# Issues of Consensus and Debate for Economic Evaluation in Rheumatology

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***ABSTRACT.*** We report initial attempts at developing standards for the conduct of economic evaluations in rheumatology. We surveyed 25 clinicians and economists with an interest in rheumatology regarding the design and reporting of economic evaluations, with particular reference to 4 clinical scenarios relating to treatment for rheumatoid arthritis, osteoarthritis, and osteoporosis. The results demonstrated widespread agreement on a number of methodological issues such as statement of funding source, perspective, discounting, and allowance for uncertainty. However, there was lack of consensus over clinical variables including sources of data for efficacy estimates, specific clinical outcomes, methods of assessing quality of life, and choice of comparators. Some of the disagreement reflects lack of consensus in current general methodological guidelines. Consensus regarding the disease-specific clinical variables is crucial to standardizing analysis and facilitating comparisons within clinical scenarios. (J Rheumatol 2001;28:642–7)

*Key Indexing Terms:*
COST-EFFECTIVENESS ANALYSIS STANDARDIZATION SURVEY METHODOLOGY

## INTRODUCTION

The increasing number of economic analyses in the general medical literature and the increasing requirements for economic evidence with regard to reimbursement of pharmaceuticals have led to a number of attempts to provide guidelines for the conduct and reporting of studies[1-5]. Guidelines can undertake 3 specific roles: to promote the standardization of methods to allow comparison across studies, to facilitate the interpolation of studies across jurisdictions, and to act as an educational tool for both users and producers of studies.

Guidelines have often focussed on promoting the use of either a set of minimum or core requirements or a reference case[1,5]. For many issues in the conduct of economic evaluations, both forms of guidelines will reflect the consensus within the research community: for example, the need for discounting, sensitivity analysis, and the separate reporting of costs and resource use. However, there are still areas where consensus has not and may never be reached. Thus, different guidelines favor different approaches with respect to issues such as the measurement of utilities, preferred study perspective, and the choice of study comparator.

Guidelines have tended to be general in nature, relating to all fields of medicine. As part of the OMERACT Health Economics Working Group, we have made attempts to produce guidelines for the standardization of the conduct and reporting of studies specifically in the field of rheumatology. These standards would go beyond the general nature of current guidelines to address specific clinical issues relating to the conduct of studies within rheumatology. Such an initiative may lead to improvements in the quality of published studies as well as facilitating direct comparison between studies and improving the transferability of studies into different jurisdictions.

Our objective is to report the initial attempts to develop standards within the conduct of economic evaluations in rheumatology highlighting those areas where consensus has not been reached.

## METHODS

### Template

For the first step in developing guidelines for rheumatology based economic evaluations, a template was developed, covering principal areas related to study conduct and reporting. The initial design of the template was developed through consultation with methodological and clinical experts working in this field.

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Templates were derived for 4 distinct clinical scenarios: the treatment of rheumatoid arthritis (RA) with disease modifying antirheumatic drugs, treatment of RA patients with nonsteroidal antiinflammatory drugs (NSAID) or selective cyclooxygenase-2 (COX-2) inhibitors, treatment of patients with osteoarthritis (OA) with NSAID or selective COX-2 inhibitors, and the treatment of patients with osteoporosis. Principal areas covered were similar to the content of most existing guidelines with additional areas pertinent to the specific clinical area, which follow.

*Study funding.* Given the potential to bias the results of economic analysis, there has been much focus on who should fund studies and how industry-funded studies should be interpreted[6,7]. However, many studies do not indicate the funding source.

A recommendation by the Canadian Coordinating Office of Technology Assessment that might alleviate such concerns is that industry funded studies investigators must state that they had independence over all aspects of study design and analysis[1].

*Study population and patient characteristics*. The results of economic analyses may be only appropriate to a specific population subgroup. For example, in the evaluation of treatments for osteoporosis, results may vary by whether the patient is peri or postmenopausal or has had previous fracture, or by age[8]. Sensitivity analysis can be conducted to assess the differences in cost-effectiveness across subgroups. However, in practice, it is necessary to define the minimum details of the patient population required for analysis, although this should include only those characteristics over which the study results may vary.

*Choice of comparators*. The results of an economic analysis of a new therapy can vary substantially by the choice of comparator therapy. There is a lack of consensus within existing guidelines on what the baseline comparator should be, i.e., which is the least costly alternative, the most common alternative, or the most effective alternative[1-5]. The comparator may vary by specific patient population and by country of study. Therefore, it is unclear whether a reference case should define a specific therapy as a comparator for all studies, or whether the approach should be less prescriptive by suggesting a specific criteria for choice of comparator, e.g., the most widely used therapy.

*Perspective*. A crucial issue in the design of any economic evaluation is the study perspective, i.e., the range of costs to be included. Studies can be conducted based on limited perspectives such as the hospital, health care budget, or third party payer; or based on a more general, societal perspective, whereby costs incurred by all parties (including patients) are included. Ideally, analysis should be conducted based on the latter perspective with the results being presented in a transparent fashion enabling specific decision makers to identify their own preferred perspective. However, in many instances funders of studies may prefer analysis to be conducted solely from a more limited perspective. Thus, it is unclear whether a guideline should be prescriptive over the choice of study perspective.

*Source and nature of clinical data*. Within an economic analysis, there are 3 important issues relating to the source of clinical data: the source of efficacy/effectiveness data, adjustment for compliance, and modeling beyond the duration of a trial.

Economic analysis can be conducted based on the results of a single clinical trial or from a metaanalysis of all existing trials. Analysis based on a single clinical trial minimizes concern over economic analysis being based on data variables from a variety of unrelated sources[9]. However, analysis based on a single trial may be open to accusations of bias, given increasing evidence that results can vary substantially by the choice of trial[10]. Thus, results based on metaanalysis may be more acceptable and more precise, as well as potentially being more generalizable.

There is evidence that results of analysis are particularly sensitive to compliance with therapy[11]. Thus, it is necessary for a guideline to determine whether estimates of a therapy's effectiveness from clinical trials should be adjusted for compliance in a real world setting.

Many economists have argued that modeling beyond a clinical trial is unavoidable due to both the characteristics of clinical trial design and their limited duration[12]. Thus, modeling approaches control for the protocol induced effects of clinical trials and allow for modeling the longterm effects of therapy beyond the trial duration[12,13]. However, because of the complexity of such models, many studies have limited themselves to data collected solely within the clinical trial (for example, Reference 14).

*Study outcomes for cost-effectiveness analysis*. In a cost-effectiveness analysis, outcome is usually expressed in terms of a natural clinical unit, i.e., final outcomes such as life-years or surrogate outcomes such as fractures or proportion of patients meeting Amercian College of Rheumatology 20% improvement criteria. The choice of surrogate outcome is of crucial importance and should be based on criteria relating to acceptability and validity in relation to disease progression.

*Quality of life and utility measurement*. Within the design of an economic analysis, it is necessary to determine whether quality of life considerations should be incorporated. If so, quality of life can be incorporated through use of generic or disease-specific quality of life measures (e.g., the Medical Outcome Survey Short Form-36, or the Arthritis Impact Measurement Scale) or through utility measurement. Although the former measures may be more acceptable to clinicians, they are generally inappropriate for economic analysis. Utilities can be measured through direct assessment using tools such as standard gambles, time tradeoff,

and visual analog scales. Alternatively, they can be estimated by the use of validated questionnaires relating to different aspects of a patient's health status; these instruments have an associated scoring system or set of utility weights (e.g., EuroQol, Health Utilities Index). In addition, there is a lack of consensus over whose utility values for health states should be employed, the patients' or general public's[15].

*Toxicities*. Certain side effects of therapies can have significant effect on economic analysis in terms of the effect on both costs and quality of life. However, other side effects may only have a marginal impact. Thus, it is necessary to decide which side effects relevant to rheumatology therapies to consider. In addition, it may be necessary to consider the relationship between side effects and discontinuation of therapy and whether estimates of this impact can be best obtained from clinical trials or observational data.

*Resource use*. In measuring resource use and costs in an economic analysis, it is important that only those resource items that are expected to vary between therapies need to be considered. Thus, the relevant range of costs and resource use for an economic analysis is dependent on both the study perspective and the therapies of interest.

There is general agreement that ideally resource quantities and costs should be reported separately, thus facilitating the transferability of results between jurisdictions[16]. In addition, standards for the costing of health care resources have general acceptance[17].

*Discounting*. There is general consensus that costs and benefits that occur in the future or in different time periods should be adjusted, or discounted, to present values. This is based on the principal of a positive value of time preference, where individuals prefer to incur benefits sooner rather than later and costs later rather than sooner. However, there is a lack of consensus over what the appropriate discount rates are, and whether both benefits and costs should be discounted at the same rate[1-5,18-21]. The effect of the choice of discount rate has been shown to affect the results of evaluations[22].

*Allowance of uncertainty*. Because of uncertainty in estimates of resource use and effectiveness, there is consensus within guidelines that analyses should be conducted to assess how sensitive study results may be to changes in the value of key variables or assumptions[23]. However, there is less consensus over the preferred nature of such analyses.

*Distributional and budgetary effects*. Certain guidelines argue that discussion relating to the distributional and budgetary effects of an intervention should be included within an economic analysis (for example Reference 1). Others argue that such issues are inappropriate since they relate to decisions on the adoption of therapy, which vary with the level and geographical location of the decision maker.

Survey

Opinion leaders representing those undertaking and using economic analyses in rheumatology were surveyed using a template (Table 1). Respondents indicated their agreement or disagreement with a proposed reference case for future economic analyses. In addition, for areas where there is a lack of consensus in the literature, respondents indicated their own preferences. There were 25 respondents. The majority of respondents were clinicians with a demonstrated knowledge of economic evaluation issues.

## RESULTS

*Study funding*. There was a broad consensus that the source of study funding should be reported and that where necessary investigators should state that they had independence over all aspects of study design and analysis.

*Study purpose and population*. Respondents were in consensus that detailed patient characteristics for which the study was conducted should be stated. Respondents generally agreed that patient characteristics such as age and sex should be required, but disagreed over which clinical characteristics should be included.

*Comparators*. Respondents were equally divided over whether we should be prescriptive over the choice of study comparator. Only a minority of respondents favored the use of a designated comparator for any of the 4 scenarios. The majority of respondents believed that the most widely used therapy should be a comparator, although a significant proportion of respondents believed that the recommendation should be even less prescriptive.

*Study perspective*. Respondents preferred where possible the adoption of a societal perspective. Reflecting that the societal perspective is not always possible, respondents were also asked whether analysis from a third party payer perspective was an acceptable minimum. A sizeable minority of respondents opposed this (29%).

*Clinical data.* All respondents favored the use of efficacy data from clinical trials. However, respondents disagreed over whether data should be from single trials or a review of all available trials. There was a lack of agreement over whether estimates of efficacy should be adjusted for patient compliance and what would be the appropriate source for data on compliance.

Respondents disagreed over whether studies should be based on trial data alone or modeling beyond the trial or on a combination of both.

*Outcomes.* For each clinical scenario respondents favored the use of the proposed outcome measure, i.e., the American College of Rheumatology 20%/50% improvement for RA patients treated with DMARD; ulcer rates for RA patients treated with NSAID; WOMAC for OA patients treated with NSAID and DMARD; and fracture rates and, where appropriate, heart disease, breast cancer and endometrial cancer, for patients with osteoporosis.

*Table 1*. Content of survey.

- Study design issues
  - Funding
    - Statement of source
    - Statement of investigator independence
  - Statement of study purpose
  - Population characteristics
    - Details on minimum specific characteristics required for each clinical scenario
  - Preferred comparators
  - Perspective
- Clinical data
  - Source of clinical data — efficacy from single trial or metaanalysis
  - Should we adjust for compliance?
  - Analysis based on trial data alone or modelling beyond trial or both
  - How should data be modeled?
- Study outcomes
  - Natural units
    - Details on preferred outcomes required for each clinical scenario
  - Quality of life measurement
    - Disease-specific and/or generic
  - Utility measurement
    - Direct or indirect utility elicitation
  - Measurement of toxicities
  - Intervention-specific side effects
    - Details on necessary side effects by clinical scenario
- Resource use and costs
  - Details on preferred practice regarding reporting
- Analysis
  - Time preference
    - Choice of discount rate
  - Incremental cost-effectiveness ratio
  - Allowance for uncertainty
    - Details of preferred analyses

However, respondents also indicated that other variables may be appropriate for modeling: disease activity score, EULAR and remission rates for RA patients treated with DMARD; liver and renal events for RA patients treated with NSAID, and the HAQ for OA patients treated with NSAID.

*Quality of life and utility measurement*. All respondents recommended the inclusion of a disease-specific quality of life measure. About two-thirds of respondents were in favor of the use of a generic measure. Respondents did not demonstrate any strong preferences for specific measures as the most appropriate. Respondents were supportive of the inclusion of utility estimates. The majority of respondents recommended both direct and indirect methods of measurement, although fewer respondents recommended the use of indirect measures. Respondents were equally supportive of the 3 main methods of direct measurement (standard gambles, time tradeoff, and visual analog scales).

*Toxicities*. All respondents recommended the incorporation of toxicities into economic analyses. However, respondents differed in their recommendations over which toxicities needed to be measured and how they should be measured. In particular, certain respondents favored the use of toxicity indices. In addition, respondents disagreed over which of the resources arising from toxicities should be included.

*Resource use*. Respondents agreed that resource units and costs must be reported separately.

*Discounting*. Respondents agreed that adjustment for time preference was necessary. However, they disagreed over which rate should be recommended, with a slight majority of respondents favoring 3 to 5%.

*Allowance for uncertainty*. Respondents generally agreed that the minimum standard for sensitivity analysis should be a simple one way analysis of the major clinical, cost, and quality of life variables. Only a small minority of respondents favored the use of multiway sensitivity analysis, statistical tests for stochastic data, or Monte Carlo simulation techniques.

*Other issues*. The majority of respondents preferred that discussion of practical implementation issues, budgetary impact, and potential for realizing resource savings should be included in the reference case.

## DISCUSSION

These attempts to derive a reference case for economic analysis are not meant to set hard and fast rules for what should and should not be done. The reference case is an attempt to derive minimum standards for future studies to facilitate interstudy comparisons. Thus, respondents have

tended to be conservative concerning certain methodological issues such as sensitivity analysis and choice of variables, while they have remained prescriptive over other issues such as disclosure of funding. This has led to a great deal of consensus over many of the items within the proposed reference case.

The specific areas where consensus is apparent mirror areas of agreement between current guidelines, e.g., agreement over the use of data from randomized controlled trials, presentation of data in disaggregated format, discounting of future costs and benefits, and the need for sensitivity analysis.

Areas of disagreement can be classified into 2 distinct categories: disagreement reflecting a lack of consensus within current guidelines and disagreement over disease-specific issues not covered by current guidelines. Generally, none of the areas of agreement were contrary to current guidelines.

Disagreement over the choice of discount rate, study perspective, the use of direct or indirect utility measurements, and the source of these values and the use of single trials versus metaanalyses reflect the lack of consensus across current guidelines. For example, respondents' choice over the appropriate discount rate was related to the recommended rate for the specific guideline within their own country.

Disagreement over areas specific to the disease process are likely more problematic. Respondents differed over their choice of which patient characteristics need to be reported, what disease-specific outcomes should be the basis of any cost-effectiveness analysis, and what toxicities need to be recorded and how. Respondents also had minor disagreements regarding what disease-specific measure should be used to facilitate modeling beyond the trial duration. The lack of consensus over such disease-specific issues is crucial in terms of standardizing analysis within the 4 clinical scenarios of interest.

In addition, there was mild disagreement over the choice of study comparator. Respondents rejected the concept of a preferred comparator for all analyses. Instead, respondents favored flexibility over study comparator, reflecting that the appropriate comparator would vary across studies and jurisdictions, with the majority of respondents endorsing the use of the most widely used therapy as one study comparator.

A further area of disagreement was whether estimates of a therapy's effectiveness should incorporate information on compliance.

Thus the lack of consensus found in this survey reflects in part the content of the currently available guidelines. Such a lack of consensus should not be seen as a deterrent to the use of economic analysis, nor should it imply that a particular form of analysis is superior to another. Rather, it reflects the nature of economics as a discipline and the need for value rather than scientific based judgments with respect to certain study design issues[24]. Many general areas of disagreement such as the choice of discount rate, source of utility values, and study perspective can be adequately addressed through appropriate sensitivity analyses[23]. Of more concern is the lack of consensus over the clinical variables within a study design. A degree of consensus is required over disease-specific study variables such as outcomes for modeling. Otherwise, attempts to standardize studies to facilitate comparison and generalizability may be unsuccessful.

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