Clinical and Economic Assessment: Infliximab for the Treatment of Crohn’s Disease
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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™)
  − 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 (RemicadeTM) 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 conduct a primary cost-utility analysis of infliximab treatment for patients with active CD resistant to conventional therapy.

Clinical 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 5mg/kg than 10 or 20mg/kg. Among subjects who responded to a blinded infliximab infusion or an open-label re-infusion (10mg/kg), re-infusions of 10mg/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...
(5mg/kg or 10mg/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 3 to 7 per cent 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 Review**

Six previous economic analyses of infliximab and two observational studies of infliximab-
associated resource utilization were identified. The only published analysis concluded that the
incremental cost-utility ratio (ICUR) of infliximab for fistulizing CD vs. usual care is high
(US$355,450/QALY). A cost-utility analysis of single-dose infliximab for treatment-resistant
CD, presented in abstract form, found its ICUR to range from US$14,200/QALY to
US$40,000/QALY. Four evaluations prepared by industry yielded favourable results, finding
infliximab to be cost saving for both indications.

**Economic Analysis**

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$2762 (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 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.
1. Introduction
Crohn’s disease (CD) is a chronic relapsing inflammatory disorder of the gastrointestinal tract characterized by segmental and transmural inflammation. Although the disorder is heterogeneous, patients with CD can be categorized by disease location, severity, and behaviour (inflammatory, fibrostenotic, fistulizing). Management strategies can be broadly dichotomized to those that treat acute, active disease and those that maintain response and prevent relapse among patients in remission. None of the available medical therapies is uniformly effective and many, like systemic corticosteroids, can cause serious side effects. Half of patients with CD require surgery over their lifetime for refractory or complicated disease, but post-operative recurrence is common.2

Improved understanding of the complex intestinal immune response 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. Infliximab is a chimeric IgG-kappa monoclonal antibody to tumor necrosis factor-alpha (TNFa), and 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.

The use of infliximab has been endorsed in recent guidelines released by the American College of Gastroenterology and the Canadian Association of Gastroenterology.3,4 However, the costs of infliximab and other biologic agents are 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. A primary economic analysis is presented for its use in treatment-refractory inflammatory CD.

2. Objectives
- Review published and unpublished evidence of the efficacy, effectiveness and adverse effects of infliximab for treatment of CD.
- Review published and unpublished economic analyses of infliximab for treatment for CD.
- Evaluate the cost-utility of infliximab for the management of treatment-resistant CD in a Canadian practice setting.

3. Clinical Review

Literature Search
A systematic search of electronic reference databases and abstract listings from major scientific meetings was undertaken. Abstract authors were contacted to identify unpublished manuscripts. Unpublished data were also sought from pharmaceutical companies that produce and distribute infliximab. Websites of relevant international government agencies were searched, and selected agencies were contacted directly for information. The titles and/or abstract listings of all citations were screened for potential relevance.
The review of clinical effectiveness considered all citations that 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. Non-randomized case series were considered for review only if they evaluated clinical outcomes of infliximab treatment in at least 100 consecutive patients with CD and were reported in English. Unpublished reports were accepted if sufficiently detailed. In reviewing adverse events, data available from eligible clinical trials were supplemented by data from case series and cohort studies, federal agencies, and industry. The reporting biases inherent to uncontrolled case reports were acknowledged.

The search identified six reports of randomized controlled efficacy trials. Of these, four were primary reports and two described secondary endpoints from another of the trials. The major design characteristics of four primary clinical trials are summarized in Table 1.

Table 1: Summary of Clinical Efficacy Trial Designs

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Present et al⁶</th>
<th>Targan et al⁸</th>
<th>Rutgeerts et al⁷</th>
<th>ACCENT¹⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre (n)</td>
<td>North America, Europe (12)</td>
<td>North America, Europe (18)</td>
<td>North America, Europe (17)</td>
<td>North America, Europe, Israel (55)</td>
</tr>
<tr>
<td>Intervention (n)</td>
<td>Infliximab 5mg/kg iv (31); Infliximab 10mg/kg iv (32) at Weeks 0,2,6</td>
<td>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)</td>
<td>Infliximab 10mg/kg iv at Weeks 12, 20, 28, 36 (37)</td>
<td>Infliximab 5mg/kg iv at Weeks 2, 6, 14, 22, 30 (113); Infliximab 5mg/kg iv at Weeks 2, 6 then 10mg/kg iv at Weeks 14, 22, 30 (112)</td>
</tr>
<tr>
<td>Comparator (n)</td>
<td>Matched placebos iv (31)</td>
<td>Matched placebos iv (25)</td>
<td>Matched placebos iv (36)</td>
<td>Infliximab 5mg/kg iv at Week 0 then matched placebos iv (110)</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Partial closure (50% reduction in draining fistulas on two consecutive study visits)</td>
<td>Clinical response at Week 4 (drop in CDAI&gt;70)</td>
<td>Sustained clinical response at Week 44 (drop in CDAI&gt;70)</td>
<td>Time to loss of clinical response from Week 2 (drop in CDAI&gt;70)</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>Remission (CDAI&lt;150)</td>
<td>Duration of response</td>
<td>Change in CDAI</td>
<td>Remission (CDAI&lt;150)</td>
</tr>
<tr>
<td>Outcome Assessments</td>
<td>Weeks 0, 2, 6, 10, 14, 18, 26, 34</td>
<td>Weeks 0, 4, 8, 12</td>
<td>Weeks 12, 16, 20, 24, 28, 32, 36, 40, 44</td>
<td>Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, 62, 70, 78, 102</td>
</tr>
</tbody>
</table>

The randomized controlled efficacy trials were considered too heterogeneous for quantitative pooling in a meta-analysis because of variation in patient population (fistulizing versus treatment-resistant disease), disease status (active 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 of at least 100 subjects. The remaining 38 citations were also reviewed for reports of rare or unusual adverse events. In addition, summary reports of cumulative efficacy and safety data from all clinical trials of infliximab were provided by Schering Canada.
**Fistulizing Crohn’s Disease**

For the treatment of fistulizing CD, only one controlled study has been reported. This multicentre, randomized, placebo-controlled, double-blind trial enrolled 94 adult subjects with CD and draining enterocutaneous or perianal fistulas for at least three months. Subjects were required to be on stable doses of 5-aminosalicylates (5ASA), corticosteroids, methotrexate or azathioprine/6-mercaptopurine (6MP). Participants were randomized to receive intravenous infliximab 5mg/kg (n=31), infliximab 10mg/kg (n=31) or placebo (n=32) at Weeks 0, 2 and 6 and were followed to Week 18. Six subjects discontinued treatment after the second infusion for lack of efficacy (three on placebo), withdrawal of consent (one on infliximab) or unspecified administrative reasons (one on placebo).

By intention-to-treat analysis, infliximab was superior to placebo in achieving the primary study endpoint, a 50% reduction in the number of draining fistulas upon gentle compression at two consecutive study visits (62% vs. 26%, p=0.002). Infliximab was also superior in achieving the secondary endpoint of complete closure of all fistulas (46% vs. 13%, p=0.001). No difference between the two infliximab doses was seen. Perianal Disease Activity Index (PDAI) scores differed significantly from placebo in both treatment groups at Week 2, but only in the 5mg/kg treatment group at Week 18.

A large, multi-centre trial (ACCENT II) is underway to confirm these results and evaluate longer-term treatment with repeated doses of infliximab. However, results of four large case series support the efficacy of infliximab for fistulizing CD. Ricart et al noted improvement in 17 of 26 patients (65%) and closure of all fistulas in 9 (35%). Of 48 subjects, Cohen et al reported improvement of fistulas in 53% and complete closure in 26% after 7 weeks. Farrell reported that 70% and 55% of 33 patients treated for fistulizing CD experienced a 50% or greater reduction in PDAI at 2 and 18 weeks, respectively, with closure of 64% and 48% of fistulas. An update of this series described clinical benefit in 84% of 72 patients. De Vos et al noted significant improvements in CDAI and Inflammatory Bowel Disease Questionnaire (IBDQ) scores in 62 patients with fistulizing CD, but did not report rates of fistula closure.

Although the number of trials of infliximab infusion for fistulizing CD is relatively small, the available literature supports its efficacy. No subgroup effects have been identified. As no dose response has been observed, the 5mg/kg dose is used clinically. However, the rationale for three serial infusions is unclear. 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) is also uncertain.

**Treatment-Resistant Crohn’s Disease**

Targan et al reported a randomized, multi-centre, placebo-controlled trial of infliximab for treatment-resistant CD. Eligible participants were required to have moderate to severe CD with CDAI scores between 220 and 400 despite treatment with 5ASA (8 weeks), systemic corticosteroids (8 weeks) or 6MP/azathioprine (6 months). Subjects were randomized to receive placebo (n=25) or one of the following infliximab doses as a single intravenous infusion: 5mg/kg (n=27); 10mg/kg (n=28) or 20mg/kg (n=28). The primary study endpoint was clinical response at Week 4, defined as a decrease of at least 70 points in the CDAI (intention-to-treat analysis). Non-responders at Week 4 were offered an open-label infusion of infliximab 10mg/kg. Follow-up extended to 12 weeks from the last infusion. All infliximab doses were superior to placebo in
achieving the primary study endpoint, but no dose-response was observed (Table 2). The rates of clinical response and clinical remission at Week 4 were both significantly higher in the combined infliximab groups than with placebo. At Week 12, the clinical response rate was significantly higher with infliximab, but the gain in clinical remission lost statistical significance. Endoscopic and histologic endpoints, reported separately for 30 European subjects, improved significantly in those treated with infliximab but not those treated with placebo.

Table 2: Short-Term Study of Infliximab in Treatment-Resistant Crohn’s Disease

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Week 4 Response</th>
<th>Week 4 Remission</th>
<th>Week 12 Response</th>
<th>Week 12 Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>4/25 (16%)</td>
<td>1/25 (4%)</td>
<td>3/25 (12%)</td>
<td>2/25 (8%)</td>
</tr>
<tr>
<td>5mg/kg infliximab</td>
<td>22/27 (81%)</td>
<td>n/r</td>
<td>13/27 (48%)</td>
<td>8/27 (30%)</td>
</tr>
<tr>
<td>10mg/kg infliximab</td>
<td>14/28 (50%)</td>
<td>n/r</td>
<td>8/28 (29%)</td>
<td>5/28 (18%)</td>
</tr>
<tr>
<td>20mg/kg infliximab</td>
<td>18/28 (64%)</td>
<td>n/r</td>
<td>13/28 (46%)</td>
<td>7/28 (25%)</td>
</tr>
<tr>
<td>Combined infliximab</td>
<td>54/83 (65%)</td>
<td>27/83 (33%)</td>
<td>34/83 (41%)</td>
<td>20/83 (24%)</td>
</tr>
</tbody>
</table>

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

Subjects who achieved clinical response at Week 8 in any arm of the Targan study were invited to join a study extension to evaluate repeated doses of infliximab to maintain the response. Seventy-three participants were randomized to receive either four intravenous doses of infliximab 10mg/kg at eight-week intervals (n=37) or a matched placebo (n=36), starting at Week 12 after their previous infusion. Treatment was discontinued in 24 subjects for lack of efficacy (12 on placebo, 4 on infliximab), adverse events (6 on infliximab), withdrawal of consent (one on placebo), or non-compliance (one on placebo). The proportion of subjects who maintained the clinical response at Week 44 was numerically higher among those receiving infliximab maintenance (62% vs. 37%, p=0.16), but this difference was not significant. Interval rates reached significance only at Week 36 (72% vs. 44%, p=0.018). The proportion of subjects in clinical remission at Week 44 was significantly higher in the infliximab group (44% vs. 20%, p=0.013). The median time to loss of response was 37 weeks with placebo, versus more than 48 weeks with infliximab (i.e. most subjects continued in clinical response at Week 48).

The interim results of a large ongoing randomized double-blind multi-centre trial evaluating acute and maintenance therapy in patients with moderately to severely active treatment-resistant CD were reported in abstract form. The ACCENT 1 trial has enrolled 573 subjects with median baseline CDAI 297 (range 193 to 488), of whom 62% were receiving corticosteroids and 29% other immunomodulators. All subjects received infliximab 5mg/kg at week 0. Those who responded at Week 2 (> 70 point drop in CDAI to < 75% of baseline) were randomized to one of three arms: (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) matched placebo. At Week 10, infliximab was superior to placebo in achieving clinical response (65% vs. 53%, p<0.05). At Week 30, infliximab was superior to placebo with respect to: (1) the proportions of subjects in clinical response (55% vs. 27%, p<0.001), clinical remission (42% vs.
21%, p<0.01); and steroid withdrawal (34% vs. 11%, p<0.01); (2) the median steroid dose; and (3) the median increase in IBDQ score. No significant difference between the maintenance regimens was observed. The trial is continuing to Week 102.

**Adverse Effects**

Table 3 summarizes adverse events experienced by more than 10 per cent of subjects in combined controlled clinical trials of infliximab for treatment of CD. Differences in event rates between infliximab and placebo are partially confounded by the longer follow-up of infliximab-treated subjects in some trials. Serious adverse events were reported among 13% of infliximab-treated subjects vs. 4% of placebo-treated subjects. There were no deaths. The reported incidences of adverse events are broadly similar to those experienced in clinical trials of infliximab in rheumatoid arthritis.

Table 3: Adverse events in clinical trials of infliximab for CD

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patient treated</td>
<td>56</td>
<td>199</td>
</tr>
<tr>
<td>Mean weeks of follow-up</td>
<td>14.7</td>
<td>27.0</td>
</tr>
<tr>
<td>One or more adverse event</td>
<td>35 (62.5%)</td>
<td>168 (84.4%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 (8.9%)</td>
<td>32 (16.1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (21.4%)</td>
<td>45 (22.6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (3.6%)</td>
<td>33 (16.6%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (3.6%)</td>
<td>24 (12.1%)</td>
</tr>
<tr>
<td>Fever</td>
<td>4 (7.1%)</td>
<td>21 (10.6%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (5.4%)</td>
<td>21 (10.6%)</td>
</tr>
</tbody>
</table>

Infusion reactions, defined as adverse events that occur during or within two hours of an infusion, can occur with administration of infliximab. Present reported dizziness, headache, low-grade fever, chest pain or flushing in 4 of 63 subjects (6.3%) treated for fistulizing CD. Targan 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 (6.9%). In the re-treatment phase of this study, Rutgeerts et al noted reversible dyspnea during an infusion in 1 of 37 subjects (2.7%). Across all published trials of infliximab for treatment of CD and rheumatoid arthritis, infusion reactions have been reported with 4.8% of infliximab infusions (vs. 2.1% of placebo infusions) and have led 1.9% of patients to discontinue treatment. Most reactions appear to be mild or moderate and respond to interrupting the infusion. Three serious reactions have been reported, but all were nonfatal and resolved within two hours. Preliminary results of the ACCENT I trial note infusion reactions in 5.5% of subjects on infliximab (of which 1.0% were “serious”) vs. 3.2% of subjects on placebo. In three large case series, the rates of infusion reaction ranged from 5.4% to 9.0%. No associated deaths have been described.

Infliximab can induce the formation of human anti-chimeric antibodies (HACA). Although their clinical significance remains unclear, HACA have been suggested to increase the risk of reactions to subsequent infusions and/or attenuate their effectiveness.
controlled trials of infliximab for CD, HACA were detected in 4% to 15% of subjects, but residual infliximab in some serum may have interfered with the assay. HACA may develop less often in subjects given concomitant immunosuppressive therapy. A small randomized controlled trial suggested that pre-treatment with intravenous hydrocortisone could reduce formation of HACA. Several patients with new antibodies to double-stranded DNA and one case of steroid-responsive lupus arthritis have also been reported in clinical trials of infliximab for CD, and a case series reported new, low-titre anti-nuclear antibodies after treatment. However, the clinical significance of these autoimmune markers remains to be defined.

Eighteen malignancies (including 5 lymphomas) have been reported within 3 years of treatment in clinical trials of infliximab for CD, and a case of NK-cell lymphoma emerged in the ongoing ACCENT1 trial. Although this observed incidence of lymphoma exceeds the rate expected in healthy population controls, there are conflicting data on the baseline risk of lymphoproliferative disorders in patients with CD. Accordingly, any increase attributable to infliximab therapy remains controversial.

As of January 3, 2001 33 cases of tuberculosis among the 115,000 patients treated with infliximab worldwide had been reported to the manufacturer. These include 13 disseminated infections and 3 deaths. Although the majority of cases occurred outside North America, both the manufacturer and recent Canadian guidelines suggest that patients be evaluated for latent or active tuberculosis prior to treatment with infliximab.

In the European subset of subjects participating in the Targan trial, 2 of 22 subjects treated with infliximab developed strictures at sites of previous ulceration. New intestinal strictures have also been described in case series, but the lack 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.

4. **Economic Review**

A systematic search identified nine studies of the economic impact of infliximab treatment for CD. Of these, only one is published in a peer-reviewed journal and four were presented as abstracts to international scientific meetings. The remaining four reports were unpublished analyses prepared and provided by industry. Six citations reported economic models, two were observational studies of resource utilization among patients treated with infliximab, and one was a descriptive analysis of infusion-related costs relative to reimbursement.

**Fistulizing Crohn’s Disease**

A published Markov model compared four strategies for treating perianal fistulizing CD with respect to their incremental cost-utility from the perspective of a U.S. third party payer. The strategies were: (1) 6MP/metronidazole; (2) infliximab with 6MP/metronidazole for failures; (3) infliximab with re-infusion for failures; and (4) 6MP/metronidazole with infliximab for failures. Surgery was not considered, and non-responders remained in a “persistent fistula” state with constant risk of abscess formation. Twelve one-month cycles were modeled, with costs and benefits discounted at an annual rate of 3%. Transition probabilities were derived from a systematic literature review, and direct medical costs (1999 US$) were acquired from an existing administrative database using cost-to-charge ratios. Health state utilities were elicited from a
convenience sample of 32 patients with CD using a standard gamble technique. In the base-case analysis, Strategies 1, 4, 2 and 3 provided progressively more QALY at progressively higher cost. However, all incremental cost-utility ratios (ICUR) were greater than US$300,000/QALY. In sensitivity analysis, reducing drug costs by 85% reduced the ICUR of Strategy 3 vs. Strategy 1 to US$54,050/QALY.

In contrast, an unpublished cost minimization study of infliximab infusion for fistulizing CD prepared by industry assembled an expert panel to profile typical resource utilization by hypothetical patients with fistulizing CD. When the direct costs of key resources were considered from the perspective of a Canadian provincial ministry of health, infliximab was concluded to generate cost savings of C$106 over one year.

**Treatment-Resistant Crohn’s Disease**

In an analysis presented in abstract form the cost-utility of infliximab for treatment-resistant CD was assessed from the perspective of a U.S. third-party payer. The authors applied 4-week efficacy data from Targan to an existing natural history Markov model constructed from observed transitions and health care charges in a cohort of CD patients in Olmsted County. Health state utilities were adapted from Gregor et al. and costs and benefits were discounted at an annual rate of 3%. When infliximab-induced remission was equated to surgical remission, infliximab was cost saving. When it was equated to “medical remission” or “mild disease”, infliximab improved outcomes with ICUR of US$14,200/QALY and US$40,000/QALY, respectively. Thus, the authors concluded infliximab to be cost-effective.

An unpublished, industry-driven cost-minimization study asked an expert panel to profile resource utilization by drug-refractory patients treated with infliximab vs. usual care. With direct medical costs considered from the perspective of a Canadian provincial ministry of health, infliximab was found to generate net annual savings of C$12,336. However, the analysis assumed that all untreated patients require a 30-day medical admission plus a hospitalization for surgery. Two Australian analyses, also prepared by industry, considered the impact of infliximab from the perspective of an Australian ministry of health. The first used efficacy data from Targan to estimate the incremental cost per clinical remission after 4 and 12 weeks as Aus$8,965 and Aus$17,929, respectively. However, the only incremental costs considered were those of the infliximab infusion. Finally, an Australian cost-utility analysis used efficacy data from Targan and Rutgeerts to assess the cost-utility of a single infliximab infusion over 48 weeks. The model used just two health states, with utilities adapted from Gregor et al. Infliximab was found to improve outcomes with an undiscounted ICUR of Aus$45,418/QALY. When the time horizon was extended to 104 weeks under various assumptions of treatment durability, the discounted ICUR were found to range from Aus$21,932/QALY to Aus$31,770/QALY.

5. **Primary Economic Analysis**

**Methods**

a) **General**
An economic analysis was undertaken to compare the expected costs and outcomes of alternative strategies for management of patients with CD resistant to conventional medical therapy. A Markov model was constructed to represent the health states experienced by a hypothetical
cohort of patients with active treatment-resistant CD. 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 8 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"):** No infliximab treatment. There exists no single, obvious alternative to infliximab in the treatment of refractory CD. Alternatives can include continued outpatient medical care (e.g. new or extended immunosuppression), inpatient medical care (e.g. intravenous corticosteroids) and surgery. Within a cohort of patients eligible for infliximab, some weighted mixture of these approaches would occur (see below).

**Strategy B ("Single Dose"):** Intravenous infusion of infliximab 5mg/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 as in Strategy A.

**Strategy C ("Re-treatment"):** Intravenous infusion of infliximab 5mg/kg at Week 0 with no maintenance infliximab therapy. However, patients who subsequently relapse are re-treated with a single infusion of infliximab 5mg/kg.

**Strategy D ("Maintenance"):** Intravenous infusion of infliximab 5mg/kg at Week 0. Patients who respond to treatment (drop in CDAI of at least 70 points) receive maintenance infusions of infliximab 5mg/kg every 8 weeks starting at Week 12. Patients who do not respond to infliximab or subsequently relapse on maintenance therapy receive usual care as in Strategy A.

**b) Transition Probabilities**
Transition probabilities were derived from two sources: (1) observed transitions in the Targan\textsuperscript{8} and Rutgeerts\textsuperscript{7} clinical trials; and (2) observed transitions in long-term population-based cohort study of 174 patients with CD in Olmsted County.\textsuperscript{40} Permission to re-analyze the latter data was obtained from the authors. The dataset was used to construct a previous natural history model of CD,\textsuperscript{40} and segregates patients among 8 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 steroids or immunosuppressives with improvement.

**Drug-Dependent:** Treatment with steroids or immunosuppressive > 6 months with improvement.

**Drug-Refractory:** Treatment with steroids >2 months or immunosuppressives >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.

**Death**

The same health states and definitions were adopted for the current Markov model of infliximab for treatment-resistant CD with one exception: no deaths were assumed within the one-year time horizon. The model cohort initially was assigned to the **Drug-Refractory** state. In Strategy A (Usual Care), transition probabilities from **Drug-Refractory** to **Drug-Responsive** and **Remission** in the first model cycle were calibrated to the rates of clinical response and remission reported at 12 weeks in the placebo arm of the Targan trial (0.04 and 0.08). In Strategies B through D, transition probabilities to **Drug-Responsive** and **Remission** in the first cycle were set to the rates of response and remission in the combined infliximab arms of that trial (0.17 and 0.24). For all strategies, the remaining transition probabilities to other health states were estimated from the Olmsted county transition data using survival analysis (SAS 6.12 LIFEREG procedure) to derive exponential hazard rates and their standard errors. These probabilities were reweighted in fixed proportion to sum to one. Transition to **Surgical Remission** was permitted only from **Surgery** or **Surgical Remission**.

In subsequent 8-week cycles, subjects in the **Remission** and **Drug Responsive** states were allowed to either remain in that state or relapse to the **Drug Refractory** state. Transition probabilities in strategies without maintenance therapy (Strategies A, B and C) were calibrated to the observed rates of clinical relapse from Week 12 to Week 44 in the placebo arm of the Rutgeerts trial assuming a constant hazard rate. Insufficient data were available from the publication to calculate separate conditional probabilities for remaining in remission (**Remission** to **Remission**) or clinical response (**Drug-Responsive** to **Drug-Responsive**). Thus, the conditional probability of remaining in each health state was estimated to be 0.7963. This approach eliminated transition between the **Remission** and **Drug-Responsive** health states.

In Strategy D, subjects who responded to the initial dose of infliximab received maintenance infusions at 8-week intervals. Those who failed the initial dose or relapsed (to the **Drug-Refractory** state) on maintenance therapy received usual care. The treatment effect of repeated infliximab infusion was represented by a multiplier variable, which increased the probabilities of remaining in the **Remission** and **Drug-Responsive** health states (Strategies A, B and C) to the conditional response rates observed from Week 12 to Week 44 in the infliximab arms of the Rutgeerts maintenance trial. Accordingly, the probability of remaining in both **Remission** and **Drug-Responsive** was estimated to be 0.9370.

Strategy C was similar to Strategy B, except that patients who relapsed (to the **Drug-Refractory** state) following an initial response to infliximab received another infusion of infliximab. The ensuing transitions were assumed to equal those seen with the initial infusion (i.e. Strategy B) but prorated to an 8-week cycle length.

For all 8-week cycles, transitions not derived from clinical trials were estimated from the Olmsted County data as described above. 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. In addition, transitions to **Surgical Remission** occurred only from **Surgery** or **Surgical Remission**. Transitions from **Surgical Remission** were permitted only to **Surgical Remission** or **Drug Refractory**.

c) **Utility Weights**  
Utility weights for each model health state were adapted from Gregor et al.41 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 were not identical to those represented in the model. Thus, model health states **Remission, Surgical Remission**, and **Mild** were equated to the mild disease scenario with utility 0.82 (95% CI 0.80 to 0.85). Model health states **Drug Responsive** and **Drug Refractory** were equated to the moderate disease scenario with utility 0.73 (0.71 to 0.77). Model health states **Drug Refractory** and **Surgery** were equated to the severe disease scenario with utility 0.54 (0.50 to 0.59).

d) **Cost Inputs**  
For each model health state, profiles of resource utilization were 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 considered. Similarly, indirect costs were not captured.

Resource profiles and unit costs for infusion-related personnel, facilities and disposable supplies were prepared by audit of current infusion protocols at the McMaster University Medical Centre. The costs of infliximab were estimated for a 70kg patient and assumed an acquisition cost C$1150/100mg vial. A 10% mark-up and $4.11 dispensing fee were assumed in accordance with Ontario Drug Benefit Plan provisions. Thus, the total cost per infusion of infliximab was estimated to be C$5338.41.

Standard profiles of prescription medications and outpatient physician contacts were developed by consensus of a three-member expert panel of clinical gastroenterologists (JKM, EJI, KC) based on text descriptions of the health states.40 Profiles for the initial **Drug Refractory** state were based on the concomitant medications reported in the two published trials of infliximab in treatment-resistant CD.7,8 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 dispensing fees, it was assumed that all medications were dispensed as 12-week supplies.

For each cycle spent in the **Surgery** health state, only one surgical admission was assumed. For each cycle spent in the **Drug Refractory** health state, 0.20 medical admissions were assumed. Costs for medical and surgical admissions for CD were obtained from the existing case-cost database of London Health Sciences Centre (LHSC, London ON). 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.

e) **Sensitivity Analyses**  
Three model parameters were subjected to deterministic one-way sensitivity analysis. Because
use of inpatient hospital resources for medical and surgical treatment of CD is a major cost driver in the management of CD, the proportion of patients with Drug-Refractory disease who received inpatient medical care was varied between 0% and 100% (base case 20%). The rate of surgical admission was also tested by varying the transition from Drug-Refractory to Surgery from 0% to 100% (base case rate approximately 13%). Finally, the impact of variation in drug costs was tested by varying the cost of infliximab infusion between 0% and 100% of its baseline value.

A probabilistic sensitivity analysis was undertaken to consider the effects of joint uncertainty across multiple parameters of the model. Distributions were specified for model parameters to reflect uncertainty in their estimates, and 10,000 Monte Carlo simulations were performed to select values at random from those distributions. Beta distributions (bounded by zero and one) were specified to parameterize transition probabilities and utility weights. For most cost parameters in the model, no distributions were specified. 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.

Because there exists uncertainty with respect to the acceptable threshold for incremental cost-utility ratios, acceptability curves were constructed from the Monte Carlo simulation to demonstrate the probabilities that each strategy would provide the greatest net benefit across a range of threshold values of C$/QALY.

Results
a) Base Case Analysis
In the base-case model analysis, no strategy was dominant (Table 4). Strategy A (Usual Care) incurred the lowest costs and generated the fewest QALY ($9941 and 0.6281 QALY over one year). Strategies B, C and D (in order) incurred increasing costs but provided progressively more QALYs. Strategies B (Single Dose) and C (Re-Treatment) 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. The rates of surgical and medical admission were lowest in the Strategy D (Maintenance), and highest in Strategy A. From Strategy A to Strategy B, the rates of medical and surgical admission fell by 40% and 26%, respectively.

Table 4: Results of Base-Case Analysis of Cost-Utility Model

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs</th>
<th>QALY</th>
<th>ICUR (C$/QALY)</th>
<th>Medical Admissions</th>
<th>Surgical Admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>C$ 9,940</td>
<td>0.6281</td>
<td>N/A</td>
<td>0.6573</td>
<td>0.4899</td>
</tr>
<tr>
<td>B</td>
<td>C$12,702</td>
<td>0.6433</td>
<td>C$181,201</td>
<td>0.3911</td>
<td>0.3640</td>
</tr>
<tr>
<td>C</td>
<td>C$13,739</td>
<td>0.6455</td>
<td>C$480,111</td>
<td>0.3290</td>
<td>0.3544</td>
</tr>
<tr>
<td>D</td>
<td>C$21,597</td>
<td>0.6568</td>
<td>C$696,078</td>
<td>0.3241</td>
<td>0.3349</td>
</tr>
</tbody>
</table>

b) Deterministic Sensitivity Analysis
Variation in the rate of surgical admission for drug-refractory CD was found to exert negligible
influence on the ICUR, all of which remained in excess of C$150,000/QALY. The model was sensitive to variation in the proportion of patients with drug-refractory disease who required hospital admission (base case assumption 20%). Higher rates of admission were associated with lower ICUR for Strategy B vs. Strategy A, and Strategy C vs. Strategy B but only small changes in that for Strategy D vs. Strategy C. If 60% were admitted, the ICUR of B vs. A fell to C$39,002/QALY. If 80% were admitted, Strategy B was dominant over Strategy A. If all were admitted, Strategy B remained dominant over Strategy A but the ICUR of C vs. B fell to C$15,824/QALY. Thus, infliximab therapy may be more economically appealing in patient subgroups with higher likelihoods of admission.

The model was also sensitive to variation in costs for drug acquisition and infusion. If these costs were reduced by 25%, the ICUR of Strategy B vs. Strategy A fell below C$100,000/QALY. If costs were reduced by 75%, Strategy B was dominant over Strategy A, and the ICUR of Strategy C vs. Strategy B fell to C$27,289/QALY. If drug and infusion costs were eliminated, Strategy C was dominant over both Strategies A and B, and the ICUR of Strategy D vs. Strategy C was small (C$1,810/QALY).

c) Probabilistic Sensitivity Analysis
A scatter plot of the incremental costs and effects of Strategies B, C and D relative to Strategy A is provided in Figure 1. Acceptability curves to demonstrate the probability that each strategy would provide the greatest net benefit across a range of threshold values of C$/QALY are provided in Figure 2. If the maximum willingness-to-pay per QALY is less than C$180,000/QALY, Strategy A is most likely to provide greatest net benefit. For values between C$180,000/QALY and C$430,000/QALY, Strategy B is favoured. For values between C$430,000/QALY and C$690,000/QALY, Strategy C is preferred. Strategy D is favoured only if decision makers are willing to pay more than C$690,000 per QALY.

Discussion and Limitations
The decision analytic model compared four alternative strategies for the treatment of active CD, with respect to their expected direct medical costs and quality-adjusted survival over one year. None of the strategies was simply or extendedly dominant over another in the base-case analysis. Usual care incurred the lowest costs (C$9941) 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 limited 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 rates of medical admission and reductions in drug costs.

In probabilistic sensitivity analysis, the distributions 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.

Acceptability curves plot the likelihood that a strategy is the most cost-effective alternative across a range of ICUR thresholds. They provide important information to decision makers faced with uncertainty about societal willingness-to-pay for QALY. 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, controversy over the selection and use of cost-effectiveness thresholds to allocate resources continues, and beyond the scope of this report. 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, for lack of Canadian data of similar detail, we estimated some transition probabilities through analysis of raw data from long-term follow-up of an established U.S. patient cohort. Because these data assigned patients to health states according to medical treatment, assumptions were required to transpose the outcomes of clinical trials that were defined in terms of disease activity. Assumptions were also required to convert published utility weights for CD to model health states that were not represented precisely in the utility data set. Furthermore, estimates of treatment effect were derived from a relatively 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. From a societal perspective, the ICUR of infliximab treatment relative to usual care could become more favourable.

It must be recognized that few medical 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 or deferring surgery. In the base case analysis, a single infliximab infusion for active CD reduces surgical admissions within one year by approximately 25%.

This analysis will require updates to assess the effects of future changes in infliximab delivery, costs and dose regimens, such as those used in the ongoing ACCENT1 trial. Despite this and other limitations, however, the model is methodologically rigorous, 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.
6. 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 both acute and maintenance therapy of treatment-resistant CD. In Canada, maintenance therapy is not an approved indication for infliximab. Additional efficacy data from large, controlled clinical trials are forthcoming.

Clinical trials and post-marketing experience suggest that the short-term tolerability of infliximab is acceptable. Acute infusion reactions are relatively common, but are self-limited and rarely severe. Cases of disseminated tuberculosis and malignancy (including lymphoma) have been observed, but their attributable risk is uncertain. New autoimmune markers and human anti-chimeric antibodies (HACA) have also developed after infliximab therapy, but their clinical significance remains unclear.

In a Markov model cost-utility analysis with both deterministic and probabilistic sensitivity analysis, the incremental cost-utility ratio of single-dose infliximab therapy for treatment-resistant CD was estimated to be C$181,201 from the perspective of a Canadian provincial ministry of health. This estimate exceeds most conventional cost-utility thresholds, but was sensitive to changes in drug infusion costs and rates of medical admission.

7. References


Figure 1: Scatter plot of incremental costs and outcomes in Monte Carlo simulation for probabilistic sensitivity analysis. Strategy A is used as the reference strategy.
Figure 2: Acceptability curves generated in probabilistic sensitivity analysis