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.

CRD summary
The aim was to evaluate the cost-effectiveness of cyclooxygenase-2 selective inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), and both of these in combination with proton-pump inhibitors, in patients with osteoarthritis. The authors concluded that it was cost-effective to add a proton-pump inhibitor to treatment with either cyclooxygenase-2 inhibitors or NSAIDs. The analysis was generally well conducted and adequately reported and the authors' conclusions appear to be appropriate.

Type of economic evaluation
Cost-effectiveness analysis, cost-benefit analysis

Study objective
The objective was to determine the cost-effectiveness of cyclooxygenase-2 selective inhibitors, alone or with proton-pump inhibitors, compared with non-steroidal anti-inflammatory drugs (NSAIDs), alone or with proton-pump inhibitors, in patients with osteoarthritis.

Interventions
The interventions compared were the NSAIDs paracetamol, diclofenac, naproxen, and ibuprofen and the cyclooxygenase-2 inhibitors etoricoxib and celecoxib (alone or with proton-pump inhibitors).

Location/setting
UK/secondary care.

Methods
Analytical approach:
A Markov model, with a lifetime horizon, was used to determine the clinical and economic impact of the alternative treatments, using published evidence. The authors stated that a health care system perspective was used.

Effectiveness data:
The clinical estimates were derived from the published literature. They were from the three largest randomised controlled trials that reported gastrointestinal and cardiovascular events, in patients treated with cyclooxygenase-2 inhibitors versus NSAIDs. These were the Celecoxib Long-term Arthritis Safety Study (CLASS), the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), and the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study. The key clinical parameters were the adverse event rates of specified conditions, which were dyspepsia, symptomatic ulcer, gastrointestinal bleed, myocardial infarction, stroke, and heart failure. These rates were adjusted to reflect the risks of events, at licensed levels, for cyclooxygenase-2 inhibitors. The effect of adding a proton-pump inhibitor to the NSAIDs was estimated from a published meta-analysis and that for cyclooxygenase-2 was from a trial. The risk reductions were assumed to be equal for all NSAIDs and for all cyclooxygenase-2 inhibitors.

Monetary benefit and utility valuations:
The utility estimates for the treatments were derived using the "transfer to utility" mapping technique. The trial outcomes of improvements in symptom control, measured by the disease-specific Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, were synthesised in a meta-analysis. The results were used as the utility...
value for an individual experiencing no adverse events. The utility weights for the adverse events were from the literature, augmented by expert opinion. All these values were multiplied by age-specific utility scores for the general UK population.

Measure of benefit:
The benefit measure was quality-adjusted life-years (QALYs) and these were discounted at an annual rate of 3.5%.

Cost data:
The analysis included the direct medical costs to the National Health Service (NHS) of drugs and the treatment of side effects. These costs were derived from a number of nationally published sources, including the Department of Health reference costs (treatment of adverse events) and the British National Formulary (drugs). The costs of out-patient and general practitioner consultations were based on national unit costs. The price year was 2007 to 2008 and all prices were given in UK pounds sterling (£). An annual discount rate of 3.5% was applied.

Analysis of uncertainty:
The uncertainty in the key assumptions and parameters (including the adverse event rate adjustments) was assessed, using both deterministic and probabilistic sensitivity analysis. Cost-effectiveness acceptability curves were presented.

Results
The results for all eleven treatment options were presented in graphs and an incremental analysis was conducted.

In summary, treatment with cyclooxygenase-2 inhibitors was generally more costly and more effective than treatment with NSAIDs. Adding a proton-pump inhibitor to cyclooxygenase-2 and NSAID treatment increased the estimated gain in QALYs, and was reported to increase costs negligibly when the savings from the treatment of adverse events were taken into account. Due to high levels of uncertainty, no conclusions could be drawn on the relative cost-effectiveness of the traditional NSAIDs.

The most cost-effective treatment was celecoxib 200mg with a proton-pump inhibitor. In patients at low risk of gastrointestinal and cardiovascular events, the cost per 10,000 people treated was £790,859 and the gain in QALYs was 92.5. Compared with the next less-effective treatment, which was etoricoxib at a cost of £580,668 and QALYs gained of 72.9, the incremental cost-effectiveness ratio was £10,745 per QALY. In patients at high risk of gastrointestinal and cardiovascular events, the incremental cost-effectiveness ratio was £10,458 per QALY, compared with no treatment.

Authors’ conclusions
The authors concluded that it was cost-effective to add a proton-pump inhibitor to either cyclooxygenase-2 inhibitors or NSAIDs for the treatment of osteoarthritis.

CRD commentary
Interventions:
The interventions were appropriate comparators. They were the licensed treatment alternatives, in the authors’ setting, at the time, and they are likely to be relevant in other settings.

Effectiveness/benefits:
The use of data from large randomised controlled trials, with head-to-head comparisons of the treatments, was appropriate, but the follow-up in these trials was not reported. This makes it difficult to determine whether they lasted long enough to capture all the relevant adverse events. It was also not clear that these were the only available evidence, as the systematic review was not described. Assumptions were made to adjust the event rates from these published trials and this resulted in more conservative estimates that reflected clinical practice. These key assumptions were discussed and evaluated in the probabilistic sensitivity analysis. The source for the utility data was reported, along with some information on the derivation of the QALY, but the details of the sources for the adverse event utility weights were not presented. Some assumptions by clinical experts were required to augment these data and further details would have allowed an assessment of the validity of these assumptions. QALYs were the most appropriate benefit measure, given the potential impact of the treatment on both quality of life and survival. There was no available data from the European Quality of life (EQ-5D) questionnaire and so the use of mapping and published data seems to have been
The perspective was clearly defined and it appears that all the relevant costs were considered. Summary costs and their sources were presented, but a detailed breakdown of the cost items was not. This does not impact on the results, but might hinder their transfer to other settings. This analysis was conducted in accordance with the National Institute for Health and Clinical Excellence (NICE) guidelines. The reporting was adequate and the key details, such as the price year and discount rate, were clearly stated.

Costs:
The issue of uncertainty was appropriately addressed, in both deterministic and probabilistic sensitivity analyses. The results of the base case and the sensitivity analyses were reported in sufficient detail and the authors highlighted the key strengths and limitations of their analysis. Cost-effectiveness acceptability curves were presented and they showed that celecoxib 200mg with a proton-pump inhibitor was likely to be the most cost-effective treatment, over a range of willingness-to-pay thresholds. The authors highlighted the uncertainty in this result, as there was only a 50% chance that it would be cost-effective. Given the number of comparators considered and the impact that this had on the construction of the curves, this result might not be as uncertain as the authors suggested.

Concluding remarks:
The cost-effectiveness analysis was generally well conducted and adequately reported. The authors' conclusions appear to be appropriate.

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