Overview of the Arthritis Cost Consequence Evaluation System (ACCES): a pharmacoeconomic model for celecoxib

D. Pettitt, J. L. Goldstein\(^1\), A. McGuire\(^2\), J. S. Schwartz\(^3\), T. Burke\(^4\) and N. Maniadakis\(^5,6\)

Outcomes Research, Pfizer Inc, New York, NY, \(^1\)Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA, \(^2\)Department of Economics, City University, Northampton Square, London, UK, \(^3\)School of Medicine and The Wharton School, University of Pennsylvania, Philadelphia, PA, \(^4\)Global Health Outcomes North America, Pharmacia Corporation, Skokie, IL, USA and \(^5\)Global Health Outcomes Europe, Pharmacia Corporation, High Wycombe, Bucks, UK

\(^6\)Present address: European Health Outcomes Research, Eli Lilly and Company Limited, Lilly Research Centre, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey GU20 6PH, UK

Abstract

Pharmacoeconomic analyses have become useful and essential tools for health care decision makers who increasingly require such analyses prior to placing a drug on a national, regional or hospital formulary. Previous health economic models of non-steroidal anti-inflammatory drugs (NSAIDs) have been restricted to evaluating a narrow range of agents within specific health care delivery systems using medical information derived from homogeneous clinical trial data. This paper summarizes the Arthritis Cost Consequence Evaluation System (ACCES)—a pharmacoeconomic model that has been developed to predict and evaluate the costs and consequences associated with the use of celecoxib in patients with arthritis, compared with other NSAIDs and NSAIDs plus gastroprotective agents. The advantage of this model is that it can be customized to reflect local practice patterns, resource utilization and costs, as well as provide context-specific health economic information to a variety of providers and/or decision makers.

KEY WORDS: NSAIDs, COX-2 inhibitors, GI discomfort, Health outcomes, Pharmacoeconomic model.

Internationally, health care decision makers are increasingly requesting that pharmacoeconomic analyses describing the economic efficiency of an intervention be completed prior to placing a drug on a national, regional or hospital formulary.

In Australia, it has already become mandatory to demonstrate a drug’s pharmacoeconomic benefit in order for it to be listed in the government’s Schedule of Pharmaceutical Benefits (Australia's national formulary) \([1]\); other countries have developed or are developing guidelines for the pharmacoeconomic evaluation of new drugs \([2, 3]\). In the USA, a recent survey suggests that pharmacoeconomic outcomes are used in making policy decisions on an occasional basis 62% of the time, and on a frequent basis >20% of the time \([4]\). In aggregate, these regulations emphasize the importance and practical utility of pharmacoeconomic decisions.

The gastrointestinal (GI) side-effects of non-steroidal anti-inflammatory drugs (NSAIDs) have been well documented, and they have a significant impact, medically and economically, on both individual patients and health care systems. These GI events range from nuisance side-effects such as dyspepsia and abdominal pain, which often require evaluation, to the more serious GI events such as bleeding and perforation that can lead to hospitalization and death \([5, 6]\). The occurrence of these events results in greater utilization of medical resources, which leads to increased costs of treatment among patients using these drugs \([7–12]\). It is clear that there is a need for safer anti-inflammatory agents associated with a reduced incidence of NSAID-associated GI toxicity and, in parallel, treatment costs \([13, 14]\).

To address the need for safer NSAIDs, the specific
cyclooxygenase-2 (COX-2) inhibitors celecoxib and 
rofecoxib were developed and have recently been 
approved for use in several countries, including the USA, 
Canada, Switzerland and Sweden, for the symptomatic 
relief of both osteoarthritis (OA) and rheumatoid arthri-
tis (RA). These selective agents inhibit the pro-inflam-
atory COX-2 isoform and spare the constitutively 
expressed COX-1 isoform, which is generally associated 
with physiological functions, including gastroprotection 
[15, 16]. It is generally believed that the inhibition of 
COX-1 by traditional non-selective NSAIDs leads to 
their GI toxicity, such as gastroduodenal ulcers and their 
complications.

While clinical trials and long-term outcomes studies 
have demonstrated the efficacy as well as the safety of 
celecoxib in patients both with OA and with RA [17, 18], 
the potential reduction in resource utilization and the 
concomitant economic benefits associated with the use 
of this drug have received less attention [19]. Indeed, 
there have been few pharmacoeconomic models de-
veloped to evaluate the comparative cost of treatment 
with specific NSAIDs, and these models were designed to 
evaluate a narrow range of comparators within specific 
health care delivery systems using medical information 
derived from homogeneous clinical trials data [20–24].

To address this deficiency, the Arthritis Cost Conse-
quence Evaluation System (ACCES) has been developed, 
which can be customized to reflect local practice patterns, 
resource utilization and costs, as well as provide context-
specific health economic information to a variety of 
providers and/or decision makers.

This paper provides an overview of ACCES and its 
capacity to assess the effectiveness of celecoxib in the 
context of available knowledge of NSAID utilization, 
outcomes and costs.

Model design

Rationale and development

The ACCES model was developed to predict and 
evaluate the costs and consequences associated with the 
use of celecoxib in patients with arthritis, compared with 
non-selective NSAIDs with or without gastroprotective 
agents. The goal was to develop a flexible model that could 
provide different levels of analyses to a variety of 
decision makers by incorporating information from both 
clinical trials and real-world observational studies. This 
model was designed to assess the various perspectives 
and can be modified to reflect specific patient popula-
tions, NSAID formulary recommendations, resource 
utilization and costs, adverse event treatment practices, 
and drug use patterns.

Decision analytical models, such as the one illustrated 
in Fig. 1 for the ACCES model, facilitate analyses of 
alternative treatment decisions under conditions of 
uncertainty. In this type of model, default values based 
on existing research may be accepted, or specific variables 
such as risks, costs and treatment choices may be 
modified at the appropriate decision points or node(s), 
producing condition-specific analyses.

Results can be presented as incremental costs and 
medical benefits (i.e. the difference in costs and clinical 
events between the proposed treatment and the 
comparator treatment) or absolute costs (i.e. total cost or 
clinical events associated with a treatment). Accordingly, 
three types of analyses can be performed using the 
ACCES model: (i) cost consequences; (ii) cost-effective-
ness (cost per life-year gained); and (iii) budget impact 
analyses.

In the cost consequences mode, the model calculates 
the medical consequences of specific interventions as 
captured by the number of clinical adverse events 
associated with the specific NSAID therapy, including 
potential deaths and life-years lost. In this mode, the 
model also calculates both the incremental and absolute 
costs of the treatment based on these consequences. The 
number-needed-to-treat to avert a GI event is derived 
from these results.

The disaggregated costs and consequences are then 
combined to generate cost-effectiveness results in terms 
of cost per GI event averted and/or life-year gained. The 
default 6% discount rate (i.e. the value used to calculate 
present-day values for future costs and benefits) can be 
varied since various countries and providers may weight 
future events or costs differently.

Next, using these cost consequence results, the 
prevalence of GI risk factors in the population and 
information on NSAID utilization within the health care 
system, a budget impact analysis can be performed. In 
this type of analysis, the budgetary impact of switching 
a proportion of patients to a new therapy can be deter-
determined. Additionally, linear programming can be 
conducted to identify the optimal safe NSAID distribu-
tion under prespecified financial constraints. This 
methodology is commonly used by financial analysts, in 
which acceptable financial risk is balanced with expected 
monetary gain to obtain the greatest return for an 
investment portfolio. This analytical strategy is useful for 
providers who need to maintain a constant budget while 
minimizing the occurrence of GI events. This analysis 
takes the cost of therapy and the number of GI events 
verted for each therapeutic option and, based on the risk 
factors of the population and the drugs used, identifies 
the required shift in NSAID prescribing that would 
maximize patients’ health while maintaining constant 
costs.

A Microsoft Excel spreadsheet (Microsoft Corp., 
Redmond, WA) is used as the calculation engine in 
conjunction with a program called Crystal Ball 
(Decisioneering Inc., Denver, CO), which uses Monte 
Carlo simulations to generate probability distributions 
and confidence intervals for selected variables to simulate 
uncertainty.

A key determinant in all pharmacoeconomic models is 
the robustness of the model, which is routinely confirmed 
by sensitivity analyses. These analyses are instrumental in 
determining the effect of methodological or clinical 
assumptions inherent in economic models. They are
performed by considering alternative assumptions that may affect the outcomes, and generally require altering key probability variables over a range of values to calculate their overall impact on the model. To confirm the strength of the ACCES model, sensitivity analyses can be performed in a variety of ways.

As with most pharmacoeconomic models, ACCES can perform one-way sensitivity analyses by varying the probability of a parameter across its 95% confidence interval to determine the threshold value that would alter the scientific conclusions of the analysis. ACCES can also perform more sophisticated analyses, such as the generation of tornado diagrams for multiple one-way analyses. Tornado diagrams reflect the relative influence of different variables in descending order (i.e. the variables with the greatest influence to the variables with the least influence) on the results based upon the extreme ranges of their values (i.e. 95% confidence intervals). These diagrams facilitate the identification of variables most likely to influence the results of the analysis. Additionally, Monte Carlo simulations can be performed to generate probability distributions of variables to determine the uncertainty of an outcome.

**Perspective**

A societal perspective is commonly perceived as the appropriate perspective for use in any pharmacoeconomic analysis because it comprehensively reflects the medical benefit of a particular intervention by taking into account direct costs (i.e. medical costs), indirect costs (i.e. lost productivity) and intangible costs (i.e. quality of life). Realistically, however, many health authorities consistently focus on direct costs and 'short-term' clinical events. The ACCES model therefore takes the perspective of a third-party health plan. A third-party health plan in the USA is the health care buyer, such as a health maintenance organization, and parallels the perspective of the national health services in many countries, especially in Europe. This represents a pragmatic perspective, as costs and savings can be readily determined. There is also the basic assumption that improvements resulting from treatment will not only reduce direct medical costs, but will carry over to societal benefits in indirect and intangible costs resulting from a reduction in the need for treatment and an improved quality of life. In addition, one of the unique aspects of the ACCES model is that it can be easily adapted to address the needs of

*FIG. 1. Decision tree used in the ACCES model for evaluating pharmacoeconomic outcomes of celecoxib vs NSAIDs. Chronological events flow from left to right, with squares indicating decision nodes, circles indicating chance nodes and triangles indicating terminal nodes; + indicates continuation of the model with similar decisions or chances as for the first node in the sequence.*
regional providers such as the national health services that are common in many European countries.

The analytical horizon

Unlike other published pharmacoeconomic models of traditional NSAIDs that have looked at short-term use utilizing fixed endpoints of up to 12 weeks [20–24], the analytical horizon in ACCES can be varied between 0 and 365 days. The GI events (consequences) for each therapy and the costs for these consequences are calculated at the end of the specified time period. This unique feature of the ACCES model allows for analyses of acute or chronic treatment, since many OA and RA patients are on long-term therapy. The flexibility of this variable is additionally important, as standard NSAIDs differ not only between OA and RA patients, but also among different countries.

Comparators

In total, there are eight therapeutic groupings defined in the decision tree (Fig. 1): celecoxib, generic NSAID, branded NSAID, NSAID + proton pump inhibitor (PPI), NSAID + H2-receptor antagonist (H2-RA), NSAID + misoprostol and Arthrotec®, (fixed-dose diclofenac/misoprostol). These treatment choices enable decision makers to compare celecoxib not only with the traditional NSAIDs used in the celecoxib randomized clinical trials—naproxen, diclofenac and ibuprofen—but also with other branded and generic NSAIDs used in clinical practice. Individual NSAIDs and/or groups of NSAIDs—an NSAID ‘basket’ that may reflect the local NSAID market and/or the standard of care—can be used in the model. This broad range of treatment options maximizes the external validity of the model to assess the value of celecoxib therapy within a variety of health care delivery settings, such as managed care organizations in the USA or government-funded national health care systems, which may have dissimilar patterns of NSAID utilization.

Furthermore, the concomitant use of gastroprotective agents such as PPIs, prostaglandin analogues (i.e. misoprostol) and H2-RAs was also taken into account in designing the model, as was use of the fixed formulation of diclofenac/misoprostol. Gastroprotective agents are generally used for the primary or secondary prophylaxis of GI symptoms and/or adverse events, and the cost of these drugs can account for a large proportion of the cost of treatment in patients taking NSAIDs [10].

The ACCES model has the capacity for comparison among individual agents or therapeutic categories (i.e. NSAIDs, NSAIDs + PPI, etc.). Yet it also has the ability to construct a ‘base-case’ scenario by weighting costs and risks of individual agents and/or therapeutic categories to reflect local market conditions or prescribing patterns among all the treatment options.

Definition of clinical outcomes

The ACCES model considers six clinical events as possible outcomes. Five of these events, mentioned below, are related to GI outcomes; the sixth is loss of efficacy, which often leads to switching of drugs. This ‘loss-of-efficacy’ outcome is not generally considered in other models, and although there do not appear to be differences in efficacy amongst NSAIDs, lack of efficacy nevertheless contributes to increased costs resulting from additional physician visits and therapeutic switching to other NSAIDs. Switching of drugs, with the associated increase in treatment costs, also occurs as a result of GI intolerability, generally due to dyspepsia, the reduction of which can also provide economic benefit [25].

The clinical importance of this issue is shown in Fig. 2, which illustrates NSAID switching during a 1-yr period in ~12 000 OA patients in a study conducted using the database of a US managed care organization [26]. The average duration of initial NSAID dispensation for individual NSAIDs is shown by the black bars. The white bars represent the total number of days of NSAID dispensation during the 1-yr period for the patients who were started on each of the drugs. Therefore, the difference between the black bars and the white bars represents switching of drugs from the original dispensation. It can also be observed in this diagram that the duration of treatment with the initial NSAID is ~60 days. These results are similar to previously reported outcomes in studies of the patterns of interchange in NSAID dispensation. In one study, 52.8% of NSAID prescriptions were followed by another prescription within 60 days, with 32.7% of this switching due to lack of efficacy [27]. In another study, 50% of discontinuations of a drug occurred within 60 days, with only 15–20% of patients remaining on the same drug at the end of 1 yr [28]. These data demonstrate the extent of NSAID switching by patients, and suggest that a drug that improves patient satisfaction with efficacy and tolerability can lead to clinical and economic benefits.

The other five clinical events incorporated into the model are the GI consequences of NSAID use, which drive resource utilization and the cost of treatment [19]. The GI events considered in the model include: (i) serious GI complications, defined as any GI event resulting in
hospitalization or death; (ii) symptomatic ulcers, defined as ulcers treated in an out-patient setting but severe enough to lead to NSAID discontinuation in clinical trials; (iii) anaemia with occult bleeding, defined as any suspected GI event with a clinical diagnosis of anaemia that required trial withdrawal; (iv) intolerable diarrhoea, defined as the number of patient withdrawals from clinical trials due to diarrhoea; and (v) GI discomfort, a combined endpoint of dyspepsia, abdominal pain and nausea.

Dyspepsia is generally the primary source of GI discomfort in NSAID patients, and it is often cited as the reason for discontinuation or switching of drugs [5, 27, 29]. Additionally, resource utilization and the overall cost of treatment have been shown to be higher in patients with dyspeptic symptoms than in those without these symptoms [25, 30]. However, it is well recognized that there is no general consensus as to the clinical definition of dyspepsia. Therefore, abdominal pain and nausea were also included in this endpoint, since there is often overlap among these symptoms and they generally lead to similar clinical interventions.

Intolerable diarrhoea was included only as a source of therapeutic discontinuation. There was no assumption of incurred costs for the management of this problem, but this can be modified on a conditional basis by the investigator. Although diarrhoea is a symptom that occurs in a small percentage of patients taking NSAIDs, the main reason for inclusion of this outcome is for comparison of celecoxib with the combination of any NSAID plus the prostaglandin analogue misoprostol, which is used as a gastroprotective agent. These combinations are associated with diarrhoea, leading to discontinuation of therapy [31].

**Determination of event rates and relative risk**

GI discomfort rates are not constant over time, with the greatest risk for GI discomfort occurring at the beginning of therapy. To adjust for the changing rate, a Weibull model was constructed [32, 33] to determine the hazard rate at any given time while on therapy. This construct model was constructed [32, 33] to determine the hazard rate of therapy. To adjust for the changing rate, a Weibull model was used with respect to the daily discomfort rates, while for NSAIDs plus gastroprotective agents, a multiplicative model was used. The rationale for using these two different types of models is that there is an underlying rate of GI discomfort in the general population, as demonstrated in placebo groups. This underlying rate may possibly be associated with non-NSAID factors, such as Helicobacter pylori status, diet, stress, as well as NSAID GI toxicity (hence an additive model), but both the NSAID and non-NSAID factors may be affected by the gastroprotective agents (hence a multiplicative model).

In contrast to GI discomfort, the risk of serious GI events with long-term NSAID exposure has been shown to be constant over time [34]. Therefore, a predictive equation was adapted from the Fries risk calculator [35]. The Fries risk equation uses information obtained from the ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System) database to assign point scores to individual clinical characteristics of the patients based on the contribution of that characteristic to the overall risk. These risk scores were derived from a logistic equation developed by the ARAMIS group. The total score is then used to estimate the risk of a serious GI event for an individual or for a population based on the mean point scores of that population. Although the population characteristics and risk scores in the ARAMIS study are those of RA patients, extrapolation to OA patients is valid since it has been shown that there is no consistent rate difference between OA and RA patients after controlling for other serious GI event risk factors [36]. The original calculator reported by Fries et al. incorporated five risk factors: age, history of previous NSAID GI side-effect, NSAID dose, prednisone use and disability index. The risk equation was further modified to reflect the impact of a history of prior serious GI events. As shown in Fig. 3, there is good correlation between the original scoring system described by Fries et al. [35] and the adapted scoring system within ACCES. The modified risk calculator is used to obtain the baseline NSAID rate of serious GI events in a population at risk by taking the mean scores for each of the risk factors of this population and entering them into the modified Fries risk calculator. This baseline rate can then be multiplied by the relative risk for celecoxib or NSAIDs plus gastroprotective agents to obtain the event rates for these therapies. Event rates for individual

![Fig. 3. Correlation between an adapted Fries scoring algorithm and the original Fries scoring algorithm.](image-url)
NSAIDs can also be calculated using naproxen as a reference according to the formula:

\[
\text{rate}_{\text{NSAID}} = \frac{\text{rate}_{\text{naproxen}}}{\text{relative risk}_{\text{NSAID}}/\text{relative risk}_{\text{naproxen}}}
\]

Naproxen was used as the reference NSAID for several reasons: (i) it has the largest sample size of the drugs used in comparative trials with celecoxib; (ii) it is the most prevalent NSAID on the US market; (iii) the trial dosage was similar to the dose used in clinical practice; and (iv) the dose was comparable to the standardized NSAID dose used by the Fries risk equation to predict GI hospitalization. For other NSAIDs, relative toxicities with respect to GI hospitalizations were determined from a study performed in the UK that calculated the relative risk of NSAIDs compared with ibuprofen [34]. The data from that study were used to determine the relative risk for the different NSAIDs compared with the reference NSAID, naproxen (S. Morant, personal communication). These relative risks are shown in Table 1, which also shows the relative risk based on dosage; the relative doses of NSAIDs in the UK have been found to be similar to those used in a managed care population in the USA [26]. This concordance of dosage is important, since the ARAMIS study indicates that NSAID toxicity is dose dependent [35], and because it validates the use of the data from the UK study. Weighted relative risk adjustment for the entire NSAID therapeutic category is calculated by taking into account the proportion of the market represented by the different NSAIDs.

The relative risk of serious GI events for celecoxib compared with standard NSAIDs was determined from clinical trials of celecoxib. The selection of trials included in the pooled analysis has been described previously [19]. For NSAID plus gastroprotective agents, the relative risks were calculated vs NSAIDs alone using data obtained from a meta-analysis of randomized, controlled trials performed for each gastroprotective agent class (three trials for NSAIDs + PPIs [37–39], five trials for NSAIDs + H2-RAs [40–44], eight trials for NSAIDs + misoprostol [31, 39, 45–50], four trials for Arthrotec® [50–53]). In these trials, serious GI events were not studied, and therefore endoscopic ulcers were used as a surrogate endpoint, with the assumption that the relative risks for endoscopic ulcers and serious GI events are the same. This is a conservative assumption because (i) it attributes benefit to the gastroprotective agents (prevention of serious GI complications) that have not been proved in clinical trials and (ii) it is likely to bias against celecoxib. A random effects model was used to summarize the outcomes of individual trials, and tests of homogeneity were performed to determine the appropriateness of combining trials.

For symptomatic ulcers and anaemia, the base rates of these NSAID-associated events were obtained as a product of the incidence rate of serious GI events obtained from the modified Fries risk calculator and the ratio of total symptomatic ulcers to total serious GI events or the ratio of anaemia to total serious GI events. These ratios were determined from data in the 6-month Misoprostol Ulcer Complications Outcomes Safety Assessment (MUCOSA) trial [31], which provides a closer approximation of real-world conditions than the celecoxib clinical trials. The event rates were used to determine incidence rates for the reference NSAID, naproxen, with incidence rates calculated for other NSAIDs based on their relative risk compared with naproxen.

Table 2 summarizes the results of the calculations for the relative risk of the various therapeutic groupings vs NSAIDs alone for the specific events considered in the ACCES model. These values were used to determine the probability for initial GI events in each treatment arm.

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Exposure patient-years</th>
<th>Complicated event (95% CI) vs ibuprofen</th>
<th>Any event (95% CI) vs ibuprofen</th>
<th>Complicated event (95% CI) vs naproxen</th>
<th>Any event (95% CI) vs naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenoprofen</td>
<td>79</td>
<td>4.74 (1.09–20.6)</td>
<td>3.08 (0.72–13.1)</td>
<td>3.43 (0.79–14.85)</td>
<td>2.15 (0.51–9.11)</td>
</tr>
<tr>
<td>Azapropazone</td>
<td>767</td>
<td>3.70 (1.85–7.42)</td>
<td>4.07 (2.45–6.74)</td>
<td>2.67 (1.31–5.47)</td>
<td>2.83 (1.69–4.75)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>2199</td>
<td>3.31 (1.89–5.79)</td>
<td>2.82 (1.51–4.38)</td>
<td>2.39 (1.45–3.94)</td>
<td>2.00 (1.31–2.93)</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>710</td>
<td>2.37 (1.04–5.40)</td>
<td>2.31 (1.22–4.38)</td>
<td>1.71 (0.76–3.86)</td>
<td>1.61 (0.85–3.03)</td>
</tr>
<tr>
<td>All others</td>
<td>1607</td>
<td>1.85 (0.96–3.57)</td>
<td>1.91 (1.16–3.15)</td>
<td>1.34 (0.70–2.54)</td>
<td>1.33 (0.82–2.17)</td>
</tr>
<tr>
<td>Diclofenac retard</td>
<td>4031</td>
<td>1.63 (0.91–2.93)</td>
<td>1.68 (1.08–2.62)</td>
<td>1.18 (0.71–1.94)</td>
<td>1.17 (0.80–1.72)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1351</td>
<td>1.35 (0.59–3.10)</td>
<td>1.35 (0.69–2.62)</td>
<td>0.97 (0.43–2.20)</td>
<td>0.94 (0.49–1.80)</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>1078</td>
<td>1.40 (0.58–3.36)</td>
<td>1.29 (0.65–2.56)</td>
<td>1.01 (0.44–2.34)</td>
<td>0.90 (0.46–1.74)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>4789</td>
<td>1.38 (0.77–2.49)</td>
<td>1.44 (0.92–2.45)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>2123</td>
<td>1.35 (0.67–2.75)</td>
<td>1.81 (1.11–2.95)</td>
<td>0.98 (0.49–1.95)</td>
<td>1.26 (0.78–2.02)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>6294</td>
<td>1.00</td>
<td>1.00</td>
<td>0.72 (0.40–1.30)</td>
<td>0.70 (0.45–1.09)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>1798</td>
<td>0.98 (0.42–2.25)</td>
<td>1.25 (0.69–2.25)</td>
<td>0.71 (0.32–1.56)</td>
<td>0.87 (0.50–1.52)</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>649</td>
<td>0.61 (0.14–2.69)</td>
<td>0.37 (0.09–1.57)</td>
<td>0.44 (0.10–1.91)</td>
<td>0.26 (0.06–1.08)</td>
</tr>
<tr>
<td>Fenbufen</td>
<td>987</td>
<td>0.43 (0.10–1.89)</td>
<td>0.50 (0.18–1.42)</td>
<td>0.31 (0.07–1.36)</td>
<td>0.35 (0.12–0.98)</td>
</tr>
<tr>
<td>Dose Low</td>
<td>10 533</td>
<td>1.00</td>
<td>1.00</td>
<td>0.65 (0.37–1.14)</td>
<td>0.87 (0.55–1.37)</td>
</tr>
<tr>
<td>Dose Medium</td>
<td>12 241</td>
<td>1.41 (1.03–1.93)</td>
<td>1.25 (0.98–1.58)</td>
<td>0.80 (0.48–1.36)</td>
<td>0.95 (0.62–1.47)</td>
</tr>
<tr>
<td>Dose High</td>
<td>5694</td>
<td>1.92 (1.18–3.14)</td>
<td>1.39 (0.93–2.07)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>
The ACCES model allows for a one-time switch associated with either loss of efficacy or adverse events, with potential for a second GI event at a risk that can be varied as a function of both the preceding event and the new therapeutic regimen. The model allows the user to determine the type of treatment initiated after the switch. For patients who switched due to lack of efficacy, the assumption was that the switch was to another drug in the same class (i.e. from one generic NSAID to another). However, for adverse events, this switch was invariably to a safer treatment based upon the input of either local experts or alternative information sources (databases). Although a prior event increases the risk for a subsequent event, the chosen therapeutic regimen (i.e. NSAID plus gastroprotective agent) that the patient was switched to may offset the increased risk. For the purposes of the ACCES model, the relative risk adjustment for serious secondary GI events was derived from the Fries risk calculator [35]. For secondary discomfort rates, information from the aforementioned Weibull model was used. These calculated risk adjustments (see Table 3) were used to determine the probability of incurring secondary GI events in order to calculate outcomes and costs for each treatment arm.

**Determination of costs**

Since the perspective taken in this model is not a societal one but rather that of a payer, the model only allows for direct medical costs to be considered. These include the cost of the NSAID itself and any resource utilization that may be associated with side-effects or the prevention of side-effects resulting from the NSAID (gastroprotective agents, additional physician visits and diagnostic tests resulting from GI discomfort, hospitalizations resulting from serious GI events, etc.).

Costs are considered within the time frame of the model and according to the periods shown in Fig. 4. Initial drug costs (arthritis therapy or arthritis therapy plus gastroprotective agent) are considered for the period from initiation of therapy to occurrence of a GI event. During the event, only costs of GI event management are considered, since arthritis therapy is discontinued until resolution of the GI event. At resolution of the GI event, the patient is switched to a new drug and subsequent drug costs are resumed until the end of the time period or occurrence of another GI event. The initial drug costs for treatment are considered to be a sunk cost component in the model if a switch occurs.

Average costs are used in the model, since health care providers are generally interested in the average cost of resource utilization, even though this variable is not normally distributed. However, costs other than the average (i.e. median costs) can be used in the model, and for sensitivity analyses this parameter can be varied. The input of actual costs will, by necessity, be based on the conditions specific to the type of analysis, i.e. country specific and/or provider specific.

<table>
<thead>
<tr>
<th>Event</th>
<th>Treatment</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI discomfort</td>
<td>NSAIDs + proton pump inhibitor</td>
<td>0.64</td>
<td>0.39–1.06</td>
</tr>
<tr>
<td></td>
<td>NSAIDs + H2-receptor antagonist</td>
<td>0.71</td>
<td>0.55–0.92</td>
</tr>
<tr>
<td></td>
<td>NSAIDs + misoprostol</td>
<td>1.19</td>
<td>0.66–1.33</td>
</tr>
<tr>
<td></td>
<td>Arthrotec</td>
<td>1.24</td>
<td>0.99–1.57</td>
</tr>
<tr>
<td></td>
<td>Celecoxib</td>
<td>0.65</td>
<td>0.54–0.78</td>
</tr>
<tr>
<td>Symptomatic ulcer</td>
<td>NSAIDs + proton pump inhibitor</td>
<td>0.33</td>
<td>0.24–0.44</td>
</tr>
<tr>
<td></td>
<td>NSAIDs + H2-receptor antagonist</td>
<td>0.65</td>
<td>0.44–0.95</td>
</tr>
<tr>
<td></td>
<td>NSAIDs + misoprostol</td>
<td>0.40</td>
<td>0.31–0.51</td>
</tr>
<tr>
<td></td>
<td>Arthrotec</td>
<td>0.66</td>
<td>0.53–0.79</td>
</tr>
<tr>
<td></td>
<td>Celecoxib</td>
<td>0.28</td>
<td>0.17–0.45</td>
</tr>
<tr>
<td>Serious GI events</td>
<td>NSAIDs + proton pump inhibitor</td>
<td>0.50a</td>
<td>–b</td>
</tr>
<tr>
<td></td>
<td>NSAIDs + H2-receptor antagonist</td>
<td>0.98a</td>
<td>–b</td>
</tr>
<tr>
<td></td>
<td>NSAIDs + misoprostol</td>
<td>0.6</td>
<td>0.36–0.98</td>
</tr>
<tr>
<td></td>
<td>Arthrotec</td>
<td>0.54a</td>
<td>–b</td>
</tr>
<tr>
<td></td>
<td>Celecoxib</td>
<td>0.39</td>
<td>0.10–1.56</td>
</tr>
<tr>
<td>Anaemia</td>
<td>NSAIDs + proton pump inhibitor</td>
<td>0.33a</td>
<td>0.20–0.44</td>
</tr>
<tr>
<td></td>
<td>NSAIDs + H2-receptor antagonist</td>
<td>0.65a</td>
<td>0.44–0.95</td>
</tr>
<tr>
<td></td>
<td>NSAIDs + misoprostol</td>
<td>0.4a</td>
<td>0.31–0.51</td>
</tr>
<tr>
<td></td>
<td>Arthrotec</td>
<td>0.33a</td>
<td>–b</td>
</tr>
</tbody>
</table>

*Endoscopic ulcer was used as a surrogate marker for serious GI events and anaemia for gastroprotective agents.

**Table 2. Relative risk of therapies compared with NSAIDs alone for the occurrence of GI events**

<table>
<thead>
<tr>
<th>Initial event</th>
<th>GI discomfort</th>
<th>Symptomatic ulcer</th>
<th>Anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of efficacy</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>GI discomfort</td>
<td>1</td>
<td>1.91</td>
<td>1.48</td>
</tr>
<tr>
<td>Symptomatic ulcer</td>
<td>1</td>
<td>1.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1</td>
<td>1.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Serious GI event</td>
<td>1</td>
<td>1.5</td>
<td>3.9</td>
</tr>
</tbody>
</table>

*Relative risks for serious GI events, ulcers and anaemia are assumed to be equivalent and values are based upon ARAMIS regression coefficients [35]; risk for GI discomfort is based upon the Weibull risk equation from celecoxib trials.

**Fig. 4. Cost estimation intervals.** The time period from baseline to end can be varied between 0 and 365 days, and a second complication interval with associated costs may occur after resumption of NSAID therapy.
Discussion and conclusions

The ACCES model was developed to evaluate the costs and consequences of the use of celecoxib compared with those of standard NSAIDs. The strengths of this model are its flexibility with regard to duration of therapy, its comparators considered and its management of uncertainty. ACCES provides the ability to vary the input parameters and time frame, obtain a variety of pharmacoeconomic outputs (incremental and/or total costs, cost per event averted, number needed to treat for averted event and cost per life-year gained) and perform multiple sensitivity analyses. Additionally, while many NSAID evaluations focus predominantly on serious GI events, the ACCES model includes GI events that are not necessarily considered serious, yet are clinically relevant and contribute to the overall cost of treatment and patient quality of life. This flexibility maximizes the generalizability of the model, so that condition- or country-specific variables can be used to mimic real-world conditions and provide accurate pharmacoeconomic analyses upon which to base health policy decisions regarding utilization of these drugs. The multiple levels of sensitivity analysis for determining the robustness of the model also ensure that any clinical or methodological uncertainties are considered, regardless of how the model is being used.

However, as with any pharmacoeconomic model, there are limitations and assumptions. One of the limitations of this model is the use of naproxen as a reference, with the assumption that the relative risk differences among NSAIDs compared with naproxen have been quantified correctly. Although data on the relative toxicity of NSAIDs were taken from one study [34], the default value used in ACCES need not be accepted, and data from other studies may be used to determine relative risks—or values can be varied over a range. However, this assumption will not introduce an overall bias either for or against celecoxib.

Another assumption is related to the calculation of the event rate of symptomatic ulcers and anaemia, which assumes that there is a correlation between these events and more serious GI events. The rationale for this is that these events probably reflect a correlated underlying disease process. While the validity of this assumption has yet to be demonstrated, it can be considered a conservative assumption that biases against celecoxib, at least when compared with gastrenteroprotective agents.

Data for NSAIDs plus gastrenteroprotective agents were obtained from a meta-analysis of trials that considered different populations. However, the use of relative risks in the ACCES model avoids any potential bias that could be introduced from the differences in populations. Furthermore, the use of endoscopic ulcers as a surrogate marker for GI events in trials of NSAIDs plus gastrenteroprotective agents also provides a conservative assumption that biases against celecoxib, since it attributes benefits to these agents that have not been formally demonstrated within the construct of a randomized clinical trial.

Given the caveats of this model, its value and validity can only be determined under conditions of utilization. The practical applications of ACCES in country-specific settings are established in the subsequent articles, which demonstrate the pharmacoeconomic benefits of the introduction of celecoxib into the NSAID market in Sweden and Norway.

References

49. Elliott SL, Yeomans ND, Buchanan RRC, Smallwood RA.


