OMERACT 6 Economics Working Group Report: A Proposal for a Reference Case for Economic Evaluation in Rheumatoid Arthritis

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ABSTRACT. Standardization of methods for economic evaluation is essential for defining the methodological research agenda that will advance the discipline. Standardization also greatly facilitates the interpretation and comparison of the results of economic analyses. For these reasons, several jurisdictions now require economic evaluation, conducted according to standardized methodological guidelines, as a key ingredient in decision making for reimbursement of health treatments and technologies. The application of these general guidelines, however, can be difficult in the absence of disease-specific information. In the case of rheumatoid arthritis (RA), the recent emergence of innovative, highly effective, but also expensive treatments has created an immediate need to more fully understand the economic implications of RA treatments. With this background, the OMERACT Economics Working Group set out in 1994 to develop an RA-specific reference case for economic evaluation. This report summarizes the OMERACT process leading to specific recommendations on the 12 key elements of a proposed "reference case" for economic evaluation in RA. These elements include: study horizon, duration of therapy, extrapolation beyond trial duration, modeling beyond therapy, synthesis of comparisons where head-to-head trials do not exist, clinical outcome measures, mortality, valuation of health states, resource utilization, discontinuation of therapy, therapeutic sequence, and population risk stratification. Through these efforts, the OMERACT Economics Working Group aims to expedite and enhance the conduct and dissemination of methodological research in economic analyses in the rheumatic diseases. (J Rheumatol 2003;30:886–90)

Key Indexing Terms:
ECONOMIC EVALUATION OMERACT REFERENCE CASE

The goal of this report is to summarize the work of the OMERACT Economics Working Group. During the last 10 years, this group has focused on developing criteria for the standardization of methods for economic evaluation in rheumatology. We describe the process and the final consensus achieved on key elements of a proposed "reference case" for economic evaluation in rheumatoid arthritis (RA).

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Standardization is an essential first step towards identifying methodological research priorities that will eventually advance the field of economic evaluation. Thus, the scientific development of this evolving field will be greatly facilitated by methodological standardization. Another important reason for standardization is the ability to compare studies in different jurisdictions. Through such comparisons, the implementation of standards would greatly increase the value of economic evaluations to health care decision making. Indeed, several jurisdictions now require economic evaluation as a part of decision making for reimbursement of health treatments and technologies, and methodological guidelines for performing such studies have already been developed in several countries[1-6] (Table 1).

In spite of the existence of these general guidelines, however, numerous important methodological choices still need to be made. These include selection/inclusion of clinical outcomes, choice of utility values, source of comparative regimens, and modeling beyond trial duration, among others. Such choices are often determined by the nature of the disease under study. Thus, the application of these general guidelines is difficult in the absence of methodological standards that apply to the specific disorder being studied. In the case of RA, the recent emergence of innova-

Table 1. Existing guidelines or standards for economic evaluation. Details of most of these sets of guidelines can be found in Hjelmgren, *et al*[6],

Source	Purpose		
	Reimbursement or listing	Methodological Standards	Ethics and Conduct
Government or Payors	Australia	Canada	—
	Ontario	Public Health Service Panel, USA	
	The Netherlands	Academy of Managed Care	
	Portugal	Pharmacy, USA	
	Finland		
	United Kingdom		
Academia	Langley, *et al* (USA)	LDI Task Force, USA	LDI Task Force (USA)
	Alban, *et al* (Denmark)	Rovira, *et al,* Spain	
		Hannover, Germany	
		Belgian Society for Pharmacoepidemiology, Belgium	
		Government/Pharmaceutical Industry Working Party, UK	
		Garattini, *et al*, Italy	
		College of Economists, France	
Industry		Pharmaceutical Research and Manufacturers of America, USA	—

tive, highly effective, but also expensive treatments has created a need to more fully understand the economic implications of RA treatments. For all the above reasons, the OMERACT Economics Working Group set out in 1994 to develop an RA-specific reference case for economic evaluation.

The OMERACT Taskforce on Economic Evaluation was first assembled at OMERACT 2 in 1994. At this time, the group reviewed the literature on the principles and application of economic analyses in the rheumatic diseases[7]. The Economic Evaluation Taskforce met next at the American College of Rheumatology national meetings in 1997 and began to identify key elements of a reference case for RA, as well as a preliminary research agenda.

The results of this work were presented at OMERACT 4 in 1998 and published shortly after[8]. In April 2000, at OMERACT 5, the members of the Economics Group presented the results of original research that was aimed at addressing the methodological gaps identified in the previous report. These were synthesized into a document that summarized the methodological elements of consensus and of debate in economic evaluation of RA[9]. A special session of the OMERACT Economics Group was held in New York in February 2001, which consisted of in-depth discussion and debate of the 13 most controversial methodological elements. Preliminary reference case recommendations for each of these 13 methodological elements across 3 common rheumatological disorders, i.e., RA, osteoarthritis, and osteoporosis, were identified[10].

A survey was developed featuring the recommendations (Table 2). The survey was circulated for feedback to 290 relevant experts, i.e., clinical rheumatologists, clinical researchers, methodological experts, industry scientists, and policy makers. The latter group included key individuals from the Agency for HealthCare Research and Quality, Academy of Managed Care Pharmacy, Canadian Coordinating Office for Health Technology Assessment, Australian Commonwealth Department of Health, US Food and Drug Administration, European League Against Rheumatism, International League of Associations for Rheumatology, and National Institute for Clinical Excellence, among others. Although excellent comments and minor changes were suggested, the results of the survey demonstrated that there was no substantive disagreement on any of the recommendations. Four elements that were judged to be most relevant to the OMERACT constituencies were selected for further small group discussion at OMERACT[6]. Following the discussions in general and breakout sessions, recommendations on these 4 items were endorsed by a majority vote (see Table 3 for voting session results). The reference case recommendations resulting from this 8-year process are summarized in Table 4 and discussed below.

While it is recognized that the ideal study horizon is lifetime, the study horizon (methodological element 1) recommended for RA economic evaluation is a minimum of one year for trial based analyses and a minimum of 5–10 years for model based economic evaluations (Table 4). Therapy is assumed to be continuous, i.e., patients with RA are assumed to always be following a disease modifying antirheumatic drug regimen (element 2). We recommend a combination of clinical trial based analyses and extrapolation beyond trial duration, using mathematical models based on a synthesis of evidence from published observational studies and other sources (element 3). Expert opinion should only be used as a last resort (i.e., in the absence of any quan-

Table 2. Reference case developement questionnaire.

Methodological Issues[10]	Preliminary Proposed Recommendation	Agree	Disagree	Don't Know	Comments
Outcomes					
1. Outcome measures	ACR 20 sustained for 6 months EULAR improvement criteria Clinical adverse events				
2. Valuation of health (ie., sources for QALY)	Values from general population using direct measurement				
3. Classification and reporting of adverse events	Report adverse events with patients as the unit of analysis using common toxicity criteria (under development by OMERACT Toxicity Working Group)				
4. Mortality	Hazard for mortality from observational studies				
Comparators					
5. Comparisons in the absence of head-to-head trials	Not recommended due to uncertain validity of transitive comparisons				
6. Therapeutic strategies	Include modeling of most commonly used therapeutic strategy with sensitivity analysis to consider other strategies.				
Modeling					
7. Model horizon	One year				
8. Duration of therapy	Continuous				
9. Modeling beyond trial duration	No benefit or harm if therapy is stopped				
10. Discontinuation of therapy	Use discontinuation rates from observational studies				
11. Extrapolation beyond trial duration	Estimates of benefit based on trial data; estimates of withdrawal and longterm outcomes based on observational data				
12. Population risk stratification	Include clear definition of underlying population, including low and high-risk groups				
Costs					
13. Resource utilization	Include all associated direct medical costs in the analysis, but report indirect and nonmedical costs separately.				

QALY: Quality-of-life-years.

Table 3. Results of economic module voting among 250 attendees of OMERACT 6, April 14, 2002.

Question	Yes/Agree (%)	No/Disagree (%)	Don't Know (%)
1. Do you understand the concept of a reference case?	87	5	8
2. Clinical outcomes — All of the following should be included in determining the responder "state" as an effectiveness measure to estimating cost effectiveness: pain, function, inflammation, HRQoL, structural damage, toxicity comorbidity	64	31	8
a. Do we want to include pain in the reference case for economics?	90	7	3
b. Pain should be measured by:	VAS 84 Categorical 16		
c. Do we want to include a physical measure of function (e.g., HAQ)?	93	5	2
d. Do we want to include a measure of inflammation?	80	15	5
e. Do we want to include HRQoL?	83	14	3
f. Do we want to include a measure of structure (e.g., x-rays) as it relates to damage?	68	29	3
g. Do we want to include a measure of toxicity?	93	6	1
h. Do we want to include a measure of comorbidities?	77	19	4
3. Valuation of health status—patient's values for clinical choices, general public's values for health policy decisions	78	12	10
4. Comparisons in the absence of head-to-head trials—synthetic comparisons by using realtive effects from controlled trials	84	13	3
5. Discontinuation of therapy			
a. Analysis of censored cost data: When estimating mean costs in the presence of censoring due to discontinuation, we should adjust using appropriate statistical methods to allow for unequal exposure to risk of resource use	88	3	9
b. Differences in trials vs observational rates of discontinuation: We propose to use discontinuation rates from trials, adjusted using observational data	81	12	7
6. Extrapolation: Report trial data alone and extrapolate (model) using a synthesis of evidence from observational studies, trials, and other sources with sensitivity analysis	79	14	7

HAQ: Health Assessment Questionnaire; HRQoL: health related quality of life; SF36: Medical Outcome Study Short Form-36.

Table 4. Reference case recommendations for economic evaluations in RA.

Methodological Element	Recommendation
1. Study horizon	Trial based analysis, minimum 1 year; Model based analyses, minimum 5–10 yrs
2. Duration of therapy	Continuous
3. Extrapolation beyond trial duration	Report clinical trial data alone and extrapolate (model) using a synthesis of evidence from observational studies, trials, and other sources with sensitivity analysis (minimize use of expert opinion)
4. Modeling beyond therapy	No additional benefit or harm after therapy is stopped
5. Synthesis of comparisons where head-to-head trials do not exist	Synthetic comparisons by using relative effects from controlled trials
6. Clinical outcome measures	Joint count, Pain by VAS, Physical measure of function (e.g., HAQ), Measure of inflammation (CRP/ESR), HRQoL, Toxicity (report adverse events with patients as the unit of analysis)
7. Mortality	Hazard rates for mortality from observational studies
8. Valuation of health states (e.g., QALY)	Patients' values for clinical choices, general population's values for health policy decisions
9. Resource utilization	Include all associated direct medical and nonmedical costs in the analysis, but report indirect costs (productivity losses) separately When estimating mean costs in the presence of censoring due to discontinuation of therapy, adjust using appropriate statistical methods to allow for unequal exposure to risk of resource use
10. Discontinuation of therapy	Use discontinuation rates from trials, adjusted using observational data
11. Therapeutic sequence	Include modeling of most commonly used therapeutic sequence with sensitivity analysis to consider other strategies
12. Population risk stratification	Include clear definition of underlying population including low and high risk groups

VAS: visual analog scale; HAQ: Health Assessment Questionnaire; HRQoL: health related quality of life; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; QALY: quality-of-life-years.

titative data) because of the potential that such opinions may introduce bias into the analysis. Sensitivity analysis should be used to test the rigor of these models. Unless there is good evidence from trials, modeling beyond therapy duration should assume no additional benefit or harm (i.e., a return to baseline) once therapy is discontinued (element 4).

Synthetic comparisons based on relative effects from controlled trials can be used where head-to-head clinical trials are not available (element 5). Clinical outcome measures (element 6) should include absolute changes in the following: joint count (swollen and tender), pain (measured by visual analog scale), a physical measure of function such as the Health Assessment Questionnaire, a measure of inflammation such as erythrocyte sedimentation rate or C-reactive protein, a measure of health related quality of life, and toxicity measures (adverse effects are to be reported with patients as the unit of analysis).

The OMERACT/World Health Organization/American College of Rheumatology (ACR) core set, containing all the above except adverse effects, is the major clinical outcome set for assessing the efficacy of new treatments in clinical trials. Currently, relative change is used to calculate the ACR 20/50/70. The OMERACT Task Force on Minimal Clinical Important Difference is developing and testing measures of absolute change and achievement of target states using the core set. This will provide an appropriate measure of beneficial clinical outcome for the reference case for economic evaluation in RA.

The hazard rates for mortality (element 7) should be incorporated based on information from observational studies. Valuation of health states (element 8) should be incorporated using patients' values for clinical choices and the general population's values for health policy decisions. In terms of resource utilization (element 9), we recommend the inclusion of all associated medical and nonmedical direct costs in the analysis, but that indirect costs (i.e., productivity losses) be reported separately. When estimating mean costs in the presence of censoring due to discontinuation of therapy, we recommend adjustment by means of appropriate statistical methods to allow for unequal exposure to risk of resource use. Discontinuation rates from clinical trials should be used with adjustment using data from observational studies (element 10). Modeling of the most commonly used therapeutic sequences should be included along with sensitivity analyses to consider the effects of other sequences (element 11). Finally, the model should include clear definitions of the underlying populations, including low and high risk groups (element 12).

The OMERACT Health Economics Working Group is an active, engaged methodological team that has reported here the first disease-specific reference case recommendations for economic evaluation. The next major challenge for this group is dissemination of this proposed reference case. It is hoped that investigators and industry sponsors will encourage the application and use of these standards in future analyses. This is vital in order to provide feedback that will serve to further improve and strengthen the quality of the reference case. Future goals for this group include replicating the process to develop reference cases for osteoporosis and for osteoarthritis. Through these efforts, we aim

to expedite and enhance the conduct of methodological research in economic analysis in rheumatology, to encourage networking among clinicians, policy makers, pharmaceutical industry scientists, health economists, and statisticians, and to stimulate the transfer of the results of economic analyses into policy and practice through the use of rigorous, consensus based methodological standards.

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