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Infliximab for the Treatment of Crohn's Disease: A Systematic Review and Cost-Utility Analysis

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Infliximab for the Treatment of Crohn's Disease: A Systematic Review and Cost-Utility Analysis

John K. Marshall M.D., M.Sc., FRCPC[1,3]
Gordon Blackhouse MBA[2,3]
Ron Goeree MA[2,3]
Nicole Brazier B.Sc.[2,3]
E. Jan Irvine M.D., M.Sc., FRCPC[1]
Lisa Faulkner Ph.D.[2,3]
Christine Dipchand M.D., FRCPC[2,3]
Bernie J. O'Brien Ph.D.[2,3]

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1. Department of Medicine, McMaster University, Hamilton, Ontario
2. Department Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario
3. Centre for Evluation of Medicines, St. Joseph's Hospital, Hamilton, Ontario

REVIEWERS

These individuals kindly provided comments on this report.

CCOHTA Scientific Advisory Panel

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Authorship

As principal investigator, Dr. Marshall led protocol development, supervised the literature review and summarized its results, assisted in economic model design and analysis and prepared the report for publication. Mr. Blackhouse constructed and analyzed the economic model, prepared related components of the report and approved its final version. Mr. Goeree assisted in protocol development and economic model design, revised the report and approved its final version. Ms. Brazier performed all literature searches and prepared related summaries, revised the report and approved its final version. Dr. Irvine assisted with literature review, assisted in economic model design, revised the report and approved its final version. Dr. Dipchand assisted in drafting inputs for the economic model, revised the report and approved its final version. Dr. Faulkner assisted in protocol development, revised the report and approved its final version. As senior investigator, Dr. O'Brien assisted in protocol development, provided advice throughout the project, revised the final report and approved its final version.

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Disclosure of Conflicts of Interest

No conflicts of interest were declared by any of the report's authors.

HIGHLIGHTS

What is already known about this topic?

- About Crohn's disease
  - Crohn's disease (CD) is a chronic, inflammatory disorder of the gastrointestinal tract that often follows a relapsing and remitting course, and can be complicated by intestinal strictures, fistulas and abscesses.
  - Some patients with CD develop refractory disease, suffer poor quality of life and consume considerable healthcare resources.
  - New treatments to attenuate inflammation, improve symptoms and avoid hospitalization are needed.
- About infliximab (Remicade^{TM})
  - Infliximab is a monoclonal antibody treatment for CD.
  - Clinical trials have evaluated infliximab for treatment of patients with fistulizing and active CD resistant to conventional therapy.
  - The costs and potential toxicity of infliximab must be weighed against its effectiveness in improving health outcomes and reducing healthcare resource use.

Assessment Objectives

1. To review available data supporting the efficacy, effectiveness and adverse effects of infliximab in the treatment of patients with CD.
2. To review available data evaluating the economic impact of infliximab used to treat patients with CD.
3. To conduct a primary cost-utility analysis of infliximab treatment for patients with active CD resistant to conventional therapy.

What new information does this assessment provide?

- Infliximab appears to be clinically effective for the treatment of fistulizing CD and active CD resistant to conventional therapy. The findings also suggest that infliximab for CD is currently outside the range of what is normally considered cost effective.
- Due to limited data availability, some simplifying assumptions about natural history, resource utilization and drug dosing were made. The analysis used a short time horizon and it did not assess indirect costs and benefits.
- The economic impact of infliximab may continue to evolve, with changes in drug delivery, dose and cost. Decision makers should recognize that infliximab offers a potential treatment to selected patients with refractory CD for whom few, if any other alternatives are available.

EXECUTIVE SUMMARY

The Issue: Crohn's disease (CD) is a chronic, inflammatory disorder of the gastrointestinal tract of uncertain etiology. The morbidity and clinical manifestations of CD are variable, and reflect the distribution and severity of the disease. CD often follows a relapsing and remitting course, and can be complicated by intestinal strictures, fistulas and abscesses. Although effective treatments are available, a minority of patients with CD develop refractory disease, suffer poor quality of life and consume considerable healthcare resources. Novel treatments to attenuate inflammation, improve symptoms, and avoid hospitalization are needed. Infliximab (Remicade^{TM}) is a chimeric human-murine monoclonal antibody to the pro-inflammatory cytokine tumour necrosis factor-alpha (TNFa), and the first biological therapy to win regulatory approval for the treatment of CD. Clinical trials have evaluated infliximab for treatment of patients with fistulizing and active CD resistant to conventional therapy. The costs and potential toxicity of infliximab must be weighed against its effectiveness in improving health outcomes and reducing healthcare resource utilization in a challenging patient population.

Objectives: (1) To review available data supporting the efficacy, effectiveness and adverse effects of infliximab in the treatment of patients with CD. (2) To review available data evaluating the economic impact of infliximab used to treat patients with CD. (3) To conduct a primary cost-utility analysis of infliximab treatment for patients with active CD resistant to conventional therapy.

Clinical Effectiveness Review: Because a limited number of clinical trials have evaluated infliximab for treatment of CD, no attempt was made to pool literature quantitatively. Rather, a qualitative summary of the available clinical data was undertaken.

For the treatment of fistulizing CD, one controlled clinical trial has been reported and another is underway. Three infusions of infliximab (5 or 10 mg/kg) at Weeks 0, 2 and 6 were superior to placebo in achieving partial (62% vs. 26%, p=0.002) and complete (46% vs. 13%, p=0.001) closure of fistulas over 18 weeks. No significant dose response was observed, although numerically higher closure rates were seen with 5mg/kg.

For the treatment of active CD resistant to conventional medical therapy, only one acute treatment trial and its extension to maintenance therapy have been fully published. The results show that a single intravenous infusion of infliximab is superior to placebo in inducing clinical response (65% vs. 16%, p<0.001) and clinical remission (33% vs. 4%, p=0.005) at four weeks. The gains in response (41% vs. 12%, p=0.008) and remission (24% vs. 8%, p=0.31) were attenuated by 12 weeks. Again, no dose-response was observed, with numerically greater treatment effects at 5 mg/kg than 10 or 20 mg/kg. Among subjects who responded to a blinded infliximab infusion or an open-label re-infusion (10 mg/kg), re-infusions of 10 mg/kg at eight-week intervals yielded significantly higher rates of clinical remission (44% vs. 20%, p=0.013) and numerically higher rates of clinical response (62% vs. 37%, p=0.16) at Week 44. Preliminary results from a larger trial evaluating maintenance strategies for subjects who achieve clinical response two weeks after infliximab infusion also suggest that repeat infusions of infliximab (5 mg/kg or 10 mg/kg) every eight weeks are numerically superior to placebo in providing

clinical response (55% vs. 27%) or remission (42% vs. 21%) at Week 30 (significance testing not reported). Full results of this trial are awaited.

No clinical subgroups in which infliximab consistently offers preferential benefit have been identified. In controlled clinical trials of CD, treatment with infliximab has been tolerated well, with mild and self-limited infusion reactions in three to seven percent of patients. Increased rates of acute respiratory infection were observed. With rare cases of reactivated tuberculosis reported in post-marketing surveillance, screening for tuberculosis is now recommended among candidates for infliximab treatment. Patients treated with infliximab have been noted to develop *de novo* autoimmune markers and human anti-chimeric antibodies (HACA), although their clinical significance remains uncertain. The long-term risks of infliximab, including malignancy and autoimmune disease, are currently unknown.

Economic Analysis and Review: Six previous economic analyses of infliximab and two observational studies of infliximab-associated resource utilization were identified. Four evaluations, submitted by industry, generated favourable results for treatment of fistulizing and active CD, and suggested it to be cost-saving. A cost-utility analysis of single-dose infliximab for the treatment of active CD estimated its incremental cost-utility ratio (ICUR) to range from US $14,200/QALY to US $40,000/QALY, but it has been published only in abstract form with limited information on methods and assumptions. The only analysis to be published in a peer-reviewed journal concluded that the ICUR of primary treatment with infliximab for fistulizing CD, relative to usual care, was US $355,450/QALY. Two pre-post observational studies noted lower resource utilization after infliximab infusion, than in a matched period before treatment.

The authors undertook a cost-utility analysis of infliximab for active CD resistant to conventional therapy. Its use for fistulizing CD was not evaluated. A Markov model was used to compare three infliximab treatment strategies to usual care, using transition data from a published natural history study of CD and estimates of treatment effects from clinical trials. From the perspective of a Canadian provincial ministry of health, no strategy was dominant in the base-case analysis. Usual care yielded the fewest QALY and incurred the lowest costs over one year. A single-infusion of infliximab was estimated to yield 0.01524 additional QALY for incremental direct medical costs of C $2,762 (ICUR C $181,201/QALY). Re-treatment of responders further improved outcomes (ICUR C $480,111/QALY) while adding maintenance therapy for responders provided the best outcome (ICUR C $696,078/QALY). In one-way sensitivity analyses, the results were sensitive to extreme reductions in the cost of infliximab and increases in the rate of medical admission for drug-refractory disease. In a probabilistic sensitivity analysis, usual care was the strategy most likely to be cost effective for QALY values less than approximately C $180,000.

Discussion: This economic analysis is methodologically rigorous and relevant to the Canadian practice setting, and used advanced probabilistic sensitivity analysis to explore the impact of parameter uncertainty. In its base-case, the economic impact of infliximab exceeded what is generally considered good value for money. However, several limitations warrant recognition. First, explicit assumptions regarding natural history, resource utilization and drug dosing were required with reliance upon expert opinion. Second, the analysis used a limited time horizon in keeping with the limited available efficacy data, and did not address long-term costs,

outcomes and adverse effects of the alternative strategies. Third, indirect costs and benefits were not assessed. Fourth, the economic impact of infliximab may continue to evolve, with changes in drug delivery, dose and cost. Finally, decision makers must recognize that infliximab offers a potential treatment to selected patients with refractory CD for whom few, if any, other alternatives are available.

Conclusions: Infliximab appears to be clinically effective for the treatment of fistulizing CD and active CD resistant to conventional therapy. While more information on the long-term consequences of infliximab therapy is needed, its short-term safety profile is acceptable. A cost-utility analysis of infliximab in treatment-resistant active CD suggests the incremental costs per additional quality-adjusted life year exceed traditional benchmarks for cost per QALY.

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ABBREVIATIONS

CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICER	Incremental Cost-Effectiveness Ratio
6MP	6-mercaptopurine
PDAI	Perianal Disease Activity Index
QALY	Quality-Adjusted Life Year
TNFa	Tumor Necrosis Factor Alpha
UC	Ulcerative Colitis

1 INTRODUCTION

1.1 Background

Crohn's disease (CD) is a chronic relapsing disorder of the gastrointestinal tract characterized by segmental and transmural inflammation. The symptoms and manifestations of CD are variable, but are largely dependent upon the site, severity and local complications of inflammation. Most patients experience abdominal pain and diarrhea, but other common symptoms include fever, malaise, weight loss, rectal bleeding and manifestations of malnutrition. Furthermore, a constellation of extra-intestinal manifestations of inflammatory bowel disease affecting the eyes, skin, joints and hepatobiliary system has been well-described. Although the inflammation of CD can affect any segment of the gastrointestinal tract, from mouth to anus, it is limited to the colon in approximately 25 percent of patients, the terminal ileum in 30 percent and both the terminal ileum and colon in 40 percent.[1] In only five percent does the disease involve the more proximal small bowel or the upper gastrointestinal tract. CD and ulcerative colitis (UC) are variants of inflammatory bowel disease (IBD), but differ with respect to their clinical manifestations, disease course and treatment alternatives. This review does not address the management of UC.

Prospective, population-based studies of CD in Western Europe and North America have derived estimates of annual incidence between three and 11 per 100,000[2]. Most population-based estimates of CD prevalence range from 50 to 150 per 100,000.[2] However, a recent study from Manitoba derived incidence and prevalence rates of 15 and 199 per 100,000 respectively, which are among the highest reported rates worldwide.[3]

Local complications of inflammatory Crohn's disease can include luminal stricture and the formation of fistulas. The latter are tracts that develop between the gastrointestinal mucosa and adjacent structures as a consequence of transmural inflammation. The lifetime risk of fistula formation among patients with CD is between 20 percent and 40 percent.[4] Fistulas are classified as internal if they penetrate adjacent organs (e.g. enteroenteric, gastrocolic, rectovaginal or enterovesical fistulas), or external if they emerge to skin (e.g. perianal, enterocutaneous or colocutaneous fistulas). Although many fistulas are asymptomatic, some incur substantial morbidity and can lead to the formation of abscesses.

In the majority of cases, CD follows a chronic relapsing course with periods of relative quiescence (remission) and periods of active disease.[5] Although the disorder is heterogeneous, patients with CD can be categorized by disease location, severity, and behaviour (inflammatory, fibrostenotic, fistulizing).[1] Management strategies can be broadly dichotomized to those which treat acute, active disease and those which maintain response and prevent relapse among patients in remission. None of the available treatments is curative and many are associated with troublesome adverse effects. For patients with acute, mild to moderately active disease, first-line therapeutic options include sulfasalazine, mesalamine, budesonide and oral antibiotics.[6] Other immunomodulatory therapies for refractory or severe disease include systemic corticosteroids, azathioprine/6-mercaptopurine, methotrexate and cyclosporine.[6] However, none of these is uniformly effective and each can cause serious side effects. In particular, the use of corticosteroids has been associated with devastating adverse effects, including osteoporosis and avascular osteonecrosis. There are few published data that characterize current practice or

identify variation in practice for the management of CD in Canada. However, a recent practitioner survey identified heterogeneity among experts with respect to their use of immunosuppressive therapy for refractory patients, with variable thresholds for use of azathioprine.[7]

The management of patients with active disease who fail standard medical therapy is challenging. Half of patients with CD require surgery over their lifetime for refractory or complicated disease. However, even ostensibly curative surgical resections are associated with endoscopic disease relapse in up to 30 percent within one year.[8] Post-operative treatment with mesalamine or azathioprine may reduce the rate of symptomatic and endoscopic relapse.[9-12]

Medical strategies to maintain medically-induced remission of CD include no treatment, long-term oral mesalamine, and chronic immunosuppressive therapy with azathioprine (or 6-mercaptopurine) or methotrexate. The approach to such patients is often individualized to reflect the combined influences of: (1) patient preference; (2) physician preference and familiarity; (3) treatment history (response and adverse effects); and (4) surgical candidacy. The latter can incorporate comorbidity, anaesthetic risk, disease distribution, prior surgical procedures and available surgical expertise.

Medical alternatives for the management of fistulas associated with CD include antibiotics and immunosuppressive agents such as 6-mercaptopurine, azathioprine, methotrexate and cyclosporine. The use of 6-mercaptopurine is supported by one controlled clinical trial, but not as a primary study endpoint.[13] The use of other agents is based on uncontrolled data and anecdotal clinical experience.[4] Many patients with fistulas require surgical intervention.

There are no published data that define the societal economic burden of Crohn's disease in Canada. However, a Markov model from Olmsted County Minnesota identified average lifetime direct medical costs of US $125,000 per patient and observed that a small proportion of patients consumed a disproportionate share of the overall resource pool.[14] In this model, and in a recent U.S. review, the major cost drivers among patients with CD were medications and in-patient medical/surgical care.[14;15] These results are consistent with earlier studies by Hay et al, in which surgery and hospitalization accounted for 70 percent of the total costs, and 2 percent of patients with CD incurred 36 percent of the total charges.[16;17] A more recent analysis of a U.S. integrated claims database revealed average annual charges of US $12,417 for patients with CD, with three-fold higher charges in the subgroup that had required hospitalization.[18] At a Canadian centre, direct medical costs for hospital admissions for medical and surgical treatment of CD have been estimated to be C $2571 and C $3427, respectively, per admission.[19] It bears emphasis that the impact of CD on morbidity and productivity may also be substantial. A recent U.S. study estimated the indirect costs of CD to be only 15 percent tof the direct costs.[15] However, a Swedish study suggested that the indirect costs of CD are at least double the direct medical costs.[20] Thus, interventions that improve the outcomes of resource-intensive patient subgroups could yield a significant societal benefit.

1.2 Technology Overview

Improved understanding of the complex inflammatory cascade and intestinal immune responses has allowed the development of targeted immunomodulatory therapies for CD and other chronic inflammatory disorders. Infliximab (Remicade™, Centocor, Malvern PA) remains the only such compound to win full regulatory approval in Europe and the North America. Previously known as cA2, infliximab was developed for the treatment of chronic inflammatory disorders, including rheumatoid arthritis and IBD. Infliximab received its Notice of Compliance from the Health Protection Branch of Health Canada on June 6, 2001 in the therapeutic class of Biologic Disease Modifiers. Remicade™ is marketed and distributed in Canada by Schering Canada Inc. (Pointe Claire QC). Infliximab is indicated for: (1) the treatment of moderate to severe CD to reduce signs and symptoms in patients who have an inadequate response to conventional therapy; and (2) the treatment of patients with fistulizing CD to reduce the number of draining enterocutaneous fistulas. Although clinical trials have evaluated the role of repeated infliximab infusions for maintaining remission of CD, this indication has not been approved in Canada.

Tumor necrosis factor-alpha (TNFa) is an endogenous pro-inflammatory cytokine which is thought to play an important role in the pathogenesis of CD. Several investigators have identified increased levels of TNFa in the stool[21] and intestinal mucosa[22-25] of patients with CD. TNFa is a T helper 1 (Th1) cytokine that exerts a number of biological effects, including stimulating IL1 and IL6 production, adhesion molecule expression and fibroblast proliferation.[26] In animal models, blocking TNFa has been shown to attenuate granuloma formation.[27]

Infliximab is a chimeric IgG-kappa monoclonal antibody to TNFa. A murine variable region is joined to a human IgG_1 constant region, such that the molecule is approximately 75 percent human in origin.[28] Infliximab has been demonstrated to bind both soluble and transmembrane TNFa and to activate complement, leading to lysis of activated CD4-positive T cells and macrophages.[29;30] Other approaches to attenuate TNF activity are under investigation for treatment of IBD, but are not addressed in this report. These include the recombinant soluble TNF receptor etanercept (Enbrel™), the humanised monoclonal antibody CDP571, the anti-sense oligonucleotide ISIS30782 and thalidomide, which inhibits TNF production.[31-36]

Infliximab is distributed commercially as a lyophilized powder for reconstitution and intravenous administration. Infusions are delivered over two to three hours through an in-line low-protein-binding filter, and require the supervision of a nurse. In Ontario, only hospital out-patient centres provide infliximab infusions. However, alternative settings, such as private offices and home-care have been evaluated in other jurisdictions.[37;38]

Recent clinical trials have evaluated the efficacy of infliximab in the treatment of inflammatory and fistulizing CD. The use of infliximab has been endorsed in recent guidelines released by the American College of Gastroenterology and the Canadian Association of Gastroenterology.[6;39] However, the cost of infliximab (and other biologic agents) is substantial. This review attempts to balance the clinical benefit of infliximab against its potential toxicity and economic impact in the treatment of CD. The available clinical and economic evidence supporting the use of infliximab in inflammatory and fistulizing CD are reviewed and summarized. However, a primary economic analysis is presented only for its use in treatment-refractory inflammatory CD.

2 OBJECTIVES

- To perform a systematic review of published and unpublished clinical studies to define and quantify, via meta-analysis if appropriate, the efficacy and effectiveness of infliximab in the treatment of CD.
- To identify and quantify any adverse events, both acute and chronic, associated with infliximab therapy for CD.
- To define the role of infliximab in the overall management of CD.
- To identify subgroups of patients, if any, where infliximab may offer preferential benefit in the management of CD.
- To perform a systematic review of published and unpublished economic analyses of infliximab in the treatment of CD.
- To construct an economic evaluation model (cost-utility analysis) to define and quantify the clinical and economic impact of introducing infliximab in the management of CD in a Canadian practice setting.

3 CLINICAL EFFECTIVENESS REVIEW

3.1 Methods

3.1.1 Literature search strategy

Six electronic reference databases were searched sequentially to identify published studies of infliximab for the treatment of CD. MEDLINE was searched first, then EMBASE, followed by Current Contents, CINAHL, HealthSTAR TOXLINE, and the Cochrane Database. A parallel search of databases that provide information on the pharmaceutical industry was undertaken including: Drug Info Full Text; Pharmaceutical & Health Care Industry News; PharmaProjects; and Pharmaceutical News Index. All databases were searched only from January 1990 to May 2001, inclusive, as infliximab was developed in the mid 1990's. Search terms included "Crohn's disease", "infliximab", Remicade™", "anti-TNF-alpha monoclonal antibody", "cA2" and "antibody to TNF-alpha". The full search strategy and results are provided in Appendix A. Although the electronic database search was last updated in May 2001, major clinical gastroenterology journals were hand-searched through August 2001 to identify recent publications.

Abstracts listings from the following major scientific meetings were also searched using a similar strategy: the American College of Gastroenterology (1995 to 2000), the Canadian Digestive Disease Week (1996 to 2001) and Digestive Diseases Week (1995 to 2001). The corresponding authors of all relevant abstracts were contacted by email or post to request full manuscripts and information on publication status. A follow-up letter was sent to authors who did not respond within three weeks. If the data provided in full publications were incomplete, principal investigators were contacted to provide clarification and/or additional outcomes.

Unpublished efficacy and effectiveness data were also sought from pharmaceutical companies involved in the production and distribution of infliximab: Schering Canada Inc. (Pointe-Claire PQ); Schering-Plough Inc. (Kenilworth NJ); and Centocor Inc. (Malvern PA). The websites of relevant international government agencies were searched, and selected agencies were contacted directly for information (Appendix A).

The titles and/or abstract listings of all citations were screened for their potential relevance to the review by a single reviewer (NB). Full offprints of all such studies were retrieved, and their reference lists scanned for additional relevant citations.

3.1.2 Inclusion criteria

All relevant citations were assessed for inclusion in the review by two independent reviewers, according to predefined inclusion criteria (JKM, NB). The review of clinical effectiveness considered all citations which satisfied the following criteria: (1) randomized; (2) controlled; (3) adult subjects; (4) infliximab in at least one study arm; (5) treatment of fistulizing or treatment-resistant CD; (6) clinical endpoints; and (7) English language. Studies of both acute treatment and maintenance of remission were eligible. Unpublished reports were accepted if sufficiently detailed. However, evaluations of other inhibitors of TNFa were excluded. Where multiple studies described the same population and endpoint, only the report with the strongest design

and/or largest sample size was included in the primary review. However any additional outcomes disclosed in such secondary reports were reviewed.

Non-randomized case series were considered for review only if they evaluated clinical outcomes of infliximab treatment in at least 100 consecutive patients with fistulizing or active CD, and were reported in English. Both published and unpublished reports were included.

In reviewing adverse events, data available from eligible clinical trials were supplemented by data from eligible and non-eligible case series and cohort studies, federal agencies, and industry to permit identification of rare events. The reporting biases inherent to uncontrolled case reports are acknowledged.

3.1.3 Data extraction

From each efficacy trial, the following data were extracted by two independent reviewers (JKM, NB): number and location of study centres; source of funding; inclusion and exclusion criteria; baseline comparability of treatment groups; treatment regimens evaluated; method of randomization; use of blinding; primary and secondary outcomes; description of screen failures, dropouts and withdrawals; and adverse events. The original authors' definitions of clinical endpoints (e.g. improvement, remission, fistula closure) were adopted.

The Jadad score was used to assess the methodologic rigour of randomized efficacy trials.[40] This score assesses the use and appropriateness of randomization, the use and appropriateness of blinding, and the description of dropouts and withdrawals (Appendix B). Two reviewers independently assigned a score to each trial, with discrepancies resolved by consensus.

3.2 Results

3.2.1 Quantity and quality of research available

The review of electronic databases and conference proceedings identified 274 potentially relevant citations as follows: MEDLINE 126 citations; EMBASE 34 citations; Current Contents 53 citations; TOXLINE seven citations; and CINHAL four citations. The search of pharmaceutical industry databases yielded four citations, and the search of abstract listings generated 50 additional citations. Of 19 letters sent to authors of published abstracts, eight responses were received. None provided new data or identified new publications.

After duplicate entries were removed, 228 unique citations remained (Appendix C). From review of abstracts, 20 were deemed ineligible because they reported data on another monoclonal antibody to TNFa (e.g. CDP571), a specific patient subpopulation (e.g. children or pregnant women) or a disorder other than CD. A further 151 citations referred to reviews, editorials, letters or guidelines, and were also excluded. No citations were excluded on the basis of their language of publication. The remaining 57 citations appeared to report new clinical data related to the use of infliximab in adults with CD, and were retrieved.

Of the 57 papers reviewed in full, six reported results of randomized controlled trials. Of these, two reported secondary endpoints from another of the clinical trials.[41;42] Thus, the literature

search identified only four eligible randomized controlled trials that evaluated the efficacy of infliximab for treatment of CD.[43-46] The major design characteristics of these studies are summarized in Table 1. The Jadad scores for the three trials published as full papers ranged from three to four (maximum five).[47] The score assigned to the trial published only in abstract form was two, in part because few methodologic details were provided.

Table 1: Summary of Clinical Efficacy Trial Designs

	Present et al[44]	Targan et al[46]	Rutgeerts et al[45]	ACCENT1[43]
Disease Category	Fistulizing CD (active treatment)	Treatment-resistant CD (active treatment)	Treatment-resistant CD (maintenance treatment)	Treatment-resistant CD (active and maintenance)
Centre Locations (n)	North America, Europe (12)	North America, Europe (18)	North America, Europe (17)	North America, Europe, Israel (55)
Intervention (n)	Infliximab 5mg/kg iv (31); Infliximab 10mg/kg iv (32) at Weeks 0,2,6	Infliximab 5mg/kg iv (27); Infliximab 10mg/kg iv (28); Infliximab 20mg/kg iv (28) at Week 0 (open-label 10mg/kg iv retreatment option)	Infliximab 10mg/kg iv at Weeks 12, 20, 28, 36 (37)	Infliximab 5mg/kg iv at Weeks 0, 2, 6, 14, 22, 30 (113); Infliximab 5mg/kg iv at Weeks 0, 2, 6 then 10mg/kg iv at Weeks 14, 22, 30 (112)
Comparator (n)	Matched placebos iv (31)	Matched placebo iv (25)	Matched placebos iv (36)	Infliximab 5mg/kg iv at Week 0, then matched placebos iv (110)
Primary Outcome	Partial closure (50% reduction in draining fistulas on two consecutive study visits)	Clinical response at Week 4 (drop in CDAI>70)	Sustained clinical response at Week 44 (drop in CDAI>70)	Time to loss of clinical response from Week 2 (drop lin CDAI>70)
Secondary Outcomes	• Complete closure (absence of draining fistulas on two consecutive study visits) • Time to response • Duration of response • Change in CDAI • Change in PDAI	• Remission (CDAI<150) • Duration of response • Change in CDAI • IBDQ scores • C-reactive protein levels • Autoimmune markers • Adverse events	• Remission (CDAI<150) • Withdrawals for treatment failure • Change in CDAI • IBDQ scores • C-reactive protein levels	• Clinical response (drop in CDAI>70) • Clinical remission (CDAI<150) • Corticosteroid use • IBDQ scores
Outcome Assessments	Weeks 0, 2, 6, 10, 14, 18, 26, 34	Weeks 0, 4, 8, 12	Weeks 12, 16, 20, 24, 28, 32, 36, 40, 44	Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, 62, 70, 78, 102
Jadad Score[37] (Maximum 5)	4	4	3	2

- One study evaluated infliximab for the treatment of fistulizing CD,[44] but no other controlled trial for this indication has been reported.

- A second study evaluated infliximab as acute therapy of treatment-refractory inflammatory CD[46]

- A third study evaluated the effect of maintenance therapy with repeated infliximab infusions in maintaining the treatment response among patients who had responded to treatment in the previous study.[45]

- The fourth study is ongoing and has not been published in full, although interim results were presented recently in abstract form at a scientific meeting.[43] This trial evaluates patients with

treatment-refractory CD with respect to their acute treatment response and their response to maintenance therapy. Although the study population and outcomes resemble those used in previous studies,[45;46] the protocol differs with respect to dose regimens and timing of responses, and incomplete outcome data have been released. Neither the industry sponsors (Centocor Inc., Malvern PA; Schering Inc., Kenilworth NJ, Schering Canada Inc., Pointe-Claire QC) nor the principal investigator was able to provide these data upon request.

The available literature was considered too heterogeneous in design for quantitative pooling in a meta-analysis because of variation in patient population (acute disease versus maintenance of disease remission), dosing schedules and timing of outcome assessments (Table 1). Thus, a qualitative review and summary of the available clinical effectiveness studies are presented.

Of the 51 citations that reported clinical data from non-randomized studies, 13 described cohorts larger than 100 subjects.[38;48-59] The remaining 38 citations were also reviewed for reports of rare or unusual adverse events. In addition, reports summarizing pooled, cumulative efficacy and safety data from all clinical trials of infliximab were received from Schering Canada.[60] Citations which were retrieved but not considered relevant to the review of clinical effectiveness are listed in Appendix D.

3.2.2 Assessment of clinical effectiveness

a) Fistulizing crohn's disease

Present et al paper

For the treatment of fistulizing CD, only one controlled study has been reported in the literature.[44] This multicentre, randomized, placebo-controlled, double-blind trial enrolled subjects at 12 centres in the United States and Europe. The published manuscript did not reveal the source of funding. The investigators screened 120 patients and enrolled 94 adult subjects with CD and draining enterocutaneous abdominal or perianal fistulas of at least three months' duration. Subjects were required to be on stable doses of 5-aminosalicylates (four weeks), corticosteroids (three weeks), methotrexate (three months) or azathioprine/6-mercaptopurine (eight weeks). Subjects were excluded if they were receiving cyclosporine or had a stricture, abscess or new stoma (six months).

Randomization to one of three treatment groups (1:1:1, method not specified) was stratified by study centre and by the number of fistulas. Two active treatment groups received intravenous infusions of infliximab 5 mg/kg (n=31) or 10 mg/kg (n=32) at Weeks 0, 2 and 6. The rationale for this infusion regimen was not provided. A control group (n=31) received three infusions of an albumin solution as matched placebo. Patients were assessed at Weeks 2, 6, 10, 14 and 18. The primary outcome was the proportion of subjects achieving a 50 percent or greater reduction in the number of draining fistulas (defined as no drainage despite gentle finger compression) at two or more consecutive study visits. Subjects who required surgery or a change in medication, or were lost to follow-up, were deemed treatment failures (intention-to-treat analysis). Secondary outcomes included: the proportion of patients achieving complete closure of all fistulas; the median time to response; the median duration of response; the mean change in Crohn's Disease Activity Index (CDAI)[61] and Perianal Disease Activity Index (PDAI);[62] and adverse events.

Treatment groups were similar with respect to age, weight, gender, duration and site of disease, number and location of fistulas, concurrent use of medication and baseline CDAI. The core study results are summarized below. Six subjects discontinued treatment after the second infusion due to lack of efficacy (three on placebo), withdrawal of consent (one on 5 mg/kg infliximab) and unspecified administrative reasons (one on placebo). By intention-to-treat analysis, both doses of infliximab were significantly superior to placebo in achieving a 50 percent or greater reduction in the number of draining fistulas (primary endpoint) and complete closure of all fistulas (secondary endpoint) (Table 2) dose response was observed between the groups treated with 5 mg/kg vs. 10 mg/kg of infliximab. Among infliximab-treated subjects who achieved the primary endpoint, the median time to onset of response was 14 days (range 14 to 42). CDAI scores differed significantly from placebo in the 5 mg/kg treatment group at Week 2 but not Week 18, and at neither time-point in the 10 mg/kg group. PDAI scores differed significantly from placebo in both treatment groups at Week 2, but only in the 5 mg/kg treatment group at Week 18.

Table 2: Results of Present Trial of Infliximab for Fistulizing Crohn's Disease

Study Arm:	50% Closure (Primary End Point)	Complete Closure Secondary End Point
Placebo	8/31 (26%)	4/31 (13%)
5mg/kg infliximab	21/31 (68%)[a]	17/31 (55%)[c]
10mg/kg infliximab	18/32 (56%)[b]	12/32 (38%)[d]
Combined infliximab	39/63 (62%)[a]	29/63 (46%)[c]

[a]p=0.002, [b]p=0.02, [c]p=0.001 and [d]p=0.04 vs. placebo

Other clinical studies

A large, multicentre trial labelled ACCENT II, which evaluates longer-term treatment with repeated doses of infliximab for fistulizing CD, is ongoing and should report its results in the next year. However, no interim data have been released for citation in this report.

The corroboration of clinical trial efficacy data with effectiveness results from large case series of patients treated for fistulizing CD is problematic, because of the variation in treatment schedules and reporting of clinical endpoints. However, Ricart et al noted improvement of fistulizing CD in 17/26 patients (65%) and a complete response, defined as closure of all fistulas, in 9/26 (35%).[55] Among 48 subjects, Cohen et al reported improvement of fistulas in 53% and complete closure in 26% at 7 weeks post infusion but did not provide the number of patients followed at each time-point and did not report response rates to serial infliximab infusions.[50] Furthermore, only a minority received the three-dose regimen studied by Present et al. Farrell reported that 70 and 55 per cent, respectively, of 33 patients treated for fistulizing CD experienced a 50 per cent or greater reduction in their PDAI at 2 and 18 weeks with the three-dose present regimen.[52] At the same time points, 32/50 (64%) and 24/50 (48%) of fistulas, respectively, had closed. In an update of this series, clinical benefit was described in 84 per cent of 72 patients.[56] De Vos et al reported significant improvements in CDAI and Inflammatory Bowel Disease Questionnaire (IBDQ) scores among 62 patients with fistulizing CD, but not rates of fistula closure.[51]

b) Treatment-resistant crohn's disease

Targan et al

A randomized, placebo-controlled trial of infliximab conducted at 18 centres in North America and Europe was reported by Targan et al.[46] The study was funded jointly by Centocor Inc. and the Food and Drug Administration's Orphan Products Development Division. Eligible participants were required to have moderate to severe CD, with CDAI scores between 220 and 400, despite treatment with mesalamine for eight weeks (stable dose for four weeks), corticosteroids for eight weeks (stable dose for two weeks), or 6-mercaptopurine/azathioprine for six months (stable dose for eight weeks). Exclusion criteria were: treatment with cyclosporine, methotrexate or experimental agents; symptomatic stenosis or stricture; subtotal or total colectomy; stoma; potential allergy to the study compound; and treatment with parenteral corticosteroids or corticotropin within four weeks. The investigators screened 203 patients to enrol 108 eligible subjects.

Subjects were randomized (1:1:1:1, method not specified) to a placebo arm (n=25) or one of three infliximab doses administered as a single intravenous infusion: 5 mg/kg (n=27); 10mg/kg (n=28) and 20 mg/kg (n=28). Controls received a 0.1% albumin solution indistinguishable from infliximab. Subjects were followed for 12 weeks after infusion. The primary study endpoint was clinical response at Week 4, defined as a decrease of at least 70 points in the CDAI. Non-responders at Week 4 were offered an open-label infusion of infliximab 10mg/kg and followed for an additional 12 weeks, and were categorized as non-responders for all subsequent end-points. Secondary endpoints included clinical response at Weeks 2 and 12, clinical remission (defined as a CDAI < 150) at Weeks 2, 4, and 12, IBDQ scores, adverse events, immunologic markers and change in C-reactive protein levels.

The treatment groups were similar at baseline with respect to their demographics, disease history and disease activity. Two patients randomized to infliximab did not receive the drug and were excluded from analysis, as the protocol had not specified an intention-to-treat analysis. All doses of infliximab were statistically superior to placebo in achieving the primary study endpoint (Table 3). No dose-response was observed, and the highest absolute response rates were seen in the 5 mg/kg group. The rates of clinical response at Week 4 were 65% for the combined infliximab groups, versus 16% for placebo ($p<0.001$). The rate of clinical remission at Week 4 was 33% in the combined infliximab groups, versus 4% in the placebo group ($p=0.005$). When followed to Week 12, the clinical response rate with infliximab remained higher than that with placebo (41% vs. 12%, $p=0.008$) but the difference in clinical remission rates was not statistically significant (24% vs. 8%, $p=0.31$). For secondary endpoints, infliximab-treated subjects differed significantly from the placebo-treated with respect to their mean increase in IBDQ scores (36 vs. 5, $p=0.001$), their mean decrease in C-reactive protein levels (16.0 vs. 3.9 mg/l, $p<0.001$) and their mean CDAI scores (201 vs. 271, $p<0.001$) at Week 4.

Table 3: Results of Targan Trial of Infliximab for Treatment-Resistant Crohn's Disease

Study Arm	Week 4 Response	Week 4 Remission	Week 12 Response	Week12 Remission
Placebo	4/25 (16%)	1/25 (4%)	3/25 (12%)	2/25 (8%)
5mg/kg infliximab	22/27 (81%)	n/r	13/27 (48%)	8/27 (30%)
10mg/kg infliximab	14/28 (50%)	n/r	8/28 (29%)	5/28 (18%)
20 mg/kg infliximab	18/28 (64%)	n/r	13/28 (46%)	7/28 (25%)
Combined infliximab	54/83 (65%)[a]	27/83 (33%)[b]	34/83 (41%)[c]	20/83 (24%)[d]

n/r=Not reported, [a]$p<0.001$, [b]$p=0.005$, [c]$p=0.008$ and [d]$p=0.31$ vs. placebo

Forty-eight subjects who did not respond to the study medication at Week 4 chose to receive an open-label infusion of infliximab at four weeks. Among 19 who had initially received placebo, the response and remission rates after 12 weeks were 58% and 47%, respectively. Among 29 who had initially received infliximab, the response and remission rates were lower, at 34% and 17%, respectively.

Endoscopic and histologic healing were assessed and reported separately in the 30 study subjects who were enrolled at European centres in this trial.[41] Mean endoscopic activity, as measured by the Crohn's Disease Endoscopic Index of Severity (CDEIS),[63] improved significantly (from 13.0 to 5.3, $p<0.001$) in subjects treated with infliximab (n=22), but not in those treated with placebo (n=8). Mean histology scores also improved significantly in infliximab-treated subjects, but not in those treated with placebo.

Rutgeerts et al

Subjects who responded to therapy in the trial reported by Targan et al were invited to participate in a study extension evaluating the effect of repeated doses of infliximab in maintaining treatment effect.[45] Enrolment in the maintenance phase was offered to subjects who had achieved a clinical response at eight weeks after treatment with either the original study medication (infliximab or placebo) or an open-label infliximab infusion. By necessity, these subjects had to have satisfied the initial inclusion and exclusion criteria of the acute-treatment study.

Participants were randomized (1:1) to one of two treatment groups: (1) four intravenous doses of infliximab 10mg/kg at eight week intervals; or (2) four intravenous infusions of a matched placebo. The first dose of study medication was given four weeks after the clinical response to acute therapy was assessed, or 12 weeks from the last dose of medication. Doses of 6-mercaptopurine/azathioprine, sulfasalazine and mesalamine were kept constant throughout the study period. Tapering of oral corticosteroids was permitted, but increasing the dose above the baseline was not.

Subjects were assessed at 4-week intervals up to Week 48. Clinical outcomes included the proportion of subjects maintaining a clinical response (defined as a drop in CDAI of at least 70 points from week 0), the proportion in clinical remission (defined as a CDAI < 150), and the proportion discontinuing therapy for lack of efficacy. Secondary endpoints included median

values of CDAI, IBDQ and C-reactive protein levels. All subjects who underwent surgery or received medication regimens excluded by the study protocol were considered treatment failures.

Seventy-three subjects were randomized to continued treatment with placebo (n=36) or infliximab (n=37). Four of these had responded to an initial infusion with placebo, while the remainder had responded to a blinded or open-label infusion of infliximab. The treatment groups were similar, although more patients randomized to active therapy were female (59.5% vs. 36.1%, p=0.053). Treatment was discontinued in 24 subjects due to lack of efficacy (12 on placebo, 4 on infliximab), adverse events (six on infliximab), withdrawal of consent (one on placebo) and non-compliance (one on placebo). The primary analysis was by intention-to-treat.

The primary study results are summarized below in Table 4. The proportion of subjects who maintained their clinical response at Week 44 was numerically higher among those receiving infliximab maintenance but this difference did not achieve statistical significance. Similar comparisons at interval time points achieved significance only at Week 36 (72% vs. 44%, p=0.018) but no significant threshold adjustment for multiple comparisons was made. The proportion of subjects in clinical remission at Week 44 was significantly higher in the infliximab group. Numeric response and remission rates at other time points were not reported, but were depicted graphically in the publication. Similarly, no subgroup analyses of subjects who entered the study in clinical remission (as opposed to clinical response) were provided. The median time to loss or response was 37 weeks with placebo, vs. more than 48 weeks with infliximab (i.e. most subjects continued in clinical response at Week 48)

Table 4: Results of Rutgeerts Trial of Infliximab to Maintain Response in Treatment-Resistant Crohn's Disease

Study Arm	Week 44 Response	Week 44 Remission
Placebo	37%	20%
Infliximab	62%[a]	44%[b]

[a]p=0.16 and [b]p=0.013 vs. placebo

c) ACCENT1 trial

A large randomized double-blind multi-centre trial evaluating acute and maintenance therapy with infliximab in patients with moderately to severely active treatment-resistant CD is underway at over 40 centres in North America and Europe. This ongoing trial has not been published, although selected preliminary data have been reported in abstract form.[43] The source of funding was not reported. Among the 573 subjects enrolled, the median baseline CDAI score was 297 (range 193 to 488). Sixty-two per cent were receiving corticosteroids and 29 per cent were receiving other immunomodulatory treatments. All subjects were given an infusion of infliximab 5mg/kg at week 0. Those who responded at Week 2 (defined as a drop of at least 70 points in the CDAI to less than 75% of baseline) were randomized (1:1:1) to one of three treatment groups: (1) infliximab infusions 5mg/kg at weeks 2 and 6 then every 8 weeks; (2) infliximab infusions 5mg/kg at weeks 2 and 6 then 10mg/kg every 8 weeks; or (3) placebo

infusions at weeks 2 and 6 then every 8 weeks. The trial will continue to 102 weeks. However, interim results at Week 30 have been reported and are summarized below in Table 5.

Table 5: Interim Results of ACCENT1 Trial of Infliximab for Treatment-Resistant Crohn's Disease

Study Arm:	Week 10 Response	Week 30 Response	Week 30 Remission	Week 30 Remission and Off Steriods
Single-Dose	58/110 (53%)	30/110 (27%)	23/110 (21%)	12/110 (11%)
Low-Dose Maintenance	n/r	58/113 (51%)[b]	44/113 (39%)[c]	35/113 (31%)[c]
High-Dose Maintenance	n/r	66/112 (59%)[b]	50/112 (45%)[c]	41/112 (37%)[c]
Combined Maintenance	146/225 (65%)[a]	124/225 (55%)[d]	94/225 (42%)[d]	76/225 (34%)[d]

(N/R=not reported, [a]$p<0.05$, [b]$p<0.001$, [c]$p<0.01$ or [d]p not reported vs. single-dose)

No significant difference between the maintenance regimens was observed. However both were significantly better than the single–dose regimen with respect to clinical response rate at Week 10. At Week 30, both maintenance regimens were significantly superior to single-dose infliximab with respect to: (1) the proportion of subjects in clinical response, clinical remission and clinical remission and off steroids; (2) the median steroid dose; and (3) the median increase in IBDQ score. Data from other time points and for other end points were not reported.

d) Adverse effects

General

Table 6, which summarizes adverse events experienced by more than 10 per cent of subjects in controlled clinical trials of infliximab for treatment of CD, is presented below.[60] Differences in event rates between infliximab and placebo are confounded by the longer follow-up of infliximab-treated subjects in the trials. The reported incidence of adverse events was broadly similar to those experienced in clinical trials of infliximab for treatment of rheumatoid arthritis.[60] In CD trials, serious adverse events were reported among 13% of infliximab-treated subjects vs. 4% of placebo-treated subjects. No deaths occurred.

Table 6: Summary of Adverse Events Reported in Clinical Trials of Infliximab for Crohn's Disease

	Placebo	Infliximab
Total patient treated	56	199
Mean weeks of follow-up	14.7	27.0
One or more adverse event	35 (62.5%)	168 (84.4%)
WHOART[a] preferred term:		
Upper respiratory tract infection	5 (8.9%)	32 (16.1%)
Headache	12 (21.4%)	45 (22.6%)
Nausea	2 (3.6%)	33 (16.6%)
Abdominal pain	2 (3.6%)	24 (12.1%)
Fever	4 (7.1%)	21 (10.6%)
Fatigue	3 (5.4%)	21 (10.6%)
Pharyngitis	3 (5.4%)	17 (8.5%)
Pain	3 (5.4%)	17 (8.5%)
Vomiting	0 (0.0%)	17 (8.5%)
Dizziness	5 (8.9%)	16 (8.0%)
Bronchitis	1 (1.8%)	14 (7.0%)
Rash	3 (5.4%)	12 (6.0%)
Rhinitis	2 (3.6%)	12 (6.0%)
Chest pain	3 (5.4%)	11 (5.5%)
Back pain	2 (3.6%)	10 (5.0%)
Sinusitis	1 (1.8%)	10 (5.0%)
Purities	1 (1.8%)	10 (5.0%)
Cough	0 (0.0%)	10 (5.0%)

[a]World Health Organization Adverse Reaction Terminology

Acute infusion reactions

In clinical trials of infliximab, infusion reactions have been defined as adverse events which occurred during an infusion or within two hours after an infusion.[60] Present et al reported infusion reactions characterized as dizziness, headache, low-grade fever, chest pain or flushing in four of 63 subjects (6%)[44] Targan et al reported no adverse events during first infusions for treatment-resistant CD, but described transient chest pain, dyspnea or nausea that required discontinuation of the second infusion in 2 of 29 subjects (7%).[46] In the re-treatment phase of this study, Rutgeerts et al noted reversible dyspnea during an infusion in one of 37 subjects (2.7%).[45] Across all published trials of infliximab for treatment of CD and rheumatoid arthritis, infusion reactions have been associated with 4.8% of infliximab infusions (vs. 2.1% of placebo infusions) and have led 1.9% of patients to discontinue treatment.[60] Most infusion reactions are mild to moderate, but three serious, nonfatal reactions among patients treated for CD were reported. These were reported as: hypotension/dyspnea; hypotension/chest pain/dyspnea/palpitations; and dyspnea/flushing/nausea. All resolved within two hours, and all led to discontinuation of treatment. Preliminary results from the ACCENT1 trial have noted infusion reactions in 5.5% of subjects receiving infliximab (of which 1.0% were "serious") vs. 3.2% of subjects given placebo infusions.[43]

Similar rates of infusion reaction have been reported in four large post-marketing case series of 100 or more patients. Farrell et al reported acute infusion reactions in 7.0% of 100 consecutive patients treated at their center.[52] In a summary of 348 infusions given to 129 patients, Cohen et al described adverse events with 5.4% and 5.9% of initial infusions for luminal and fistulizing CD, respectively, and 8.6% of second infusions.[50] Similarly, Ricart et al observed acute reactions in association with 21 of 234 infusions (9.0%) given to 100 patients, of which 2 were severe.[55] No information on infusion reactions was reported by De Vos et al, in their summary of 146 treated patients.[51] No deaths were described in any of these reports.

Human anti-chimeric antibodies

As a partly foreign protein, infliximab can induce a host immune response including the production of antibodies to the drug, called human anti-chimeric antibodies (HACA). High titres of HACA have been suggested to increase the risk of subsequent infusion reactions and may attenuate the effectiveness of subsequent infliximab doses.[64;65] HACA were detected in only 6 of 101 subjects treated with infliximab by Targan et al, but residual infliximab in two-thirds of serum samples may have interfered with the assay.[46] In the re-treatment extension of this study, HACA were found in seven of 47 subjects whose serum contained no infliximab.[45] In the Present trial, HACA were found in three of 79 such subjects.[44] HACA assay results from the ACCENT1 study have not been reported. HACA may develop less often among subjects receiving concomitant immunosuppressive therapy.[65] A randomized controlled trial in 40 subjects suggested that pre-treatment with intravenous hydrocortisone reduces the incidence of HACA,[65] but this awaits confirmation and is not yet standard practice.

Autoimmune disorders

Among the 161 subjects treated acutely with infliximab in studies reported by Targan and Present, 11 (6.8%) developed antibodies *de novo* to double-stranded DNA.[44;46] Two additional patients developed antibodies to double-stranded DNA in Rutgeert's re-treatment extension.[45] One subject also developed a lupus arthritis that responded to prednisone. In a series of 116 patients, the prevalence of low-titre anti-nuclear antibodies (ANA) increased from 6.9% before treatment with infliximab to 50.0% following treatment.[58] The clinical significance of these antibodies remains to be defined.

Malignancy

Eighteen of 771 patients (2.3%) treated with infliximab in controlled clinical trials for CD and rheumatoid arthritis were diagnosed with a malignancy during the trial or within three years of follow-up, compared to two of 192 subjects (1.0%) treated with placebo.[60] Five malignancies among infliximab-treated patients were lymphomas, and one additional case of NK-cell lymphoma in the ACCENT1 trial for CD has since been reported.[66] The observed incidence of lymphoma exceeds the expected rate among population controls,[60] but not necessarily controls with CD. There are conflicting data on the baseline risk of lymphoproliferative disorders and other malignancies in patients with CD.[67;68] Accordingly, the component of risk of lymphoma attributable to infliximab therapy remains controversial.[69]

Infection

As of January 3, 2001 33 cases of tuberculosis among the 115,000 patients treated with infliximab worldwide had been reported to the manufacturer.[70] These included 13 disseminated infections and three deaths, of which two were attributed to tuberculosis. The majority of cases

(20 of 33) occurred outside North America. Both the manufacturer and current Canadian guidelines now suggest that patients be evaluated for evidence of latent or active tuberculosis prior to treatment with infliximab.[39;70] However, no Canadian guidelines for tuberculosis screening in this setting have been published.

Upper respiratory tract infections occurred with increased frequency among infliximab-treated patients across clinical trials, relative to those treated with placebo (see Table 6). Other acute infections associated with infliximab therapy in sporadic case reports have included three cases of invasive pulmonary aspergillosis.[71] However the incremental risk of such events is uncertain and their cause-effect relationship to drug treatment is undefined.

Intestinal stricture

In the European subset of subjects participating in the Targan trial, two of 22 subjects treated with infliximab developed strictures at sites of previous ulceration (one with stenosis). De novo strictures have also been described in uncontrolled case series of infliximab therapy.[72;73] However the absence of controls and potential reporting bias make these data difficult to interpret. Current Canadian guidelines suggest that infliximab be administered with caution to patients with intestinal obstructive symptoms or documented intestinal narrowing.[39]

e) Subgroup effects

Subgroup effects observed in clinical trials of infliximab should be considered speculative, as all represent *post hoc* analyses and no trial has stratified subjects by putative predictors of response. In the study by Present of fistulizing CD, treatment effects remained qualitatively similar across demographic subgroups.[42] The effect was less strong among females (OR 2.0, p=0.28) than among males (OR 13.3, p<0.001), but women experienced higher placebo response rates.[42] The effect was also less strong among users of 6MP/azathioprine (OR 1.8, p=0.46) than among non-users (OR 8.3, p=0.001). The treatment effect achieved statistical significance among subjects with a single fistula (OR 12.9, p=0.02) or with multiple fistulas at baseline (OR 3.8, p=0.03).

Targan et al did not report subgroup analyses from their study of treatment-resistant CD.[46] Rutgeerts et al observed that the rate of sustained response among infliximab-treated subjects was marginally higher if those subjects were also treated with 6MP/azathioprine (75% vs. 50%, p=0.17)[45] However, preliminary reports from the larger ACCENT1 trial described no significant difference in Week 30 remission rates among the infliximab-treated subjects receiving concomitant immunomodulatory therapy.[43] No other subgroup analyses from this trial have been released.

Ricart, Cohen and Farrell noted no significant predictors of clinical response in their published series of 100, 129 and 100 treated patients, respectively.[50;52;55] Other potential biochemical and demographic predictors of response are currently being studied.[49;53;54;59;74]

f) Outcome measures

The Crohn's Disease Activity Index (CDAI) is the conventional outcome used in clinical trials of treatments for CD, and was developed and revised in conjunction with the National Cooperative Crohn's Disease Study.[61;75] A point system is used to weight clinical, physical examination and laboratory parameters on a scale from 0 to 600 (Appendix E).[75] Various clinical trials have used

changes of 70 or 100 points to signify clinically-significant change in disease status.[33;76] The CDAI has been validated against clinicians' global impression; scores under 150 correlate with clinical remission, while those over 450 suggest severe disease.

The Perianal Disease Activity Index (PDAI) measures the severity of perianal CD using five elements rated on 5-point Likert scales.[62] This instrument correlates well with physician and patient global assessments of perianal disease but not with CDAI or other global measures of CD activity. It is also responsive to clinically-significant changes in perianal disease activity.

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a disease-specific instrument that measures health-related quality of life among patients with IBD.[77] The questionnaire contains 32 questions across four domains (bowel, systemic, social and emotional) and scores range from 32 to 224. The IBDQ has been shown to correlate well with disease activity, to be responsive to changes in disease status and to perform well whether self-administered or administered by interview.[78] A short version of the IBDQ has been developed and shown to correlate well with the longer instrument.[78]

The Crohn's Disease Endoscopic Index of Severity (CDEIS) is used to grade the severity of CD detected endoscopically.[63] The score sums endoscopic activity scores for five ileo-colonic segments: terminal ileum; right colon; transverse colon; sigmoid and left colon; and rectum. Each segment is graded using a point system that measures the presence of deep and superficial ulceration, the presence of ulcerated and non-ulcerated stenosis and the total surface area diseased and/or ulcerated. This score correlates well with the endoscopist's global appraisal of severity ($r=0.83$) and is responsive to clinically significant changes in endoscopic activity ($r=0.72$).[63]

3.3 Discussion of Results

Although the number of clinical trials of infliximab for which results are available is relatively small, qualitative review of this literature provides evidence supporting the efficacy of infliximab infusion for both fistulizing and treatment-resistant CD. In the case of fistulizing CD, Present et al demonstrated superiority of three serial infliximab infusions over placebo in achieving fistula closure. However, the rationale and requirement for three serial infusions, and the clinical relevance of the primary study endpoint (a 50% reduction in the number of fistulas that drain upon compression by the examiner on two consecutive visits) are unclear. A larger clinical trial in fistulizing CD is underway.[44]

For treatment-resistant inflammatory CD, Targan et al showed a single infliximab infusion to be superior to placebo in achieving clinical improvement and clinical remission after 4, 8 and 12 weeks.[46] A randomized maintenance-phase extension of this study demonstrated that repeat infusions of infliximab at eight-week intervals in initial responders were significantly superior to placebo in maintaining clinical remission to 44 weeks, with a non-significant trend to maintaining clinical response (defined as a 70-point improvement in CDAI with or without clinical remission).[45] Preliminary results from a fourth, much larger study have provided further evidence that serial infliximab infusions are superior to a single infusion in achieving clinical response and remission for up to 30 weeks.[6] Full results of this trial are awaited.

No consistent subgroup effects have been demonstrated in clinical trials of infliximab for CD. In addition, trials that have compared infliximab doses have established no clear dose response relationship. Certainly, no advantage to doses higher than 5 mg/kg has been demonstrated. Doses lower than 5 mg/kg have not been studied. As a result, the standard dose for infusion is 5 mg/kg.

The short-term tolerability of infliximab appears favourable, although 10 to 15 per cent of treated subjects appear to suffer adverse effects including respiratory tract infections, nausea and abdominal pain. Clinical trials and case series have described infusion reactions associated with three to seven percent of infusions, although these appear generally to be mild and respond to interrupting the infusion and/or treating with steroids, antihistamine and acetaminophen. Anaphylaxis has been reported but appears to be rare, and no infusion-related deaths have been reported. Preliminary evidence suggests that the development of HACA may increase the risk of future infusion reactions. As with many immunosuppressive medications, infliximab infusion also appears to increase the incidence of infection, particularly in the respiratory tract. Rare cases of pulmonary aspergillosis and 33 cases of tuberculosis (13 disseminated and three fatal) have been reported worldwide. Although the true frequency of such complications among treated patients in Canada remains unclear, both the manufacturer and Canadian guidelines recommend that physicians consider screening treatment candidates for latent tuberculosis.[39] Similarly, sporadic cases of *de novo* intestinal stricture following infliximab infusion have led guidelines to suggest that infliximab be administered with caution to patients with documented luminal narrowing. The chronic sequellae of short- and long-term infliximab treatment are even less certain, and observational data continue to accumulate. Sporadic malignancies including lymphomas have developed in patients treated with infusion, although the attributable risk remains undefined. Similarly, new autoimmune markers have been observed in treated patients, although their clinical significance is unclear.

In summary, infliximab infusion appears to be effective for the acute treatment of fistulizing and treatment-resistant CD, and for maintaining clinical response among the latter. The short-term toxicity of infliximab seems minimal, and infusion reactions are rarely severe. Further data on the long-term adverse effects of infliximab treatment, particularly long-term maintenance, are needed.

4 ECONOMIC ANALYSIS

4.1 Review of Economic Evaluations

4.1.1 Methods

a) Search strategy

All citations retrieved for the review of clinical effectiveness were also reviewed for relevance to the review of economic analyses. Additional searches were performed to identify other published and unpublished economic evaluations of infliximab for treatment of CD from 1990 to 2001. Published evaluations were identified through on-line searches of MEDLINE, EMBASE, Current Contents, CINAHL and HealthSTAR using the search terms "Crohn's disease", "infliximab" and "economics" (Appendix F). The Health Economics Evaluations Database (OHE-HEED, United Kingdom Office of Health Economics) and various health economic websites were also reviewed (Appendix F). The authors of relevant abstracts were contacted to request full manuscripts and information on their publication status. Schering Canada and Centocor Inc. were asked to provide additional, unpublished economic evaluations of infliximab for treatment of CD. Finally, international health economic institutes such as the United Kingdom's National Institute for Clinical Excellence (NICE) were contacted for further information and in-house reviews (Appendix F).

b) Inclusion criteria

All citations were assessed for potential relevance by a single reviewer (NB). Because of the small volume of literature, inclusion criteria were broad. All searches were constrained to the years 1990 to 2001, inclusive, and to English-language publications. Studies accepted for review were required to be original reports of primary economic analyses of infliximab in the treatment of CD. Eligible studies could have assumed any of the following designs: burden of illness, cost-minimization, cost-effectiveness, cost-utility and cost-benefit. Because of the small volume of literature available and to avoid publication bias, the review considered both published and unpublished evaluations.

c) Data extraction

Owing to significant design heterogeneity among the few efficacy studies retrieved, no attempt was made to extract data systematically, or to quantitatively pool their results. Rather, each report was summarized and reviewed qualitatively.

4.1.2 Results

a) Search results

Nine studies that examined economic aspects of infliximab treatment for CD were retrieved (see Appendix F). Of these, five were identified in the search strategy for review of clinical effectiveness. Only one of these was published in full in a peer-reviewed journal.[79] The remaining four studies had been presented at international meetings and were published in abstract form.[80-83] Four additional analyses were provided by Schering Canada.[84] These were unpublished economic evaluations prepared by industry for reimbursement submissions in Canada and Australia. Of the nine economic citations, six reported economic models,[79;83;84] two

were observational studies of resource utilization among patients treated with infliximab,[81;82] and one was a descriptive analysis of infusion-related costs relative to reimbursement (Appendix G).[80]

b) Fistulizing crohn's disease

American cost-utility analysis: Arseneau et al

To date, only one economic analysis of infliximab therapy for CD has appeared in a peer-reviewed journal. This model assumed the perspective of a third-party payer in the United States (U.S.) and used a Markov process to compare incremental cost-utility among four strategies for treating perianal fistulizing CD:[79] (1) treatment with 6MP/metronidazole alone (the comparator strategy); (2) primary treatment with infliximab, with 6MP/metronidazole for failures; (3) primary treatment with infliximab, with re-infusion of infliximab for failures; and (4) primary treatment with 6MP/metronidazole, with infliximab for failures. Surgical fistula repair was not modeled as an alternative for failures. Non-responders to model strategies were assigned to a "persistent fistula" state with fixed risk of abscess formation per cycle.

Markov processes for the four strategies segregated patients among 11, 14, 6 and 16 health states, respectively, over twelve one month cycles (time horizon one year). Both costs and benefits were discounted at an annual rate of 3 per cent. Transition probabilities were derived from a systematic literature review. The key model assumptions were stated explicitly. Consistent with clinical trials,[44] fistula improvement was defined as a 50% reduction in the number of draining fistulas. Direct medical costs were acquired from an existing administrative database using cost-charge ratios, and reported in 1999 U.S. dollars (US$1.00 = C$1.53). Utility weights for nine discrete health states were elicited from a convenience sample of 32 patients with CD using a standard gamble technique: fistula on 6MP/metronidazole or infliximab; improved fistula on 6MP/metronidazole or infliximab; perianal abscess; pancreatitis +/- fistula on 6MP/metronidazole; and paraesthesias +/- fistula on 6MP/metronidazole.

The base-case results of the model are summarized below in Table 7. Incremental cost-effectiveness ratios (ICER) were reported only in relation to Strategy 1.

Table 7: Base Case Results of Arseneau Cost Utilitiy Analysis of Infliximab for Fistulizing Crohn's Disease

Strategy:	QALY:	Cost:	ICER (vs. Strategy 1):
1	0.76	US$ 2,894	--
4	0.77	US$ 6,664	US$377,000/QALY
2	0.78	US$10,003	US$355,450/QALY
3	0.78	US$10,112	US$360,900/QALY

Throughout the one-way deterministic sensitivity analyses, the ICER of infliximab strategies relative to the comparator (Strategy 1) remained above US$100,000/QALY or revealed dominance of the comparator (lower cost with equal or greater effectiveness). The results were

highly sensitive to variation in the cost of infliximab: an 85% reduction in drug costs was required to reduce the ICER of Strategy 3 to US$54,050/QALY. A two-way sensitivity analysis testing simultaneous variation in utility weights for fistula health states found ICER to fall below US$150,000/QALY only at extreme values.

Canadian cost-minimization analysis: Schering

An unpublished cost minimization study of infliximab infusion for fistulizing CD was provided by Schering Canada.[84] The study was conducted and funded by the company, and assumed the perspective of a Canadian provincial ministry of health. Expert opinion from a four-member panel was used to estimate the proportionate reduction in key resource utilization that would occur if patients with fistulizing CD receive infliximab. Cost weights were assigned to each resource and to infliximab infusion; the latter included infusion-related supplies but not markup or dispensing fees. By comparing cost profiles with and without infliximab, the authors estimated net cost savings of C$106 per year with infliximab therapy. A stochastic sensitivity analysis, varying infliximab dose requirements, key resource reductions and surgery costs, found the impact of infliximab treatment to vary from an annual savings of C$4,214 to annual incremental costs of C$8,260.

c) Treatment-resistant crohn's disease:

American cost-utility analysis: Wong et al

A cost-utility analysis of infliximab therapy for treatment-resistant CD was presented in abstract form by Wong et al.[83] The source of funding was not disclosed. The authors applied four-week efficacy data from Targan et al (all dose groups combined)[46] to an existing natural history Markov model of CD[14] constructed from observational transitions in a cohort of patients with CD followed in Olmsted County for up to 24 years. Cost weights for Markov states were estimated from observed charges in the Olmsted cohort, with the perspective of a U.S. third-party payer. Utility weights were adapted from Gregor et al.[85] Both costs and benefits were discounted at an annual rate of three percent.

If infliximab-induced remission was assumed equivalent to surgical remission, treatment was found to be cost saving. If equivalent to medically-induced remission or "mild disease", the incremental cost effectiveness ratios of infliximab therapy were US$14,200/QALY and US$40,000 respectively. The authors concluded infliximab treatment to be cost-effective. However, few details of the model are provided in the published abstract and full publication is awaited.

Canadian cost-minimization analysis: Schering

An unpublished cost-minimization analysis of infliximab infusion for treatment-resistant CD was provided by Schering Canada.[84] The analysis was conducted for Canadian provincial health plans, and followed an approach identical to that used in the cost-minimization study of fistulizing CD with infliximab-associated changes in resource utilization estimated by an expert panel. Importantly, it was assumed in the base case that all subjects not given infliximab would require one hospitalization for surgery within one year (cost C$9,250), plus a 30-day non-surgical admission (cost C$20,430). The latter is at odds with U.S. data suggesting the average duration of hospitalization for CD is seven days.[15] The analysis concluded that infliximab treatment yielded net cost savings of C$12,336 per patient, largely from avoidance of in-patient

care. In stochastic sensitivity analysis, the estimated annual cost savings varied between C$4,130 and C$22,551 per patient.

Australian cost-utility analysis: Schering

An unpublished cost-utility analysis of infliximab infusion for treatment-resistant CD was also provided by Schering Canada.[84] The study was conducted by the company for Australian provincial health plans, and assumed the perspective of an Australian ministry of health. The primary analysis compared the costs and effects (in quality-adjusted life-years) over 48 weeks of treatment with a single infliximab infusion.

The model used two health states: response and non-response. Efficacy estimates were derived from the response rates (change in CDAI of ate least 70 points from baseline) among the subsets of patients reported by Targan et al and Rutgeerts et al who received a single infusion of infliximab 5 mg/kg or placebo.[45;46] For subjects whose data were missing or who received another infliximab infusion, the last reported response status was carried forward. Accordingly, only seven of 27 subjects in the treatment group had usable, complete response data to 48 weeks after a single infusion. It is unclear from the model report how placebo-associated 48-week response rates were derived, as Rutgeerts et al do not provide full follow-up of the cohort of 26 subjects randomized by Targan et al to initial treatment with placebo.[45;46]

Background costs of care for the response and non-response health states were obtained from an unpublished Australian cost-of-illness study, which estimated annual direct costs for patients with drug refractory and non-refractory CD. Infliximab infusion was assigned a cost of Aus$3,944, with drug and non-drug components. Utility weights for the two health states were adapted the standard gamble measurement of Gregor et al.[85] Thus, annualized estimates of cost and effects (QALY) were calculated for each trial subject as a weighted average of time spent in the response and non-response health states. Costs were expressed in 1998 Australian dollars (Aus$1.00 = C$0.80).

In the base-case, infliximab treatment was concluded to incur additional costs of Aus$3,011 and gain 0.0619 QALY for an incremental cost-effectiveness ratio of Aus$45,418/QALY (undiscounted). In a limited one- and two-way sensitivity analysis testing the impact of variation in background costs of care and health state utilities, the costs per QALY ranged from Aus$25,480 to Aus$63,483.

In a secondary analysis, the authors extended the model time horizon to 104 weeks (two years). Because the durability of treatment response is unknown the analysis tested three scenarios: that 25%, 50% and 75% of responders at 48 weeks lost their response by 76 weeks (the half-way point of the 56-week extension). Costs and benefits were discounted at an annual rate of 5%. The estimated costs per QALY over two years were Aus$21,932, Aus$26,296, and Aus$31,770, respectively, under assumptions of high, medium and low response durability. In a sensitivity analysis of the medium response durability scenario, the costs per QALY ranged from Aus$12,663 to Aus$36,587.

Australian cost-effectiveness analysis: Schering

An unpublished cost-effectiveness analysis of infliximab for treatment-resistant CD was provided by Schering Canada.[84] Like the previous study (4.1.2.3.3.), the analysis was performed

by the company for submission to Australian provincial health plans, and assumed the perspective of an Australian ministry of health. The primary outcomes of the analysis were the estimated incremental costs per clinical response and remission at 4 and 12 weeks associated with infliximab infusion. The assumed incremental rates of response (drop in CDAI of 70 points and more) and remission (CDAI less than 150) were those reported by Targan et al.[46]

However, the only incremental costs considered were those of the infliximab infusion (Aus$3,944 for drug and non-drug components).

The base-case analysis revealed incremental costs per clinical response of Aus$6,068 and Aus$10,957 after four and 12 weeks, respectively, and costs per clinical remission of Aus$8,965 and $17,929. In sensitivity analysis, the treatment effect was varied in accordance with the 95% confidence intervals of the differences in treatment effect from the clinical trial. The incremental cost per clinical response varied from Aus$4,993 to Aus$23,202, while the incremental cost per clinical remission varied from Aus$6,261 to Aus$98,610.

Other economic data

Two pre-post analyses have observed reductions in resource consumption in association with infliximab therapy.[81;82] In the year after infliximab infusion, Rubenstein et al observed significant reductions in use of endoscopy and emergency room visits compared to the year pre-treatment, with similar trends in use of surgery, outpatient clinics and radiology among 57 patients with inflammatory and fistulizing disease.[81] In a Belgian cohort, Rutgeerts et al estimated average direct medical costs of 4,566Euros per patient in the year prior to infusion, and 3,089Euros per patient in the year following infusion, excluding the cost of infliximab itself (1.00Euro = C$1.35).[82] However, without untreated control groups pre-post analyses cannot differentiate natural history from treatment effect.

Finally, a micro-costing review of 48 infusions given at an outpatient infusion centre in the U.S. concluded that reimbursement by insurers was adequate to cover infusion-related costs.[80]

4.1.3 Discussion of results

The economic analyses reviewed for this report have produced discrepant results. For the treatment of fistulizing CD, a fully-published Markov model found infliximab strategies to incur incremental costs per QALY well above accepted benchmarks.[79] In contrast, a cost-minimization analysis provided by industry concluded infliximab provides small net cost savings in treating patients with fistulizing CD.[84] However, this study used a relatively simple approach that relied largely on expert opinion and its results were relatively unstable in limited stochastic sensitivity analysis.

For treatment-resistant CD, the economic analyses reviewed yielded more consistently favourable results. A Markov model published only in abstract form concluded that the incremental cost per QALY of infliximab infusion (versus usual care) was US$14,200 if infliximab-induced remission resembled medical remission, and US$40,000 if it resembled mild disease (as defined in the Silverstein natural history model).[14] Full publication of this model and its assumptions is awaited. Two economic analyses prepared by industry for reimbursement applications in Australia revealed the costs of achieving a clinical response with infliximab

infusion were Aus$6,068 at 4 weeks and Aus$10,957 at 12 weeks, respectively. A cost utility analysis revealed that a single infliximab infusion yielded a favourable ICER of Aus$45,418/QALY over 48 weeks and that this estimate was robust to sensitivity analysis. Finally an industry-driven Canadian cost-minimization study similar to that reported for fistulizing disease concluded infliximab infusion to yield net cost savings, using expert opinion to profile resource utilization with and without infliximab.

These analyses have several obvious limitations. First, only one has been fully published in a peer-reviewed journal with full disclosure of its methods and assumptions. Second, at least four of the analyses were supported and/or conducted by companies involved in the sale and distribution of infliximab.[84] Third, none of the models provided cost-utility analyses relevant to a Canadian practice setting. Fourth, none has assessed the impact of maintenance infliximab therapy. Although chronic repeat infusions have not won regulatory approval, emerging data from large-scale clinical trials support maintenance therapy and it may emerge as a practice standard. Finally, it is important to recognize that simplified economic analysis with relatively short time horizons (1 to 2 years) cannot fully reflect the downstream clinical and economic impact of conventional therapy for CD, such as repeated surgeries with peri-operative morbidity and risks of malabsorption and short gut syndrome. Decision makers must weigh economic analyses against these risks and the unknown long-term effects of chronic immunosuppression when assessing the place of infliximab in the CD therapeutic armamentarium.

4.2 Primary Economic Analysis

4.2.1 Methods

a) Objective

This economic analysis was conducted to compare the expected costs and outcomes of alternative strategies for management of patients with CD resistant to conventional medical therapy.

b) Overview of analytic approach

A Markov model was constructed to represent the health states experienced by a hypothetical cohort of patients with active CD resistant to conventional therapy. Transition probabilities were determined by quantitative literature review and analysis of an existing usual care database. Principles of cost-effectiveness analysis were used to compare treatment strategies in terms of weak and strong dominance and incremental-cost-effectiveness. One-way and probabilistic sensitivity analyses were conducted to evaluate uncertainty.

The analysis was performed from the perspective of a Canadian provincial ministry of health, and included direct medical costs. All costs are reported in 2001 Canadian dollars (C$). The time horizon of the analysis was 52 weeks. The first cycle was 12 weeks in duration, and four subsequent cycles were each eight weeks. The primary measure of effect was quality-adjusted life years (QALY) and the principal measure outcome was the incremental cost per QALY. Neither costs nor effects were discounted, as the time horizon was limited to one year.

The model considered four alternative treatment strategies:

- **Strategy A ("Usual Care")**
- **Strategy B ("Single Dose"):** Intravenous infusion of infliximab 5 mg/kg at Week 0 with no maintenance infliximab therapy and no re-treatment with infliximab. Patients who do not respond to infliximab or who subsequently relapse receive usual care (Strategy A).
- **Strategy C ("Re-treatment"):** Intravenous infusion of infliximab 5 mg/kg at Week 0 with no maintenance infliximab therapy. Patients who subsequently relapse are retreated with a single infusion of infliximab 5 mg/kg.
- **Strategy D ("Maintenance"):** Intravenous infusion of infliximab 5 mg/kg at Week 0. Patients who respond to treatment (drop in CDAI of at least 70 points) receive maintenance infusions of infliximab 5 mg/kg every 8 weeks starting at Week 12. Patients who do not respond to infliximab or subsequently relapse on maintenance therapy receive usual care (Strategy A).

The infliximab treatment regimens evaluated in the ACCENT1 study were not modeled, as insufficient outcome data had been released at the time of submission of this report to allow model construction.

c) Usual care strategy (Strategy A)

There exists no single, obvious alternative to infliximab in the treatment of refractory CD. Treatment alternatives are individualized to patient characteristics, patient preference, disease parameters and history, prior treatment and response, physician preference, and access to care. Alternatives to infliximab infusion can include continued outpatient medical care (e.g. new or extended immunosuppression), inpatient medical care (e.g. intravenous corticosteroids) and surgery. A cohort of patients considered eligible for infliximab would otherwise receive some weighted mixture of these three approaches.

Observed transition data from long-term follow-up of a population-based cohort of patients with CD in Olmsted County Minnesota were used to estimate transition probabilities in usual care. Literature searches and expert consultation could identify no comparable source of adequate data on health outcomes and transition probabilities in Canadian patients. The Olmsted County data have been used previously to construct a natural history Markov model of CD,[14] and segregate patients among seven discrete health states:

Remission:	No medication for CD (excluding anti-diarrheals).
Mild:	Treatment with sulfasalazine, oral 5ASA, antibiotics, or rectal therapy (including steroids).
Drug-Responsive:	Treatment with oral steroids or immunosuppressive medications with documented improvement.
Drug-Dependent:	Treatment with oral steroids or immunosuppressive medications for more than 6 months with documented improvement.

Drug-Refractory:	Treatment with oral steroids (>2 months) or immunosuppressive medications (>6 months) with no clinical improvement, or high disease activity despite treatment with steroids for >6 months.
Surgery:	Inpatient surgery for CD.
Post-Surgical Remission:	No medication for CD after a surgical procedure for CD.

The cohort evaluated in the economic model was presumed to resemble patients in the **Drug-Refractory** health state, as clinical trials have assessed its use predominantly among patients who fail conventional medical therapy with corticosteroids and immunosuppressive agents. Thus, the initial 12-week cycle of Strategy A assigned the full hypothetical cohort to the following health state:

Drug-Refractory-A:	Drug refractory disease receiving usual care (12 weeks).

Transition probabilities from the initial cycle were derived from outcomes observed in the Targan trial,[46] and from the Olmsted County data by means of survival analysis (SAS 6.12 LIFEREG procedure). Full details of the methodology and resulting transition matrices are provided in Appendix H. The estimated transition probabilities from **Drug-Refractory-A** were 0.0800 to **Remission** and 0.0400 to **Drug-Responsive**, in keeping with rates observed in the Targan placebo arm. The Olmsted County data were used to estimate the probability of transition from **Drug-Refractory-A** to **Surgery** as 0.1338.

Transition probabilities for subsequent 8-week cycles were derived from outcomes observed in the Rutgeerts clinical trial,[45] and from the Olmsted County data (see Appendix H). From this, the probabilities of remaining in remission (**Remission** to **Remission**) or clinical response (**Drug-Responsive** to **Drug-Responsive**) were both estimated to be 0.7963. All patients who did not remain in clinical response or remission were assumed to re-enter to the **Drug-Refractory** state. The remaining probabilities were estimated using the Olmsted County data.

d) Treatment strategies:

For the initial cycle of all infliximab treatment strategies (Strategies B, C and D), patients were assigned to the following health state:

Drug-Refractory-BCD:	Drug refractory disease receiving infliximab (12 weeks) For subsequent cycles of these strategies, two additional health states were introduced to permit modeling of treatment effects:
Infliximab-Remission:	Clinical remission (CDAI<150) following an infusion of infliximab.
Infliximab-Responsive:	Clinical response (drop in CDAI >70 points) but no remission (CDAI>150) following an infusion of infliximab.

Transition probabilities from **Drug-Refractory-BCD** (Cycle 1) to **Infliximab-Remission** and **Infliximab-Responsive** were set to equal the 12-week rates of remission and response observed by Targan et al in the combined infliximab treatment groups[46] (see Appendix I). Thus, the

Drug-Refractory-BCD to **Infliximab-Remission** transition probability was 0.2400 and that for **Drug-Refractory-BCD** to **Infliximab-Responsive** was 0.1700.

Single dose strategy (Strategy B)

Strategy B assumed that no further doses of infliximab would be given. Thus, patients who failed the initial dose, or who relapsed (to the **Drug-Refractory** state) following initial response, would receive usual care. Those who responded to the initial infliximab dose were permitted only to remain in the **Infliximab-Remission/Responsive** health state, or enter the **Drug-Refractory** state to simulate loss of response/remission. As no persistent treatment effect was assumed, these 8-week transition probabilities were set at 0.7963, to parallel the placebo arm of the Rutgeerts maintenance trial[76] (see Appendix I). Transition probabilities emanating from the **Drug-Refractory** state were the 8-week transition probabilities for usual care (Strategy A).

Re-treatment strategy (Strategy C)

Strategy C was similar to Strategy B, except that patients who relapsed (to the **Drug-Refractory** state) following an initial response to infliximab would receive another infusion of infliximab. The rates of response and remission with repeat infusions were assumed to equal those seen with the initial infusion (i.e. Strategy B).

Maintenance strategy (Strategy D)

Strategy D assumed that patients who responded to the initial dose of infliximab would continue to receive infusions at 8-week intervals. Those who failed the initial dose, or who relapsed (to the **Drug-Refractory** state) on maintenance therapy, would receive usual care. The treatment effect of repeated infliximab infusion was represented by a multiplier variable, which increased the probabilities of remaining in **Infliximab-Remission/Responsive** health state to the conditional response rates observed in the infliximab arm of the Rutgeerts maintenance trial. The trial results were converted to transition probabilities as described in Appendix I. The 8-week transition probabilities from **Infliximab-Remission** to **Infliximab-Remission** and **Infliximab-Responsive** to **Infliximab-Responsive** were thus estimated to be 0.9370.

e) Utility inputs

Utility weights for each model health state were adapted from the published values estimated by Gregor et al.[85] A cohort of patients with CD was asked to rate three hypothetical disease states representing mild, moderate and severe disease using a standard gamble approach. These disease states are not identical to those represented in the model. Thus, assumptions were made to map model health states to those described by Gregor et al. (Appendix J).

f) Cost inputs

For each model health state, a profile of resource utilization was prepared in five categories: (1) infliximab infusion; (2) outpatient prescription medications related to CD; (3) outpatient physician visits; (4) medical hospital admissions for CD; and (5) surgical hospital admissions for CD. Utilization of other resources, and of resources not directly related to management of CD, was not assessed. Similarly, indirect costs were not captured.

A single infusion of infliximab 5 mg/kg was assumed in Cycle 1 for Strategies B, C and D, and in subsequent cycles of Strategies C and D as determined by the model. The costs of infliximab

were estimated for a 70 kg patient, to reflect the median weight among patients enrolled in published clinical trials in treatment-resistant CD.[45;46] Thus, each infusion would require four vials of 100 mg (total 400 mg). The estimated cost per vial of infliximab was C$1150 (Schering Canada), plus 10 percent mark-up and dispensing fees of C$4.11 (C$6.11 minus C$2.00 co-payment, as per the Ontario Drug Benefit Plan reimbursement). A profile of facility, personnel and supply costs for administering the infliximab infusion was prepared by audit of current infusion protocols at the McMaster University Medical Centre (MUMC) Infliximab Infusion Centre (see Appendix K).

Standard profiles of prescription medications and outpatient physician contacts for each model health state (Appendices L and M) were developed by consensus of a three-member expert panel of clinical gastroenterologists (JKM, EJI, KC) based on text descriptions of the health states.[12] Medication profiles for the initial states were constructed to resemble those reported in clinical trials of infliximab.[43;46] Medication costs were obtained from the 2001 Drug Benefits Formulary of the Ontario Ministry of Health and Long-Term Care, or the MUMC outpatient pharmacy. In calculating the associated dispensing fees, it was assumed that all medications were dispensed as 12-week supplies.

For each cycle spent in the **Surgery** health state, one surgical admission was assumed. For each cycle spent in the **Drug Refractory** health state, 0.20 medical admissions were assumed in the base-case analysis. Costs for medical and surgical admissions for CD were obtained from the existing case-cost database of London Health Sciences Centre (LHSC, London ON). LHSC was an original participant in the Ontario Case Cost Project, and maintains a fully-allocated database indexed by individual patient encounter with regular auditing and quality assurance. LHSC is a tertiary care teaching hospital similar to MUMC. Among 80 medical admissions with a primary ICD-9 discharge diagnosis of 555.XX (CD), the average length of stay and per diem costs (excluding physician reimbursement) were 7.86 days and C$492.58, respectively. Among 49 surgical admissions with ICD-9 discharge diagnosis of 555.XX and procedure code 45.73 (ileocolonic resection), the average length of stay and per diem costs were 13.16 days and C$804.44, respectively. For each medical admission, a gastroenterologist's fees for partial consultation at admission and daily follow-up visits for duration of hospitalization were assumed. Surgical admissions assumed a general surgeon's fees for consultation and laparotomy with ileo-colonic resection, a gastroenterologist's fees for one hospital visit and an anaesthetist's fees for general anaesthetic (two hours). Post-operative care is included in the surgeon's procedure fee. Rates of physician reimbursement for these services were obtained from the Ontario Hospital Insurance Plan (OHIP) Schedule of Benefits (July 2001). Use of all outpatient resources in the **Drug-Refractory** health state was reduced in a prorated fashion to reflect the proportion and duration of in-patient care.

g) Additional assumptions

The model made several explicit assumptions in addition to those described above:

A. That all members of the model cohort had undergone full gastrointestinal diagnostic imaging at baseline (i.e. colonoscopy plus small bowel radiography), and thus required no repeat imaging within the one-year model horizon.

B. That approximately 20 percent of patients in the **Drug-Refractory** health state would be admitted, while the remainder would receive outpatient care. Thus, the cost per cycle

reflected a weighted mixture outpatient and inpatient care (assumed length of stay eight days). Use of inpatient services is considered a major cost driver in the management of CD. However, no reliable data from which to estimate this proportion were identified. Thus, this parameter was one of the few subjected to both one-way and probabilistic sensitivity analyses.

C. That infliximab infusions of 5 mg/kg, 10 mg/kg and 20 mg/kg are equivalent in their efficacy for acute treatment and maintenance of response/remission. Thus, clinical effectiveness data from all doses were pooled for analysis. The approved dose for treatment of CD, 5 mg/kg, was assumed in the model.

D. That acute infusion reactions would be mild, and would neither attenuate treatment efficacy nor incur additional infusion-related costs.

E. That methotrexate and cyclosporine would not be used by the model cohort. These were prohibited in clinical trials of infliximab, and thus were not included in the outpatient drug profiles used for costing.

F. That patients in the model cohort who received surgery would not be given medication as post-operative prophylaxis. This was assumed because the Silverstein health state, **Surgical-Remission** was defined by the absence of medication for CD.

h) One-way deterministic sensitivity analyses

As a full probabilistic sensitivity analysis was planned, only three model parameters were subjected to deterministic one-way sensitivity analysis. Use of inpatient hospital resources for medical and surgical treatment of CD is considered to be a major cost driver in the management of CD. Thus, the proportion of patients with **Drug-Refractory** disease who received inpatient medical or surgical care were subjected to broad one-way sensitivity analysis. The effect of uncertainty in the rate of medical admission was tested by varying the proportion of patients hospitalized in the **Drug-Refractory** state between 0% and 100% (base case 20%). The rate of surgical admission was tested by varying the transition probability from **Drug-Refractory** to **Surgery** between 0% and 100% (base case approximately 13%). Finally, the impact of variation in drug costs was tested by varying the costs of infliximab infusion between 0% and 100% of their baseline value.

i) Probabilistic sensitivity analysis

Probabilistic sensitivity analysis considers the effects of joint uncertainty across multiple parameters of a decision model. This is accomplished by specifying distributions for model parameters to represent uncertainty in their estimation, and using Monte Carlo simulation to select values at random from those distributions.[86,87] For the probabilistic analysis of the present model, we performed 10,000 Monte Carlo simulations with distributions specified for transition probabilities, utility values, and key unit cost parameters (Appendix N).

Beta distributions (bounded by zero and one) were specified to parameterize all transition probability variables. For transition probabilities taken from clinical trials results,[46,82] Beta distribution parameters (alpha, beta) were estimated directly from the number of successes (alpha) and failures (beta) reported for each probability of interest. For transition probabilities estimated from the Olmstead county data, Beta distributions were fitted by method of moments[88] using means and standard errors estimated by survival analysis. For all utility variables, beta

distributions were fitted by method of moments using mean and standard error estimates reported by Gregor et al.[85]

For most cost parameters in the model, no distributions were specified as they were considered fixed (e.g. by provincial formularies and/or benefits schedules). However, normal distributions were specified for the hospital costs for surgical and medical admission, with arbitrary standard errors equal to 20% of their respective means. A summary of the parameters used for probabilistic sensitivity analysis is provided in Appendix N.

4.2.2 Results

a) Base case analysis

The base-case model analysis is summarized in Appendix O. No strategy was dominant. The usual care strategy (Strategy A) incurred the lowest costs and generated the fewest QALY ($9941 for 0.6281 QALY over one year). Strategies B, C and D, in order, incurred increasing costs but provided progressively more QALYs. Strategies B and C differed only marginally with respect to costs and effects. The incremental cost-utility ratios (ICUR) associated with advancing to more costly but more effective strategies were: $181,201 for Strategy B vs. Strategy A; $480,111 for Strategy C vs. Strategy B; and $696,078 for Strategy D vs. Strategy C.

b) One-way sensitivity analysis

The full results of selected one-way deterministic sensitivity analyses are summarized in Appendix P. Variation in the rate of surgical admission for drug-refractory CD was found to exert a negligible influence on the ICUR, all of which remained above C$150,000/QALY. Variation in the proportion of patients with drug-refractory disease treated medically fell to C$39,000/QALY at 60 per cent and showed dominance of Strategy B at 80 per cent. However the ICUR of Strategy D vs. Strategy C remained over C$600,000/QALY. Variation in the cost of infliximab infusion revealed that the ICUR of Strategy B vs. Strategy A fell below C$100,000/QALY when the cost was reduced by 25%. Usual care was dominated by Strategy B when the drug costs were reduced by at least 75%.

c) Probabilistic sensitivity analysis

The full results of the probabilistic sensitivity analysis are presented in Appendix Q. Through 10,000 Monte Carlo simulations, Strategies A, B, C and D formed part of the efficiency frontier in 99.95%, 92.10%, 72.60% and 95.52% of the time, respectively. A scatter plot of incremental costs and effects of Strategies B, C and D relative to Strategy A is provided in Appendix R. The distributions of incremental cost-effect pairs for Strategies B and C overlapped considerably. However, Strategies B and C did not overlap with Strategies A or D. The scatter distribution of incremental cost-effect pairs for each strategy was oblong along a horizontal axis, suggesting that there was more uncertainty with respect to effects than costs. Because of uncertainty with respect to the acceptable threshold for incremental cost-utility ratios, acceptability curves were constructed to demonstrate the probability that each strategy will provide the greatest net benefit across a range of threshold values of C$/QALY (Appendix S). If the maximum willingness-to-pay per QALY was less than C$180,000/QALY, the Strategy A was most likely to provide the greatest net benefit. For values between C$180,000/QALY and C$430,000/QALY, Strategy B was favoured. For values between C$430,000/QALY and C$690,000/QALY, Strategy C was preferred. Strategy D was favoured only if the willingness-to-pay per QALY exceeded C$690,000/QALY.

4.2.3 Discussion of results

We constructed a decision analytic model to compare four alternative strategies for the treatment of active CD, with respect to their expected direct medical costs and quality-adjusted survival over one year. The comparator strategy was designed to represent usual care, while the remainder represented three alternative approaches to the use of infliximab in treatment-resistant patients; a single infusion with no re-treatment; a single infusion with maintenance treatment for responders; and a single infusion with re-treatment only for subsequent relapses. The effects of parameter uncertainty in the model were tested in selected deterministic sensitivity analyses and in a probabilistic sensitivity analysis using a Monte Carlo simulation.

None of the strategies was simply or extendedly dominant over another in the base-case analysis. Usual care incurred the lowest costs (C$9,941) but also generated the fewest QALYs (0.6281). The infliximab strategies provided progressively more QALYs, but at progressively greater cost. The incremental cost-utility ratio (ICUR) of the single infusion strategy relative to usual care was C$181,201/QALY. The ICUR of switching to the next more costly strategy, single infusion with re-treatment, was C$480,111/QALY. Finally, ICUR of moving from the re-treatment strategy to the maintenance strategy was C$696,078/QALY. In deterministic sensitivity analyses, these estimates were robust to variation in the rate of surgical admission for drug refractory disease but sensitive to extreme increases in the rate of medical admission and reductions in drug costs.

In probabilistic sensitivity analysis using 10,000 Monte Carlo simulation, the distribution of incremental costs and effects for Strategy D relative to Strategy A did not overlap appreciably with any other strategy. However, the distributions of Strategies B and C overlapped considerably with each other and were virtually indistinguishable. This suggests that their relationship in the base-case analysis is unstable, and highly sensitive to parameter uncertainty. Furthermore, Strategies B and C were rarely dominated, as they remained part of the efficiency frontier in 94 and 73 percent of simulations, respectively.

Acceptability curves provide important information to decision makers faced with uncertainty about societal willingness-to-pay for QALY. The selection and use of cost-effectiveness thresholds to allocate resources on the basis of ICUR remain controversial, and a full discussion of this issue is beyond the scope of this report. Acceptability curves are produced through Monte Carlo simulations, and plot the likelihood that a strategy is the most cost-effective alternative for each ICUR threshold. In this analysis, usual care was preferred for all thresholds below approximately C$180,000/QALY. This threshold exceeds most proposed benchmarks for ICUR, and suggests that infliximab therapy for CD is not favoured on grounds of cost-effectiveness. However, ICUR alone are not sufficient to determine whether programs should receive funding. It remains up to health care payers, patients and physicians to review the parameters and assumptions of this model, weigh the opportunity costs, consider the alternatives, and determine whether infliximab therapy for CD makes appropriate use of resources.

Several limitations of this analysis warrant specific mention. First, few prospective observational data on the "natural history" of CD provide sufficient detail to inform a Markov model of usual care. We analyzed raw data from long-term follow-up of an established U.S. patient cohort, but their relevance to modern-day treatment in a Canadian setting cannot be proven. Furthermore, these data assigned patients to health states according to their medical

treatment, and assumptions were required to transpose the outcomes of clinical trials that defined outcomes in terms of disease activity indices. Similar assumptions were also required to convert published utility weights for CD to model health states that were not represented fully in the utility data set. Estimates of treatment effect were derived from a small number of clinical trials, and expert opinion was required to inform several aspects of resource utilization.

This economic analysis assumed the perspective of a provincial ministry of health, and assessed only direct medical costs. It bears recognition that active CD imposes significant morbidity that may limit productivity. Thus, reducing disease activity could yield indirect cost savings by attenuating productivity losses. If a societal perspective were assumed, the ICUR of infliximab treatment relative to usual care might become more favourable. However, detailed data on productivity changes with CD activity are not available to inform such an analysis.

It must be recognized that few treatment alternatives are available to patients with severe, refractory CD. Policy advisors must consider this predicament in evaluating the results of economic analyses. Furthermore, because this model does not capture the considerable longer-term morbidity of repeated surgical resection of diseased bowel segments, it may underestimate the downstream clinical benefits of infliximab treatment in avoiding surgery. In base case analysis, this model shows that a single infliximab infusion for active CD reduces surgical admissions within one year by approximately 25 percent. Longer-term data on the efficacy and safety of infliximab are not currently available.

Despite these limitations, this economic analysis of infliximab treatment in CD is methodologically rigorous, is based the best available clinical data, reflects a Canadian practice setting, and uses state-of-the art techniques to measure the impact of parameter uncertainty. Probabilistic sensitivity analysis allows simultaneous variation in multiple model parameters, and provides estimates of uncertainty for the model results, including its incremental cost-effectiveness ratios. As such, decision makers gain insight into the strengths and limitations of the model's conclusions.

Our results differ from those of two other economic analyses that evaluated the cost-utility of infliximab in treatment-resistant CD. An unpublished, industry-funded analysis reported an ICUR of Aus$45,418/QALY for a single-dose strategy vs. usual care, but used a relatively simple model with two health states and Australian resource data.[84] A second analysis, reported only in abstract form, estimated the ICUR to be between US$14,200/QALY and US$40,000/QALY.[83] Although this model used sources of transition probabilities and utility weights similar to those used in our analysis, its resource costs were of U.S. origin. The published abstract provides insufficient information on other assumptions and model structure for further comparison. Ours is the first cost-utility analysis of infliximab therapy in a Canadian practice setting.

This economic analysis will require updates to assess the effects of future changes in infliximab delivery, costs and dose regimens. Sensitivity analyses suggest that reductions in cost and/or treatment dose could reduce the expected costs per QALY gained with infliximab, and make infliximab more economically attractive. However, important efficacy data emerging from the ACCENT1 clinical trial assess a more intense treatment regimen, wherein infusions of

infliximab 5 mg/kg at 0, 2 and 6 weeks are followed by maintenance infusions of 5 or 10 mg/kg at 8-week intervals. We chose not to model this strategy because insufficient outcome data had been released at the time of report submission to inform the model. However, as drug costs are a major determinant of the cost-effectiveness of infliximab, the multiple-dose ACCENT1 regimen is unlikely to yield a more favourable ICUR and may not provide substantial gains in efficacy. Future evaluations should assess this strategy in detail.

5 HEALTH SERVICES IMPACT

The cost-utility analysis of infliximab for the treatment of treatment-resistant CD, presented in this report, suggests that a single-dose infliximab infusion incurs additional costs of C$2762 per patient but offers 0.01524 additional QALY for an ICER of C$181,201/QALY. The national impact of infliximab was not directly assessed by this report, but given a prevalence of 100 per 100,000, there are approximately 30,000 individuals in Canada with CD. If only five percent of those individuals were to receive infliximab treatment within a given year, a crude calculation suggests that the additional direct medical costs could exceed C$4 million. However, further information on the spectrum of disease severity and practice variation in Canada would be required to measure this impact more accurately.

Infliximab currently is administered in hospital-based infusion centres under nursing supervision with a specialist physician on-call for infusion reactions. Although this practice may create geographic inequity in access to care, and places a strain on scarce acute-care resources, infliximab treatment can also be argued to avert some hospitalizations and free those resources for other use. The analysis presented in this report suggests that a single-infusion infliximab strategy reduces the rates of medical and surgical hospitalization by 40 and 25 percent, respectively. Furthermore, alternative approaches to infliximab delivery, such as home-care and office-based infusion, are being explored.[37,38]

The health services impact of new recommendations that patients considered for infliximab infusion be screened for latent tuberculosis is unclear, and was not addressed in this report. Future studies should consider the impact and yield of routine chest radiography and tuberculin skin testing, including the follow-up and treatment of false-positive results.

Finally, future trends in drug costs are often difficult to predict. The cost-utility analysis summarized in this report assumed a cost per infusion (400mg) of C$5,338 (including dispensing fees, mark-up, supplies and labour). However, the ICER of the single-infusion infliximab strategy (relative to usual care) falls to C$15,190/QALY if the costs of infliximab are reduced by 50 per cent, and shows dominance of infliximab infusion if its costs are reduced by 75 percent.

6 ETHICAL, LEGAL AND SOCIAL IMPLICATIONS

Ethical, legal and social implications were not assessed directly in this review. CD is a chronic, relapsing disorder whose severity and morbidity span a broad spectrum. For the minority of patients with chronic, severe and treatment-resistant disease there are few, if any, therapeutic alternatives. Surgery is neither universally feasible nor universally effective, and carries both acute and long-term risks, including short gut syndrome. This review endorses the efficacy of infliximab in treating these patients, although the incremental costs per gain in QALY exceed conventional benchmarks. This analysis was limited necessarily to a relatively short time horizon, did not recognize long-term complications of infliximab its alternatives, and did not address the indirect costs of chronic refractory CD. Health care providers, payers and policy advisors must weigh the available efficacy, safety and economic data to determine whether to make infliximab available to patients with a debilitating disease and few satisfactory treatment alternatives.

7 CONCLUSIONS

Clinical trials of infliximab for treatment of CD are too few and too heterogeneous to allow quantitative review and pooling. However, the available literature supports the efficacy and effectiveness of infliximab for the acute treatment of fistulizing CD, and for acute and maintenance treatment of treatment-resistant inflammatory CD. In Canada, maintenance therapy is not an approved indication for infliximab. Additional efficacy data from large, controlled clinical trials are awaited.

Clinical trials and post-marketing experience suggest that the short-term tolerability of infliximab is acceptable. Acute infusion reactions, experienced by three to seven percent of patients, are usually mild and self-limited but can be severe. Other adverse events associated with infliximab in placebo-controlled trials include upper respiratory infection, nausea and abdominal pain. Adverse events which occurred rarely or never in controlled trials, but which have been associated with infliximab therapy in uncontrolled, post-marketing experience include severe infections (including tuberculosis), malignancy (including lymphoma), autoimmune sero-conversion and clinical syndromes, and the development of human anti-chimeric antibodies (HACA). However, the true frequency, attributable risk and clinical significance of these events are unclear.

Published controlled trials of infliximab for the treatment of CD have not demonstrated consistent patient subgroups wherein infliximab offers preferential benefit.

Previous economic analyses of infliximab for CD vary in their methodologic rigour and conclusions. A number of analyses submitted by the manufacturer have been favourable. However, the only analysis published in a peer-reviewed journal estimated the impact of infliximab for treatment of fistulizing CD to exceed traditional thresholds of cost per QALY. A U.S. cost-utility analysis presented in abstract form yielded more favourable cost-utility ratios for treatment-resistant CD, but details of the model structure and assumptions are not available.

A cost-utility analysis of infliximab for the treatment of patients with active CD resistant to conventional therapy was conducted using a Markov model. The incremental cost-utility ratio of a single-dose infliximab treatment strategy, relative to a usual care alternative was estimated to be C$181,201, from the perspective of a Canadian provincial ministry of health. A probabilistic sensitivity analysis using Monte Carlo simulations demonstrated that, for cost-effectiveness thresholds less than C$180,000/QALY, usual care was more likely to maximize net benefit than infliximab treatment strategies.

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Appendix 1: Search Strategy – Clinical Effectiveness

DATABASE	LIMITS	KEYWORDS
MEDLINE® HealthSTAR®	1990 to 2001/Jan W1	1. Crohn's disease! 2. Crohn's disease/mp 3. infliximab?/tw OR Remicade?/tw OR anti(w)TNF(w)alpha(w) monoclonal(w)antibody?/tw,sh 4. CDP571?/tw 5. dt=clinical trial OR dt=clinical trial, phase iii OR clinical trial,phaseivO dt=meta-analysis OR dt=controlled clinical trial OR dt= randomized controlled trial OR dt=multicenter study 6. clinical trials! OR comparative study/de OR double-blind method/deO random allocation/de 7. random?/sh,tw OR controlled(w)trial?/sh,tw OR double(w)blind/sh,twO meta(w)analy?/sh,tw OR research(w)overview?/sh,tw OR methodologic(w)overview?/sh,tw OR systematic(w)overview?/sh,tw 8. (1 OR 2) AND (3 OR 4) 9. Set 8/1990-2001 10. Set 9/human 11. Set 10/English
EMBASE®	1990 to 2001/Jan W3	12. Crohn's disease! 13. (12) AND (3 OR 4) 14. Set 13/human 15. Set 14/1990-2001 16. Set 15/English (There were hits (refs) in MEDLINE and, in EMBASE, prior to final removal ofduplicates)
CURRENT Contents® CINAHL®	1990 to 2001/May W5	17. Crohn's disease?/mp 18. 17 AND (3 OR 4) 19. set 18/human 20. set 19/1990:2001 21. set 20/English
TOXLINE		22. infliximab/pr OR Remicade/br
Pharmaceutical News Drug Info Pharmaceutical & Health Care Industry News PharmaProjects Pharmaceutical News Index		23. infliximab/mp OR Remicade/mp 24. Crohn's disease/mp 25. 23 AND 24 26. set 25/English
		Reduce Duplicates: 26 = 228 refs **Total refs = 228**

Appendix 2: Jadad Score for Evaluating the Quality of Clinical Trials[47]

Criteria

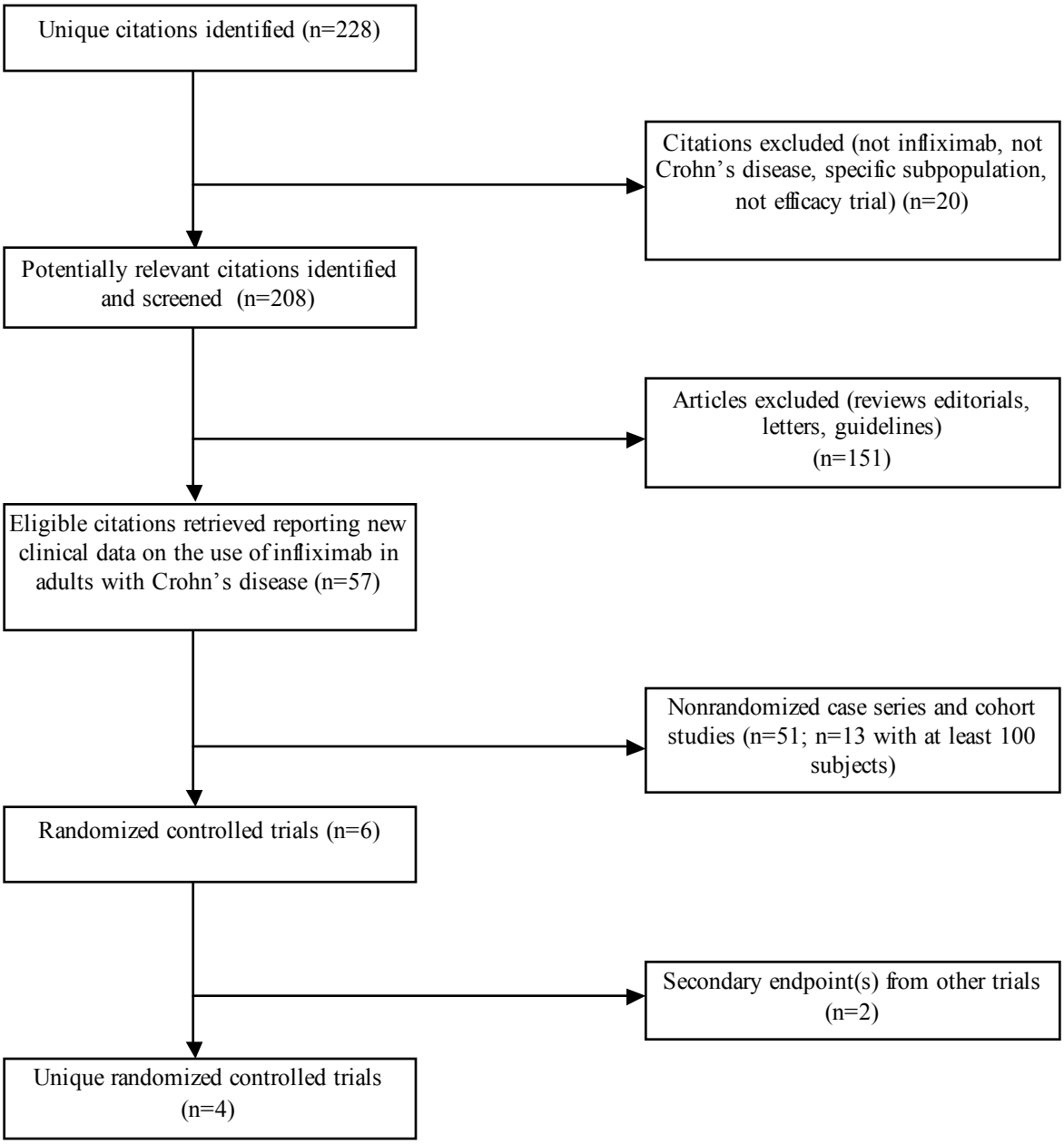
1. Was the study described as randomized?
2. Was the study described as double-blind?
3. Was there a description of withdrawals and dropouts?

Score

- Give a score of one point for each "yes".
- Give an additional point if:
  - For (A), the method to generate the sequence of randomization was described and was appropriate.
  - For (B), the method of double blinding was described and was appropriate.
- Deduct one point if:
  - For (A), the method to generate the sequence of randomization was described and was inappropriate.
  - For (B), the study was described as double-blind but the method was inappropriate.

MAXIMUM SCORE = 5

Appendix 3: Quorom Flow Diagram (Clinical Effectiveness - Literature Search)[40]



Appendix 4: Studies Retrieved but not cited in the Clinical Effectiveness Review

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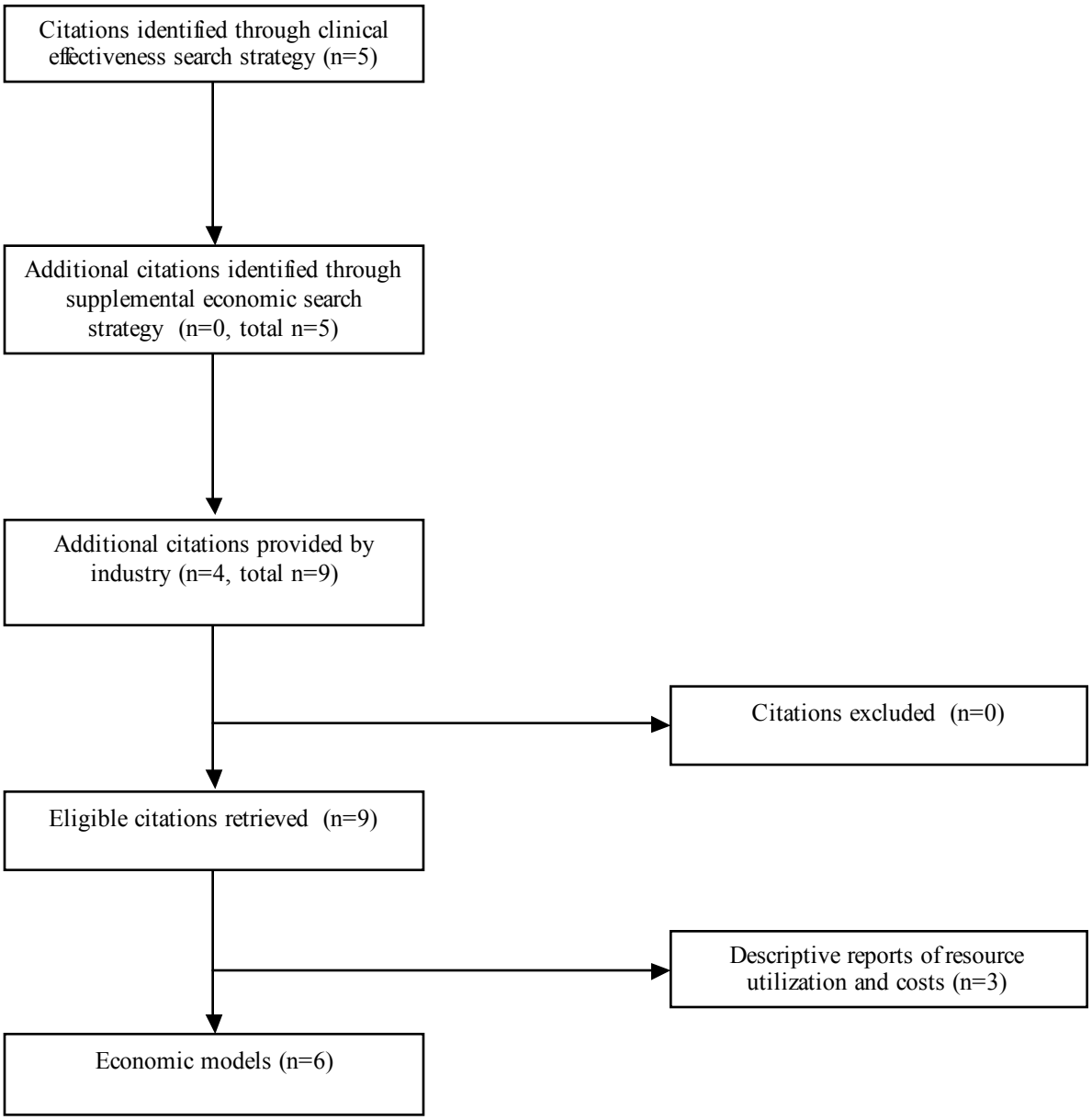
Appendix 5: Crohn's Disease Activity Index[61,75]

1. Number of liquid or very soft stools in one week:	_____	(Multiply by 2)	= _____
2. Sum of seven daily abdominal pain ratings: (0=none; 1=mild; 2=moderate; 3=severe)	_____	(Multiply by 5)	= _____
3. Sum of seven daily ratings of general well-being: (0=well; 1=slightly below par; 2=poor; 3=very poor; 4=terrible)	_____	(Multiply by 7)	= _____
4. Symptoms or findings presumed related to Crohn's disease (Add 1 for each of: arthritis or arthralgia; iritis or uveitis; erythema nodosum or pyoderma gangrenosum or aphthousstomatitis; anal fistula or fistula or perirectal abscess; other fistula; febrile during past week)	_____	(Multiply by 20)	= _____
5. Taking loperamide or opiates for diarrhea (0=no; 1=yes)	_____	(Multiply by 30)	= _____
6. Abdominal mass (0=none; 0.4=questionable; 1=present)	_____	(Multiply by 10)	= _____
7. For males: 47 minus hematocrit For females: 42 minus hematocrit	_____	(Multiply by 1)	= _____
TOTAL SCORE:			= _____

Appendix 6: Supplemental Search Strategy - Economic

DATABASES	LIMITS	KEYWORDS
MEDLINE® HealthSTAR®	1990 to 2001/Jan W5	 (1 OR 2) AND (3 OR 4) economics! economic?/tw,sh,ti OR cost?/ti,ab OR cost(w)effectiveness(analysis)/tw,sh OR economic(w)analysis/tw,sh OR cost(w)utility(w)analysis/tw,sh (1 OR 2 OR 3 OR 4) AND (28 or 29) set /1990:2001
EMBASE®	1990 to 2001/Feb W4	(11 or 3 or 4) AND economic aspect!
Clinical Search	1990 to 2001	Based on previous literature search
		Reduce Duplicates: 31 OR 32 = 6 refs
Cochrane Library	Performed 02/15/2001	Crohn's disease*:me infliximab*me: OR Remicade OR anti TNF alpha OR anti-TNF alpha monoclonal antibody 1and 2 3 and 1990:2001 = 10 hits Cochrane Database of Systematic Reviews = 0 Database of Reviews of Effectiveness. Abstracts of Quality Assessed Systematic Reviews = 0 Cochrane Reviews/Protocols Listed by Collaborative Review Group = 0 Cochrane Trials Register. References = 9 Health Technology Assessment Database. Abstracts from INAHTA and other healthcare agencies = 1 NHS Economic Evaluation Database. Abstracts of Economic Evaluation of Health Care Technologies = 0
Unpublished Data Clinical investigator Manual (Centocor)	Received Jan 2001	Pharmacoeconomic Analysis
		TOTAL REFS: 10 REFS
		REDUCE DUPLICATES: 9 REFS

Appendix 7: Quorom Flow Diagram (Economic Evaluation Literature Search)[40]



Appendix 8: Calculation of Transition Rates from Olmsted County Cohort

Transition probabilities which presumed no infliximab treatment effect were generated through secondary analysis of raw transition data from prospective observation of a defined cohort of patients with CD. These data were also used to derive 8-week transition probabilities for a Markov model of CD published by Silverstein et al.[14] Permission to re-analyze the raw data was obtained from a senior author[89] for two reasons. First, the "death" health state was removed as the time horizon for the infliximab model was one year, and no increase in mortality has been attributed to infliximab. Secondly, a probabilistic sensitivity analysis was planned, which required estimates of uncertainty estimates for each transition probability. These were not provided in the original analysis.

The Silverstein data were derived from a cohort of 174 Olmsted County, Minnesota residents with CD observed between 1970 and 1993, inclusive, with mean follow-up 7.3 years. The data classified patients as being in one of 9 health states at a given time: Pre-Study; Remission; Mild Disease; Drug Refractory; Drug Responsive; Drug Dependent; Surgery; Post-surgery Remission; and Dead. Each transition between health states was entered as a separate record, containing patient identification number; previous health state; current health state; next health state; and time between transitions (current health state to next health state).

Aggregate probabilities for each transition were estimated by performing a survival analysis on all related data records using the LIFEREG procedure in SAS 6.12 and assuming an exponential distribution. The LIFEREG model is dependant upon both the "time on study" and censor status of observations. "Time on study" reflects the time between transitions in the data set. An observation is considered censored if the transition occurred to a health state other than the one being analyzed. For example when analyzing the transition from Mild to Remission, the survival analyses will include not only records with transitions from Mild to Remission, but also records with transitions from Mild to other health states, up to the time of transition. The LIFEREG procedure estimates a daily exponential hazard rate for transitioning from one health state to another, along with the standard error of that hazard rate. This approach is similar to that used by Silverstein et al in their analysis, and assumes a constant risk over time. The hazard rate can be converted to a cumulative transition probability for any time period using the following equation, where "t" is the period length in days and hazard is the daily hazard rate:

P(t) = exp(-hazard(t))

Several adjustments were made to the derived transition matrices:

- To ensure that all transition probabilities emanating from a given health state summed to one, the probability of staying in the health state was set equal to the probability generated by survival analysis and the remaining probabilities were re-weighted in fixed proportions to equal the complement of that probability.
- Transitions to the Surgical Remission state occurred only from the Surgery and Surgical Remission states.

- Transitions from the Surgical Remission state were permitted only to the Surgical Remission and Drug Refractory states.The Death state was removed.
- Transitions from the Remission and Drug Responsive states were dichotomized and estimated using probabilities observed in the placebo arm of the Rutgeerts trial,[45] rather than those derived from the Silverstein cohort (see Appendix I). This was done for calibration of the matrix, such that the model cohort would resemble patients considered for infliximab in clinical trials in their rates of disease relapse under usual care.
- Similarly, transitions from the Drug Refractory state to Remission and Drug Responsive were estimated using probabilities observed in the placebo arm of the Targan trial[46](see Appendix I). Transition probabilities from the Drug Refractory state to other health states were derived from analysis of the Silverstein data and re-weighted in fixed proportion to sum to one.

The following 8-week transition probabilities were used in the model:

	Next State						
Current State	**Remission**	**Mild**	**Drug Responsive**	**Drug Dependant**	**Drug Refractory**	**Surgery**	**Surgical Remission**
Remission	0.7963[a]	0.0000	0.0000	0.0000	0.2150[a]	0.0000	0.0000
Mild	0.0618	0.8985	0.0130	0.0064	0.0118	0.0085	0.0000
Drug Responsive	0.0000	0.0000	0.7963[a]	0.0000	0.2150[a]	0.000	0.0000
Drug dependent	0.0524	0.0326	0.0021	0.8902	0.0062	0.0165	0.0000
Drug refractory	0.0540[b]	0.0490	0.0270[b]	0.0230	0.7722	0.0956	0.0000
Surgery	0.0000	0.0778	0.0142	0.0422	0.0329	0.3821	0.4508
Surgical Remission	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9761

The following 12-week transition probabilities were used in the first cycle of the model:

	Next State						
Current State	**Remission**	**Mild**	**Drug Responsive**	**Drug Dependant**	**Drug Refractory**	**Surgery**	**Surgical Remission**
Drug refractory	0.0800[a]	0.0696	0.0400[b]	0.0327	0.6786	0.1338	0.0000

[a]Estimated from the Rutgeerts study placebo arm.[45]
[b]Estimated from the Targan study placebo arm.[46]

Appendix 9: Calculation of Transition Rates from Infliximab Trials

Specific transition probabilities in the Usual care and infliximab treatment strategies were derived from event rates observed in clinical trials, rather than the Silverstein patient cohort. Twelve-week transition probabilities from the Drug Refractory for the first cycle were derived from the Targan acute treatment trial, which noted clinical response and remission at Week 12 in 12% and 8% of subjects treated with placebo, versus 41% and 24% of subjects treated with infliximab (all doses combined).[46] Thus, the proportion of subjects who experience clinical response but not clinical remission was 4% on placebo (12% minus 8%) and 17% on infliximab (41% minus 24%). Eight-week transition probabilities from the Drug Refractory state for subsequent cycles were then estimated as follows:

$$p_{8wks} = 1-((1-p_{12wks})^{8/12})$$

Eight-week transition probabilities from the Remission and Drug-Responsive health states were derived from the Rutgeerts maintenance trial, wherein patients who achieved clinical response in the acute treatment trial were randomized to receive infliximab or placebo every 8 weeks for an additional 32 weeks.[45] Data provided in the publication included the proportion of patients in clinical response and clinical remission at each time point, among those in clinical response at baseline. Unfortunately, the published report did not provide conditional remission rates (i.e. the probabilities of remaining in remission if in remission for the current cycle), and neither the investigators nor the trial sponsor could provide further data. Thus, the conditional probabilities of remaining in clinical remission (i.e. **Remission** to **Remission** transition) and clinical response without full remission (i.e. **Drug-Responsive** to **Drug-Responsive** transition) were both assumed to equal the observed conditional probability of remaining in clinical response and/or remission (Figure 3 in Rutgeerts et al[45]). While this approach ensured that the probabilities of clinical response and remission were calibrated to those observed in the clinical trial, it eliminated transitions between the **Remission** to **Drug-Responsive** health states.

Placebo Arm:
Proportion of patients with clinical response at Week 0 = 0.920
Proportion of patients with clinical response at Week 32 = 0.370
Proportion of patients with clinical response at baseline who remain in clinical response at Week 32 = 0.370/0.920 = 0.402
Eight-week probability of remaining in clinical response = $0.402^{8/32}$ = 0.796

Infliximab Arm:
Proportion of patients with clinical response at Week 0 = 0.870
Proportion of patients with clinical response at Week 32 = 0.670
Proportion of patients with clinical response at baseline who remain in clinical response at Week 32 = 0.670/0.870 = 0.770
Eight-week probability of remaining in clinical response = $0.770^{8/32}$ = 0.937

Appendix 10: Assumed Health State Utility Weights

Model Health State (see Text):	**Evaluated Health State [85]:**	**Standard Gamble Utility (95% CI):**
Remission	Mild[a]	0.82 (0.80 to 0.85)
Infliximab-Remission	Mild[a]	0.82 (0.80 to 0.85)
Surgical-Remission	Mild[a]	0.82 (0.80 to 0.85)
Mild-Disease	Mild[a]	0.82 (0.80 to 0.85)
Drug-Responsive	Moderate[b]	0.73 (0.71 to 0.77)
Infliximab-Responsive	Moderate[b]	0.73 (0.71 to 0.77)
Drug-Dependent	Moderate[b]	0.73 (0.71 to 0.77)
Drug-Refractory	Severe[c]	0.54 (0.50 to 0.59)
Drug-Refractory-BCD	Severe[c]	0.54 (0.50 to 0.59)
Drug-Refractory-A	Severe[c]	0.54 (0.50 to 0.59)
Surgery	Severe[c]	0.54 (0.50 to 0.59)

[a] Mild: Four or fewer bowel movements per day, occasional abdominal pain, able to attend work/school with only occasional absences, little fatigue or sleep disturbance.

[b] Moderate: Five to eight bowel movements per day, tolerable abdominal pain related to bowel movements, occasional blood, tired most days, frustrated at times, concerned about the side effects of medication, able to work or go to school but misses days because of illness.

[c] Severe: More than eight bowel movements per day, frequent severe abdominal pain, frequent bloody stools, tired, difficulty sleeping, depressed and frustrated, worried about surgery and side effects of medication, unable to attend work/school or participate in social activities.

Appendix 11: Profile Of Infliximab Infusion Costs

Item	Total Cost (C$)
Infliximab (4 x 100 mg vials @ $1,150.00/vial)	4,600.00
Markup (10% of above)	460.00
Dispensing fee (minus co-payment)	4.11
Subtotal	**5,064.11**
Nursing supervision (2.5 hours @ $26.50/hour)	79.50
Gastroenterologist partial assessment	24.40
250 mL saline bag	1.02
Alaris IV infusion set	3.32
Alaris IV secondary set	1.69
0.22 micron filter	2.27
Needle lock device	0.68
20 inch extension tubing	0.95
#22 1” In-Syte	0.96
Tegaderm	0.16
Alcohol swab	0.01
Chlorhexidine swab	0.05
2x2” gauze	0.03
Subtotal	**227.60**
Chest x-ray (first infusion only)	46.70
Total	**5,338.41**

Appendix 12: Profiles of Physician Contact Frequencies

	Family Physician		Gastroenterologist		General Surgeon:	
	per 8 weeks	per year	per 8 weeks	per year	per 8 weeks	per year
Remission	0.00	0.00	0.15	1.00	0.00	0.00
Mild	0.15	1.00	0.31	2.00	0.00	0.00
Drug-Responsive	1.00	6.19	2.00	12.38	0.00	0.00
Drug-Dependent	0.15	1.00	0.62	4.00	0.00	0.00
Drug-Refractory	1.00	6.19	2.00	12.38	0.15	1.00
Surgery	1.00	6.19	1.00	6.19	0.23	1.50
Surgical Remission	1.00	6.19	0.50	3.10	1.00	6.19

Appendix 13: Profiles of Outpatient Prescription Drug Costs

Health State:	Medication:	Proportion Using:	Daily Dose:	Drug Cost per Cycle (8-weeks)[a]:	Total Cost of Health State per Cycle:
Remission	None	N/A	N/A	N/A	C$0.00
Mild Disease	Oral 5-ASA	0.90[c]	4g po	C$233.46[b]	
	Metronidazole	0.10	1,000 mg po	C$11.11	
	Ciprofloxacin	0.10	1,000 mg po	C$31.51	
	Hydrocortisone enema	0.05	100 mg pr od	C$16.16	
	Mesalamine enema	0.05	4 g pr	C$18.69	C$310.93
Drug-Responsive	Prednisone	0.60	20 mg po	C$ 5.17	
	Azathioprine/6-MP[b]	0.40	150/75 mg po	C$50.93[c]	
	Budesonide CIR	0.10	9 mg po	C$30.58	
	Oral 5-ASA[c]	0.60	4g po	C$154.53[b]	C$241.22
Drug-Dependent	Prednisone	0.30	10 mg po	C$2.25	
	Azathioprine/6-MP[b]	0.70	150/75,mg po	C$89.13[c]	
	Oral 5-ASA[c]	0.60	4g po	C$154.53[b]	C$245.92
Drug-Refractory	Prednisone	0.07	40 mg po	C$ 7.58	
	Azathioprine/6-MP[b]	0.40	150/75 mg po	C$50.93[b]	
	Budesonide CIR	0.10	9 mg po	C$30.58	
	Oral 5-ASA[c]	0.60	4g po	C$154.53[c]	C$243.63
Surgery	None	N/A	N/A	N/A	C$0.00
Surgical Remission	None	N/A	N/A	N/A	C$0.00

[a] assumes 12-week prescriptions with 10% markup and C$4.11 dispensing fee
[b] assumes 10:25:45:10 split of sulfasalazine:Asacol™:Pentasa™:Salofalk™
[c] assumes 70:30 split of azathioprine:6-MP

Appendix 14: Monte Carlo Distribution Parameters

(A) Beta distribution parameters for health state utility weights

Health State	Alpha	Beta
Mild (remission, infliximab/surgical remission, mild)	743.93	163.30
Moderate (drug/infliximab responsive, drug dependent)	614.16	227.15
Severe (drug refractory, surgery)	254.47	216.77

(B) Normal distribution parameters for inpatient hospital costs

Type	Mean	Standard Error
Surgical admission	10586.47	2117.294
Medical admission	3871.68	774.336

(C) Beta distribution parameters for transition probabilities under infliximab treatment effect

Transition From	Transition to	Duration (Wks)	Alpha	Beta
Drug Refractory	Remission	12*	20	63
Drug Refractory	Drug Responsive	12*	14	69
Remission	Remission	8	34.66	2.34
Drug Responsive	Drug Responsive	8	34.665	2.34

*8-week transition probability parameters derived from 12-week parameters

(D) Beta distribution parameters for transition probabilities without infliximab treatment effect

Transition From	Transition to	Duration (wks)	Alpha	Beta
Drug Refractory	Remission	12*	2	23
Drug Refractory	Drug Responsive	12*	1	24
Drug Refractory	Mild	12	21.13	253.75
Drug Refractory	Drug Dependent	12	12.41	329.97
Drug Refractory	Drug Refractory	12	116.59	55.22
Drug Refractory	Remission	12	2	23
Drug Refractory	Drug Responsive	12	1	24
Drug Refractory	Mild	8	21.37	390.03
Drug Refractory	Drug Dependant	8	12.50	501.39
Drug Refractory	Drug Refractory	8	179.40	52.91
Remission	Remission	8	28.67	7.33
Drug Responsive	Drug Responsive	8	28.67	7.33
Mild	Remission	8	4251.06	3485.50
Mild	Drug Responsive	8	253.58	309.41
Mild	Mild	8	57.42	4207.36
Mild	Drug Dependant	8	29.25	4770.83
Mild	Drug Refractory	8	19.28	4270.99
Mild	Surgery	8	50.52	4515.37
Drug Dependent	Remission	8	37.07	655.86
Drug Dependent	Drug Responsive	8	25.27	734.24
Drug Dependent	Mild	8	5.20	2453.93
Drug Dependent	Drug Dependent	8	352.90	43.53
Drug Dependent	Drug Refractory	8	8.33	1309.41
Drug Dependent	Surgery	8	15.24	893.36
Surgery	Drug Responsive	8	25.90	256.44
Surgery	Mild	8	8.27	483.26
Surgery	Drug Dependent	8	16.30	311.87
Surgery	Drug Refractory	8	13.74	340.13
Surgery	Surgery	8	113.71	183.86
Surgery	Surgical Remission	8	147.41	129.92

*8-week transition probability parameters derived from 12-week parameters

Appendix 15: Base Case Model Results

Strategy	Costs	QALY	ICUR	Med. Admissions	Surg. Admissions
A (Usual Care)	C$9,940	0.6281	--	0.6573	0.4899
B (Single-Dose)	C$12,702	0.6433	C$181, 201/QALY	0.3911	0.3640
C (Re-Treatment)	C$13,739	0.6455	C$480, 111/QALY	0.3290	0.3544
D (Maintenance)	C$21,597	0.6568	C$696, 078/QALY	0.3241	0.3349

Appendix 16: One-way Deterministic Sensitivity Analyses

(A) Rate of Surgical Admission following Drug-Refractory Disease (Base-Case Value 15%):

		0%	15%	25%	50%	75%	100%
Strategy A	Costs (C$)	5,140	9,940	13,576	17,531	19,464	20,578
	QALY	0.6139	0.6281	0.6391	0.6560	0.6670	0.6741
Strategy B	Costs (C$)	9,113	12,702	15,589	18,839	20,557	21,592
	QALY	0.6336	0.6434	0.6511	0.6631	0.6710	0.6764
Strategy C	Costs (C$)	10,446	13,739	16,627	19,689	21,244	22,187
	QALY	0.6360	0.6455	0.6533	0.6650	0.6728	0.6779
Strategy D	Costs (C$)	20,126	21,597	24,465	27,033	28,307	29,075
	QALY	0.6477	0.6568	0.6645	0.6758	0.6831	0.6880
ICUR ($C/QALY)							
Strategy A		Reference	Reference	Reference	Reference	Reference	Reference
Strategy B		202,585	181,201	167,550	183,903	267,061	446,885
Strategy C		546,585	480,111	474,530	423,444	393,017	Dominate (ext)
Strategy D		823,116	696,078	699,112	686,344	683,694	686,808

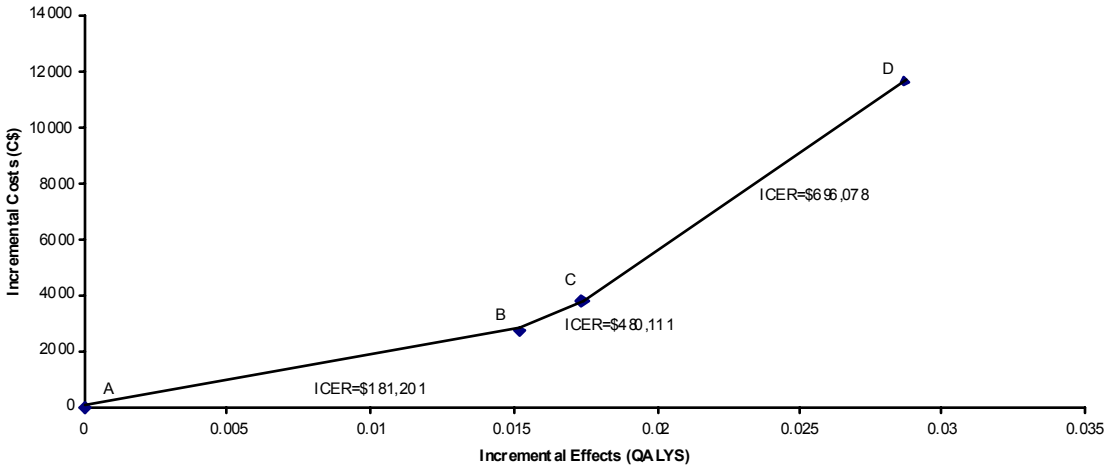
(B) Rate of Medical Admission for Drug-Refractory Disease (Base-Case Value 20%):

		0%	20%	40%	60%	80%	100%
Strategy A	Costs (C$)	7,265	9,940	12,616	15,292	17,968	20,644
	QALY	0.6281	0.6281	0.6281	0.6281	0.6281	0.6281
Strategy B	Costs (C$)	11,110	12,702	14,294	15,886	17,479	19,071
	QALY	0.6434	0.6434	0.6434	0.6434	0.6434	0.6434
Strategy C	Costs (C$)	12,398	13,739	15,081	16,422	17,764	19,105
	QALY	0.6455	0.6455	0.6455	0.6455	0.6455	0.6455
Strategy D	Costs (C$)	20,278	21,597	22,917	24,237	25,557	26,876
	QALY	0.6568	0.6568	0.6568	0.6568	0.6568	0.6568
ICUR (C$/QALY)							
Strategy A		Reference	Reference	Reference	Reference	Dominated	Dominated
Strategy B		252,300	181,201	110,101	39,002	Reference	Reference
Strategy C		596,185	480,111	364,042	247,968	131,894	15,824
Strategy D		698,025	696,078	694,130	692,183	690,236	688,289

(C) Drug Costs of Infliximab Relative to Base-Case (Base-Case Value 100%):

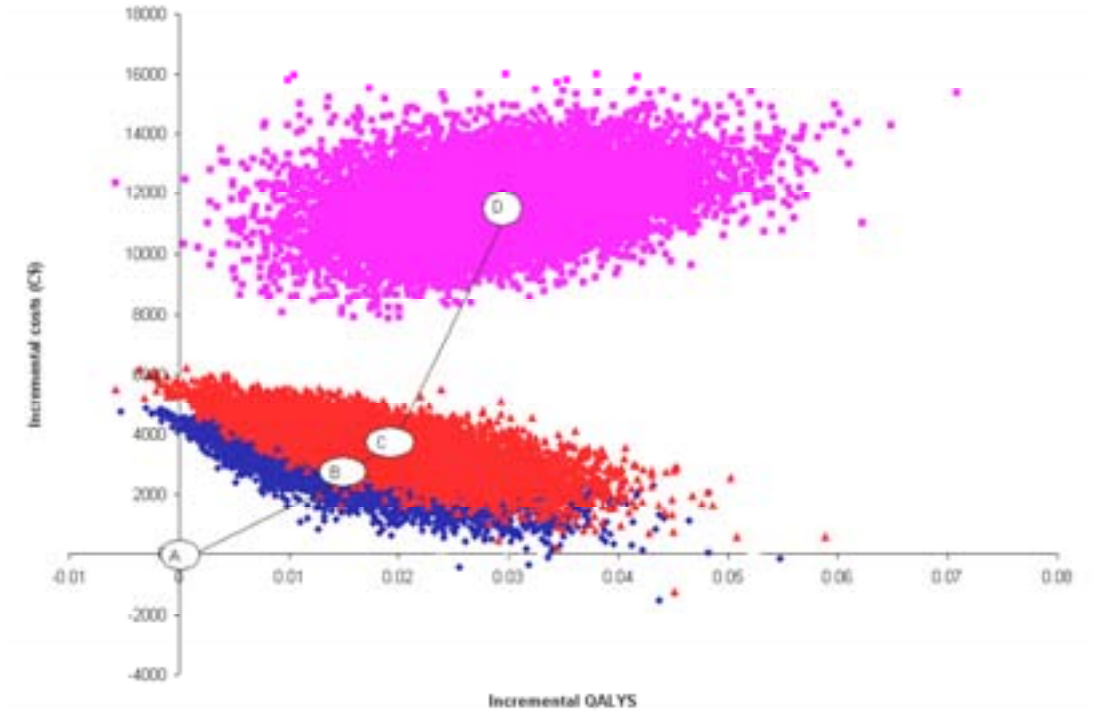
		0%	25%	50%	75%	100%
Strategy A	Costs (C$)	9,940	9,940	9,940	9,940	9,940
	QALY	0.6281	0.6281	0.6281	0.6281	0.6281
Strategy B	Costs (C$)	7,642	8,907	10,172	11,437	12,702
	QALY	0.6433	0.6433	0.6433	0.6433	0.6433
Strategy C	Costs (C$)	7,375	8,966	10,557	12,148	13,739
	QALY	0.6455	0.6455	0.6455	0.6455	0.6455
Strategy D	Costs (C$)	7,395	10,946	14,496	18,047	21,597
	QALY	0.6568	0.6568	0.6568	0.6568	0.6568
ICUR (C$/QALY)						
Strategy A		Dominated	Dominated	Reference	Reference	Reference
Strategy B		Dominated	Reference	15,190	98,186	181,201
Strategy C		Reference	27,389	178,296	329,204	480,111
Strategy D		1,810	175,376	348,944	522,511	696,078

Appendix 17: Graph of Base-Case Analysis



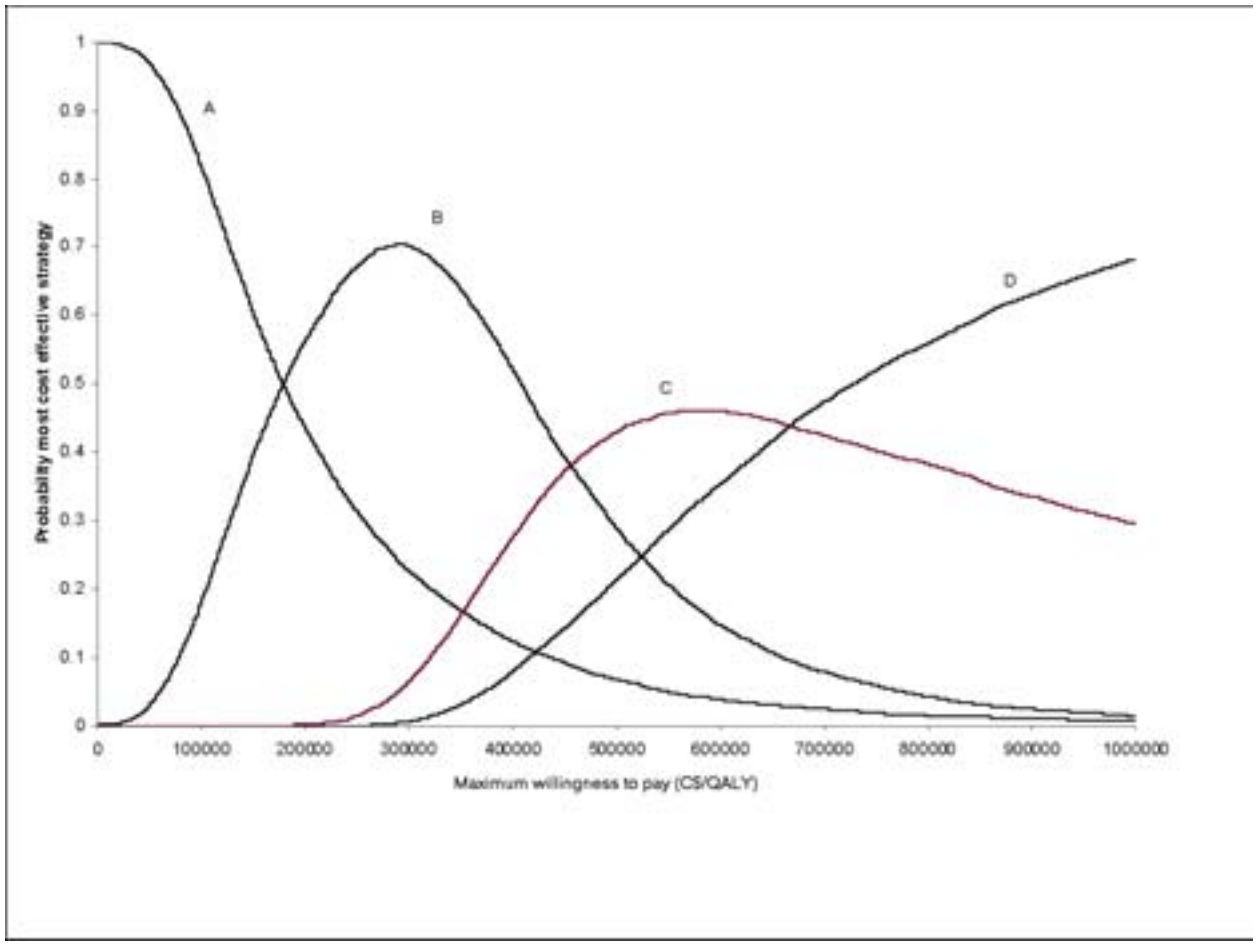
Legend:
A = Strategy A (" Usual Care")
B = Strategy B (" Single Dose")
C = Strategy C (" Re-treatment")
D = Strategy D (" Maintenance")

Appendix 18: Scatter Plot of Monte Carlo Simulation for Probabilistic Sensitivity Analysis



Legend:
A = Strategy A (" Usual Care")
B = Strategy B (" Single Dose")
C = Strategy C (" Re-treatment")
D = Strategy D (" Maintenance")

Appendix 19: Acceptability Curves from Probabilistic Sensitivity Analysis



Legend:
A = Strategy A (" Usual Care")
B = Strategy B (" Single Dose")
C = Strategy C (" Re-treatment")
D = Strategy D (" Maintenance")