

Protocol for technology assessment report: Cyclooxygenase-2 (COX-2) selective inhibitors for osteoarthritis and rheumatoid arthritis

A. Final version (5 November 2003).

B. Details of review team

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C. Full title of research question

Clinical effectiveness and cost-effectiveness of cyclooxygenase-2 (COX-2) selective inhibitors (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis or rheumatoid arthritis.

D. Clarification of research question and scope

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for symptomatic treatment of osteoarthritis (OA) and rheumatoid arthritis (RA). They exert anti-inflammatory and analgesic effects by inhibiting cyclooxygenase (COX) which facilitates the production of prostanoids, including prostaglandins, prostacyclin and thromboxanes. At least three isoforms of COX have been identified: COX-1 is responsible for the production of prostanoids which are involved in the protective mechanisms of the gastrointestinal (GI) tract and maintain renal and platelet functions; COX-2 is an inducible form of COX that mediates the production of prostanoids associated with inflammation; COX-3 is a recently discovered isoform, the functions of which are yet to be investigated.¹ NSAIDs may cause stomach ulcers, GI haemorrhage or perforation by inhibiting the protective functions of COX-1 in the stomach. This toxicity has important clinical and economic implications.

COX-2 selective NSAIDs inhibit COX-2 to a greater extent than COX-1, depending on selectivity, which aims to reduce their GI toxicity while maintaining their anti-inflammatory and analgesic benefits. The determination of COX-2 selectivity however depends on the laboratory assay used and selectivity may vary 10-fold depending on assay systems. Currently, there appears to be no consensus on a precise definition of a COX-2 selective agent and the necessity of demonstrating clinical benefits has been emphasised.^{2,3}

The effectiveness and cost-effectiveness of four COX-2 selective inhibitors, namely celecoxib, rofecoxib, etodolac and meloxicam, for RA and OA have been assessed in a previous technology assessment report published by the National Institute of Clinical Excellence (NICE)⁴ in 2000/2001 and subsequently in two Cochrane reviews

¹ Schwab JM, Schluesener HJ, Laufer S. Cox-3: just another COX or the solitary elusive target of paracetamol? *Lancet* 2003;361:981-982.

² Hawkey CJ. COX-2 inhibitors. *Lancet* 1999;353:307-314.

³ Vane JR, Warner TD. Nomenclature for COX-2 inhibitors. *Lancet* 2000;356:1373-1374.

⁴ NICE appraisal team. The clinical effectiveness and cost effectiveness of celecoxib, rofecoxib, meloxicam and etodolac (Cox-II inhibitors) for rheumatoid arthritis and osteoarthritis. The National Institute for Clinical Excellence, London, UK. November 2000. Available at: <http://www.nice.org.uk/pdf/coxihtareport.pdf>

published by the same group of authors.^{5,6} The evidence base on these drugs continues to grow rapidly, and three additional COX-2 selective inhibitors (etoricoxib, valdecoxib, lumiracoxib) have been licensed since. Therefore, an update of currently available evidence in this field is needed.

The aims of this technology assessment report are:

- (1) To update the systematic review⁴⁻⁶ on the clinical effectiveness and cost-effectiveness of celecoxib, rofecoxib, etodolac, and meloxicam for OA and RA.
- (2) To undertake a systematic review on the clinical effectiveness and cost-effectiveness of etoricoxib, valdecoxib and lumiracoxib for OA or RA.
- (3) To assess the cost-effectiveness of COX-2 inhibitors from a National Health Services (NHS) perspective.

Within the general aims mentioned above and where evidence permits, this technology assessment has the following *exploratory objectives*:

- (4) To explore the potential impact of concomitant gastroprotective agents, with either COX-2 selective inhibitors or other NSAIDs, on the incidence of symptomatic gastrointestinal perforations, ulcers, bleeds (PUBs) and obstructions.
- (5) To take into account the effects of co-existing *Helicobacter pylori* infection.
- (6) To explore the impact of concomitant low dose aspirin and COX-2 selective inhibitors on the incidence of cardiovascular adverse events, PUBs and obstructions.

E. Report methods

Search strategy

Clinical effectiveness

A search for systematic reviews and RCTs will be undertaken for all the drugs (meloxicam, etodolac, celecoxib, rofecoxib etoricoxib, valdecoxib, and lumiracoxib) for the indications of OA or RA based on the previous assessment report and current Cochrane reviews. The following sources will be searched for RCTs:

- Bibliographic databases as follows: Cochrane Library, MEDLINE, pre-MEDLINE and EMBASE.

⁵ Garner S, Fidan D, Frankish R, et al. Celecoxib for rheumatoid arthritis (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2003. Oxford: Update Software.

⁶ Garner S, Fidan D, Frankish R, et al. Rofecoxib for rheumatoid arthritis (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2003. Oxford: Update Software.

Index and text words representing the drug names will be combined with terms for OA and RA. Depending on the yield of references, a trial filter will also be incorporated.

- Internet sites of regulating authorities, e.g. European Agency for the Evaluation of Medicinal Products (EMA) and the Food and Drug Administration (FDA)
- Citations of relevant studies
- Contact with experts
- Invited pharmaceutical company submissions

Because of the change of inclusion criteria from the previous assessment report (see next section), databases will be searched from the inception date for all drugs. The searches will not be restricted by language. Published and unpublished studies will be sought.

Conference abstracts will be sought for years 2001 to 2003 such as annual meetings of the American College of Rheumatology/Association of Rheumatology Health Professionals.

Cost-effectiveness

For all drugs, the searches for clinical effectiveness will be amplified to identify any existing economic models and information on costs, cost effectiveness and quality of life from the following sources:

- Bibliographic databases: MEDLINE, pre-MEDLINE, EMBASE, NHS EED, DARE, HEED.
- Internet sites of national economic units
- Internet sites of regulating authorities, e.g. FDA, EMA

Databases will be searched from the inception date of the databases for all drugs.

Inclusion and exclusion criteria

Given the broad scope of the technology assessment, different sets of criteria will be adopted for each of the three parts of the review: clinical effectiveness, safety, and cost-effectiveness.

Inclusion criteria for the review on clinical effectiveness

Study design	RCTs with duration of treatment \geq 2 weeks (no restriction on the number of patients)*; systematic reviews of RCTs
Population	Patients with OA or RA; other forms of arthritis are excluded
Intervention	Celecoxib, rofecoxib, meloxicam, etodolac, etoricoxib, valdecoxib and lumiracoxib, with or without aspirin
Comparator	Placebo, non-COX-2 NSAIDs, or direct comparisons of the intervention drugs**
Outcome	<ul style="list-style-type: none">• Any accepted measure of clinical disease activity or progression except radiographic outcomes. The following outcome measures will be particularly sought: American College of Rheumatology core set of disease activity measures for RA clinical trials; Outcome Measures for Rheumatoid Arthritis Clinical Trials (OMERACT) measures: number of tender joints per patient, number of swollen joints per patient, pain, physician global assessment, patient global assessment, functional status, acute phase reactants; WOMAC Osteoarthritis Index• Quality of life

*RCTs with less than 50 patients in each arm and with duration of treatment less than 4 weeks were excluded from the previous assessment report and Cochrane reviews.

**Dose-finding studies of the intervention drugs without a comparator will be excluded.

Inclusion criteria for the review on safety

Study design	RCTs with duration of treatment \geq 2 weeks (no restriction on the number of patients)*; systematic reviews**
Population	Patients with OA or RA; other forms of arthritis are excluded
Intervention	Celecoxib, rofecoxib, meloxicam, etodolac, etoricoxib, valdecoxib; lumiracoxib, with or without aspirin
Comparator	Placebo; Non-COX-2 NSAIDs with or without gastroprotective agents; COX-2 selective inhibitors with or without gastroprotective agents; COX-2 selective inhibitors with low dose aspirin
Outcome	<ul style="list-style-type: none"> • Total adverse events (AEs) • Total withdrawals • Withdrawals due to AEs • Withdrawals due to gastrointestinal AEs • Withdrawal due to lack of efficacy • Number of patients with perforations and/or ulcers and/or obstructions and/or bleeds – ulcers detected by endoscopy will be considered separately from ulcers presented clinically • Number of patients with cardiovascular thrombotic event(s), including myocardial infarction and stroke • AEs associated with therapy, including oedema, hypertension, and changes in renal function • Deaths

*RCTs with less than 50 patients in each arm and with duration of treatment less than 4 weeks were excluded from the previous assessment report and Cochrane reviews.

**If identified RCTs and systematic reviews did not provide sufficient information to address the *exploratory objectives*, key studies of best research design (according to the hierarchy of quasi-experimental studies, cohort studies, case-control studies, observational studies without control groups) will be sought. Long-term follow-up or observational studies of patients included in key trials of COX-2 selective inhibitors will be identified from searches, pharmaceutical company submissions and data from regulatory agencies, such as the EMEA and the FDA, in order to assess long-term drug safety.

Inclusion criteria for the review on cost-effectiveness

Study design	Cost-consequence analysis, cost-minimisation analysis, cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis; cost studies* (UK only), quality of life studies*
Population	People with OA or RA; other forms of arthritis are excluded
Intervention	Celecoxib, rofecoxib, meloxicam, etodolac, etoricoxib, valdecoxib and lumiracoxib, with or without aspirin
Comparator	Non-COX-2 NSAIDs with or without gastroprotective agents, COX-2 selective inhibitors with or without gastroprotective agents
Outcome	Quality of life estimates, cost estimates, cost-effectiveness

*Not included in the previous assessment report.

Based on these inclusion criteria, study selection will be carried out independently by two reviewers. Disagreements will be resolved by discussion. A third person, whose decision is final, will be consulted when disagreements persist after discussion.

Data extraction strategy

Clinical effectiveness and safety review

Data extraction for RCTs not included in the previous assessment report and Cochrane reviews will be carried out by a reviewer using a form adopted from the previous assessment report. Data from RCTs included in the previous assessment report and Cochrane reviews will be taken by a reviewer directly from the reports and via contact with the authors, and the data incorporated into the current assessment report. All included data will be checked by a second reviewer. The following data will be extracted:

- Details of the study population and baseline characteristics of the intervention and control groups, with particular reference to concomitant drug and non-drug therapies and *H. pylori* infection.
- Details of the intervention and comparator, such as dose, frequency of administration and duration of treatment.
- Details of completion rates across the groups, reasons for withdrawal, loss to follow up, and compliance.
- Details of individual outcomes for effectiveness and adverse events.

Results will be extracted, where possible for the intention to treat population, as raw numbers, plus any summary measures with standard deviations, confidence intervals and p-values where given. Disagreements will be resolved by discussion. A third person, whose decision is final, will be consulted when disagreements persist after discussion.

Cost-effectiveness review

Data will be extracted from included studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion. A third person, whose decision is final, will be consulted when disagreements persist after discussion. It is anticipated that data will be extracted on the following:

- Study characteristics such as form of economic analysis, population, interventions, comparators, perspective, time horizon, and modelling used.
- Effectiveness and cost parameters such as effectiveness data, health state valuations (utilities), resource use data, unit cost data, price year, discounting, and key assumptions.
- Results and sensitivity analyses.

Quality assessment strategy

Clinical effectiveness and safety review

The methodological quality of RCTs will be assessed on the basis of randomisation, adequate concealment of randomisation, level of blinding, use of intention to treat analysis, and description of loss to follow up. An overall quality score (Jadad) will be assigned to each study. Quality assessment will be conducted by a reviewer and checked by second. Disagreements will be resolved by discussion. A third person, whose decision is final, will be consulted when disagreements persist after discussion.

Cost-effectiveness review

The quality of included studies will be assessed independently by two reviewers using checklists suggested by Drummond and Jefferson⁷ and by Soto⁸. The study question, selection of alternatives, form of evaluation, effectiveness data, costs, benefit measurement and valuation, decision modelling, discounting, allowance for uncertainty and presentation of results will all be evaluated as part of this process.

⁷ Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996;313:275-283.

⁸ Soto J. Health economic evaluations using decision analytic modeling: Principles and practices - Utilization of a checklist to their development and appraisal. *International Journal of Technology Assessment in Health Care* 2002;18:94-111.

Methods of analysis/synthesis

Clinical effectiveness & safety review

Data on clinical effectiveness and safety will be presented in tabulated format with narrative summaries. A decision on whether to pool efficacy and safety outcomes will be taken following the updated search and based on the level of clinical and statistical heterogeneity and the range of outcome measures reported. Data will be pooled using a fixed effect model unless statistical heterogeneity between studies is found, in which case a random effect model will be used.

Where possible the clinical effectiveness and safety results for each of the seven drugs will be presented separately for OA and RA patients. Direct comparisons between COX-2 selective inhibitors will be presented separately for each combination. Separate comparisons will be carried out for drug versus placebo and drug versus NSAIDs.

Subgroup analysis

Data on the following subgroups will be sought specifically:

- (1) the effects of gastroprotective agents (including the prostaglandin analogue misoprostol, H₂-receptor antagonists, and proton pump inhibitors) on the risk of NSAID induced PUBs and obstructions;
- (2) the effects of concomitant low dose aspirin (up to 325 mg/day) on the risk of cardiovascular events, PUBs and obstructions;
- (3) the impact of *H. pylori* infection and eradication of *H. pylori* on the risk of NSAID induced PUBs and obstructions.

Where data on these subgroups are available within trials or pharmaceutical company submissions, results will be abstracted and presented separately. Such data may be pooled if appropriate.

Cost-effectiveness

The characteristics and main results of included economic evaluations, cost studies (UK only), and quality of life studies will be summarised in a tabulated format. A commentary for the models included in these studies and pharmaceutical company submission will be provided. The commentary will be fuller and more technical for the pharmaceutical company submissions given the availability of the computer files of these models.

Methods for estimating quality of life, costs and cost-effectiveness

The decision to develop a *de novo* decision analytic model or to adapt an existing model will be made following a detailed review of published decision analytic models examining the cost-effectiveness of COX-2 inhibitors. Given that there are no important interaction issues to consider here, a Markov model may be sufficient. Model outcome parameters (e.g. quality of life estimates) will be obtained from published sources identified by the search methods described above. Model costs data will be sourced from published literature, NHS sources and pharmaceutical company submissions. Costs to be considered include the costs of the drug treatment and the costs of management of clinical events including adverse drug events. The perspective of the economic analysis will be that of the NHS.

The final outcome measures used will depend on the literature retrieved but is likely to include cost per quality adjusted life year (QALY) gained. Inadequacies of QALYs in dealing with short-term outcomes (e.g. GI bleeds) will be considered. A sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the treatments, with the objective of identifying how secure the results of the economic analysis are, given the current level of evidence.

In all other respects the economic analysis component of the project will seek to follow the current NICE guidelines on methods for technology appraisal.

F. Handling the company submission(s)

All data submitted by pharmaceutical companies by 9th February 2004 will be examined in detail. Studies not identified in our searches that meet inclusion criteria will be quality assessed and data extracted as described above. Confidential information will be clearly underlined in the final report (followed by an indication of the relevant company name in brackets). Tabulated summaries and technical commentaries on the economic models used in pharmaceutical company submissions will be provided.

G. Project management

a. Timetable/milestones – submission of:

Draft protocol: 16th October 2003

Final protocol: 6th November 2003

Progress report: 16th February 2004

Complete and near final draft to external reviewers and NICE project team: 21st June 2004

Assessment report: 19th July 2004

b. Competing interests

Rod Taylor has undertaken paid educational presentation for Roche. Paresh Jobanputra has received funding from Pfizer for two research studies: (1) Quality of care in patients with musculoskeletal pain who use NSAIDs; (2) Perception of risk in relation to NSAID use for patients with RA and OA. He has also been entertained, paid to speak and provided with financial assistance for educational purposes by many manufacturers of NSAIDs, new and old. Andreas Maetzel is currently a consultant to Cerner Zynx Inc., a company carrying out research on behalf of Novartis. He has also been paid entertained, paid to speak and provided with financial assistance for educational purposes by manufacturers of NSAIDs, specifically Merck and G.D. Searle Inc. (now Pharmacia-Pfizer). The other members of the review team have no competing interest.

c. External reviewers

The technology assessment report will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, but if the current technology assessment report encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the technology assessment report and will understand that their role is part of external quality assurance. All reviewers are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking form. We will send external reviewers' signed copies to NCCHTA. Comments from external reviewers and NICE technical leads, together with our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

H. Appendices (optional)

None submitted