Summary

OMERACT 5 Economics Working Group: Summary, Recommendations, and Research Agenda

INTRODUCTION

Numerous reasons exist for the need to achieve consensus on economic evaluation methods. First, the recent explosion in the number of published economic analyses makes it important to identify key methodologic standards so that studies can be appropriately compared and critically appraised. Second, one of the primary objectives of economic evaluations is to make informed choices regarding the allocation of resources. This objective can only be achieved if the methodology of studies is broadly comparable. Otherwise, apparent differences in the relative cost-effectiveness of treatments may be attributable to differences in study methodology rather than to true differences in the cost-effectiveness of the therapies/interventions. Third, since the field of economic evaluation is still in development, the discussion of standardization of methods is an essential first step toward identifying research priorities. Fourth, several jurisdictions are now requiring economic evaluations as part of the decision-making process for reimbursement of health treatments and technologies. This has identified a number of methodological issues that require more discussion and debate. Finally, the emergence of innovative, highly effective, but costly new treatments for rheumatoid arthritis (RA) has created a need to more fully understand the economic implications of RA treatments.

With these reasons in mind, the OMERACT Economics Working Group developed a template for an economic evaluation reference case (or core data set) and undertook a survey of key opinion leaders, as outlined by Coyle, *et al* in these proceedings[1]. The survey indicated that, while there was consensus on some aspects of study methodology, there were a number of areas where additional discussion and debate are needed. Through these efforts, 6 major questions (and associated subquestions) were identified for discussion at the OMERACT 5 conference. This paper reports the responses, among approximately 150 participants, to those questions, summarizes the associated discussions, and identifies areas for further research.

RESPONSES TO QUESTIONS

1. Outcomes for cost-effectiveness analysis

Economic evaluations typically relate a change in a health outcome to a change in cost. However, there is a large potential set of outcomes that could be used. Some are clinical endpoints, such as ulcer bleeding rates or endoscopically determined lesions. Others are composite scores or descriptive measures of quality of life [e.g., the American College of Rheumatology (ACR) 20% Improvement Criteria, ACR 50, Western Ontario McMaster University Osteoarthritis Index]. Yet others are health utility measures used for the calculation of quality adjusted life years (QALY). The discussions under this question focused on the selection of outcome measures.

1a. Should we have preferred outcomes for cost-effectiveness analysis?

Yes	94%
No	1%
Don't know	5%

Although the preferred outcomes would depend on the disease, a large majority of participants felt that existing measures should be reviewed to determine those most useful for economic evaluation. For example, within RA, the "core set" could be reviewed to assess which of these measures best predicts longterm outcomes.

1b. Should these outcomes relate to intermediate outcomes (e.g., ACR20, bone mineral density) or final outcomes (e.g., workers, joint replacement, life years gained, QALY)?

Intermediate	1%
Final	6%
Both	92%
Don't know	1%

There was general agreement this was critically dependent on the stage of development of the drug or health technology being evaluated. At the time of launch of a new drug, it is rarely possible to have data on final outcomes. Therefore, modeling from intermediate endpoints is necessary. However, at a later stage, when the drug has been used in clinical practice, data on final outcomes may be available from longterm trials or from observational studies. The group was unified in their opinion that longterm outcomes data are most relevant from a patient's perspective and can be very useful in influencing payors.

1c. Should the effects of toxicity be included in economic analyses?

Yes	90%
No	3%
Don't know	1%

This response reflected the opinion that a complete evaluation of therapies in rheumatology must include toxicity. Indeed, it was pointed out that, for certain topics (i.e., the evaluation of nonsteroidal antiinflammatory drugs) adverse events (e.g., gastrointestinal bleeds) were the main discriminatory factor between alternative therapies. In addition, the group expressed some doubt about whether QALY could adequately capture all the consequences of toxicity. Instead, it was suggested that other measures also be used to more fully describe toxicity. The group deferred to the expertise of the OMERACT Toxicity Working Group.

1d. Should toxicity rates be based solely on the results of clinical trials, or should data from observational studies be used?

Clinical trials	4%
Observational studies	4%
Both	91%
Don't know	2%

Participants recognized that, while clinical trials presented an opportunity to measure toxicity, data from observational studies were also required because these more accurately reflect the use of drugs in the community over the long term. There was agreement that enrollees in clinical trials were not representative of people in the general community with the disease under study. Moreover, clinical trials of 3 or even 6 months' duration provide little insight into the toxicities that may occur after one or more years of treatment.

2. Source of data on clinical effectiveness for economic evaluations

Economic evaluation is critically dependent on data describing the relative effectiveness of the therapies being compared. These data should be unbiased, but should also be relevant to the setting under study. For example, clinical data from studies performed early in the life cycle of a health technology (e.g., prior to the launch of a new drug) are likely to relate to efficacy as opposed to effectiveness.

2a. Should analyses be based on results from single trials or from a metaanalysis of all available trials?

Single trials	10%
Metaanalysis	10%
Both	78%
Don't know	2%

Discussion reflected that complete reliance on one source of data is neither desirable nor feasible in all situations. Economic evaluations based on data from single trials could be biased if the trial or trials selected were not representative of all the available clinical effectiveness data. On the other hand, participants expressed a lack of confidence regarding the methodology of metaanalysis, and noted that such analyses may also be biased if based on a biased sample of small, poorly conducted, clinical trials. Moreover, a metaanalysis based on trials from a range of settings may not be relevant in the particular setting where the economic evaluation is being conducted. The group agreed, therefore, that choosing the most appropriate source of data depends on the specific circumstances of the study. A comprehensive, methodologically rigorous metaanalysis, if available, should be the first choice in most circumstances. However, a large well conducted controlled clinical trial in one's own setting may be the most appropriate source for clinical data for an economic evaluation. Finally, the group agreed that the use of both clinical trial and metaanalysis data would be ideal and would also provide us the opportunity to compare the influence of these 2 data sources on the results of the economic evalution.

3. Source of utilities

Elsewhere in these proceedings Suarez-Almazor, *et al*[2] illustrate that there are a number of methods for obtaining utilities for the calculation of QALY to be used in economic analyses. Their data indicate that the different methods can yield very different results. Further, some methods involve direct measurement from the patient or other respondent, while others involve indirect measurement, i.e., the patient's health state is first categorized (by using the HUI questionnaire, for example) and then assigned a utility weight derived from a previous survey (usually of the general population).

3a. What should be the preferred method for measuring utilities in a clinical trial including a cost-utility analysis?

Patient derived utilities	25%
Utilities obtained from the general public	9%
Both	61%
Don't know	5%

These responses partly reflected participants' uncertainties regarding the complex methodologies used for obtaining utility values. There was also recognition of the different purposes for obtaining utilities (e.g., broad allocation of health care resources or choosing treatments within rheumatology). Participants agreed that the purpose of a given study should always be stated. The group indicated a preference for patient derived utilities over indirect utilities, but acknowledged that indirect measurement may be useful in certain circumstances. Some participants also noted that it would be of interest to measure health professionals' utilities. It was recognized that these responses are in sharp contrast with the recommendations of health economists, which generally support the use of the general public's values. This is obviously an area where more discussion and debate must take place.

4. Use of modeling in economic evaluation

Since many clinical trials are of short duration, only rarely are final outcomes (e.g., survival) measured. The question arises whether observational data should be used to extrapolate outcomes beyond the end of the trial, in order to calculate life years or QALY gained.

4a. Is modeling beyond trial duration desirable?

Yes	63%
No	10%
Don't know	27%

Although a majority of participants were in favor of modeling, a significant proportion expressed concerns about the methods used in economic analysis models. For example, some models may not have provided good predictions in the past, and many have not been adequately validated. Clearly, the desirability of relying on models depends on the stage of development of the treatment or technology. At the time of drug launch it may be necessary to rely on the predictions of longterm outcomes, from a model. However, at a later stage it may be possible to produce actual data on longterm outcomes. The latter may be encouraged where possible.

It was also thought that consideration should be given to lengthening the followup period in clinical trials, since models constructed from a more lengthy observation period may be more valid. Also, consideration may also be given to gaining access to the data (e.g., from administrative databases) that would enable the construction of more comprehensive models.

5. Choice of comparator

Economic evaluation typically involves a comparison of 2 or more therapies; the selection of the comparator (to the therapy of interest) is an important methodologic decision, since the results of the evaluation can differ depending on the comparator chosen. Existing economic evaluation guidelines vary on this issue. Some argue that the comparator should be a single, widely used therapy, or a combination of a number of the most used treatments. Others suggest that the lowest cost therapy or no therapy should also be considered as comparators.

5a. What would be the desired comparator therapy for modeling studies?

Most widely used in your country	14%
Combination of commonly used	11%
Cheapest	0%
Most effective	12%
No therapy	0%
All of these	19%
Don't know	44%

The wide diversity of views on this topic partly reflected that the choice of comparator depends largely on the purpose of the study. However, it is clear that participants were against the use of the cheapest therapy or no therapy as the sole comparator in modeling studies. The group identified a number of other issues that may be important when deciding on the comparator. These include type of disease, disease severity, the country or setting, and the audience for the economic evaluation.

6. Compliance

Lack of compliance by patients can affect both efficacy and cost. Therefore, compliance can be an important determinant of cost-effectiveness and it is well known that compliance in usual clinical practice in the community differs from that observed in clinical trials. Thus, extrapolating compliance rates from clinical trials was not favored.

6a. Should we allow for compliance within economic analyses in rheumatology?

Yes	89%
No	3%
Don't know	8%

The large majority in favor of including compliance measures in economic analyses is consistent with the views of health economists, who believe that, as far as possible, economic evaluations should reflect the "real world." However, there was much more disagreement on how compliance should be measured, as indicated below.

6b. What measure of compliance should we use?

Withdrawal rate in clinical trials	6%
Patient questionnaire	6%
Pill counts	1%
Administrative datasets	2%
Other	6%
Don't know	21%
Combination of all of these	57%

Participants identified drawbacks with each of the methods; hence the view that a combination might be the optimal approach. In particular, it was emphasized that withdrawal from therapy during a controlled clinical trial is unlikely to be a good indicator of compliance in usual clinical practice, given the special context of trials. It was also noted that physician compliance may be of interest, although most of the discussion focused on measuring patient compliance. Finally, promising new methods currently being developed for measuring compliance (such as electronic pill boxes) were discussed.

RESEARCH AGENDA

A number of priorities for future research emerged during the discussions. They are listed below according to broad categories.

Outcomes

1. Determine the minimum set of clinical outcomes for each disease state.
2. Revisit the "core set" of outcomes to identify those measures that best predict longterm outcomes (such as QALY, work loss, etc.).
3. Assess how the results of the OMERACT Toxicity Study can be relevant to economic evaluation.
4. Develop a toxicity index suitable for use in economic evaluations.

5. Develop an observational database to assess longterm outcomes.

Source of effectiveness

Explore the feasibility of a 2 stage approval process for health technologies, giving preliminary approval at launch using efficacy data (combined with modeling), followed by a review at a later stage using data gathered in usual clinical care in a community setting.

Utilities

1. Undertake more comparative studies of direct and indirect utility measurement on arthritis patients.
2. Conduct international comparisons examining the validity and interpretability of utility scenarios.

Modeling

Develop methods for assessing the validity of models and undertake more validity checks of models used in the arthritis field.

Comparators

Determine which is the most relevant comparator (or comparators) for each of the clinical indications in which new therapies are being developed.

Compliance

Explore novel approaches to measuring compliance in clinical trials and incorporate these into economic evaluations.

CONCLUSIONS

Considerable progress has been made in defining standards for economic evaluation since OMERACT 2, where this topic was first discussed. A key goal throughout this process has been to build interdisciplinary collaborations among academic investigators, clinicians, regulatory experts, third party payors, and industry representatives. Through the OMERACT process, we have begun to build those critical collaborations. Beginning at OMERACT 4, we have carefully examined key methodological issues in economic evaluation in rheumatology, identifying those on which there is general agreement and those that require additional methodological research. As evidenced by the articles in this issue of *The Journal of Rheumatology*, we have already taken steps to begin to resolve some of these key methodological questions. The challenge before us now is to build upon and extend these initial findings, which will lead to a substantive methodological body of literature on economic evaluation in the rheumatic diseases. This body of work is the necessary next step to achieving our ultimate goal of creating common standards for economic evaluation in our discipline. Moreover, this effort will constitute an important contribution towards improving the science of economic evaluation.

SHERINE GABRIEL, MD, MSc, Department of Health Sciences Research and Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905. E-mail: gabriel.sherine@mayo.edu ; MICHAEL DRUMMOND, PhD, Centre for Health Economics, University of York, UK; DOUG COYLE, MS, Clinical Epidemiology Unit, Ottawa Hospital, Ottawa, Canada; MARIA E. SUAREZ-ALMAZOR, MD, Health Services Research, Baylor College of Medicine, Houston, TX, USA; BRIAN RUFF, FCP, Discovery Health, Parkview, South Africa; FRANCIS GUILLEMIN, MD, PhD, School of Public Health, Faculty of Medicine, Vandoeuvre-les-Nancy, France; CLAIRE BOMBARDIER, MD, University Health Network, Toronto, Canada; MAARTEN BOERS, MD, MSc, PhD, Department of Clinical Epidemiology, VU University Hospital, Amsterdam, The Netherlands; ANDREAS MAETZEL, MD, MSc, University Health Network, Toronto, Canada; JORGE RUOF, MD, Division of Rheumatology, Hannover Medical School, Hannover, Germany; ANN CRANNEY, MD, MSc, Department of Medicine, University of Ottawa, Ottawa; MICHAEL MARENTETTE, MBA, Health Economics, Patient Health Management, Merck Frosst Canada & Co., Kirkland, Quebec, Canada; PETER TUGWELL, MD, Department of Medicine, University of Ottawa, Ottawa, Canada.

Address reprint requests to Dr. Gabriel.

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