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Infliximab and Etanercept in Rheumatoid Arthritis: Systematic Review of Long-term Clinical Effectiveness, Safety, and Cost-Effectiveness
Until April 2006, the Canadian Agency for Drugs and Technologies in Health (CADTH) was known as the Canadian Coordinating Office for Health Technology Assessment (CCOHTA).


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Infliximab and Etanercept in Rheumatoid Arthritis:
Systematic Review of Long-term Clinical Effectiveness,
Safety, and Cost-effectiveness

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Zulma Ortiz participated in the design of the project, screening of literature, data abstraction, analysis and interpretation of the data, and revision of the report.

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Conflicts of Interest

Chris Skedgel has received research funding from Pfizer, AstraZeneca, and Eli Lilly.
Infliximab and Etanercept in Rheumatoid Arthritis: Systematic Review of Long-term Clinical Effectiveness, Safety, and Cost-Effectiveness

Technology and Condition
Biologic agents intended to reduce tumor necrosis factor (TNF) in the treatment of rheumatoid arthritis (RA): infliximab (IFX) and etanercept (ETN)

Issue
It is estimated that 150,000 to 300,000 Canadians have been diagnosed with RA. There is uncertainty about the long-term (>12 months) effectiveness and safety of anti-TNF agents. It is unknown whether the increased cost of anti-TNF agents compared with the cost of traditional disease-modifying anti-rheumatic drugs (DMARDs) in the long term is justifiable with limited available resources.

Methods and Results
A systematic review of the clinical literature was done to compare IFX and ETN at recommended dosages with placebo or other therapies. The literature search resulted in eight health technology assessment reports, 14 systematic review articles, 30 original publications on long-term effectiveness, 160 on safety, and 22 economic evaluations.

Implications for Decision Making

- **IFX and ETN are moderately effective at one year.** Evidence suggests that IFX and ETN, used concomitantly with MTX, improve surrogate and composite outcomes, such as delay in radiological progression and American College of Rheumatology improvement criteria. The long-term impact on functionality, survival, or quality of life has not been demonstrated.

- **Concerns remain regarding long-term harm.** Evidence suggests that risks for some serious complications, such as tuberculosis and autoimmune disorders, are greater with IFX than with ETN. Half of patients receiving IFX and a third of patients receiving ETN discontinued therapy by the third year of treatment. Patients receiving therapy should be monitored.

- **IFX and ETN are not cost-saving.** Economic evidence suggests that ETN and IFX, when used concomitantly with MTX, is only cost-effective for the treatment of RA after the failure of other DMARDs, and if society is willing to pay >$100,000 to obtain a quality-adjusted life-year.

EXECUTIVE SUMMARY

The Issue

Rheumatoid arthritis (RA), which is a chronic inflammatory disorder of uncertain etiology, is characterized by a chronic polyarthritis causing potentially severe pain and disability. The morbidity and clinical course of RA reflect its distribution and severity. Although effective treatments are available, many patients with RA develop refractory disease and functional impairment, with a deleterious impact on their quality of life.

Etanercept (ETN, brand name Enbrel®) and infliximab (IFX, brand name Remicade®) are agents that are intended to reduce tumour necrosis factor (TNF) activity. Both have been approved in Canada for use in patients with RA and other inflammatory arthritis. They have also been approved for use in other patient populations.

These agents are thought to work more quickly than traditional disease-modifying anti-rheumatic drugs (DMARDs) to reduce inflammation. The costs and potential toxicity of IFX and ETN must be weighed against their effectiveness in improving health outcomes and reducing health care resource utilization.

Objectives

To review the available data on the long-term effectiveness, safety, and cost effectiveness of IFX and ETN in the treatment of patients with RA.

Methods

Using a defined search strategy, published and unpublished literature was searched in March 2005 (without publication date restrictions) and the search systematically updated until September 2005. For the review on effectiveness, we included studies with a duration of ≥1 year, and we evaluated randomized controlled trials (RCTs) and observational studies. Outcome measures included American College of Rheumatology (ACR) improvement criteria (ACR50: 50% improvement in the number of swollen and tender joints, and 50% in at least three of the other five core set measures), Disease Activity Scores (DAS), functional status, and radiological progression. A meta-analysis was performed to synthesize and combine the results of RCTs. Data from observational studies was synthesized but not combined. For the review of cost-effectiveness, we included all studies reporting costs and outcomes.

Results

A total of eight health technology assessments, 14 systematic reviews, 30 original publications on long-term effectiveness, 160 on safety, and 22 on economic evaluations were analyzed. The original publications on clinical effectiveness and safety included RCTs, observational studies, pharmacovigilance reports, and case reports and series.

Long-term effectiveness: RCTs of ≥1 year duration showed that anti-TNF agents have a small to moderate effect in clinical outcomes. A clinical and significant improvement in ACR50 improvement criteria and DAS28 scores was observed for IFX+methotrexate (MTX) and ETN+MTX, compared with MTX alone. A statistically significant pooled result was observed for the Short Form 36 (SF-36) physical component with IFX 3 mg/kg every eight weeks, but the effect was not clinically
meaningful (1.77, with an effect size of 0.15). The beneficial effects of anti-TNF agents were revealed on radiological progression: Significant differences were observed between the treatment and control groups, even when the clinical differences were not significant. ETN alone did not offer a clear benefit over MTX alone, but ETN+MTX was better than MTX alone. Observational studies in clinical practice or as follow-up studies of trials showed high discontinuation rates for all causes after several years of treatment.

**Safety:** Anti-TNF agents are well tolerated in the short term (generally $\leq 6$ months). Concerns remain about their longer-term safety with respect to infections (i.e., tuberculosis, histoplasmosis, listeriosis, and coccidiomycosis), development of tumors (e.g., lymphomas), autoimmunity [i.e., antinuclear antibodies (ANAs), anti-deoxyribonucleic acid (DNA), anti-histone and anticardiolipin, systemic lupus], and demyelination (i.e., encephalopathies, transverse myelitis, optic neuritis, and peripheral neuritis).

**Economic Review:** Economic evidence suggests that treatment with ETN and IFX, each used concomitantly with MTX, is only cost-effective for the treatment of RA after the failure of other DMARDs, and if a high threshold for cost-effectiveness is used [$>$100,000 per quality-adjusted life-year (QALY)].

**Discussion**

ETN and IFX have been shown to be cost-effective at current thresholds as a second-line therapy after the failure of a traditional DMARD. IFX+MTX may be more effective during the first year of treatment than ETN alternatives, particularly at higher dosages. The two-year data and the longer-term results of cohort studies do not show better efficacy for either drug. The discontinuation rates are similar to those observed for other traditional DMARDs, such as MTX, and perhaps higher for IFX, which appears to be more effective than ETN.

There are several limitations. First, because of ethical and feasibility concerns, the duration of RCTs is generally $<6$ months, which hinders the assessment of long-term effectiveness in trials. Second, there are no well-designed observational studies comparing IFX and ETN head to head to determine the differences in efficacy or risk for infrequent but serious adverse events. Third, for economic evaluations, explicit assumptions based on expert opinion were required regarding natural history and resource utilization.

**Health Services Impact**

Anti-TNF therapies are only cost-effective if a large threshold is used, and if indirect costs are considered. Decision makers must recognize that TNF blockers offer a potential treatment to selected patients with refractory RA for whom few other alternatives are available because other treatments have failed.

In practice, the utilization patterns of TNF antagonists diverge from the experience in trials, and can result in unexpected use and costs. Moreover, the demand for these therapies is likely to increase over time with their increased availability.

The widespread adoption of these therapies will require changes in the infrastructure needed to deliver services. IFX is administered intravenously and therefore an outpatient setting is required. This suggests that a large initial investment is needed for outpatient space and training in the delivery
of IFX. The average cost of delivery is likely to decrease over time as more RA patients use the services. ETN is delivered in a self-administered injection. This suggests that the increasing use of ETN will not have a large initial cost, but it will not have a decreasing average cost with additional patients.

**Conclusions**

IFX and ETN, each used concomitantly with MTX, have moderate efficacy in the long-term treatment of active RA that is resistant to conventional therapy. Indirect comparisons showed a trend favouring the use of IFX+MTX over ETN+MTX, and no advantage to using ETN alone over MTX.

The short-term (<12-month) safety profile of TNF antagonist therapy is acceptable, but concerns remain about the long-term consequences, particularly with respect to infections, lymphomas, autoimmunity, and demyelination.

The economic review shows that costs per QALY are high, surpassing in many evaluations the generally accepted thresholds for cost-effectiveness. The results suggest that IFX+MTX and ETN+MTX are only cost-effective as second-line therapies after failure with traditional DMARDs if society is willing to pay >$100,000 for a QALY. Longer-term clinical studies and economic evaluations need to take into account community practice patterns to better reflect the realistic benefits and costs of these therapies.
ABBREVIATIONS

aCL  anticardiolipin antibodies
ACR  American College of Rheumatology
ADM  adalimumab
AE   adverse events
ANA  antinuclear antibodies
ANAK anakinra
ANCA anti-neutrophilic cytoplasmic antibodies
anti-dsDNA anti-double stranded deoxyribonucleic acid
anti-RNP anti-ribonucleoprotein antibodies
anti-Sm anti-Smith antibodies
aPL  anti-phospholipid antibodies
ARAMIS Arthritis, Rheumatism, and Aging Medical Information System
ARMADA Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab [D2E7] in Rheumatoid Arthritis
AS   ankylosing spondylitis
ASPIRE Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group
ATC  Anatomic Therapeutic Chemical
ATTRACT Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group
AUC  area under the curve
BD   benefit difference
bid  twice a day
BIOBADASER Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología
biw  biweekly
BPM  Birmingham preliminary model
BRAM Birmingham Rheumatoid Arthritis Model
CCT  controlled clinical trial
CD   Crohn’s disease
CDC  Centers for Disease Control
CE   cost-effective
CEA  cost-effectiveness analysis
CI   confidence interval
CRP  C-reactive protein
DAS  Disease Activity Score
DD   disease duration
DKK  Danish kroner
DMARD disease modifying anti-rheumatic drug
DNA  deoxyribonucleic acid
dsDNA double-stranded deoxyribonucleic acid
ENA  extractable nuclear antigen antibodies
ERA  early rheumatoid arthritis
ESR  erythrocyte sedimentation rate
ETN  etanercept
EULAR European League Against Rheumatism
RR relative risk (or relative benefit when measuring effectiveness)
SC subcutaneous
SD standard deviation
SE standard error
SEK Swedish kronor
SF-36, SF-6 Short Forms 36 and 6
SIR standardized incidence ratio
SJC swollen joint counts
SLE systemic lupus erythematosus
SMD standardized mean difference
SSATG South Swedish Arthritis Treatment Group
SSZ sulfasalazine
TB tuberculosis
TEMPO Trial of Etanercept and Methotrexate with Radiographic Patients Outcomes
TJC tender joint counts
TNF tumour necrosis factor
UK United Kingdom
US United States
VAS visual analogue scale
vdH-S van der Heijde-Sharp score
wk week
WMD weighted mean difference
WTP willingness to pay
y year
β2GPI beta₂ glycoprotein-1 antibodies
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXECUTIVE SUMMARY</td>
<td>iv</td>
</tr>
<tr>
<td>ABBREVIATIONS</td>
<td>vii</td>
</tr>
<tr>
<td>1 INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.1 Background</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Overview of Technology</td>
<td>2</td>
</tr>
<tr>
<td>1.2.1 Description of technology</td>
<td>2</td>
</tr>
<tr>
<td>1.2.2 Infliximab</td>
<td>2</td>
</tr>
<tr>
<td>1.2.3 Etanercept</td>
<td>2</td>
</tr>
<tr>
<td>2 THE ISSUE</td>
<td>3</td>
</tr>
<tr>
<td>3 OBJECTIVES</td>
<td>3</td>
</tr>
<tr>
<td>4 CLINICAL REVIEW</td>
<td>4</td>
</tr>
<tr>
<td>4.1 Methods</td>
<td>4</td>
</tr>
<tr>
<td>4.1.1 Literature search strategy</td>
<td>4</td>
</tr>
<tr>
<td>4.1.2 Selection criteria and method</td>
<td>4</td>
</tr>
<tr>
<td>4.1.3 Safety</td>
<td>5</td>
</tr>
<tr>
<td>4.1.4 Data extraction strategy</td>
<td>6</td>
</tr>
<tr>
<td>4.1.5 Strategy for quality assessment</td>
<td>6</td>
</tr>
<tr>
<td>4.1.6 Data analysis methods</td>
<td>6</td>
</tr>
<tr>
<td>4.2 Results</td>
<td>7</td>
</tr>
<tr>
<td>4.2.1 Clinical effectiveness</td>
<td>7</td>
</tr>
<tr>
<td>4.2.2 Safety</td>
<td>17</td>
</tr>
<tr>
<td>4.3 Discussion</td>
<td>20</td>
</tr>
<tr>
<td>4.3.1 Long-term effectiveness</td>
<td>20</td>
</tr>
<tr>
<td>4.3.2 Safety</td>
<td>21</td>
</tr>
<tr>
<td>5 ECONOMIC ANALYSIS</td>
<td>21</td>
</tr>
<tr>
<td>5.1 Methods</td>
<td>21</td>
</tr>
<tr>
<td>5.1.1 Literature search strategy</td>
<td>21</td>
</tr>
<tr>
<td>5.1.2 Selection criteria and method a) Selection criteria</td>
<td>21</td>
</tr>
<tr>
<td>5.1.3 Data extraction strategy</td>
<td>22</td>
</tr>
<tr>
<td>5.1.4 Data analysis methods</td>
<td>22</td>
</tr>
<tr>
<td>5.2 Results</td>
<td>22</td>
</tr>
<tr>
<td>5.2.1 Quantity of research available</td>
<td>22</td>
</tr>
<tr>
<td>5.2.2 Study Characteristics</td>
<td>23</td>
</tr>
<tr>
<td>5.2.3 Data analysis and synthesis</td>
<td>23</td>
</tr>
<tr>
<td>5.3 Discussion</td>
<td>34</td>
</tr>
<tr>
<td>6 HEALTH SERVICES IMPACT</td>
<td>35</td>
</tr>
<tr>
<td>7 DISCUSSION</td>
<td>35</td>
</tr>
<tr>
<td>7.1 Summary of Results</td>
<td>35</td>
</tr>
<tr>
<td>7.2 Study Limitations</td>
<td>36</td>
</tr>
<tr>
<td>7.3 Generalizability of Findings</td>
<td>37</td>
</tr>
</tbody>
</table>
7.4 Knowledge Gaps

8 CONCLUSIONS

9 REFERENCES

APPENDICES – available from CADTH’s web site www.cadth.ca

APPENDIX 1: Literature search strategy
APPENDIX 2: Outcome Measures for Clinical Review
APPENDIX 3: Selection Criteria Forms
APPENDIX 4: Data Extraction Forms
APPENDIX 5: Quality Assessment Instruments
APPENDIX 6: Clinical Review – Excluded Studies
APPENDIX 7: Clinical Review – Study Characteristics
APPENDIX 8: Clinical Review Results – IFX RCTs
APPENDIX 9: Clinical Review Results – ETN RCTs
APPENDIX 10: Clinical Review Results – Effectiveness, Observational Studies
APPENDIX 11: Clinical Review Results – Safety
APPENDIX 12: Economic Review – Excluded Studies
APPENDIX 13: Economic Review – Study Characteristics
APPENDIX 14: Economic Review Results
1 INTRODUCTION

1.1 Background

Rheumatoid arthritis (RA), which is a chronic inflammatory disorder of unknown etiology, is characterized by a chronic polyarthritis causing pain and disability that can be severe. The clinical course is variable. Most patients experience flares and remissions, but the remissions tend to be partial, and for most patients, inflammatory disease activity is always present. About a third of patients have a non-remittent, progressive course. A few patients have a flare that lasts months or years, followed by prolonged remission. The prevalence of RA varies from 0.5% to 1.5% of the adult population, ages ≥18 years. RA is more common in women (3:1) and may appear at any age, most often in the fifth or sixth decade of life.

The etiology of RA appears to be multi-factorial. An association with human leukocyte antigens (HLA), specifically HLA DR4, occurs in many, but not all patients. It is thought that disease occurs because of an interaction between these genetic factors, which influence immune responses, and environmental factors such as infections. No single environmental factor has yet been identified.

RA has an impact on quality of life. Over the years, structural damage occurs, often leading to articular deformities, muscular atrophy, and functional impairment. The mortality rates of patients with RA are increased, compared with those of the general population. The reduction in survival of patients with advanced RA is similar to that observed in patients with coronary artery disease and Hodgkin’s lymphoma.

The current clinical treatment of RA includes several drug therapies. Non-steroidal anti-inflammatory drugs (NSAIDs) are usually the first medications that are prescribed. The main clinical effect of these drugs is a reduction in joint pain, stiffness, and swelling, which occurs within days of starting the therapy. In theory, the sustained suppression of inflammation could prevent more joint damage. There is no evidence to date that NSAIDs can slow the rate of joint destruction. Disease-modifying anti-rheumatic drugs (DMARDs) have a more profound effect — modifying RA’s natural course. With DMARDs, clinical effects usually take several weeks or months to appear. DMARDs interfere with inflammatory and immunologic pathways, depending on the drug, though their mechanisms of action are often unclear. Commonly used DMARDs include methotrexate (MTX), sulfasalazine (SSZ), antimalarials, leflunomide (LEF), gold salts, cyclosporin and cytotoxic agents (azathioprine and cyclophosphamide). An increasing trend is the use of ≥2 drugs in combination. Although not all DMARD combinations have been proven to be more efficacious than their single counterparts, many — particularly those including MTX — have a beneficial effect. None of these drugs is curative, and their discontinuation often leads to a relapse with increased disease activity. Therefore, for most patients, DMARD therapy is continued throughout their lives. Patients with active disease who are treated continuously have better outcomes than those who receive therapy intermittently.

A delay in starting therapy has adverse effects. Structural damage, which is seen in radiological erosions, occurs in many patients during the first year of disease and is generally irreversible. Systematic reviews show that a delay in therapy is related to deleterious outcomes. The current recommendation is to treat patients with active RA early and aggressively within months from the onset of the disease.
A new approach in the treatment of RA is the use of biologic therapies. Several biologic agents that have been developed in the past decade, target specific cytokines or cell markers, which are crucial to the pathogenesis of RA. The first biologic therapy to gain approval for use in RA were agents against tumour necrosis factor (TNF) α, a cytokine that plays a role in the chronic joint inflammation of RA.

1.2 Overview of Technology

1.2.1 Description of technology

Three anti-TNF agents have been approved as treatment for RA: etanercept (ETN; Enbrel®; marketed by Amgen Canada), infliximab (IFX; Remicade®; marketed by Schering Canada Inc.), and adalimumab (ADM; Humira®, marketed by Abbott Canada). This report evaluates the long-term effectiveness and cost-effectiveness of the first two anti-TNF agents to obtain approval for use in RA: IFX and ETN. The Anatomical Therapeutic Chemical (ATC) therapeutic classification for IFX and ETN is selective immunosuppressive agents. The ATC classification of IFX is L04AA12, and the ATC classification of ETN is L04AA11. Dose and unit cost information is provided in Table 1.

<table>
<thead>
<tr>
<th>Drug</th>
<th>DIN</th>
<th>Strength/Dosage Form</th>
<th>Cost per Unit</th>
<th>Dose Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX</td>
<td>02244016</td>
<td>100 mg/vial</td>
<td>$940.00 (^{12})</td>
<td>3 mg/kg intravenously, every 4 to 8 weeks after loading dose of 3 doses of 3 mg/kg</td>
</tr>
<tr>
<td>ETN</td>
<td>02242903</td>
<td>4 vials of 25 mg</td>
<td>$740.00 (^{13})</td>
<td>25 mg subcutaneous injection twice a week</td>
</tr>
</tbody>
</table>

ETN=etanercept; IFX=infliximab; DIN=drug identification number.

1.2.2 Infliximab

IFX is a chimeric human-murine monoclonal antibody targeted against TNF. About 30% of the recombinant antibody is murine, and 70% is human. The murine portion comprises the region that binds to TNF. IFX binds to membrane-bound and soluble TNF. The recommended dose is 3 mg/kg at weeks zero, two, six, and every eight weeks thereafter. The approved dose range per infusion is from 3 mg/kg to 10 mg/kg.

1.2.3 Etanercept

ETN is a genetically engineered fusion protein: two chains of a recombinant human p75 TNF soluble receptor are linked to the Fe domain of human immunoglobulin G (IgG). ETN only binds soluble TNF. The initially recommended dosage was 25 mg subcutaneously twice weekly. Recent evidence suggests that 50 mg weekly is as effective, and this preparation is increasingly being used.

IFX and ETN were approved for use in patients with moderate to severe RA in Canada in 2000 and 2001 respectively. They have also been approved for use in other patient populations.
2 THE ISSUE

This project is aimed at clarifying the issues of long-term effectiveness, sustainability of results, toxicity, and cost of IFX and ETN therapy for RA.

Questions linger about the long-term effectiveness and safety of these treatments. Randomized controlled trials (RCTs) and systematic reviews have shown that these agents are efficacious in the short term, decreasing pain and swelling, and improving function. Radiological progression is slower in patients who are treated with anti-TNF agents, when compared with patients treated with MTX. Yet questions remain unanswered in relation to the longer-term effects and the sustainability of the initial beneficial effects. Short-term toxicity is not severe.

The long-term side effects include an increase in the rate of infections, particularly tuberculosis. It is unclear whether these agents increase the risk of hematologic and solid tumours. Because the available efficacy and toxicity data from RCTs are short-term (<12 months), larger and longer-term studies are required.

This report also investigates issues related to the cost-effectiveness of these agents. The annual cost for administration of a biologic agent is approximately $10,000. Therefore, most health care agencies and drug plans only approve the use of biologic therapies in RA after failure with the use of usually ≥2 other traditional DMARDs is demonstrated. The cost-effectiveness of anti-TNF agents in comparison to other agents remains unclear. Most economic analyses have been based on data from short-term trials and often sponsored by the pharmaceutical industry. The analyses compare the benefits and costs of anti-TNF agents in relation to placebo or to remaining on a DMARD (usually MTX) and assume an inadequate response. These control scenarios are unlikely in medical practice, because most patients with RA who have one DMARD fail will switch rheumatic agents or receive combination therapy (the addition of a DMARD). This approach has been inadequately compared with biologic therapy, and the use of therapeutically ineffective control arms can bias the results by suggesting better relative benefits than would be observed in clinical practice.

The evidence from clinical trials suggest better short-term efficacy for anti-TNF agents than for other DMARDs, but larger studies of long-term effectiveness and safety are required. While the cost-effectiveness of these biologic agents has been evaluated by various groups, the methods and clinical settings vary. Our systematic review may assist in determining the cost-effectiveness of these agents under varying clinical scenarios.

3 OBJECTIVES

The objective of the report is to provide the best up-to-date evidence of the safety, long-term effectiveness, and costs of anti-TNF agents in the treatment of RA. To accomplish this, we present a systematic review of the literature that includes RCTs, observational studies, and economic evaluations from the time when anti-TNF agents were first available. Two questions are implied in our objective.

- What is the evidence (clinical trials or observational studies) of the long-term effectiveness and safety of IFX and ETN for RA?
- What is the evidence of cost-effectiveness for IFX and ETN for RA?
The information in this report is intended to help health providers, policy makers, and consumers make decisions about the clinical use of IFX and ETN for RA.

4 CLINICAL REVIEW

4.1 Methods

4.1.1 Literature search strategy

Data identification and retrieval was done according to the recommendations in the Guidelines for Authors of CCOHTA Health Technology Assessment Reports. A comprehensive, single search strategy (Appendix 1) was designed to identify published and unpublished (grey) literature covering the safety, clinical effectiveness, cost-effectiveness, therapeutic timing, dose escalation, and switching of IFX and ETN in the treatment of patients with RA. Because of the potential overlap among these issues, literature searches were combined, and the relevant retrieved references were categorized and synthesized by review topic. When the report was written, it became apparent that the large volume of information would be best presented by dividing the document into two reports. Thus, this report includes the safety, long-term clinical effectiveness, and cost-effectiveness analyses, and another CADTH report discusses the results of the therapeutic timing, dose escalation, and switching analyses.

On the DIALOG® system, the MEDLINE®, EMBASE®, BIOSIS Previews®, and ToxFile databases were searched on March 16, 2005. This search was systematically updated and results incorporated on a biweekly basis until September 4, 2005. Parallel searches were conducted on PubMed. There were no publication date restrictions on any of the searches. All searches were limited to human studies. The 2005, Issue 1 of The Cochrane Library was searched and results updated to 2005, Issue 3. Grey literature was retrieved by searching the web sites of health technology assessment (HTA) and related agencies. Only English, Spanish, French, Italian, Portuguese or German original publications were included because of the availability of translation. Reviews were mostly retrieved to identify additional information that may have been missed in the searches, and were only examined further if they were published in English. The only exceptions were two HTA reports (from Denmark and Hungary) that provided enough information from tables that could be used to extract overall results. The two were also hand-searched to identify additional citations.

All databases and sources of information were cross-referenced to check for duplicate citations. These searches were supplemented by the hand-searching of bibliographies of retrieved relevant articles, systematic reviews, and HTA reports for additional references. The manufacturers of ETN (Amgen Canada) and IFX (Schering Canada, Inc.) were contacted for additional relevant information.

4.1.2 Selection criteria and method

a) Selection criteria

The inclusion criteria used to select publications for review of clinical effectiveness and safety are as follows.
Long-term effectiveness

- study design included RCTs, controlled clinical trials (CCTs), quasi-randomized studies, cohort studies (prospective or retrospective), and case-control studies
- population included patients with RA; results specified for RA patients if the study included >1 disease
- intervention was IFX or ETN at recommended dosages: IFX (≥3 mg/kg every eight weeks), ETN (<50 mg/week); other therapies allowed; we only considered publications providing separate results for IFX and ETN
- comparator was placebo or other therapies (for RCTs and CCTs); for observational studies, no comparator was required
- duration of therapy and follow-up ≥1 year (reported as mean or average, or for all patients)
- outcomes were ≥1 of Disease Activity Score (DAS); responders to American College of Rheumatology (ACR) improvement criteria (ACR20, ACR50, ACR70) or European League against Rheumatism (EULAR) improvement criteria; health-related quality of life; radiological damage; and drug terminations (Appendix 2); we decided a priori to use ACR50 and ACR70 responses because ACR20 (20% improvement) indicates a small response, which may fail to differentiate benefit between active therapies\(^{20,21}\)
- for observational studies, a minimum sample size of 30 was required; per the central limit theorem, the number is based on assumptions about the normal distribution of parameters (mean) when the sample is <30.

4.1.3 Safety

All publications with information about adverse events (AEs) and safety were included. We included all observational studies reporting data primarily on safety.

- study design included pharmacovigilance reports, cohort studies (prospective or retrospective), case-control studies, case series, and case reports
- population was patients with RA as specified
- intervention was IFX or ETN
- outcomes were ≥1 of drug terminations, serious AEs, total serious and specific morbidity (e.g., cancer, infections), total hospitalizations, and mortality.

Technology assessment reports and systematic reviews examining the effectiveness and safety of IFX or ETN in RA patients were reviewed and preliminarily included if they complied with the following criteria derived from Cook\(^{22}\):
- explicit sources for identification and retrieval of data
- search strategy described.

Reviews that complied with these criteria were considered potentially systematic and screened using the QUOROM instrument for the assessment of reviews\(^{23}\). We considered as systematic those reviews with a score of ≥10 (out of a possible 18). This was decided by consensus. There are no published cut-offs for QUOROM, but two clusters >10 and <10, could be seen in our sample of reviews.

a) Selection method

The process for selecting articles followed three steps. At each step, two raters (BK, CP, MK, MLO, MM, or ZO) independently examined each citation. Agreement for inclusion or exclusion was by consensus. A third reviewer (MSA) assisted if consensus could not be reached. Selection criteria forms appear in Appendix 3.
Step 1: All potentially eligible publications were selected for review if the title and abstract appeared related to the objectives of this report. Selected publications were then obtained for full review. When reviewing titles and abstracts, the approach was always inclusive, i.e., when unclear, the reference was included for review of the full publication.

Step 2: The full publications of selected references were reviewed. Articles were excluded if they were unrelated to the issues of interest. Publications were categorized according to topic, i.e., clinical effectiveness or economic evaluation. When possible, inclusion or exclusion was decided based on information from the abstract.

Step 3: The specified inclusion criteria were applied. Appendices 6 and 12 list the excluded literature.

4.1.4 Data extraction strategy

The content of each study was abstracted by one reviewer (MLO) and independently cross-checked by a second reviewer [IFX (ZO); ETN (MSA)]. Disagreements were resolved by consensus. Extracted content included:

- publication characteristics (year of publication, language of publication, country, sources of funding)
- study characteristics (study design, duration of follow-up, sample size)
- population characteristics (age, sex, disease duration, clinical characteristics, previous therapies)
- intervention characteristics (drug, dosing)
- outcome measures (disease activity, functional impairment) (Appendix 2).

Data extraction forms appear in Appendix 4.

4.1.5 Strategy for quality assessment

The quality of each study was assessed by two independent raters. Differences were resolved by consensus, and if agreement was not achieved, a third rater was the adjudicator. For RCTs and CCTs, we used the Jadad score, which takes into account randomization, blinding, and description of withdrawals. We also rated allocation concealment as adequate, inadequate, or unclear. For observational studies, we used the Newcastle-Ottawa Scale (NOS), which evaluates the quality of non-randomized studies. This instrument provides subscales to assess the methodological quality of cohort and case-control studies on the basis of three design characteristics: selection of the study groups, comparability of the groups, and ascertainment of the exposure or outcome of interest for case-control or cohort studies respectively (Appendix 5).

4.1.6 Data analysis methods

a) Randomized clinical trials

RCT data were quantitatively analyzed using meta-analysis and an intention-to-treat model whenever possible. Continuous data were analyzed using weighted mean differences (WMDs) and standardized mean differences (SMDs) to estimate the effect sizes. An effect size of 0.80 was considered to be large, 0.50 moderate, and 0.20 small. Dichotomous data were reported as relative benefit (RB) or absolute benefit difference (BD) for improvements in health, and as relative risk (RR) for AEs. A chi-squared test [using n−1 degrees of freedom (n=number of studies) and a p value of ≤0.05] was performed to test the homogeneity of the data. A fixed-effects model was used for pooling studies to calculate a pooled estimate of effect. When heterogeneity was present, random effects models were
used. The mean and standard deviations (SDs) were used when available. If unavailable, the SD was estimated from confidence intervals (CIs) whenever possible. When only median and interquartile ranges were reported, the median was used as the mean, and half of the difference between the first and third quartile ranges was used as the SD.\textsuperscript{16} When only the baseline SD was available, it was used as the end-of-study SD. When numerical data were reported graphically only, the values were extracted from the graph. We estimated the percent or mean change from baseline when the data for these calculations were available.

We used the following outcome measures determined a priori:
- ACR50 and ACR70 improvement responses, shown as RB and BD
- physical functional status [Health Assessment Questionnaire (HAQ)], shown as WMD and SMD
- radiological scores, reported as WMD and SMD because all radiological data had been evaluated using van der Heijde-Sharp scores;\textsuperscript{26} a difference of $\geq 5$ is considered to be clinically meaningful with the van der Heijde-Sharp score, which is also the smallest detectable difference after accounting for reliability in readings.\textsuperscript{27}
- discontinuations (all, lack of efficacy, AEs), reported as RR.

All meta-analyses were conducted using the Cochrane Collaboration RevMan 4.2.7 software.

\textbf{b) Observational studies}
We included studies that reported at least one year of follow-up for patients on anti-TNF agents, with separate results for IFX and ETN. Data were extracted and synthesized without meta-analysis, and results were tabulated according to the primary outcome measure of the study, including:
- discontinuations (all, lack of efficacy, AEs)
- ACR responses
- swollen joint counts
- functional status
- radiological outcomes
- safety.

4.2 Results

4.2.1 Clinical effectiveness

\textbf{a) Quantity of research available}

The literature search is shown in Figure 1. Excluded citations are listed in Appendix 6. Although the manufacturers of IFX and ETN responded to our requests, no new information was obtained beyond the data that had been published.

At each step, two raters independently examined each citation. Kappa agreement scores were calculated for each pair of reviewers. Kappa coefficients ranged between 0.56 and 0.83 (agreement between 83\% and 92\%). The kappa score for all ratings combined was 0.81 [standard error (SE)=0.03].

A total of 3,620 possibly relevant citations were found after an electronic search (n=3,422) and hand searching (n=198). Two reviewers independently screened each title and abstract for relevance; 1,403 citations were excluded and 2,217 were selected for review of the full publication. Most of the excluded citations were related to diseases other than RA, were laboratory studies, or reported...
different therapies. The selected citations were obtained in full text and reviewed. This review excluded 1,530 articles, most of which were excluded because they:

- were abstracts from meetings or from published full papers
- contained citations related to diseases other than RA
- were comments or editorials
- contained insufficient information.

We did not contact authors to ask for more information. We excluded 65 articles in languages other than English, Spanish, French, Italian, Portuguese, and German.

Finally, 687 publications were selected to which the specific inclusion criteria were applied. In 33 cases, the full publication could not be retrieved. After this step, our literature search resulted in eight HTA reports, 14 systematic review articles, 177 original publications on clinical review, and 22 original publications on economic review. Of the 14 systematic reviews, eight were included in the set of articles for clinical review, and seven in the set of articles for economic review (one was included in both). There were 30 original publications on long-term clinical effectiveness (nine RCTs and 21 observational studies), 160 including safety data, and 22 on economic evaluation.

Some of the included references relate to the dose escalation and drug switching components in the second report.28

b) Study characteristics

Health technology assessments: Seven HTAs on the use of biologic agents for RA were conducted in five countries between 2001 and 2006: Germany,29,30 UK,31-33 Denmark,18 Hungary,19 and Canada.34 Each HTA involved its own literature review, for which search dates ranged from 1991 to 2003. Of the eight publications, three were updates. The reports included data on clinical effectiveness and safety. Study characteristics appear in Appendix 7 Table 1.

Systematic reviews: The characteristics of eight systematic reviews15,16,35-40 on the clinical effectiveness of anti-TNF agents appear in Appendix 7 Table 2. Two reviews, one on ETN15 and the other on IFX,16 included a meta-analysis of RCTs only, with safety and efficacy results, and a follow-up of six to 12 months in 955 and 529 subjects respectively. The other six reviews were non-quantitative and included mainly RCTs (two37,38 included observational studies) with at least six months follow-up, an examination of IFX or ETN with other agents, and between 902 and 3,907 subjects. The authors of three reviews disclosed an association with a pharmaceutical company.

Original publications

IFX RCTs: The study characteristics appear in Appendix 7 Table 3. Four trials presented in five publications41-45 met the inclusion criteria. The four RCTs included 428, 1,049, 24, and 20 patients respectively (1,113 IFX, 408 control). Three studies41,43,44 had a follow-up of one year, and two studies42,45 had a follow-up of two years. All four studies were double-blinded for the first year. The two studies with a follow-up of two years became open after the first year. The Jadad quality scores ranged between 3 and 5 (first year). All studies used an IFX dose of 3 mg/kg q8wk, except one study,44 which used a dose of 5 mg/kg q8wk. Doses of 3 mg/kg q4wk, 10 mg/kg q8wk, and 10 mg/kg q4wk were used in the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) trial.41,42 The Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) trial43 used 6 mg/kg q8wk. In all trials, the treatment and control groups received oral MTX. In two studies, MTX treatment had failed, and patients had high disease activity despite
Infliximab and Etanercept in Rheumatoid Arthritis: Systematic Review of Long-term Clinical Effectiveness, Safety, and Cost-effectiveness

In the other two studies, patients had no prior treatment with DMARDs and started oral MTX at the time of the trial. In the other two studies, patients had no prior treatment with DMARDs and started oral MTX at the time of the trial.41,42,44

**ETN RCTs:** The study characteristics are shown in Appendix 7 Table 4. We identified two RCTs of ETN presented in four publications with a duration of at least 12 months: the Etanercept and versus Methotrexate in Patients with Early Rheumatoid Arthritis (ERA)46-48 and the Trial of Etanercept and Methotrexate with Radiographic Patients Outcomes (TEMPO)49 studies. The two RCTs included 632 and 682 patients (869 ETN and 445 controls). The allocation concealment was unclear in the ERA trial46 and adequate in the TEMPO study.49 The Jadad quality scores were 2 and 4 respectively. The ERA48 trial became open after the first year and had a two-year follow-up.48 A dose of ETN 25 mg subcutaneous (SC) biw was used for both studies; a dose of 10 mg SC biw was also used in the ERA study. Control groups received oral MTX.

**Observational studies:** The study characteristics appear in Appendix 7 Table 5. A total of 21 publications were included and all reported cohort studies: four retrospective, 16 prospective, and one with retrospective and prospective studies. Ten studies included patients on IFX only, seven included patients on ETN only, and four included patients on either drug. Several were open follow-up cohort studies of patients who were previously included in RCTs.

Sixteen studies reported discontinuation rates (all causes and lack of efficacy). Five studies reported clinical outcomes only, and eight included both. We included the following outcomes in our synthesis: swollen joint counts, DAS, ACR responses, functional status, and radiological progression. Most studies did not have control groups comprised of patients not receiving TNF antagonists. The quality of the studies was assessed using the NOS; scores ranged between 2 and 9.

c) **Data analysis and synthesis**

**Health technology assessments**

**German HTA reports:** Corzilius et al.29 assessed the efficacy of anti-TNF agents in treating RA symptoms and severe disease activity, and when used at early stages before conventional treatments. The authors performed a systematic review and found 137 publications, including RCTs, observational studies, case reports, and surveillance registries. Clinical trials data in short-term studies showed statistically significant differences in rates of remission of disease activity and slowing of structural joint damage, and an increased risk for serious infectious complications. The authors concluded that TNF antagonists are effective in RA patients with no or an incomplete response to MTX and recommended this therapy after the failure of conventional DMARD treatment. A second report30 updated this publication and investigated related pharmacoeconomic studies.

**British HTA reports:** In 2001, Jobanputra et al.31 conducted a comprehensive systematic review and identified 118 publications. Results showed that ETN and IFX improved outcomes in adults with RA when compared with placebo. One trial failed to find a difference between ETN and MTX. Their second report32 updated this literature review regarding the clinical effectiveness and cost-effectiveness of new drug treatments for RA. In this update, the authors recommended:

- more research and development of economic models
- comparative studies of anti-TNF agents and other DMARDs
- studies of the quality of life of RA patients in the long term
- studies on how DMARDs and other interventions affect quality of life.
**Infliximab and Etanercept in Rheumatoid Arthritis: Systematic Review of Long-term Clinical Effectiveness, Safety, and Cost-effectiveness**

*Figure 1: Searches*

Step 1: Review of titles and abstracts
- Dialog N=2536
- other electronic databases N=886
- hand searching N=198

unique citations N=3,620

excluded N=1,403

potentially relevant citations N=2,217

excluded N=1,530

potentially relevant citations N=687

Step 2: Review of full paper

HTA-CPG N=30
- excluded N=22
- HTA N=8

reviews N=328
- excluded N=314
- reviews N=14

clinical review* N=299
- excluded N=122
- clinical review N=177

economic review* N=33
- excluded N=11
- economic review N=22

*Three original citations included in both reviews. HTA-CPG=health technology assessment-clinical practice guidelines.*
Danish HTA report: Kristensen et al.\textsuperscript{18} performed a systematic review of the management of RA, including the role of early referrals, diagnosis, and pharmacotherapy. It evaluated the efficacy, price, and role of IFX and ETN relative to other available treatments. The study compared three possible treatment models – a regimen of DMARDs alone, a regimen of new agents for new patients and for those in whom DMARDs are ineffective, and a regimen switching from DMARDs to new agents on an as-needed basis. The study recommended using anti-TNF agents after the failure of traditional DMARDs.

Hungarian HTA report: In a systematic review, Gulácsi et al.\textsuperscript{19} compared relevant meta-analyses in RA therapy to determine the efficacy, effectiveness, and efficiency of IFX therapy in terms of epidemiology, morbidity, mortality, clinical aspects, and economic burden. The review recommended additional studies to adapt current information to the epidemiological and health economic characteristics of RA in Hungary.

Canadian HTA report: Coyle et al.\textsuperscript{34} conducted a literature search from 1996 to 2003, and performed a systematic review of IFX and ETN in the treatment of RA. Results and conclusions were drawn from one-year data taken from trials. Three RCTs comparing IFX+MTX with MTX only, and three RCTs comparing ETN with placebo, were identified. The report was partly based on a previous HTA.\textsuperscript{32} Although ETN and IFX were found to be effective in controlling symptoms and retarding radiologic progression, the authors concluded that neither agent was cost-effective under conventionally applied criteria.

Systematic reviews

Quantitative (meta-analyses performed): Blumenauer et al.\textsuperscript{16} examined IFX for the treatment of RA. The review included two trials with a total of 529 patients. The dosages tested included IFX 1 mg/kg (with or without MTX), 3 mg/kg (with or without MTX), 10 mg/kg (with or without MTX), or placebo infusion plus MTX. Infusions were given every four or eight weeks. Treatment with IFX for six and 12 months significantly reduced RA disease activity and had an acceptable safety profile in these trials. The number needed to treat (NNT) with IFX to achieve an ACR20, ACR50, or ACR70 response in patients with refractory RA ranged from 2.78 to 3.33 for ACR20, 3.57 to 4.76 for ACR50, and 5.88 to 12.5 for ACR70, depending on the dose. Total radiographic scores improved, fewer patients showed radiographic progression, and more patients showed radiographic improvement with IFX treatment at 12 months compared with controls. Based on these results, the authors concluded that IFX was efficacious for the treatment of RA, based on short-term data.

In another review, Blumenauer et al.\textsuperscript{15} studied ETN for the treatment of RA. The review included three trials of at least six months duration. Two trials compared the experimental group, who were started on ETN, with a control group; in one trial, one group was on stable MTX. ACR20, ACR50, and ACR70 response rates at six months were statistically significant and clinically important with ETN 25 mg SC twice weekly: 39% of those receiving ETN achieved an ACR50 response compared with 4% taking control treatment (NNT=3); 15% achieved a ACR70 compared with 1% of controls (NNT=7). In the third trial, where patients started on ETN or MTX, no significant differences were observed in ACR responses, but ETN showed a beneficial statistically significant effect on radiological progression.

Non-quantitative (no meta-analyses performed): de Vries et al.\textsuperscript{35} published a review evaluating the efficacy of TNF antagonists in people with RA. The authors concluded that ETN and IFX were more effective than placebo in people with active RA that is insufficiently controlled with DMARDs.
ETN and IFX reduced clinical and non-clinical signs of disease severity, and prevented progressive joint damage in patients with severe RA not responding to conventional treatment.

Rubio-Terres et al. conducted efficacy and macro-economic analyses of the treatment of RA with LEF, a DMARD, in comparison with IFX+MTX. LEF and the IFX+MTX combination had similar efficacy and safety after one year of use.

Culy et al. examined ETN use in RA, psoriatic arthritis, and juvenile RA. They concluded that ETN was an important treatment option in inflammatory arthritis, providing rapid and sustained improvements in disease activity in early RA patients and patients with DMARD-refractory RA. ETN was shown to inhibit radiographic disease progression in those with early disease.

Keating et al. evaluated the role of ETN in the management of RA. They found that ETN provided a rapid and sustained reduction in disease activity, and inhibited the progression of structural damage in patients with early active RA. The improvement in disease activity and slowing of joint damage were more rapid than those with MTX treatments. The review found ETN to be effective in treating patients with active DMARD-refractory RA.

Hochberg et al. compared the efficacy of the TNF alpha blocking agents ADM, ETN, and IFX when added to MTX in patients with active RA. ADM, ETN, and IFX had similar efficacy when added to MTX in treating patients with active RA and an incomplete response to MTX alone.

Jones et al. examined the effect of various drugs, including IFX, on the radiological progression of RA in a systematic review of placebo-controlled RCTs. Published evidence supported the efficacy of IFX and eight other agents in decreasing radiological progression in RA.

**IFX RCTs**

Results from the analyses of IFX effectiveness appear in Appendix 8. Most of the meta-analysis results are reported as fixed effects pooling because no significant heterogeneity was observed. For results showing significant heterogeneity (p<0.05), random and fixed effects are shown.

**ACR improvement responses:** At one year, ACR responses were significantly improved in all IFX+MTX arms compared with MTX-only controls in the ATTRACT, ASPIRE, and Quinn trials. Taylor et al. reported no significant differences between IFX 5 mg/kg q8wk and controls. In the ASPIRE study, ACR-N results showed a better percent improvement in patients treated with IFX versus controls (p=0.001). Pooled RB for IFX 3 mg/kg q8wk versus MTX (the recommended dosage) was 1.52 (95% CI: 1.25, 1.85) for ACR50, and 1.63 (95% CI: 1.26, 2.12) for ACR70. The NNTs for ACR50 and ACR70 were 7 and 9 respectively. Similar relative pooled results were observed for ACR50 with IFX 5 to 6 mg/kg q8w; the results showed an RB for IFX of 1.59 (95% CI: 1.30, 1.94). The NNT was lower in this pooled group (NNT 3), but the difference compared to the standard dose was not statistically significant. Only the ATTRACT trial examined other dosing regimens: 3 mg/kg q4wk, 10 mg/kg q8wk, and 10 mg/kg q4w. These regimens showed similar results for ACR50 (NNTs 3 to 4) and ACR70 (NNTs 4 to 7), but the results were not significantly different from those of the 3 mg/kg q8wk dose.

Only the ATTRACT and Quinn trials presented two-year data. The pooled RB for 3 mg/kg q8wk compared with MTX was 1.97 (95% CI: 0.94, 4.13) for ACR50 and 1.43 (95% CI: 0.61, 3.37) for ACR70, and did not reach statistical significance. NNTs were 6 for ACR50 (p<0.05) and 17 for ACR70 (not significant). No clear dose effect was observed at two years (ATTRACT study only).
Although the NNTs were lower for 3 mg/kg q4wk and 10 mg/kg q8wk, the differences were not statistically significant. The highest dosage (10 mg/kg q4wk) was lower than the previous two dosing schemes; the highest dosage results were similar to those of the 3 mg/kg q8wk dosage (NNTs for ACR50 were 7 and 6 respectively; NNTs for ACR70 were 14 and 17 respectively).

The results for ACR responses appear in Appendix 8 Tables 1 and 2, and Figures 1 to 8.

**DAS28:** Three trials\(^43-45\) reported DAS28 results at year one; two\(^43,45\) reported an improvement for IFX+MTX that was statistically significantly better than MTX alone (Appendix 8 Table 3, Figures 9 to 12). Because the results showed heterogeneity, random effects models were also used. The difference between the trials was not in the population, but in the design, with the largest study showing less benefit than the smaller ones. In year one, using random effects, no statistically significant differences were observed in the pooled WMD between IFX 3 mg/kg q8wk+MTX and MTX was 1.26 (95% CI: -2.82, 0.31); the SMD was -1.37 (95% CI: -1.43, -0.30), with a SMD of -1.03 (-2.25, 0.18). A DAS28 <0.6 indicates no response; 0.6 to 1.2, a moderate response; and >1.2, a moderate to good response.\(^50\)

At 54 weeks in the ASPIRE analysis of completers,\(^43\) 31% of the patients receiving 6 mg/kg q8wk achieved remission, compared with 21% in the 3 mg/kg q8wk group, and 15% of the patients receiving MTX only. The differences were not statistically significant. For the small Taylor trial,\(^44\) 25% of IFX patients had a good DAS response compared with 18% of patients on MTX (difference not significant).

The results for DAS28 appear in Appendix 8 Table 3, and Figures 9 to 12.

**Functional outcomes:** Three RCTs\(^41,43,45\) reported HAQ results at one year, and two\(^42,45\) reported results at two years. In year one, the WMD from baseline between IFX 3 mg/kg q8wk+MTX and MTX was 0.13 (95% CI: 0.05, 0.22), with an SMD of 0.21 (95% CI: 0.08, 0.35). The differences were statistically significant. The threshold of clinical efficacy for the HAQ is considered to be 0.22.\(^51\) In year two, the HAQ WMD between the IFX 3 mg/kg q8wk and control groups was 0.32 (95% CI: 0.15, 0.50), and the SMD was 0.53 (95% CI: 0.25, 0.82). No differences were observed in HAQ changes among the ATTRACT dose groups.

Two studies reported SF-36 results.\(^41,45\) The pooled results of the SF-36 physical component at one year showed small but statistically significant differences between the IFX 3 mg q8wk group and MTX controls; the WMD was 1.77 (95% CI: 0.19, 3.36) and the SMD was 0.15 (95% CI: 0.02, 0.29). The results with other dosages (3 mg/kg q4 wk, 10 mg/kg q8 and 4 wk) were reported only in the ATTRACT study\(^41\) and showed significantly better scores for the IFX groups, ranging from a mean difference from baseline between 10.8 to 13.5, with no clear dosing effect. Only ATTRACT data were available for SF-36 in year two; no significant differences were observed between the IFX groups (mean changes between 4.6 and 6.9) and the MTX-only controls (mean change=2.8). No differences were observed for the SF-36 mental component at either timepoint.

The results for functional outcomes appear in Appendix 8 Table 4, and Figures 13 to 18.

**Radiological outcomes:** Four studies presented one-year data for radiological outcomes.\(^41,43-45\) For year one, statistically significant benefits were observed for pooled dosages of 3 mg/kg q8wk and
5 mg/kg to 6 mg/kg q8wk, compared with MTX only. For IFX 3 mg/kg q8wk, the total score WMD was −3.69 (95% CI: −4.85, −2.53) and the SMD −0.47 (95% CI: −0.61, −0.33). For 5 mg/kg to 6 mg/kg q8wk, the WMD was −3.44 (95% CI: −4.67, −2.20) and the SMD −0.44 (95% CI: −0.60, −0.29). Similar results were observed for the erosion and joint space narrowing subscores. Patients on 3 mg/kg q8 wk had a decreased risk of major radiographic progression compared with the controls (RR=0.32, 95% CI: 0.20, 0.53). Only the ATTRACT study\textsuperscript{42} reported data for year two, but the analysis did not include all patients. Statistically significant differences were observed for all IFX dosages, with decreased progression compared with MTX controls. All ATTRACT IFX groups showed little or no progression from baseline (mean changes in total scores ranging from −0.42 to 1.14), but progression was observed in the MTX-only group (mean change in total score of 12.59).

The results for radiographic outcomes appear in Appendix 8 Table 5, and Figures 19 to 34.

**Discontinuation rates:** The results for discontinuation rates are shown in Appendix 8 Table 6, and Figures 35 to 48. The pooled total withdrawals were lower for IFX 3 mg/kg q8w; the RR was 0.74 (95% CI: 0.58, 0.95) for year one and 0.59 (95% CI: 0.43, 0.80) for year two.

**ETN RCTs**

The effectiveness analyses appear in Appendix 9 Tables 1 to 6, and Figures 1 to 74. The meta-analyses results are reported mostly as fixed effects pooling, because no significant heterogeneity was observed. Random effects are only shown when significant heterogeneity (p<0.05) was observed.

The ETN dose of 10 mg biw was less beneficial than MTX. This is below the recommended dosage. Therefore, specific results are not discussed in the text, although they are shown in the tables and figures.

**ACR improvement responses:** The ERA\textsuperscript{46} and TEMPO\textsuperscript{49} studies reported one-year data. At one year, no significant differences were observed between ETN 25 mg biw and MTX; the ACR50 RB for ETN was 1.13 (95% CI: 0.97, 1.30) and for ACR70, 1.21 (95% CI: 0.94, 1.54). The BD for ETN for ACR50 and ACR70 was 5% (95% CI: −1%, 12%) and 4% (95% CI: −1%, 10%) respectively, with NNTs of 20 and 25. Statistically significant differences were observed when comparing the combination of ETN 25 mg biw+MTX to ETN alone, or MTX alone in the TEMPO trial.\textsuperscript{49} The RB compared with that of ETN alone was 1.43 (95% CI: 1.22, 1.69) for ACR50 and 1.77 (95% CI: 1.34, 2.33) for ACR70. The RB compared with that of MTX alone was 1.60 (95% CI: 1.35, 1.90) for ACR50 and 2.27 (95% CI: 1.67, 3.09) for ACR70. The NNTs ranged from 4 to 5.

Only the ERA trial\textsuperscript{48} reported results at two years. No significant differences were observed between ETN 25 mg biw and MTX. The RBs for ACR50 and ACR70 were 1.16 (95% CI: 0.94, 1.44) and 1.21 (95% CI: 0.88, 1.66), with NNTs of 14 and 20 respectively.

The results for ACR responses are shown in Appendix 9 Tables 1 and 2, and Figures 1 to 16.

**DAS28:** Only the TEMPO trial\textsuperscript{49} reported DAS28 responses at one year. In the study, 35% of patients receiving ETN 25 mg biw+MTX achieved remission compared with 16% and 13% with ETN alone and MTX alone respectively. Patients receiving ETN 25 mg biw+MTX showed a mean change from baseline of −3.2 compared with −2.7 (ETN alone) and −2.5 (MTX alone). The differences were statistically significant, but of small magnitude (−0.5 and −0.7 respectively).
The results for DAS responses appear in Appendix 9 Table 3.

**Functional outcomes:** Both trials\(^{47,49}\) reported HAQ results at one year, and the ERA trial\(^{48}\) reported results at two years. When pooling the results comparing ETN 25 mg biw and MTX, significant heterogeneity was observed, so a random model was used for pooling. Although the fixed effects models were statistically significant, the random effects were not. The WMD for improvement between groups was small: overall $-0.03$ for fixed effects and $0.02$ for random effects; $0.22$ is considered to be a clinically significant change.\(^{51}\) A statistically significant difference was observed in the TEMPO study\(^{49}\) between ETN+MTX and ETN alone, or MTX alone, with mean differences of $0.3$ and $0.4$ respectively. A statistically significant difference was reported for year two in the ERA. ETN patients had a mean percent improvement from baseline of $55\%$, compared with $37\%$ in the MTX group.\(^{48}\)

The ERA trial\(^{47}\) reported SF-36 results at year one. No significant differences were observed between ETN and MTX.

The results for functional outcomes appear in Appendix 9 Table 4, and Figures 17 to 20.

**Radiological outcomes:** Pooled results showed a statistically significant WMD between ETN 25 mg and MTX in the total scores ($-1.78$, 95% CI: $-3.32$, $-0.25$). The difference was small and not significant when using SMD ($-0.14$, 95% CI: $-0.27$, $0$) or random effects models. In the TEMPO trial,\(^{49}\) a statistically significant difference of $-3.3$ (95% CI: $-5.12$, $-1.56$) was observed in the total score between patients taking ETN+MTX and those taking MTX alone (SMD=$-0.36$, 95% CI: $-0.55$, $-0.17$) (Appendix 9 Figure 29). A statistically significant difference was also observed in the percentage of patients who showed no progression after a year (80% in the ETN+MTX group versus 57% in the MTX-only group). Only the ERA study\(^{48}\) presented results for year two. A small difference was observed between patients receiving ETN 25 mg and MTX, $-1.90$ (95% CI: $-4.83$, $1.03$; SMD=$-0.14$, 95% CI: $-0.35$, $0.08$) (Appendix 9 Figure 43). This difference was reported as statistically significant by the authors, but we could not replicate the results, possibly because the exact number of patients included in each group varied between their estimates and ours.

The results for radiographic outcomes appear in Appendix 9 Table 5, and Figures 21 to 50.

**Discontinuation rates:** Discontinuations (all causes) at year one were significantly lower for the ETN-only group (pooled results) and the ETN+MTX group compared with MTX only, with RRs of $0.76$ (95% CI: $0.59$, $0.97$) and $0.54$ (95% CI: $0.38$, $0.77$) respectively. Discontinuations due to lack of efficacy were significantly lower only for the ETN+MTX group compared with MTX alone, RR=$0.28$ (95% CI: $0.12$, $0.69$).

The two-year results observed in the ERA study\(^{48}\) showed that discontinuations due to all causes and to lack of efficacy were significantly lower in the ETN 25 mg patients compared with those receiving MTX alone, RR=$0.57$ (95% CI: $0.36$, $0.91$).

The complete results for discontinuation rates appear in Appendix 9 Table 6, and Figures 51 to 74.

**Observational Studies: IFX and ETN**

**Discontinuations (all causes):** The results for discontinuations from all causes appear in Appendix 10 Table 1.
• **IFX versus ETN:** Four studies\(^{52-55}\) included patients on IFX (N=677) and on ETN (N=846). One study\(^{54}\) followed patients for up to three years. For the first year, the discontinuation rates varied between 16% and 42% for IFX, and 8% and 31% for ETN. The three-year study reported a discontinuation rate of 52% for IFX compared with 17% for ETN.

• **IFX only:** Seven studies\(^{56-61,65}\) included patients receiving IFX, with a follow-up of three years in three\(^{58,60,65}\) and four years in one\(^{60}\) (N=898). The discontinuation rates for year one ranged between 7% and 36%, for year three between 30% and 70%, and for year four between 58% and 70%.

• **ETN only:** Five studies\(^{62-64,66,67}\) included patients receiving ETN with follow-up of one to four years (N=2,539). The discontinuation rates were 24% in year one\(^{63}\) and between 29% and 38% for year three.\(^{52,64}\) One study\(^{67}\) reported data for year four, with a discontinuation rate of 18%.

**Discontinuations (lack of efficacy):** The results for discontinuations due to lack of efficacy appear in Appendix 10 Table 2.

• **IFX versus ETN:** Three studies\(^{52,53,55}\) reported discontinuation rates due to lack of efficacy for IFX and ETN. The rates were similar: 8 to 20% for IFX in year one, and 8% in year two; 5% to 18% for ETN in year one, and 8% in year two.

• **IFX:** The discontinuation rates were 2% to 22% at year two.\(^{56,57,60,65}\) One study\(^{60}\) reported data for year four comparing IFX+LEF with IFX alone, with discontinuation rates due to lack of efficacy of 46% and 22% respectively.

• **ETN:** Three studies\(^{62,64,67}\) reported discontinuation rates because of lack of efficacy at year three or four, ranging from 4% to 9%.

**Swollen joint counts:** The results for swollen joint counts appear in Appendix 10 Table 3.

• **IFX:** One study\(^{68}\) reported swollen joint counts for IFX, with a median count of two at one year.

• **ETN:** Four studies\(^{62,64,67,69}\) reported changes in swollen joint counts at up to three years follow-up in patients receiving ETN. The mean (or median) swollen joint counts at three years ranged from 3.5 to 7.5, but most studies reported only patients continuing therapy, without data on withdrawals.

**ACR responses:** The results for ACR responses appear in Appendix 10 Table 4.

• **IFX versus ET:** One study\(^{52}\) reported ACR responses when comparing patients receiving IFX or ETN after one year. No major differences were observed. An ACR50 response was seen in 38% of patients receiving IFX versus 46% of patients receiving ETN.

• **IFX:** Three studies\(^{56,65,68}\) reported ACR responses in patients receiving IFX. ACR50 responses ranged between 49% and 67%.

• **ETN:** Six studies\(^{62,64,67,69-71}\) evaluated ACR responses in patients treated with ETN; ACR50 responses ranged between 40% and 58%.

**DAS28:** The results for DAS28 appear in Appendix 10 Table 5.

• **IFX:** One study\(^{60}\) reported DAS28 in patients treated with IFX+LEF or IFX alone. After three years, the mean DAS28 decreased from 5.7 to 5.0 in patients receiving IFX+LEF, and from 5.9 to 4.7 in patients receiving IFX alone.

• **ETN:** Two studies\(^{56,69}\) measured DAS28 in patients receiving ETN. The first study\(^{69}\) was a follow-up of the ERA RCT reporting the results of patients who remained on 25 mg ETN, those who switched from 10 mg to 25 mg ETN, and those who switched from MTX to 25 mg ETN. DAS28 scores at year three were 2.6, 3.0, and 2.8 for each of these groups respectively.
**Functional status:** The results for functional status appear in Appendix 10 Table 6.

- **IFX:** One study\textsuperscript{56} that examined the changes in HAQ among patients receiving IFX, showed a decrease of 0.3 from baseline to year two.
- **ETN:** Four studies\textsuperscript{62,64,67,69} evaluated HAQ changes in patients receiving ETN. One study\textsuperscript{64} showed a decrease in HAQ scores of approximately 0.7 among patients with recent or established RA. A follow-up of the ERA study\textsuperscript{69} showed that patients maintained their functional status over three years. Three studies\textsuperscript{62,64,67} reported that from 14% to 26% of patients maintained normal function (HAQ=0) after three years of treatment.

**Radiological progression:** The results for radiological progression appear in Appendix 10 Table 7. Two open follow-up studies from RCTs reported long-term radiological outcomes, one for ETN\textsuperscript{69} and one for IFX.\textsuperscript{72}

- **IFX:** A two-year follow-up of the ATTRACT study\textsuperscript{72} reported a mean radiological progression of 25.03 in patients receiving MTX only, compared with those on IFX, who showed no change or slight mean improvement in their scores (from −2.51 to 1.67 based on the IFX dose).
- **ETN:** A follow-up of the ERA study\textsuperscript{69} of up to five years in the subgroup of patients who remained or switched to ETN 25 mg showed stable radiological scores.

### 4.2.2 Safety

#### a) Quantity of research available

A combined literature search was conducted for safety and clinical effectiveness. After applying the inclusion criteria, there were 30 original publications on long-term clinical effectiveness (nine RCTs and 21 observational studies) and 160 on safety. We report the safety results from the clinical effectiveness studies and from studies specifically reporting on safety issues. These included 18 pharmacovigilance reports, 34 observational safety studies, and 79 case series and reports. One publication\textsuperscript{73} included a pharmacovigilance study and a case report. We conducted a review of case series and reports because many rare AEs may be initially reported as cases. We considered the following to be pharmacovigilance reports: safety studies in a defined population (geographical or in a registry) that included spontaneous or voluntary reports by institutions or health providers (passive surveillance) or regular monitoring of AEs (active surveillance).

#### b) Study characteristics

**Clinical effectiveness studies:** The study characteristics of the RCTs and observational studies of clinical effectiveness appear in Appendix 7 Tables 3 to 5.

**Pharmacovigilance reports:** Nine studies were from the US,\textsuperscript{74-82} four from Sweden,\textsuperscript{52,83-85} two from Spain,\textsuperscript{86,87} and the others from France,\textsuperscript{88} Canada,\textsuperscript{89} and The Netherlands.\textsuperscript{90} Most of the studies from the US derived their data from the Federal Drug Administration’s Adverse Events Reporting System or MedWatch (passive surveillance). The Canadian study gathered data from a similar database sponsored by Health Canada. Both Spanish studies collected data from the Society of Rheumatology’s BIOBADASER database — an active, non-compulsory, long-term follow-up registry. The Swedish studied gathered data from a compulsory surveillance database hosted by the Medical Product Agency. The French study used a multi-centre retrospective survey. The number of cases reported ranged from three to 697 (Appendix 8 Table 6). Many of these included diseases other than RA: juvenile RA,\textsuperscript{75-77,79,81} psoriatic arthritis,\textsuperscript{74,77,79,81} AS,\textsuperscript{76,79} inflammatory arthritis,\textsuperscript{80} dermatomyositis,\textsuperscript{75} and CD.\textsuperscript{74-79,82}
Other observational safety studies: Six studies reported AEs in general, and the remainder focused on specific AEs or complications, such as infections or autoimmunity (Appendix 7 Table 7).

Case series and reports: The case series and reports described safety issues in patients receiving IFX (73 cases) or ETN (45 cases) (Appendix 7 Table 8).

c) Data analysis and synthesis

RCTs

Major AEs in IFX and ETN trials appear in Appendix 11 Tables 1 and 2 respectively. Statistically significant differences were observed between the IFX and control groups for non-serious infusion reactions, RR=3.09 (95% CI: 1.95, 4.90); development of anti-nuclear antibodies (ANAs), RR=3.16 (95% CI: 2.38, 4.19); and anti-DNA antibodies, RR=47.19 (96% CI: 9.36, 237.81). No statistically significant differences were observed between patients receiving ETN versus controls (oral MTX) other than for injection site reactions (favouring the control group).

Observational studies or pharmacovigilance reports

Discontinuations: The discontinuations from AEs in cohort studies appear in Appendix 11 Table 3. Three studies evaluated IFX and ETN, seven IFX, and five ETN. In the head-to-head cohort studies and in the indirect comparisons, IFX was more frequently discontinued because of AEs than ETN: by year three, 19% to 37% of patients on IFX had stopped treatment because of toxicity compared with 7% to 9% receiving ETN. The three-year data for ETN appear in Appendix 10 Tables 1 and 2.

Tuberculosis: Eight pharmacovigilance studies reported the occurrence of active tuberculosis (TB) in patients who are treated with anti-TNF agents. In general, IFX (more than ETN) increased the risk of TB. In two Spanish studies, the incidence of TB was higher before guidelines for screening prior to anti-TNF therapy were implemented, compared with the incidence after the guidelines were implemented.

In two cohorts of several thousand patients in the US and Spain, the incidence of TB in patients who were treated with biologic agents was <1%. In the US report, the incidence was 52.5 per 100,000 patient-years (0.52%). In the Spanish report, the incidence was 4,878 per 100,000 patient-years (0.48%).

Serious infections: Serious infections such as histoplasmosis, listeriosis, and coccidiodomycosis were reported in several observational studies. Generalized sepsis has also been reported.

Two case series assessed the risk of postoperative infections in patients with RA receiving IFX or ETN, who underwent orthopedic surgery. No unexpected increases in infection were noted, but the number of patients was small (<50).

Autoimmunity: Ten studies reported an increase in serologic autoimmune phenomena with the use of IFX. Several autoantibodies have been observed in patients receiving IFX, including ANA, anti-DNA, anti-histone, and anticardiolipin. Occurrences of fully developed autoimmune disease have also been reported, including lupus erythematosus and vasculitis. Leukocytoclastic vasculitis has been identified in patients receiving IFX and ETN.

Tumours: The incidence of tumours in general is not increased among RA patients receiving TNF antagonists compared with traditional therapy. Three studies assessed the development of
lymphomas in patients receiving anti-TNF agents.\textsuperscript{74,84,105} The incidence of lymphoma was increased among RA patients in general, but it is difficult to attribute the cause to therapy because those with more active disease, who are more likely to receive biologic therapy, are more likely to develop lymphoproliferative disorders.

Brown \textit{et al.}\textsuperscript{74} reported data from MedWatch identifying 26 cases of lymphoproliferative disorders (mostly non-Hodgkin’s lymphomas) in patients receiving ETN or IFX. In two cases, the lymphoma regressed after discontinuation of therapy. Wolfe\textsuperscript{105} evaluated the risk for lymphoma in a population of 18,572 patients who were prospectively enrolled in the National Data Bank for Rheumatic Diseases, and used Survey, Epidemiology and End Results (SEER) data to estimate the expected number of lymphomas in this cohort of RA patients. The overall standardized incidence ratio (SIR) for lymphoma in RA patients was 1.9 (95\% CI: 1.3, 2.7). The SIR was 2.6 for IFX, 3.8 for ETN, 1.7 for MTX, and 1.0 for those not receiving biologics or MTX. The differences in SIR between groups were not statistically significant because of the rarity of the outcome: lymphoma occurred in only 29 of the 18,572 patients. The authors could not determine if the increase in lymphoma was attributable to therapy or to indication bias (because of the high disease activity leading to anti-TNF treatment). In a study of the South Swedish Arthritis Treatment Group (SSATG) register,\textsuperscript{84} the standardized incidence of total tumors was increased in patients with RA, but there was no increased association with anti-TNF agents. There was an increased risk for lymphoproliferative disorders (RR=11.5, 95\% CI: 3.7, 26.9) in patients treated with anti-TNF compared with the population, but not in RA patients receiving other treatments (RR=1.3, 95\% CI: 0.2, 4.5). Lymphomas occurred in patients receiving IFX and in those receiving ETN.

A study examining the incidence of cutaneous squamous cell carcinoma in 1,442 RA patients treated with ETN for up to five years did not show any increase compared with that of the general population.\textsuperscript{106}

\textbf{Demyelination:} Neurologic events, including encephalopathies, transverse myelitis, optic neuritis, and peripheral neuritis related to demyelination have been reported with the use of ETN and IFX.\textsuperscript{80,90} The discontinuation of therapy resulted in partial or total improvement. The incidence of these disorders and the causal attribution to TNF antagonists remain unclear.

\textbf{Other:} The development or worsening of heart failure has been reported through pharmacovigilance, but the attribution is unclear.\textsuperscript{77} Many patients improved after discontinuation of therapy. In a study from the National Data Bank of Rheumatic Diseases, heart failure in >13,000 patients with RA was not associated with the use of anti-TNF agents.\textsuperscript{107}

An increase in the number of serious hepatic events in RA patients treated with biologics has been reported.\textsuperscript{108} An increased risk of hepatotoxicity with isoniazid in patients receiving TNF antagonists was observed in one study.\textsuperscript{109}

The effect of anti-TNF on pregnancy is unknown, but a report on 131 women receiving IFX mostly for Crohn’s disease (eight patients with RA) showed no increase in the risk of adverse outcomes to the mother and fetus.\textsuperscript{110}

\textbf{Case series and reports} 

The case series and reports are listed in Appendix 7 Table 8. These publications reported a total of 71 patients treated with IFX who experienced AEs (the number of cases shown in parentheses): sepsis (four), meningitis (one), TB (10), pulmonary infections (eight), general infections (seven), drug-induced
systemic lupus erythematosus (SLE) (six), discoid lupus (two), pulmonary autoimmune reactions (three), vasculitis (nine), accelerated cutaneous nodulosis (one), skin reactions (11), neurological involvement (three), polymyositis (one), cancer-related disorders (two), late onset of long-lasting fever (one), sudden death (one), and bone marrow toxicity (one). One publication\textsuperscript{111} that focused on RA patients with hepatitis C virus (HCV) reported no adverse reactions from concomitant IFX treatments.

A total of 37 patients treated with ETN experienced AEs: sepsis (one), meningitis (one), TB (three), pulmonary infections (two), general infections (three), drug-induced SLE (seven), discoid lupus (two), pulmonary autoimmune reactions (three), vasculitis (five), skin reactions (six), mononeuritis (one), orbital myositis (one), progressive neutropenia (one), and atrial fibrillation (one). One case report\textsuperscript{112} described one RA patient receiving ETN and treated for infertility, who underwent ovulation induction, followed by conception and normal delivery. A case series of five patients\textsuperscript{111} with HCV treated with anti-TNF agents reported no reactivations.

4.3 Discussion

4.3.1 Long-term effectiveness

\textbf{a) ACR responses}

The results of RCTs of >1 year’s duration showed that anti-TNF agents have a small to moderate effect in clinical outcomes. Compared with MTX alone, the beneficial effects were modest at the recommended dosages of 3 mg/kg for IFX and 25 mg biw for ETN, ranging between 1.13 and 1.60 for relative ACR50 benefits. When compared with MTX alone, the NNTs at year one for ACR50 improvement were seven for IFX+MTX, four for ETN+MTX, and 20 for ETN alone. A trend for better outcomes was observed with increased dosages of IFX. Compared with MTX, ETN was only effective when used with MTX.

\textbf{b) Disease activity}

Compared with MTX alone, a clinical and significant improvement in DAS28 scores was observed for IFX+MTX and ETN+MTX. Despite being statistically significant, the degree of improvement was often small, below the 0.6 cut-off for clinical relevance.\textsuperscript{50}

\textbf{c) Functional status}

The long-term impact of IFX and ETN on functional status was modest. Although some statistically significant comparative results were observed for HAQ, the size of the effects was generally small, below the 0.22 threshold used for minimal clinical significance.\textsuperscript{51} A statistically significant pooled result was observed for the SF-36 physical component with IFX 3 mg/kg qw8, but the effect was not clinically meaningful (1.77, with an effect size of 0.15). Better results were observed with increasing dosages of IFX. The difference between ETN and MTX in SF-36 results was neither clinically nor statistically significant.

\textbf{d) Radiological outcomes}

The beneficial effects of anti-TNF agents were seen on radiological progression. Not all statistically significant differences between treatment and control groups were found to be clinically significant. For IFX+MTX versus MTX, the SMD was close to 0.50, suggesting a moderate effect. Based on the minimal clinically important difference of 5,\textsuperscript{27} many of the radiological differences between groups that reached statistical significance could not be considered to be clinically relevant. Disease progression occurred in almost a third of patients receiving MTX alone compared with <6% in the
IFX groups combined. Approximately half of the patients on IFX+MTX showed radiological improvement, compared with 14% in the MTX-only group. Similar results were observed for the ETN+MTX group. Although there were no differences in clinical outcomes between the ETN-only and MTX groups, statistically significant differences favouring ETN only were observed for radiological outcomes, although of a small magnitude (SMD effect size 0.14).

4.3.2 Safety

The discontinuation rates for all causes after several years of treatment were high. Approximately half of the patients receiving IFX and a third of patients receiving ETN discontinued therapy by the third year of treatment.

Anti-TNF agents were well tolerated in the short term, but concerns remain about their long-term safety with respect to infections, lymphomas, autoimmunity, and demyelination. Although the rates of these events are low, the seriousness of these diseases demands that they be considered when evaluating potential treatment with anti-TNF agents. Patients should be monitored if treatment with anti-TNF agents is initiated. The risk for some serious complications, such as TB and autoimmune disorders, is greater with IFX than ETN, although there are no well-designed observational studies comparing the two agents head-to-head to determine their differences in risk for infrequent, but serious, AEs.

5 ECONOMIC ANALYSIS

5.1 Methods

5.1.1 Literature search strategy

The search strategy paralleled the clinical literature search strategy, except an economics filter was used instead of a clinical filter. Unlike the clinical review, there were no language restrictions on any of the searches. In addition, the Health Economics Evaluations Database (HEED) was searched.

5.1.2 Selection criteria and method

a) Selection criteria
Economic evaluations were eligible for inclusion if they met the following criteria:

- RA specified by the author(s)
- treatment with ETN or IFX at adequate dosages
- at least six months’ time horizon
- estimate of direct costs (minimum) and not drug costs only
- adequate data on costs and therapeutic effects.

Unlike our clinical studies review (for which we set a minimum follow-up of one year), the time horizon for our economic evaluation was six months. We used this because there were fewer economic analyses, and we wanted a broader inclusion criterion to evaluate how the time frame affected the studies’ conclusions.
b) **Selection method**
The selection method was the same as that used for the clinical review.

5.1.3 **Data extraction strategy**

The content of each study was abstracted by one reviewer (MLO) and independently cross-checked by a second reviewer (MM). Disagreements were resolved by consensus.

The extracted content included:
- publication characteristics (year of publication, language of publication, country, sources of funding)
- study characteristics (study design, duration of follow-up, sample size)
- population characteristics (age, sex, disease duration, clinical characteristics, previous therapies)
- intervention characteristics (drug, dosing)
- outcome measures (Appendix 2)
- analytic technique (cost analysis, cost minimization, cost-consequence, cost-effectiveness, cost-utility, cost-benefit)
- perspective of study (societal, health care system, provider, third-party payer, patient)
- source of preference (direct elicitation, indirect instrument elicitation, professional opinion, literature review)
- cost valuation (direct medical, direct non-medical, indirect)
- transition rate probabilities
- sensitivity analysis (deterministic, probabilistic, acceptability curves).

The data extraction forms appear in Appendix 4.

5.1.4 **Data analysis methods**

We extracted, tabulated, and analyzed the data. No attempt was made to pool the results from original economic evaluations because of the heterogeneity in study designs. Each report was reviewed and summarized. In the summary for each study, the costs and cost-effectiveness ratios are reported in the units that are used in the evaluation. One study used the Canadian dollar.34

We present a summary of the studies using the 2004 Canadian dollar as the currency unit. The currency was converted into Canadian dollars in the reporting year of the study and then inflated to 2004 prices. The currency exchange rates and inflation calculators were based on those reported by the Organisation for Economic Co-operation and Development.

5.2 **Results**

5.2.1 **Quantity of research available**

The literature searches retrieved 86 citations related to economic issues. After review, 33 original publications were retained. After the selection criteria were applied, 22 were left for inclusion in
the review. We identified seven reviews with adequate economic data and seven technology assessment reports.

We excluded 28 reviews that provided insufficient information, three economic reports that had insufficient data, 11 abstracts with insufficient data, and eight publications that were mostly unrelated to the topic of interest (Appendix 12).

5.2.2 Study Characteristics

a) Health technology assessments
Five countries conducted HTAs between 2001 and 2006 on the use of biologic agents for RA (search dates ranged from 1991 to 2003): Germany, UK, Denmark, Hungary, and Canada. Those including an economic section are described in this report. The study characteristics appear in Appendix 13 Table 1. While Jobanputra et al., Barton et al., and Coyle et al. present economic analyses, the purpose of their HTAs was different from that of the original articles.

b) Systematic reviews
In total, 33 publications were identified as reviews. Seven had enough data to be included in this report (they provided the database sources and the search strategy that was used in conducting the review). The characteristics of the seven reviews appear in Appendix 13 Table 2.

c) Individual economic evaluations
Appendix 13 Table 3 lists the 22 original publications with an economic evaluation included in this report. Of these, nine were cost-utility analyses, two were cost-effectiveness analyses, one was a cost-effectiveness with minimization analysis, six were cost analyses, and three were benefit analyses. A budget impact evaluation was also described in one publication. More than half of the studies were funded by the pharmaceutical industry.

5.2.3 Data analysis and synthesis

A synthesis and tabulation of the results of the publications included in this report appear in Appendix 14.

a) Health technology assessments
Five countries conducted HTAs evaluating the use of biologic agents for RA (Appendix 14 Table 1). Of the eight publications, three were updates. Seven publications presented economic evaluations. Three reports were written in languages other than English, and translation difficulties prevented a comprehensive review.

British HTA reports
Two technology assessments included the following:
- an economic evaluation of ETN
- trial data from Wyeth on the treatment costs and effectiveness of ETN
- trial data from Schering-Plough on the costs and effectiveness of IFX
- findings from a simulation model created by the authors to evaluate the incremental cost-effectiveness ratios (ICERs) of treatment strategies for RA patients.
Quality-adjusted life-years (QALYs) were used as the outcome units. The base case ICERs for ETN ranged from £9,942 to £48,454. The base case ICERs for IFX ranged from £29,008 to £40,766. The simulation model known as the Birmingham Preliminary Model (BPM) estimated the ICER to be £47,000 to £128,000 for ETN and £62,000 to £169,000 for IFX when used after traditional DMARDs fail. The BPM included potential benefits in health-related quality of life (HRQOL), but it did not model potential benefits from reductions in mortality or decreased future health care utilization. One technology assessment evaluated the use of modelling to estimate the clinical and economic benefits and costs of anti-TNF strategies for the treatment of RA. The study presented the Birmingham Rheumatoid Arthritis Model (BRAM) — a modification of the BPM — as discussed by Jobanputra et al. The BRAM estimated offsetting costs that decreased health care utilization. The BRAM simulation model estimated the ICER to be £47,117 to £49,938 for ETN and £63,040 to £70,025 for IFX.

**Canadian HTA report and cost-utility analysis**

Coyle et al. evaluated the cost utilities of ETN and IFX+MTX versus a baseline strategy. The study used a decision analytic Markov model with a five-year time horizon comprised of six-month cycles. Each RA patient was assumed to start with MTX and then switched therapies because of toxicity or lack of efficacy. The therapies that were considered included gold, IFX+MTX, ETN, and palliative care. These therapies could be switched again because of toxicity or lack of efficacy. The baseline for analysis was the switching from gold to palliative care. IFX+MTX and ETN were evaluated separately as to whether they were used before or after gold.

The perspective of the study was that of a third-party payer, in this case, the Ministry of Health. The estimated costs included those for management of AEs, routine monitoring, drugs, and palliative care. Monitoring costs were derived from the Ontario Schedule of Benefits, and drug costs were extracted from the Ontario Drug Formulary. The utility estimates for the strategies were based on the HTA from Jobanputra et al. The costs and utilities were discounted at 5%.

The study concluded that from a third-party payer’s perspective, there was no therapy that included ETN or IFX+MTX that was cost-effective when applying $50,000 per QALY as the threshold.

**Danish HTA report**

Kristensen et al. simulated the impact of three scenarios for IFX and ETN on the health care system in Denmark. The first scenario envisioned not using ETN or IFX in the Danish health care system. Danish patients with RA use anti-TNF as part of their therapy, so this scenario was not elaborated. The second scenario involved the use of IFX or ETN as first-line therapy for all newly diagnosed RA patients. The budget impact in Danish kroner (DKK) for this scenario (assuming IFX) was DKK136 million in the first year to DKK505 million by the fifth year after adoption. For ETN, the costs were DKK169 million in the first year to DKK942 million by the fifth year. The final scenario used ETN or IFX after failure of a traditional DMARD therapy. The estimated financial impact of this scenario was DKK57 million (year one) to DKK126 million (year five) for IFX and DKK71 million (year one) to DKK240 million (year five) for ETN. The benefit of an increased ability to work was not modelled in any scenario, and the cost of early diagnosis and referral was not modelled. The team recommended the use of anti-TNF agents as a second-line therapy after the failure of traditional DMARDs.
We did not translate the percentage increase to Canadian dollars, because this would exaggerate the impact of these therapies. Canada’s economy is six times greater than that of Denmark. Therefore, the budget impact of funding ETN and IFX would be different in Canada compared to Denmark.

**German HTA report**
Kulp et al. included the results from the BPM (Jobanputra et al.) and from two cost analyses (Choi et al. and Nuijten et al.). Their conclusions were driven primarily by the BPM. The study concluded that pharmacoeconomic studies are lacking, but decision analytic models of anti-TNF drugs for RA treatment exist.

**Hungarian HTA report**
Gulácsi et al. reviewed the use of IFX for the treatment of RA. The report used data from the ATTRACT trial, which, when modelled, generally found that IFX is cost-effective. The HTA called for central registration of RA patients to follow the effects, side effects, and health care utilization for a future evaluation of IFX. Because of the language of the report, the information for economic evaluation was extracted primarily from tables. The review recommended additional studies to adapt current information to the health economic characteristics of RA in Hungary.

**b) Economic reviews**
Seven publications were identified as economic reviews of anti-TNF agents that provided sufficiently robust methods and information to be included in this report (Appendix 14 Table 2). We ordered them by type of study (CUA, cost analysis) and then by drug (ETN, IFX, both) (Appendix 13) ETN and IFX were not assumed to be equivalent therapies.

Lyseng-Williamson et al. evaluated the cost effectiveness of IFX in RA patients. The reviewed articles included two studies that used effectiveness data from the ATTRACT trials and two cost studies. The ATTRACT study provides strong evidence that the use of IFX+MTX is more effective and more economical than MTX monotherapy for RA patients who are MTX-resistant. Nuijten et al. used administrative cost data to compare IFX and ETN and found that the total medical costs were lower for ETN. Ollendorf et al. used administrative cost data to compare LEF, ETN, and IFX, and found that LEF had the lowest direct medical costs. The review concluded that IFX is likely to be cost-effective. This result should be verified by long-term studies that include the benefit of delayed radiographic progression due to IFX.

Nahar et al. examined the cost effectiveness of IFX for RA patients. The reviewed articles included two studies that used effectiveness data from the ATTRACT trials. The review concluded that the cost-effectiveness depended largely on the modelling of the long-term effects and costs of IFX therapy. It concluded that long-term studies should be conducted.

Lyseng-Williamson et al. reported on the cost-effectiveness of ETN use in RA patients. They included articles from primary economic evaluations of the ERA trial and SSATG longitudinal data. The studies using the SSATG data concluded that ETN+MTX is more cost-effective than MTX alone. The study that was based on ERA suggested that ETN may be a cost-effective first-line strategy — better than waiting for DMARDs to fail. The conclusion of the review was that ETN may be cost-effective for DMARD-naïve and DMARD-resistant RA patients. Bansback et al. evaluated the cost-effectiveness of IFX and ETN for use in RA patients. The two studies included for the IFX review used effectiveness data from the ATTRACT trials. Three studies included for the ETN review used effectiveness data from the ERA trial and Choi, and
SSATG. The review concluded that ETN or IFX may be cost-effective compared with DMARD monotherapy. No conclusion could be made as to which anti-TNF therapy was more cost-effective.

Emery et al. assessed the cost-effectiveness of treating RA with IFX or ETN. They included studies that used effectiveness data from the ERA trial for ETN evaluation. The review included studies that used the ATTRACT trial for the evaluation of IFX. The cost studies largely used administrative cost databases. The review concluded that IFX and ETN may be cost-effective for the treatment of RA, and that ETN may be more cost-effective than IFX.

Merkesdal et al. reported the cost-effectiveness of treating RA with IFX or ETN. In general, the included studies concluded that IFX and ETN were cost-effective. Some studies found that ETN was effective, but expensive. The review concluded that RA treatment with ETN or IFX may not be cost-effective for the population. It also recommended identifying specific subgroups in which biologics are cost-effective therapies.

Rubio-Terres et al. compared one-year treatment costs for LEF and IFX+MTX. The studies reviewed generally concluded that there is no statistically or clinically meaningful difference in efficacy between LEF and IFX+MTX in the treatment of RA. Direct medical costs were included in the study. The review concluded that LEF monotherapy is more effective than IFX+MTX with respect to ACR20 response rate and equivalent with respect to ACR50 response. The authors estimated that one year of IFX+MTX treatment costs more than a year of LEF treatment by a factor of 8.24.

c) Original economic evaluations
A summary of the results appears in Appendix 14 Table 3.

Cost-utility analyses

**British and Swedish cost-utility analysis:** Kobelt et al. estimated the cost-effectiveness of IFX+MTX versus that of MTX alone. The efficacy data were 54-week results from the ATTRACT study. Direct and indirect costs were included for the UK and Sweden scenarios.

Table 2 reports lifetime results that were discounted at 3% for cost and outcomes. It shows the base-case results for the cost-effectiveness analyses (CEAs) and the ICERs reported for IFX+MTX versus MTX.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>QALY</th>
<th>Total Costs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX (Sweden)</td>
<td>4.417</td>
<td>SEK1,250,406</td>
<td>N/A</td>
</tr>
<tr>
<td>IFX+MTX (Sweden)</td>
<td>4.648</td>
<td>SEK1,187,780</td>
<td>dominant</td>
</tr>
<tr>
<td>MTX (UK)</td>
<td>3.694</td>
<td>£40,468</td>
<td>N/A</td>
</tr>
<tr>
<td>IFX+MTX (UK)</td>
<td>4.031</td>
<td>£44,434</td>
<td>€19,000</td>
</tr>
</tbody>
</table>

ICER = incremental cost-effectiveness ratio; IFX = infliximab; MTX = methotrexate; SEK = Swedish kroner; QALY = quality-adjusted life-year; N/A = not applicable.

In the Swedish data, the increased cost due to the cost of IFX was more than offset by the indirect cost savings, because of the increased effectiveness of the treatment strategy. IFX was found to be cost-effective.

**Swedish cost-utility analysis:** Kobelt et al. evaluated the cost-effectiveness of TNF antagonists. The data for IFX and ETN patients were combined, and the comparator was assumed to be a
continuance of DMARDs. Patients had to have failed to respond to ≥2 DMARDs. The data for the analysis were from a Swedish registry of patients receiving IFX or ETN for the treatment of RA (160 patients total/116 used in base case analysis).

Table 3 compares the cost-effectiveness of TNF antagonists to continued treatment on DMARDs. The time frame was one year with no discounting. The subgroups were based on the baseline HAQ scores for the patients.

The cost per QALY decreased with higher baseline disability (higher HAQ scores). The anti-TNF treatments were found to be cost-effective, but no conclusion could be reached as to whether IFX or ETN is more cost-effective.

<table>
<thead>
<tr>
<th>Group (Baseline HAQ)</th>
<th>QALY Gain</th>
<th>Incremental Cost</th>
<th>Cost/QALY ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>0.28</td>
<td>€12,184</td>
<td>€43,500</td>
</tr>
<tr>
<td>HAQ&lt;0.6</td>
<td>0.11</td>
<td>€14,131</td>
<td>€128,500</td>
</tr>
<tr>
<td>HAQ 0.6&lt;1.1</td>
<td>0.18</td>
<td>€11,131</td>
<td>€61,800</td>
</tr>
<tr>
<td>HAQ 1.1&lt;1.6</td>
<td>0.25</td>
<td>€15,241</td>
<td>€61,000</td>
</tr>
<tr>
<td>HAQ 1.6&lt;2.1</td>
<td>0.30</td>
<td>€11,176</td>
<td>€37,300</td>
</tr>
<tr>
<td>HAQ ≥2.1</td>
<td>0.16</td>
<td>€6,888</td>
<td>€43,000</td>
</tr>
</tbody>
</table>

HAQ=health assessment questionnaire; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year.

**British cost-utility analysis:** Barbieri et al.\textsuperscript{115} examined the cost utility of IFX+MTX versus MTX alone in patients with severe RA. Therefore, the base case analysis was from the ATTRACT study.\textsuperscript{41} The ATTRACT data were for one year. Additional year transition probabilities were extrapolated from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), and costs were extrapolated from the Norfolk Arthritis Register (NOAR) cohort. QALYs were based on patients’ self-reported VAS and on HAQ scores. The perspective was the UK National Health Service (NHS) and Personal Social Service in the UK. The ICER for the one-year base case analysis (using a 6% discount rate for cost and 1.5% for benefits) was £40,453 per QALY. The lifetime ICER was estimated at £34,680 per QALY. The inclusion of direct non-medical and indirect costs would lower the cost-effectiveness ratio. The authors concluded that IFX may be a cost-effective treatment for patients who fail to respond to MTX alone.

**US cost-utility analysis:** Wong et al.\textsuperscript{116} compared the cost-effectiveness of IFX+MTX versus MTX monotherapy. The data for the study were from the ATTRACT study,\textsuperscript{41} which measured the clinical benefit of IFX+MTX use with a 54-week timeframe. The authors used ARAMIS to extrapolate lifetime cost and effectiveness measures.

Table 4 reports the base case results for the CEA. The ICERs are reported for IFX+MTX versus MTX. The table reports lifetime results discounted at 3% for cost and outcomes.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>QALY</th>
<th>Direct Costs</th>
<th>Direct+ Indirect Costs</th>
<th>ICER (direct costs only)</th>
<th>ICER (direct+ indirect costs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>9.11</td>
<td>US$84,100</td>
<td>US$313,200</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>IFX+MTX</td>
<td>9.40</td>
<td>US$93,000</td>
<td>US$315,800</td>
<td>US$30,690</td>
<td>US$8,966</td>
</tr>
</tbody>
</table>

ICER=incremental cost-effectiveness ratio; IFX=infliximab; MTX=methotrexate; QALY=quality-adjusted life-year; N/A=not applicable.
The ICER from the health care system perspective (US$30,690) fell within generally accepted ranges for being cost-effective. The cost difference between IFX+MTX versus MTX narrowed as analysis went from direct costs to direct+indirect costs. The narrowing was due to cost offsets resulting from the improved IFX effectiveness. Although the cost of the IFX was incompletely offset, the resultant ICER (US$8,966) was significantly reduced. Therefore, the report concluded that IFX was a cost-effective add-on strategy under ATTRACT treatment considerations.

The U.S. Panel on Cost-effectiveness in Health and Medicine recommends not using a defined threshold, but using ICERs instead to rank potential treatment strategies by value per dollar spent. The range of $20,000 to $100,000 per QALY reported in a Canadian study (Laupacis et al., CMAJ 1992;146:473-81) was not updated for inflation.

**British cost-utility analysis:** Brennan et al. tested the cost utility of ETN as a third-line RA treatment, based on the British Society for Rheumatology guidelines. The guidelines recommend that ETN be considered after patients fail to respond to two DMARDs. The effectiveness data were from a phase two study of ETN by Moreland et al. The QALY scores were based on a calculation from patient HAQ scores. Only direct medical costs were included. Six-month efficacy data were used to model lifetime cost-effectiveness ratios.

ETN was found to be cost-effective compared with non-biologic agents. The ICERs are reported for IFX+MTX versus MTX. Table 5 reports lifetime results discounted at 6% for costs and 1.5% for benefits.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>QALY</th>
<th>Total Costs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMARD</td>
<td>5.87</td>
<td>£9,199</td>
<td>N/A</td>
</tr>
<tr>
<td>ETN</td>
<td>7.53</td>
<td>£36,213</td>
<td>£16,330</td>
</tr>
</tbody>
</table>

DMARD=disease modifying anti-rheumatic drug; ETN=etanercept; ICER=incremental cost-effectiveness ratio; IFX=infliximab; QALY=quality-adjusted life-year; N/A=not applicable.

**Swedish cost-utility analysis:** Kobelt et al. investigated the cost-effectiveness of ETN versus MTX. The data for the study were from the TEMPO trial of ETN and MTX. The timeframe in the TEMPO trial was two years. A five- and 10-year timeframe was modelled for this analysis. A societal perspective was used. The costs and effects were discounted at 3%. The EuroQol mapping of visual analogue scale (VAS) utility scores was used to estimate QALYs. Table 6 summarizes the 10-year cost-effectiveness findings.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>QALY</th>
<th>Total Costs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>3.08</td>
<td>€162,695</td>
<td>N/A</td>
</tr>
<tr>
<td>ETN</td>
<td>3.23</td>
<td>€181,271</td>
<td>€123,840</td>
</tr>
<tr>
<td>ETN+MTX</td>
<td>3.46</td>
<td>€176,915</td>
<td>€37,421</td>
</tr>
</tbody>
</table>

ETN=etanercept; ICER=incremental cost-effectiveness ratio; MTX=methotrexate; QALY=quality-adjusted life-year; N/A=not applicable.

The ETN monotherapy was a dominated strategy. The concomitant use of ETN and MTX was cost-effective and resulted in greater health improvements at a lower total cost than ETN alone.

**Dutch cost-utility analysis:** Welsing et al. evaluated the cost utility of five treatment strategies for RA:
1. usual care (U)
2. LEF, switch to usual care for non-response (LEF)
3. ETN, switch to usual care for non-response (TNF)
4. LEF, switch to ETN for non-response (LEF-TNF)
5. ETN, switch to LEF for non-response (TNF-LEF).

A Markov analysis with a five-year timeframe and a 4% discount rate was used to model cost-effectiveness. The data for the study were from a private dataset owned by Wyeth Pharmaceuticals (Table 7).

<table>
<thead>
<tr>
<th>Strategy</th>
<th>QALY</th>
<th>Medical Costs (including RA medication)</th>
<th>Total Costs</th>
<th>ICER (medical costs only)</th>
<th>ICER (total costs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>2.86</td>
<td>€5,869</td>
<td>€13,212</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>LEF versus U</td>
<td>2.93</td>
<td>€7,333</td>
<td>€13,921</td>
<td>€20,914</td>
<td>€10,129</td>
</tr>
<tr>
<td>LEF-TNF versus LEF</td>
<td>2.99</td>
<td>€29,493</td>
<td>€35,038</td>
<td>€369,333</td>
<td>€351,950</td>
</tr>
<tr>
<td>TNF versus U</td>
<td>3.00</td>
<td>€53,889</td>
<td>€58,975</td>
<td>€343,000</td>
<td>€326,879</td>
</tr>
<tr>
<td>TNF-LEF versus TNF</td>
<td>3.01</td>
<td>€54,101</td>
<td>€59,037</td>
<td>€21,200</td>
<td>€6,200</td>
</tr>
</tbody>
</table>

ICER=incremental cost-effectiveness ratio; MTX=methotrexate; LEF=leflunomide; TNF=tumour necrosis factor; U=usual care; N/A=not applicable.

ETN was not shown to be cost-effective in this study, compared with usual care or LEF, a newer RA therapy often used as an alternative to MTX.

**Swedish cost-utility analysis**: Bansback et al. evaluated the cost utilities of ADM and ADM+MTX compared with traditional DMARDs, ETN, ETN+MTX, and IFX+MTX. The data for the analysis were from literature searches and include the Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab [D2E7] in Rheumatoid Arthritis (ARMADA) trial, the ATTRACT study and a study on ETN funded by Immunex. QALY estimates were determined through conversion of the HAQ to utilities. Bansback’s reference for the HAQ to QALY conversion was a 2002 International Society for Pharmacoepidemiology and Outcomes Research (ISPOR) abstract. Resource use and cost were determined through expert opinion and modelling.

Table 8 reports the base-case results for the CEA. The ICERs are reported using the traditional DMARD as the comparator. The table reports six-month results discounted at 3% for cost and benefits.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>QALY</th>
<th>Total Medical Costs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMARD</td>
<td>1.1818</td>
<td>€70,387</td>
<td>N/A</td>
</tr>
<tr>
<td>ADM</td>
<td>1.6551</td>
<td>€90,058</td>
<td>€41,561</td>
</tr>
<tr>
<td>ADM+MTX</td>
<td>2.3114</td>
<td>€108,982</td>
<td>€34,167</td>
</tr>
<tr>
<td>ETN</td>
<td>2.0493</td>
<td>€102,421</td>
<td>€36,927</td>
</tr>
<tr>
<td>ETN+MTX</td>
<td>2.0974</td>
<td>€103,129</td>
<td>€35,760</td>
</tr>
<tr>
<td>IFX+MTX</td>
<td>1.8379</td>
<td>€102,099</td>
<td>€48,334</td>
</tr>
</tbody>
</table>

ADM= adalimumab; DMARD=disease modifying anti-rheumatic drug; ETN=etanercept; ICER=incremental cost-effectiveness ratio; IFX=infliximab; MTX=methotrexate; QALY=quality-adjusted life-year; N/A=not applicable.

The study concluded that ADM was as cost-effective as ETN or IFX, as a monotherapy or used concomitantly with MTX.

**US cost-utility analysis**: Chiou et al. evaluated the cost-effectiveness of treating RA with IFX, ETN, and ADM compared with anakinra (ANAK), another biologic therapy for RA that targets
interleukin-1. The review included two cost-effectiveness evaluations that used the ATTRACT study\textsuperscript{113,116} and one that used the TEMPO trial (Table 9).

| Table 9: Chiou cost-utility analysis, US (2004) |
|---|---|
| **Treatment** | **ICER (versus ANAK+MTX)** |
| ETN+MTX | US$7,925 |
| ADM+MTX | US$10,909 |
| IFX+MTX | US$114,463 |

ANAK=anakinra; ETN=etanercept; ICER=incremental cost-effectiveness ratio; IFX=infliximab; MTX=methotrexate.

The review concluded that anti-TNF agents may be cost-effective for RA patients who fail traditional DMARD therapy. ETN (monotherapy and with MTX) was the most cost-effective. The authors also addressed the need for more research on switching rules for biologics.

**Cost-effectiveness analyses**

Three studies reported an cost-effectiveness analysis — one from Spain and two from the US.

**US cost-effectiveness analysis**: Choi et al.\textsuperscript{122} tested second-line therapies for the treatment of RA after monotherapy with MTX failed. The strategies tested were:

- ETN+MTX
- ETN alone
- cyclosporine+MTX
- triple therapy (hydroxychloroquine, SSZ, and MTX)
- continue MTX alone
- no second-line therapy.

The data for the study were extracted from several double-blind RCTs. The outcomes of interest in the study were the ACR20 and a weighted average of proportions of patients achieving ACR70 (ACR70WR). A societal perspective was assumed for the costs. Indirect costs were based on capacity to work and estimated from the HAQ scores.

The base-case results for the CEA are reported in Table 10. The ICERs are reported against the no second-line agent. The study had a six-month timeframe, and no discounting of costs or benefits were reported.

| Table 10: Choi cost-effectiveness analysis, US (2000) |
|---|---|---|---|---|
| **Strategy** | **ACR20** | **ACR70WR** | **Total Costs US$** | **ICER, ACR20** | **ICER, ACR70WR** |
| no second line | 0.11 | 0.06 | US$12,842 | N/A | N/A |
| continue MTX | 0.27 | 0.11 | US$13,810 | US$6,050 | US$19,360 |
| triple DMARD therapy | 0.55 | 0.27 | US$13,492 | US$1,477 | US$4,467 |
| cyclosporine+MTX | 0.55 | 0.27 | US$14,780 | US$4,405 | US$9,229 |
| ETN alone | 0.61 | 0.40 | US$18,180 | US$10,676 | US$15,700 |
| ETN+MTX | 0.68 | 0.43 | US$19,083 | US$10,949 | US$16,868 |

ACR=American College of Rheumatology; DMARD=disease modifying anti-rheumatic drug; ETN=etanercept; ICER=incremental cost-effectiveness ratio; MTX=methotrexate; N/A=not applicable.
There are no published decision rules regarding the cost per ACR20 or cost per ACR70WR. The ICER of ETN+MTX versus continuing MTX alone — the relevant comparison in other studies — is $12,861 per ACR20 and $16,478 per ACR70WR. The most cost-effective therapy in this scenario was a triple DMARD combination.

US cost-effectiveness analysis: Choi et al.\textsuperscript{123} compared monotherapies of ETN, LEF, MTX, SSZ, and placebo. The strategies tested were:
- ETN
- LEF
- MTX
- SSZ
- no second-line therapy.

The data for the study were extracted from several clinical trials. The outcomes of interest were the ACR20 and a weighted average of proportions of patients achieving ACR70 (ACR70WR). A societal perspective was assumed for the costs. Indirect costs were based on capacity to work and estimated from the HAQ scores.

Table 11 reports the base case results for the CEA. The ICERs are reported against the no second-line agent. The study had a six-month timeframe, and no discounting of costs or benefits were reported.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>ACR20</th>
<th>ACR70WR</th>
<th>Total Costs $</th>
<th>ICER, ACR20</th>
<th>ICER, ACR70WR</th>
</tr>
</thead>
<tbody>
<tr>
<td>no second line</td>
<td>0.27</td>
<td>0.15</td>
<td>US$11,379</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>SSZ</td>
<td>0.56</td>
<td>0.31</td>
<td>US$11,027</td>
<td>cost saving</td>
<td>cost saving</td>
</tr>
<tr>
<td>MTX</td>
<td>0.55</td>
<td>0.33</td>
<td>US$10,926</td>
<td>cost saving</td>
<td>cost saving</td>
</tr>
<tr>
<td>LEF</td>
<td>0.55</td>
<td>0.33</td>
<td>US$11,428</td>
<td>US$175</td>
<td>US$272</td>
</tr>
<tr>
<td>ETN</td>
<td>0.68</td>
<td>0.46</td>
<td>US$16,165</td>
<td>US$11,673</td>
<td>US$15,439</td>
</tr>
</tbody>
</table>

ACR=American College of Rheumatology; ETN=etanercept; ICER=incremental cost-effectiveness ratio; LEF=leflunomide; MTX=methotrexate; SSZ=sulfasalazine; N/A=not applicable.

ETN was the most effective strategy and the most costly. The CERs for ETN were US$41,900 (versus SSZ) and US$40,800 per ACR70WR (versus MTX).

Spanish cost-effectiveness/minimization analysis: Rubio-Terres et al.\textsuperscript{124} compared the one-year treatment costs between LEF+MTX and IFX+MTX. The article was organized as a cost-minimization analysis with an assumption that there is no statistically or clinically meaningful difference in efficacy between LEF and IFX+MTX in the treatment of RA. Direct medical costs were included in the study. Indirect costs and non-medical direct costs were excluded. The health resource use was determined through dosage and treatment guidelines. The pharmaceutical costs were obtained from the Spanish Catalogue of Pharmaceutical Specialties.

The cost per patient of a six-month treatment with LEF+MTX or with IFX+MTX is estimated to be €2,823 and €11,489 respectively.

Cost analyses
US cost analysis: Ollendorf et al.\textsuperscript{125} compared the costs of treating RA using LEF versus ETN or IFX. The study had a retrospective design using data from the PharMetrics Integrated Outcomes...
Database. The direct costs of care — including inpatient, outpatient, and pharmacy care — were included.

The LEF was found to have the lowest cost of administration, followed by ETN and then IFX. The mean total charges were US$9,618 for LEF, US$16,534 for ETN, and US$20,263 for IFX.

**US cost analysis:** Ollendorf et al.\(^{126}\) examined dosing patterns and costs among RA patients newly treated with IFX. The study had a retrospective design using data from the PharMetrics’ Integrated Outcomes Database. The study analyzed follow-up duration and annualized costs among treatments with upward dose and treatments without adjusting dose. It concluded that annualized RA-related costs are higher by >50% among patients with upward dose adjustment.

**US cost analysis:** Yazdani et al.\(^{127}\) compared the costs of care for six months after initial treatment of RA with LEF and ETN. The study used a retrospective cohort design with the PharMetrics Integrated Outcomes Database used to link medical and pharmaceutical claims. In total, 527 patients were assigned to the LEF cohort, and 281 patients were assigned to the ETN cohort. For both cohorts, approximately 85% of patients were receiving ≥4 medications for RA.

The resource use costs were separated into emergency department, inpatient, ancillary, outpatient, and pharmacy costs. Only the mean charges for pharmacy were significantly different between the cohorts. The total post-index charges were US$2,683.17 for the LEF group, compared with US$7,733.94 for the ETN group.

**US cost analysis:** Yelin et al.\(^{128}\) assessed the effects of ETN use on employment status and work loss due to RA. Two data sources were used to identify the employment status for RA patients using ETN and patients not using ETN. The data for ETN users were collected through the Rheumatoid Arthritis Pharmacoeconomic and Outcomes Longitudinal Observational Study (RAPOLO) that enrolled patients for ETN clinical trials. The non-ETN data were collected through a structured telephone interview via the University of California at San Francisco RA Panel Study.

The ETN patients were more likely to be employed compared with the non-ETN group (71% versus 55%). This difference did not significantly change after controlling for age, gender, race, education, marital status, and health status. The findings suggest that the cost of ETN use is at least partially offset by the increased employability of the RA patient. This is an important consideration in any economic evaluation that assumes a societal perspective using the human capital approach to estimate indirect costs.

**US cost analysis:** Gilbert et al.\(^{129}\) compared the one-year costs of treatment for ETN and IFX. The data for the study were from the PharMetrics Patient-Centric Database. The study accounted for variability in cost estimates due to dose escalation. There were 598 IFX patients and 950 ETN patients.

Dose escalation is more common for IFX patients than for ETN (60% versus 18%). IFX had higher one-year medical costs than ETN, primarily due to the dose escalation. The study did not compare differences in the effectiveness of treatment due to the dose escalation.

**Dutch cost analysis:** Nuijten et al.\(^{130}\) compared the costs of treating RA using ETN or IFX. The analysis used a one-year time horizon. The resource use was estimated using a Delphi panel. The study measured only differences in resource utilization between the two drugs. IFX was found to
have a significantly higher annual cost (direct and indirect) than ETN. The total costs in Netherlands guilders (NLG) were 45,115 for IFX and 31,621 for ETN.

**Benefit analyses**

**US utility analysis:** Kosinski et al.\(^{47}\) compared the HRQOL for RA patients treated with ETN+placebo tablet versus MTX+placebo injection. The study population consisted of 424 patients with early RA participating in a double-blind, randomized controlled trial. HRQOL was measured through SF-36 and HAQ instruments. The trial did not measure costs (direct or indirect). The Klippel\(^{147}\) cost estimate for ETN use was cited, but no CEA was performed.

ETN and MTX improved the quality of life over a one-year period. The improvement with ETN happened earlier than with MTX. This may have implications if the patient’s adherence to treatment is influenced by the realized benefit.

**US utility analysis:** Kavanaugh et al.\(^{131}\) examined the relationship between functional status and employability in patients treated with IFX+placebo tablet or MTX+placebo infusion. The study population consisted of 428 patients with early RA participating in a double-blind, randomized controlled trial. The functional status was measured by using a HAQ instrument. The author used cost data collected during the ATTRACT study.\(^{41}\) No comparisons between treatments were made, and no CEA was performed. The study concluded that patients who achieved a clinically important improvement in functional status have significant improvement in their employability, time lost from work, total or direct medical costs, and quality of life.

**Danish willingness-to-pay analysis:** Slothuus et al.\(^{132}\) estimated the willingness to pay (WTP) for alleviating RA symptoms with IFX. The data for this study were collected from RA patients. The domains of activity used for the valuation of RA treatment were duration of morning stiffness, pain measured by VAS, and the number of swollen joints. Two methods were used to estimate WTP to alleviate stiffness, pain, and swollen joints: the double-bounded method and the contingent ranking method. Both extracted a dollar value that a patient was willing to pay in addition to the current costs of treatment. The report implied a one-time WTP for relief from RA symptoms. A treatment exceeding cost could be adopted for factors affecting other direct medical, direct non-medical, or indirect costs of RA.

Using the double-bounded method, it was estimated that marginal WTP to alleviate symptoms was DKK581; with the contingent ranking method, DKK643. This is equivalent to C$115 to C$127 (as of September 1, 2005).

**Budget impact analysis**

**Danish budget impact analysis:** Sorensen et al.\(^{133}\) evaluated the budget impact of prescribing ETN and IFX in the Danish health care system. The prevalence of RA was estimated at 0.8% among adults (≥18 years old), approximately half of whom received care from a rheumatologist. The budget impact analysis was performed for two strategies. In the first strategy, it was assumed that anti-TNF would be the first drug of choice for newly diagnosed RA. In the second strategy, it was assumed that patients were started on a DMARD and then switched to an anti-TNF if they failed to respond.

The primary difference in the annual costs of treatment was due to differences in the administration of the drugs. The estimated per dose charge was higher for IFX than for ETN (€583 versus €158). IFX was administered intravenously under clinical supervision, while ETN was self-injected. The
additional burden of ETN and IFX on the Danish system was estimated at €6 million to €188 million for the first strategy and €17 million to €49 million for the second strategy. Because Canada has an economy that is six times greater than Denmark, translating the percentage increase to Canada would likely exaggerate the cost impact.

d) Synthesis of studies in Canadian dollars (CAD)
The ICER results for cost-utility analyses reported in the HTA and individual studies were reported, and the costs in the individual studies that performed cost-utility evaluations were converted to Canadian dollars at the purchasing power parity conversions reported by the Organisation for Economic Co-operation and Development for the dollar base year reported in each article. The amounts converted to 2004 dollars were based on the inflation calculator using the health care services component of the consumer price index as reported by Statistics Canada. One caveat is that the purchasing power parity transformation assumes that different countries consume resources in similar ways. The 2004 Canadian dollar provides a common metric in which to compare the ICERs from the cost-utility analyses.

Appendix 14 Table 4 summarizes the results of the HTA reports in Canadian dollars. The ICERs estimated in these HTAs were generally higher than the C$100,000 per QALY threshold commonly used for CUA.

Appendix 14 Table 5 summarizes the ICERs from studies reporting cost-utility evaluations. The results for these studies varied from cost-effective ICERs <C$50,000 in some scenarios, to >C$500,000 in one of the studies comparing TNF antagonists with leflunomide.

5.3 Discussion

The results of the economic review suggest that ETN and IFX, each used concomitantly with MTX, may be cost-effective for the treatment of RA after failure with other DMARDs. In many economic evaluations, the costs per QALY were high, surpassing the generally accepted thresholds for cost-effectiveness. There was insufficient information to suggest that these agents are cost-effective as initial therapy.

The economic literature on ETN and IFX was dominated by three clinical studies, all funded by industry. The three studies included patients with RA who had failed at least one DMARD. For ETN, the clinical data came largely from a study funded by Immunex or from the TEMPO study. The Immunex data suggested that ETN was more cost-effective than non-biologic agents. The TEMPO trial found that the concomitant use of ETN and MTX was more cost-effective than MTX or ETN alone; no differences were observed between MTX and ETN. For IFX, the economic analysis was dominated by the ATTRACT study funded by Centocor. The study found that IFX+MTX was more cost-effective than MTX alone. No studies directly compare the cost-effectiveness of IFX versus ETN. Although mixed, most of the evidence indicates that ETN is probably not cost-effective as a monotherapy.

Variation was observed in the results reported by type of publication, and individual studies showed large variation associated with whether the study was funded or authored by the pharmaceutical industry. In general, HTA reports showed modest cost-effectiveness for TNF antagonists in most scenarios. From a cost-utility perspective, the use only in serious active disease not responding to other treatments seemed to be appropriate. The cost-effectiveness of anti-TNF agents was sensitive to
the choice of comparator. For example, LEF was shown to be more cost-effective than ETN and IFX. Many of the evaluations were based on trials using an ineffective comparator (e.g., MTX after therapeutic failure with this drug), so some cost-effective scenarios may not represent current best practice. Indirect costs also played a role in determining the cost-effectiveness of these biologic agents in RA; therefore, a societal perspective should always be used in these analyses.

The one economic evaluation that included an analysis of IFX and ETN in the Canadian health care system — Coyle et al. — found that neither was cost-effective from a health care system perspective, compared with a baseline strategy of MTX followed by a switch to gold (due to toxicity or lack of efficacy) and then to palliative care if gold failed. The study assumes no cost offsets due to therapeutic benefit, a defined limitation to Jobanputra et al. Including offsets (such as societal costs) would improve the ICER and imply that Coyle et al. would produce an upper bound result. Although the methods for estimating indirect and direct non-medical costs in Coyle et al. are not as developed as those used for the direct medical costs, the effects of anti-TNF on these costs are evident. The therapies are more cost-effective from a societal perspective than from a ministries of health perspective.

6 HEALTH SERVICES IMPACT

Based on our results, we cannot declare that ETN or IFX is unequivocally cost-effective. Studies where a societal perspective was taken — rather than a health care system perspective — were more likely to find the therapies to be cost-effective. More research is needed on the long-term cost-effectiveness of ETN and IFX. The short-term improvements in clinical endpoints are large enough to warrant further evaluation.

In practice, the utilization patterns of TNF antagonists diverge from the experience in trials and can result in unexpected use and costs. From an economic perspective, there is a budget impact to the adoption and funding of anti-TNF therapies for the treatment of RA. Moreover, the demand for these therapies is likely to increase over time with their increased availability. The widespread adoption of these therapies will require changes in the infrastructure needed to deliver services. IFX is administered intravenously, and therefore requires administration in an outpatient setting. This suggests a large initial investment with respect to availability of outpatient space and training in the delivery of IFX. The average cost of delivery is likely to decrease over time as more RA patients use the services. ETN is a self-administered injection.

This suggests that the increasing use of ETN will not have a large initial cost, but it will not have a decreasing average cost with additional patients.

7 DISCUSSION

7.1 Summary of Results

The long-term clinical effectiveness of anti-TNF agents is small to moderate. Many studies were conducted in patients who had not responded to MTX, but despite this failure, a significant — albeit modest — response to anti-TNF agents was observed. IFX and ETN were most effective when used in
combination with MTX. The use of ETN alone did not have an advantage in the long term over the use of MTX alone. The beneficial effects of anti-TNF agents were on radiological progression. More research is needed to establish how these effects translate to clinical benefits and enhanced quality of life.

The discontinuation rates for all causes after several years of treatment were high. The rates were higher with IFX than with ETN. Anti-TNF agents were well tolerated in the short term, but concerns remain about their long-term safety with respect to infections, lymphomas, autoimmunity, and demyelination. The risk for some serious complications, such as TB and autoimmune disorders, is greater with IFX than with ETN, although head-to-head comparative risk studies are needed.

ETN and IFX were shown to be clinically effective, but with a substantial budget impact. Many studies suggest that ETN and IFX, when concomitantly administered with MTX, may be cost-effective if society is willing to pay $100,000 for a QALY and if prescribed after therapeutic failure with traditional DMARDs. There was insufficient information to suggest that these agents are cost-effective as initial therapy when a similar threshold is applied.

7.2 Study Limitations

This report has limitations inherent to the quality of the data that it synthesizes. Few trials have examined the long-term effectiveness of anti-TNF agents. Because of ethical concerns and the methodological difficulties associated with extending trials in patients who are failing the treatment interventions, few studies go beyond one or two years. Head-to-head comparisons between biologic agents are unavailable. Therefore, many recommendations are based on indirect comparisons. Because of the heterogeneity of the evidence, the economic results were difficult to synthesize, but enough information was gathered to project what is clinically relevant.

Many RCTs did not follow current clinical practice. Studies often compared IFX or ETN to MTX using a control group of patients who had already failed MTX. When the trials included a “true” MTX control group of naïve patients, the results showed less benefit with IFX or ETN (compared with MTX) than in trials that “added on” patients who had already failed with MTX. In real practice, patients seldom remain on the same treatment if they fail. Often, other DMARDs are added. At the time of our literature search, a comparison between biologic agents and combination therapy of traditional trials had not been published.

Only moderate overall quality scores were obtained for the observational studies that we included in this report. Observational studies are needed to establish the long-term clinical effectiveness of IFX and ETN. The methodological rigour applied to RCTs, however, is not commonly used in observational studies. Because all the included clinical trials were adjusted for covariates such as age, gender, and ethnicity, these covariates probably had minimal, if any, impact on our results.

For the economic review, most of the studies that we included were sponsored by the pharmaceutical industry, which may have influenced the cost-effectiveness evaluations and interpretation of results. Many of the limitations that we identified involved the modelling of trial information, which often did not correspond to best, or even usual, clinical practice. For example, dose escalation and switching TNF-antagonists play roles in clinical practice (their significance in the clinical effectiveness of IFX and ETN is described in a separate CADTH report\(^{28}\)). These effects should be considered in economic evaluations. Most of the economic evaluations were based on six-month or one-year data (with longer-term projections), whereas our review of the literature on clinical
effectiveness showed that anti-TNF agents may be less effective in the long term. Long-term discontinuation rates were similar to those observed for other traditional DMARDs such as MTX. Our review of the clinical literature showed that the difference between anti-TNF agents and other traditional DMARDs was their effect on radiological progression, although the clinical significance on long-term outcomes remains unclear. Improved radiographic progression, however, is often not modelled in the long-term effects of either therapy. The cost-effectiveness of TNF antagonists may depend on the long-term impact of improved radiographic progression on health care utilization, joint replacement, health-related quality of life, and ability to work.

7.3 Generalizability of Findings

In general, the findings of our clinical review are similar to those presented in HTA reports. Because of our focus on long-term effectiveness, however, our results show a more modest impact of anti-TNF agents on clinical outcomes after a year of treatment. Because our review covered literature from many countries, with no differences among them, these findings are generalizable to many countries in the western world. Some of the issues examined, such as safety, particularly in relation to infections, may be different among vulnerable populations in the western world and in developing countries. The findings of our economic assessment are generally consistent with those of other reviews. The models used in economic evaluations, however, often omitted common practice patterns.

7.4 Knowledge Gaps

The knowledge gaps in this report relate mostly to areas of clinical effectiveness. The scientific knowledge gaps that hinder evidence-based decision-making and recommendations are the lack of information in the following areas:

- information on the effects of radiological progression on long-term patient outcomes (such as joint replacement) and quality of life
- safety data for longer-term use of anti-TNF agents (particularly with respect to tumors, infection, demyelinating diseases, and autoimmunity)
- longer-term observational information comparing usual therapy patterns with biologic agents to other alternatives (such as combination therapy with traditional DMARDs).

Many of the RCTs in this review included patients from Canada, but separate studies in Canadian populations were scarce. It would be beneficial to have additional information on current practice patterns in Canada and safety issues in vulnerable Canadian populations.

8 CONCLUSIONS

IFX and ETN, each used concomitantly with MTX, have moderate efficacy in the long-term treatment of RA after failure with conventional therapy. Indirect comparisons showed a trend favouring the use of IFX+MTX over ETN+MTX, and no advantage to using ETN alone over MTX. The short-term safety profile for these anti-TNF agents is acceptable, but concerns remain about their long-term safety with respect to infections, lymphomas, autoimmunity, and demyelination.
The results of the economic review suggest that ETN and IFX, each used concomitantly with MTX, is only cost-effective as second-line therapy after failure with a traditional DMARD if society is willing to pay $100,000 for a QALY. There was insufficient information to suggest that these agents are cost-effective as initial therapy when a similar threshold is applied.

Longer-term studies and economic evaluations need to take into account community practice patterns to better reflect the realistic benefits and costs of these therapies.

9 REFERENCES


Infliximab and Etanercept in Rheumatoid Arthritis: Systematic Review of Long-term Clinical Effectiveness, Safety, and Cost-effectiveness


Infliximab and Etanercept in Rheumatoid Arthritis: Systematic Review of Long-term Clinical Effectiveness, Safety, and Cost-effectiveness


Infliximab and Etanercept in Rheumatoid Arthritis: Systematic Review of Long-term Clinical Effectiveness, Safety, and Cost-effectiveness


232. de'Clari F, Salani I, Safwan E, Giannacco A. Sudden death in a patient without heart failure after a single infusion of 200 mg infliximab: does TNF-alpha have protective effects on the failing heart, or does infliximab have direct harmful cardiovascular effects? *Circulation* 2002;105(21):E183.


APPENDICES

Available from CADTH’s web site
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