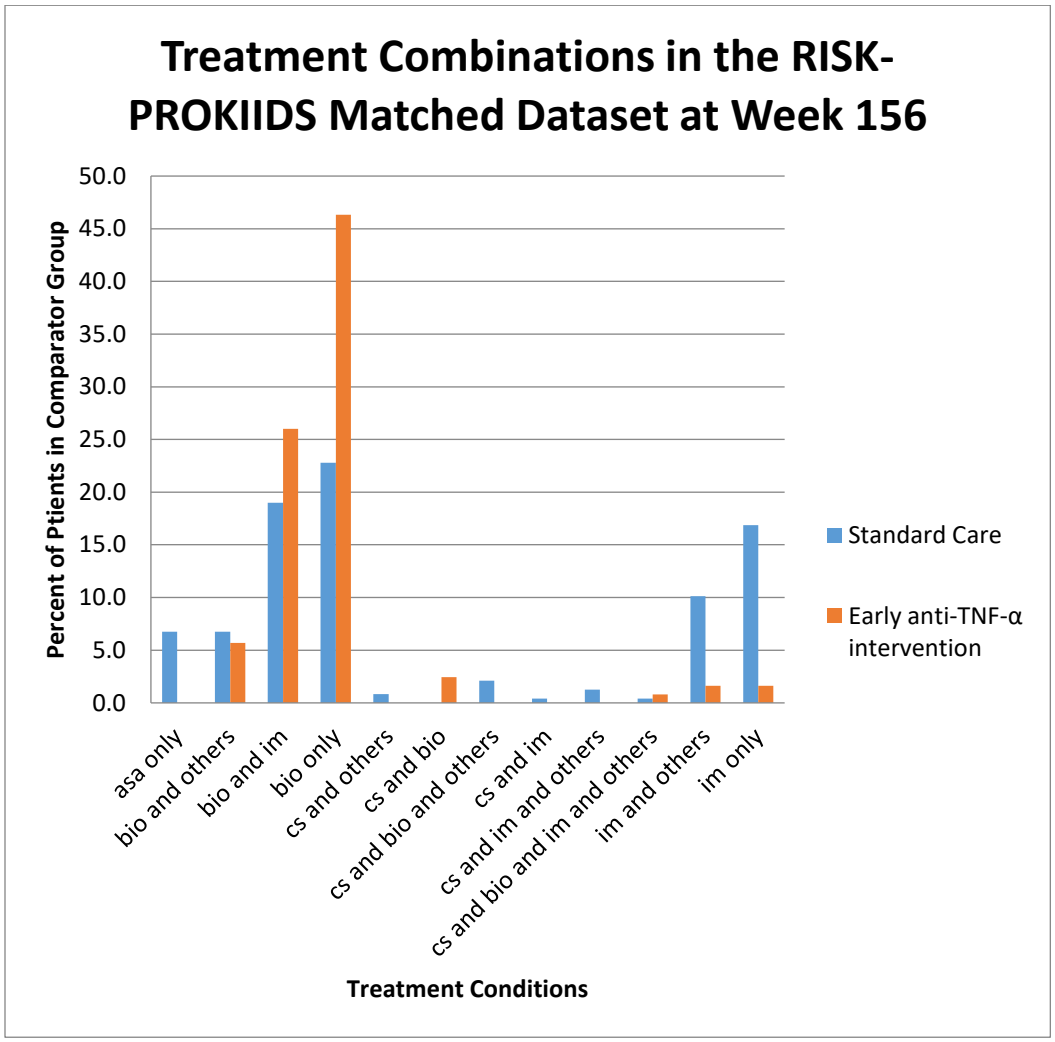
Abbreviations: cs = corticosteroids; im = immunomodulators; bio =biologics, en = enteral nutrition; anti = antibiotics; asa = oral 5-aminosalicylate; others = and/or asa and/or anti and/or en.

Figure 3.6-6. Drug Treatment Combinations in the RISK-PROKIIDS Comparator Groups 105 Weeks After Diagnosis.



Abbreviations: cs = corticosteroids; im = immunomodulators; bio =biologics, en = enteral nutrition; anti = antibiotics; asa = oral 5-aminosalicylate; others = and/or asa and/or anti and/or en.

Figure 3.6-7. Drug Treatment Combinations in the RISK-PROKIIDS Comparator Groups 156 Weeks After Diagnosis.



Abbreviations: cs = corticosteroids; im = immunomodulators; bio =biologics, en = enteral nutrition; anti = antibiotics; asa = oral 5-aminosalicylate; others = and/or asa and/or anti and/or en.

3.7 Cost-effectiveness Analysis

The goal of the work so far was to prepare inputs to inform the cost-effectiveness analysis of early intervention (intervention within the first three months of diagnosis) with anti-TNF-α compared to standard step-up care where anti-TNF-α can be introduced only after the first three months of diagnosis in newly diagnosed pediatric patients with moderate to severe Crohn's disease. Where patient level data was needed to inform transition probabilities or costs, the propensity score matched RISK-PROKIIDS data set (assembled using the Across method) was used for the results shown below.

Using a Markov two-dimensional microsimulation model, which modeled the movement of Crohn's disease patients between states of remission and active disease, the incremental cost per week in steroid-free remission of early anti-TNF-α intervention was determined. The incremental cost per additional week in steroid-free medical remission was the representative incremental cost effectiveness ratio (ICER) for the primary cost-effectiveness analysis. Healthcare public payer, and societal perspectives were examined and are described below. In addition to determining the incremental cost per additional week in steroid-free medical remission, the incremental cost per additional week in medical remission irrespective of steroid use was also determined as a secondary analysis.

3.7.1 Cost-effectiveness in the Healthcare Public Payer Reference (Base) Case

The Ontario public health care system was used to represent the health care public payer. A discount rate of 1.5% and a three-year time horizon were used for the reference case. The seven health states of "active disease", "active disease experiencing adverse events of special interest", "active disease requiring surgery or hospitalization", "medical remission", "surgical remission", "surgical complications" and "death" were modelled in the Markov microsimulation model (see Figure 2.5.6.1-1 for the health state transition diagram). The number of weeks (or cycles) in medical remission without taking corticosteroids was the primary effectiveness outcome. Costs and outcomes for the early anti-TNF-α treatment and standard care treatment

strategies were determined and averaged for 50 samples of 10,000 individual microsimulations representing a probabilistic (2-D) analysis.

The results of the cost-effectiveness analysis are summarized in Table 3.7.1-1. In the reference case, early anti-TNF-α intervention was more costly than the standard care intervention over three years by $31,112. Early anti-TNF-α intervention was also more effective with 11.3 more weeks in steroid-free medical remission. The incremental cost per steroid-free remission week was $2,755.70 for the early anti-TNF-α intervention for the reference case from a health care payer perspective.

The early anti-TNF-α intervention was more costly but more effective than standard care. However, there was considerable uncertainty in the results as demonstrated by the incremental cost-effectiveness scatter plots and the cost-effectiveness acceptability curves. The reference case incremental cost effectiveness scatter plot for the two dimensional probabilistic analysis with 50 samples of 10,000 microsimulations is shown in Figure 3.7.1-1. All of the 50 samples showed a positive incremental effect of steroid-free remission weeks for the early anti-TNF-α intervention, but at increased cost and most of the samples fell within the 95% confidence ellipse.

The incremental cost effectiveness scatter plot for one sample of 10,000 microsimulations is shown in Figure 3.7.1-2. Figure 3.7.1-2 shows that within one sample of 10,000 microsimulations within the 95% confidence interval ellipse, most simulations showed a positive incremental effect and positive incremental cost for the early anti-TNF-α intervention. However, some simulations fell within other quadrants of the cost-effectiveness plane. Sixty-seven percent of simulations (dots in ICE scatterplot) fell within the northeast quadrant of the cost-effectiveness plane showing increased cost and increased effectiveness. Fourteen percent of simulations were dominated and fell within the northwest quadrant of the cost-effectiveness plane with increased cost and less effectiveness. Sixteen percent of simulations were dominant and fell within the southeast quadrant) of the cost-effectiveness plane and were more effective and less costly. Three percent of simulations fell within the southwest quadrant and were less

costly and less effective. The scattering of simulations in all quadrants from the one-dimensional microsimulation indicates that there is uncertainty within the results. For this particular sample, of 10,000 microsimulations, the incremental cost for early anti-TNF-α intervention was $30,448 (95%CI -36708, 117,265), the incremental effect was 11.19 (95%CI -31.04, 47.97) steroid-free remission weeks, and the incremental cost-effectiveness ratio was $2,720 per additional week in steroid-free remission.

The use of tracker variables in the microsimulation model allowed the tracking of individuals as they went through the model and allowed the determination of how many individuals experienced various events such as surgery, death, and adverse events. The wide confidence interval for the incremental cost in Table 3.7.1-1 reflects the large range of costs incurred by individuals in each comparator arm. Higher costs were accrued by individuals that experienced surgeries, or multiple adverse events in either comparator group.

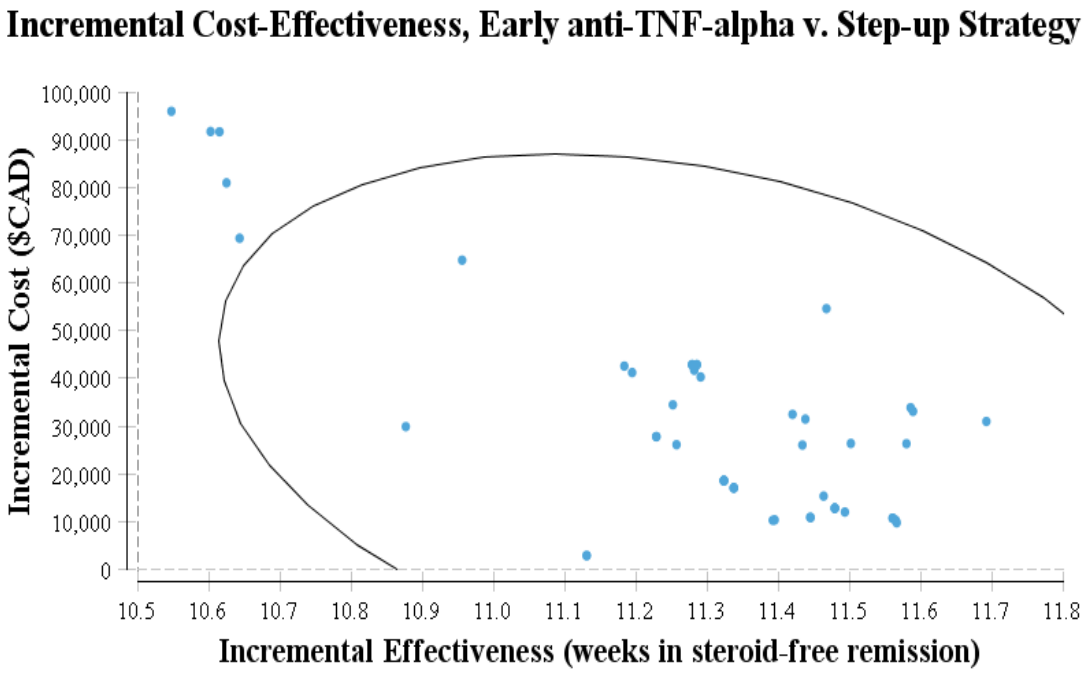
The cost-effectiveness acceptability curve from the 2-D microsimulation for the reference case from a health care payer perspective is shown in Figure 3.7.1-3. These curves, reflective of uncertainty in the ICER, represent the proportion of microsimulations wherein each strategy is cost-effective (the dollar value of effectiveness exceeds the costs) over a range of willingness-to-pay thresholds. The curve shows that the standard care intervention was cost-effective below a willingness-to-pay threshold of $2,000 per week in steroid-free remission, but above this threshold, the early anti-TNF-α intervention does become cost-effective in some iterations. At a willingness-to-pay threshold of approximately $3,500 per week in steroid-free remission, neither strategy is dominant over the other as both strategies are cost-effective 50% of the time. Above a willingness to pay threshold of $3,500, the early anti-TNF-α intervention becomes cost-effective an increasing number of times compared to the standard care strategy. Above a willingness-to-pay of $6,000 per week in steroid-free remission, the early anti-TNF-α intervention becomes the dominant cost-effective strategy.

Table 3.7.1-1. Cost-effectiveness Analysis Results Summary from a Health Care Payer Perspective.

Strategy	Annual Discount Rate	Mean Cost ($CAD)	Incremental Cost (ΔCost) ($CAD)	95% Confidence Interval for ΔCost	Mean Effect (weeks in steroid-free remission)	Incremental Effect (ΔEffect)	95% Confidence Interval for Δ Effect	Incremental Cost-effectiveness Ratio (ICER)
Standard Care (Step-up)	1.5% (reference case)	96,516.42			83.07			
Early anti-TNF-α Intervention	1.5% (reference case)	127,628.05	31,111.63	(2,939.44, 91,715.06)	94.36	11.29	(10.60,11.59)	**2,755.70**

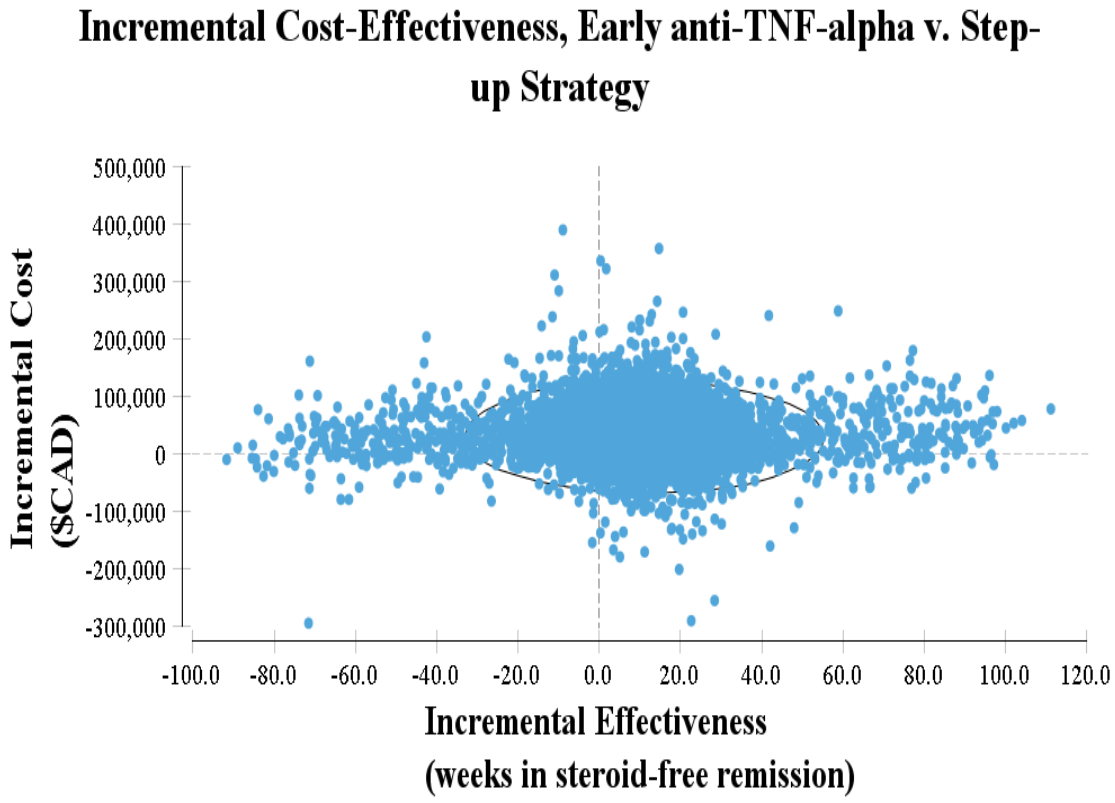
Probabilistic analysis results from a two-dimensional Markov microsimulation model with 50 samples of 10,000 microsimulations. Costs are presented in 2017 Canadian dollars ($CAD).

Figure 3.7.1-1. Incremental Cost-effectiveness Scatter Plot of the Probabilistic (2-D) Cost-effectiveness Analysis of Early anti-TNF-α Intervention vs. Standard Care from a Public Healthcare Perspective.



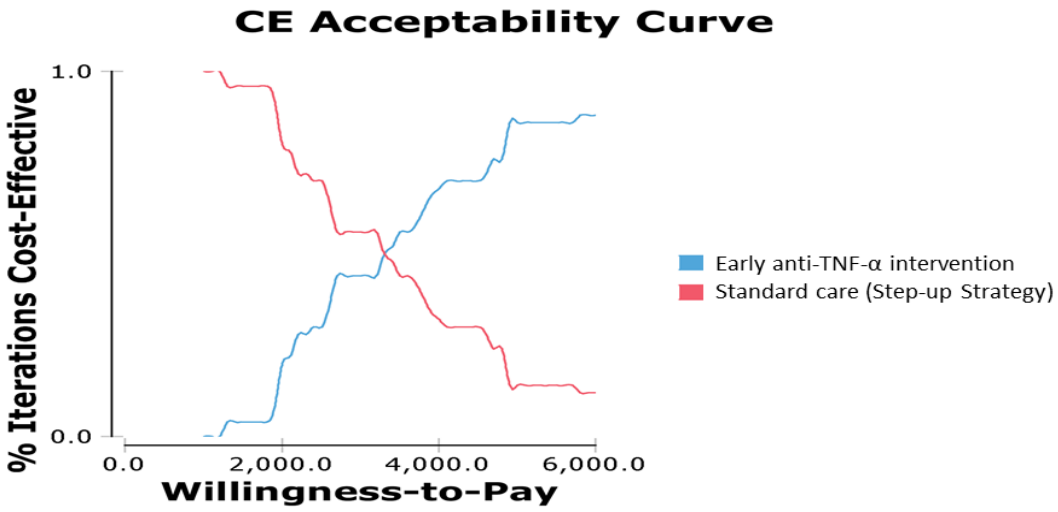
Results from the probabilistic analysis, two dimensional microsimulation of 50 samples of 10,000 microsimulations cost-effectiveness analysis are shown. All 50 samples fell within the northeast quadrant of the cost-effectiveness plane. Each dot represents the mean incremental costs and mean incremental effectiveness of one sample of 10,000 microsimulations. The incremental cost is presented in Canadian dollars and the incremental effectiveness is presented in weeks in steroid-free remission. Ellipse represents the 95% confidence interval.

Figure 3.7.1-2. Incremental Cost-effectiveness Scatter Plot of the One Dimensional Microsimulation Cost-effectiveness Analysis of Early anti-TNF-α Intervention vs. Standard Care from a Public Healthcare Perspective.



Results from the one dimensional Markov microsimulation with 10,000 microsimulations cost-effectiveness analysis are shown. Each dot represents the incremental cost and incremental effectiveness of one microsimulation. The incremental cost is presented in Canadian dollars and the incremental effectiveness is presented in weeks in steroid-free remission. The partially visible ellipse represents 95% confidence interval.

Figure 3.7.1-3. Cost-effectiveness Acceptability Curve of the Probabilistic (2-D) Cost-effectiveness Analysis of Early anti-TNF-α Intervention vs. Standard Care from a Public Healthcare Perspective.



Results from the probabilistic analysis, two dimensional microsimulation of 50 samples of 10,000 microsimulations cost-effectiveness (CE) analysis are shown. The willingness-to-pay (WTP) is presented in Canadian dollars.

3.7.2 Cost-effectiveness with the Societal Payer Perspective Reference (Base) Case

The cost-effectiveness analysis from the societal perspective was identical to the health care public payer perspective except for the addition of costs associated with caregiver time losses required for the care of their children afflicted with Crohn's disease. Therefore, the incremental cost-effectiveness ratio from the societal perspective is slightly higher than that of the healthcare public payer perspective. Similar to the healthcare perspective, a discount rate of 1.5%, and a three-year time horizon were used for the reference case from the societal perspective.

The results of the cost-effectiveness analysis from a societal perspective are summarized in Table 3.7.2-1. In the reference case, early anti-TNF-α intervention was more costly over the standard care intervention over three years by $33,509. Early anti-TNF-α intervention was also more effective with 11.3 more weeks in steroid-free medical remission. The incremental cost per additional steroid-free remission week was $2,968 for the early anti-TNF-α intervention for the reference case from a societal payer perspective. The societal perspective had the same outcome measures and only a marginal increase in cost than the healthcare public payer perspective, and, as a result, the early anti-TNF-α intervention had a similar ICER from a societal perspective.

As with the healthcare public payer perspective, the early anti-TNF-α intervention from a societal perspective was more costly but more effective than standard care. However, there was considerable uncertainty in the results. The reference case incremental cost effectiveness scatter plot for the two dimensional probabilistic analysis with 50 samples of 10,000 microsimulations is shown in Figure 3.7.2-1. All of the samples showed a positive incremental effect of steroid-free remission weeks for the early anti-TNF-α intervention, but at increased cost. Ninety percent of the samples fell within the 95% confidence ellipse.

The cost-effectiveness acceptability curve from the 2-D microsimulation for the reference case from a societal perspective is shown in Figure 3.7.2-2. The curve shows that the standard care

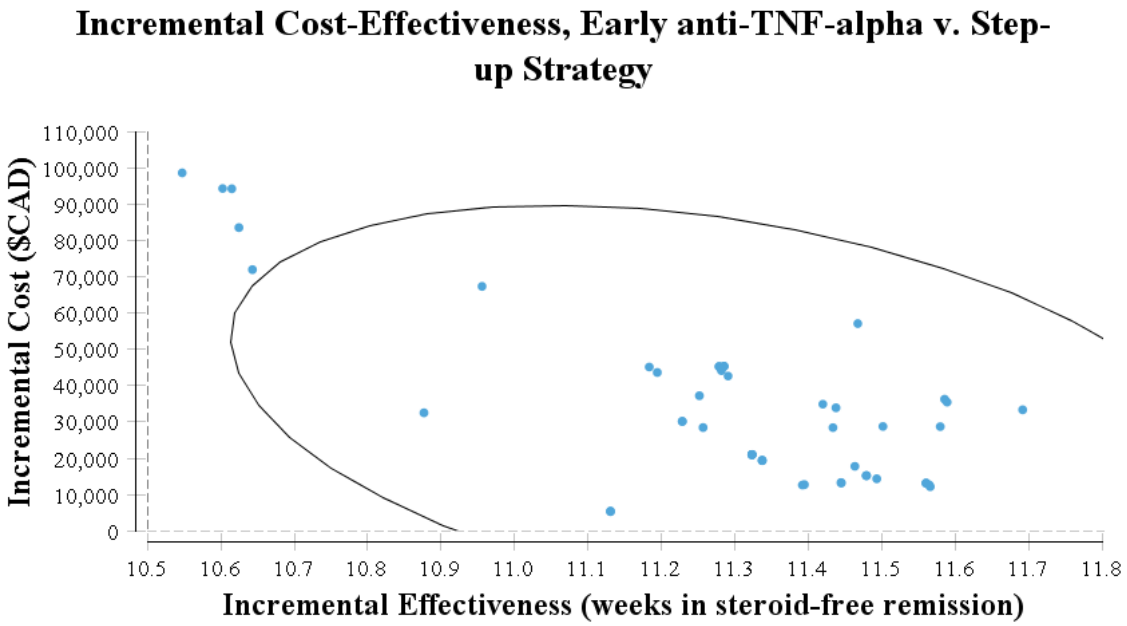
intervention was cost-effective below a willingness-to-pay threshold of $4,000 per week in steroid-free remission, but above this threshold, the early anti-TNF-α intervention does become cost-effective in some iterations. At a willingness-to-pay threshold of approximately $5,000 per week in steroid-free remission, neither strategy is dominant over the other as both strategies are cost-effective 50% of the time. Above a willingness to pay threshold of $8,000, the early anti-TNF-α intervention becomes cost-effective an increasing number of times compared to the standard care strategy. Above a willingness-to-pay of $10,000 per week in steroid-free remission, the early anti-TNF-α intervention becomes the dominant cost-effective strategy.

Table 3.7.2-2. Cost-effectiveness Analysis Results Summary from a Societal Perspective.

Strategy	Annual Discount Rate	Mean Cost ($CAD)	Δ Cost	Δ Cost (95%CI)	Mean Effect (weeks in steroid-free remission)	Δ Effect	Δ Effect (95%CI)	ICER
Standard Care (Step-up)	1.5% (reference case)	100,955.65			83.07			
Early anti-TNF-α Intervention	1.5% (reference case)	134,464.29	33,508.64	(5436.27, 94,308.26)	94.36	11.29	(10.60,11.59)	2,968.02

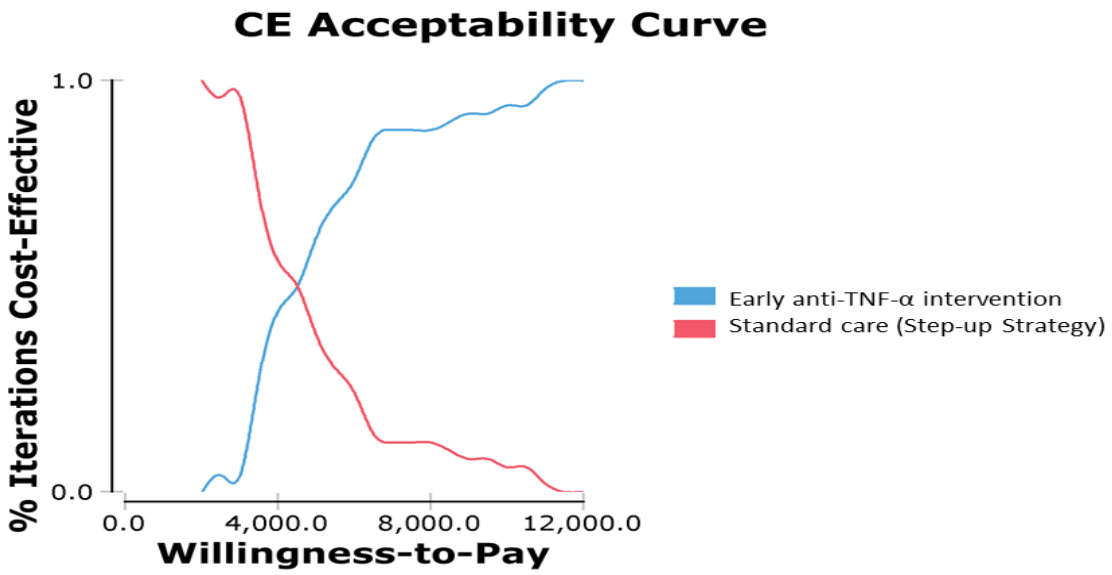
Probabilistic analysis results from a two-dimensional Markov microsimulation model with 50 samples of 10,000 microsimulations. Costs are presented in 2017 Canadian dollars. ICER=incremental cost-effectiveness ratio.

Figure 3.7.2-1. Incremental Cost-effectiveness Scatter Plot of the Probabilistic (2-D) Cost-effectiveness Analysis of Early anti-TNF-α Intervention vs. Standard Care from a Societal Perspective.



Results from the probabilistic analysis, two dimensional microsimulation of 50 samples of 10,000 microsimulations cost-effectiveness analysis are shown. Each dot represents the mean incremental cost and mean incremental effectiveness of one sample population. All dots fell within the northeast quadrant of the cost-effectiveness plane. The incremental cost is presented in Canadian dollars and the incremental effectiveness is presented in weeks in steroid-free remission.

Figure 3.7.2-2. Cost-effectiveness Acceptability Curve of the Probabilistic (2-D) Cost-effectiveness Analysis of Early anti-TNF-α Intervention vs. Standard Care from a Societal Perspective.



Results from the probabilistic analysis, two dimensional microsimulation of 50 samples of 10,000 microsimulations cost-effectiveness (CE) analysis are shown. The willingness-to-pay (WTP) is presented in Canadian dollars.

3.7.3 Additional Cost-effectiveness Analysis

In addition to conducting a cost-effectiveness analysis of early intervention with anti-TNF-α compared to standard step-up care where the outcome measure was weeks in steroid-free medical remission, the cost-effectiveness model was run comparing the two strategies using the outcome measure of weeks in medical remission irrespective of steroid use as a secondary analysis. All model inputs were identical to the previous analysis except that all weeks in medical remission were counted and not just the ones without steroid-use. The incremental cost of early intervention with anti-TNF-α per week in medical remission was determined. Similar to the above analysis, the "Across" method of imputed data set assembly was used in the preparation of the matched RISK-PROKIIDS data set. Summary results of the cost-effectiveness analysis from a healthcare public payer perspective using a reference case discounting rate of 1.5% is shown in Table 3.7.3-1.

In the reference case, early anti-TNF-α intervention was more costly than the standard care intervention over three years by $31,112. Early anti-TNF-α intervention was also more effective with an additional 6.65 weeks in medical remission. The incremental cost per additional medical remission week was $4,679 for the early anti-TNF-α intervention from a health care payer perspective. The ICER was higher when remission weeks were considered as the effectiveness measure because the difference between the early anti-TNF-α intervention and the standard care strategy was smaller when total remission weeks were considered. This suggests that the early anti-TNF-α intervention may be more favorable for the pediatric population since steroid use is of particular concern.

The summary results of the cost-effectiveness analysis with weeks in remission as the effectiveness measure with or without steroids, from a societal perspective, including caregiver productivity losses (similar to the previous societal cost-effectiveness analysis), are shown in Table 3.7.3-2. The incremental cost-effectiveness scatter plot for the societal perspective and the cost-effectiveness acceptability curve are shown in Figures 3.7.3-1 and Figure 3.7.3-2. The patterns for the incremental cost-effective scatter plot and the cost-effectiveness acceptability

curve were similar to those of the plots with steroid-free remission weeks as the effect measure.

In addition to comparing the ICERs without steroids and irrespective of steroid use in remission, the additional cost-effectiveness analysis was used to compare the difference in the ICER between the model using transition probabilities from the RISK-PROKIIDS matched data assembled using the “Across” method with data assembled using the “Within” approach.

Table 3.7.3-1. Cost-effectiveness Analysis Results Summary from a Public Health Care Payer Perspective Using Remission as the Outcome.

Strategy	Annual Discount Rate	Mean Cost ($CAD)	Δ Cost	Δ Cost (95%CI)	Mean Effect (weeks in remission)	Δ Effect	Δ Effect (95%CI)	ICER ($/weeks in remission)
Standard Care (Step-up)	1.5% (reference case)	96,516.42			97.50			
Early anti-TNF-α Intervention	1.5% (reference case)	127,628.05	31,111.63	(2,939.43, 91,715.06)	104.15	6.65	(5.92, 7.00)	4,679.24

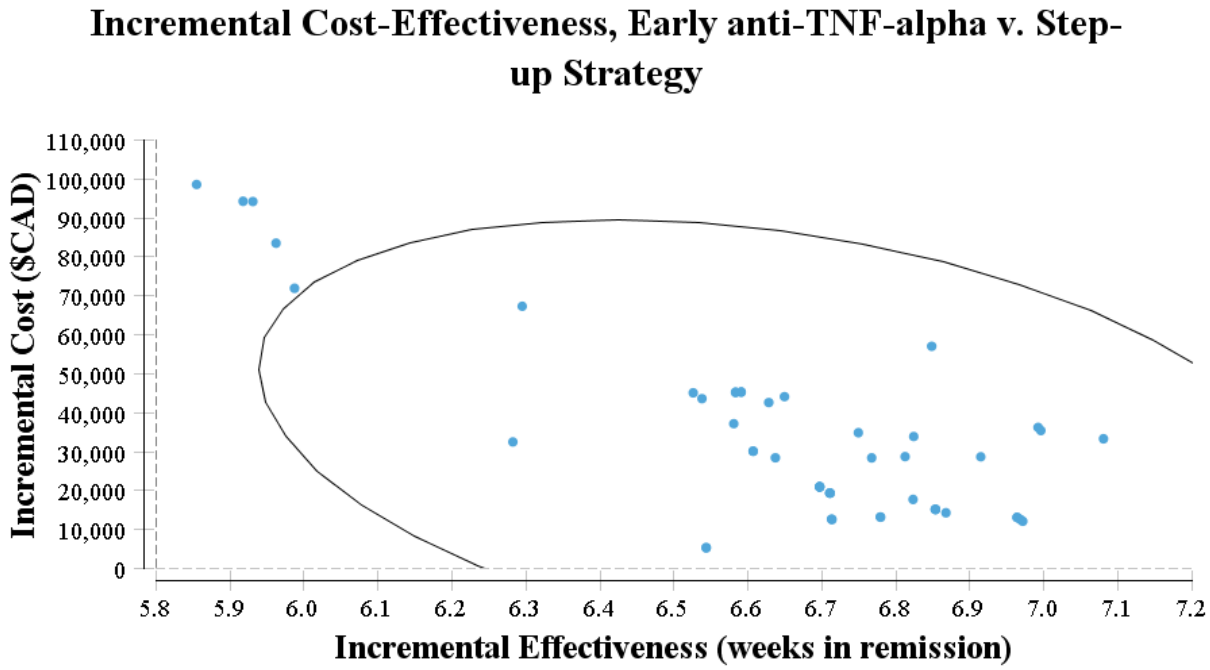
Probabilistic analysis results from a two-dimensional Markov microsimulation model with 50 samples of 10,000 microsimulations. Costs are presented in 2017 Canadian dollars. The effect measured was weeks in medical remission with or without the use of steroids. Abbreviation: ICER = incremental cost-effectiveness ratio.

Table 3.7.3-2. Cost-effectiveness Analysis Results Summary from a Societal Payer Perspective Using Remission as the Outcome.

Strategy	Annual Discount Rate	Mean Cost ($CAD)	Δ Cost	Δ Cost (95%CI)	Mean Effect (weeks in remission)	Δ Effect	Δ Effect (95%CI)	ICER
Standard Care (Step-up)	1.5% (reference case)	100,955.65			97.50			
Early anti-TNF-α Intervention	1.5% (reference case)	134,464.29	33,508.64	(5,436.27, 94,308.26)	104.15	6.65	(5.92, 7.00)	5,039.76

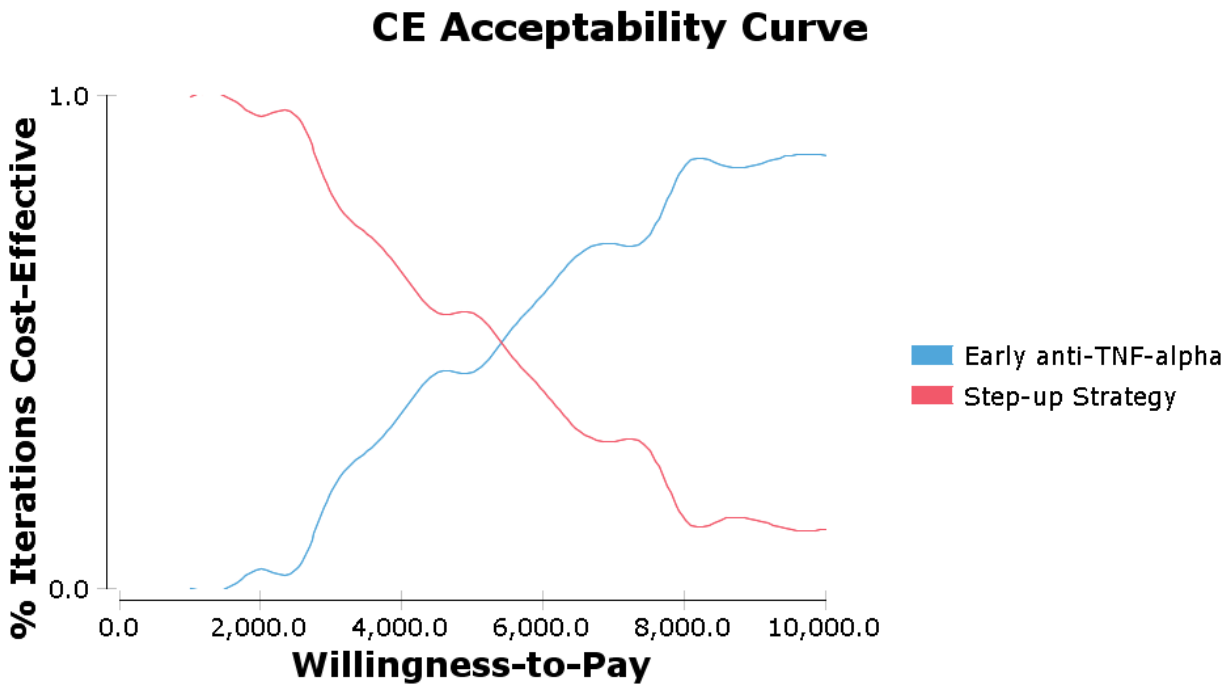
Probabilistic analysis results from a two-dimensional Markov microsimulation model with 50 samples of 10,000 microsimulations. Costs are presented in 2017 Canadian dollars. The effect measured was weeks in medical remission with or without the use of steroids. Abbreviation: ICER = incremental cost-effectiveness ratio.

Figure 3.7.3-1. Incremental Cost-effectiveness Scatter Plot of the Probabilistic (2-D) Cost-effectiveness Analysis of Early anti-TNF-α Intervention vs. Standard Care from a Societal Perspective with Medical Remission with or without Steroids as the Effect Measure.



Results from the probabilistic analysis, two dimensional microsimulation of 50 samples of 10,000 microsimulations cost-effectiveness analysis are shown. Each dot represents the mean incremental cost and mean incremental effectiveness of one sample population. The incremental cost is presented in Canadian dollars and the incremental effectiveness is presented in weeks in medical remission. All points fell within the northeast quadrant of the cost-effectiveness plane. The ellipse represents the 95% confidence interval.

Figure 3.7.3-2. Cost-effectiveness Acceptability Curve of the Probabilistic (2-D) Cost-effectiveness Analysis of Early anti-TNF-α Intervention vs. Standard Care from a Societal Perspective with Medical Remission With or Without Steroids as the Effect Measure.



Results from the probabilistic analysis, two dimensional microsimulation of 50 samples of 10,000 microsimulations cost-effectiveness (CE) analysis are shown. The willingness-to-pay (WTP) is presented in Canadian dollars.

3.7.4 Comparison of Cost-effectiveness Analyses with Different Matched Datasets

As stated previously, the RISK-PROKIIDS matched dataset used to determine health state transition probabilities for the cost-effectiveness model was created following imputation of missing data in the original data. In section 2.3.2 and 3.3 two methods of handling imputed data were described—the "Across" method and the "Within" method. The "Within" approach, calculated propensity scores on each imputed dataset separately and created ten matched data sets and the "Across" approach, took the mean of the propensity score for each subject across the ten imputed datasets and then used that average propensity score to create one matched population. The above cost-effectiveness analysis was conducted using transition probabilities primarily derived from the RISK-PROKIIDS dataset that had been matched following assembly of one dataset using the "Across" method. Propensity matching using the "Within" approach created ten matched data sets each with a slightly different, but equally representative patient population. Since transition probabilities were determined by counting the number of people in a health state over time, each patient population within each of the ten data sets resulted in slightly different transition probabilities. Transition probabilities calculated for each of the ten imputed, "Within" matched datasets that were dependent on the RISK-PROKIIDS data are shown in Appendix 21.

Since this secondary analysis of comparing ICERs using different datasets was not the primary goal of this study, medical remission irrespective of steroid use was used as the effectiveness measure. Examining steroid-free remission would have required additional analysis for each dataset. The different incremental costs of early anti-TNF-α intervention per additional week in medical remission using transition probabilities informed by each of the ten imputed matched RISK-PROKIIDS datasets are shown in Tables 3.7.4-1. A reference case discount rate of 1.5% was used in the analysis. As stated in section 3.7.3, using transition probabilities derived from the RISK-PROKIIDS matched imputed dataset assembled with the "Across" approach, the incremental cost of early anti-TNF-α intervention per additional week gained in medical remission over three years was $4,679 compared to standard care in a 2-D microsimulation of

50 samples of 10,000 microsimulations. When the 2-D microsimulation cost-effectiveness analysis was conducted using transition probabilities informed by each imputed dataset separately, the ICERs of early anti-TNF-α intervention compared to standard care ranged from $2,236 to $12,464 per additional week gained in medical remission. This represented a wide range of ICERs and illustrated the structural uncertainty introduced by the imputation of missing data and subsequent propensity score analysis. The mean ICER from the ten cost-effectiveness analyses was $5,047 (SD = $2,880) which was similar to the ICER determined using from the cost-effectiveness analysis informed by RISK-PROKIIDS probabilities assembled from the averaged "Across" approach ($4,679). The incremental cost per additional week of medical remission of early anti-TNF-α intervention in the ten cost-effective analyses ranged from $26,028 [95% CI (-1,937, 85,861)] to $36,301 [95% CI (7,606, 96,938)] and the incremental effect ranged from 2.91 [95% CI (2.51, 3.13)] to 11.64 [95% CI (11.40, 11.83) to 2.91 (2.51, 3.13)] weeks in medical remission. The confidence interval for the smallest incremental cost passed through zero suggesting a cost savings. However, all the other confidence intervals are positive indicating a net cost for 95% of simulations, albeit in a wide range. There is some overlap between the confidence intervals in incremental cost and incremental effectiveness among the ten cost-effectiveness analyses. Nevertheless, there appears to be uncertainty in the model which is discussed further in the next section.

Table 3.7.4-1. Summary Results of the Cost-effectiveness Analysis from a Public Health Care Payer Perspective Using Remission as the Outcome with Imputed RISK-PROKIIDS Datasets.

Matched Datasets	Strategy	Mean Cost ($CAD)	Δ Cost	Δ Cost (95%CI)	Mean Effect (weeks in remission)	Δ Effect	Δ Effect (95%CI)	ICER
"Across" Matched Dataset	Standard Care	96,516.42			97.50			
	Early anti TNF-α	127,628.05	31,111.63	(2,939.43, 91,715.06)	104.15	6.65	(5.92, 7.00)	4,679.24
"Within" Matched Datasets								
1	Standard Care	96,951.75			98.20			
	Early anti TNF-α	126,565.13	29,613.38	(2172.50, 89,241.80)	104.38	6.18	(5.46, 6.52)	4,793.14
2	Standard Care	104,258.76			98.58			
	Early anti-TNF-α	133,962.55	28,532.25	(1672.91, 89,698.48)	106.44	7.79	(7.47, 8.14)	3,783.31
3	Standard Care	103,467.70			98.35			
	Early anti-TNF-α	136,082.94	32,615.23	(4049.46, 92,406.36)	105.55	7.20	(6.68,7.43)	4,529.02
4	Standard Care	103,393.01			98.95			
	Early anti-TNF-α	136,516.94	33,123.93	(5205.94, 92818.47)	104.77	5.81	(5.40, 6.00)	5,697.86
5	Standard Care	104,142.61			100.06			
	Early anti-TNF-α	136,248.85	32,106.24	(4618.70, 91736.94)	105.02	4.96	(4.57, 5.24)	6,469.83

Matched Datasets	Strategy	Mean Cost ($CAD)	Δ Cost	Δ Cost (95%CI)	Mean Effect (weeks in remission)	Δ Effect	Δ Effect (95%CI)	ICER
6	Standard Care	107,572.13			94.57			
	Early anti TNF-α	133,600.44	26,028.32	(-1,937.16, 85,861.34)	106.21	11.64	(11.40,11.83)	2,235.70
7	Standard Care	107,476.15			97.23			
	Early anti-TNF-α	136,226.81	28,750.66	(613.82, 88,741.23)	104.99	7.76	(7.31, 8.00)	3,707.25
8	Standard Care	105,208.15			96.03			
	Early anti-TNF-α	136,529.35	31,321.2	(2,828.40, 91,121.28)	104.77	8.74	(8.40, 8.98)	3,583.38
9	Standard Care	100,175.74			101.69			
	Early anti-TNF-α	136,476.54	36,300.79	(7,606.00, 96,938.27)	104.76	2.91	(2.51,3.13)	12,464.20
10	Standard Care	107,643.60			95.49			
	Early anti-TNF-α	136,821.24	29,177.65	(437.65, 89,320.62)	104.59	9.10	(8.68,9.35)	3,204.99

Probabilistic analysis 2-D Markov microsimulation with 50 samples of 10,000 microsimulations. The results represent the base case with a 1.5% discount rate.

3.7.5 Uncertainty Analysis

Uncertainty analysis was conducted to assess the robustness in the cost-effectiveness model. Parameter uncertainty was assessed through probabilistic analysis. Structural uncertainty in the model was assessed via scenario analysis. Uncertainty in the estimated costs, outcomes and incremental cost-effectiveness ratio for the early anti-TNF-α intervention and standard care (step-up) treatment strategies was demonstrated with the cost-effectiveness acceptability curves. All types of uncertainty analyses are described below.

3.7.5.1 Structural and Methodological Uncertainty

The cost-effectiveness model used some health state transition probabilities derived from an imputed and subsequently propensity matched data set. Since two approaches, the "Across" method and the "Within" method, could be used to assemble the imputed data set for propensity matching and resultant transition probabilities, choosing one approach over the other in deriving inputs for the model introduced methodological uncertainty into the model. The probabilities of transitioning from "active disease" to "medical remission", "active disease" to "active disease requiring surgery or hospitalization", medical remission to medical remission (continued medical remission), and from "surgical remission" to "active disease", varied depending on the probabilities calculated from each of the ten imputed data sets ("Within" data sets) and the average "Across" data set (see Appendix 21 for transition probabilities from the "Within" data sets and Tables 2.5.6.3-1 and 2.5.6.3-2 for transition probabilities from the "Across" data set). The transition probabilities varied among datasets because when matched, sampling caused each of the ten matched data sets to contain a slightly different mix of patients and patient experiences. The slight differences in transition probabilities resulted in a wide range of ICERs. ICERs from the "Within" data sets ranged from $2,236 to $12,464 per additional week gained in remission and the average ICER from these data sets (calculated by taking the mean of each individual ICER from each "Within" dataset) was $5,047 (SD = $2,880) which was similar to the ICER determined using the averaged "Across" approach ($4,679). When the mean incremental cost was divided by the mean incremental effect of the "Within" datasets, the ICER was $4,266. The range in ICERs demonstrates the degree of methodological

uncertainty introduced by different approaches of assembling imputed data sets and subsequent propensity score matching using patient-level data. The structural uncertainty was compared using the incremental cost of an additional week in medical remission irrespective of steroid use for simplicity when altering model parameters.

Uncertainty in the discount rate was assessed in a sensitivity analysis using discount rates of 0% and 3% as recommended by CADTH guidelines (Canadian Agency for Drugs and Technologies in Health (CADTH), 2017). The incremental cost of early anti-TNF-α treatment per additional steroid-free remission week compared to the standard care intervention using discount rates of 0% and 3% from a health care public perspective and a societal perspective are shown in Tables 3.7.5.1-1 and 3.7.5.1-2. With a 3% discount rate, the incremental cost per steroid-free remission week was $2,771 and without discounting it was $2,740 from a public health care payer perspective. There was very little difference between the ICERs with the different discounting rates since the time horizon was only three years. With a 3% discount rate, the incremental cost per steroid-free remission week was $2,982 and without discounting it was $2,954 from a societal perspective.

The ICER was also determined from a health care payer perspective and a societal perspective using a 3% discount rate and a 0% discount rate with the outcome of remission irrespective of steroid use shown in Tables 3.7.5.1-3 and 3.7.5.1-4. With a 3% discount rate, the incremental cost per remission week was $4,698 and without discounting it was $4,661 per remission week for the health care payer perspective. With a 3% discount rate, the incremental cost per remission week was $5,055 and without discounting it was $5,024 per remission week gained for the societal payer perspective.

Table 3.7.5.1-1. Sensitivity Analysis of Cost-effectiveness Results Summary from a Public Health Care Payer Perspective with Different Discount Rates.

Strategy	Annual Discount Rate	Mean Cost ($CAD)	Incremental Cost (ΔCost) ($CAD)	95% Confidence Interval for ΔCost	Mean Effect (weeks in steroid-free remission)	Incremental Effect (ΔEffect)	95% Confidence Interval for Δ Effect	Incremental Cost-effectiveness Ratio (ICER)
Standard Care (Step-up)	0%	98,957.20			85.22			
Early anti-TNF-α Intervention	0%	130,209.14	31,251.94	(2,665.24, 93,016.74)	96.63	11.41	(10.70,11.71)	2,740.18
Standard Care (Step-up)	3%	94,186.15			81.02			
Early anti-TNF-α Intervention	3%	125,162.92	30,976.77	(3,199.68, 90,469.91)	92.20	11.18	(10.51,11.47)	2,771.13

Probabilistic analysis results from a two-dimensional Markov microsimulation model with 50 samples of 10,000 microsimulations. Costs are presented in 2017 Canadian dollars. ICER=incremental cost-effectiveness ratio.

Table 3.7.5.1-2. Sensitivity Analysis of Cost-effectiveness Results Summary from a Societal Perspective with Different Discount Rates.

Strategy	Annual Discount Rate	Mean Cost ($CAD)	Δ Cost	Δ Cost (95%CI)	Mean Effect (weeks in steroid-free remission)	Δ Effect	Δ Effect (95%CI)	Incremental Cost-effectiveness Ratio (ICER)
Standard Care (Step-up)	0%	103,479.01			85.22			
Early anti-TNF-α Intervention	0%	137,168.68	33,689.67	(5,205.29, 95,654.58)	96.63	11.41	(10.70, 11.71)	2,953.92
Standard Care (Step-up)	3%	98,546.34			81.02			
Early anti-TNF-α Intervention	3%	131,881.26	33,334.92	(5,655.27, 93,020.47)	92.20	11.18	(10.51, 11.47)	2,982.09

Probabilistic analysis results from a two-dimensional Markov microsimulation model with 50 samples of 10,000 microsimulations. Costs are presented in 2017 Canadian dollars. ICER=incremental cost-effectiveness ratio.

Table 3.7.5.1-3. Sensitivity Analysis of Cost-effectiveness Results Summary from a Public Health Care Payer Perspective Using Remission as the Outcome with Different Discount Rates.

Strategy	Annual Discount Rate	Mean Cost ($CAD)	Δ Cost	Δ Cost (95%CI)	Mean Effect (weeks in remission)	Δ Effect	Δ Effect (95%CI)	Incremental Cost-effectiveness Ratio (ICER)
Standard Care (Step-up)	0%	98,957.20			99.81			
Early anti-TNF-α Intervention	0%	130,209.14	31,251.94	(2,665.24, 93,016.74)	106.51	6.71	(5.95, 7.06)	4,660.91
Standard Care (Step-up)	3%	94,186.15			95.29			
Early anti-TNF-α Intervention	3%	125,162.92	30,976.77	(3199.69, 90,469.91)	101.89	6.59	(5.88, 6.93)	4,697.66

Probabilistic analysis results from a two-dimensional Markov microsimulation model with 50 samples of 10,000 microsimulations. Costs are presented in 2017 Canadian dollars. The effect measured was weeks in medical remission with or without the use of steroids.

Table 3.7.5.1-4. Sensitivity Analysis of Cost-effectiveness Results Summary from a Societal Payer Perspective Using Remission as the Outcome with Different Discount Rates.

Strategy	Annual Discount Rate	Mean Cost ($)	Δ Cost	Δ Cost (95%CI)	Mean Effect (weeks in remission)	Δ Effect	Δ Effect (95%CI)	Incremental Cost-effectiveness Ratio (ICER)
Standard Care (Step-up)	0%	103,479.01			99.81			
Early anti-TNF-α Intervention	0%	137,168.68	33,689.67	(5,205.29, 95,654.58)	106.51	6.71	(5.95, 7.06)	5,024.48
Standard Care (Step-up)	3%	98,546.34			95.29			
Early anti-TNF-α Intervention	3%	131,334.92	33,334.92	(5,655.27, 93,020.47)	101.89	6.59	(5.88,6.93)	5,055.28

Probabilistic analysis results from a two-dimensional Markov microsimulation model with 50 samples of 10,000 microsimulations. Costs are presented in 2017 Canadian dollars. The effect measured was weeks in medical remission with or without the use of steroid.

3.7.5.2 Parameter uncertainty

Parameter uncertainty was addressed in the model by running the reference case as a probabilistic analysis via a two-dimensional Monte Carlo microsimulation. All variable distributions that were not fixed were varied simultaneously in the model. Considerable variation in the patient population and treatment patterns within each strategy arm were addressed through the probabilistic analysis by simultaneously sampling variable distributions. There was uncertainty surrounding the health state transition probabilities due to patient variation and the limitation of using one data set. Therefore, a probabilistic approach was taken and these probabilities were assigned a beta distribution with the distribution being sampled every cycle for each microsimulation. A deterministic approach would not be amenable to the multiple sampling. While prices and doses for drugs were fixed, costs varied based on the weights for which there was a range for a particular age and gender. In addition, costs for each drug class were averaged among the common drugs used with a wide range of prices. These parameters introduced uncertainty and therefore sampling from a distribution for each individual was performed. The reported cost of hospitalization varied considerably based on Ontario Case Costing Data most likely due to varying lengths of stays and complications, therefore hospitalization cost was sampled from a distribution each time an individual entered the hospitalization health state. The probabilistic analysis was run with 50 samples of 10,000 trials in the reference case. The one-dimensional Monte Carlo microsimulation was also run probabilistically since all variable distributions were varied simultaneously for the 10,000 microsimulations. The incremental cost-effectiveness scatter plot of the one-dimensional microsimulation showed that the 10,000 ICER points of one population fell within all quadrants of the cost-effectiveness plane (see Figure 3.7.1-2).

Cost-effectiveness acceptability curves (CEACs) demonstrated uncertainty in the estimated costs, outcomes and incremental cost-effectiveness ratio for the early anti-TNF-α intervention and standard care (step-up) treatment strategies. The CEACs from a health care public payer and societal perspectives are shown in Figure 3.7.1-3 and Figure 3.7.2-2, respectively. The CEACs show that no one intervention is dominantly cost-effective in a range of willingness to

pay between $2,000 and $4,500. Hence, there is uncertainty in the model, and a difficulty in unequivocally stating that one strategy is more cost-effective than the other strategy.

3.7.5.3 Scenario Analysis

Scenario analyses to examine how the cost of infliximab, the rate at which anti-TNF-α is adopted in the standard care (step-up group), and the cost of immunomodulators (in comparison to the cost of infliximab) affect the incremental cost-effectiveness ratio. For the scenario analyses, two-dimensional microsimulations of 50 samples of 10,000 trials were conducted using reference case parameters of a 1.5% discount rate, three-year time horizon and a public health care payer perspective. In each scenario, or one-way sensitivity analysis, only the parameter of interest was altered prior to running the cost-effectiveness model. The difference in the ICER between the health care public payer perspective and the societal perspective was minimal and therefore sensitivity analyses were only performed using the health care public payer perspective.

It was hypothesized that the cost of anti-TNF-α treatment, particularly the cost of infliximab, could be a major driver of the uncertainty in the incremental cost-effectiveness ratio (ICER). Infliximab was the chosen target since it was the predominant anti-TNF-α treatment used in the RISK-PROKIIDS study. The price of one vial of infliximab was fixed at $987.56 in the reference case probabilistic analysis. However, costing of infliximab treatment was complex since the number of vials was based on weight (5mg/kg), the cost of infusion administration was added, and the cost of different dosing regimens depended on whether the patient was in the induction phase (“active”) or in the maintenance phase of treatment. A one-way sensitivity analysis was conducted by varying the price of infliximab by a multiplier. The effect of varying the price of one vial by 150%, 87.5%, 75%, 62.5%, 50%, 37.5%, and 25% of the reference case ($987.56) was tested. These ranges were used to examine at what range biologic treatment could potentially be cost-effective. Biosimilar infliximab (Inflectra®) is 53% of the cost of originator infliximab (Remicade®) in the Ontario Drug Formulary. The results are shown in Table 3.7.5.3-1, and the range in ICERs when altering the price of infliximab is shown in the tornado diagram (Figure 3.7.5.3-1).

To compare the impact of altering the cost of immunomodulators on the ICER with the impact of altering the cost of infliximab, a one-way sensitivity analysis was conducted to test the effect of alternative costs of immunomodulators. The cost of immunomodulators was based on the average cost of the drug class per week, and this average cost was multiplied by a factor of 2 or a factor of 0.5 in the sensitivity analysis. This range was chosen to reflect the variance in prices of the different immunomodulators within this drug class and the potential variance in preference and use. The weighted average cost based on RISK-PROKIIDS use for the class of immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate) was calculated for a range of weights per week and hence the range in the sensitivity analysis could account for variances in the weighted average cost per week of immunomodulators. Since the determination of treatment cost varied by weight of the patient and varied over time by health state, using a multiplier was the simplest way of varying the cost. A one-dimensional Monte Carlo analysis with 10,000 microsimulations was conducted using reference case parameters from a health care payer public perspective for the one-way sensitivity analysis. When the cost of immunomodulators was doubled, the incremental cost of early anti-TNF-α treatment compared to standard care was $2737 per additional steroid-free week in remission and when the cost of immunomodulators was halved the incremental cost of early anti-TNF-α treatment compared to standard care was $2712 per additional steroid-free week in remission (see Figure 3.7.5.3-1 for tornado diagram). This indicates that the incremental cost-effectiveness ratio was not sensitive to the cost of immunomodulators.

It was hypothesized that the rate of escalation to anti-TNF-α treatment in the standard care group introduced uncertainty in the model since it was based on the RISK-PROKIIDS study and may not be reflective of more current patient treatment patterns. The proportion of patients that switched to anti-TNF-α treatment in the standard care group over three years based on the RISK-PROKIIDS matched population was shown in Figure 3.6-2. The rate of escalation to anti-TNF-α treatment was not linear and changed over time. A one-way sensitivity analysis was conducted using reference case parameters with a health care public perspective to examine the impact on the ICER of varying the rate of escalation to anti-TNF-α treatment after three

months post-diagnosis. The probability of being on anti-TNF-α treatment was multiplied by a factor of the current weekly probability. The factors used to change the probability of escalation are shown in Table 3.7.5.3-2 and the comparative tornado diagram is shown in Figure 3.7.5.3-1). As expected, reducing the probability of switching to anti-TNF-α in the standard care group increased the incremental cost per additional week of steroid-free remission for the early anti-TNF-α strategy (see Table 3.7.5.3-2). Increasing the probability of switching to anti-TNF-α four-fold starting at three months and throughout the three years minimally increased the ICER to $2,750 from $2,720 in a one dimensional microsimulation. As seen in Figure 3.7.5.3-1 the ICER was most sensitive to the price of infliximab compared to the probability of escalating to anti-TNF-α and the cost of immunomodulators.

Table 3.7.5.3-1. The Impact on the Incremental Cost-effectiveness Ratio Following a Reduction in the Price of Infliximab.

Percent of Original Infliximab Price	Price of 1 Vial of Infliximab ($CAD)	Δ Cost ($CAD)	Δ Cost (95%CI)	Incremental Cost-effectiveness Ratio (ICER) (cost per steroid-free remission week)
150%	1,481.34	53,522.63	(-30,0001.57,157,993.92)	4,781.83
100%	**987.56**	30,447.61	**(-36,707.98, 117,265.37)**	**2,720.25**
87.5%	864.12	24,678.86	(-39,044.64, 107,820.96)	2,204.86
75%	740.67	18,910.10	(-41,968.18, 98,034.78)	1,689.47
62.5%	617.23	13,141.35	(-45,410.63, 89,796.17)	1,174.08
50%	493.78	7,372.60	(-49,931.63, 81,789.86)	658.68
37.5%	370.34	1,603.86	(-55,230.77, 75,305.40)	143.29
25%	246.89	-4,164.91	(-59,476.36, 69,907.01)	-372.10

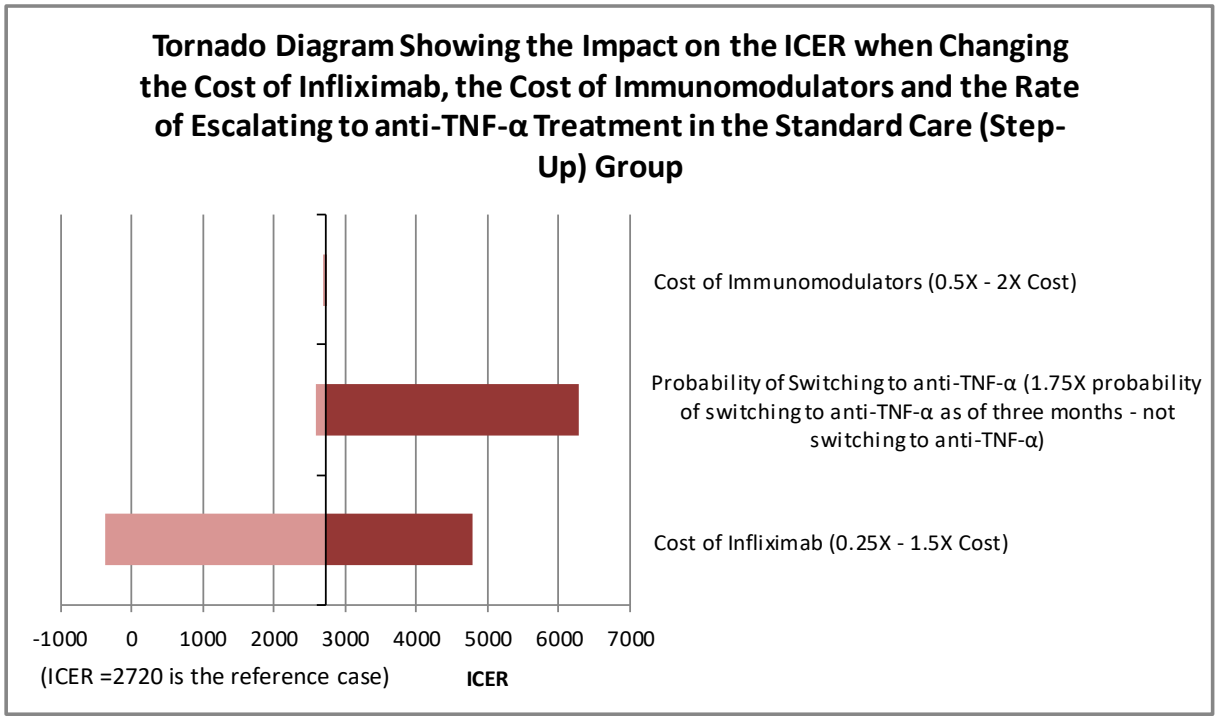
The incremental effect for all scenarios was 11.19 steroid-free remission weeks for all cost changes. Probabilistic analysis results from a one-dimensional Markov microsimulation model with 10,000 microsimulations. Costs are presented in 2017 Canadian dollars.

Table 3.7.5.3-2. The Impact on the Incremental Cost-effectiveness Ratio With Changes to the Rate of Escalation to Anti-TNF-α Treatment in the Standard Care Group.

Multiplying Factor for Probability of Switching to anti-TNF-α by Standard Care Group	Increase or Decrease in Escalation Rate to anti-TNF-α after 3 months	ICER (cost per steroid-free remission week)
1 x switch rate (reference case, used RISK-PROKIIDS study)	No change	2,720.25
4x	Increase	2,750.16
0.75x	Decrease	2,845.98
0.5x	Decrease	3,174.66
0.25x	Decrease	3,890.08
No switching to anti-TNF-α	Decrease	6,291.22

Probabilistic analysis results from a one-dimensional Markov microsimulation model with 10,000 microsimulations. Costs are presented in 2017 Canadian dollars. Abbreviation: ICER= incremental cost-effectiveness ratio.

Figure 3.7.5.3-1. Tornado Diagram Showing the Impact on the ICER when Changing the Cost of Infliximab, the Cost of Immunomodulators and the Rate of Escalating to anti-TNF-α Treatment in the Standard Care (Step-Up) Group.



The ICER is stated in $CAD per steroid-free remission week for the early anti-TNF-α treatment. Abbreviation: ICER = incremental cost-effectiveness ratio. Note the effect on the ICER of altering the cost of immunomodulators was miniscule.

3.7.6 Validation and Calibration of the Cost-effectiveness Model

The cost-effectiveness model was validated and calibrated as much as possible according to International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines (Eddy et al., 2012) considering the lack of external validation and calibration sources with pediatric data. The mean number of steroid-free medical remission weeks in three years, the mean number of medical remissions weeks in three years (steroid-free or on steroids), and the number of surgeries in three years from the RISK-PROKIIDS study were used as calibration targets for the cost-effectiveness model. The model outputs were compared to the actual values observed in the RISK-PROKIIDS study to calibrate the model (see Table 3.7.6-1). The model generated similar results as the RISK-PROKIIDS study and did not require adjustments or further calibration. The number of surgeries observed in the cost-effectiveness model was compared to the number of surgeries observed in the RISK-PROKIIDS matched population using a Chi-squared goodness of fit test and the null hypothesis of the two populations having a similar distribution was not rejected (p=0.944).

The number of subjects in medical remission at one year from diagnosis served as an external parameter for model validation. The number of remissions (irrespective of steroid use) in the cost-effectiveness model were validated against another small pediatric observational study which examined the use of early intervention with infliximab in pediatric CD (see Table 3.7.6-2) (Kim et al., 2011), (Y. M. Lee, Kang, Lee, Kim, & Choe, 2015). The Kim et al., 2011 and the Lee et al., 2015 studies described the same cohort of patients with patients on maintenance infliximab up to one year. The number of remissions (irrespective of steroid use) at one year in the present study was also compared to an earlier published study of a portion of the RISK-PROKIIDS subjects examining early intervention with anti-TNFα treatment (see Table 3.7.6-2) (Walters et al., 2014). Fifty-two percent of patients in the standard care (step-up) group were in remission at one year in the present study while 45% of step-up patients were in remission in the Kim et al, 2011 and Lee et al, 2015 study and 54% were in remission in the Walters et al., 2014 study. Sixty-six percent of early anti-TNF-α intervention patients were in remission at one year in the present study and 83% and 85% of early anti-TNF-α intervention patients were in

remission in the Kim et al., (2011) and Walters et al., (2014) studies respectively. Sixty-three percent of patients in the early anti-TNF-α group were in remission in the RISK-PROKIIDS population. The RISK-PROKIIDS study informed the Walters (2014) study but patients were allocated differently than in the present study. It is possible that the patients included in the Walters (2014) study were not all the same patients that were included in our study. The Kim et al., (2011) study was a small study population with only 18 patients treated with early anti-TNF-α intervention and 11 patients in the step-up group. Therefore, the percentage of patients in remission at one year may seem high compared to the results of our model.

The percent of pediatric Crohn's disease-related surgeries among CD patients in Ontario in three years (14.7%) based on an epidemiological study also served as an external validation target for the model (Eric I Benchimol et al., 2014). In the present study, 15.3% (1,527/10,000) of CD patients across both comparator groups, had surgery within three years. Due the scarcity of studies examining early anti-TNFα treatment in naïve pediatric CD subjects, the model could not be validated more extensively. However, the model appeared to have good face validity based on the limited comparisons conducted and did not require further calibration.

Table 3.7.6-1. Validation of the Cost-effectiveness Model with Internal Parameters.

Validation Target	Early anti-TNF-α (RISK-PROKIIDS dataset) n=123	Step-up Treatment (RISK-PROKIIDS dataset) n=237	Early Biologics (C-E Model, 10,000 microsimulations)	Step-up Treatment (C-E Model 10,000 microsimulations)
Mean number in steroid-free medical remission in 3 years, weeks, (SD)	98.72 (50.70)	91.27 (43.32)	94.37 (14.52)	83.17 (13.03)
Mean number of medical remission weeks (SD) in 3 years	101.46 (49.65)	98.19 (42.52)	104.16 (15.19)	97.62 (14.08)
Number of surgeries in 3 years	11/123 (8.9%)	14/237 (5.9%)	911/10,000 (9.1%)	616/10,000 (6.2%)

The number of surgeries in 3 years was determined based on the number of individuals out of 10,000 in the microsimulation model who entered the surgery health state over three years. C-E = cost-effectiveness; SD= standard deviation.

Table 3.7.6-2. Validation of the Cost-effectiveness Model with the External Parameter of Percent of Subjects in Remission at One Year.

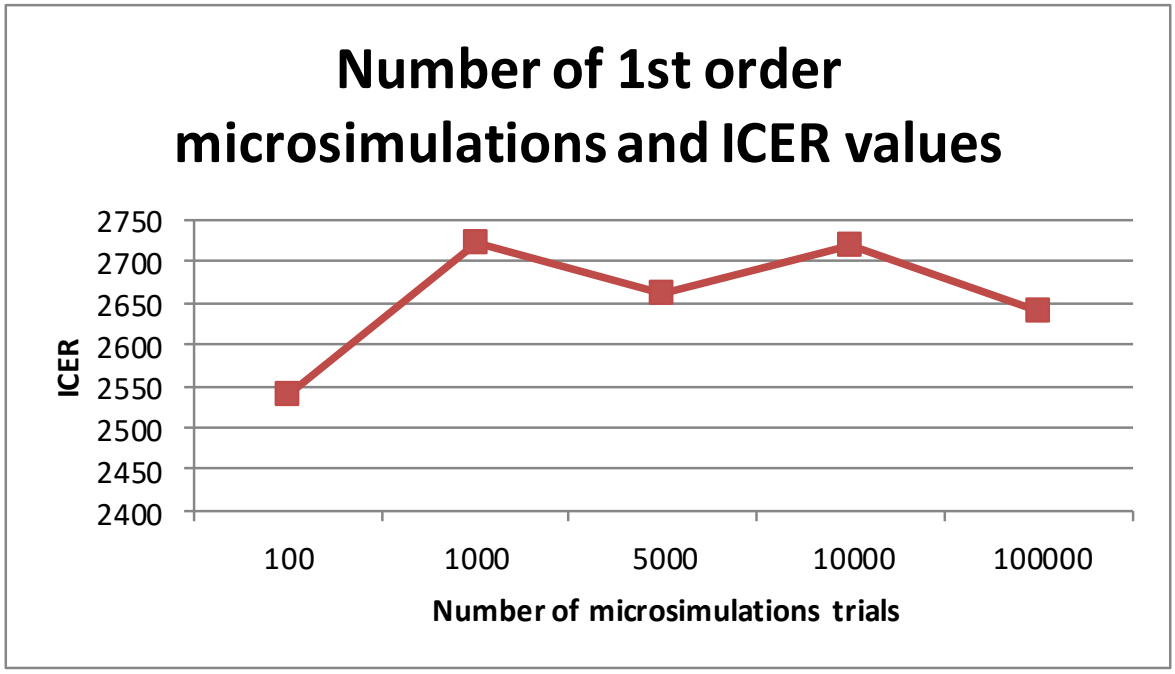
Strategy	**C-E Model** (10000 microsimulations) (% of subjects in remission at one year)	**RISK-PROKIIDS dataset** Step-up (n=237); Early intervention (n=123) (% of subjects in remission at one year)	**Kim et al., 2011** (n=29) (% of subjects in remission at one year)	**Walters et al., 2014** (n=68) (% of subjects in remission at one year)
Standard Care (Step-Up Strategy)	52%	57%	45%	54%
Early anti-TNFα	66%	63%	83%	85%

Remission was considered as medical remission irrespective of steroid use. Abbreviations: C-E = cost-effectiveness.

3.7.7 Microsimulations and Sampling in the Cost-effectiveness Model

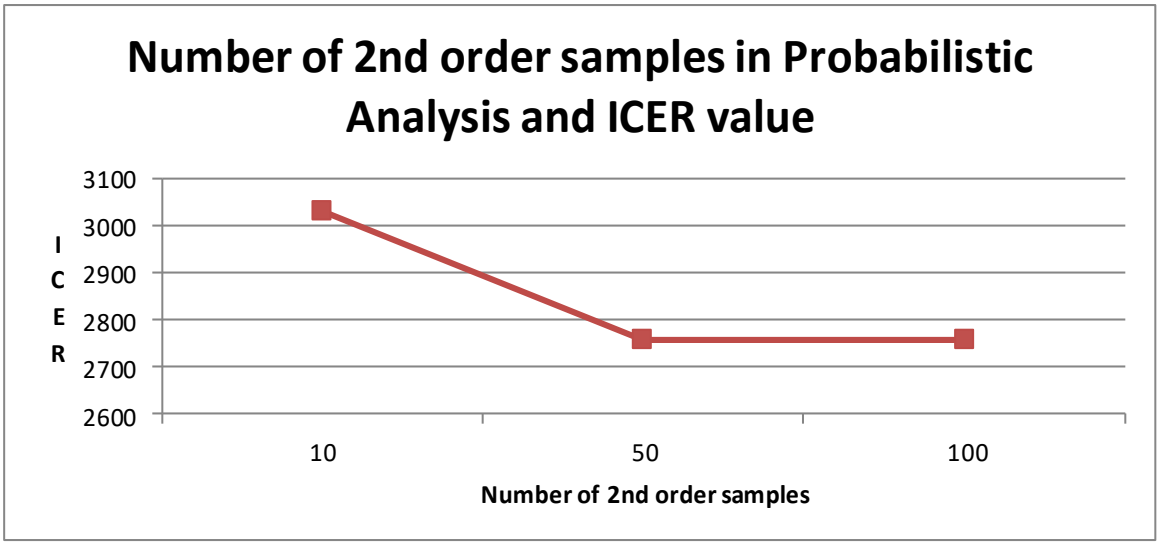
Ten thousand individual-level (one dimensional) Monte Carlo microsimulations were conducted to exceed the minimum 5,000 simulations recommended by CADTH guidelines (Benchimol et al., 2017; Canadian Agency for Drugs and Technologies in Health (CADTH), 2017). To confirm that 10,000 microsimulations was adequate, the incremental cost-effectiveness ratio (ICER) was compared with several numbers of microsimulations (see Figure 3.7.7-1). Figure 3.7.7-1 shows that the ICER value (over three years and with a 1.5% annual discount rate using a health payer perspective) is similar between 1,000 and 100,000 microsimulations. The graph suggests that 10,000 microsimulations are adequate to yield a robust ICER in the cost-effectiveness model. The probabilistic analysis was undertaken, whereby all distributions were sampled using a two-dimensional (2-D) microsimulation which sampled 50 samples of 10,000 individuals. Fifty samples were chosen as this was the minimum number of samples that showed a consistent ICER (see Figure 3.7.7-2).

Figure 3.7.7-1. The number of 1st order microsimulation trials and the variation in the ICER value.



This graph shows that the ICER value is similar regardless of the number of 1st order microsimulations over 1,000. The model used was a three-year model with a 1.5% annual discount rate and had the health payer perspective. Abbreviation: ICER= incremental cost-effectiveness ratio.

Figure 3.7.7-2. The Number of Second Order Samples Used for the Probabilistic Analysis and the Variation in the ICER in the 2-D microsimulation.



This graph shows that the ICER value stabilized beyond 50 samples. The model used was a three-year model with a 1.5% annual discount rate and had the health payer perspective with 10,000 1st order microsimulation trials. The graph indicates that 50 2nd order samples are sufficient for consistency within the 2-D microsimulation. Abbreviation: ICER = incremental cost-effectiveness ratio.

3.7.8 Summary of Cost-effectiveness Analysis

A two-dimensional Markov microsimulation model with incorporated probabilistic analysis was used to determine the incremental cost-effectiveness of early anti-TNF-α intervention compared to standard care in moderate to severe pediatric Crohn's disease patients. The early anti-TNF-α intervention was more costly but more effective than standard care of step-up therapy over three years in a population of children with moderate-to-severe Crohn's disease. The incremental cost of early anti-TNF-α intervention per additional steroid-free remission week was $2,756 for the reference case compared to standard care. The incremental cost of early anti-TNF-α intervention per additional steroid-free remission week was $2,968 for the reference case from a societal payer perspective compared to standard care. If steroid use was not taken into account, then the incremental cost of early anti-TNF-α intervention per additional remission week was $4,679 for the reference case from a health care payer perspective and $5,040 from a societal perspective. There was uncertainty in the model arising from the imputation of missing data and propensity score matching of the reference patient population used to inform health state transition probabilities. The cost-effectiveness model run using probability inputs from an averaged population of patients was different than the cost-effectiveness model run with separate imputed datasets and the mean of the mean incremental cost-effectiveness ratios (using the "Within" datasets) was higher than the incremental cost-effectiveness ratio from the averaged population. Parameter uncertainty was due to the large variation in health state transitions and treatment regimens of the patients. The incremental cost effectiveness ratio was sensitive to the price of infliximab based on a one-way sensitivity analysis and to the rate at which the standard care group adopted anti-TNF-α treatment three months after diagnosis.

4 Discussion

4.1 Overview

Since there is a keen interest to introduce effective treatment as early as possible and to maintain remission for as long as possible, a cost-effectiveness analysis was conducted comparing early intervention with anti-TNF-α treatment and standard care (step-up treatment) in children with moderate-to-severe Crohn's disease from a health care public payer perspective and a societal perspective. The incremental cost per additional steroid-free remission week was $2,756 ($CAD) for the early anti-TNF-α intervention for the reference case from a public health care payer perspective. From a societal perspective, the incremental cost per additional steroid-free remission week was $2,968 ($CAD) for the early anti-TNF-α intervention for the reference case. With both perspectives, the early anti-TNF-α intervention was more costly but more effective than standard care. However, there was considerable uncertainty in the results as reflected by the cost-effectiveness acceptability curves, which showed that at a hypothetical willingness-to-pay threshold of approximately $3,500 per week in steroid-free remission, neither strategy is dominant over the other. An actual willingness-to-pay threshold on behalf of the health care public payer for a week in steroid-free remission is unknown.

The following chapter will discuss the results of the cost-effectiveness analysis of early intervention with anti-TNF-α treatment compared to standard, step-up care in children with moderate-to-severe Crohn's disease. The results of this research will be compared to other economic evaluations of anti-TNF-α treatments in Crohn's disease. Since economic evaluations that take a societal perspective are rare but highly relevant to economic evaluations in child health, the differences in the cost-effectiveness outcomes between the societal and public health care payer perspectives will be discussed. Following the discussion on perspectives, the strengths, limitations and generalizability of the study will be discussed.

Based on the Crohn's Disease health technology assessment theoretical framework presented in Figure 1.7-1, an economic evaluation may have an impact on clinical practice policies or

clinical management practices, and drug coverage and pricing policies. In line with this framework, the results of the economic evaluation presented here will be discussed in terms of its potential impact on current clinical practice, and CD treatment coverage policies. How various stakeholders such as clinicians, policy makers, researchers, manufacturers, patients and caregivers may use the information of the cost-effectiveness analysis will also be examined. Since Crohn's disease treatment is rapidly evolving and recent changes may not have been incorporated into the present study, a discussion of the impact of biosimilars and new biologic market entrants and their potential impact on cost-effectiveness of pediatric CD treatments will be discussed. Finally, future research and concluding remarks will be outlined.

4.2 The Cost-Effectiveness of Early Anti-TNF-αTreatment in Pediatric Crohn's Disease and Related Research

This study represents the first cost-effectiveness analysis examining early intervention with anti-TNF-α treatment in treatment-naïve pediatric Crohn's disease and comparing it to standard care defined as traditional step-up therapy with biologics. Using anti-TNF-α treatment earlier in the treatment process in newly-diagnosed pediatric CD patients has been shown to improve clinical remission outcomes compared to standard care (Walters et al., 2014). Other economic evaluations examining anti-TNF-α treatments in children with Crohn's disease conducted comparisons in children refractory to conventional treatments or used previous or older versions of standard care comparator arms that did not contain the anti-TNF-α treatment at all (Punekar et al., 2010; Veereman et al., 2013). This study is novel in that it represents the current standard care of step-up therapy in which patients can be placed on anti-TNF-α treatment later in their course of treatment after trying other non-biologic treatments. Therefore, the main difference to published work is the timing of initiating anti-TNF-α treatment. The other main difference in this study is the primary clinical outcome of number of steroid-free remission weeks experienced by patients as compared to the number of patients in remission at a certain time point (Walters et al., 2014), or quality of life (Assasi et al., 2009; Blackhouse et al., 2012b; Jaisson-Hot et al., 2004; Punekar et al., 2010; Reinink et al., 2011).

Having steroid-free remission weeks as a clinical outcome is particularly relevant for a pediatric population since steroids have been shown to affect growth and brain development in children and therefore there is a desire to minimize steroid use (Heuschkel et al., 2008; Mrakotsky, Watson, Waber, Grand, & Rivkin, 2013). In the cost-effectiveness analysis presented here, steroid-free remission weeks were used as the effect measure but weeks in remission irrespective of steroid use were also determined. The incremental effect of early anti-TNF-α treatment compared to standard step-up care was greater with an outcome of steroid-free remission weeks (11.3 weeks in steroid-free remission) than weeks in remission irrespective of steroid use (6.7 more weeks in remission for early anti-TNF-α treatment compared to standard care), thus making the early anti-TNF-α intervention more advantageous than standard care when considering that it was more effective at prolonging steroid-free remission. Anti-TNF-α treatments (infliximab and adalimumab) have been shown to be clinically effective at maintaining steroid-free remission status at weeks 48-52 in a significantly greater number of adult CD patients than placebo (Jean–Frédéric Colombel et al., 2007; Hanauer SB, 2002; Hanauer et al., 2002; Peyrin-Biroulet et al., 2008). Sustained corticosteroid-free remission has been recommended as a primary clinical outcome for pediatric CD clinical trials (F. M. Ruemmele et al., 2014). Perhaps it should be considered in future pediatric CD cost-effectiveness analysis studies as well.

While measuring health-related quality of life is relevant to a pediatric patient population, preference-based quality of life, i.e. utilities, have not been established in a pediatric Crohn's disease population and therefore only surrogate measures such as adult Crohn's disease utilities have been used in cost-utility analyses in children (Gregor et al., 1997). Whether the adult CD utilities are a sufficient representation of child CD utilities remains to be established.

A cost-effectiveness analysis with a specific clinical outcome is difficult to compare to other economic evaluations with anti-TNF-α treatments since most other economic evaluations in inflammatory bowel diseases are cost-utility analyses (Jean, Audrey, Beauchemin, & Consortium, 2018). To compare the results of this cost-effectiveness analysis to other economic evaluations, one would need to convert steroid-free remission weeks to quality-adjusted life

years (QALYs). To do so certain assumptions need to be made in an unvalidated and hypothetical exercise. In the absence of childhood utilities, if adult CD utilities were used based on work done by Gregor et al, 1997, then the remission health state would be allocated a value 0.96 based on the time trade off method and 0.88 based on the standard gamble method for those with moderate CD (Gregor et al., 1997). If it is assumed that a steroid-free remission year is allocated a utility weight of 0.88-0.96, then a steroid-free remission week could represent 0.017-0.018 QALYs, and the incremental effect (11.29 weeks) of early anti-TNF-α treatment would be approximately 0.19-0.21 QALYs compared to standard step-up care. Hence an incremental cost per steroid-free remission week of $2,755.70 for early anti-TNF-α intervention compared to standard care (step-up therapy) could be roughly translated into an incremental cost per QALY of $149,266-$162,836 ($CAD) for early anti-TNF-α treatment compared to standard care (step-up) treatment over three years.

In a review of economic evaluations in adult and pediatric inflammatory bowel disease, Jean et al., 2018 stated that all studies comparing biologic treatments to standard care in CD resulted in an ICER above the $100,000 ($CAD)/QALY willingness to pay threshold in the Canadian setting (Jean et al., 2018). In pediatric economic evaluations reporting QALY's, adult CD utilities were used as utility measures in the absence of pediatric CD utilities (Jean et al., 2018). Standard care in these cases was not defined as step-up treatment with biologics. Recent reviews of cost-effectiveness studies of biological agents including anti-TNF-α treatments for the treatment of inflammatory bowel disease showed a wide range of costs per QALYs owing to the diverse outcomes, treatment paradigms and patient populations (Huoponen & Blom, 2015; Jean et al., 2018; Pillai, Dusheiko, Burnand, & Pittet, 2017). A systematic review of studies in adults of biological treatments for inflammatory bowel disease concluded that while biologics improved outcomes, they were not cost-effective for maintenance therapy (Pillai et al., 2017). Among the patients refractory to conventional medical treatment, the incremental cost-effectiveness ratio for biologics compared to conventional, non-biologic medical treatment ranged from dominance to $CAD 836,064/QALY in 2017 dollars (€549,335 /QALY in 2014 euros) (Huoponen & Blom, 2015). A European cost-utility analysis comparing first-line infliximab to non-biologic

standard care treatment for peri-anal fistulae in adult CD showed an incremental cost per QALY of $CAD 667,556 in 2017 dollars (€438,617 in 2014 euros) over one year (Arseneau, Cohn, Cominelli, & Connors Jr, 2001; Huoponen & Blom, 2015). A recent review examining the efficacy of early anti-TNF-α treatment (also called top-down treatment) vs a step-up strategy for the treatment of Crohn's disease concluded that for pediatric patients, a top-down strategy showed positive clinical outcomes in larger studies but were inconclusive in smaller studies, however only a small number of studies were reviewed (Tsui & Huynh, 2018). Overall, research and evidence supporting top-down therapy remain limited in adult and pediatric CD, and further studies are needed to determine the most appropriate CD patients to receive a top-down treatment approach (Tsui & Huynh, 2018).

An economic evaluation similar to our analysis is a cost-utility analysis conducted by Marchetti et al., (2013) (Marchetti et al., 2013). Marchetti et al., conducted a cost-effectiveness study in newly diagnosed luminal CD adults comparing treatment with infliximab plus azathioprine plus corticosteroids if necessary at diagnosis (referred to as the top-down strategy in their study) to treatment with corticosteroids and azathioprine with infliximab only if necessary in refractory patients (referred to as step-up strategy in their study) over a five year time horizon (as opposed to a three year time horizon in our study). Many of their model inputs were based on one randomized clinical trial conducted in adults with newly-diagnosed CD (Geert D'Haens et al., 2008). They determined that the incremental effect of the top-down strategy was 0.14 QALYs over five years and that their top-down strategy was dominant yielding a cost-savings of $CAD 1,120 in 2017 dollars (€773 in 2013 euros) compared to their step-up strategy over a five-year time horizon from the Italian health care payer perspective. Interestingly, effectiveness results were similar to our study but in the Italian study, cost-savings were observed. In their study the price of infliximab was lower than in our study by about $245 per vial and their hospitalization cost due to adverse events was almost ten-fold less in the Italian health perspective than in our study. The Marchetti et al. analysis was sensitive to the time horizon with a $CAD 130,431/QALY in 2017 dollars (€90,000/QALY in 2013 euros) for their top-down strategy after one year, $CAD 43,477/QALY in 2017 dollars (€30,000/QALY in 2013 euros) after

two years and a cost-savings only after five years. Their base case discount rate was higher at 3.5% and their relapse rate was also lower than our study (Marchetti et al., 2013).

Another challenge in conducting cost-effectiveness analysis in CD is the fact that the decision-maker's willingness to pay (WTP) for an additional week in steroid-free remission is unknown, and a formal willingness-to-pay threshold for a QALY in Canada has not been published. In the United Kingdom a willingness to pay threshold of £20,000 - £30,000 has been published and the United States commonly uses a threshold of $50,000 per QALY (Shiroiwa et al., 2010; Woods, Revill, Sculpher, & Claxton, 2016). For low to middle income countries, the World Health Organization (WHO) has suggested a willingness-to-pay threshold of one to three times the gross domestic product (GDP) per capita per disability-adjusted life-year (DALY) averted, but this would not apply to Canada since Canada is not considered a low to middle income country (Woods et al., 2016; World Health Organization (WHO), 2001). Since a true Canadian WTP is unknown, cost-effectiveness over a range of WTP's can only be estimated as shown by the cost-effectiveness acceptability curves.

The cost-effectiveness acceptability curves shown in Figures 3.7.1-3 and 3.7.2-2 demonstrate the uncertainty of the cost-effectiveness analysis. In Figure 3.7.1-3, for early anti-TNF-α intervention, there is a 50% or less chance that the additional cost of a week of steroid-free is at or less than $3,500, and at a threshold of $6,000 per week of steroid-free remission there is about a 80% or less chance that the additional cost of a week of steroid-free remission is cost-effective compared to standard step-up care.

The unknowns relative to willingness to pay in Canada for steroid-free remission weeks and the uncertainty around the ICER makes making a definitive conclusion about cost-effectiveness of early anti-TNF-α compared to standard care of step-up treatment challenging. However, decision makers can still find the information of the cost-effectiveness analysis informative in their decision making process. The cost-effectiveness analysis has shown that the early intervention with anti-TNF-α is more costly but more effective at increasing steroid-free remission time compared to standard step-up care. The analysis of treatment patterns in the

RISK-PROKIIDS patients showed that while over fifty percent of patients in the standard care step-up group adopt anti-TNF-α treatment by the end of three years from diagnosis, some patients are not taking anti-TNF-α, possibly indicating a preference for not taking anti-TNF-α or indicating that a clinical need for anti-TNF-α was not determined by the physician. Public decision makers take several aspects of a treatment strategy, such as clinical effectiveness, cost-effectiveness, patient preferences, ethical and legal considerations, and equity issues into consideration before making a decision on whether to fund a treatment strategy (Canadian Agency for Drugs and Technologies in Health (CADTH), 2017; Health Quality Ontario, 2018). The analysis presented in this research provides information on the cost-effectiveness and the clinical effectiveness of early anti-TNF-α. The research also showed that not all pediatric patients with moderate to severe CD adopt an anti-TNF-α strategy within the first three years of diagnosis. Decision makers also need to be aware that long-term data on the clinical effectiveness and cost-effectiveness of early anti-TNF-α treatment beyond three years is not available. Another difference between the cost-effectiveness analysis presented here and other studies is the incorporation of the societal perspective in the analysis as well as the public health payer's perspective.

4.3 The Societal and Public Health Care Payer Perspectives

A common criticism of economic evaluations of biologics in the treatment of inflammatory bowel disease has been that many of them have taken a health care public payer perspective and not a societal perspective thus not including all costs such as caregiver costs and loss of productivity costs related to Crohn's disease management (Huoponen & Blom, 2015; Pillai et al., 2017; D H Tang, A R Harrington, J K Lee, M Lin, & E P Armstrong, 2013). A societal perspective is always recommended for economic evaluations in child health (W. Ungar & Gerber, 2010) . The cost-effectiveness analysis in this study has taken both a health care public payer perspective and a societal perspective. However, the differences in the findings were not substantial. From a public health care payer perspective, the incremental cost per steroid-free remission week for early anti-TNF-α treatment compared to step-up standard care was $2,756 and from a societal perspective it was $2,968. The difference between the two perspectives

was the inclusion of indirect costs (in the form of caregiver loss of productivity costs) in the societal perspective in addition to the costs incurred by the Ontario health care public payer. The main reason for the slight difference in outcomes between the different perspectives is due to the nature of pediatric drug coverage in Ontario and the disproportionate direct cost of treatment compared to the indirect costs in Crohn's disease management, particularly if a child is on anti-TNF-α treatment. Loss of productivity costs are of particular importance since they account for an overall cost to society due to the illness. Since children are dependent on caregivers, loss of productivity costs for caregivers of children with CD can be significant over time since CD is a chronic illness that requires ongoing physician visits, possible infusion clinic visits and possible hospital stays. Once the child grows to adulthood, his or her own loss of productivity due to illness would be included in the societal perspective. The time horizon in our economic evaluation was only three years. Hence the long term loss of productivity cost to society of caregivers and of CD-afflicted adults was not considered in societal costs. A life time horizon is suggested for economic evaluations (Canadian Agency for Drugs and Technologies in Health (CADTH), 2017). A lifetime horizon would allow the inclusion of loss of productivity of caregivers and afflicted adults over the lifetime of the patient impacting the cost-effectiveness analysis. However, a three year time horizon was chosen since long-term effects of early anti-TNF-α are unknown. If early anti-TNF-α were found to reduce productivity loss over the long-term, the strategy may have been found to be more cost-effective than standard step-up care. Anti-TNF-α treatment has become the major cost in CD treatment in recent years (van der Valk et al., 2014). Recently Ontario has introduced provincial public drug coverage for all children under the age of 25 (Ontario Ministry of Health and Long-Term Care, 2018b). This change may reduce the role of the private insurance payer for pediatric drug coverage in Ontario until full public coverage is completely implemented. Therefore, it was assumed that all treatment costs were attributed to the provincial public payer. While some costs, such as infusion clinic expenses, may be administered by private clinics, in our study, it was assumed that the Ontario public payer was responsible for these costs. It is also important to remember that Crohn's disease is a chronic disease that requires management in the form of drug treatments and physician visits during the active phase of the disease and the remission phase of the disease.

Hence, during the remission phase of the disease, loss of caregiver productivity is still an issue albeit less frequent.

4.4 Biologics Drug Policy

Drug coverage for biologics is complex, varies from province to province, and is costly for the provincial health care systems. Since January 2018, Ontario has implemented comprehensive drug coverage for children. Quebec has mandated private or public drug coverage for all residents and other provinces have a mixture of private and public plans depending on age and financial need (Fiona M. Clement, Lesley J.J. Soril, Herbert Emery, David J.T. Campbell, & Braden J. Manns, 2016). In a recent study of people surveyed in four western provinces, 61.2% (British Columbia) to 76.4% (Alberta) of people under the age of 65 had private drug coverage insurance while 18.9 % (British Columbia) to 24.4% (Manitoba) of people with an income of lower than $30,000 had private insurance (Fiona M. Clement et al., 2016). Due to the high costs of biologic treatments and financial constraints of most families, the burden of paying for anti-TNF-α treatments falls to the public payer. Anti-TNF-α drugs account for the highest proportion of public drug spending in Canada at 8.7% (Canadian Institute for Health Information, 2017). Therefore, ensuring that treatment with anti-TNF-α is done in a medically and financially responsible way is of particular concern to provincial health ministries.

The current anti-TNF-α treatments (both brand name and biosimilar versions) and newer biologic treatments have different public coverage rules depending on the province (Gastrointestinal Society, 2017). For example, naïve CD patients are now forced to start on the biosimilar version of infliximab, Inflectra® instead of choosing the brand name Remicade® in all provinces except for Saskatchewan (Gastrointestinal Society, 2017). In Ontario, Remicade® is not on the Ontario Drug Benefit Formulary and is only available through the Exceptional Access Program (Ontario Ministry of Health and Long-Term Care, 2018a). Applications to the Exceptional Access Program are filed by the attending medical practitioner. In addition, with the newly-elected provincial government, recent changes to the Ontario OHIP+ program have extended private drug coverage for children who have private insurance plans prior to

accessing the publicly funded program. Rapid changes to drug funding programs for children can create confusion on where to apply for drug coverage for children's drugs and may create unnecessary delays. (Ontario Ministry of Health and Long-Term Care, 2016a). Constraints and delays for patients covered through public payers may delay access to treatments and affect subsequent clinical outcomes for CD patients (Rumman et al., 2017). Rumman et al., 2017 showed that IBD patients in Ontario with public drug coverage experienced greater delays in access to anti-TNF-α therapy than privately insured patients, and had a higher rate of hospitalization and emergency room visits related to IBD. Since many Ontario pediatric CD patients may now be relying exclusively on the province for their drug coverage, their clinical outcomes may be negatively affected as well. Research evaluating the new drug program in Ontario is required to examine whether the OHIP+ program affects timely access to anti-TNF- α therapy. The changes and uncertainty regarding the OHIP+ program in Ontario and evolving private and public drug coverage policies could raise access and equity issues with respect to biologic treatment. Those with private insurance may receive treatment sooner than those who do not. Those in provinces with established systems and policies in place on how to cover expensive provinces may receive treatment sooner than those in provinces where changes to coverage policy are evolving. Nevertheless, our cost-effectiveness model shows that intervention with anti-TNF-α sooner than later results in a better clinical outcome in the form of time in steroid-free remission even though it is more costly from a societal and public payer perspective. Our results did not indicate that hospitalization was reduced with early anti-TNF-α intervention. Decision makers should be aware that earlier intervention may result in better clinical outcomes and not create unnecessary delays in treatment due to policy or administrative issues.

4.5 Strengths and Limitations

4.5.1 Strengths of the Study

There are five main strengths of the cost-effectiveness analysis that was conducted: 1) it is the first cost-effectiveness analysis in pediatric Crohn's disease examining early anti-TNF-α intervention to incorporate a societal perspective; 2) it uses the clinical outcome of steroid-free

remission weeks as the effectiveness measure which is particularly relevant to pediatric CD concerned with growth; 3) it uses a large multi-centre North American observational study to inform model inputs to increase generalizability; 4) it uses an individual microsimulation model that incorporates the wide variability in patient characteristics and health experiences; and 5) it assesses different methods of propensity score analysis and data assembly when dealing with patient-level data. Each of these strengths will be discussed further below.

This study was the first economic evaluation of early introduction of anti-TNF-α treatments in pediatric Crohn's disease that examined the health care public payer and societal perspectives. The societal payer perspective took into account the economic burden experienced by caregivers through loss of productivity as a result of managing a child's Crohn's disease. It was important to consider caregiver costs because children are dependent on their caregivers for support such as time spent in caregiving.

A cost-effectiveness analysis (CEA) was chosen for this economic evaluation as opposed to a cost-utility analysis (CUA) (the recommended approach) because of the lack of established childhood health utilities in this patient population. The CEA allowed the comparison to other studies (see section 4.2) based on clinically relevant outcomes in pediatric CD such as the effectiveness measure of steroid-free remission weeks, which is of particular concern in children with CD, since the disease and corticosteroid use can negatively impact their growth.

The study data were drawn from the RISK-PROKIIDS study, a large North American observational study of newly-diagnosed CD children where patients were treated according to the physician's discretion. Hence the data were pragmatic and reflected actual clinical practice as opposed to the controlled situation in a randomized controlled trial. This increased the generalizability and external validity of the results as the patient population reflected a diverse North American population as shown by the patient characteristics. The generalizability of the results is discussed in more detail in the next section.

Since patients were not treated according to a strict protocol and in a randomized controlled trial, the possibility of selection bias in treatment selection was not accounted for, thus

questioning the comparability and internal validity of the comparator groups without adjustments for potential bias. The observational database, with patient-level data, provided another advantage in that it reflected the variation in characteristics, disease and treatments received in patients as opposed to a clinical trial which can be constrained by a regimented treatment pattern. The patient-level data informed the microsimulation model which could accurately account for an individual's characteristics and their individual experience of going back and forth between the active disease and remission health states. A cohort model would not be able to capture all the variation in the patient population compared to the microsimulation model.

The disadvantage of the observational data is that selection bias may be present such as the possibility of patients of a particular ethnic background being treated with more aggressive treatments than other patients despite similar disease severity. By treating all patients in a similar fashion, and randomizing patients, an RCT would avoid an imbalance in allocation to treatment group based on patient characteristics. To account for this, propensity score analysis was used to construct the comparator groups. The strength of propensity score analysis was that it aided in defining comparator groups in observational data to mimic the randomization of a randomized controlled trial by choosing patients in treatment and control arms that had the same propensity to receive each treatment. In preparing data for the cost-effectiveness model, several propensity score analysis methods were assessed and the method that optimized balance between the comparator groups was chosen. While unknown at the start of this study, the presence of missing data in the patient-level data triggered the imputation of missing data to maintain a large sample population and also highlighted the options of combining imputed data sets which had not been previously discussed within the context of preparing inputs for a microsimulation cost-effectiveness model. The study conducted here examined the "Across" and "Within" methods and highlighted the fact that additional research should be conducted on this issue.

4.5.2 Limitations of the Study

A potential limitation of the study was that the study population may not reflect community or rural CD patients since all the recruiting sites are in major urban centers. Another limitation of the RISK-PROKIIDS data source was that it could be skewed towards reflecting U.S. clinical CD practice as opposed to Canadian practices since most of the sites are in the United States. To account for this difference Canadian costing was used, and the RISK-PROKIIDS data was mainly used to inform health state transition probabilities. There was no apparent difference among the health states of Canadian patients and American study patients, which is discussed in more detail in the next section.

The study conducted was based on observational data. A limitation of using observational data was that it had the potential to introduce several sources of bias into the study. The fact that the study was not blinded and that subjects were treated accorded to the physician's discretion could have led to selection bias in which clinicians may have selected certain patients to receive a particular treatment over others. Selection bias was accounted for through propensity score analysis. Recall bias on behalf of patients may have been present when relaying disease activity for assessment of the Pediatric Crohn's Disease Activity Index and response bias may have been present on behalf of clinicians who may have reported favourable outcomes in patients treated more aggressively. However, it was assumed that physical assessment of disease and laboratory values would support the subjective assessment of disease. Endoscopies were conducted at the discretion of the physician and therefore physical assessment of disease and mucosal healing were not part of the assessment of remission in this study. Therefore, internal validity may have been limited, but pragmatically, endoscopies are not always conducted regularly therefore supporting the generalizability and external validity of the assessments. The study patients were a subset of the larger, ongoing, observational RISK-PROKIIDS study which included patients with ulcerative colitis and Crohn's disease. Patients included in the economic evaluation met the study's inclusion criteria and therefore patients had to have health state data for a minimum of three years past diagnosis. Loss to follow-up was recorded as part of the RISK-PROKIIDS data and none of the included patients were recorded as being lost to follow-up.

It should also be noted that while the outcome has been presented as weeks in remission. Outcomes were based on the RISK-PROKIIDS study which only recorded health states every six months or so. Hence, the health state between the six month study visits was an assumption which was translated to the weekly cycle of the model. To compensate for the parameter uncertainty within the six month interval, a probabilistic analysis was conducted using beta distributions assigned to health state transition probabilities.

The observational nature of the RISK-PROKIIDS study included a wide variety of patients with various baseline characteristics. To account for the variation in baseline characteristics of patients among the treatment groups, propensity scoring analysis was used. A limitation of propensity scoring analysis is that while it can serve to reduce imbalanced allocation within an observational study, the methodology can reduce the sample size of the comparator groups. From an unadjusted population of 573 patients, the adjusted population included 360 patients with 237 in the standard care group and 123 in the early anti-TNF-α intervention group. Compared to other small pediatric CD studies of fewer than a hundred patients, this study still maintained a reasonable sample size. An argument could be made that the propensity score matching process with a resultant 123 patients in the early anti-TNF-α group could have excluded patients with a high propensity score to be treated (see Figure 3.4.5-1 for unmatched treatment group) thus creating differential bias. If those patients had shown a greater response to the anti-TNF-α, the early anti-TNF-α intervention may have shown to be more cost-effective. However, this does not seem to be the case, since when comparing the proportion of patients in remission and steroid-free remission between the unadjusted and adjusted populations, the results are very similar. For example, at one year the proportion of patients in the early anti-TNF-α group in the unadjusted population (n=131) in steroid free remission was 61.1% and 61.0% in the adjusted population. The differences in proportion of patients in remission and steroid-free remission between the standard care group and the early anti-TNF-α group in the adjusted and unadjusted populations were also similar.

Another limitation of this study was that the RISK-PROKIIDS study was originally designed to investigate the genetic, microbial and environmental impacts on children with CD. As such, the

data collected address those questions and not the clinical efficacy or cost-effectiveness of anti-TNF-α treatments *per se*. As a result, certain relevant economic inputs such as outpatient resource use, parental costs or productivity losses, drug dosages, or clinical outcomes such as mucosal healing, anti-TNF-α trough level results or therapeutic drug monitoring were not assessed for patients (Al Hadithy et al., 2005; G. D'Haens, 2004; Vande Casteele et al., 2013). The lack of these data may affect current practice, costing, and clinical effectiveness assessments and hence may affect the external validity of this study. Similarly, the rapid evolution of treatments in CD, with the entry of new biologics and biosimilars into the market, was not included in the study. The study was limited in that it only included the costs of brand name infliximab and adalimumab because these were the treatments used by the RISK-PROKIIDS patients. Not including more recently introduced biologic treatments and biosimilars may have affected the external validity of the study since the variation in current treatment costs were not taken into account. However, to compensate for this limitation, a scenario analysis of altering the price of infliximab was conducted.

A criticism of this study may be that for a chronic life-long illness, a 3-year time horizon is too short and that a life time horizon would be more suitable. However, at the moment, there is very limited long-term safety and efficacy data beyond three years in newly-diagnosed children with CD prescribed anti-TNF-α treatments as first line therapy. One argument could be that adult data could have been used to model outcomes and extrapolate beyond a pediatric time frame, however, pediatric patients respond differently to anti-TNFα treatments than adults so it is possible that children who have received infliximab in childhood and graduate to adulthood may have different outcomes than adult patients thus increasing parameter uncertainty (Hanauer SB, 2002; Gary R Lichtenstein, 2013). The choice of a 3-year time horizon allowed the results to be more easily compared to other economic evaluations in pediatric CD (Punekar et al., 2010) and studies in adult Crohn's patients (Assasi et al., 2009; Blackhouse et al., 2012a; Canadian Agency for Drugs and Technologies in Health (CADTH), 2009; Lindsay et al., 2008).

Another challenge in assessing long-term outcomes is the uncertainty in the loss of response to treatment. Loss of response to anti-TNF-α treatment is a concern and can occur in

approximately 30% of patients over time (Gouldthorpe et al., 2013). At this time, it is difficult to know which patients would lose response and whether their treatment options would be dose escalation or a switch to another treatment. Since there is considerable uncertainty and a lack of long-term data, a longer term or lifetime time horizon would not be robust. The effect of discounting in the long-term model would likely decrease the gap between the clinical effectiveness of early anti-TNF-α treatment and standard step up care since clinical results would be realized early in treatment, and more patients in the step-up strategy would be on anti-TNF-α treatment later on. Hence the early anti-TNF-α may be even less cost-effective over a longer term.

Another limitation of the study was a lack of balance between the first order and second order microsimulations due to limitations in computing power. There were 10,000 first order microsimulations, and 50 second order microsimulations.

4.6. Generalizability of the Study

The RISK-PROKIIDS study, a multi-centre, observational cohort of pediatric Crohn's disease patients, analyzed retrospectively, informed the health state transition probabilities and served as the representative pediatric Crohn's disease patient population in the cost-effectiveness study. Patients in the RISK-PROKIIDS study were treated according to the physician's discretion and not according to a particular protocol. Hence, treatment of patients was pragmatic and reflected actual clinical practice as opposed to a randomized clinical trial. This increased the generalizability and external validity of the results as the results reflected a diverse North American CD population. The study included 25 sites in the United States and 3 Canadian sites. All the sites were in major urban centres and almost all of them identified themselves as having an affiliation with an academic institution. Therefore, while they were scattered across the U.S. and Canada, they may not reflect the treatment patterns of a rural CD population.

As mentioned in the previous section, from a Canadian perspective, a limitation of the study could be that since there were fewer Canadian sites, treatment practices could be skewed towards U.S. clinical practice. Following propensity score matching, 57 out of 237 (24.1%)

Canadian patients were in the standard step-up care group, and 12 out of 123 (9.8%) Canadian patients were in the early anti-TNF-α group. The treatment and health state of the Canadian patients and their health state did not appear to differ substantially from their American counterparts. The rate at which Canadian patients adopted anti-TNF-α treatment compared to their American counterparts in the propensity matched standard care group from the RISK-PROKIIDS study was similar. After one year, 30% of Canadian CD patients were on anti-TNF-α and 26% of Americans in the standard care group were on anti-TNF-α, and at three years post-diagnosis, 63% of the Canadians and 53% of Americans on anti-TNF-α treatment (see Appendix 22).

A recent survey of pediatric IBD clinicians that examined regional differences in anti-TNF-α practice patterns in children with IBD showed somewhat different results with a median of 36% of Canadian practitioners treating luminal CD pediatric patients with anti-TNF-α treatment compared to a median of 50% for U.S. practitioners (Peter C Church et al., 2018). The same study showed that anti-TNF-α therapy in pediatric IBD patients was more prevalent in North America compared to Europe and other countries (Peter C Church et al., 2018). Therefore, the cost-effectiveness analysis presented here would be more applicable to a North American practice setting. Despite the possibility that Canadian treatment practices may differ slightly from American treatment practices, the cost-effectiveness analysis could still be applicable to a Canadian population since treatment costs were based on Canadian costs and Canadian resource use.

Certain aspects of the cost-effectiveness analysis would be of interest to decision makers in jurisdictions within Canada and outside of Canada when making funding decisions. The scenario analysis of the price of infliximab affecting the cost-effectiveness early anti-TNF-α is of particular interest to decision makers in various jurisdictions. Inflectra®, the biosimilar version of infliximab, ranges from $CAD 525 in Alberta to $CAD 650 per vial in Saskatchewan. The scenario analysis showed that at 50% of the price of Remicade®, the cost of an additional week of steroid-free remission was $CAD 659 which is approximately the cost of an additional dose of infliximab in Canada. This analysis shows that, depending on the willingness to pay in a

particular jurisdiction for an additional week of steroid-free remission, early anti-TNF-α with biosimilar infliximab may be cost-effective compared to standard step-up care. While infliximab is indicated in patients refractory to other treatments, the steroid-sparing nature of early anti-TNF-α therapy as determined by our cost-effectiveness analysis, would be of interest to European decision makers as there is preference for steroid-sparing treatments in European guidelines for pediatric CD management and in the United Kingdom, National Institute of Health and Care Excellence guidelines (National Institute of Health and Care Excellence, 2016) (F. Ruemmele et al., 2014).

4.7 Implications for Stakeholders

The results of this cost-effectiveness analysis may impact various stakeholders in different ways depending on their individual mandates. How the various stakeholders, such as clinicians, policy makers, researchers, manufacturers, patients and caregivers can use the information from the cost-effectiveness study is discussed below.

4.7.1. Implications for Clinical Practice

The results of the cost-effectiveness analysis comparing early anti-TNF-α treatment to standard, step-up care have some notable points for the clinical management of Crohn's disease in children. Compared to standard step-up care, intervention with anti-TNF-α within the first three months of diagnosis resulted in: 1) a greater number of steroid-free semesters or weeks in remission over a three year period; 2) a greater number of consecutive steroid-free remission semesters over a three year period; and 3) a greater number of patients in steroid-free remission at six months (see Table 3.5-4).

Interestingly, over three years, the number of people in steroid-free remission at one year, and at six month intervals thereafter, was not significantly different among the two comparator groups. This may have been observed because the endpoint of people in remission at a given point is a snapshot in time and does not account for the individual's experience and number of relapses prior to that point. Observations at approximately six month intervals in the RISK-PROKIIDS data showed that many patients moved frequently and unpredictably between active

and remission phases of diseases. Hence, the number of people in steroid-free remission at any one time could vary. Clinical researchers should be aware that the endpoint of the number of people in remission at any given time may not be an adequate endpoint on its own to measure efficacy of anti-TNF-α treatment and that multiple clinical endpoints should be assessed and reported to avoid reporting bias. In addition, the number of hospitalizations did not differ significantly between the two comparator groups, which is also seen in some studies (Tsui & Huynh, 2018). While this cost-effectiveness analysis used time in remission as the outcome measure, this outcome can also be described as the relapse free rate. Lee et al., showed that top-down, or early anti-TNF-α intervention had a longer remission period than a step-up strategy based on relapse free rate over three years in pediatric Crohn's disease over three years (Y. M. Lee et al., 2015).

Our results also highlight the difference between remission irrespective of steroid treatment and steroid-free remission. The cost-effectiveness analyses showed that early anti-TNF-α treatment had a greater impact on steroid-free remission weeks (11.3 more weeks than standard care) than simply weeks in remission (6.65 more weeks). This result demonstrates the reduction in steroid dependency for the early anti-TNF-α treatment, and its steroid-sparing qualities, compared to standard care and supports the recommendation to incorporate steroid use in measuring outcomes for children with CD (Griffiths et al., 2005).

The cost-effectiveness analysis conducted here adds to the sparse literature regarding anti-TNF-α treatment in pediatric CD. The size of the RISK-PROKIIDS study is large compared to other pediatric studies examining top-down treatments with biologics (Tsui & Huynh, 2018). The time horizon of three years can be considered a longer term study than most studies that end after a year (Y. S. Lee et al., 2012).

From a clinical management perspective, our results seem to support the use of anti-TNF-α treatments within the first three months of diagnosis. However, due to constraints from the public payers restricting use of anti-TNF-α to those who have had inadequate response to conventional treatments, it may be difficult to implement such a strategy. The use of anti-TNF-α

treatments as first line treatment in pediatric patients is considered off-label use. The positive clinical outcome of increased weeks in steroid-free remission with early anti-TNF-α treatment compared to standard step-up care may lead clinicians to increase off label use of anti-TNF-α earlier in the treatment of pediatric patients.

Since the results of the cost-effectiveness analysis were based primarily on inputs and experiences of patients in the RISK-PROKIIDS study, there are several rapidly evolving aspects of clinical practice that were not addressed. These include assessing the outcome of mucosal healing, dose escalation of infliximab or adalimumab, assessing a patient's preference for a particular anti-TNF-α treatment, and therapeutic drug monitoring. These issues were not incorporated into the cost-effectiveness model because they are not part of current clinical practice guidelines or they were not recorded in the RISK-PROKIIDS data. In pediatric luminal CD, early anti-TNF-α intervention was significantly better than traditional step-up treatment at improving mucosal healing, which is assessed endoscopically, and is being touted as a predictor of sustained remission (Kang et al., 2016; Nuti et al., 2013). Therapeutic drug monitoring, and management of loss of response to biologics are also becoming more common in clinical practice but were not modeled in the cost-effectiveness model since they are newer practices, not widely accessible for all patients and were not observed in the RISK-PROKIIDS data (Ding, Hart, & De Cruz, 2016). The anti-TNF-α treatment used in the RISK-PROKIIDS study was primarily infliximab since it was the first anti-TNF-α available for pediatric CD and some patients started the study in 2009. Since then, adalimumab, administered by injection, has also become more prevalent as an anti-TNF-α treatment option. Early use of adalimumab showed positive clinical outcomes in pediatric CD (Kierkus et al., 2013). With increased treatment and management options, clinicians need to be aware that treatment is increasingly more individualized and that initial aggressive therapy, while clinically effective in some patients, may not be necessary in all patients (J.-F. Colombel, Narula, & Peyrin-Biroulet, 2017; Rogler, 2013; Torres, Mehandru, Colombel, & Peyrin-Biroulet, 2017).

4.7.2 Implications for Policy

The purpose of this study was to provide additional evidence to support policy decision making regarding the use and timing of anti-TNF-α treatments for the treatment of moderate to severe pediatric Crohn's disease. Cost-effectiveness analyses from both the health care public payer perspective and a societal perspective provide a more comprehensive analysis of the costs and consequences involved in the management of pediatric CD with anti-TNF-α therapy. Since the analyses incorporated an Ontario health care public payer perspective, all treatment costs were assumed to be the responsibility of the public payer, with societal costs incorporating only the addition of caregiver productivity costs. The incremental cost effectiveness ratios from the societal perspective and the health care public payer perspectives were very similar, as that the main driver of costs was the cost of treatment. The cost-effectiveness analyses showed that early anti-TNF-α treatment was more effective than standard step-up care but more costly and that there was considerable uncertainty surrounding the ICER. The uncertainty surrounding the ICER made it difficult to state unequivocally that the early anti-TNF-α strategy was not cost-effective compared to standard care particularly since the willingness to pay for a week in steroid-free remission was unknown. The results of the study did suggest that the sooner a child with moderate to severe CD receives anti-TNF-α treatment, the greater likelihood of greater time in steroid-free remission over three years. Therefore, policies regarding anti-TNF-α treatment should ensure that treatment is accessed and administered as quickly as possible and that administrative delays in processing applications for access are avoided. Currently observed delays due to public payer involvement in treatment management with biologics should be addressed to avoid needlessly delaying treatment (Office of the Auditor General of Ontario, 2017; Rumman et al., 2017; Sher, 2018). In 2016 to 2017, the time between the Ontario Ministry of Health and Long-term Care receiving requests for coverage for infliximab and adalimumab to when it replied with its coverage decision averaged approximately seven to eight weeks (Office of the Auditor General of Ontario, 2017). Therefore, in Ontario, the implementation of treatment with anti-TNF-α after diagnosis faces an administrative challenge.

While the cost-effectiveness analysis suggests that early anti-TNF-α intervention could improve clinical outcomes, it is unlikely that drug coverage policies will change to allow the use of anti-TNF-α treatment as first line therapy unless Health Canada approvals are amended to include first-line treatment use. Currently anti-TNF-α treatment is indicated in patients refractory to other conventional treatments. Other constraints for anti-TNF-α also exist. In Ontario, Remicade® is available only through the Exceptional Access Program and is no longer recommended for anti-TNF-α treatment-naïve patients. In Ontario, public drug coverage for Inflectra® (biosimilar infliximab) is considered limited use (Ontario Ministry of Health and Long-Term Care, 2016b). The limited use notes, posted on the Ontario Ministry of Health Long-Term Care e-formulary (Ontario Ministry of Health and Long-Term Care, 2016b) , do not specify a patient's age and state the following: "the limited use is authorized for one year for the treatment of moderate to severe (luminal) Crohn's Disease in patients who meet the following criteria:

- HBI (Harvey Bradshaw Index) score greater than or equal to 7; and
- failed to respond to conventional treatment with a corticosteroid equivalent to a daily dose of prednisone 40mg daily for at least 2 weeks;
- OR the patient is stabilized on corticosteroid but cannot be tapered to a corticosteroid dose below prednisone 20mg daily or equivalent;
- failed to respond to an immunosuppressive agent (azathioprine, 6-mercaptopurine, methotrexate, or cyclosporine) tried for at least 3 months (or where the use of immunosuppressants is contraindicated);
- the recommended dosing regimen is 5mg/kg/dose at 0, 2 and 6 weeks followed by 5mg/kg/dose every 8 weeks. (note: higher doses up to 10mg/kg/dose may be considered in patients who have failed to respond to lower doses);
- maintenance therapy is funded for patients who meet the Ministry initiation criteria and whose disease is maintained with a 50% reduction in the Harvey Bradshaw Index from pre-treatment measurement, AND improvement of symptoms (for example: absence of bloody diarrhea, weight is stable or increased), AND the use of

corticosteroids and/or other immunosuppressive therapy is reduced, being tapered, or discontinued;

- for funding beyond the second year, the patient must continue to demonstrate benefit and if unable to be discontinued on corticosteroids, the physician may wish to consider other funded alternatives;
- the recommended dosing regimen is 5mg/kg/dose every 8 weeks."

The Harvey Bradshaw Index (HBI) is a Crohn's disease activity index (Harvey & Bradshaw, 1980). To ensure that patients receive appropriate and timely treatment, policy makers should ensure that meeting these conditions is not cumbersome, difficult to achieve, or overly time-consuming for clinicians, patients and administrators.

The one-way sensitivity analysis showed that a reduction in the price of infliximab could result in cost-savings. This result corresponds with another economic impact study that examined the impact of biosimilars on inflammatory bowel disease treatment which found that a price reduction in anti-TNF-α therapy such as with biosimilars, could result in significant cost-savings for the Dutch healthcare system (Severs et al., 2016). Policy makers could leverage this knowledge in negotiating prices with manufacturers to ensure that covered treatments and corresponding policies are aligned to manage pediatric CD in a clinically effective and cost-effective manner. Since the budget for Crohn's disease treatment in Ontario was unknown, the budget impact of early anti-TNF-α treatment could not be established. In 2016, the class of anti-TNF-α drugs which are also used to treat rheumatoid arthritis, accounted for the highest proportion of public drug spending in Canada at over $800 million and the third highest proportion of Ontario's public drug expenditure at over $264 million (Canadian Institute for Health Information, 2017). Remicade® (infliximab) is the fourth costliest drug in Ontario and comprised 2.4% of the total drug costs in 2015/2016. Early anti-TNF-α treatment could increase drug costs in Ontario. However, the introduction of biosimilars, which would reduce Remicade® use, may reduce overall drug costs which could compensate for earlier anti-TNF-α use.

4.7.3. Implications for Manufacturers

The cost-effectiveness analysis results could be informative for manufacturers. The one-way sensitivity analysis examining the cost of infliximab showed that the ICER was sensitive to the price of infliximab and that a price of 25% of the current price of Remicade® may result in cost savings with early anti-TNF-α treatment. A cost-saving and clinically effective strategy, i.e. a dominant strategy would be more amenable to the payer. Knowing the approximate price at which cost-savings could occur assists manufacturers in pricing their drugs and in negotiations with the pan-Canadian Pharmaceutical Alliance (pCPA). The pan-Canadian Pharmaceutical Alliance (pCPA) includes thirteen Canadian provinces and territories and the Federal Government, and negotiates prices of both generic and brand name drugs for Canadians (Husereau, Dempster, Blanchard, & Chambers, 2014).

Currently biologic treatments are only recommended for use after an inadequate response to conventional treatment and are used off-label in pediatric patients because they have not specifically been approved for a pediatric population by Health Canada. If manufacturers desire unrestricted access to their pharmaceutical products they would have to provide sufficient evidence, preferably from randomised clinical trials in children, proving the safety and efficacy of their products in a particular population such as treatment naïve patients. In addition, appropriate economic evaluations would have to be performed for inclusion in publicly funded drug formularies. Our results, based on retrospective observational data, suggest that early anti-TNF-α treatment may improve time in steroid-free remission in children with moderate to severe CD, therefore manufacturers of existing or new anti-TNF-α products may want to consider sponsoring a pediatric randomized clinical trial to support this new indication. A multi-centre randomized clinical trial in a pediatric CD population has begun examining early intervention with infliximab, and may provide additional evidence for the support of early anti-TNF-α intervention in pediatric CD (Cozijnsen et al., 2016).

4.7.4. Implications for Patients and Caregivers

Patients and caregivers are interested in receiving appropriate and timely treatments. In Ontario, out-of-pocket drug expenses may be reduced due to the OHIP+ program which provides publicly funded drug coverage for drugs on the Ontario Drug Benefit Formulary for those under the age of 25 and not covered by private plans. In other provinces, a mix of private and public insurance remains. Safety of biologic treatments is a concern for patients, particularly the risk of cancer (Norton, Thomas, Lomax, & Dudley-Brown, 2012). However, a recent study concluded that infliximab exposure did not increase the incidence of malignancy in pediatric IBD patients (Jeffrey S Hyams et al., 2017). For caregivers and patients, the results of this study can provide information in their advocacy efforts in conjunction with organizations, such as Crohn's and Colitis Canada, with provincial governments in advocating for timely access to appropriate medications. The results demonstrating that early anti-TNF-α intervention may provide better clinical outcomes can be used as evidence to support the elimination of delays and restrictions in getting treatment coverage for initial treatment or adjustments to treatment. Other concerns for parents include long-term quality of life and disease burden for their children (Teitelbaum, Rajaraman, Jaeger, Para, & Rakitt, 2013). The decision to start anti-TNF-α treatment is difficult for parents with children with Crohn's disease owing to the limited long-term safety and efficacy data of anti-TNF-α treatment in children (Lipstein et al., 2013). While still only a three-year study, the results of this study, particularly the positive clinical outcome of increasing steroid-free remission, add to the body of knowledge related to the efficacy of early anti-TNF-α treatment which may provide some additional information to parents faced with the decision of starting anti-TNF-α treatment for their children.

4.7.5. Implications for Researchers

The cost-effectiveness analysis presented here raises some noteworthy issues for researchers in pediatric IBD and for researchers conducting economic evaluations with patient-level data. When the cost-effectiveness analyses using an outcome of weeks in steroid-free remission was compared to the outcome of weeks medical remission irrespective of steroid-use, the results of the model suggested that the early anti-TNF-α was more steroid sparing than standard step-up

care. The outcome of medical remission alone did not expose the added advantage of early anti-TNF-α treatment particularly in pediatric CD. The steroid sparring nature of early anti-TNF-α treatment has also been supported in adult CD (D. T. Rubin, Uluscu, & Sederman, 2012) and in an adolescent case study (Persley, Scherl, & Rubin, 2001). The differences in steroid-related outcomes in the cost-effectiveness model support the recommendation of using steroid-free remission as a preferred outcome in pediatric IBD studies (Griffiths et al., 2005). While steroid-sparing outcomes are preferable in pediatric IBD, a clear, quantified relationship between the amount of steroid-free remission time and health care cost savings or steroid-free remission time and increased quality of life has yet to be determined.

The secondary objective of this study was to examine the impact of different methods of propensity score analysis within the context of a cost-effectiveness analysis. The cost-effectiveness analysis and the preparation of model inputs provided insight for researchers in health technology assessment. The pediatric RISK-PROKIIDS study was the primary source for health state transition probabilities in the Markov model. Since the RISK-PROKIIDS study was an observational study, analyzed retrospectively, to avoid selection bias, propensity score analysis was used to create comparator groups. In the absence of a randomized controlled trial, propensity score analysis allocated individuals to each treatment group based on their similarities on several covariate characteristics. In the study, it was determined that the propensity to be assigned a particular treatment may be based on the following variables: age at diagnosis, sex, disease activity at diagnosis, African heritage, disease location, the presence of peri-anal disease, height z-score, steroid-related health state at diagnosis, albumin lab values, and whether the subject was recruited at a large clinical site. When the unadjusted RISK-PROKIIDS CD study population was assessed, there were 64 patients with missing values for the continuous variable of albumin. Instead of arbitrarily excluding these patients and reducing the potential sample size, and since there was a small proportion of patients with missing values and the missing values were for a continuous variable, imputation was chosen as a viable option for maintaining these patients as part of the unadjusted study population. Multivariate imputation by chained equations (MICE) using the predictive mean matching

method was conducted for ten iterations resulting in ten separate imputed data sets. Clear guidance on how to proceed for subsequent propensity score analysis within the context of a cost-effectiveness analysis was not found among the economic evaluation literature. Typically, imputed datasets are pooled to present an outcome determined with a regression model (Buuren & Groothuis-Oudshoorn, 2011; D. B. Rubin, 2004). Rubin's rules, based on asymptotic theory on the normal distribution, guide the combination of the separate estimates and standard errors from each of the imputed datasets into an overall estimate with standard error, confidence intervals and p-values when pooling the estimates (Buuren & Groothuis-Oudshoorn, 2011). There is uncertainty regarding pooling imputed datasets if parameters do not have a normal distribution or if the distribution is unknown, such as in estimating propensity scores or for survival model estimates (Leyrat et al., 2017; White, Royston, & Wood, 2011).

Two approaches were proposed to estimate propensity scores: the "Within" method or the "Across" method (Mitra & Reiter, 2016). The "Within" method calculates propensity scores on each imputed dataset separately and creates multiple matched data sets with the intention of averaging results for the final outcome estimate (Mitra & Reiter, 2016). The "Across" method averages the propensity score for each subject from each imputed dataset and then uses that mean propensity score to create one matched population (Mitra & Reiter, 2016). The "Within" method has also been called the "MIte" method and the "Across" method has also been called the "MIps" by Leyrat et al., (2017) (Leyrat et al., 2017). While Mitra and Reiter (2016) suggest using the "Across" method as a default method since it can provide greater bias reductions, both methods could provide similar point estimates with the "Within" method having a lower variability (Mitra & Reiter, 2016). Mitra and Reiter (2016) used simulations with complete and missing data, variance estimates, and mean squared error estimates to compare bias from actual data between the "Across" and "Within" methods (Mitra & Reiter, 2016). In our cost-effectiveness analysis mean squared errors were not determined, since complete data without missing data was not available. Therefore, an assessment of bias could not be determined in our dataset. Standard deviations between the two methods were determined and discussed further below. A criticism of the "Across" method is that it doesn't take into account the

variance estimator due to the estimation of the propensity score and the variance of the imputation of missing data (Leyrat et al., 2017). The "Within" method does account for the variance in both estimates as it is based on Rubin's rules (D. B. Rubin, 2004). Mitra and Reiter (2016) concluded that both methods should be assessed depending on whether missing data is in one or multiple covariates that influence treatment selection and treatment effect. Leyrat et al., (2017), concluded that the "Within" method showed greater covariate balance when the inverse probability of treatment weighting propensity score analysis was performed. While a comprehensive analysis of combining data following imputation with subsequent propensity score analysis was not the primary focus of this research, it was determined that data combination methods could affect cost-effectiveness analysis results. The results of this research highlight the need for further research and guidance in handling missing data and propensity score methods within the context of economic evaluations. The differences between the "Across" and "Within" methods are discussed further below.

This cost-effectiveness study also involved examining different propensity score analysis methods to create comparator groups from patient-level data within the context of an economic evaluation. Propensity score methods are often chosen arbitrarily to create comparator groups from observational data (Austin, 2011a). However, the method which optimizes covariate balance should be chosen among the various methods available (Austin, 2011a). Since randomized controlled trials are rare in pediatrics and studies often rely on retrospective, observational data, appropriate propensity score analysis is of particular relevance to pediatric research. This study examined four methods of propensity score analysis: propensity score matching, propensity score weighting using the inverse of the probability of treatment assignments as a weight, the covariate balancing propensity score (CBPS) method, and propensity score with subclassification. The propensity score methods with the greatest degree of balance included those with the most covariates with mean standardized differences below 0.1 and variance ratios closest to 1. The weighting method, the CBPS method and the nearest neighbour matching method using a caliper constraint of 0.2 and using a 2:1 or 3:1 ratio of standard care to early anti-TNF-α intervention patients were the optimal methods based on

covariate balance. While all these methods met the criteria for acceptable covariate balance, for the purposes of determining health state probabilities at various time points, separate matched comparator groups needed to be extracted from the propensity score analysis software. Therefore, due to the technical ability to extract the full matched dataset with individual characteristics, the nearest neighbour matching with a caliper of 0.2 in a 2:1 control (standard care) to treatment (early anti-TNF-α intervention) was chosen as the propensity score method of choice.

Multiple health state transition probabilities needed to be determined for the Crohn's disease Markov model. Transition probabilities were based on the number of individuals in a particular health state at a given time using the method described in Briggs et al., (2006) (Briggs, Sculpher, & Claxton, 2006). Using this method, the number of patients in each comparator group in the adjusted data set was counted. Using the "Across" method of combining data, prior to propensity score analysis transition probabilities came from one data set. However, when using the 'Within" method, ten matched data sets were created. Each matched data set had a slightly different population of individuals resulting in a slightly different combination of people in each health state over time. Hence, ten models with ten different sets of health state transition probabilities were also created. In all, the RISK-PROKIIDS population provided eleven data sets to inform health state transition probabilities. The eleven data sets resulted in eleven different point estimates for the incremental cost-effectiveness ratio (ICER). The question arises as to which data set(s) to use to inform model inputs. If the primary outcome was a treatment effect for a clinical trial, the mean of the "Within" estimates would be determined thus pooling the results. However, within the context of a cost-effectiveness analysis there is no clear guidance on which point estimate would serve as a better representative of the ICER. In this study, following a two dimensional probabilistic analysis of 50 samples of 10,000 microsimulations, the mean ICER determined based on the "Across" method of data assembly was $4,818 and the mean point estimate ICERs based on the "Within" method of data combination ranged from $2,250 to $12,870 for an additional week of remission with the early anti-TNF-α treatment compared to standard step-up care. The average of the mean point estimates of the ten ICERs

using the “Within” approach was $5,157 which was higher than the point estimate ICER using the “Across” approach. The standard deviation of the ICER using the “Across” approach was $3,865 and the pooled standard deviation of the ten datasets using the “Within” method was $4,366. The standard deviation and the variance of the “Across” method was slightly lower than the standard deviation and variance of the “Within” method. Mitra and Reiter (2016) found that the “Within” method had lower variability. It should be noted that the point estimates in Mitra and Reiter’s study were singular study outcomes. However, the point estimates that were compared in this cost-effectiveness analysis were incremental cost-effectiveness ratios. Typically, standard deviations of ICER’s are not reported but confidence intervals for the incremental costs and incremental effects are reported separately. Nevertheless, these two methods of data combinations added to the methodological uncertainty in the cost-effectiveness model. Researchers conducting cost-effectiveness analysis imputing missing data and then performing propensity score analysis should be aware of the uncertainty and differences in the ICERs based on different methods of obtaining model inputs. Additional research needs to be performed to provide guidance on which methods are best suited for determining health state transition probabilities with patient-level data. Possible suggestions for additional research could include running simulated cost-effectiveness analyses with multiple complete data sets. Comparisons of cost-effectiveness analysis results using health state transition probabilities determined from the complete dataset and health state transition probabilities determined with imputed data after artificially creating missing data could be used to determine the differences between the “Across” and “Within” methods of data assembly. Studies examining how missing data coming from control, or treated, or both groups affects the outcome of a cost-effectiveness analysis can also be conducted. A minimum number of datasets to impute and their effect on the ICER should be determined. Comparisons between determining each health state transition probability using regression modelling as opposed to counting the number of individuals within a health state over time can also be examined when missing data in patient-level data are involved.

4.8 Biosimilars and Other New Biologic Market Entrants

The biologic treatments for inflammatory bowel disease are rapidly evolving with biosimilars and new biological drugs entering the market. A discussion on the cost-effectiveness of anti-TNF-α treatments in Crohn's disease would be incomplete if it did not mention the impact of biosimilars on clinical practice and drug policy. Biosimilars or biosimilar biologic drugs are highly similar to biologic drugs that were already authorized for sale. Biosimilars, or subsequent entry biologics, are manufactured in living cells and hence not completely identical to their originator biological drugs but can enter the market following regulatory approval and patent expiry of the originator biological drug (Health Canada, 2017). Similar to generic drugs, it is expected that biosimilars would enter the market at a lower price than the originator biologic drug (Canadian Agency for Drugs and Technologies in Health (CADTH), 2018). In 2016, Inflectra® and Remsima® , the biosimilar versions of infliximab were approved by Health Canada for inflammatory bowel disease in adults with moderate to severe disease who have not responded to conventional treatments such as corticosteroids (Canadian Agency for Drugs and Technologies in Health (CADTH), 2018; Health Canada, 2016). Currently the price for a 100 mg vial of Inflectra® is $CAD 525, which is 53% of the cost of Remicade® at $CAD 987.56 in Ontario. Based on provincial formularies, in Canada the price for Remicade® ranged from $CAD 940 to $1036 following negotiations through the pan-Canadian Pharmaceutical Alliance (Canadian Agency for Drugs and Technologies in Health (CADTH), 2018). The efficacy of Inflectra® has been demonstrated in clinical trials (Deiana, Gabbani, & Annese, 2017; Gecse et al., 2015; Jørgensen et al., 2017). In 2018, Health Canada issued a summary basis for the approval of Renflexis®, another infliximab biosimlar, which specifically included the use of Renflexis® for the treatment of pediatric patients with moderate to severe Crohn's disease over the age of nine who have not responded adequately to conventional treatments (Health Canada, 2018). Currently Renflexis® or Remsima® are not yet listed on provincial formularies for inflammatory bowel disease.

Other new biologic market entrants for the treatment of inflammatory bowel disease include Entyvio® (vedolizumab) and Stelara®(ustekinumab). Entyvio®, a biologic treatment targeting integrin was approved in 2016 for adults with moderate-to-severe Crohn's disease with an

inadequate response to other immunomodulators or other anti-TNF-α treatments (Takeda Pharmaceutical Company Limited, 2016). Entyvio® is available through the Exceptional Access Program in Ontario and costs $3,290 for 300 mg (Ontario Ministry of Health and Long-Term Care, 2018a). In 2016, Stelara® a biologic therapy targeting interleukin 12 (IL-12) and interleukin 23 (IL-23), was approved for adults with moderate-to-severe Crohn's disease with an inadequate response to other immunomodulators or other anti-TNF-α treatments. However, Stelara® is not listed in the Ontario Drug Benefit (ODB) formulary for Crohn's disease at this time. All these examples illustrate the rapidly changing treatment options for Crohn's disease. However, it is important to note that coverage for these biologics and biosimilars come with constraints on their use in terms of dosing frequency, no pediatric indications, and the caveat that they can only be used in patients with inadequate responses to conventional treatments. Imposing such restrictions which may need to be reconciled on a case by case basis within a special access program can delay access to these medications (Office of the Auditor General of Ontario, 2017). Children with IBD, often have different dosing requirements and imposing restrictions can limit the speed at which clinicians can make adjustments to treatment and also cause delays in treatment (Sher, 2018). Crohn's and Colitis Canada, a not-for-profit organization that raises funds for IBD research and advocates on behalf of IBD patients stated that "Doctors and their patients must be able to select the treatment option best suited to each patient's individual circumstances, without undue interference from government or private payers," as part of their position statement on biosimilars. As mentioned previously, IBD patients relying on public drug plan coverage may experience different clinical outcomes than those on private drug plans due to delays and restrictions in access to appropriate treatments (Rumman et al., 2017).

Our results suggest that early anti-TNF-α intervention is clinically more effective with regard to weeks with steroid-free remission compared to standard step-up care. However, it was more costly. A one-way sensitivity analysis was conducted to determine the sensitivity of the results of the cost-effectiveness analysis to the price of infliximab treatment. While our study did not model the incorporation of biosimilars into the treatment regimen, the sensitivity analysis could

serve to simulate the incremental cost per additional steroid-free remission week in the event that the cost was similar to that of the biosimilar Inflectra® or one that could be introduced at a lower price. The one-way sensitivity analysis was conducted with the price of infliximab varying by 150%, 87.5%, 75%, 62.5%, 50%, 37.5%, and 25% of the reference case ($987.56) (see Table 3.7.5.3-1 for ICERs). The incremental cost per additional steroid-free remission week at 50% the cost of Remicade® (similar to Inflectra®), was $CAD 659 for early anti-TNF-α treatment compared to standard step-up care. Hypothetically, if infliximab was 25% of its current cost, early anti-TNF-α treatment would provide a cost savings of $CAD 372 per steroid-free remission week gained. However, anti-TNF-α treatment is not currently indicated as first line treatment which would be considered off-label treatment. Over 75% of medicines prescribed to children are prescribed off-label since a pediatric population is often not specified as a treatment target in the product monograph due to a lack of safety and efficacy data (Standing Senate Committe on Social Affairs Science and Technology, 2014). Reimbursement of drugs prescribed for off-label indications through publicly funded provincial/territorial drug plans may not be consistent across jurisdictions (Standing Senate Committe on Social Affairs Science and Technology, 2014), and therefore may cause differences in treatment and access across provinces particularly for pediatric illness. This may raise concerns about patients getting timely access to appropriate treatments through public pediatric drug coverage systems such as with the OHIP+ program in Ontario.

4.9 Future Research

Similar to other cost-effectiveness analyses overall show conflicting results regarding the cost-effectiveness of anti-TNF-α for the treatment of inflammatory bowel disease, in this study, there is considerable uncertainty as to whether the early use of anti-TNF-α use is cost-effective compared to standard, step-up care in pediatric moderate to severe Crohn's disease (Huoponen & Blom, 2015; Tsui & Huynh, 2018). With respect to pediatric studies, due to the lack of randomized controlled trials, small sample sizes in retrospective studies, and a lack of standardization among studies, the efficacy and cost effectiveness of early anti-TNF-α treatment remain ambiguous (Tsui & Huynh, 2018). This study showed that while early anti-

TNF-α treatment was clinically more effective at increasing the time in steroid-free remission, the difference compared to standard step-up care was marginal over three years as patients in the standard care group also experienced weeks in steroid-free remission and several patients achieved remission in the absence of anti-TNF-α treatment. A concern with early anti-TNF-α treatment is that it is an aggressive therapy that may not be necessary for all moderate-to-severe patients (Hanauer, 2005). Determining which patients would be best served with early anti-TNF-α and which patients would be most responsive to early anti-TNF-α needs to be defined (Tsui & Huynh, 2018). Research into prognostic Crohn's disease biomarkers may yield promise into predicting which patients may require or respond to particular treatments (J. Lee et al., 2017).

Cost-effectiveness research into therapeutic drug monitoring in conjunction with early anti-TNF-α is needed to optimize the efficacy and cost-effectiveness of treatment. Therapeutic drug monitoring through the assessment of drug trough levels and correlating disease symptoms may also serve to optimize the efficacy of anti-TNF-α treatments on an individual basis (Casteele et al., 2015; Crowley et al., 2017; Hoekman et al., 2014). Therapeutic drug monitoring may also be more cost-effective and efficacious in patients who initially lose response to an anti-TNF-α treatment (Steenholdt et al., 2013).

With increasing calls to personalize treatment, research into appropriate cost-effectiveness models also needs to be done (Conti, Veenstra, Armstrong, Lesko, & Grosse, 2010). While clinical efficacy is challenged by relying on large randomized clinical trials to show statistically significant differences among treatments, individual microsimulation models using patient-level data may be able to incorporate individualized treatment and patient heterogeneity into cost-effectiveness studies.

The cost-effectiveness study performed here identified other gaps where research is needed. The willingness to pay for time is steroid-free remission is unknown. A study examining parents' preferences for willingness to pay for biologic treatments in Crohn's disease, similar to that conducted by Burnett et al., in juvenile idiopathic arthritis may be conducted (Burnett, Ungar,

Regier, Feldman, & Miller, 2014). In addition, the health utility of growth restoration as a result of steroid-free remission in children with Crohn's disease has not been quantified. The broader issue of health utilities, or the assignment of quality-adjusted life years to health states in children with Crohn's disease is undetermined. The determination of QALYs in pediatric Crohn's disease can allow the comparison of Crohn's disease treatments to treatments for other diseases. A survey of parent proxies of children or of children with Crohn's disease assessing their response to generic quality of life questionnaires designed for determining child health utilities can be performed (W. J. Ungar, 2010).

Another area of needed research identified by this study is in handling imputed patient-level data from clinical studies and propensity score analysis within the context of informing economic evaluations. Simulation studies with different sets of patient level data can be conducted with and without missing data to examine its impact on the cost-effectiveness results with different methods of data combinations and different methods of propensity score analysis. Guidance is needed as to the best practice when conducting economic evaluation with missing patient-level data.

In summary, this study contributed additional information regarding the cost-effectiveness of early anti-TNF-α treatment to the limited body of economic evaluations in pediatric Crohn's disease. Early anti-TNF-α treatment was more costly but more effective than standard, step-up care in increasing steroid-free remission weeks in children with moderate to severe Crohn's disease. Methodological uncertainty in the model identified that additional research is needed in how to handle missing patient-level data and choosing propensity score analysis methods within the context of economic evaluations. Steroid-free remission weeks were used as the effectiveness measure but if QALYs in pediatric Crohn's disease had been determined, a cost-utility analysis could have been conducted and the results could have been compared to other cost-utility analyses. As treatments become optimized and more personalized, cost-effectiveness models that incorporate personalized treatments such as therapeutic drug monitoring and dose adjustment may help to identify the most cost-effective treatment and monitoring strategies in children with Crohn's disease over the long term.

4.10 Conclusion

The cost-effectiveness of treatment with anti-TNF-α treatment within the first three months of diagnosis was compared to standard step-up care with the option of anti-TNF-α treatment only after three months following diagnosis in children with moderate to severe Crohn's disease. Concomitant medications such as corticosteroids and immunomodulators were allowed in both treatment arms. Due to the lack of randomized controlled pediatric studies in newly-diagnosed patients, the RISK-PROKIIDS study, an observational, North American multi-centre study, analyzed retrospectively, served as the source of patient health state transition probabilities and treatment patterns. The results of this research showed that early anti-TNF-α intervention is more effective but more costly than standard step-up care over three years in children with moderate to severe Crohn's disease. A microsimulation cost-effectiveness model showed that the incremental cost per additional steroid-free remission week was $2,755.70 ($CAD) for the early anti-TNF-α intervention for the reference case from a public health care payer perspective and the incremental cost per additional steroid-free remission week was $2,968.02 ($CAD) for the early anti-TNF-α intervention from a societal perspective. From a public health payer perspective, the early anti-TNF-α treatment strategy resulted in 11.3 more weeks of steroid-free medical remission than standard step-up treatment and was $31,112 ($CAD) more costly over three years. From a societal perspective, early anti-TNF-α treatment was more costly than the standard care intervention over three years by $33,508.64 ($CAD) and also resulted in 11.3 more weeks of steroid-free remission. There was considerable uncertainty in the model due to methodological and structural uncertainty and considerable individual variation in disease characteristics among patients. A willingness to pay for a steroid-free week in remission is unknown. The improvement on quality of life of being in a health state of steroid-free remission is also unknown in children with Crohn's disease. Therefore, there is a need to establish generic health utilities and a better understanding of willingness to pay for remission in pediatric Crohn's disease.

The cost-effectiveness model was sensitive to the price of anti-TNF-α treatment (infliximab) with early anti-TNF-α treatment having the potential to be the dominant strategy if anti-TNF-α

was reduced to 25% of its current price. The cost-effectiveness model also showed that early anti-TNF-α was more effective at reducing steroid use during remission than standard step-up care since early anti-TNF-α resulted in 11.3 more steroid-free remission weeks over three years and 6.65 more remission weeks irrespective of steroid use compared to standard step-up care. These results suggest that time in steroid-free remission may be a preferred clinical outcome in pediatric Crohn's disease.

The process of preparing inputs for the cost-effectiveness model highlighted that when dealing with patient-level data with missing values, the imputation of missing data, and subsequent combination of data and propensity score analysis can impact cost-effectiveness results and introduce methodological uncertainty into the cost-effectiveness model. The incremental cost-effectiveness ratio of an additional week of remission irrespective of steroid use ranged from $CAD 2,250 to $CAD 12,870 depending on the method of data assembly following imputation of missing data. This range suggests that guidelines need to be established on how to handle patient-level data with missing values that inform a cost-effectiveness model and on how to report results within the context of an economic evaluation.

The results of the cost-effectiveness model examining early anti-TNF-α treatment for Crohn's disease suggest that early anti-TNF-α treatment has potential to improve clinical outcomes in pediatric Crohn's disease, but may be a costly strategy unless anti-TNF-α prices come down. While over fifty percent of patients in the step-up strategy from the RISK-PROKIIDS study were on anti-TNF-α treatment at three years, some patients entered remission without the need for anti-TNF-α treatment suggesting that aggressive anti-TNF-α treatment is not necessary for all patients. With better therapeutic management techniques such as therapeutic drug monitoring, research into which patients would be better responders, early anti-TNF-α treatment may be a clinically effective and cost-effective strategy in a subpopulation of patients. Additional research is required to identify this sub-population. In any case, early anti-TNF-α intervention was shown to be clinically effective at increasing the steroid-free remission weeks in children with moderate to severe Crohn's disease and therefore policies or

administrative delays that would delay treatment in patients that could benefit from early intervention should be adjusted.

Appendices

Appendix 1. Methods for Scoping Literature Review for Pediatric Clinical Studies with Anti-TNF-α Treatments as First Line Therapy in Crohn's Disease.

The following method was used in the scoping literature review.

The following databases were searched:

- MEDLINE from 1946-May 2018
- EMBASE from 1980-May 2018
- ClinTrials.gov
- Cochrane Central Register of Controlled Trials and the Cochrane Library

Filters based on age < 18 years and for human studies were used. Anti-TNF-α products did not reach the market until the late 1990's and therefore it is not likely that studies in children with these products were conducted prior to 1980. As this was a preliminary review, other databases, such as CINAHL, Scopus and Web of Science will be searched at a later time.

The following search terms were used:

Crohn disease (MeSH heading), infliximab, adalimumab, certolizumab, cost-effectiveness, cost-benefit analysis, cost-utility analysis.

Infliximab, adalimumab and certolizumab were searched as key words in Medline and as subject headings in EMBASE. For the purposes of this review, searches were limited to English language articles for which abstracts were available.

The following inclusion criteria were used:

- Studies where the main focus of the study is to assess the clinical effectiveness of an anti-TNF-α treatment (infliximab, adalimumab or certolizumab pegol).

- Studies with pediatric patients with moderate-to-severe CD that were not grouped with another indication such as ulcerative colitis.

- Studies with only pediatric patients or where pediatric data can be segregated from adult data.

- Studies in which the anti-TNF-α intervention is used alone as first-line therapy and not concomitantly with other medications in at least one arm of the study.

- Studies can be RCTs, cohort or case-control studies. Where appropriate, studies can be prospective or retrospective.

- Any doses and routes of administration of the interventions (anti-TNF-α and comparator interventions)

- All English language abstracts even if the study in another language

- Where the primary outcome is measured in terms of remission and/or Pediatric Crohn's Activity Index (PCDAI) score

In EMBASE, when the search terms Crohn disease and infliximab were combined and a filter for child references was applied, there were 101 search results. Similarly, when adalimumab was used as a term instead of infliximab, 45 search results were found. Certolizumab produced 1 result. In Medline, a similar search strategy produced 43 results. When the abstracts of all of these results were reviewed, only 1 result (Walters et al., 2014) met the clinical inclusion criteria and examined the early intervention of anti-TNF-a treatments in newly diagnosed children with CD. Subsequently, the inclusion criteria was relaxed to include studies that examined the effectiveness of infliximab or adalimumab in children with CD that did not have only monotherapy arms and which had refractory patients as well, as opposed to a study in newly diagnosed, naïve patients.

Appendix 2. Methods for Scoping Literature Review for Health Technology Assessments of anti-TNF-α Treatments in Pediatric Crohn's Disease

The following method was used in the literature search.

The databases used for the search of clinical studies were also used to search for the economic evaluations. Health technology assessments in Crohn's disease were also searched for on websites of governmental agencies such as Canadian Agency for Drugs and Technology in Health (CADTH) and National Institute for Health and Care Excellence (NICE).

The following criteria were used as inclusion criteria for cost-effectiveness or cost-utility analyses:

- Studies that provide economic evaluations of anti-TNF-α treatments in children with moderate-to-severe Crohn's disease

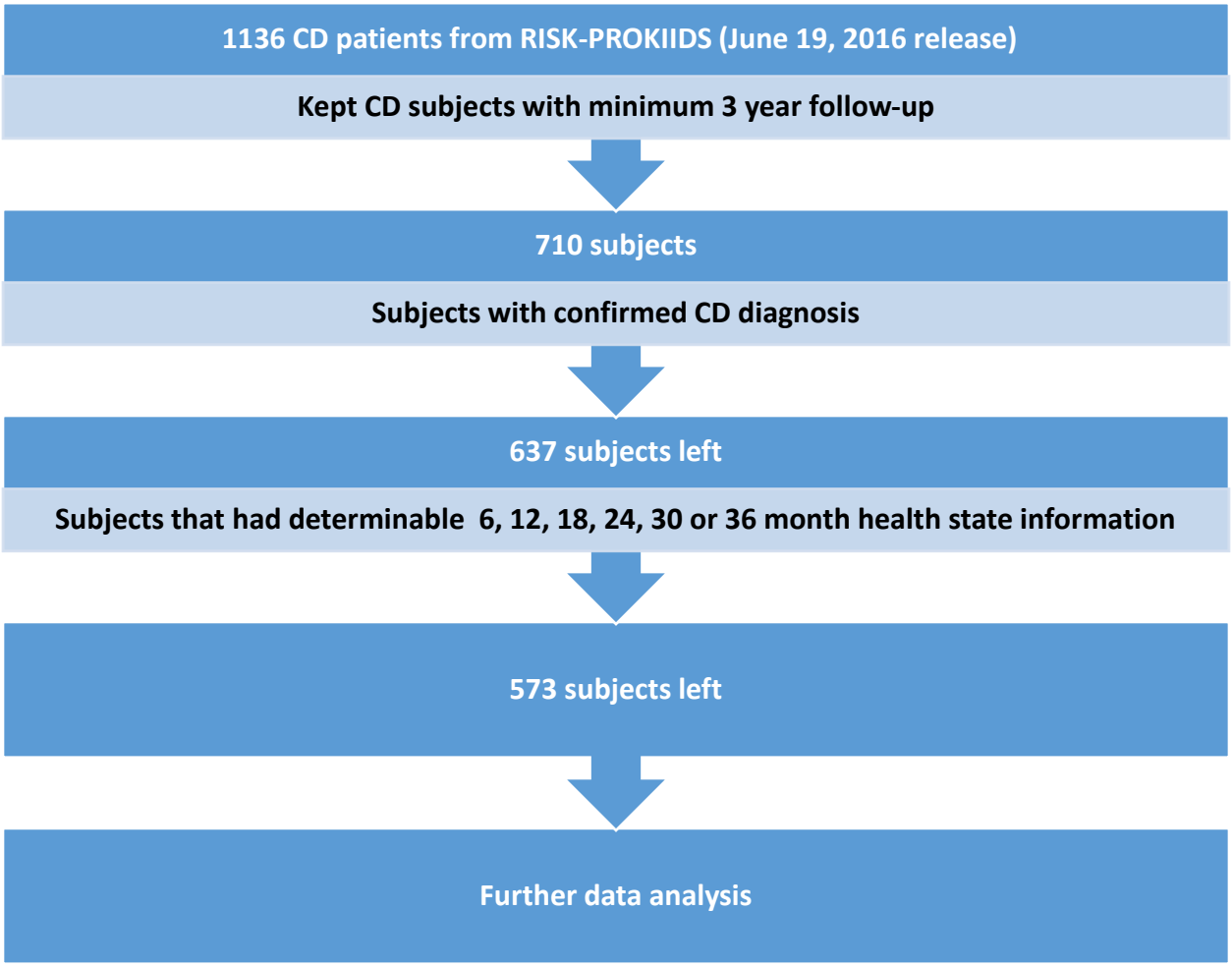
- Studies that provide economic evaluation of anti-TNF-α treatments in adults moderate-to-severe Crohn's disease (luminal or fistulizing CD is not excluded)

Searches including the terms Crohn disease, infliximab or adalimumab, or certolizumab, and cost-effectiveness or cost-utility analysis with a filter for child studies yielded no results in either Medline or EMBASE. Removal of the pediatric filter yielded approximately 33 search results.

Appendix 3. North American Pediatric Inflammatory Bowel Disease Clinical Centres of the RISK-PROKIIDS Study.

Clinical Site	Site Name	Number Crohn's Patients per site with minimum 3 years follow-up (573pts)	% Patients per site (out of 573)
Emory (Georgia)	01	24	4.2
CSMC (Cedar Sinai, Los Angeles)	02	25	4.4
CHOP (Philadelphia)	03	44	7.7
Cincinnati	04	51	8.9
Connecticut	05	72	12.6
Wisconsin	06	33	5.8
Schneider (Cohen Centre, New Hyde Park, New York)	07	16	2.8
San Francisco	08	8	1.4
Nationwide (Ohio)	09	29	5.1
Harvard	10	32	5.6
Texas Childrens	11	5	0.9
Chapel Hill (North Carolina)	12	14	2.4
Sick Kids (Toronto)	13	62	10.8
Goryeb NJ	14	31	5.4
IWK Health Centre (Halifax)	15	14	2.4
Riley CHIU (Indianapolis)	16	16	2.8
CCDH (Illinois)	17	7	1.2
U of Utah	18	3	0.5
Hasbro RI	19	22	3.8
Johns Hopkins (Maryland)	20	6	1.0
U of Pittsburg	21	11	1.9
Vanderbilt (Nashville)	22	11	1.9
U of Chicago	23	2	0.3
Dallas	24	2	0.3
UCLA	25	2	0.3
Nemours (Jacksonville, FL)	26	4	0.7
U of Buffalo	27	7	1.2
CHEO (Ottawa)	29	20	3.5

Appendix 4. Included Subjects from the RISK-PROKIIDS Study.



Appendix 5. wPCDAI Perirectal Disease Scoring Assignment Scheme.

Datasheet parameter	Field value (1= Yes; 0=No)	Number of Missing fields	wPCDAI Perirectal score assigned
Drainage	1	0-5	15
Active fistula	0 or 1		
Indolent fistula	0 or 1		
Fissure	0 or 1		
Inflamed tags	0 or 1		
Asymptomatic tags	0 or 1		
Drainage	0 or 1		
Active fistula	1	0-5	15
Indolent fistula	0 or 1		
Fissure	0 or 1		
Inflamed tags	0 or 1		
Asymptomatic tags	0 or 1		
Drainage	0	0-5	7.5
Active fistula	0		
Indolent fistula	1		
Fissure	0 or 1		
Inflamed tags	0		
Asymptomatic tags	0 or 1		
Drainage	0	0-5	7.5
Active fistula	0		
Indolent fistula	0 or 1		
Fissure	1		
Inflamed tags	0		
Asymptomatic tags	0 or 1		
Drainage	0	0-5	7.5
Active fistula	0		
Indolent fistula	0 or 1		
Fissure	0 or 1		
Inflamed tags	1		
Asymptomatic tags	0 or 1		
Drainage	0	0-5	0
Active fistula	0		
Indolent fistula	0		
Fissure	0		
Inflamed tags	0		
Asymptomatic tags	0 or 1		

Appendix 6. Spearman's Correlation Between PGA and wPCDAI in RISK-PROKIIDS Subjects.

Table A6-1. Spearman's correlation between PGA and wPCDAI in 710 RISK-PROKIIDS CD subjects.

Time Point	n (N=710 CD subjects, excluding unknown)	Spearman's correlation (P=<0.001 for all)
All visits combined	5324	0.702
Visit 0	678	0.494
Visit 1	626	0.566
Visit 2	629	0.577
Visit 3	575	0.598
Visit 4	579	0.542
Visit 5	485	0.588
Visit 6	480	0.616
Visit 7	395	0.584
Visit 8	339	0.632
Visit 9	267	0.601
Visit 10	180	0.616
Visit 11	52	0.713
Visit 12	39	0.841

Subjects may have had fewer than three years of follow-up. Abbreviations: PGA = Physician Global Assessment; wPCDAI = weighted Pediatric Crohn's Disease Activity Index

Appendix 7. Formulas to Convert Probabilities from One Cycle Length to Another

The following equations were used to convert transition probabilities from one cycle length to another (Briggs et al., 2006) . Probabilities were converted to a rate and then to the desired probability for the cycle length.

Probability to Rate: Rate = $-\ln (1-p)/t$

Rate to Probability: Probability = $1- e^{(-rt)}$

Where r = rate, p= probability, t= time

Appendix 8. Probabilities of Switching to an Anti-TNF-α Treatment Each Week for the Standard Care Group Over Three Years.

Table A8-1. The probability of switching to an anti-TNF-α treatment each week for the standard care group over three years.

Week	Prob.	Week	Prob.	Week	Prob.	Week	Prob.	Week	Prob.	Week	Prob.
1	0.000	27	0.118	53	0.274	79	0.392	105	0.456	131	0.502
2	0.000	28	0.122	54	0.278	80	0.392	106	0.464	132	0.515
3	0.000	29	0.131	55	0.278	81	0.397	107	0.464	133	0.519
4	0.000	30	0.131	56	0.291	82	0.397	108	0.464	134	0.523
5	0.000	31	0.148	57	0.300	83	0.401	109	0.468	135	0.519
6	0.000	32	0.156	58	0.300	84	0.414	110	0.473	136	0.519
7	0.000	33	0.173	59	0.316	85	0.418	111	0.473	137	0.527
8	0.000	34	0.181	60	0.312	86	0.418	112	0.477	138	0.527
9	0.000	35	0.181	61	0.316	87	0.422	113	0.489	139	0.527
10	0.000	36	0.186	62	0.329	88	0.422	114	0.498	140	0.527
11	0.000	37	0.190	63	0.325	89	0.426	115	0.494	141	0.523
12	0.000	38	0.194	64	0.338	90	0.430	116	0.494	142	0.523
13	0.000	39	0.203	65	0.342	91	0.430	117	0.494	143	0.519
14	0.008	40	0.211	66	0.342	92	0.430	118	0.494	144	0.523
15	0.034	41	0.211	67	0.342	93	0.443	119	0.498	145	0.523
16	0.038	42	0.207	68	0.354	94	0.443	120	0.494	146	0.527
17	0.042	43	0.215	69	0.350	95	0.439	121	0.494	147	0.536
18	0.051	44	0.228	70	0.359	96	0.439	122	0.498	148	0.532
19	0.059	45	0.236	71	0.363	97	0.443	123	0.498	149	0.536
20	0.068	46	0.241	72	0.367	98	0.447	124	0.502	150	0.536
21	0.080	47	0.249	73	0.367	99	0.439	125	0.502	151	0.544
22	0.089	48	0.253	74	0.371	100	0.435	126	0.498	152	0.549
23	0.101	49	0.257	75	0.371	101	0.435	127	0.498	153	0.549
24	0.110	50	0.262	76	0.380	102	0.447	128	0.502	154	0.553
25	0.114	51	0.262	77	0.384	103	0.451	129	0.502	155	0.544
26	0.114	52	0.266	78	0.388	104	0.456	130	0.506	156	0.540

The probabilities were based on the Across data set from the RISK-PROKIIDS study. Prob. = probability of switching to anti-TNF-α.

Appendix 9. All Causes Mortality Table For Ages 1-18 Years.

Table A9-1. Canadian age-adjusted all causes mortality for 1 to18 years of age.

Age (years)	Weekly Mortality Probability
1	5.19E-06
2	2.31E-06
3	2.31E-06
4	1.15E-06
5	1.35E-06
6	1.54E-06
7	2.50E-06
8	1.54E-06
9	5.77E-07
10	1.73E-06
11	3.08E-06
12	1.73E-06
13	2.12E-06
14	2.31E-06
15	3.85E-06
16	3.85E-06
17	5.58E-06
18	6.92E-06

Source: (Canadian Human Mortality Database. Department of Demography Université de Montréal (Canada), 2014).

Appendix 10. The Proportion of Subjects on Each Drug Class Per Week.

Table A10-1. The proportion of subjects in each comparator group on a particular class of drug in each week for three years.

	CS		IM		Biol		Anti		5-ASA		EN	
Week	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)
0	65.4	58.5	17.7	4.1	0.0	14.6	27.0	40.7	34.2	13.0	6.8	2.4
1	67.5	56.1	25.3	8.9	0.0	26.8	27.0	40.7	35.0	15.4	7.6	2.4
2	66.2	56.9	35.4	12.2	0.0	49.6	25.7	39.8	40.1	16.3	8.0	2.4
3	66.2	57.7	38.0	14.6	0.0	59.3	27.4	38.2	41.8	14.6	8.9	1.6
4	66.7	56.9	44.3	15.4	0.0	66.7	25.7	36.6	42.2	15.4	8.9	1.6
5	66.7	55.3	46.4	16.3	0.0	71.5	25.3	35.8	42.6	15.4	8.4	1.6
6	67.9	50.4	48.5	17.9	0.0	74.0	25.3	30.1	43.5	15.4	8.9	1.6
7	66.2	46.3	51.1	18.7	0.0	77.2	24.9	30.1	43.5	15.4	8.4	0.8
8	62.4	43.9	51.9	19.5	0.0	80.5	24.5	26.8	43.5	15.4	7.2	0.0
9	58.6	37.4	51.9	18.7	0.0	82.1	24.9	26.8	43.5	14.6	6.3	0.0
10	53.6	33.3	53.6	19.5	0.0	91.1	23.2	24.4	43.9	14.6	5.9	0.0
11	51.1	30.9	55.3	19.5	0.0	96.7	23.6	23.6	43.9	14.6	5.9	0.0
12	43.5	30.1	56.1	19.5	0.0	100.0	24.1	22.8	43.9	13.8	5.9	0.0
13	40.1	26.8	57.8	20.3	0.8	100.0	22.4	20.3	43.9	13.8	5.1	0.0
14	38.8	24.4	59.9	20.3	3.4	100.0	22.8	21.1	43.9	14.6	4.6	0.0
15	37.6	21.1	59.1	20.3	3.8	100.0	23.2	21.1	44.3	14.6	5.1	0.0
16	35.9	21.1	58.6	22.8	4.2	100.0	23.2	20.3	43.9	14.6	5.5	0.8
17	34.2	19.5	59.1	24.4	5.1	99.2	24.1	16.3	42.6	13.8	5.1	0.0
18	32.5	17.1	59.5	24.4	5.9	100.0	22.8	15.4	43.0	13.8	5.1	0.0
19	31.6	17.1	59.5	23.6	6.8	99.2	21.5	15.4	42.6	13.8	5.1	0.0
20	32.1	14.6	60.3	24.4	8.0	99.2	22.4	15.4	43.0	13.8	4.6	0.0
21	30.0	13.0	59.5	25.2	8.9	99.2	21.5	14.6	42.6	13.8	4.6	0.0

	CS		IM		Biol		Anti		5-ASA		EN	
Week	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)
22	27.0	12.2	59.9	23.6	10.1	99.2	20.3	16.3	42.6	13.8	4.6	0.0
23	24.1	10.6	59.5	24.4	11.0	97.6	20.3	16.3	42.6	13.0	4.6	0.0
24	22.4	11.4	59.5	24.4	11.4	98.4	20.3	15.4	42.6	13.8	4.6	0.0
25	22.4	10.6	60.3	25.2	11.4	98.4	19.4	14.6	42.2	13.8	5.1	0.0
26	21.1	9.8	60.3	25.2	11.8	98.4	19.4	12.2	42.6	14.6	4.6	0.0
27	19.0	9.8	59.9	27.6	12.2	97.6	18.6	10.6	42.6	13.8	4.2	0.0
28	16.9	8.1	59.9	27.6	13.1	97.6	19.4	11.4	42.6	13.0	4.6	0.0
29	17.7	8.1	60.8	27.6	13.1	96.7	19.0	11.4	42.6	13.0	4.2	0.0
30	17.3	7.3	60.3	27.6	14.8	96.7	19.0	9.8	41.8	13.0	4.2	0.0
31	16.9	7.3	59.9	28.5	15.6	96.7	19.0	9.8	41.8	13.0	4.2	0.0
32	17.3	7.3	60.8	29.3	17.3	95.1	19.4	8.9	41.8	13.0	4.2	0.0
33	17.3	5.7	59.9	28.5	18.1	94.3	18.6	8.9	41.8	13.0	4.2	0.0
34	16.5	6.5	59.9	30.1	18.1	95.1	17.7	8.9	41.4	13.0	4.6	0.0
35	16.0	6.5	59.9	29.3	18.6	95.1	16.5	8.9	41.4	12.2	4.6	0.0
36	15.6	4.9	60.3	29.3	19.0	95.1	16.0	8.9	41.4	12.2	4.2	0.0
37	14.3	4.9	59.9	29.3	19.4	95.1	15.2	8.1	40.9	12.2	4.2	0.0
38	13.5	4.9	60.3	30.1	20.3	95.1	15.2	8.1	41.4	12.2	4.2	0.0
39	13.9	4.1	60.8	30.1	21.1	95.1	14.8	8.1	41.4	12.2	4.2	0.0
40	14.8	4.9	59.9	30.9	21.1	95.1	14.3	8.9	41.8	12.2	3.4	0.0
41	14.3	4.9	59.5	31.7	20.7	94.3	15.2	8.9	41.4	13.0	3.8	0.0
42	14.8	4.1	59.9	31.7	21.5	94.3	15.2	8.1	41.4	13.0	3.4	0.0
43	14.8	4.1	59.1	32.5	22.8	94.3	15.2	8.1	41.4	13.0	3.4	0.0
44	14.8	4.1	60.3	31.7	23.6	94.3	14.8	7.3	41.4	13.0	3.4	0.0
45	14.8	4.1	59.9	31.7	24.1	94.3	13.5	7.3	40.9	13.0	3.4	0.0
46	13.9	4.1	58.6	31.7	24.9	94.3	13.9	7.3	40.5	13.0	3.4	0.0
47	13.9	4.1	59.1	31.7	25.3	94.3	14.3	8.1	40.5	13.0	3.8	0.0

	CS		IM		Biol		Anti		5-ASA		EN	
Week	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)
48	13.1	4.9	58.6	31.7	25.7	94.3	14.8	8.1	40.5	12.2	3.8	0.0
49	12.2	4.1	58.6	30.9	26.2	94.3	14.8	8.9	40.5	12.2	3.8	0.0
50	13.5	4.1	58.2	31.7	26.2	94.3	14.3	8.9	40.5	12.2	3.8	0.0
51	13.9	4.9	59.1	31.7	26.6	94.3	14.8	8.9	40.5	12.2	3.8	0.0
52	13.1	4.9	57.8	33.3	27.4	95.1	14.8	8.9	40.5	12.2	3.4	0.0
53	13.5	3.3	57.0	32.5	27.8	95.1	14.3	8.1	40.5	12.2	3.4	0.0
54	13.5	3.3	57.4	32.5	27.8	95.1	14.3	8.1	40.1	12.2	3.0	0.0
55	12.7	3.3	57.8	32.5	29.1	95.1	14.8	6.5	40.1	12.2	3.0	0.0
56	12.2	3.3	58.2	32.5	30.0	95.1	15.6	6.5	40.1	13.0	3.0	0.0
57	11.0	2.4	57.8	31.7	30.0	95.1	16.0	7.3	40.1	12.2	3.0	0.0
58	11.0	2.4	57.4	31.7	31.6	95.1	15.6	7.3	40.1	12.2	3.0	0.0
59	9.7	2.4	57.0	32.5	31.2	95.1	15.2	6.5	40.1	13.0	3.0	0.0
60	8.9	2.4	57.4	33.3	31.6	95.9	14.3	5.7	40.1	13.0	3.0	0.0
61	8.9	2.4	58.2	33.3	32.9	95.1	14.3	5.7	40.5	13.0	3.4	0.0
62	8.9	2.4	58.6	34.1	32.5	95.9	13.9	6.5	40.1	13.0	3.4	0.0
63	9.3	2.4	58.6	34.1	33.8	95.9	13.9	7.3	39.7	13.0	3.0	0.0
64	8.4	2.4	58.2	33.3	34.2	96.7	13.1	7.3	38.8	13.0	3.4	0.0
65	7.6	2.4	59.1	33.3	34.2	96.7	13.1	6.5	38.8	13.0	3.8	0.0
66	8.4	2.4	59.9	33.3	34.2	96.7	13.1	5.7	38.0	13.0	3.4	0.0
67	7.6	3.3	59.9	32.5	35.4	96.7	13.5	5.7	38.4	13.0	3.4	0.0
68	8.0	4.1	60.3	33.3	35.0	96.7	14.3	5.7	38.4	13.0	3.4	0.0
69	8.4	4.1	59.9	33.3	35.9	96.7	14.8	4.1	38.4	13.0	3.4	0.0
70	8.4	4.9	58.6	33.3	36.3	96.7	14.3	4.1	38.4	13.0	3.4	0.0
71	8.9	4.9	58.2	33.3	36.7	96.7	13.1	4.1	38.4	13.0	3.0	0.8
72	8.9	4.1	57.8	34.1	36.7	96.7	14.3	4.1	38.4	13.0	3.0	0.8
73	8.4	3.3	57.8	35.0	37.1	96.7	14.3	3.3	38.0	13.0	3.0	0.8

	CS		IM		Biol		Anti		5-ASA		EN	
Week	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)
74	7.2	4.9	59.5	35.8	37.1	97.6	14.3	3.3	37.1	13.0	3.0	0.8
75	6.8	4.1	58.6	36.6	38.0	95.9	14.8	3.3	37.1	13.0	3.0	0.8
76	8.4	4.9	58.6	37.4	38.4	95.9	14.8	3.3	37.1	13.0	3.0	0.8
77	9.3	4.9	58.6	37.4	38.8	96.7	14.3	4.1	37.1	13.0	3.0	0.8
78	9.7	5.7	58.6	37.4	39.2	96.7	13.5	4.1	36.7	13.0	3.0	0.8
79	9.7	5.7	59.5	36.6	39.2	95.9	12.7	4.1	36.7	13.0	3.0	0.8
80	11.0	5.7	58.6	36.6	39.7	96.7	12.7	5.7	36.7	13.0	3.0	0.8
81	11.0	6.5	59.5	36.6	39.7	96.7	12.7	5.7	35.9	13.0	3.0	0.8
82	10.5	6.5	59.5	37.4	40.1	96.7	13.1	5.7	35.4	13.0	3.0	0.8
83	10.1	5.7	58.6	38.2	41.4	96.7	13.1	4.9	35.4	13.0	3.0	0.8
84	10.1	5.7	59.1	38.2	41.8	96.7	13.1	4.9	35.4	13.0	3.4	0.8
85	9.7	5.7	59.1	39.0	41.8	96.7	13.1	4.9	35.0	13.0	3.4	0.8
86	8.0	4.1	59.1	39.0	42.2	96.7	12.7	4.9	35.0	13.8	3.4	0.8
87	7.6	4.1	59.1	37.4	42.2	96.7	12.2	4.9	34.6	13.8	3.4	0.8
88	7.6	4.1	59.1	37.4	42.6	95.9	12.7	4.9	34.2	13.8	3.4	0.8
89	7.6	4.9	59.5	37.4	43.0	96.7	12.7	4.9	34.2	13.8	3.0	0.8
90	7.6	4.9	59.5	37.4	43.0	96.7	12.2	5.7	34.2	13.8	3.0	0.8
91	8.0	4.9	59.5	37.4	43.0	96.7	12.2	5.7	33.8	13.8	3.0	0.8
92	8.4	4.9	58.6	39.0	44.3	97.6	12.7	5.7	32.9	13.8	3.0	0.8
93	7.6	4.9	59.5	38.2	44.3	95.9	12.7	5.7	33.3	13.8	3.0	0.8
94	7.2	4.9	58.6	39.0	43.9	95.9	13.1	5.7	32.5	13.8	3.0	0.8
95	6.8	6.5	58.2	39.0	43.9	96.7	13.5	7.3	32.5	13.8	3.0	0.8
96	6.8	7.3	59.1	39.0	44.3	96.7	13.5	8.1	32.5	13.8	2.5	0.8
97	7.2	7.3	58.6	39.0	44.7	96.7	12.2	8.1	32.1	13.8	2.5	0.8
98	6.8	6.5	58.2	38.2	43.9	95.9	12.7	8.9	32.1	13.0	2.5	0.8
99	8.0	7.3	57.8	37.4	43.5	94.3	12.7	9.8	32.1	13.0	2.5	0.8

	CS		IM		Biol		Anti		5-ASA		EN	
Week	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)
100	8.0	7.3	57.4	38.2	43.5	94.3	12.2	7.3	32.1	12.2	2.5	0.8
101	7.2	6.5	56.5	38.2	44.7	94.3	12.7	7.3	32.5	12.2	2.1	0.8
102	6.3	5.7	57.4	38.2	45.1	93.5	12.2	7.3	31.6	12.2	2.1	0.8
103	6.3	4.9	57.0	39.0	45.6	94.3	12.7	7.3	31.2	12.2	2.1	0.8
104	5.9	4.9	57.8	39.0	45.6	94.3	12.2	7.3	30.8	11.4	2.1	0.8
105	6.3	4.1	58.6	39.0	46.4	92.7	12.7	7.3	30.8	11.4	2.1	0.8
106	5.9	4.1	57.8	39.8	46.4	92.7	12.7	7.3	30.4	11.4	2.1	0.8
107	6.3	4.1	57.4	39.0	46.4	92.7	12.7	7.3	30.4	11.4	2.1	0.8
108	5.9	4.1	57.8	39.8	46.8	92.7	12.7	6.5	30.0	11.4	2.1	0.8
109	6.8	4.1	57.8	39.8	47.3	93.5	12.7	6.5	30.4	11.4	2.1	0.8
110	5.9	4.1	57.4	39.8	47.3	93.5	12.7	5.7	30.0	11.4	2.1	0.8
111	5.5	4.1	57.4	40.7	47.7	93.5	12.7	6.5	30.0	11.4	2.1	0.8
112	5.9	4.9	57.4	40.7	48.9	93.5	12.7	6.5	30.0	11.4	2.1	0.8
113	4.6	4.1	56.5	40.7	49.8	93.5	13.1	7.3	29.5	11.4	2.1	0.8
114	5.9	4.1	55.7	40.7	49.4	93.5	12.2	6.5	29.1	11.4	2.1	0.8
115	6.3	4.1	56.1	40.7	49.4	93.5	12.2	4.9	29.1	11.4	2.1	0.8
116	6.8	4.1	55.7	40.7	49.4	93.5	12.2	5.7	28.7	11.4	2.1	0.8
117	5.9	4.1	55.7	40.7	49.4	94.3	12.2	5.7	28.7	11.4	2.1	0.8
118	5.5	4.1	55.7	40.7	49.8	94.3	12.2	4.9	28.7	11.4	2.1	0.8
119	5.1	4.1	55.3	40.7	49.4	93.5	12.2	4.9	28.7	10.6	2.1	0.8
120	4.6	3.3	55.3	40.7	49.4	93.5	12.2	4.9	28.7	10.6	2.1	0.8
121	4.6	3.3	54.9	40.7	49.8	93.5	12.2	4.9	28.3	10.6	2.1	0.8
122	4.6	4.1	54.9	40.7	49.8	93.5	11.8	4.9	27.4	10.6	2.1	0.8
123	4.6	4.1	54.4	40.7	50.2	91.9	11.0	4.9	27.0	10.6	2.1	0.8
124	4.2	4.1	54.0	40.7	50.2	91.9	11.0	4.9	27.0	10.6	2.1	0.8
125	4.6	4.1	54.0	40.7	49.8	91.9	11.8	4.9	27.0	10.6	1.7	0.8

	CS		IM		Biol		Anti		5-ASA		EN	
Week	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)
126	5.1	4.1	54.0	40.7	49.8	91.1	11.4	4.9	27.0	10.6	2.1	0.8
127	4.2	4.1	54.0	40.7	50.2	91.1	10.5	4.9	27.0	10.6	2.1	0.8
128	3.8	3.3	53.6	40.7	50.2	91.1	11.4	4.9	27.0	10.6	2.1	0.8
129	4.6	3.3	53.6	40.7	50.6	91.9	11.8	5.7	27.0	10.6	2.1	0.8
130	4.6	3.3	53.6	40.7	50.2	91.9	11.4	5.7	27.0	10.6	2.1	0.8
131	4.2	2.4	52.7	40.7	51.5	91.9	11.0	6.5	27.4	10.6	2.1	0.0
132	4.2	2.4	52.7	40.7	51.9	91.9	10.5	6.5	27.0	10.6	2.1	0.0
133	3.8	2.4	52.3	40.7	52.3	91.9	10.1	6.5	27.0	10.6	2.1	0.0
134	3.4	2.4	52.3	40.7	51.9	91.9	10.5	6.5	27.0	10.6	2.1	0.0
135	4.2	4.1	52.3	40.7	51.9	91.9	11.0	6.5	27.0	10.6	2.1	0.0
136	4.6	2.4	52.7	40.7	52.7	91.1	11.0	5.7	27.0	10.6	2.1	0.0
137	4.6	2.4	52.7	40.7	52.7	90.2	10.5	5.7	27.0	10.6	2.1	0.0
138	4.2	2.4	52.7	40.7	52.7	90.2	10.5	4.9	26.6	10.6	2.1	0.0
139	3.4	2.4	52.7	39.0	52.7	90.2	11.0	4.1	26.6	10.6	2.5	0.0
140	3.0	2.4	53.2	39.0	52.3	89.4	11.0	4.9	26.6	10.6	2.1	0.0
141	3.0	1.6	53.2	38.2	52.3	89.4	11.8	5.7	26.6	10.6	2.1	0.0
142	3.0	1.6	53.2	39.0	51.9	89.4	12.2	5.7	26.6	11.4	2.1	0.0
143	3.4	1.6	53.2	39.0	52.3	89.4	12.2	5.7	26.6	11.4	2.1	0.0
144	3.4	2.4	53.2	39.0	52.3	90.2	11.8	6.5	26.6	11.4	2.1	0.0
145	3.4	3.3	53.6	39.0	52.7	90.2	12.2	6.5	26.6	10.6	2.1	0.0
146	3.4	3.3	53.2	39.0	53.6	90.2	12.7	5.7	26.6	10.6	2.1	0.0
147	3.4	3.3	53.6	39.0	53.2	90.2	11.8	5.7	26.6	10.6	2.1	0.0
148	3.4	4.1	53.2	39.0	53.6	90.2	11.8	5.7	26.6	10.6	2.1	0.0
149	4.2	4.1	53.6	39.0	53.6	90.2	11.8	5.7	26.6	10.6	2.1	0.0
150	3.8	4.1	53.6	39.0	54.4	90.2	11.8	5.7	26.2	10.6	2.1	0.0
151	5.1	4.9	54.0	39.8	54.9	90.2	12.7	4.9	26.6	10.6	2.1	0.0

	CS		IM		Biol		Anti		5-ASA		EN	
Week	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)	Std. Care (%)	Early Int. (%)
152	4.6	4.9	53.6	39.8	54.9	90.2	13.1	4.9	27.0	10.6	2.1	0.0
153	4.6	4.9	53.6	39.8	55.3	90.2	13.1	4.9	26.6	10.6	2.1	0.0
154	5.1	4.9	53.6	39.8	54.4	90.2	13.1	4.9	26.6	10.6	2.1	0.0
155	5.1	4.9	53.6	39.0	54.0	90.2	13.9	4.9	26.6	9.8	2.1	0.0
156	4.6	4.9	52.7	39.0	53.6	90.2	13.9	4.9	26.6	9.8	2.1	0.0

Note that proportions do not take concomitant therapy into account. Abbreviations: CS=corticosteroid; IM= immunomodulator; Biol= anti-TNF-α; Anti = antibiotic; 5-ASA = Oral 5-ASA, EN = enteral nutrition; Std. Care = standard care group; Early Int. = early anti=TNF-α intervention group.

Appendix 11. The Weighted Average Cost of Immunomodulators Per Week and Per Weight.

Table A11-1. The weighted average cost of immunomodulators per week and per weight for the standard care comparator group.

Weight (kg)	Week 0 to 26 mean	Week 0 to 26 SD	Week 27 to 52 mean	Week 27 to 52 SD	Week 53 to 78 mean	Week 53 to 78 SD	Week 79 to 104 mean	Week 79 to 104 SD	Week 118 to 130 mean	Week 118 to 130 SD	Week 131 to 156 mean	Week 131 to 156 SD
10	10.93	0.63	9.56	0.24	8.58	0.38	7.73	0.25	7.27	0.13	7.16	0.09
20	10.99	0.63	9.67	0.22	8.74	0.37	7.92	0.24	7.47	0.12	7.40	0.09
30	11.60	0.58	10.33	0.23	9.40	0.36	8.60	0.23	8.17	0.12	8.09	0.09
40	21.66	1.29	18.79	0.53	16.65	0.81	14.89	0.54	13.90	0.26	13.60	0.16
50	22.16	1.25	19.33	0.53	17.17	0.80	15.42	0.53	14.45	0.26	14.17	0.16
60	22.23	1.24	19.44	0.52	17.34	0.79	15.61	0.52	14.65	0.26	14.40	0.17
70	32.51	1.92	28.09	0.84	24.68	1.26	21.94	0.82	20.43	0.41	20.00	0.26
80	32.57	1.91	28.20	0.83	24.84	1.24	22.12	0.81	20.64	0.40	20.23	0.27
90	33.01	1.88	28.63	0.85	25.20	1.25	22.46	0.81	20.98	0.41	20.56	0.27
100	33.01	1.88	28.63	0.85	25.20	1.25	22.46	0.81	20.98	0.41	20.56	0.27
110	43.29	2.56	37.28	1.17	32.54	1.72	28.79	1.11	26.76	0.56	26.16	0.35
120	43.29	2.56	37.28	1.17	32.54	1.72	28.79	1.11	26.76	0.56	26.16	0.35
130	43.74	2.53	37.71	1.19	32.90	1.73	29.13	1.10	27.10	0.56	26.49	0.36
140	53.57	3.24	45.93	1.50	39.88	2.19	35.12	1.41	32.53	0.71	31.75	0.44
150	54.02	3.21	46.36	1.52	40.24	2.20	35.46	1.40	32.87	0.71	32.08	0.44
160	54.02	3.21	46.36	1.52	40.24	2.20	35.46	1.40	32.87	0.71	32.08	0.44
170	64.29	3.89	55.01	1.84	47.58	2.67	41.79	1.71	38.65	0.86	37.68	0.53
180	64.29	3.89	55.01	1.84	47.58	2.67	41.79	1.71	38.65	0.86	37.68	0.53
190	64.74	3.85	55.44	1.86	47.94	2.68	42.13	1.70	38.99	0.86	38.01	0.53
200	64.74	3.85	55.44	1.86	47.94	2.68	42.13	1.70	38.99	0.86	38.01	0.53

Table A11-2. The weighted average cost of immunomodulators per week and per weight for the early anti-TNF-α intervention comparator group.

Weight (kg)	Week 0 to 26 mean	Week 0 to 26 SD	Week 27 to 52 mean	Week 27 to 52 SD	Week 53 to 78 mean	Week 53 to 78 SD	Week 79 to 104 mean	Week 79 to 104 SD	Week 118 to 130 mean	Week 118 to 130 SD	Week 131 to 156 mean	Week 131 to 156 SD
10	8.38	1.32	6.23	0.29	5.82	0.11	5.62	0.29	5.18	0.19	4.83	0.12
20	8.59	1.22	6.58	0.29	6.22	0.11	6.02	0.29	5.61	0.19	5.27	0.12
30	9.13	1.23	7.15	0.27	6.80	0.11	6.59	0.27	6.19	0.18	5.88	0.11
40	16.11	2.95	11.40	0.61	10.44	0.24	10.01	0.59	9.05	0.39	8.31	0.27
50	16.48	2.94	11.81	0.59	10.89	0.23	10.43	0.58	9.50	0.38	8.79	0.26
60	16.69	2.84	12.16	0.58	11.29	0.23	10.83	0.58	9.93	0.38	9.23	0.26
70	23.45	4.61	16.16	0.90	14.73	0.37	13.97	0.89	12.54	0.58	11.44	0.41
80	23.66	4.51	16.50	0.90	15.13	0.36	14.37	0.89	12.97	0.58	11.88	0.40
90	23.81	4.60	16.57	0.88	15.19	0.36	14.39	0.88	12.99	0.56	11.92	0.40
100	23.81	4.60	16.57	0.88	15.19	0.36	14.39	0.88	12.99	0.56	11.92	0.40
110	30.57	6.38	20.56	1.20	18.63	0.50	17.54	1.20	15.60	0.76	14.13	0.55
120	30.57	6.38	20.56	1.20	18.63	0.50	17.54	1.20	15.60	0.76	14.13	0.55
130	30.72	6.47	20.63	1.19	18.69	0.50	17.55	1.19	15.62	0.75	14.17	0.55
140	37.33	8.16	24.56	1.53	22.07	0.63	20.68	1.52	18.21	0.96	16.35	0.71
150	37.48	8.25	24.63	1.51	22.13	0.64	20.70	1.51	18.23	0.95	16.38	0.71
160	37.48	8.25	24.63	1.51	22.13	0.64	20.70	1.51	18.23	0.95	16.38	0.71
170	44.24	10.03	28.62	1.83	25.57	0.77	23.84	1.83	20.84	1.15	18.59	0.86
180	44.24	10.03	28.62	1.83	25.57	0.77	23.84	1.83	20.84	1.15	18.59	0.86
190	44.40	10.13	28.69	1.82	25.63	0.78	23.86	1.82	20.86	1.14	18.63	0.86
200	44.40	10.13	28.69	1.82	25.63	0.78	23.86	1.82	20.86	1.14	18.63	0.86

A gamma distribution was assigned to the weekly cost for the probabilistic sensitivity analysis. SD= standard deviation. Costs are presented in 2017 Canadian dollars.

Appendix 12. The Weighted Average Cost of Corticosteroids Per Week and Per Weight.

Table A12-1. The weighted average cost of corticosteroids per week and per weight for the standard care comparator group.

Weight (kg)	Week 0 to 26 mean	Week 0 to 26 SD	Week 27 to 52 mean	Week 27 to 52 SD	Week 53 to 78 mean	Week 53 to 78 SD	Week 79 to 104 mean	Week 79 to 104 SD	Week 118 to 130 mean	Week 118 to 130 SD	Week 131 to 156 mean	Week 131 to 156 SD
10	9.28	2.49	12.27	1.24	14.32	2.04	15.35	1.26	18.77	2.66	19.66	2.20
20	10.19	2.37	13.04	1.29	15.23	2.19	16.28	1.29	19.91	2.46	20.81	2.34
30	10.85	2.36	13.59	1.38	15.94	2.40	17.03	1.38	20.89	2.43	21.83	2.59
40	10.85	2.36	13.76	1.33	16.28	2.42	17.41	1.36	21.48	2.46	22.59	2.67
50	10.85	2.36	13.93	1.29	16.62	2.44	17.79	1.34	22.06	2.49	23.34	2.76
60	10.85	2.36	14.11	1.26	16.95	2.47	18.17	1.33	22.65	2.53	24.10	2.85
70	10.85	2.36	14.28	1.24	17.29	2.49	18.56	1.32	23.23	2.57	24.85	2.93
80	10.85	2.36	14.46	1.22	17.63	2.52	18.94	1.31	23.82	2.62	25.61	3.02
90	10.85	2.36	14.63	1.22	17.96	2.55	19.32	1.31	24.40	2.66	26.36	3.12
100	10.85	2.36	14.80	1.22	18.30	2.58	19.70	1.30	24.99	2.71	27.12	3.21
110	10.85	2.36	14.98	1.23	18.64	2.61	20.08	1.30	25.57	2.77	27.87	3.31
120	10.85	2.36	15.15	1.26	18.97	2.64	20.46	1.31	26.16	2.82	28.63	3.41
130	10.85	2.36	15.33	1.29	19.31	2.68	20.85	1.31	26.74	2.88	29.38	3.51
140	10.85	2.36	15.50	1.33	19.65	2.71	21.23	1.32	27.33	2.94	30.14	3.61
150	10.85	2.36	15.67	1.38	19.98	2.74	21.61	1.33	27.91	3.00	30.90	3.71
160	10.85	2.36	15.85	1.43	20.32	2.78	21.99	1.34	28.50	3.07	31.65	3.81
170	10.85	2.36	16.02	1.49	20.65	2.81	22.37	1.36	29.08	3.13	32.41	3.92
180	10.85	2.36	16.20	1.55	20.99	2.85	22.75	1.38	29.66	3.20	33.16	4.02
190	10.85	2.36	16.37	1.62	21.33	2.89	23.14	1.40	30.25	3.27	33.92	4.13
200	10.85	2.36	16.54	1.70	21.66	2.93	23.52	1.42	30.83	3.34	34.67	4.23

A gamma distribution was assigned to the weekly cost for the probabilistic sensitivity analysis. SD= standard deviation. Costs are presented in 2017 Canadian dollars.

Table A12-2. The weighted average cost of corticosteroids per week and per weight for the early anti-TNF-α intervention comparator group.

Weight (kg)	Week 0 to 26 mean	Week 0 to 26 SD	Week 27 to 52 mean	Week 27 to 52 SD	Week 53 to 78 mean	Week 53 to 78 SD	Week 79 to 104 mean	Week 79 to 104 SD	Week 118 to 130 mean	Week 118 to 130 SD	Week 131 to 156 mean	Week 131 to 156 SD
10	9.28	2.49	12.27	1.24	14.32	2.04	15.35	1.26	18.77	2.66	19.66	2.20
20	10.19	2.37	13.04	1.29	15.23	2.19	16.28	1.29	19.91	2.46	20.81	2.34
30	10.85	2.36	13.59	1.38	15.94	2.40	17.03	1.38	20.89	2.43	21.83	2.59
40	10.85	2.36	13.76	1.33	16.28	2.42	17.41	1.36	21.48	2.46	22.59	2.67
50	10.85	2.36	13.93	1.29	16.62	2.44	17.79	1.34	22.06	2.49	23.34	2.76
60	10.85	2.36	14.11	1.26	16.95	2.47	18.17	1.33	22.65	2.53	24.10	2.85
70	10.85	2.36	14.28	1.24	17.29	2.49	18.56	1.32	23.23	2.57	24.85	2.93
80	10.85	2.36	14.46	1.22	17.63	2.52	18.94	1.31	23.82	2.62	25.61	3.02
90	10.85	2.36	14.63	1.22	17.96	2.55	19.32	1.31	24.40	2.66	26.36	3.12
100	10.85	2.36	14.80	1.22	18.30	2.58	19.70	1.30	24.99	2.71	27.12	3.21
110	10.85	2.36	14.98	1.23	18.64	2.61	20.08	1.30	25.57	2.77	27.87	3.31
120	10.85	2.36	15.15	1.26	18.97	2.64	20.46	1.31	26.16	2.82	28.63	3.41
130	10.85	2.36	15.33	1.29	19.31	2.68	20.85	1.31	26.74	2.88	29.38	3.51
140	10.85	2.36	15.50	1.33	19.65	2.71	21.23	1.32	27.33	2.94	30.14	3.61
150	10.85	2.36	15.67	1.38	19.98	2.74	21.61	1.33	27.91	3.00	30.90	3.71
160	10.85	2.36	15.85	1.43	20.32	2.78	21.99	1.34	28.50	3.07	31.65	3.81
170	10.85	2.36	16.02	1.49	20.65	2.81	22.37	1.36	29.08	3.13	32.41	3.92
180	10.85	2.36	16.20	1.55	20.99	2.85	22.75	1.38	29.66	3.20	33.16	4.02
190	10.85	2.36	16.37	1.62	21.33	2.89	23.14	1.40	30.25	3.27	33.92	4.13
200	10.85	2.36	16.54	1.70	21.66	2.93	23.52	1.42	30.83	3.34	34.67	4.23

A gamma distribution was assigned to the weekly cost for the probabilistic sensitivity analysis. SD= standard deviation. Costs are presented in 2017 Canadian dollars.

Appendix 13. The Weighted Average Cost of Antibiotics Per Week and Per Weight.

Table A13-1. The weighted average cost of antibiotics per week and per weight for the standard care and early anti-TNF-α intervention comparator groups.

Weight (kg)	Standard Care		Early anti-TNF-α Intervention		Distribution for PA
	cost per week $ mean	cost per week $ SD	cost per week $ mean	cost per week $ SD	
10	3.28	1.68	1.48	0.98	gamma
20	5.45	3.32	2.10	1.88	
30	6.94	3.34	3.35	1.94	
40	8.50	3.37	4.66	2.05	
50	7.47	3.33	3.86	1.94	
60	9.03	3.36	5.18	2.06	
70	10.44	3.38	6.37	2.19	
80	10.73	3.37	6.69	2.16	
90	12.46	3.41	8.13	2.36	
100	12.46	3.41	8.13	2.36	
110	13.95	3.44	9.38	2.55	
120	13.52	3.39	9.16	2.39	
130	15.09	3.43	10.47	2.60	
140	15.54	3.42	10.92	2.61	
150	15.54	3.42	10.92	2.61	
160	17.10	3.47	12.23	2.83	
170	17.55	3.46	12.69	2.84	
180	19.12	3.51	14.00	3.08	
190	19.57	3.50	14.45	3.08	
200	19.57	3.50	14.45	3.08	

PA= probabilistic analysis; SD = standard deviation. Costs are presented in 2017 Canadian dollars.

Appendix 14. The Weighted Average Cost of Oral 5-Aminosalicylates Per Week and Per Weight.

Table A14-1. The weighted average cost of oral 5-ASA's per week and per weight for the standard care and early anti-TNF-α intervention comparator groups.

Weight (kg)	Standard Care		Early anti-TNF-α intervention		Distribution for PA
	Cost per week $ mean	Cost per week $ SD	Cost per week $ mean	Cost per week $ SD	
10	35.21	0.52	33.77	0.83	gamma
20	35.61	0.47	34.32	0.74	
30	35.80	0.44	34.60	0.69	
40	36.20	0.38	35.15	0.61	
50	36.40	0.35	35.42	0.56	
60	36.80	0.30	35.97	0.47	
70	37.00	0.27	36.25	0.43	
80	37.39	0.22	36.80	0.34	
90	37.59	0.19	37.08	0.30	
100	37.99	0.13	37.63	0.21	
110	38.19	0.10	37.90	0.17	
120	38.59	0.05	38.45	0.08	
130	38.78	0.02	38.73	0.03	
140	39.18	0.03	39.28	0.05	
150	39.38	0.06	39.55	0.10	
160	39.78	0.12	40.10	0.19	
170	39.98	0.15	40.38	0.23	
180	40.37	0.20	40.93	0.32	
190	40.57	0.23	41.20	0.36	
200	40.97	0.29	41.75	0.45	

PA= probability sensitivity analysis; SD = standard deviation. Costs are presented in 2017 Canadian dollars.

Appendix 15. The Mean Cost Per Week for Enteral Nutrition Supplements.

Table A15-1. The age-dependent mean weekly cost of enteral nutrition supplements for males.

Age (years)	Minimum cost per week ($)	Maximum cost per week ($)	Mean cost per week ($)	SD cost per week ($)	Distribution for PA
4	66.92	615.44	341.18	387.86	gamma
5	66.92	615.44	341.18	387.86	gamma
6	66.92	692.37	379.65	442.26	gamma
7	83.65	692.37	388.01	430.43	gamma
8	83.65	846.23	464.94	539.23	gamma
9	66.92	846.23	456.58	551.06	gamma
10	66.92	1000.09	533.51	659.85	gamma
11	83.65	1000.09	541.87	648.02	gamma
12	100.38	1000.09	550.24	636.19	gamma
13	83.65	1000.09	541.87	648.02	gamma
14	83.65	1077.02	580.34	702.42	gamma
15	100.38	1153.95	627.17	744.99	gamma
16	117.11	1153.95	635.53	733.16	gamma
17	117.11	1153.95	635.53	733.16	gamma

PA= probabilistic analysis. SD= standard deviation Costs are in 2017 Canadian dollars.

Table A15-2. The age-dependent mean weekly cost of enteral nutrition supplements for females.

Age (years)	Minimum cost per week ($)	Maximum cost per week ($)	Mean cost per week ($)	SD cost per week ($)	Distribution for PA
4	66.92	615.44	341.18	387.86	gamma
5	66.92	615.44	341.18	387.86	gamma
6	66.92	692.37	379.65	442.26	gamma
7	66.92	692.37	379.65	442.26	gamma
8	83.65	846.23	464.94	539.23	gamma
9	66.92	769.30	418.11	496.66	gamma
10	66.92	1000.09	533.51	659.85	gamma
11	66.92	846.23	456.58	551.06	gamma
12	83.65	923.16	503.41	593.62	gamma
13	66.92	923.16	495.04	605.45	gamma
14	83.65	1000.09	541.87	648.02	gamma
15	83.65	846.23	464.94	539.23	gamma
16	100.38	923.16	511.77	581.79	gamma
17	100.38	923.16	511.77	581.79	gamma

PA= probabilistic sensitivity analysis. SD= standard deviation. Costs are in 2017 Canadian dollars

Appendix 16. Distribution of Imputed of Albumin.

Figure A16-1. Distribution of Albumin (g/d/L) in the 10 imputed data sets (red lines) compared to the original distribution (blue line) among the 573 RISK-PROKIIDS subjects.

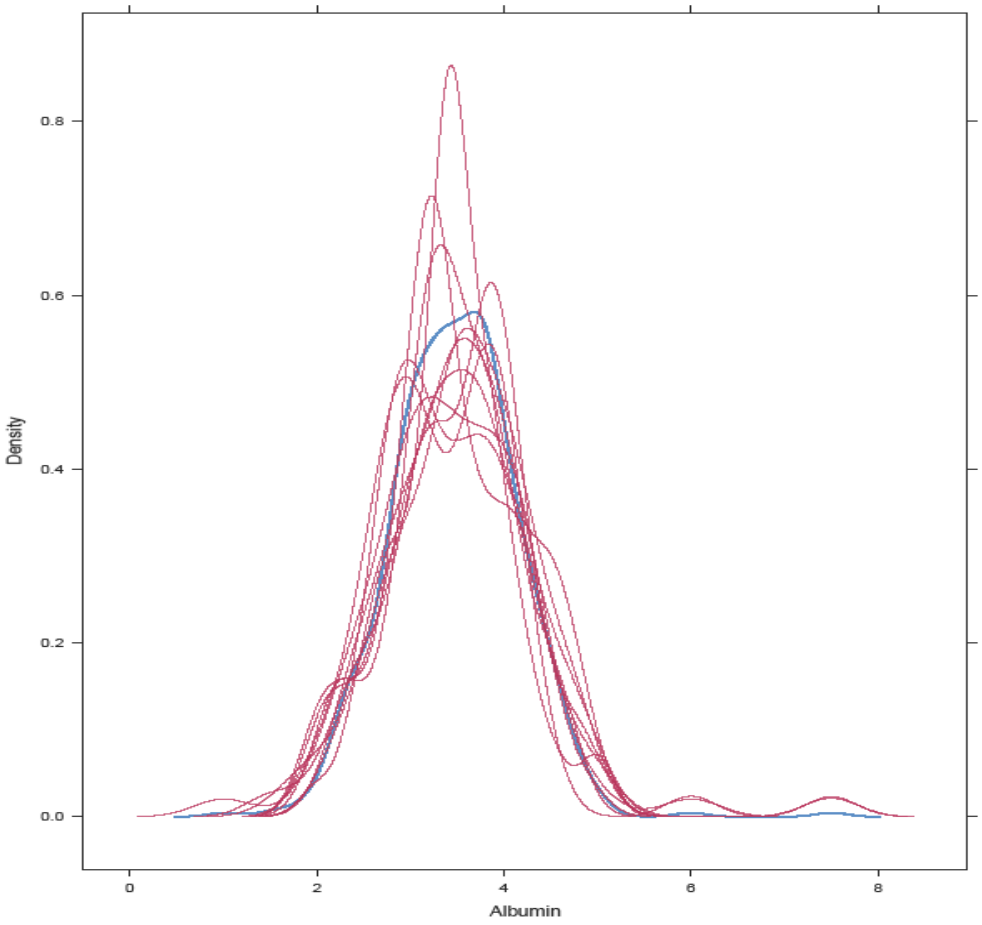
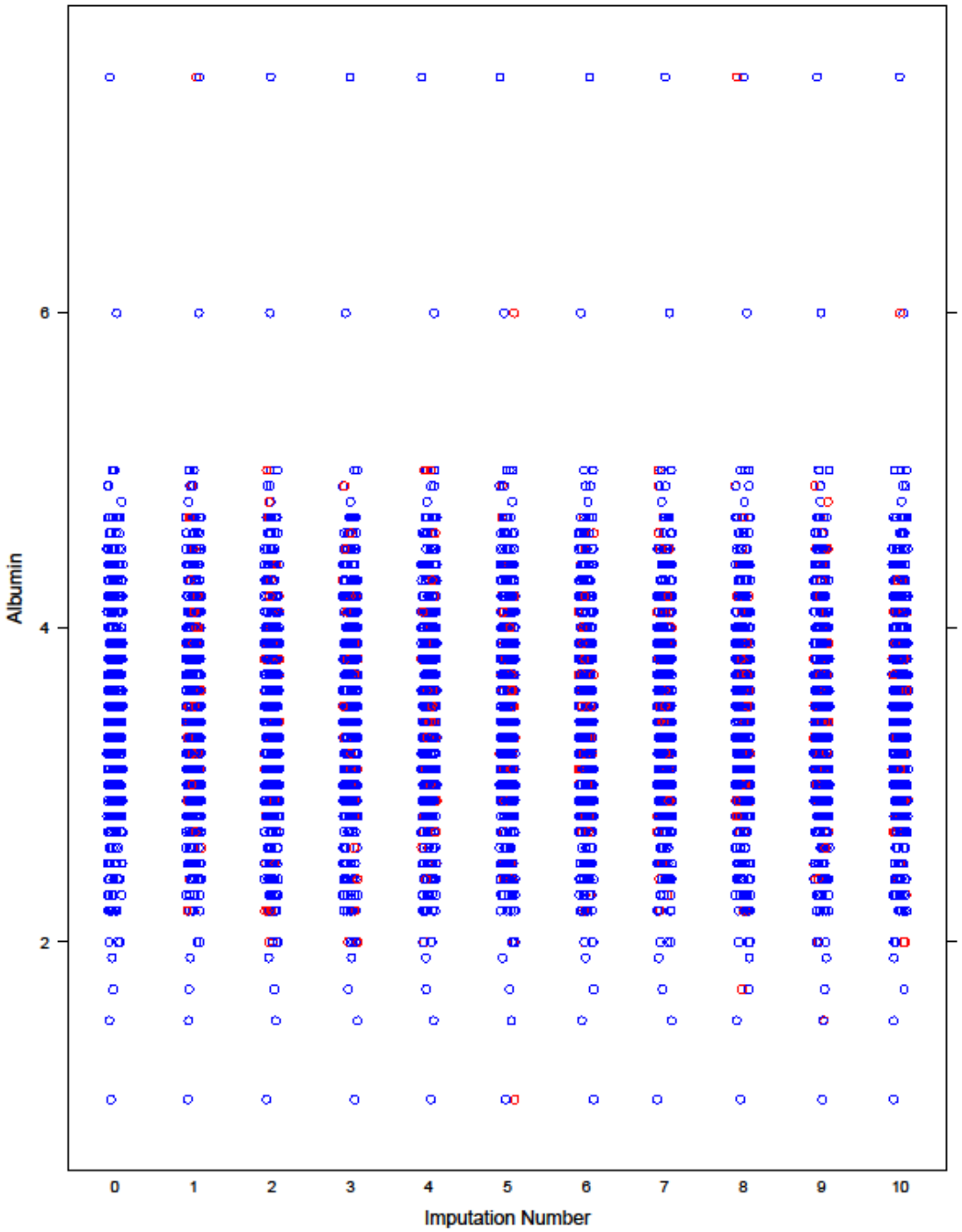
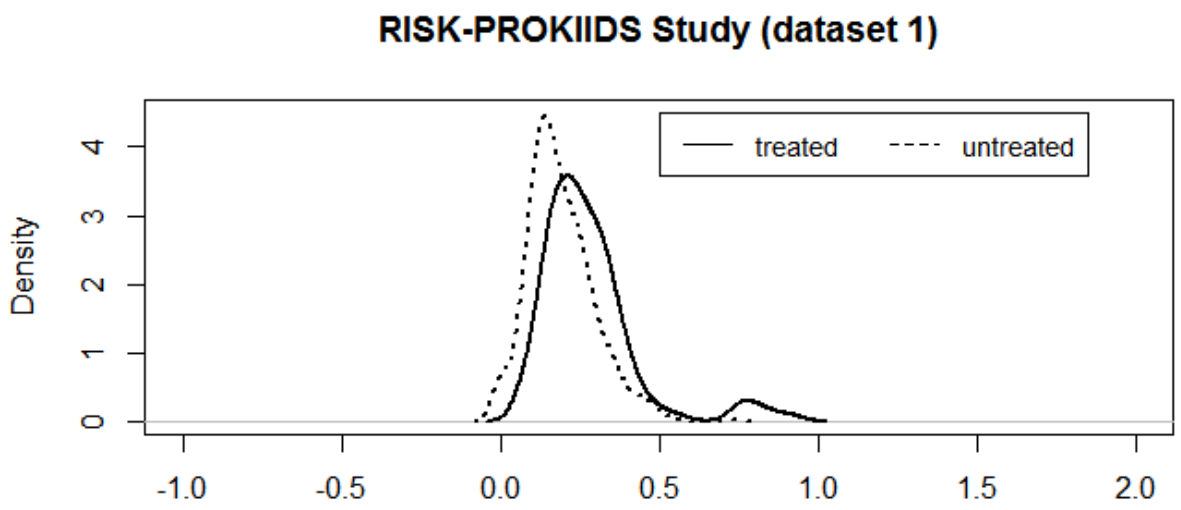


Figure A16-2. Strip plot showing the distribution of the imputed (red) values among the sample values (blue) for each of ten imputed data sets.



Appendix 17. Propensity Score Differences in Unadjusted CD RISK-PROKIIDS Patient Population.

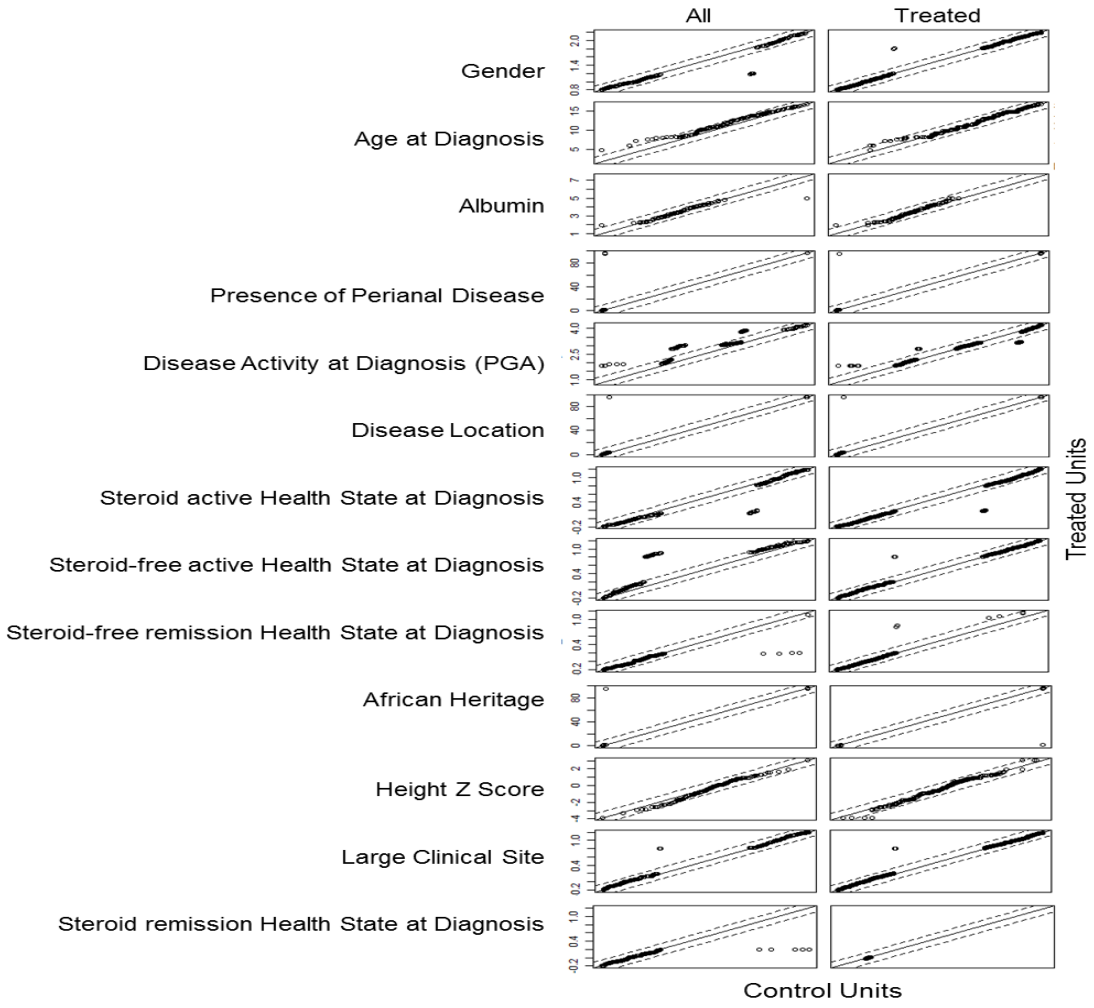
Figure A17-1. Propensity scores densities in early anti-TNF-α intervention (treated) and standard care (untreated) samples in the unadjusted RISK-PROKIIDS Patient Population.



Note that there is some overlap in the propensity scores in the unadjusted sample even prior to propensity score adjustment. Imputed dataset 1 was arbitrarily chosen as a representative data set of the unadjusted population.

Appendix 18. Quantile-quantile Plots Showing Covariate Balance.

Figure A18-1. Quantile-quantile plots of covariates in unadjusted and adjusted populations.



The Q-Q plot shows the efficacy of the propensity matching in unadjusted (left) and adjusted (right) populations by showing that the two populations, treated (anti-TNF-α) and control (standard care) come from the same distribution. The closer the points come to the 45-degree reference line, the more likely the two populations come from the same distribution and are well matched.

Appendix 19. Balance diagnostics for Propensity Score Analysis Methods on the Ten Imputed RISK-PROKIIDS Data Sets

Table A19-1. Balance diagnostics for nearest neighbour matching with 1:1 ratio of treatment:control propensity score analysis method on the individual ten imputed data sets.

Imputed Data set	Propensity Score Analysis Method	Treated Adjusted	Control Matched	Number of Imbalanced Covariates with Mean Standard Difference >0.1	Covariate with Highest Mean Standard Difference	Highest Mean Standard Difference	Age Variance Ratio	Albumin Variance Ratio	Height Z Score Variance Ratio
1	nearest, 1:1	131	131	5	Perianal Disease	0.1529	1.1022	1.3404	1.3295
2	nearest, 1:1	131	131	3	Perianal Disease	0.1875	1.1923	1.0645	1.3757
3	nearest, 1:1	131	131	5	Large Site	0.1828	1.1273	1.1347	1.2776
4	nearest, 1:1	131	131	1	Perianal Disease	0.1879	1.1914	1.0701	1.2433
5	nearest, 1:1	131	131	3	Perianal Disease	0.1522	1.0258	1.0629	1.3192
6	nearest, 1:1	131	131	2	Perianal Disease	0.1871	1.1522	1.0911	1.3240
7	nearest, 1:1	131	131	2	Perianal Disease	0.1871	1.0335	1.0092	1.1423
8	nearest, 1:1	131	131	2	Perianal Disease	0.1914	1.0354	1.4243	1.3374
9	nearest, 1:1	131	131	5	Large Site	0.1523	1.0559	1.3128	1.4551
10	nearest, 1:1	131	131	4	Albumin	0.1575	1.0881	1.0697	1.3873

Table A19-2. Balance diagnostics for nearest neighbour matching with 1:2 ratio of treatment:control propensity score analysis method on the individual ten imputed data sets.

Imputed Data set	Propensity Score Analysis Method	Treated Adjusted	Control Matched	Number of Imbalanced Covariates with Mean Standard Difference >0.1	Covariate with Highest Standard Difference	Highest Mean Standard Difference	Age Variance Ratio	Albumin Variance Ratio	Height Z Score Variance Ratio
1	nearest, 1:2	131	262	1	Perianal Disease	0.1887	1.0204	1.1331	1.2738
2	nearest, 1:2	131	262	1	Perianal Disease	0.1873	1.0655	1.2613	1.4403
3	nearest, 1:2	131	262	2	Perianal Disease	0.1883	1.0194	1.0952	1.2735
4	nearest, 1:2	131	262	1	Perianal Disease	0.1875	1.0307	1.1948	1.3239
5	nearest, 1:2	131	262	1	Perianal Disease	0.1877	1.0539	1.3001	1.3794
6	nearest, 1:2	131	262	1	Perianal Disease	0.1875	1.066	1.0642	1.3099
7	nearest, 1:2	131	262	2	Perianal Disease	0.1881	1.0157	1.149	1.2214
8	nearest, 1:2	131	262	1	Perianal Disease	0.1879	1.0259	1.2337	1.3082
9	nearest, 1:2	131	262	3	Perianal Disease	0.1881	1.0652	1.2328	1.315
10	nearest, 1:2	131	262	1	Perianal Disease	0.1887	1.011	1.1999	1.3174

Table A19-3. Balance diagnostics for nearest neighbour matching with 1:3 ratio of treatment:control propensity score analysis method on the individual ten imputed data sets.

Imputed Data set	Propensity Score Analysis Method	Treated Adjusted	Control Matched	Number of Imbalanced Covariates with Mean Standard Difference >0.1	Covariate with Highest Standard Difference	Highest Mean Standard Difference	Age Variance Ratio	Albumin Variance Ratio	Height Z Score Variance Ratio
1	nearest, 1:3	131	393	7	Disease Activity (PGA)	0.4028	1.1401	1.1798	1.3222
2	nearest, 1:3	131	393	6	Disease Activity (PGA)	0.4028	1.1258	1.1682	1.3323
3	nearest, 1:3	131	393	7	Disease Activity (PGA)	0.4028	1.1211	1.0895	1.3253
4	nearest, 1:3	131	393	6	Disease Activity (PGA)	0.4028	1.1407	1.1493	1.3308
5	nearest, 1:3	131	393	6	Disease Activity (PGA)	0.4028	1.1258	1.1947	1.3323
6	nearest, 1:3	131	393	6	Disease Activity (PGA)	0.4028	1.1212	1.1409	1.3337
7	nearest, 1:3	131	393	6	Disease Activity (PGA)	0.4028	1.1215	1.108	1.333
8	nearest, 1:3	131	393	6	Disease Activity (PGA)	0.4028	1.1405	1.2384	1.3298
9	nearest, 1:3	131	393	6	Disease Activity (PGA)	0.4028	1.1258	1.2042	1.3323
10	nearest, 1:3	131	393	7	Disease Activity (PGA)	0.4068	1.119	1.1653	1.3154

Table A19-4. Balance diagnostics for nearest neighbour matching with 1:1 ratio of treatment:control: and caliper of 0.2 propensity score analysis method on the individual ten imputed data sets.

Imputed Data set	Propensity Score Analysis Method; caliper =0.2	Treated Adjusted	Control Matched	Number of Imbalanced Covariates with Mean Standard Difference >0.1	Covariate with Highest Standard Difference	Highest Mean Standard Difference	Age Variance Ratio	Albumin Variance Ratio	Height Z Score Variance Ratio
1	nearest, 1:1, c =0.2	122	122	2	Large Site	0.1308	1.112	1.1591	1.412
2	nearest, 1:1, c =0.2	122	122	1	Disease Location	0.1549	1.0558	1.0725	1.4074
3	nearest, 1:1, c =0.2	122	122	1	Albumin	0.1085	1.0859	1.1364	1.0665
4	nearest, 1:1, c =0.2	122	122	2	Disease Activity at Dx	0.1287	1.2994	1.0716	1.6363
5	nearest, 1:1, c =0.2	122	122	0	Health State at Dx	0.0978	1.0527	1.0075	1.1635
6	nearest, 1:1, c =0.2	122	122	0	Health State at Dx	0.0815	1.1013	1.3877	1.1357
7	nearest, 1:1, c =0.2	122	122	1	Disease Activity at Dx	0.1287	1.0916	1.0487	1.1565
8	nearest, 1:1, c =0.2	122	122	0	Health State at Dx	0.0978	1.016	1.407	1.3224
9	nearest, 1:1, c =0.2	122	122	1	African	0.1243	1.0595	1.1636	1.3677
10	nearest, 1:1, c =0.2	122	122	1	African	0.1145	1.075	1.0224	1.148

Table A19-5. Balance diagnostics for nearest neighbour matching with 1:2 ratio of treatment:control: and caliper of 0.2 propensity score analysis method on the individual ten imputed data sets.

Imputed Data set	Propensity Score Analysis Method; caliper =0.2	Treated Adjusted	Control Matched	Number of Imbalanced Covariates with Mean Standard Difference >0.1	Covariate with Highest Standard Difference	Highest Mean Standard Difference	Age Variance Ratio	Albumin Variance Ratio	Height Z Score Variance Ratio
1	nearest, 1:2, c =0.2	122	234	0	Large Site	0.0572	1.0061	1.3041	1.1913
2	nearest, 1:2, c =0.2	123	236	0	Disease Activity at Dx (PGA)	0.0772	1.0111	1.0255	1.2554
3	nearest, 1:2, c =0.2	122	235	0	HtZDx	0.065	1.0025	1.1572	1.1943
4	nearest, 1:2, c =0.2	122	234	0	HtZDx	0.0715	1.0346	1.1324	1.2363
5	nearest, 1:2, c =0.2	123	235	0	Disease Activity at Dx (PGA)	0.0965	1.0888	1.1796	1.3102
6	nearest, 1:2, c =0.2	123	237	1	Disease Location	0.1021	1.0336	1.0433	1.1871
7	nearest, 1:2, c =0.2	122	234	1	Sex	0.1115	1.0605	1.1426	1.2864
8	nearest, 1:2, c =0.2	123	234	1	Sex	0.1286	1.0201	1.2255	1.3434
9	nearest, 1:2, c =0.2	123	233	0	HtZDx	0.0783	1.0316	1.3724	1.2449
10	nearest, 1:2, c =0.2	123	235	0	Age	0.0684	1.1693	1.2589	1.2491

Table A19-6. Balance diagnostics for nearest neighbour matching with 1:3 ratio of treatment:control: and caliper of 0.2 propensity score analysis method on the individual ten imputed data sets.

Imputed Data set	Propensity Score Analysis Method; caliper =0.2	Treated Adjusted	Control Matched	Number of Imbalanced Covariates with Mean Standard Difference >0.1	Covariate with Highest Standard Difference	Highest Mean Standard Difference	Age Variance Ratio	Albumin Variance Ratio	Height Z Score Variance Ratio
1	nearest, 1:3, c =0.2	122	293	0	Disease Location	0.0801	1.0098	1.1386	1.1782
2	nearest, 1:3, c =0.2	123	293	0	Disease Location	0.0683	1.0245	1.2035	1.3778
3	nearest, 1:3, c =0.2	122	293	0	Disease Location	0.0756	1.0109	1.136	1.2338
4	nearest, 1:3, c =0.2	123	289	0	Disease Activity at Dx (PGA)	0.0901	1.0637	1.198	1.2317
5	nearest, 1:3, c =0.2	123	285	0	Disease Location	0.0739	1.0102	1.1305	1.3237
6	nearest, 1:3, c =0.2	123	289	1	Disease Location	0.1117	1.0637	1.1077	1.2353
7	nearest, 1:3, c =0.2	123	292	0	Disease Activity at Dx (PGA)	0.0686	1.0694	1.1166	1.187
8	nearest, 1:3, c =0.2	123	290	0	Disease Location	0.0735	1.0276	1.1518	1.2531
9	nearest, 1:3, c =0.2	123	289	0	Disease Location	0.0783	1.0048	1.0803	1.2406
10	nearest, 1:3, c =0.2	123	295	0	Disease Location	0.0707	1.0042	1.209	1.2754

Table A19-7. Balance diagnostics for the inverse weighting on the propensity score propensity score analysis method on the individual ten imputed data sets.

Imputed Data set	Propensity Score Analysis Method	Treated Adjusted	Control Matched	Number of Imbalanced Covariates with Mean Standard Difference >0.1	Covariate with Highest Standard Difference	Highest Mean Standard Difference	Age Variance Ratio	Albumin Variance Ratio	Height Z Score Variance Ratio
1	weighting	131	244	1	Perianal Disease	0.1015	1.0211	1.264	1.244
2	weighting	131	240.7	0	Perianal Disease	0.0866	1.0169	1.0382	1.2508
3	weighting	131	244.3	1	Perianal Disease	0.1011	1.0246	1.0276	1.2466
4	weighting	131	242.2	0	Perianal Disease	0.0901	1.0205	1.0709	1.2482
5	weighting	131	240.7	0	Perianal Disease	0.0867	1.0168	1.1036	1.2466
6	weighting	131	240.4	0	Perianal Disease	0.0863	1.0174	1.0562	1.249
7	weighting	131	243.3	0	Perianal Disease	0.0931	1.0273	1.0327	1.2524
8	weighting	131	237.8	0	Perianal Disease	0.0923	1.018	1.6013	1.2475
9	weighting	131	242.3	0	Perianal Disease	0.0908	1.0213	1.1081	1.2483
10	weighting	131	243.3	0	Perianal Disease	0.0987	1.026	1.0895	1.2499

Table A19-8. Balance diagnostics for the covariate balance propensity score analysis method on the individual ten imputed data sets.

Imputed Data set	Propensity Score Analysis Method	Treated Adjusted	Control Matched	Number of Imbalanced Covariates with Mean Standard Difference >0.1	Covariate with Highest Standard Difference	Highest Mean Standard Difference	Age Variance Ratio	Albumin Variance Ratio	Height Z Score Variance Ratio
1	CBPS	131	235.2	0	Perianal Disease	0.0731	1.0291	1.2302	1.247
2	CBPS	131	230.6	0	Perianal Disease	0.0575	1.0235	1.0482	1.258
3	CBPS	131	232.9	0	Perianal Disease	0.0678	1.0301	1.0531	1.2507
4	CBPS	131	229.7	0	Perianal Disease	0.0568	1.0281	1.0863	1.2532
5	CBPS	131	227	0	Perianal Disease	0.0513	1.0218	1.1203	1.2499
6	CBPS	131	230.6	0	Perianal Disease	0.0585	1.0237	1.0596	1.2529
7	CBPS	131	232.6	0	Perianal Disease	0.0626	1.0394	1.0523	1.2598
8	CBPS	131	213.8	0	Perianal Disease	0.0295	1.0015	1.5961	1.2552
9	CBPS	131	227.1	0	Perianal Disease	0.0512	1.0296	1.1208	1.2544
10	CBPS	131	231.5	0	Perianal Disease	0.0647	1.0338	1.1174	1.2566

Table A19-9. Balance diagnostics for the subclassification propensity score analysis method on the individual ten imputed data sets.

Imputed Dataset	Subclass	Method	Treated Adjusted	Control Adjusted	# Imbalanced Covariates with Std. Difference >0.1
1	1	Subclassification	33	250	7
1	2	Subclassification	32	90	3
1	3	Subclassification	33	61	8
1	4	Subclassification	33	41	11
2	1	Subclassification	33	247	6
2	2	Subclassification	32	95	5
2	3	Subclassification	33	54	9
2	4	Subclassification	33	46	10
3	1	Subclassification	33	253	6
3	2	Subclassification	32	81	3
3	3	Subclassification	33	65	7
3	4	Subclassification	33	43	11
4	1	Subclassification	33	252	6
4	2	Subclassification	32	85	2
4	3	Subclassification	33	61	8
4	4	Subclassification	33	44	9
5	1	Subclassification	33	247	6
5	2	Subclassification	32	95	5
5	3	Subclassification	33	55	9
5	4	Subclassification	33	45	9
6	1	Subclassification	33	247	6
6	2	Subclassification	32	95	5
6	3	Subclassification	33	55	9
6	4	Subclassification	33	45	9
7	1	Subclassification	33	248	5

Imputed Dataset	Subclass	Method	Treated Adjusted	Control Adjusted	# Imbalanced Covariates with Std. Difference >0.1
7	2	Subclassification	32	89	2
7	3	Subclassification	33	61	8
7	4	Subclassification	33	44	9
8	1	Subclassification	33	251	5
8	2	Subclassification	32	85	2
8	3	Subclassification	33	63	8
8	4	Subclassification	33	43	9
9	1	Subclassification	33	253	5
9	2	Subclassification	32	83	6
9	3	Subclassification	33	61	8
9	4	Subclassification	33	45	9
10	1	Subclassification	33	243	5
10	2	Subclassification	32	93	4
10	3	Subclassification	33	65	7
10	4	Subclassification	33	41	11

Appendix 20. Treatment Class Combinations Over Three Years in the RISK-PROKIIDS Comparator Groups.

Table A20-1. All treatment class combination used in the RISK-PROKIIDS CD patients over three years in the Standard Care Step-up group and the Early anti-TNF-α.

Treatment Combination	Week 13 SC (%)	Week 13 Early anti-TNFα (%)	Week 26 SC (%)	Week 26 Early anti-TNFα (%)	Week 52 SC (%)	Week 52 Early anti-TNFα (%)	Week 105 SC (%)	Week 105 Early anti-TNFα (%)	Week 156 SC (%)	Week 156 Early anti-TNFα (%)
anti and en	1.3	0.0	0.4	0.0	0.4	0.0	0.4	0.0	0.4	0.0
anti only	1.7	0.0	3.0	0.0	3.0	0.8	0.4	0.0	0.4	0.0
asa and/or anti and/or en	6.8	0.0	4.6	0.0	4.2	0.0	3.4	0.0	2.1	0.0
asa only	7.2	0.0	13.5	0.0	9.7	0.8	5.5	0.0	6.8	0.0
bio and/or asa and/or anti and/or en	0.0	16.3	0.0	14.6	3.4	10.6	5.1	8.9	6.8	5.7
bio and im	0.0	0.8	1.7	9.8	8.0	21.1	18.1	26.8	19.0	26.0
bio and im and/or asa and/or anti and/or en	0.0	3.3	2.1	4.1	2.1	8.1	4.2	6.5	3.4	7.3
bio only	0.0	19.5	0.0	43.9	5.9	50.4	15.6	48.8	22.8	46.3
cs and/or asa and/or anti and/or en	20.3	0.0	6.8	0.0	3.8	0.0	2.5	0.0	0.8	0.0
cs and bio	0.0	14.6	0.8	10.6	0.8	1.6	1.7	0.0	0.0	2.4

Treatment Combination	Week 13 SC (%)	Week 13 Early anti-TNFα (%)	Week 26 SC (%)	Week 26 Early anti-TNFα (%)	Week 52 SC (%)	Week 52 Early anti-TNFα (%)	Week 105 SC (%)	Week 105 Early anti-TNFα (%)	Week 156 SC (%)	Week 156 Early anti-TNFα (%)
cs and bio and/or asa and/or anti and/or en	0.0	25.2	1.3	5.7	1.7	1.6	1.3	1.6	2.1	0.0
cs and im	27.8	0.0	15.2	0.0	6.8	0.0	3.0	0.0	0.4	0.0
cs and im and/or asa and/or anti and/or en	21.5	0.0	13.5	0.0	3.4	0.0	3.4	0.0	1.3	0.0
cs and im and bio	0.0	9.8	3.4	8.1	3.0	1.6	0.0	3.3	0.8	1.6
cs only	2.1	0.0	1.3	0.0	0.8	0.8	0.0	0.8	0.4	0.0
cs and bio and im and/or asa and/or anti and/or en	0.0	10.6	1.7	3.3	1.7	0.8	0.4	2.4	0.4	0.8
en only	1.7	0.0	0.8	0.0	0.8	0.0	0.4	0.0	0.0	0.0
im and/or asa and/or anti and/or en	6.8	0.0	12.7	0.0	17.7	0.0	15.6	0.0	10.1	1.6
im only	1.7	0.0	14.3	0.0	20.3	0.8	16.9	0.8	16.9	1.6
no treatment	1.3	0.0	3.0	0.0	2.5	0.8	2.1	0.0	5.1	6.5

Abbreviations: cs = corticosteroids; im = immunomodulators; bio =biologics (anti-TNF-α), en = enteral nutrition; anti = antibiotics; asa = oral 5-aminosalicylate; others = and/or asa and/or anti and/or en.

Appendix 21. Transition Probabilities for Each of the Ten Matched RISK-PROKIIDS Datasets.

Table A21-1. Weekly Transition Probabilities for the "Active Disease" to "Medical Remission" Health States Derived from the Ten RISK-PROKIIDS Matched Imputed Datasets over Three years for the Standard Care Comparator Group.

Dataset	Active Disease to Medical Remission	0-6 months	6-12 months	12-18 months	18-24 months	24-30 months	30-36 months
1	Probability	0.0279	0.0263	0.0301	0.0255	0.0207	0.0290
	SE	0.0011	0.0022	0.0026	0.0027	0.0032	0.0035
2	Probability	0.0283	0.0277	0.0220	0.0279	0.0242	0.0286
	SE	0.0011	0.0022	0.0027	0.0026	0.0035	0.0037
3	Probability	0.0302	0.0249	0.0251	0.0267	0.0222	0.0274
	SE	0.0010	0.0023	0.0026	0.0026	0.0032	0.0036
4	Probability	0.0285	0.0284	0.0276	0.0267	0.0204	0.0308
	SE	0.0011	0.0022	0.0028	0.0027	0.0034	0.0035
5	Probability	0.0295	0.0249	0.0280	0.0280	0.0242	0.0298
	SE	0.0011	0.0023	0.0027	0.0027	0.0036	0.0036
6	Probability	0.0271	0.0244	0.0233	0.0241	0.0214	0.0263
	SE	0.0010	0.0021	0.0026	0.0025	0.0031	0.0033
7	Probability	0.0298	0.0229	0.0279	0.0280	0.0168	0.0301
	SE	0.0011	0.0023	0.0026	0.0027	0.0032	0.0033
8	Probability	0.0273	0.0257	0.0244	0.0252	0.0239	0.0258
	SE	0.0011	0.0022	0.0025	0.0025	0.0032	0.0037
9	Probability	0.0278	0.0270	0.0235	0.0247	0.0336	0.0308
	SE	0.0011	0.0022	0.0028	0.0027	0.0033	0.0035
10	Probability	0.0271	0.0241	0.0255	0.0245	0.0180	0.0238
	SE	0.0011	0.0021	0.0026	0.0024	0.0030	0.0035

Probabilities were determined every six months; SE= Standard error

Table A21-2. Weekly Transition Probabilities for the "Active Disease" to "Medical Remission" Health States Derived from the Ten RISK-PROKIIDS Matched Imputed Datasets over Three years for the Early anti-TNF-α Comparator Group.

Dataset	Active Disease to Medical Remission	0-6 months	6-12 months	12-18 months	18-24 months	24-30 months	30-36 months
1	Probability	0.0309	0.0190	0.0255	0.0174	0.0179	0.0263
	SE	0.0020	0.0046	0.0054	0.0055	0.0071	0.0071
2	Probability	0.0305	0.0197	0.0246	0.0174	0.0179	0.0286
	SE	0.0020	0.0045	0.0055	0.0055	0.0071	0.0071
3	Probability	0.0302	0.0185	0.0255	0.0179	0.0187	0.0275
	SE	0.0020	0.0045	0.0054	0.0057	0.0074	0.0073
4	Probability	0.0298	0.0192	0.0247	0.0179	0.0167	0.0286
	SE	0.0020	0.0044	0.0053	0.0057	0.0072	0.0071
5	Probability	0.0298	0.0192	0.0239	0.0174	0.0179	0.0286
	SE	0.0020	0.0044	0.0054	0.0055	0.0071	0.0071
6	Probability	0.0305	0.0197	0.0246	0.0174	0.0179	0.0263
	SE	0.0020	0.0045	0.0055	0.0055	0.0071	0.0071
7	Probability	0.0298	0.0192	0.0239	0.0174	0.0179	0.0286
	SE	0.0020	0.0044	0.0054	0.0055	0.0071	0.0071
8	Probability	0.0298	0.0192	0.0247	0.0179	0.0167	0.0286
	SE	0.0020	0.0044	0.0053	0.0057	0.0072	0.0071
9	Probability	0.0298	0.0192	0.0247	0.0179	0.0167	0.0286
	SE	0.0020	0.0044	0.0053	0.0057	0.0072	0.0071
10	Probability	0.0305	0.0185	0.0247	0.0174	0.0179	0.0286
	SE	0.0020	0.0045	0.0053	0.0055	0.0071	0.0071

Probabilities were determined every six months; SE= Standard error

Table A21-3. Weekly Transition Probabilities for the Continued "Medical Remission" Health State Derived from the Ten RISK-PROKIIDS Matched Imputed Datasets over Three years for the Standard Care Comparator Group.

Dataset	Medical Remission to Medical Remission	6-12 months	12-18 months	18-24 months	24-30 months	30-36 months
1	Probability	0.0429	0.0386	0.0600	0.0617	0.0730
	SE	0.0018	0.0016	0.0011	0.0010	0.0008
2	Probability	0.0426	0.0441	0.0622	0.0626	0.0670
	SE	0.0017	0.0015	0.0011	0.0009	0.0008
3	Probability	0.0422	0.0398	0.0541	0.0659	0.0808
	SE	0.0017	0.0016	0.0013	0.0009	0.0006
4	Probability	0.0442	0.0404	0.0598	0.0617	0.0726
	SE	0.0017	0.0016	0.0011	0.0010	0.0008
5	Probability	0.0453	0.0406	0.0630	0.0596	0.0708
	SE	0.0016	0.0016	0.0011	0.0010	0.0008
6	Probability	0.0426	0.0395	0.0582	0.0605	0.0710
	SE	0.0018	0.0016	0.0012	0.0010	0.0008
7	Probability	0.0444	0.0408	0.0598	0.0631	0.0738
	SE	0.0017	0.0016	0.0011	0.0009	0.0008
8	Probability	0.0414	0.0385	0.0569	0.0643	0.0677
	SE	0.0018	0.0017	0.0013	0.0010	0.0008
9	Probability	0.0466	0.0452	0.0603	0.0639	0.0699
	SE	0.0017	0.0015	0.0011	0.0009	0.0008
10	Probability	0.0442	0.0366	0.0592	0.0688	0.0685
	SE	0.0018	0.0017	0.0012	0.0009	0.0008

Probabilities were determined every six months; SE= Standard error

Table A21-4. Weekly Transition Probabilities for the Continued "Medical Remission" Health State Derived from the Ten RISK-PROKIIDS Matched Imputed Datasets over Three years for the Early anti-TNF-α Comparator Group.

Dataset	Medical Remission to Medical Remission	6-12 months	12-18 months	18-24 months	24-30 months	30-36 months
1	Probability	0.0590	0.0529	0.0886	0.0674	0.0666
	SE	0.0024	0.0025	0.0010	0.0016	0.0016
2	Probability	0.0617	0.0539	0.0890	0.0679	0.0645
	SE	0.0022	0.0023	0.0010	0.0015	0.0017
3	Probability	0.0611	0.0529	0.0886	0.0674	0.0666
	SE	0.0023	0.0025	0.0010	0.0016	0.0016
4	Probability	0.0584	0.0550	0.0890	0.0679	0.0666
	SE	0.0024	0.0024	0.0010	0.0015	0.0016
5	Probability	0.0611	0.0534	0.0886	0.0674	0.0641
	SE	0.0023	0.0024	0.0010	0.0016	0.0017
6	Probability	0.0617	0.0539	0.0890	0.0679	0.0645
	SE	0.0022	0.0023	0.0010	0.0015	0.0017
7	Probability	0.0611	0.0534	0.0886	0.0674	0.0641
	SE	0.0023	0.0024	0.0010	0.0016	0.0017
8	Probability	0.0584	0.0550	0.0890	0.0679	0.0666
	SE	0.0024	0.0024	0.0010	0.0015	0.0016
9	Probability	0.0584	0.0550	0.0890	0.0679	0.0666
	SE	0.0024	0.0024	0.0010	0.0015	0.0016
10	Probability	0.0590	0.0529	0.0886	0.0674	0.0666
	SE	0.0024	0.0025	0.0010	0.0016	0.0016

Probabilities were determined every six months; SE= Standard error

Table A21-5. Weekly Transition Probabilities for the "Active Disease" to "Active Disease Requiring Surgery or Hospitalization" State Derived from the Ten RISK-PROKIIDS Matched Imputed Datasets over Three years for the Standard Care and Early anti-TNF-α Comparator Groups.

Dataset	Active Disease to Surgery/ Hospitalization	Standard Care	Early anti-TNF-α Intervention
1	Probability	0.0004	0.0005
	SE	0.0002	0.0006
2	Probability	0.0004	0.0005
	SE	0.0003	0.0006
3	Probability	0.0004	0.0006
	SE	0.0003	0.0007
4	Probability	0.0005	0.0006
	SE	0.0003	0.0007
5	Probability	0.0005	0.0006
	SE	0.0003	0.0007
6	Probability	0.0005	0.0005
	SE	0.0003	0.0006
7	Probability	0.0005	0.0006
	SE	0.0003	0.0007
8	Probability	0.0004	0.0006
	SE	0.0003	0.0007
9	Probability	0.0004	0.0006
	SE	0.0002	0.0007
10	Probability	0.0005	0.0006
	SE	0.0003	0.0007

SE= Standard error

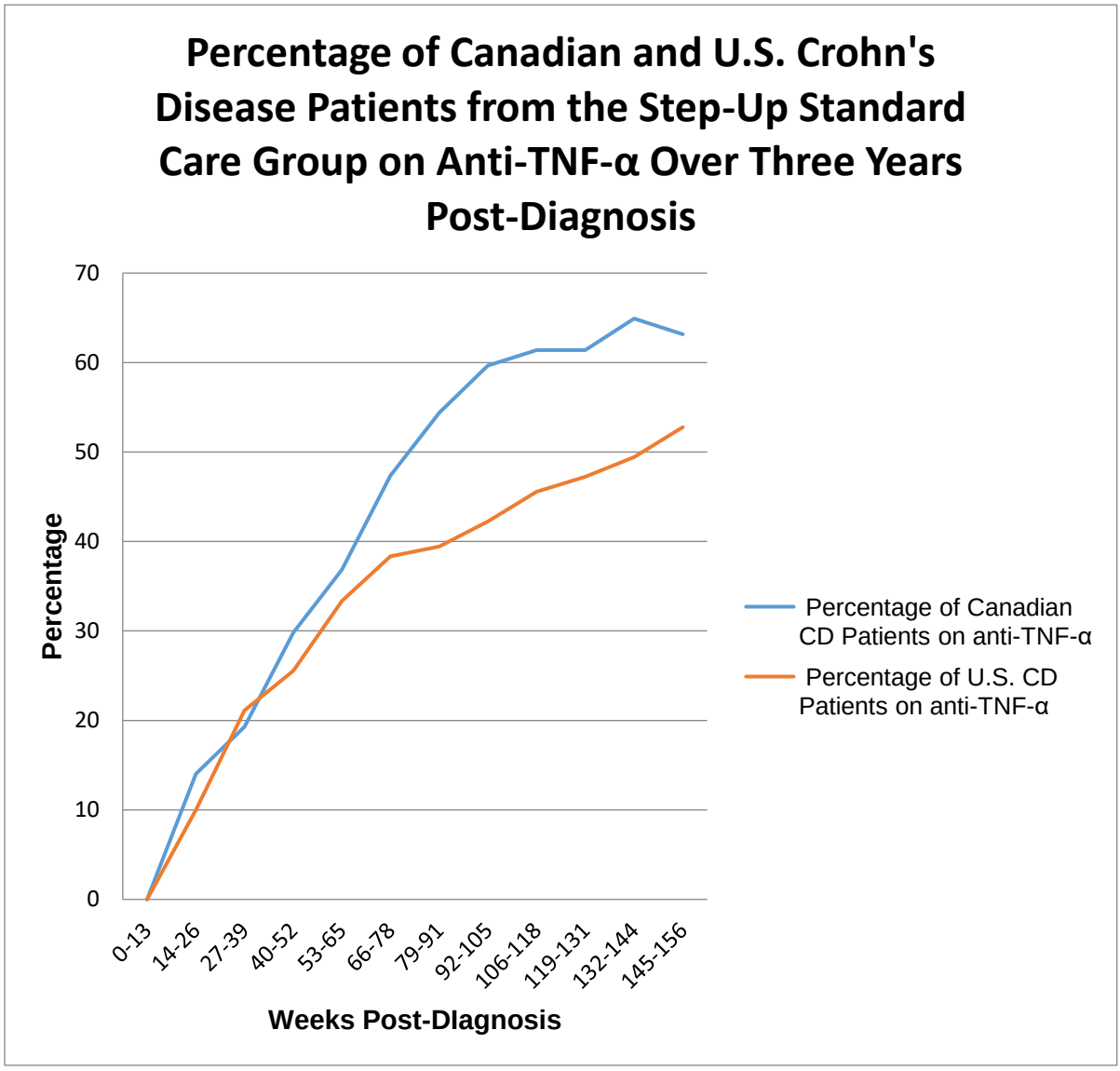
Table A21-6. Weekly Transition Probabilities for the “Surgical Remission” to “Active Disease” State Derived from the Ten RISK-PROKIIDS Matched Imputed Datasets over Three years for the Standard Care and Early anti-TNF-α Comparator Groups.

Dataset	Surgical Remission to Active Disease	Standard Care	Early anti-TNF-α Intervention
1	Probability	0.0040	0.0077
	SE	0.0178	0.0191
2	probability	0.0053	0.0077
	SE	0.0145	0.0191
3	probability	0.0049	0.0065
	SE	0.0156	0.0193
4	probability	0.0041	0.0065
	SE	0.0138	0.0193
5	probability	0.0053	0.0065
	SE	0.0145	0.0193
6	probability	0.0044	0.0077
	SE	0.0132	0.0191
7	probability	0.0048	0.0065
	SE	0.0125	0.0193
8	probability	0.0049	0.0065
	SE	0.0156	0.0193
9	probability	0.0049	0.0065
	SE	0.0178	0.0193
10	probability	0.0052	0.0065
	SE	0.0130	0.0193

SE= Standard error

Appendix 22. Anti-TNF-α Use Over Three Years in Canadian and U.S. Patients in the RISK-PROKIIDS Study

Figure A22-1. Comparison of Anti-TNF-α Use Between Canadian and U.S. Crohn's Disease Patients in the Standard Care Step-Up Group from the RISK-PROKIIDS Study Over Three Years.



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