The Cost-Effectiveness of Celecoxib and Rofecoxib in Patients with Osteoarthritis or Rheumatoid Arthritis

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The Cost-Effectiveness of Celecoxib and Rofecoxib in Patients with Osteoarthritis or Rheumatoid Arthritis

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HIGHLIGHTS

What is already known about this topic?

- About NSAIDs
  - Nonsteroidal anti-inflammatory drugs (NSAIDs) are a core modality for the management of rheumatoid arthritis (RA) and are a valuable alternative for patients with osteoarthritis (OA).
  - However, some users of NSAIDs experience gastrointestinal side effects and a few develop stomach and duodenal ulcers.
  - A new generation of NSAIDs that more selectively inhibit cyclo-oxygenase type-2, called COX2 NSAIDs, have been promoted as being associated with fewer upper gastrointestinal (UGI) side effects when compared with therapy using other NSAIDs.

- About rofecoxib (Vioxx®) and celecoxib (Celebrex®)
  - Both drugs are approved for acute and chronic treatment of OA in Canada. At the time of this review, only celecoxib had been approved for the treatment of RA.
  - Their analgesic activity is similar to that of other NSAIDs.
  - Concern exists about an increase in cardiovascular events from celecoxib and rofecoxib vs comparator NSAIDs.

Assessment Objective

To determine the cost-effectiveness of:

1. celecoxib in comparison to the “traditional” NSAIDs diclofenac and ibuprofen, and
2. rofecoxib in comparison to the “traditional” NSAID naproxen,

in patients with OA and RA who are not on low-dose aspirin for the prevention of cardiovascular disease. The findings are based on the clinical outcomes in the CLASS and VIGOR trials.

What new information does this assessment provide?

- Average risk patients
  - Rofecoxib and celecoxib were not found to provide cost-effective therapy in patients who are at average risk of UGI events or in a population with a typical mix of average risk and high risk patients. Average risk patients are those who have not experienced UGI events, defined as either (i) prior complicated UGI events (GI perforation, obstruction or major bleeding) or (ii) prior clinical symptomatic ulcers, as shown by endoscopy.
  - The two drugs provide cost-effective therapy for patients without additional risk factors when these patients are over the age of 76 for rofecoxib and age 81 for celecoxib.

- High risk patients
  - Rofecoxib and celecoxib were found to provide cost-effective therapy for patients with proven histories of UGI events (as defined above).
  - However, these drugs may no longer be cost-effective in comparison to therapy combining a traditional NSAID with a proton pump inhibitor (PPI) if a low priced PPI becomes available, with the threshold PPI price dependent on the particular treatments being compared.
EXECUTIVE SUMMARY

The Issue: Nonsteroidal anti-inflammatory drugs (NSAIDs) are core therapeutics in the management of inflammatory musculoskeletal conditions such as rheumatoid arthritis (RA). They are also a valuable therapeutic alternative for patients with osteoarthritis (OA) who fail to respond to acetaminophen or non-pharmaceutical interventions. The gastrointestinal (GI) adverse effects are hypothesized to be due to the inhibition of cyclo-oxygenase 1 and, therapeutic effects due to the inhibition of cyclo-oxygenase 2. The synthesized NSAIDs, rofecoxib and celecoxib, have demonstrated a selective COX2 inhibition with sparing of COX1 that may prevent the development of GI adverse effects. While sparing of COX1 leads to less GI adverse events, inhibition of COX2 produces therapeutic analgesic, anti-inflammatory and anti-pyretic effects, but may also lead to an increase in cardiovascular (CV) thrombotic events by inhibiting prostacyclin. Both rofecoxib and celecoxib have shown clinical efficacy similar to regular NSAIDs and an improved GI safety profile, but concerns exist about an increase in CV adverse events.

Objective: The purpose of this assessment is to evaluate the long-term cost-effectiveness of the COX2 NSAIDs celecoxib, in comparison to diclofenac and ibuprofen, and rofecoxib in comparison to naproxen, in patients with OA and RA who are not on low-dose aspirin for the prevention of CV disease. Analyses are performed for patients at average risk of upper gastrointestinal (UGI) events, and for higher risk patients with a history of a UGI event that is either (a) a clinical UGI event (a symptomatic ulcer), as shown by endoscopy, or (b) a complicated UGI event (a GI perforation, obstruction or major bleeding).

Methods: A decision-analysis model was constructed where GI and CV events were modelled as a consequence of NSAID-intake. The model used the Markov technique and extrapolated clinical trial results over a 5-year timeframe. Major events were 1) clinical UGI events, 2) complicated UGI events (excluding symptomatic ulcers), and 3) nonfatal myocardial infarctions (MIs). Key estimates of event rates, and the relative effectiveness of COX2 NSAIDs in reducing these, were based on data from two key clinical trials, which were submitted to the US Federal Drug Administration. These trials were the Vioxx® Gastrointestinal Outcomes Research (VIGOR) study and the Celecoxib Long-Term Arthritis Safety Study (CLASS). In the VIGOR study, rofecoxib was used to treat patients with RA, although it is not currently approved by Health Canada for the treatment of RA. Remaining probability estimates were obtained through a comprehensive literature search of MEDLINE®, supplemented by bibliographies of relevant articles. Standard gamble utility estimates for arthritis health states that are complicated by GI events were gathered through a separate study of 60 randomly selected members of the general public. Cost estimates were obtained from provincial databases.

Incremental cost-effectiveness, defined as the additional cost of the COX2 strategy divided by its additional clinical benefit, was calculated from the perspective of the Ontario Ministry of Health in 1999 dollars. COX2 NSAIDs were priced at dosages consistent with the proportion of RA and OA populations in the respective trials: (i) celecoxib 100 – 200mg bid was compared to diclofenac 50mg tid and ibuprofen 800mg tid, and (ii) rofecoxib 25mg qd was compared to naproxen 500mg bid. A number of other assumptions were made, including: 1) patients who were considered at high risk of recurrent GI bleeding received a co-prescription of proton pump inhibitors (PPIs); 2) the relative GI benefit of PPIs is the same in patients treated with COX2s
and regular NSAIDs; and 3) the cost/day of rofecoxib in RA patients was assumed to be that of 25mg qd in the absence of a regulatory-approved dosage regimen. The sensitivity of the cost-effectiveness results to changes in individual variables was tested, as well as the effect of an additional risk factor.

**Results:** For average-risk patients, base case results were more than $200,000 per quality-adjusted life-year (QALY) gained for rofecoxib vs naproxen and for celecoxib vs ibuprofen. Diclofenac was more effective and less costly than celecoxib in average-risk patients. Cost-effectiveness results for average-risk patients did not fall below $86,000 per QALY gained for either COX-2 NSAID in any sensitivity analysis performed. For high risk patients, the base case results showed the COX-2 NSAIDs to be more effective and less costly for rofecoxib vs naproxen + PPI and for celecoxib vs ibuprofen + PPI. Diclofenac had a cost per QALY gained of $255,000 compared to celecoxib in high risk patients. In sensitivity analysis, results fall below $50,000 per QALY gained when high risk patients are treated with regular NSAIDs + a low priced PPI (< $1.90 per day) compared to COX2 NSAIDs, with the threshold PPI price dependent on the particular treatments being compared. Analysis by age group showed that the results for rofecoxib and celecoxib fall below $50,000 per QALY gained in patients without additional risk factors over age 76 and 81, respectively.

**Conclusion:** The findings are based on the clinical outcomes (including upper gastrointestinal events and myocardial infarctions) in the CLASS and VIGOR trials and pertain only to patients with OA and RA who do not require low-dose aspirin therapy. In the analysis, rofecoxib and celecoxib:

(i) are not cost-effective treatments in patients at average risk of upper gastrointestinal events (symptomatic ulcers or complicated UGI events) or in a population with a typical mix of average risk and high risk patients;

(ii) are cost-effective treatments for patients who are considered at high risk for gastrointestinal events by having a history of upper gastrointestinal events;

(iii) become less cost-effective in high risk patients as the rate of co-prescription of PPIs increase, and may lose their cost-effective advantage altogether if the price of PPIs was to decrease, with the threshold PPI price dependent on the particular treatments being compared; and

(iv) become cost-effective treatments for patients without additional risk factors over the age of 76 for rofecoxib and 81 for celecoxib.

It is noted that rofecoxib is currently not approved in Canada for the treatment of RA. Uncertainty remains about the correct method for deriving utilities for short-term health states.
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1 INTRODUCTION

1.1 General Comments on the Disease or Condition

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed to patients with conditions as diverse as dysmenorrhoea, acute pain episodes, lower back pain, rheumatoid arthritis (RA) and osteoarthritis (OA). Individuals with inflammatory musculoskeletal conditions often need NSAIDs because of the limited activity of non-NSAID analgesics (e.g. acetaminophen) and the unacceptable side-effect profiles of corticosteroids. NSAIDs are usually prescribed on a long-term basis for patients with RA, and are recommended in therapeutic guidelines as an option for individuals with OA.1,2

NSAIDs are generally prescribed with some hesitation, due to the possibility of rare but serious upper gastrointestinal (UGI) events.3 Endoscopic studies have demonstrated the presence of gastric and duodenal ulcers in approximately 21% of users of standard NSAIDs.4 Many such ulcers are sub-clinical and only 15% of them precipitate a clinical (symptomatic) UGI event,5 however, approximately half of that 15% show signs of active bleeding and are, therefore, defined as complicated. NSAID-users are at almost four times greater risk than non-users of developing a clinical UGI event.6

1.2 Product Description

At the molecular level NSAIDs are believed to inhibit the activity of two isoforms of the enzyme cyclooxygenase.7 Cyclo-oxygenase 1 (COX1) is constitutively expressed in most cells and is responsible for the production of prostaglandins, which protect the gastrointestinal mucosa and regulate renal blood flow. In platelets, COX1 mediates production of thromboxane A2, which is responsible for vasoconstriction and platelet activation and aggregation. COX2, an inducible enzyme, is active in the kidney, brain, and sites of inflammation, where it produces prostaglandins and prostacyclin, a vasodilator and inhibitor of platelet aggregation.

Inhibition of COX1, therefore, leads to a disruption of the defence mechanisms in the gastric mucosa and subsequent development of gastrointestinal (GI) lesions. Inhibition of COX1 also leads to inhibition of platelet aggregation. Inhibition of COX2 produces therapeutic analgesic, anti-inflammatory and anti-pyretic effects, but might also lead to an increase in cardiovascular thrombotic events by inhibiting prostacyclin.

Most NSAIDs that were introduced subsequent to the discovery of acetyl salicylic acid or aspirin inhibit both enzymes and therefore incur both desirable and undesirable consequences. Some NSAIDs that were introduced more recently, e.g. nabumetone or meloxicam, claim to incur less of the undesirable properties than regular NSAIDs, such as naproxen or indomethacin. It is believed that the more an NSAID spares COX1, the less it is expected to be toxic on the gastric mucosa.8 The COX2 NSAIDs rofecoxib and celecoxib are the most selective NSAIDs and thus should impart the least gastrointestinal adverse events.9 They are believed to interact with only one of the two isoforms of the cyclo-oxygenase (COX) enzyme.7,9 Rofecoxib and celecoxib have been demonstrated to have similar analgesic activity to standard NSAIDs,10,11 while being somewhat less likely to precipitate a UGI event.12-14 The reduction in UGI events is not seen in comparison to all standard NSAIDs, and is questionable in patients given low-dose aspirin.13
Moreover, inhibition of prostacyclin may lead to increased cardiovascular thrombotic events, a hypothesis that seems supported by physiological and clinical evidence.\textsuperscript{15}

### 1.2.1 Therapeutic classification

Rofecoxib and celecoxib are anti-inflammatory analgesic agents, also called nonsteroidal anti-inflammatory drugs (NSAIDs) that exhibit anti-inflammatory, analgesic, and antipyretic activities in animal models.

### 1.2.2 Approved indications

Celecoxib and rofecoxib are both approved by the US Federal Drug Administration and the Canadian Health Protection Branch for acute and chronic treatment of the signs and symptoms of OA in adult patients. Celecoxib is also approved in Canada for the treatment of the signs and symptoms of RA, while rofecoxib is also approved for relief of pain in adults and for treatment of primary dysmenorrhea.

In Ontario, rofecoxib and celecoxib are approved for prescription reimbursement to patients with OA who have failed an adequate trial of acetaminophen, (e.g. acetaminophen 1000mg qid for several weeks) and have had: 1) a positive history of a serious ulcer-related complication (i.e. perforation, GI bleed, or clinically significant ulcer), or 2) failure or intolerance to at least three listed NSAIDs. Furthermore, celecoxib is approved for prescription reimbursement to patients with RA with the same restrictions as listed for patients with OA, without the need for a trial of acetaminophen.

### 1.2.3 Indications subjected to economic evaluation

Indications subjected to this economic evaluation will be those adopted in two key clinical trials, the Celecoxib Long-Term Arthritis Safety Study (CLASS) and the Vioxx\textsuperscript{®} Gastrointestinal Outcomes Research (VIGOR) study, the detailed data of which were submitted to the Federal Drug Administration.

Briefly, in CLASS, 7,968 patients with RA (28%) or OA (72%) were randomised to celecoxib 400mg bid (n=3,987), diclofenac 75mg bid (n=1,996) or ibuprofen 800mg tid (n=1985).\textsuperscript{13} A total of 3409 patients completed the study and had at least 9 months of exposure to treatment: 1779 (45%) receiving celecoxib, 939 (47%) receiving diclofenac, and 691 (35%) receiving ibuprofen. In CLASS, 1.5% of patients had a history of a GI bleed and 8.2% had a history of a UGI event (ulcer). Celecoxib was comparable to diclofenac and ibuprofen (at the doses studied in these trials) in treating the signs and symptoms of OA and RA, as measured by the patient’s assessment of arthritis pain on a visual analog scale from 0 mm (no pain) to 100 mm (most severe pain), the patient’s global assessment of arthritis based on a scale of 1 (very good) to 5 (very poor) and the health assessment questionnaire (HAQ).

In VIGOR, 8,076 patients with definite RA and who did not receive low-dose aspirin were randomised to rofecoxib 50mg qd (n=4,047) or naproxen 500mg bid (n=4,029).\textsuperscript{14} In the patient population, 2.6% had a history of a GI bleed and 8% had a history of an ulcer. Discontinuations due to NSAID-related AE’s such as renal, liver, HTN and edema-related AE’s were numerically higher (and some statistically significantly higher) in the rofecoxib group. Adverse events related
to coronary heart failure were also higher in the rofecoxib group. No differences could be observed in efficacy parameters as measured by Patient’s and Investigator’s Global Assessment of Disease Status, on the Likert scale from 0 to 4, the modified HAQ, consisting of 8 questions on a scale of 0 to 3, and discontinuations due to lack of efficacy.

While twice the recommended doses were required for COX2 to be used in these safety trials, the lower dosages of COX2 NSAIDs as recommended in patients with OA and RA were used for this analysis. Therefore, celecoxib (100-200mg bid) was compared to diclofenac (75mg bid) and ibuprofen (800mg tid) in patients with OA or RA and rofecoxib (25mg qd) was compared to naproxen (500mg bid) in patients with RA. All comparisons were performed for patients who do not require treatment with low-dose aspirin.

1.3 Objectives

The objective of this assessment is to evaluate the cost-effectiveness and cost-utility of celecoxib in comparison to diclofenac and ibuprofen, and that of rofecoxib in comparison to naproxen in patients with OA and RA who do not require treatment with low-dose aspirin. Analyses are performed for patients at average risk of gastrointestinal (GI) events, and for higher risk patients with a history of a UGI event that is either (a) a clinical UGI event (a symptomatic ulcer), as shown by endoscopy, or (b) a complicated UGI event (a GI perforation, obstruction or major bleeding).
2 METHODS

2.1 Type of Analyses

This pharmacoeconomic evaluation of COX2 NSAIDs consists of a cost-effectiveness and cost-utility analysis. Effectiveness was modelled as a change in the type and frequency of GI adverse events occurring as a consequence of taking COX2 NSAIDs as compared to regular NSAIDs. Utility was modelled as quality-adjusted life-years determined for the relevant GI events from members of the general public in a separately conducted utility survey. The analysis was conducted within a decision analysis framework over a 5-year time horizon.

2.2 Cost-Effectiveness and Cost-Utility Analysis

The cost-effectiveness analysis of COX2 NSAIDs is supported by a comprehensive decision analysis model of the relevant GI events that may occur as a consequence of prescribing NSAIDs to patients with OA or RA. The following paragraphs will explain the decision analysis framework, the flow of events, the underlying assumptions and the analytic approach.

2.2.1 Target population

The target populations are patients with RA or OA, who do not require low-dose aspirin and who may be at different risk levels of developing GI events through influences such as increased age, a history of GI events, corticosteroid use, or decreased health status.

2.2.2 Strategies to be compared

Two strategies will be compared separately for each disease. Strategy 1 comprises prescription of regular NSAIDs and strategy 2 prescription of COX2 NSAIDs.

2.2.3 Structure of the decision analysis model

A Markov-model\(^\text{16}\) was developed in which each 3-month Markov cycle was a period during which a patient might experience GI or cardiovascular events (Figure 1). GI events were classified as follows: dyspeptic symptoms (symptoms severe enough to require a medical consultation, with or without prescription of antacids); clinical UGI events (symptomatic ulcers); and complicated UGI events (symptomatic ulcers with bleeding). Some complicated UGI events may require hospitalization, or even surgery, whereas others can be managed on an outpatient basis. Recurrent bleeding was modelled in a separate cycle, because patients who bleed are at higher risk of recurrent GI bleeding, the management of which is identical to that of 1st bleeds. A small fraction of patients with a bleed was modelled to receive NSAIDs again with co-prescription of PPIs, but the majority received non-NSAID analgesics. All patients who experienced a second bleed were switched to non-NSAID analgesics. Exact rates of myocardial infarctions (MIs), observed under treatment with COX2 NSAIDs in the CLASS and VIGOR studies, were modelled as well as the estimated increase in mortality post MI. At each cycle, patients are subject to age-specific mortality.

Once started on a treatment, the events experienced by a patient determined the Markov state he or she moved to subsequently. Average risk individuals who did not experience a clinical UGI
event in any one cycle remained average risk in the next. Those who experienced a clinical (but not complicated) UGI event were considered high risk and received PPIs, even if on COX2 NSAIDs, while those with a complicated UGI event were assigned to the 'post-bleed' state and then transferred to 'non-NSAID analgesics and PPIs' unless NSAIDs were retriied in combination with PPIs. Patients who experienced an MI were modelled to continue their respective NSAID with co-prescription of low-dose aspirin, in the case of which we credited no GI safety benefits to COX2 NSAIDs.

Figure 1: Decision Tree used for the cost-effectiveness and cost-utility evaluation.

2.2.4 Differences in the model between COX2 and regular NSAIDs

While the clinical stages and the events are very similar for patients on COX2 or regular NSAIDs, there are differences between these NSAIDs that have been modelled. COX2 NSAIDs have been shown to be safer on the gastric mucosa and to significantly reduce the number of clinical and complicated UGI events. Moreover, patients on COX2 NSAIDs had significantly reduced co-prescription of antacids. Therefore, the probability of “clinical UGI events” and “complicated UGI events” in the model, and the probability of co-prescription of antacids to patients with dyspepsia, are reduced for patients on COX2 NSAIDs. The relative reductions will
match those that were observed in the phase IV clinical trials of celecoxib and rofecoxib for these groups of events. As a consequence of this, patients on COX2 NSAIDs experience fewer downstream hospitalizations and surgery, fewer recurrences of complicated UGI events and less co-prescription of antacids. This is associated with reductions in the healthcare costs incurred by patients on COX2 NSAIDs.

2.2.5 Scenarios used for comparing regular NSAID and COX2 strategies

The following scenarios will be used to determine the cost-effectiveness and cost-utility of COX2 NSAIDs:

1) **Average risk scenario**: In this scenario all patients are considered average risk and will all receive either regular NSAIDs in strategy 1 or COX2 NSAIDs in strategy 2.

2) **High risk scenario**: In this scenario all patients are considered high risk and will receive regular NSAIDs with co-prescription of PPIs in strategy 1, COX2 NSAIDs without co-prescription of PPIs in strategy 2, and COX2 NSAIDs with co-prescription of PPIs in strategy 3.

2.2.6 Definition of effectiveness used for the model

The more narrowly defined “Complicated UGI Event” and the “Clinical UGI Event”, which includes “symptomatic ulcers” and “complicated UGI events”, will be considered as clinical units for the purpose of the cost-effectiveness analysis. During each cycle, a small fraction of patients will experience these events, which will be added up over the 5-year model duration. The total number of accumulated events in the two groups will then be compared in the cost-effectiveness analysis.

Definitions of UGI events employed in the literature vary and are inconsistent, often making hospitalization a necessary requirement. For the purpose of this analysis we adopt the definitions of UGI events used in the recent phase IV clinical trials of the COX2 NSAIDs celecoxib and rofecoxib. In VIGOR, GI outcomes were assessed by a blinded expert committee, who classified gastrointestinal perforation, obstruction or major bleeding as a “complicated upper GI (UGI) event”, and all complicated UGI events including symptomatic ulcers as “clinical UGI event”. Identical definitions of clinical and complicated UGI event were used in the CLASS study, where a blinded GI events committee adjudicated all events.

2.2.7 Calculation of QALYs used in the model

Utility rewards were assigned to the following events:

1. Dead
2. Alive, No GI event
3. Alive, Dyspepsia
4. Alive, Symptomatic ulcer requiring endoscopy
5. Alive, complicated UGI event requiring medical management
6. Alive, complicated UGI event requiring surgical management
7. Alive, MI event followed by coronary heart disease
Utilities for the above health states were elicited from the general public for the purpose of performing the cost-utility analysis. In the cost-utility analysis, the time a patient spends in the various health states during a 3-month cycle is adjusted by the utility value of this health state to determine the quality-adjusted life-year (QALY) equivalent to spending 5 years in the model. For example, if each cycle is equivalent to perfect health, i.e. $\frac{1}{4}$ year would be worth 0.25 (1 divided by 4), then the time a perfectly health patient spends in the model would be worth 5 QALYs, i.e. $20\times0.25$ QALYs. However, because the model health states are worth less than perfect health, i.e. each cycle is worth less than 0.25, adding all cycles’ QALY values over the 5-year timeframe will provide less than 5 QALYs for the patients.

### 2.2.8 Model Assumptions

a) **Assumption 1: UGI events in patients not taking NSAIDs**

We assumed that the rates of UGI events in patients not on NSAIDs, i.e. analgesics, equal the rates observed in patients on COX2 NSAIDs in the major trials. This assumption is supported by the finding of equal rates of clinical UGI events in patients on COX2 NSAIDs or placebo in a meta-analysis of placebo-controlled COX2 trials.\(^{12}\) This information could also be taken from the placebo groups of the large cardiovascular prevention trials. However, these trials likely recruited patients with higher CV co-morbidity, and the definitions of UGI events were not the same as the ones used for the COX2 trials.\(^{19}\)

**Implication:** The effects of this assumption might be a potential reduction of the cost-effectiveness ratios in favour of COX2 NSAIDs, but only if placebo rates are lower than the rates observed in the COX2 arms. Evidence to date shows that the rates are similar. Thus, this assumption seems to have a neutral effect.

b) **Assumption 2: Effectiveness of PPIs**

We assumed that PPIs co-prescribed with NSAIDs were associated with a constant relative risk reduction in the rate of UGI events, irrespective of whether the NSAID was COX2 specific or not. There are no direct comparisons between COX2 NSAIDs and COX2 NSAIDs + PPIs and, therefore, no data about the efficacy of PPIs in patients on COX2 NSAIDs.

**Implication:** The cost-effectiveness ratios would be slightly higher for COX2 NSAIDs, if the relative risk reduction with PPIs is less with COX2 NSAIDs than with regular NSAIDs.

c) **Assumption 3: Mortality of patients with medically or surgically treated UGI events**

Complicated UGI events among long-term NSAIDs users are rare and even studies with large sample sizes do not include sufficiently large numbers to accurately estimate mortality and recurrence rates of complicated UGI events. Mortality data are available from larger patient-cohorts, which generally study patients admitted to hospital with an UGI bleed, often gastric or duodenal ulcer-related. Evidence about differences in mortality between surgically or medically treated patients does not exist. It is, therefore, assumed that the mortality of surgically or medically managed patients is identical and equals the mortality observed among patients with UGI bleeds.

**Implication:** This assumption has no significant impact on other downstream events in the model, nor does it bias the comparison of COX2 and regular NSAIDs. Any differential reduction in complicated UGI events due to COX2 NSAIDs will reduce mortality to the same degree.
d) Assumption 4: Percentage of patients with complicated UGI event retrying NSAIDs
No data are available to estimate the percentage of patients with complicated UGI events who retry NSAIDs. Therefore, we modelled this percentage based on expert opinion. The basic model will assume that physicians retry NSAIDs in ~ 5% of patients. This variable was analyzed in sensitivity analyses. **Implication:** The lower the percentage of patients retrying NSAIDs, the more this assumption might skew cost-effectiveness ratios against COX2 NSAIDs, because those patients who retry NSAIDs are at risk again of experiencing a new bleed.

e) Assumption 5: Clinical and complicated GI events occur at a constant rate
Most of the studies, in particular the clinical trials, are of limited duration, which makes it impossible to examine whether the rate of clinical or complicated UGI events stays constant or declines over time. It is conceivable that the rate declines over time because patients who take long-term NSAIDs are assumed to develop tolerance towards the GI adverse events of NSAIDs. However, no information exists in the literature to support this claim and it will thus be assumed that the rate of UGI events is constant, which is a conservative assumption. **Implication:** This assumption reduces the cost-effectiveness ratios in favour of COX2 NSAIDs.

f) Assumption 6: No GI benefit of COX2 NSAIDs in patients on low-dose aspirin
We assumed that COX2 NSAIDs would have no GI benefit in patients who experienced an MI in the model and then received low dose aspirin. At present, it is too early to conclude from the small aspirin subgroup recruited into the CLASS study, where no GI benefit was seen in aspirin users, whether aspirin use completely eliminates the GI protective effects of COX2 NSAIDs. **Implication:** Modelling a GI benefit in patients on aspirin would only minimally improve the cost-effectiveness ratio of COX2 NSAIDs due to the small number of patients who experience MIs in the model.

g) Assumption 7: GI toxicity of COX2 NSAIDs at lower doses
Although trial doses of COX2 NSAIDS were 2–4 times higher than recommended, we assumed that the GI toxicity of COX2 NSAIDs is identical at the lower doses which are recommended in patients with OA or RA and that were used in this analysis. The assumption is supported by the fact that the relative reduction of GI events is identical in studies that examine lower doses of rofecoxib. Furthermore, GI event-rates in the placebo groups of four large cardiovascular prevention trials were similar to, and sometimes higher than, the rates observed in the rofecoxib or celecoxib groups of the VIGOR and CLASS trials. The relative effectiveness of COX2 might thus hit a maximum ceiling between 50% and 60% relative risk reduction. **Implication:** A reduced GI toxicity at lower doses would lead to more favourable cost-effectiveness ratios for the COX2 NSAIDs.

h) Assumption 8: Continuous NSAID use
We assumed that NSAID use was sustained for both groups, in the absence of complications, for the full five-year period. There are no trials evaluating the GI safety of NSAIDs when given intermittently or on an “as needed” basis, which is how NSAIDs are frequently taken by OA patients. Modelling the intermittent use of NSAIDs would require additional information, such as whether patients on COX2 NSAIDs, taken intermittently, are clinically better off. **Implication:** Without data suggesting a benefit of an intermittent use of COX2 NSAIDs, the cost-effectiveness ratios for intermittent use would be identical to those for continuous use, since both
numerator and denominator of the cost-effectiveness ratio would decrease by the same relative amount.

i) Assumption 9: Five-year time-horizon
Although the clinical trials extend to only one year, we adopted a 5-year time horizon to capture the cumulative long-term consequences of cardiovascular and GI outcomes.

j) Assumption 10: Use of exact event rates
Exact event rates for GI and CV events were used from the VIGOR and CLASS studies, whether or not they were statistically significant.

2.3 Target Audience
The results of the study will be helpful to provincial/territorial Ministries of Health in their assessment of COX2 NSAIDs for drug formulary reimbursement. Similarly, third party payers such as private insurance companies may use the study in their consideration for formulary inclusion.

2.4 Viewpoint
The viewpoint of this analysis is the third party payer, more specifically, the Ontario Ministry of Health. Utilities however, were derived from informed members of the general public rather than arthritis patients, as recommended for health policy analysis. The analysis comes close to adopting a societal perspective, because indirect costs are partially captured in the utility estimates.

2.5 Treatment Comparators
Treatment comparisons matched those that were performed in the clinical trials of celecoxib and rofecoxib. Lower doses as used in the trial and as recommended for OA and RA patients were assumed for the COX2 NSAIDs. Rofecoxib (25mg qd) was thus compared to naproxen (500mg bid) and celecoxib (100 to 200mg bid), with dosages weighted by the proportion of OA (72% on 100mg bid) and RA (28% on 200mg bid) patients in the trial, was compared to diclofenac (75mg bid) and ibuprofen (800mg tid).

The regular NSAID comparators share a large proportion (> 70%) of the market for regular NSAIDs (Table 1). Data from the IMS HEALTH “CompuScript” database show that naproxen, diclofenac and ibuprofen make up over 70% of all prescriptions issued for the regular NSAIDs.
Table 1: Estimated nation-wide number of prescriptions issued for regular NSAIDs, Arthrotec and COX2 NSAIDs, and percentage share among prescriptions for 1999 and the 12-month period ending September 2000*

<table>
<thead>
<tr>
<th></th>
<th>1999 # of prescriptions</th>
<th>1999 %</th>
<th>12 months up to Sept. 2000 # of prescriptions</th>
<th>2000 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regular NSAIDs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>2,460,317</td>
<td>37.2</td>
<td>2,012,015</td>
<td>37.7</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1,154,268</td>
<td>17.5</td>
<td>943,144</td>
<td>17.7</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1,118,583</td>
<td>16.9</td>
<td>1,048,262</td>
<td>19.6</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>635,256</td>
<td>9.6</td>
<td>551,485</td>
<td>10.3</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>288,417</td>
<td>4.4</td>
<td>147,807</td>
<td>2.8</td>
</tr>
<tr>
<td>Etodolac</td>
<td>197,319</td>
<td>3.0</td>
<td>97,551</td>
<td>1.8</td>
</tr>
<tr>
<td>Tiaprofenic Acid</td>
<td>178,113</td>
<td>2.7</td>
<td>130,489</td>
<td>2.4</td>
</tr>
<tr>
<td>All Others</td>
<td>580,382</td>
<td>8.8</td>
<td>411,483</td>
<td>7.7</td>
</tr>
<tr>
<td><strong>Diclofenac / Misoprostol</strong></td>
<td>1,342,231</td>
<td>--</td>
<td>1,068,871</td>
<td>--</td>
</tr>
<tr>
<td><strong>Cox2 NSAIDs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1,846,130</td>
<td>96.8</td>
<td>3,830,557</td>
<td>69.8</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>60,450</td>
<td>3.2</td>
<td>1,656,394</td>
<td>30.2</td>
</tr>
</tbody>
</table>

*Source: IMS Health, Compuscript database

The CompuScript sample is drawn from a panel of over 4,700 pharmacies, which represents approximately two-thirds of all retail pharmacies in Canada. The sample, stratified by province, store type (chain or independent), and store size (large or small), comprises over 2,000 stores and is representative of stores in Canada. Records are collected electronically each month from the pharmacies. After passing through various quality control checks the sample data are projected to each province and provincial totals are added together to provide a national estimate.

### 2.6 Time Horizon

The comparison will be modelled over five years within a Markov model framework with cycles of 3 months duration.

### 2.7 Outcome Measures

#### 2.7.1 Effectiveness and probability estimates

Key estimates of event rates and the relative effectiveness of COX2 NSAIDs in reducing these were derived from the data of the VIGOR and CLASS studies that were submitted to the Federal Drug Administration Arthritis Advisory Panel. Rates were used regardless of whether they were statistically significant or not. Remaining probability estimates were obtained through a comprehensive literature search of Medline (up to December 2000), supplemented by bibliographies of relevant articles. Estimates were only selected from studies that included patients receiving long-term NSAIDs, preferentially with a diagnosis of OA or RA. The study providing the best evidence was used to provide the baseline estimate. Confidence intervals (95%) or estimates from other studies were used to support the lower and upper plausible range for each variable for the purposes of sensitivity analysis. All rates and probabilities were converted to 3-month probabilities using appropriate conversion formulae.
**a) Probability of clinical and complicated UGI events and of myocardial infarctions**

Probabilities for rofecoxib and naproxen were based on the exact rates observed for these events in RA patients recruited into the VIGOR study (Table 2). The VIGOR study recruited 100% RA patients and excluded patients treated for CV diseases with aspirin, anti-platelet agents or anticoagulants. In this study, an event-rate of 4.5 clinical UGI events (including complicated) per 100 person-years was observed in the naproxen group. Patients randomised to rofecoxib experienced 2.1 clinical or complicated UGI events per 100 person-years. The rates of complicated UGI events in the naproxen and rofecoxib groups respectively, were 1.4 and 0.6 per 100 person-years. The relative reductions in clinical and complicated UGI events due to rofecoxib were thus calculated to be 53.7% and 56.9%, respectively.

<table>
<thead>
<tr>
<th></th>
<th>VIGOR</th>
<th>CLASS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rofecoxib</td>
<td>Naproxen</td>
</tr>
<tr>
<td><strong>Total patient years</strong></td>
<td>2697</td>
<td>2694</td>
</tr>
<tr>
<td><strong>Clinical UGI events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>56</td>
<td>121</td>
</tr>
<tr>
<td>Rate / 100 patient-years</td>
<td>2.08</td>
<td>4.49</td>
</tr>
<tr>
<td>RRR COX2 vs. regular NSAID</td>
<td>--</td>
<td>53.7%*</td>
</tr>
<tr>
<td><strong>Complicated UGI events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>16</td>
<td>37</td>
</tr>
<tr>
<td>Rate / 100 patient-years</td>
<td>0.59</td>
<td>1.37</td>
</tr>
<tr>
<td>RRR COX2 vs. regular NSAID</td>
<td>--</td>
<td>56.9%*</td>
</tr>
<tr>
<td><strong>MIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Rate / 100 patient-years</td>
<td>0.74</td>
<td>0.15</td>
</tr>
<tr>
<td>RRR COX2 vs. regular NSAID</td>
<td>--</td>
<td>4.93%*</td>
</tr>
</tbody>
</table>

RRR: relative risk reduction; RR: relative risk; UGI: upper gastrointestinal; MI: myocardial infarction
*: p<0.05

The rates for clinical UGI events observed in the CLASS study were slightly lower with 3.2, 1.2 and 1.2 clinical UGI events per 100 person-years, respectively, in the ibuprofen, celecoxib, and diclofenac groups. Rates for complicated UGI events were 1.1, 0.5 and 0.4 per 100 person-years, respectively. The relative reductions in clinical and complicated UGI events due to celecoxib and in comparison to ibuprofen were 63.8% and 61.4%, while no difference in event rates were observed between celecoxib and diclofenac (Table 2). Rates observed in CLASS may have been lower than in VIGOR as a result of differences in patient populations. CLASS recruited a patient population that consisted of a mix of OA (72%) and RA (28%) patients with ~ 40% having a positive history of CV diseases and ~22% taking aspirin, while VIGOR preferably recruited RA patients on corticosteroids (56%).

**b) Probability of dyspepsia requiring medical consultation**

The probability of dyspepsia requiring medical consultation was available from only one study (Table 3). Jones and colleagues studied patients, who received NSAID prescriptions for at least nine of the preceding 12 months, from the registries of eight rural practices in the UK. Using a
validated questionnaire the authors asked patients about the occurrence of dyspeptic symptoms in the preceding year and whether or not they prompted medical consultations. Questionnaires were returned by 89% of the patients; 185 of 472 (39.2%) patients from a subset of practices said they had consulted a physician about their symptoms. When converted into a 3-month probability, this translated into a probability of 10.7% (95% CI: 7.7% - 13.7%) for dyspepsia-related consultations.

Table 3: Clinical estimates used in the decision analysis model

<table>
<thead>
<tr>
<th>Model Events</th>
<th>Base Case Values (Range)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia requiring consultation (per 3 months)</td>
<td>10.7 (7.7 – 13.8)</td>
<td>21</td>
</tr>
<tr>
<td>RRR: clinical/complicated UGI due to PPIs</td>
<td>40.0 (37.5 – 42.5)</td>
<td>5</td>
</tr>
<tr>
<td>RRR: antacid use due to COX2</td>
<td>22.8 (19.3 – 26.1)</td>
<td>14</td>
</tr>
<tr>
<td>Hospitalised if complicated UGI event</td>
<td>62.7 (51.1 - 74.3)</td>
<td>5,14</td>
</tr>
<tr>
<td>Surgery if hospitalised</td>
<td>8.5 (4.0 – 35.7)</td>
<td>22,24</td>
</tr>
<tr>
<td>Mortality in pat. with 1st GI bleed</td>
<td>4.3 (1.9 - 5.13)</td>
<td>25,26</td>
</tr>
<tr>
<td>Recurrence of bleed</td>
<td>11.5 (10.1 - 12.8)</td>
<td>25,26</td>
</tr>
<tr>
<td>Surgery in pat. with 2nd GI bleed</td>
<td>71.1 (62.1 - 80.2)</td>
<td>27</td>
</tr>
<tr>
<td>Mortality in pat. with 2nd GI bleed</td>
<td>38.7 (12.4 - 44.8)</td>
<td>25,27</td>
</tr>
<tr>
<td>% retrying NSAIDs after GI bleed</td>
<td>5.0 (0.0 – 100.0)</td>
<td>--</td>
</tr>
<tr>
<td>RR increase due to prior UGI event</td>
<td>2.6 (2.0 – 5.9)</td>
<td>14</td>
</tr>
<tr>
<td>Mortality after experiencing nonfatal MI (%)</td>
<td>3.5</td>
<td>28</td>
</tr>
<tr>
<td>Utility of experiencing an MI</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Utility for coronary artery disease</td>
<td>0.97 (0.875 – 1.0)</td>
<td>29</td>
</tr>
</tbody>
</table>

PPI: proton pump inhibitor, GI: gastrointestinal, RRR: relative risk reduction

**c) Prescription of antacids for patients with dyspeptic symptoms**

There are very few data in the literature that provide information on the use of antacids among NSAID-users. In one Canadian study of NSAID-users over age 65, insured under the Quebec Health Insurance Plan, 22.7% of patients used gastroprotective agents, including antacids, during a 2-year period.\(^{30}\) No information is provided on the duration of each prescription. If each patient only received a one-time prescription of less than 3 months duration, the percentage of NSAID-users receiving antacids or GPAs during a 3-month period would be approximately 3.2% (95% CI: 2.6 – 3.7). However, if each patient received a second prescription of GPAs during the 2-year period, the average 3-month probability of GPA use would be 6.2% (95% CI: 5.4 – 7.0).

Utilization of antacids only, excluding misoprostol or PPIs, was permitted and recorded in the VIGOR study. In this study, 11.2% (453 out of 4047, 16.85 per 100 person-years) of the patients randomized to rofecoxib used antacids vs. 14.5% (584 out of 4029, 21.78 per 100 person-years) in the naproxen group. The relative risk reduction of 22.8% was statistically significant (p < 0.001). For the purpose of converting the observed percentages into rates and then 3-month probabilities, it was assumed that no patients received repeat prescriptions or that intake of antacids lasted less than 3 months. This translated into a 3-month probability of 5.3% (95% CI: 4.59 – 6.01). This probability is slightly higher than the one found in the Quebec study, when
assuming one-time prescription, or slightly lower, when assuming repeat prescriptions. We chose to use the VIGOR data, as they were prospectively recorded and fell between the upper and lower estimates from the Quebec study (Table 3).

d) Effectiveness of proton pump inhibitors
There is no GI outcomes study evaluating the effectiveness of PPIs. However, misoprostol has been shown to reduce UGI events by 40.0% (95% CI: 37.5 – 42.5).5 The effectiveness of PPIs was modelled based on the evidence available for misoprostol, and may in fact underestimate the actual benefit of PPIs, because omeprazole has been demonstrated to be associated with better healing of NSAID-induced endoscopic ulcers than misoprostol31 (Table 3).

e) Risk factors for increased UGI events
Many risk factors are reported to play a role in increasing the risk of UGI events. Among the more prominent ones are history of a clinical or complicated UGI event, age, use of oral corticosteroids or anticoagulants, and cardiovascular and general co-morbidity.3,6,32,33 Very few prospective studies are available that examine the relationships between these risk factors and the size of their independent contribution to an increased risk of UGI events. Those that do, either find that some of the independent factors cancel each other out6 or that a large relative risk, found in univariable comparison, is reduced to a small independent risk, when estimated in multivariable comparisons.33

History of a clinical UGI event is the most prominent risk factor and has been estimated to increase risk of future UGI events by up to 5.9 times.6 However, in CLASS this relative risk was only 2.6, after adjusting for history of NSAID intolerance, global disease status, history of cardiovascular disease and aspirin use.18 Given the prospective nature of the CLASS study, we used the estimate from the CLASS study as our baseline estimate and included the other estimate in a confidence interval for the sensitivity analysis (Table 3).

Age is the next most important risk factor for UGI events, but the risks for specific age brackets were not analysed in either VIGOR or CLASS. Moreover, both study populations were limited to elderly patients. In a recent meta-analysis, the risk associated with specific age groups, compared to the reference group of 25-49 year olds, was summarized to be: 1.8 (age 50-59), 2.4 (60-69), 4.5 (70-79) and 9.2 (80+).6 A regression line was fitted to the log-transformed risks in order to determine a risk function based on age: [risk = exp(-2.18 + 0.05*age)]. According to this function, risk increased by approximately 5% per year. This estimate was slightly higher than the one found by Singh and associates who estimated the risk to increase by 4% for each year of age. We evaluated the effect of age in secondary analyses.

f) Hospitalization and surgery
The percentage of patients with a complicated UGI event who require in-hospital management is known from only one source, a randomised controlled trial comparing misoprostol to placebo in > 8,000 patients with RA for a period of 6 months.5 In this study the proportion of patients with a complicated UGI event that were managed in hospital was not significantly different between patients on misoprostol or placebo. The proportion of hospitalised patients among those with a complicated UGI event within the entire patient population was 62.7% (95% CI: 51.1% - 74.3%) (Table 3).
The proportion of patients with a serious GI event who undergo surgery was estimated from studies that examine cohorts of patients who are hospitalised with a GI bleed. Estimates from these studies vary between 3.3% and 35.7%. The baseline estimate was taken from a prospective study of patients admitted for upper GI bleed in Atlanta. This study was chosen because the investigators provided results for 218 patients on NSAIDs who had a proven ulcer as cause of the upper GI bleed. The observed proportion of patients undergoing surgery was 8.5% (95% CI: 4.8% - 12.2%). The lower range for this estimate was provided by a study of 1026 patients in the USA, Sweden and Hungary who were hospitalised for a first episode of major upper GI bleeding caused by gastric or duodenal ulcer. In this study, 7 of 177 patients who took NSAIDS underwent surgery (3.95%; 95% CI: 1.1% - 6.8%). The upper range for this estimate is taken from the MUCOSA study, where 14 of the 42 (35.7%) hospitalised patients underwent surgery (95% CI: 21.2% - 50.2%) (Table 3).

g) Mortality in first-bleeders, probability of recurrence, surgery and mortality in re-bleeders
Similar to surgery estimates, several case-series provide estimates of the mortality among patients with a serious GI bleed admitted to hospital. However, it was important to find studies that separate first-bleeders from re-bleeders. Detailed information on the desired estimates was provided by three studies. The study by Katschinski and associates was used as a reference for the baseline probabilities of mortality in first-bleeders, recurrence and mortality in re-bleeders, because the study provided estimates for all three events. The authors studied a large population of 2217 patients who were admitted for haematemesis and melena (any pathology) to the Nottingham University and City Hospital between 01/1980 and 04/1986. In this population, 4.3% (95% CI: 3.4% - 5.1%) died from a first bleed, 11.5% rebled (95%CI: 10.1 – 12.8) and 38.7% died from a second bleed (95% CI: 32.6 – 44.8). Data were taken from all patients because mortality data were not different between NSAID users and non-users.

Estimates for the lower and upper ranges were provided by the two other studies. Branicki and associates studied 701 Hong Kong patients admitted with a bleed related to a peptic ulcer, and Zimmerman and associates reported on 321 Israeli patients who were admitted to hospital with major upper GI bleed (including varices). The only value available for the proportion of re-bleeders undergoing surgery was provided by Branicki and associates who followed 701 Hong Kong patients with peptic ulcer bleeds. In this population there were 14.3% of patient who rebled (95% CI: 11.7 – 16.9) and of those 71.1% (95% CI: 62.1 – 80.1) underwent surgery (Table 3).

h) Mortality in the general population and following a nonfatal MI
Annual mortality rates for women and men, starting at age 50, were used to model the percentage of patients dying from natural causes as a function of age. An excess mortality among patients who had experienced an MI (3.5 deaths per 100 person-years) was determined from the 10-year survival of patients from the Framingham Heart Study who had experienced a Q-wave MI.

i) Utility of MI event and subsequent coronary heart disease
For those patients surviving an MI event, the utility is assumed to be 0 for the three-month period immediately following the event. In the period following this initial three months, chronic coronary heart diseases resulting from a MI event had a utility of 0.97, based on the median utility results for patients with moderate chronic stable angina (Class II using the Canadian Cardiovascular Society classification system), as shown in a study by Nease using the standard-
gamble approach (Table 3.3). In sensitivity analysis, this utility was varied from 0.875 (median value for Class III / IV severe chronic stable angina) to 1.00.

2.7.2 Utility Estimates

a) Introduction

In accordance with health policy recommendations, the present analysis used utilities to value model health states from the perspective of the general public. A survey was undertaken to elicit rating scale and standard gamble utilities for both long-term and short-term health states represented in the model.

b) Methods

Study Design

This study was a cross-sectional survey of randomly selected members of the city of Sudbury, Ontario, a small city with inhabitants of mainly English and French origin. We utilized two approaches to utility assessment.

For the baseline analysis, we utilized the conventional QALY method. Utilities were elicited for both short-term and long-term outcomes using standard-gamble and rating scale methods. Utilities for both short-term and long-term outcomes, expressed on a 0-1 scale, were used to weight time spent in each health state in order to estimate quality-adjusted life expectancy.

We also employed an alternate method, the Health Path approach, to estimate utilities for the purpose of sensitivity analysis. Some investigators have pointed out that the conventional QALY method may underestimate the severity of short-term events. For example, consider sitting in a dentist’s chair for 6 hours. The maximum penalty allowable under the QALY model is 6 hours, or a utility of zero for time spent in that health state. However, this is arguably not consonant with true preferences. Many individuals would trade more than 6 hours of their life to avoid experiencing pain in the dentist’s chair. This same general insight led Gafni and colleagues to develop the concept of Healthy Year Equivalents, an alternative to the QALY. While we, in general, believe that the QALY model is perfectly adequate for most purposes, this particular decision problem is one in which its potential shortcomings may qualitatively change the results of the analysis. In the present analysis, the central valuation problem is how to properly estimate the value associated with gastrointestinal bleeding. In our exploratory study of utilities, we consider an alternate method of valuing short-term outcomes.

In general, decision models describing health outcomes disaggregate a decision problem into a set of health paths (the sequence of events described within the time horizon of the model) and a set of health outcomes. A value (utility, quality-adjusted life years, life expectancy etc.) is obtained for each health outcome. The expected value for each modeled strategy is calculated by weighting each health outcome by its path probability and summing across all possible paths. The implicit assumption of this method is that the value for a health outcome is independent of its path. Some investigators, notably those incorporating the Healthy Years Equivalent (HYE) approach, have circumvented this assumption by separately estimating the value for each possible health path. As the current CCOHTA guidelines state, “Measuring preferences over a path of health states has merit, and indeed is theoretically superior to the traditional QALY approach”. However, this approach has not been considered to be feasible when there are many
health paths, as in a complex decision tree or a tree that incorporates Markov processes. The approach, which is described below, is a modification of the Health Path approach used in HYE calculation, applied to a Markov model using quality-adjusted life years.

This method involves the following steps:

i) Consider a selected subset of paths, not all paths represented in the model.

ii) Consider paths that both **include** and **exclude** key short-term health outcomes (those involving gastrointestinal bleeding).

iii) Estimate global utility values (0-1 scale) for those paths.

iv) Calculate expected QALYs for each health path by multiplying global utility by life expectancy.

v) Estimate the QALYs associated with short-term outcomes by calculating the difference between QALYs for health paths that do and those, which do not incorporate short-term outcomes.

vi) Use these QALY estimates to value short-term outcomes in the Markov model.

Note that this approach makes no assumption about the limits associated with short-term QALY estimates, and indeed allows these QALYs to be negative. Note also that this approach is theoretically superior, because it does not separate the valuation of short- and long-term health states, but provides a realistic estimate of short-term health states within the context of the full health path experienced by patients. However, this approach must be considered exploratory as it has not been validated, and does not incorporate health path estimation for all health outcomes represented in the model.

**Subject Selection**
The selection of subjects was based upon a random sample of listed residential telephone numbers purchased from Infodirect, a service of Bell Canada. Infodirect provided an updated sample of telephone numbers drawn from the telephone area-code-prefix combinations used in the study area. The sampling frame was approximately equivalent to the published telephone directory at the date of the latter’s publication, last update on April 4, 2000. Households were selected in random order from the list provided by Infodirect. Because the number of households without a telephone, or with an unlisted number, is relatively small (<20%), the sample was thought to be fairly representative of all households in the selected areas.

Households on the list were telephoned at scheduled times (morning, afternoon, evening) until 60 households were contacted that agreed to participate. At least five attempts were made to reach individuals in non-responding households. A single message was left in households with an answering service. During the initial contact, the purpose of the study was explained, and potential participants enumerated. Subjects were reimbursed $25 dollars to compensate for their time.

**Subject Recruitment**
During the initial telephone contact with the research assistant, the subject was introduced to the purpose of the study, and, if willing to participate, a meeting time was arranged in the subject’s home to conduct the interview. A written consent was obtained at the time of the interview. The
subject was administered a questionnaire inquiring about demographic information before proceeding with the utility questionnaires. All subjects aged 18 years and over, who were fluent in English, and had no known cognitive impairment were included in the study.

Procedures- Conventional QALY Approach
All interviews followed a standardized script. Subjects were introduced to rating scale and standard gamble assessments with specific training tasks, using feeling thermometer and standard gamble props. First, subjects were asked to rank and then rate, with a 3-month perspective, the following health states in comparison to “perfect health” (best=100) and the worst short-term health state “complicated UGI event requiring surgical management” (worst = 0): 1) Dyspepsia; 2) Symptomatic – Endoscopy but no Ulcer; 3) Symptomatic Ulcer; 4) Complicated UGI event – medical management (Figure 4).

We assumed the worst short-term health state had a utility of zero because of the difficulty in using death as an anchor for short-term health states. Subjects have difficulty imagining or believing that death is truly a short-term health state. Short descriptions of approximately 250 words described what it is like to live with arthritis (Figure 2), and to experience a bleeding ulcer with or without surgery (Figure 3).

Figure 2: Detailed scenario describing how it is to live with arthritis

Living With Arthritis

There are many forms of arthritis, but osteoarthritis and rheumatoid arthritis are the most common forms of arthritis. Common joints affected are those of the hands and feet, but larger joints can be affected as well.

Many forms of arthritis are chronic, meaning they can last a lifetime. Arthritis affects your body and the way you feel. The pain and limited movement can make ordinary tasks difficult. Simply getting out of bed, dressing, bathing, walking, or opening doors can become major chores. The daily pain can lead to stress and fatigue. This pain, stress, and fatigue can lead to anger and depression. This may put strains on relationships between people with arthritis and their families or friends.

Pain is present, at least some of the time, for all forms of arthritis. It can be severe and lifelong. People with arthritis need to recognize pain as a warning signal and take appropriate steps to manage it. Pain requires treatment, and the treatment frequently depends on the type of arthritis. Treatment may include medication, rest, an exercise program taught by a therapist, tips on how to protect your joints and the application of heat or cold.
Figure 3: Detailed scenario describing how it is to suffer from a bleeding ulcer that requires surgery

<table>
<thead>
<tr>
<th>Bleeding Ulcer - Hospitalization - Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>One evening, you are awakened from sleep by severe nausea and pain in your upper abdomen. You vomit material that looks bloody. You feel weak and dizzy. An ambulance is called and you are taken to the emergency room. The emergency room doctors recommend a procedure called endoscopy to determine the presence of an ulcer. You are taken to a special room, which looks like an operating room, for this procedure. You must lie on your back for 20 minutes. An intravenous line is placed in your arm. You are given some medication which makes you drowsy but you remain awake. A spray is sprayed on the back of your mouth and throat which makes them numb. You must swallow a long black tube which is about a half inch wide. It is very uncomfortable but you feel no sharp pain. The procedure is over in 20 minutes. Afterwards you are drowsy and have a sore throat. You are told that you have a bleeding stomach ulcer which has created a hole in your stomach. You must have surgery to repair this hole. You are taken to the operating room for surgery. When you wake up you are in the Intensive Care Unit (ICU). You have severe pain in your abdomen and require injections of morphine every four hours to control the pain. You have a tube going from your nose into your stomach. You have an intravenous line in each arm. You cannot eat or drink. You have a mask on your mouth and nose for oxygen. You must stay in bed. You remain in this state for 4 days. On the fifth day, the tube in your nose is removed, and you are allowed to drink water and other clear fluids. You feel stronger and have less pain each day. You are moved from the ICU to a regular patient room. This is more comfortable and much quieter. In the following days you are allowed to eat regular food, have one of your intravenous lines removed and begin walking around the hospital ward. On the tenth day you are dismissed from the hospital, feeling weak and tired.</td>
</tr>
</tbody>
</table>

All health states were then presented in itemized form. For example, a bleeding ulcer requiring hospitalization and surgery was presented as follows:

- Sudden weakness and bloody vomiting → Emergency Room
- Endoscopy shows stomach ulcer
- Emergency Surgery → in hospital 10 days
- Begin ulcer medication
- Stop arthritis medication → arthritis worse.
- Flushing and occasional diarrhea after large meals because of surgery

In the standard gamble interview, subjects were asked to make a choice between one of the short-term health states as a certain outcome for the next 3 months, or a gamble with the worst health state (“complicated UGI event requiring surgery”) and the best health state (“arthritis alone”) as outcomes. The chances associated with these outcomes were varied systematically with a 0% chance of “arthritis alone” and 100% chance of “complicated UGI event requiring surgery” as being the least attractive scenario, and 100% chance of “arthritis alone” and 0% “complicated UGI event requiring surgery” the most attractive. The chance of the best health state that made subjects indifferent as to whether they preferred the certain health state (i.e. one of the four listed above) or the gamble was then recorded as the SG utility for the subjects certain health state.
The sole long-term outcome represented in the model (“arthritis”) was also rated using rating scale and standard gamble scaling methods. Again, the latter incorporated a choice between a certain outcome (“moderate arthritis” for the rest of their life) and a gamble (“immediate death” or “perfect health”) (Figure 4).

**Procedures- Health Path Approach**
An additional gamble was performed, as described in Figure 4. This gamble involved evaluation of a long-term outcome (“arthritis”) during which the worst short-term outcome (“Complicated UGI event requiring surgical management”) was also experienced.

**Analysis- Conventional QALY Method**
Descriptive statistics were tabulated for all rating scale and standard gamble utilities. Final utilities for short-term health states were calculated by rescaling the short-term utilities from their original scale (“arthritis” to worst short-term health state) to the final scale (“full health” to “immediate death”). Thus, final short-term utilities for states represented in the model ranged from 0 (“Complicated UGI event requiring surgical management”) to 0.668 (“arthritis” only, SG method).

As is customary in cost-effectiveness analyses, the time each patient spent in one of the model health states was multiplied by the utility for the respective health state. For example, a year of life spent in a health state with a utility of 0.5 would only be worth 0.5 years QALYs. A three-month period spend in the worst short-term health state (utility=0) would be worth 0 QALYs.

**Analysis-Health Path Method**
The utility value for the health path consisting of the worst short-term health state (“Complicated UGI event requiring surgical management”) followed by arthritis was also elicited using the standard gamble and rating scale methods (Figure 5). Utilities for health paths consisting of other
short-term outcomes were calculated by transforming the short-term utility scale on to the long-term scale for health paths, as shown in (Figure 5).

**Figure 5:** Inference of lifetime utilities for short-term health state followed by arthritis from short-term health state rating scale and standard gamble utilities

For example, the utility of the health path “dyspepsia followed by arthritis”, \( u(L[S1]) \), would be calculated as follows:

\[
\begin{align*}
u(L[S1]) &= u(L2) + u(S1) \times [u(L1) - u(L2)] \\
\text{Example: } u(L[\text{dyspepsia}]) &= 0.648 + 0.734 \times (0.688 - 0.648) = 0.677
\end{align*}
\]

QALYs for health paths \( L[S1] \ldots L[S4] \) were calculated by multiplying path utilities by life expectancy. Finally, QALY values for short term outcomes were estimated by calculating the difference between QALY values for the health path without a short-term adverse event and those with a short-term adverse event (e.g. \( u(L1)\times \text{LE} - u(L[S1])\times \text{LE} \)). In order to represent this QALY estimate in the model, the utility for a 3 month period (the cycle length of the model) that generated a 3 month QALY estimate equivalent to the QALY difference for each health path (e.g. \( u(L1)\times \text{LE} - u(L[S1])\times \text{LE} \)) was calculated and used to weight time spent in the short-term health state.

**Sample Size Calculations**

Experts generally recommend a sample size between 30 and 60 subjects for standard gamble utilities. We aimed at recruiting about 60 subjects in order to filter some of the noise that usually can accompany the measurement of standard gamble utilities.
c) Results
Sixty subjects participated, with a mean age of 51.3 years (SD: 15.9). The youngest participant was 19 and the oldest 85 years old. The majority of study participants were female (n=46 [76.7%]) and 27 (45.0%) said they were diagnosed by a health professional to have arthritis. Of those 27, there were 3 (11.1%) who described their arthritis pain in the past month as severe, 12 (44.4%) as moderate, 7 (25.9%) as mild, 4 (14.8%) as very mild and 1 (3.7%) as none.

Educational attainment varied, with 3 (5.0%) participants having achieved grade 8 or less, 6 (10.0%) higher than grade 8 but no graduation from high school, 11 (18.3%) high school, 25 (41.7%) 1-4 years of college or university, 10 (16.7%) graduation from university, and 5 (8.3%) professional or graduate school. A third of the participants were employed full time (n=20 [33.3%]) and another third were retired (n=19 [31.7%]). The remaining subjects were homemakers (n=5 [8.3%]), employed part-time (n=7 [11.7%]), unemployed (n=2 [3.3%]), students (n=3 [5.0%]) or on disability leave (4 [6.7%]). Finally, household income varied broadly, with 11 (18.3%) reporting an annual household income of over $80,000, 10 (16.7%) an annual income between $60,000 and $80,000, 6 (10.0%) between $40,000 and $60,000, 9 (15.0%) between $20,000 and $40,000, 4 (6.7%) between $12,000 and $20,000, and 3 (5.0%) between $6,000 and $12,000. Seventeen subjects (28.3%) refused to indicate their annual household income.

The 3-month rating scale and SG utility values for gastrointestinal health states were fairly evenly distributed between 1 (perfect health) and 0 (bleeding ulcer requiring surgery) (Table 4).

<table>
<thead>
<tr>
<th>SG Utilities</th>
<th>SG Utilities 3 Month*</th>
<th>SG Utilities Life*</th>
<th>Standard QALYs Estimate (95% CI)</th>
<th>Health Path QALYs Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfect Health</td>
<td>n/a</td>
<td>1</td>
<td>0.25</td>
<td>.250</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1</td>
<td>0.688 (0.207)</td>
<td>0.172</td>
<td>0.172</td>
</tr>
<tr>
<td>Arthritis &amp; dyspepsia</td>
<td>0.734 (0.204)</td>
<td>0.677</td>
<td>0.126</td>
<td>0.006</td>
</tr>
<tr>
<td>Arthritis &amp; unconfirmed ulcer</td>
<td>0.669 (0.214)</td>
<td>0.675</td>
<td>0.115</td>
<td>-0.034</td>
</tr>
<tr>
<td>Arthritis &amp; confirmed ulcer</td>
<td>0.555 (0.208)</td>
<td>0.670</td>
<td>0.095</td>
<td>-0.105</td>
</tr>
<tr>
<td>Arthritis &amp; complicated UGL, medical</td>
<td>0.454 (0.260)</td>
<td>0.666</td>
<td>0.078</td>
<td>-0.168</td>
</tr>
<tr>
<td>Arthritis &amp; complicated UGL, surgical</td>
<td>0</td>
<td>0.648 (0.251)</td>
<td>0</td>
<td>-0.455</td>
</tr>
<tr>
<td>Immediate Death</td>
<td>n/a</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*: values are means (standard deviation); **: values in italics are indirectly calculated

As expected, SG utilities were higher than rating scale values. Utility values for arthritis were lower than those reported in the Beaver Dam study43 (0.815 for arthritis). On average, subjects were willing to risk a gamble with a 31.2% chance of death in order to avoid living with arthritis for the rest of their lives (Table 4). QALY estimates using the standard QALY approach and the
Health Path method for each 3-month period are shown as well. The Health Path approach results in a much greater weight being associated with short-term adverse effects of treatment.

2.8 Cost Measurement and Valuation

All costs were determined, where possible, from the Ontario Ministry of Health perspective and according to the recommendations set out in the National List of Provincial Costs for Health Care: Canada 1997/8.44

2.8.1 Costs of managing clinical events

Gastrointestinal events requiring in hospital management were first classified into codes according to the International Classification – Version IX – with Clinical Modification (ICD-9-CM). Costs for these codes were requested from the Ontario Case Costing Project (OCCP) database, which provides cost estimates generated from 5 major Ontario hospitals.45 Hospitals participating in the OCCP agreed to use a Case Mix Group (CMG) coding algorithm based on ICD-9-CM codes with adjustment for co-morbidity developed by the Canadian Institute of Health Information,46 and to allocate costs through simultaneous allocation equations. Hospitals are audited on a regular basis. The costs of managing clinical events in the decision analysis model are shown in Table 5.

The most recent useable data were those for the fiscal year 1994/1995, which were updated according to the increase in the healthcare portion of the Canadian Consumer Price Index, which was estimated to be 7.8% from 1994 to 1999.

Costs of hospitalisation were also estimated using resource intensity weights (RIW) published by the Canadian Institute for Health Information for CMGs, by 3 age groups (0 –17, 18 – 69, 70+) and for four complexity levels. RIW values were provided by the Ontario Joint Policy and Planning Committee.47

The average RIW for each CMG was weighted by the number of cases in this CMG in Ontario.47 CMG 255 (less extensive oesophageal, stomach and duodenal procedures) was used for “Complicated UGI event – surgical management”, the resulting RIW being 2.65 for patients aged 18 and over and all complexity levels. CMG 281 (G.I. Hemorrhage) and CMG 285 (Complicated Ulcer) were combined for “Complicated UGI event – medical management” giving an RIW of 1.06. RIWs were multiplied with the published cost per weighted case (CPWC) for Ontario, which was $2,755 for 1997/844 and which we updated to $2,817 using the 2.27% increase in the health care portion of the CPI from 1998 to 1999. We also calculated the CPWC from original data for over 100 large Ontario hospitals, which we found to be $2,838.
Table 5: Costs of management for clinical events in decision analysis model

<table>
<thead>
<tr>
<th>Item</th>
<th>Source / Code*</th>
<th>$/Unit</th>
<th>Frequency</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated UGI event – surgical management</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization (CMG)</td>
<td>n.a.</td>
<td>$7,470.11</td>
<td>1</td>
<td>$7,470.11</td>
</tr>
<tr>
<td>Emergency Officer</td>
<td>C003</td>
<td>$48.90</td>
<td>1</td>
<td>$48.90</td>
</tr>
<tr>
<td>Gastroenterologist</td>
<td>A135</td>
<td>$106.95</td>
<td>1</td>
<td>$106.95</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Z400</td>
<td>$116.75</td>
<td>1</td>
<td>$116.75</td>
</tr>
<tr>
<td>Coagulation</td>
<td>E701</td>
<td>$30.65</td>
<td>1</td>
<td>$30.65</td>
</tr>
<tr>
<td>Biopsy</td>
<td>E702</td>
<td>$14.10</td>
<td>1</td>
<td>$14.10</td>
</tr>
<tr>
<td>In-hospital visit /day</td>
<td>C132</td>
<td>$17.35</td>
<td>3</td>
<td>$52.05</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>$7,839.51</td>
</tr>
<tr>
<td>Complicated UGI event – medical management</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization (CMG)</td>
<td>n.a.</td>
<td>$2,987.81</td>
<td>1</td>
<td>$2,987.81</td>
</tr>
<tr>
<td>Emergency Officer</td>
<td>C003</td>
<td>$48.90</td>
<td>1</td>
<td>$48.90</td>
</tr>
<tr>
<td>Gastroenterologist</td>
<td>A135</td>
<td>$106.95</td>
<td>1</td>
<td>$106.95</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Z400</td>
<td>$116.75</td>
<td>1</td>
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</tr>
<tr>
<td>Biopsy</td>
<td>E702</td>
<td>$14.10</td>
<td>1</td>
<td>$14.10</td>
</tr>
<tr>
<td>In-hospital visit /day</td>
<td>C132</td>
<td>$17.35</td>
<td>3</td>
<td>$52.05</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>$3,326.56</td>
</tr>
<tr>
<td>Complicated UGI event – outpatient management</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulatory Care Costs</td>
<td>Alberta Health</td>
<td>$233.00</td>
<td>1</td>
<td>$233.00</td>
</tr>
<tr>
<td>Gastroenterologist</td>
<td>A135</td>
<td>$106.95</td>
<td>1</td>
<td>$106.95</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Z400</td>
<td>$116.75</td>
<td>1</td>
<td>$116.75</td>
</tr>
<tr>
<td>Coagulation</td>
<td>E701</td>
<td>$30.65</td>
<td>1</td>
<td>$30.65</td>
</tr>
<tr>
<td>Biopsy</td>
<td>E702</td>
<td>$14.10</td>
<td>1</td>
<td>$14.10</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>$501.45</td>
</tr>
<tr>
<td>Symptomatic Ulcer – outpatient management</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulatory Care Costs</td>
<td>Alberta Health</td>
<td>$233.00</td>
<td>1</td>
<td>$233.00</td>
</tr>
<tr>
<td>Gastroenterologist</td>
<td>A135</td>
<td>$106.95</td>
<td>1</td>
<td>$106.95</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Z400</td>
<td>$116.75</td>
<td>1</td>
<td>$116.75</td>
</tr>
<tr>
<td>Biopsy</td>
<td>E702</td>
<td>$14.10</td>
<td>1</td>
<td>$14.10</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>$470.80</td>
</tr>
<tr>
<td>Consultation for dyspepsia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family Physician</td>
<td>A007</td>
<td>$26.00</td>
<td>1</td>
<td>$26.00</td>
</tr>
<tr>
<td>Hematology tests</td>
<td>L418/417/399/3-7</td>
<td>$5.69</td>
<td>1</td>
<td>$5.69</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>$31.69</td>
</tr>
<tr>
<td>Costs of managing MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Managing patients with prior MI (per 3 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Physician Services Codes for the Ontario Schedule of Benefits

Ambulatory care costs were derived from the 1999 Annual Report of Ambulatory Care Costing Results for the province of Alberta. Average costs for general gastrointestinal diagnostic investigation for the age group > 45 years were used. All physician costs billed to the Ministry of Health were determined separately by looking up the billing records of a hospital-based gastroenterologist for the respective diagnoses. Codes for all billing items were recorded and costs for these items, excluding the technical component, were derived from the 1999 Ontario Schedule of Benefits. The cost of $31.69 was used to for the cost of a consultation for dyspepsia, including the costs of a family physician consultation and the costs of laboratory tests. The costs for acute CAD were derived from published cost estimates measured in 1,259 Canadian patients enrolled in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) trial. The average annual costs for patients with chronic
CAD were determined through physicians’ focus group assessments of three typical scenarios of patients with chronic CAD.50

2.8.2 Costs of drugs
Celecoxib (Celebrex®) and rofecoxib (Vioxx®) are the two COX2 selective NSAIDs that have been approved for the Canadian market. The daily costs of treatment with these agents are identical at the low doses that are intended for the treatment of OA, i.e. $1.25 per day (excluding mark-up and prescription fee), however, Celebrex® costs $2.50 per day at the doses required for RA patients, while the price of Vioxx® is $1.25 per day. Because rofecoxib is not currently approved by Health Canada for the treatment of RA, the cost/day of rofecoxib in RA was assumed to reflect double the dose used in OA patients and has not been derived from a regulatory-approved dosage regimen.

Table 6: Costs of drugs as permitted under the Ontario Drug Benefit Plan, excluding 10% pharmacy price mark-up and prescription fee51

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dosage</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>800mg tid</td>
<td>$0.22</td>
</tr>
<tr>
<td>Naproxen</td>
<td>500mg bid</td>
<td>$0.42</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>75 mg bid</td>
<td>$1.14</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>100 / 200 / 400mg bid</td>
<td>$1.25 / $2.50 / $5.00</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>12.5 / 25 / 50 mg qd</td>
<td>$1.25 / $1.25 / $2.50</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>1000mg qid</td>
<td>$0.37</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>400mg bid</td>
<td>$0.27</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40mg qd</td>
<td>$1.90</td>
</tr>
</tbody>
</table>

All drug costs were multiplied by a factor of 1.1 to account for the 10% mark-up in the price allowed under the Ontario Drug Benefit Plan.51 As well, a prescription fee of $6.47 was added to each individual prescription per 3-month period.

2.9 Sensitivity Analysis
One-way sensitivity analyses were performed for the comparison of rofecoxib and naproxen in patients at average risk. Each individual probability estimate was varied over its range, to explore the sensitivity of the cost-effectiveness and cost-utility ratios. One-way sensitivity analyses were also carried out for the comparison in high-risk patients on the price of PPIs and the relative risk for UGI events associated with a history of clinical UGI events. Cost-effectiveness and cost-utility ratios were also calculated for the prices corresponding to the dosages of COX2 NSAIDs that were used in the clinical trials. The effect of age and a potential additional risk factor was explored for the average risk comparisons of rofecoxib and naproxen, and that of celecoxib and ibuprofen. Finally, the potential impact of allowing QALYs to become negative, was evaluated in a sensitivity analysis for the comparison of rofecoxib and naproxen.
3 RESULTS

3.1 Trial-based Comparisons: Average Risk Patients

For patients at average risk, rofecoxib increased costs relative to naproxen ($3,173 vs $1,576), but also decreased clinical GI events by 13% and complicated GI events by 4.3% in absolute terms. The marginal cost for each QALY gained was high, at $271,188 (Table 7, following page).

Use of the CLASS data generated similar results. Celecoxib increased costs relative to diclofenac and ibuprofen ($3,371 vs $2,503 vs $1,141), but reduced the absolute risk of GI events. However, in the CLASS study, celecoxib reduced GI events by a very modest amount in comparison with diclofenac. In addition, cardiovascular events were in fact slightly more common in the celecoxib group, albeit not statistically significantly. Thus, neither of the more effective strategies (celecoxib and diclofenac) appear to be economically attractive in comparison with the least costly strategy (ibuprofen). The incremental cost effectiveness ratio for diclofenac in comparison with ibuprofen is unattractive (> $100,000/QALY), and celecoxib is even less attractive (dominated by) than diclofenac, because of its similar efficacy and worse cardiovascular profile.

3.1.1 High risk strategies

In patients with a history of a clinical UGI event, rofecoxib alone is both less costly and more effective than naproxen, co-prescribed with a PPI (Table 7). Adding a PPI to rofecoxib is not an economically attractive strategy in comparison with rofecoxib alone, in view of the high cost-utility ratios of $281,244 per QALY gained (Table 7). Similarly, celecoxib alone is less costly and more effective in comparison to ibuprofen. Celecoxib alone is the most economically attractive strategy, as the strategies which are marginally more effective (celecoxib + PPI, diclofenac + PPI) are not economically attractive.
Table 7: Baseline cost-effectiveness and cost-utility ratios ($CAD) for the 5-year comparison of 1) rofecoxib to naproxen in patients with rheumatoid arthritis and 2) celecoxib to diclofenac and ibuprofen in patients with osteoarthritis (72%) or rheumatoid arthritis (28%)

<table>
<thead>
<tr>
<th>Costs*</th>
<th>Clinical UGI events</th>
<th>Complicated UGI events</th>
<th>QALYs*</th>
<th>Life-years*</th>
<th>Cost/clinical UGI event</th>
<th>Cost/complicated UGI event</th>
<th>Cost/QALY gained</th>
<th>Cost/life-year gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average-risk patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VIGOR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen (500mg bid)</td>
<td>$1,576</td>
<td>25.10%</td>
<td>7.70%</td>
<td>2.894</td>
<td>4.358</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Rofecoxib (25mg qd)</td>
<td>$3,173</td>
<td>12.10%</td>
<td>3.39%</td>
<td>2.900</td>
<td>4.361</td>
<td>$12,287</td>
<td>$37,060</td>
<td>$271,188</td>
</tr>
<tr>
<td><strong>CLASS</strong></td>
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<td></td>
</tr>
<tr>
<td>Ibuprofen (800mg tid)</td>
<td>$1,141</td>
<td>17.80%</td>
<td>6.36%</td>
<td>2.899</td>
<td>4.360</td>
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<tr>
<td>Diclofenac (75mg bid)</td>
<td>$2,503</td>
<td>6.64%</td>
<td>2.68%</td>
<td>2.910</td>
<td>4.365</td>
<td>$12,204</td>
<td>$36,989</td>
<td>$119,395</td>
</tr>
<tr>
<td>Celecoxib (100/200mg bid)</td>
<td>$3,371</td>
<td>6.50%</td>
<td>2.48%</td>
<td>2.909</td>
<td>4.365</td>
<td>$633,431</td>
<td>$440,508</td>
<td>dominated by diclofenac **</td>
</tr>
<tr>
<td>Celecoxib (100/200mg bid) vs. Ibuprofen</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>$19,735</td>
<td>$57,477</td>
<td>$212,593</td>
</tr>
<tr>
<td><strong>High risk patients</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>VIGOR</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib (25mg qd)</td>
<td>$4,090</td>
<td>26.50%</td>
<td>7.45%</td>
<td>2.885</td>
<td>4.354</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Naproxen (500mg bid) + PPI</td>
<td>$4,766</td>
<td>36.80%</td>
<td>11.31%</td>
<td>2.882</td>
<td>4.352</td>
<td>dominated by rofecoxib **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib (25mg qd) + PPI</td>
<td>$6,486</td>
<td>18.20%</td>
<td>5.13%</td>
<td>2.894</td>
<td>4.359</td>
<td>$28,870</td>
<td>$103,284</td>
<td>$281,244</td>
</tr>
<tr>
<td><strong>CLASS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib (100/200mg bid)</td>
<td>$4,327</td>
<td>14.60%</td>
<td>5.54%</td>
<td>2.900</td>
<td>4.360</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Ibuprofen (800mg tid) + PPI</td>
<td>$4,414</td>
<td>26.60%</td>
<td>9.49%</td>
<td>2.889</td>
<td>4.354</td>
<td>dominated by celecoxib **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac (75mg bid) + PPI</td>
<td>$5,881</td>
<td>10.18%</td>
<td>4.11%</td>
<td>2.906</td>
<td>4.363</td>
<td>$35,149</td>
<td>$108,389</td>
<td>$254,803</td>
</tr>
<tr>
<td>Celecoxib (100/200mg bid) + PPI</td>
<td>$6,746</td>
<td>9.93%</td>
<td>3.81%</td>
<td>2.906</td>
<td>4.363</td>
<td>$346,120</td>
<td>$292,331</td>
<td>dominated by diclofenac **</td>
</tr>
</tbody>
</table>

Strategies are ordered by increasing cost. The more expensive strategy is compared to the less expensive, non-dominated strategy.
UGI: Upper Gastrointestinal Events; QALY: Quality Adjusted Life Year; PPI: proton pump inhibitor (lansoprazole)
*
: future QALYs and life-years are discounted by 5%
**: i.e. is a more costly and less efficacious strategy
### 3.2 Results of Sensitivity Analyses

Most single variable sensitivity analyses for the comparison of rofecoxib and naproxen in RA patients at average-risk showed only a relatively minor impact on the cost-effectiveness ratios (Table 8). Results for rofecoxib in RA patients of average-risk were sensitive to the relative risk reduction in clinical UGI events and complicated UGI events, but were still not cost-effective. Sensitivity analysis around the utility for coronary artery disease showed that, assuming a utility for Class III coronary artery disease, would increase the cost-effectiveness ratio for rofecoxib to $651,033. On the other hand, assuming no difference in MI event rates between rofecoxib and naproxen would lower the cost-effectiveness ratio to $86,054 per QALY gained. A much less dramatic effect is seen for the comparison of celecoxib to ibuprofen for the same variables (Table 8). Celecoxib is also unlikely to be cost-effective for average risk patients in all other sensitivities examined.

Sensitivity analyses results limited to high-risk patients revealed that cost-effectiveness ratios were sensitive to the price of PPI and the percentage of patients receiving rofecoxib plus a concomitant PPI. Specifically, prescription of rofecoxib to RA patients at high risk is more expensive than naproxen plus a PPI if the daily price of PPIs (before mark-up and prescription fee) drops below $1.35, and would achieve reasonable cost-effectiveness thresholds of $50,000 per QALY gained as long as PPIs cost no less than $1.20. Prescribing rofecoxib would also become more expensive than prescribing naproxen if more than 28% of RA patients on rofecoxib were co-prescribed PPIs. Likewise, celecoxib is cost-saving compared to ibuprofen in combination with PPIs down to a daily price of $1.83 for PPIs and would still be reasonably cost-effective ($50,000 / QALY) as long as PPIs cost no less than $1.38 per day. Diclofenac becomes cost-effective ($50,000 / QALY) compared to celecoxib when the price of PPIs falls below $0.90 and diclofenac is a cost savings strategy when the PPI price falls below $0.65 (Figure 6). Furthermore, cost-effectiveness ratios would be higher, if COX2 NSAIDs were costed according to dosages used in the clinical trials (Table 8).

**Figure 6:** Sensitivity analysis on the price of proton pump inhibitors (PPIs) in high risk patients for all three comparisons. Cost-effectiveness ratios were calculated for rofecoxib in comparison to naproxen based on VIGOR data, for celecoxib in comparison to ibuprofen and for diclofenac in comparison to celecoxib based on CLASS data.
Table 8: Sensitivity analysis of model estimates in the comparison of rofecoxib and naproxen

<table>
<thead>
<tr>
<th>Variables changed in sensitivity analysis</th>
<th>Cost per QALY gained *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Range</td>
</tr>
<tr>
<td><strong>Average Risk: Rofecoxib 25mg qd vs. Naproxen 500mg bid</strong></td>
<td></td>
</tr>
<tr>
<td>RRR clinical UGI events (36.0% - 67.0%)</td>
<td>$536,852</td>
</tr>
<tr>
<td>RRR complicated UGI events (22.0% - 76.0%)</td>
<td>$560,091</td>
</tr>
<tr>
<td>Hospitalisation if complicated UGI event (51.1% - 74.3%)</td>
<td>$292,606</td>
</tr>
<tr>
<td>Surgery if hospitalized (4.0% - 35.7%)</td>
<td>$275,522</td>
</tr>
<tr>
<td>Mortality in patients with first bleed (1.9% - 5.3%)</td>
<td>$315,289</td>
</tr>
<tr>
<td>RRR UGI events due to PPI (37.5% - 42.5%)</td>
<td>$267,341</td>
</tr>
<tr>
<td>Discount rate (0% and 3%)</td>
<td>$267,431</td>
</tr>
<tr>
<td>Relative risk if positive history of UGI bleed (2.0 - 5.9)</td>
<td>$292,547</td>
</tr>
<tr>
<td>All Resource Utilization costs ± 25%</td>
<td>$278,024</td>
</tr>
<tr>
<td>Daily cost of lansoprazole (less markup, fee) ($0.10 - $2.00)</td>
<td>$289,475</td>
</tr>
<tr>
<td>Percent with UGI event retrying NSAIDs (0 – 100)</td>
<td>$272,561</td>
</tr>
<tr>
<td>QALY for arthritis (0.159 - 0.185)</td>
<td>$330,986</td>
</tr>
<tr>
<td>QALY for dyspepsia (0.108 - 0.145)</td>
<td>$285,365</td>
</tr>
<tr>
<td>QALY for symptomatic ulcer (0.080 - 0.112)</td>
<td>$226,397</td>
</tr>
<tr>
<td>QALY for compl. UGI event with medical mgmt. (0.062 - 0.096)</td>
<td>$256,026</td>
</tr>
<tr>
<td>Utility for coronary artery disease (0.875 - 1)</td>
<td>$651,033</td>
</tr>
<tr>
<td>No difference in MI event rates</td>
<td><strong>$86,054</strong></td>
</tr>
</tbody>
</table>

**Average Risk: Celecoxib 100/200mg bid vs. Ibuprofen 800mg tid**

Utility for coronary artery disease (0.875 - 1) | $226,276   | $209,410   |

No difference in MI event rates | **$181,802** |              |

**High Risk: Rofecoxib 25mg qd vs. Naproxen 500mg bid + PPI**

Price of PPIs ($0.10 - $2.00) | $438,161   | dominance ** |

Relative risk if positive history of UGI bleed (2.0 - 5.9) | dominance ** | dominance ** |

**High Risk: Celecoxib 100/200mg bid vs. Ibuprofen 800mg tid + PPI**

Price of PPIs ($0.10 - $2.00) | $193,259   | dominance ** |

Relative risk if positive history of UGI bleed (2.0 - 5.9) | dominance ** | dominance ** |

**High Risk: Celecoxib 100/200mg bid vs. Diclofenac 75mg bid + PPI**

Price of PPIs ($0.10 - $2.00) | diclofenac dominates*** | $283,633   |

Relative risk if positive history of UGI bleed (2.0 - 5.9) | diclofenac dominates | dominance ** |

**Trial dosages of COX2 NSAIDs for patients at average risk**

Average risk: Rofecoxib 50mg qd vs. Naproxen 500mg bid | $638,240   |

High risk: Rofecoxib 50mg qd vs. Naproxen 500mg bid + PPI | $420,112   |

Average risk: Celecoxib 400mg bid vs. Ibuprofen 800mg tid | $774,929   |

High risk: Celecoxib 400mg bid vs. Ibuprofen 800mg tid + PPI | $526,236   |

High risk: Celecoxib 400mg bid vs. Diclofenac 75mg bid + PPI | diclofenac dominates |

RRR: relative risk reduction; PPI: proton pump inhibitor; UGI: upper gastrointestinal event

*: future QALYs discounted by 5%

**: COX2 less costly and more efficacious than regular NSAIDs

***: diclofenac dominates at a price of $0.10, its CE ratio increases to $283,633 at a price of $2.00.
The influence of age and a potential additional risk factor was examined in a sensitivity analysis of average-risk patients (Figure 7 and Figure 8). The results showed that rofecoxib became reasonably cost-effective in comparison to naproxen below thresholds of $100,000 and $50,000 per QALY gained in patients aged greater than 68 and 76, respectively. Presence of an additional risk factor that increases risk twofold reduces the age thresholds to 54 and 62, respectively (Figure 7).

**Figure 7:** Sensitivity analysis on age and the influence of a potential additional risk factor conferring a relative risk (RR) of 1.5 or 2 times the baseline rate in average-risk patients with RA. Cost-effectiveness ratios were calculated for rofecoxib in comparison to naproxen based on VIGOR data.

Analysis of age without an additional risk factor for celecoxib in comparison to ibuprofen in patients with RA or OA led to age thresholds of 70 and 81 for cost-effectiveness ratios of $100,000 and $50,000 per QALY gained. Analysis of age and an additional risk factor that increases risk by a factor of 2 reduced the age-thresholds to 56 and 67, respectively (Figure 8).

**Figure 8:** Sensitivity analysis on age and the influence of a potential additional risk factor conferring a relative risk (RR) of 1.5 or 2 times the baseline rate in average-risk patients with OA or RA. Cost-effectiveness ratios were calculated for celecoxib in comparison to ibuprofen based on CLASS data.
Use of Health Path Method to Estimate Utilities for Short-term Events

When values for short-term events, which were estimated using the Health-Path approach were utilized in the model, the analytic results changed. More favourable cost-utility ratios were observed in all scenarios (Table 9). In low-risk patients, use of the Health-Path approach results in lower cost-utility ratios for COX-2 inhibitors, although Celecoxib is dominated by Diclofenac. The analysis appears to be somewhat sensitive to values placed on short-term events.

Table 9: Use of negative QALY penalties and resulting cost-utility ratios

<table>
<thead>
<tr>
<th></th>
<th>Costs</th>
<th>QALYs</th>
<th>Cost/QALY gained</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average-risk patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VIGOR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen (500mg bid)</td>
<td>$1,576</td>
<td>2.625</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib (25mg qd)</td>
<td>$3,173</td>
<td>2.654</td>
<td>$54,890</td>
</tr>
<tr>
<td><strong>CLASS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen (800mg tid)</td>
<td>$1,141</td>
<td>2.643</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen &amp; Diclofenac</td>
<td>$1,864</td>
<td>2.904</td>
<td>-$6,535</td>
</tr>
<tr>
<td>Diclofenac (75mg bid)</td>
<td>$2,503</td>
<td>2.674</td>
<td>$43,738</td>
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<tr>
<td>Celecoxib (100/200mg bid)</td>
<td>$3,371</td>
<td>2.673</td>
<td></td>
</tr>
<tr>
<td><strong>High risk patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VIGOR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib (25mg qd)</td>
<td>$4,090</td>
<td>2.614</td>
<td></td>
</tr>
<tr>
<td>Naproxen (500mg bid) + PPI</td>
<td>$4,766</td>
<td>2.592</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib (25mg qd) + PPI</td>
<td>$6,486</td>
<td>2.637</td>
<td>$103,732</td>
</tr>
<tr>
<td><strong>CLASS</strong></td>
<td></td>
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<tr>
<td>Celecoxib (100/200mg bid)</td>
<td>$4,327</td>
<td>2.650</td>
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<tr>
<td>Ibuprofen (800mg tid) + PPI</td>
<td>$4,414</td>
<td>2.617</td>
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<tr>
<td>Diclofenac (75mg bid) + PPI</td>
<td>$5,881</td>
<td>2.663</td>
<td>$111,827</td>
</tr>
<tr>
<td>Celecoxib (100/200mg bid) + PPI</td>
<td>$6,746</td>
<td>2.663</td>
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</tr>
<tr>
<td>Ibuprofen &amp; Diclofenac</td>
<td>$5,249</td>
<td>2.886</td>
<td></td>
</tr>
</tbody>
</table>

Strategies are ordered by increasing cost. The more expensive strategy is compared to the less expensive, non-dominated strategy.

UGI: Upper Gastrointestinal events; QALY: Quality Adjusted Life Year; PPI: proton pump inhibitor (lansoprazole)

*: Future QALYs and life-years are discounted by 5%

**: i.e. is a more costly and less efficacious strategy
4 DISCUSSION

The results of this analysis show that prescribing either celecoxib or rofecoxib to patients without a prior clinical UGI event and who do not receive low-dose aspirin is associated with costs per quality-adjusted life-year gained that far exceed reasonable thresholds of $100,000 per QALY gained. Both celecoxib and rofecoxib are the most economically attractive strategies in high risk patients. Analysis by age groups and assuming a threshold of $50,000 per QALY gained, showed that rofecoxib or celecoxib would be cost-effective in patients aged over 76 and 81 respectively, without additional risk factors.

The findings of the cost-effectiveness and cost-utility analysis are closely influenced by the rates of clinical and complicated UGI events reported in two major trials of celecoxib and rofecoxib.\textsuperscript{13,14} The rates observed in the VIGOR study are higher than those observed in the CLASS study, which may be due to the inclusion of only RA patients, while in CLASS, 72\% of the patients had OA. The CLASS study found no difference in rates between OA and RA patients,\textsuperscript{52} in contrast to other evidence suggesting that GI events are more common in RA patients.\textsuperscript{33} However, OA and RA patients have never been observed in a prospective study with the same drug regimens, which raises the possibility that differences in rates between the two diseases are entirely due to NSAID dosages and regimens. In view of the fact that the cost of both drugs is similar at OA doses, and that the absolute risk reduction in GI events was similar in both CLASS and VIGOR, we believe that the qualitative results observed in this analysis (economically attractive in high risk patients, not so in average risk patients) most likely apply to both celecoxib and rofecoxib for OA patients. We also believe that the qualitative results of this analysis also apply to RA patients, although celecoxib may be somewhat less attractive at the higher doses (200mg bid) suggested for RA patients, (which, in Ontario, is twice as expensive as the recommended dose of rofecoxib (25mg qd)).

Two large new trials of celecoxib and rofecoxib have been recently published in abstract form and are worth mentioning. The SUCCESS-1\textsuperscript{53} study was a multinational, randomized controlled trial that compared celecoxib 100-200mg/d to naproxen 1000mg/d or diclofenac 100mg/d in 13,274 patients with osteoarthritis during a 12 week period. Incidence of complicated UGI events per 100 person-years were reported to be 0.8 in the NSAIDs group and 0.1 in the celecoxib group, while incidence of clinical UGI events was reported to be 2.1 in the NSAID group and 1.0 in the celecoxib group. All event rates were lower than reported in the CLASS study and their use would lead to higher cost-effectiveness ratios for celecoxib. In the ADVANTAGE\textsuperscript{54} trial, 5,597 patients with OA were treated for 3-months and were randomized to naproxen 1000mg/d or rofecoxib 25mg/d. The primary hypothesis was that there would be a lower incidence of discontinuations due to GI adverse events in patients treated with rofecoxib. However, rates of clinical or complicated UGI events were not reported. The data of these two large studies have been published in abstract form only and do not invalidate the findings of this cost-effectiveness analysis, but rather corroborate the present results.

We are less confident about the extrapolation of the rate of UGI events observed in the study populations to specific age strata. Precise estimates for the relationship between age and UGI event rates were not available from the VIGOR and CLASS studies. Hence, conclusions about precise age thresholds should be viewed with caution. Similarly, extrapolation to patients on aspirin is uncertain. Our baseline analysis assumes that the gastroprotective effect of COX2
NSAIDs does not extend to aspirin users, because aspirin increases bleeding risk and because clinical UGI events in the CLASS study were not different, and were in fact slightly higher in aspirin users who took celecoxib versus those who took ibuprofen or diclofenac. However, this conclusion must be regarded as uncertain, as this interpretation is based on results from a small subgroup of the CLASS study.

We also specifically excluded from this analysis consideration of adverse events other than MIs and UGI events. In fact, higher event rates of so-called serious adverse events were reported for celecoxib and rofecoxib, and higher withdrawal rates due to NSAID-related adverse events were reported for rofecoxib. However, while UGI events and MIs (VIGOR only) were classified according to their clinical relevance, this was not the case for other adverse events which precluded their use in this analysis.

Some controversy has arisen about the adequacy of measuring QALYs for short term states using conventional methods because they do not allow for values less than zero for the period of the short-term. We used a second method to derive utilities for the short-term states that resulted in negative utilities. Substitution of the baseline short-term QALYs with these negative QALYs would have led to more favourable cost-effectiveness ratios. This method is not commonly accepted and results should, therefore, be regarded as preliminary. Further empirical research is needed to clarify the best method to value short-term health states as this can have important implications in establishing the cost-effectiveness of new pharmaceuticals.

Our cost estimates were not based on measured costs, but were derived from provincial and national databases according to recently published recommendations. Potential inaccuracies in the cost-estimates were accounted for in the sensitivity analysis, where increases or decreases in the cost estimates by 25% could show only a very small influence on the final cost-effectiveness and cost-utility estimates. The relative insensitivity of the model to the cost-estimates is due to the fact that probabilities for the highly expensive events are very low, and that Cox-2 NSAIDs have only a small effectiveness on the reduction of dyspepsia-related visits.

In order to judge the cost-effectiveness of the COX2 drugs from the perspective of public health care payers / decision-makers in Canada, the following benchmarks were loosely inferred from previous reimbursement decisions of health technologies: (i) “likely to be cost-effective” if below $50,000 per QALY gained; (ii) “marginally cost-effective” if between $50,000 and $100,000 per QALY gained; and (iii) “unlikely to be cost-effective” if above $100,000 per QALY gained. Caution should be used when interpreting these benchmarks. These are not strict thresholds but reflect, in general terms, what is considered to be the current judgements of Canadian decision-makers. In addition, other factors, such as confidence in the clinical results, are often taken into account by decision-makers when considering whether to reimburse a health technology.

For high-risk patients, the cost-effectiveness of both celecoxib and rofecoxib were shown to be sensitive to the cost of PPIs used in combination with a regular NSAID. The analysis showed that treatment of high risk patients with regular NSAIDs combined with a PPI could become cost-effective (< $50,000 / QALY) for high risk patients, should a generic PPI become available at a price that is less than that used in the Base Case ($1.90). Relatively small changes in the price of PPIs can have a pronounced impact on the cost-effectiveness results, particularly in the
case of diclofenac vs celecoxib, given the marginal differences in QALYs gained and the high cost of PPIs relative to regular NSAIDs. However, these findings should be viewed cautiously as they are based on modeling the effectiveness of PPIs when used in combination with regular NSAIDs, and not on actual head-to-head trials compared to COX2 NSAIDs.

The results here are comparable to those observed in other cost-effectiveness analyses. A previous analysis comparing standard NSAIDs with and without the co-prescription of misoprostol showed that misoprostol was not cost-effective in patients at low risk, but was cost-effective among high risk individuals. The results were somewhat similar to the present findings as both economic evaluations were based on clinical UGI events observed in large randomised controlled trials. Most other economic evaluations comparing standard NSAIDs to co-prescription with gastroprotective agents usually had overstated cost-effectiveness estimates because of their reliance on extrapolated endoscopic evidence, rather than clinically important GI events. A similar overestimation would have occurred here, had the analysis been based on the very positive endoscopic findings among patients taking COX2 NSAIDs.
5 CONCLUSION

The findings are based on the clinical outcomes (including upper gastrointestinal events and myocardial infarctions) in the CLASS and VIGOR trials and pertain only to patients with OA and RA who do not require low-dose aspirin therapy. In the analysis, rofecoxib and celecoxib:

(i) are not cost-effective treatments in patients at average risk of upper gastrointestinal events (symptomatic ulcers or complicated UGI events) or in a population with a typical mix of average risk and high risk patients;
(ii) are cost-effective treatments for patients who are considered at high risk for gastrointestinal events by having a history of upper gastrointestinal events;
(iii) become less cost-effective in high risk patients as the rate of co-prescription of PPIs increase, and may lose their cost-effective advantage altogether if the price of PPIs was to decrease, with the threshold PPI price dependent on the particular treatments being compared; and
(iv) become cost-effective treatments for patients without additional risk factors over the age of 76 for rofecoxib and 81 for celecoxib.

It is noted that rofecoxib is currently not approved in Canada for the treatment of RA. Uncertainty remains about the correct method for deriving utilities for short-term health states.
6 REFERENCES


