Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of rofecoxib versus nonselective non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of osteoarthritis (OA). Three daily dosages of rofecoxib could be administered, 12.5, 25 or 50 mg (the average daily dose was 24.7 mg). The NSAIDs considered were ibuprofen (2,400 mg/day), diclofenac (150 mg/day), or nabumetone (1,500 mg/day). These nonselective NSAIDs could be combined with a proton-pump inhibitor, an H2-receptor antagonist, or misoprostol for the prophylaxis and/or treatment of gastrointestinal adverse events (GIAEs).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with OA. A hypothetical cohort of 10,000 patients was considered, with the characteristics of the included patients being described in a published meta-analysis (Langman et al., see Other Publications of Related Interest).

Setting
The setting was a health service since a combination of primary, secondary and tertiary care was considered at analysis. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data appear to have been collected from studies published between 1989 and 2001. The cost data seem to have been obtained mainly from studies published between 1988 and 1999. The price year was 1998.

Source of effectiveness data
The effectiveness data were derived from a non-systematic review of published studies.

Modelling
A decision tree model was developed to estimate the health benefits and costs associated with the alternative therapies considered at analysis for the treatment of OA. The model assumed that there was no difference in efficacy between the alternative therapies, as already demonstrated in published clinical studies. The time horizon was 1 year.

Outcomes assessed in the review
The outcomes assessed for both OA treatments (rofecoxib and nonselective NSAIDs) were:

- the probability of potential resource-generating NSAID-related GIAEs;
- the probability of perforation, ulcer or bleed (PUB);
- the probability of a suspected PUB given that a GIAE occurred; and
- the probability of a patient requiring hospital treatment given that a non serious GIAE occurred.

**Study designs and other criteria for inclusion in the review**
The review was mainly based on a meta-analysis of 8 double-blind, randomised controlled trials (Langman et al., see Other Publications of Related Interest). Some other studies appear to have been reviewed, but their designs were not described.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
It appears that the effectiveness results collected from the meta-analysis included in the review (and, more specifically, the identification of a GIAE) were based on a blinded assessment performed by an expert panel.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
At least 12 published studies were included in the review.

**Methods of combining primary studies**
The methods used to combine the results of the primary studies were not reported, but it appears that a narrative method has been used.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The probability of potential resource-generating NSAID-related GIAEs was 0.299 for rofecoxib versus 0.295 for nonselective NSAIDs.

The probability of PUB given that a GIAE occurred was 0.050 for rofecoxib versus 0.091 for nonselective NSAIDs.

The probability of a suspected PUB given that a GIAE occurred was 0.028 for rofecoxib versus 0.072 for nonselective NSAIDs.

The probability that a patient required hospital treatment given that a non serious GIAE occurred was 0.241 for rofecoxib versus 0.370 for nonselective NSAIDs.
**Methods used to derive estimates of effectiveness**
Authors’ assumptions and assumptions derived from an expert panel were used to obtain some of the estimates of effectiveness.

**Estimates of effectiveness and key assumptions**
The authors formulated the following assumptions:

- minor GIAEs (i.e. those that did not lead to a diagnostic test or therapeutic intervention) were not included;
- GIAEs occurred at the midpoint of the time horizon considered in analysis;
- misoprostol and proton-pump inhibitors were equally effective (i.e. 40% risk reduction) in reducing the incidence of NSAID-induced gastroduodenal ulcers, whilst H2-receptor antagonists were ineffective;
- prophylactic gastroprotective agents (GPAs) were used 75% less with rofecoxib than with nonselective NSAIDs; and
- 8.3% of the total number of hospitalisations related to GIAEs resulted in death.

**Measure of benefits used in the economic analysis**
The estimation of health benefits was modelled, considering a time horizon of 1 year. The outcome measures used in the economic analysis were:

- the number of PUBs avoided and the number of deaths avoided, per 10,000 patients, with rofecoxib compared with NSAIDs; and
- the number-needed-to-treat (NNT) to avoid one PUB, one PUB-related hospitalisation, and one PUB-related death. The number of years of life saved with rofecoxib, compared with NSAIDs, was also estimated from the number of deaths avoided (although these results were only reported in combination with the estimated cost). In obtaining this estimate, the authors assumed a life expectancy of 18.3 years; the value was already discounted at a rate of 3%.

**Direct costs**
The direct costs considered in the economic analysis were those of the third-party payer. These were for medication (drugs and dispensing), office visits, outpatient and inpatient testing and procedures, surgeries (including anaesthesia), and physician services (both primary care and specialists). Average prices and fees were used, instead of costs. The categories of resources used were identified. The probabilities of using some of these resources and several unit costs were reported separately. The sources of the estimated costs were published studies. An expert's validation, based on a medical chart review of a series of PUB episodes, was used to validate the collected data. The cost estimation was therefore based on actual data. The price year was 1998. The estimated costs were not discounted as the period considered at analysis was 1 year.

The costs reported were the expected cost per patient per day, the iatrogenic cost factor, and the expected costs offset with rofecoxib compared with nonselective NSAIDs per patient per day. The iatrogenic cost factor was calculated as the ratio between the total direct costs and the drug costs per patient per day. The expected costs offset with rofecoxib were calculated as the expected cost-savings associated with the treatment and prevention of GIAEs with rofecoxib versus nonselective NSAIDs, independent of the drug costs.

**Statistical analysis of costs**
No statistical analyses of the costs were reported.

**Indirect Costs**
The indirect costs were not estimated.
Currency
US dollars ($).

Sensitivity analysis
Extensive one-way and multi-way sensitivity analyses were performed to assess the robustness of the results when several parameters and assumptions were modified. Variables included the rate of prophylactic GPA use, the rate of hospitalisation treatment for minor GIAE, and the relative risk of PUB. The authors did not fully justify the ranges of variation used. The results of a 3-month study of endoscopically detected lesions, adjusted for a silent ulcer rate equal to 40% and 85%, were used to reassess the cost-effectiveness results. Also, to evaluate the daily costs offset with rofecoxib when different cost scenarios were considered (i.e. a low-cost scenario considering Medicare reimbursement fee schedules, and a high-cost scenario considering the 90th percentile of usual, customary and reasonable fees). A threshold analysis was also performed to identify the NSAID drug cost above which rofecoxib would be cost-saving. Therefore, the areas of uncertainty investigated were variability in the data.

Estimated benefits used in the economic analysis
The numbers of PUBs and deaths avoided per 10,000 patients with rofecoxib, compared with nonselective NSAIDs, were 100 (PUBs) and 2 (deaths), respectively.

The NNT was 100 to avoid one PUB, 481 to avoid one PUB-related hospitalisation, and 5,771 to avoid one PUB-related death.

Cost results
The expected costs per patient per day were $2.86 with rofecoxib versus $2.73 with nonselective NSAIDs.

The iatrogenic cost factor was 1.18 for rofecoxib versus 1.86 for nonselective NSAIDs.

The cost offset per day with rofecoxib in comparison with NSAIDs was $0.81.

Synthesis of costs and benefits
The estimated health benefits and costs were combined through incremental cost-effectiveness ratios. These were calculated as the additional costs that had to be spent on rofecoxib, compared with nonselective NSAIDs, in order to avoid one further PUB and to avoid one further death and to save an additional year of life.

The additional cost incurred with rofecoxib to prevent a further PUB was $4,738, while $274,749 had to be additionally spent to avoid one death with rofecoxib in comparison with nonselective NSAIDs.

The cost per year of life saved with rofecoxib versus nonselective NSAIDs was $18,614.

The sensitivity analyses showed that the results were more sensitive to the rate of prophylactic GPA use and the reduction in the prescribing of prophylactic GPAs with rofecoxib versus nonselective NSAIDs.

In analyses based on endoscopic data, rofecoxib was cost-saving versus nonselective NSAIDs regardless of the cost scenario or the assumed rate of silent ulcer.

Rofecoxib was cost-saving versus nonselective NSAIDs at any NSAID daily cost higher than $1.60.

Authors' conclusions
The differences in drug cost between rofecoxib and non-steroidal anti-inflammatory drugs (NSAIDs) were markedly offset by expected cost-savings in gastro-intestinal adverse events (GIAEs) and co-medications averted with rofecoxib, although the iatrogenic costs were not completely eliminated. The cost per year of life saved with rofecoxib versus
nonselective NSAIDs was within the accepted threshold of $50,000 per year.

**CRD COMMENTARY - Selection of comparators**

NSAIDs were chosen as the comparator because they were one of the currently used OA therapies in the authors’ setting. It is worth noting that rofecoxib was withdrawn from the market in September 2004 because of the serious cardiovascular risks associated with this drug.

**Validity of estimate of measure of effectiveness**

The authors did not report that a systematic review of the literature was performed. The methods used to find and select the primary studies were unclear. The review was mainly based on the results of a meta-analysis of randomised clinical trials, but it was not possible to infer whether there were any biases around the effectiveness estimators derived from this meta-analysis and from the other studies included. The assumptions formulated were conservative and were expected to bias the results against rofecoxib. Sensitive analyses were performed in order to reduce the uncertainty that these assumptions introduced into the effectiveness results.

**Validity of estimate of measure of benefit**

The estimation of health benefits was modelled. The decision tree used to derive the measures of health benefit appears to have been appropriate. The authors considered measures of benefit that appear to have been relevant for the evaluated treatments. However, the risk of serious cardiovascular effects, which is a very relevant side effect associated with the administration of rofecoxib, was not considered in the analysis. Moreover, as the authors acknowledged, quality of life was not considered in the analysis. The use of alternative measures that include quality of life, such as the number of quality-adjusted life-years gained, would have been useful for comparing the results of this study with those of different interventions.

**Validity of estimate of costs**

All the relevant costs associated with the perspective adopted (i.e. the third-party payer) appear to have been included. Prices were used instead of costs, which may have been appropriate given the perspective adopted. The resources used were identified, but the quantities were not reported. In addition, some but not all of the unit costs were reported separately. This may hinder reflation exercises in other settings. The costs were obtained from a variety of sources including expert’s validation data and published sources. The price year was reported, which will facilitate any possible inflation exercises. Discounting was appropriately not performed, owing to the study period considered at analysis (i.e. 1 year). Extensive sensitivity analyses were performed on to cost estimators so as to reduce uncertainty.

**Other issues**

The authors commented that the iatrogenic cost factor was lower for this study than for prior studies. In addition, the time horizon considered at analysis was longer than that used in earlier studies. The authors highlighted the fact that the cost data were based on national averages and, therefore, they may not represent costs in all areas and settings because of the variations in different geographic regions. Thus, the results may not be generalisable to other settings. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis.

The authors reported a number of further limitations to their study. First, the scope of the model was limited to gastrointestinal-related problems and did not extend to any cardiovascular risks, thus the results of this study should be limited to GIAEs only. The patients' quality of life was not considered in the study.

**Implications of the study**

The authors questioned whether the economic benefits of rofecoxib will be realised in clinical practice. They implicitly recommend further research to obtain gastrointestinal outcome data from a mature marketplace.

Since the risk of serious cardiovascular adverse events associated with the consumption of rofecoxib were not
considered in the study, and these are very relevant, the results of this study should not be considered for application in clinical practice. Moreover, this drug has already been withdrawn from the market because of associated serious cardiovascular effects.

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**Bibliographic details**

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**Other publications of related interest**


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