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The ISPOR Good Practices for Quality Improvement of Cost-Effectiveness Research Task Force Report

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ABSTRACT

Objectives: The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Health Science Policy Council recommended and the ISPOR Board of Directors approved the formation of a Task Force to critically examine the major issues related to Quality Improvement in Cost-effectiveness Research (QICER). The Council's primary recommendation for this Task Force was that it should report on the quality of cost-effectiveness research and make recommendations to facilitate the improvement of pharmacoeconomics and health outcomes research and its use in stimulating better health care and policy. Task force members were knowledgeable and experienced in medicine, pharmacy, biostatistics, health policy and health-care decision-making, biomedical knowledge transfer, health economics, and pharmacoeconomics. They were drawn from industry, academia, consulting organizations, and advisors to governments and came from Japan, the Netherlands, Canada and the United States.

Methods: Face-to-face meetings of the Task Force were held at ISPOR North American and European meetings and teleconferences occurred every few months. Literature reviews and surveys were conducted and the first preliminary findings presented at an open forum at the May 2008 ISPOR meeting in Toronto. The final draft report was circulated to the expert reviewer group and then to the entire membership for comment. The draft report was posted on the ISPOR Web site in April 2009. All formal comments received were posted to the association Web site and presented for discussion at the Task Force forum during the ISPOR 14th Annual International Meeting in May 2009. Comments and feedback from the forums, reviewers and membership were considered in the final report. Once Task Force consensus was reached, the article was submitted to Value in Health.

Conclusions: The QICER Task Force recommends that ISPOR implement the following:

- With respect to CER guidelines, that ISPOR promote harmonization of guidelines, allowing for differences in application, regional needs and politics; evaluate available instruments or promote development of a new one that will allow standardized quantification of the impact of CER guidelines on the quality of CER studies; report periodically on those countries or regions that have developed guidelines; periodically evaluate the quality of published studies (those journals with CER guidances) or those submitted to decision-making bodies (as public transparency increases).
- With respect to methodologies, that ISPOR promote publication of methodological guidelines in more applied journals in more easily understandable format to transfer knowledge to researchers who need to apply more rigorous methods; promote full availability of models in electronic format to combat space restrictions in hardcopy publications; promote consistency of methodological review for all CER studies; promote adoption of explicit best practices guidelines among regulatory and reimbursement authorities; periodically update all ISPOR Task Force reports; periodically review use of ISPOR Task Force guidelines; periodically report on statistical and methodological challenges in HE; evaluate periodically whether ISPOR's methodological guidelines lead to improved quality; and support training and knowledge transfer of rigorous CER methodologies to researchers and health care decision-makers.
- With respect to publications, that ISPOR develop standard CER guidances to which journals will be able to refer their authors and their reviewers; lobby to establish these guidances within the International Committee for Medical Journal Editors (ICMJE) Requirements to which most journals refer in their Author Instructions; provide support in terms of additional reviewer expertise to those journals lacking appropriate reviewers; periodically report on journals publishing CER research; periodically report on the quality of CER publications; and support training and knowledge transfer of the use of these guidelines to researchers and reviewers.
- With respect to evidence-based health-care decision-making, that ISPOR recognize at its annual meetings those countries/agencies/private companies/researchers using CER well, and those practitioners and researchers supporting good patient use of CER in decision-making; and promote public presentation of case studies of applied use of CER concepts or guidelines.

Keywords: cost-effectiveness, guidelines, health economics, quality improvement.

Background to the Task Force

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Health Science Policy Council recommended that the ISPOR Board of Directors establish a Task Force to critically examine the major issues related to Quality Improvement in Cost-effectiveness Research (QICER) in July 2005. The Council's primary recommendation for this new Task Force was that it should report on the quality of cost-effectiveness research and make recommendations to facilitate the improvement of pharmacoeconomics and health outcomes research and its use in stimulating better health care and policy. The ISPOR Board of Directors approved creation of the Task Force in December 2005. An email was sent to all ISPOR members in March 2006 seeking candidates interested in serving on the leadership group or the expert reviewer group. Task Force leadership and reviewer groups were finalized by October 2006. Task Force members were knowledgeable and experienced in medicine, pharmacy, biostatistics, health policy and health care decision-making,

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biomedical knowledge transfer, health economics and pharmacoeconomics. They were drawn from industry, academia, consulting organizations, and advisors to governments and came from Japan, The Netherlands, Canada and the United States.

Face-to-face meetings of the Task Force were held at ISPOR North American and European meetings and teleconferences occurred every few months. Literature reviews and surveys were conducted and the first preliminary findings presented at an open forum at the May 2008 ISPOR meeting in Toronto. The final draft report was circulated to the expert reviewer group in March 2009 and then to the entire membership for comment in April 2009. The draft report was posted on the ISPOR web site in April 2009; 26 responses were received. All formal comments received were posted to the ISPOR Web site and presented for discussion at the Task Force forum during the ISPOR 14th Annual International Meeting in May 2009. Comments and feedback from the forums, reviewers and membership were considered in the final report. Once Task Force consensus was reached, the article was submitted to Value in Health.

Introduction

Quality assessment and continuous quality improvement has long been recognized as a vital process in all societal systems and organizations. In health care, critical review of interventions and reports on the quality of outcomes can help correct deficiencies and further advance efficiency and quality. Continuous quality improvement is integral to our global efforts to improve the economics and quality of life in all health care sectors and all patient populations. There is an important role for ISPOR in macro review and examination of quality and trends in pharmacoeconomics, health care economics research, and their resulting impact on global policies and practice.

Mission

The mission of the ISPOR Task Force on Quality Improvement in Cost-effectiveness Research (QICER) is to generate periodic quality reports and make recommendations to facilitate the improvement of pharmacoeconomics and health outcomes research, and its use in stimulating better health care and policy. This will be accomplished through periodic systematic reviews and surveys. The results and findings will be made available to ISPOR membership for comments and published as white papers and reports, including recommendations for future ISPOR initiatives, educational programs, and member services.

In this first report, the task force has focused primarily on cost-effectiveness research (CER). While broader topics in health economics and outcomes research (HEOR), such as patient reported outcomes, health-related quality of life, training, software, etc., are beyond the range of this first report, they are envisioned as targets for future work. The HEOR scope was, however, considered in our discussion of journals to capture a more holistic view of the current state of peer-reviewed publication and to position CER within a broader perspective.

As summarized in Figure 1, organizationally and individually, we embrace patients, providers, researchers, regulators, and payers to collectively advocate that scarce health care resources are allocated wisely, fairly, and efficiently. These health sector linkages are promoted through organizational services that facilitate education, communications, research, and international cooperation. Continuous quality improvement efforts are vital for improving activities and outcomes from international policies to individual patient care. The outside ring in the diagram depicts the classic phases for quality improvement that include: developing guidelines, designing guideline implementation, conducting interventions, measuring impact, analyzing outcomes, and the feedback for improved guidelines.

The Role of Guidelines in Quality Improvement

What role do guidelines play in promoting the quality and improvement of CER? It is usually assumed that the presence of guidelines leads to quality improvement, assuming that established guidelines increase credibility and usefulness by defining generally accepted standards and the requirements of specific users. However, in this field, there is not much evidence to support or disprove this assumption. A number of studies have evaluated the quality of research, but few have examined the relationship between the presence of guidelines and the quality of research. Two topics were examined: the availability of HEOR guidelines and the impact of guidelines on the quality of CER.

A few authors have reviewed available guidelines, comparing and contrasting them [1–3], and other resources are also available at: http://www.ISPOR.org; http://www.biomedcom.org/en/resources-BMC-databases.html. Most guidances have similar content with minor variations, but some significant differences do exist among them, most generally because of their intended purpose, the audience to be addressed, regional, cultural or political variation, or author or sponsor preferences.

How can the impact of guidelines on CER quality be measured? Most journals neither have specific guidelines or requirements for HEOR (see further discussion), nor do authors normally reveal which guidelines, if any, they observe. So despite easy accessibility of published articles, their quality, and the improvement of their quality, is not easily linked to specific guidelines. Those who measure the quality of HEOR publications [1,4–8] choose their own quality measures from those guidelines currently available and generally accepted standards.

Several formulary evaluation bodies (such as NICE in the UK [9], Canadian Agency for Drugs and Technology in Health (CADTH) in Canada [10], and PBS in Australia [11–13]) have developed specific guidances and requirements for HEOR studies submitted, but these studies are often not publicly available for evaluation in the short term. Some of these bodies have performed, or allowed, quality evaluation of studies submitted to them, which have been presented publicly [14] or published [15,16]. These often use small samples, are qualitative, and more importantly, not easily comparable across jurisdictions.

The Evolution of Guidelines

Guideline development began in Australia in 1992, followed closely by Canada and a few academic groups in the United States [17–19]. Their form has tended to reflect their purpose, e.g., those intended for reimbursement decision-making tend to be more prescriptive, while those with more academic purposes more descriptive (discussion of the appropriateness of each will be left to a future report focused specifically on guidelines).

Over the last decade, many countries have produced their own guidances and others are in development. There are currently about 39 CER guidances from 34 countries (with multiples from some countries). These have been produced by government bodies, by academic groups, and health-care insurers, and fre-

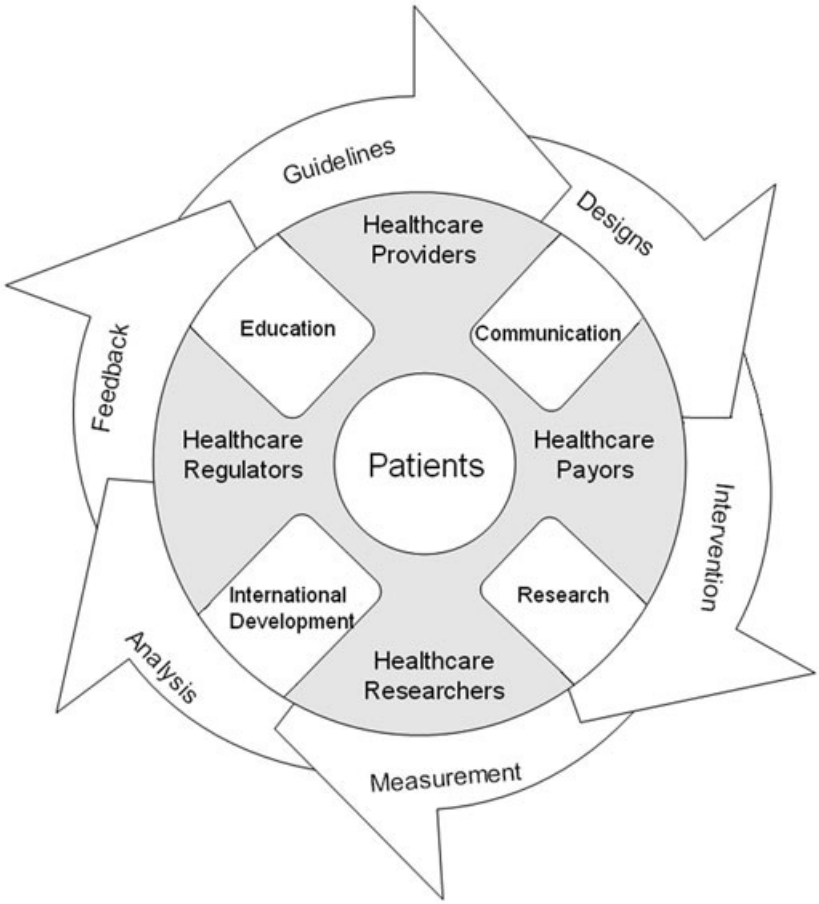

Figure 1 ISPOR vision and continuous quality improvement.

quently as collaborations among all three groups. Over half of these were prepared as part of formulary submission guidances or requirements. Table 1 summarizes those guidelines of which we are currently aware. The task force welcomes all feedback on publicly available new guidelines or updates not included here.

Measuring and Improving Guideline Quality

No instrument has been found that permits quantitative measurement of guideline quality, or comparison of guidelines. What publicly available information there is has been rather qualitative; for example, in the early days of guideline development, Regence BlueShield found that guidelines were practical from a logistics perspective, improving the relevance and timeliness of information available for decision-makers [54].

Although guidelines have not been quantitatively evaluated, there are some studies published evaluating the quality of studies submitted to the guideline-producing bodies. In one of these, Hill et al. evaluated 326 Australian studies and found significant issues in the interpretation of guidelines and in the conduct of studies [16]. In another, Colmenero et al. analyzed 53 economic studies submitted to US-managed care organizations and found low levels of compliance with accepted standards of CER research [55]. One pilot study did measure the relationship between specific guidelines and the quality of studies submitted [56]. Unfortunately, among published studies of the quality of studies, the measures used are not easily comparable.

If the impact of guidelines on quality of studies, and improvement of quality, is to be assessed rigorously, a tool is required that is quantifiable, anchored to guidelines, and to generally accepted practices, and comparable across guidelines, studies, and time. There does not appear to be an instrument that yet fits this objective, but possibly, one might be developed incorporating the most relevant aspects of existing tools. Some already in use that might be considered include: 1) Neumann et al. measured the quality of economic analyses in several studies over the last decade [5,6]; 2) Chiou et al. developed a grading system to measure the value and quality of CER analyses using the QHES instrument [1]; and 3) Goetghebeur et al. evaluated quality of 10 submissions to the Canadian Common Drug Review, assessing the studies submitted with respect to the CADTH requirements [56,57].

Future Work

Based on this preliminary review, there are a number of promising steps that could be taken with regard to guidelines as instruments in measuring and improving quality in CER:

1. Perform a formal evaluation of currently available instruments that might be used to quantify and compare the value of CER guidelines. If none are found that meet this need, adapt, develop, or promote the development of one.
2. Once an instrument is available to assess guideline quality, promote the harmonization of guidelines, allowing for differences in application, regional needs, and politics.

Table 1 Countries, regions, or groups with publicly available health economic research guidances

	Source
Australia	[11–13]
The Baltics (Latvia, Estonia & Lithuania)	[20]
Austria	[21]
Belgium	[22]
Brazil	[23]
Canada (CADTH, Ontario)	[24]
China	[25]
Finland	[26]
France	[27,28]
Germany	[29]
Hungary	[30]
Ireland	[31]
Israel	[32]
Italy	[33]
Mexico	[34]
The Netherlands	[35]
New Zealand	[36]
Norway	[37]
Poland	[38,39]
Portugal	[40]
Russia	[41]
Scotland	[42]
Singapore	[43]
Slovak Republic	[44]
South Korea	[45]
Spain	[46]
Sweden	[47]
Switzerland	[48]
Taiwan	[43]
UK (England and Wales)	[49]
USA (task force, Gold Panel, AMCP, WellPoint)	[50–53]

3. Concurrently, evaluate available instruments or promote development of one to quantify the impact of CER guidelines on the quality of CER studies. The outcomes of such an instrument should allow comparison across guidelines as well as comparison over time, to allow rigorous longitudinal evaluation of quality improvement.
4. Encourage adoption of and adherence to CER guidelines through training and knowledge transfer.

Statistics and Science

Introduction

There are a number of statistical issues in CER, which could benefit from standard approaches to address these issues. Recommendations for improving the statistical methods applied in the cost-effectiveness literature are presented. The statistical issues and their solutions are discussed separately for the two most common approaches to cost-effectiveness analyses, namely, clinical trial-based economic evaluations and decision modeling-based studies. Economic evaluations based on registry and administrative data sets have started gaining popularity in recent years, and several of the issues discussed herein also apply to such analyses. However, a comprehensive discussion of all the statistical issues and approaches to address such issues that arise in analyses of nonrandomized observational data are beyond the scope of this first article.

Statistical Issues in Clinical Trial–Based Economic Evaluations

A critical source of the evidence on costs and cost-effectiveness of new medical treatments comes from analyses of patient-level data on cost and effect collected as part of randomized clinical trials. The number of clinical trial–based economic evaluations has increased considerably over the last decade. In the same time frame, the field has matured substantially, including the advancement of, and a growing consensus about, appropriate statistical methods for analysis of costs and cost-effectiveness alongside clinical trials [58]. Systematic reviews suggest that published studies on clinical trial based economic evaluations have begun to use some of these new statistical techniques [59,60]. Nevertheless, there are still a substantial number of studies using statistical methods of poor quality. In addition, there still remain areas needing further research.

Joint comparison of costs and effects and estimation of sampling uncertainty. A joint comparison of costs and effects using the incremental cost-effectiveness ratio (ICER) or the incremental net monetary (health) benefit is a useful decision tool to help determine whether the new therapy offers good value relative to the alternative. The use of this tool is particularly important when there is a trade-off between costs and effects; that is, one therapy is both significantly more effective and more costly compared with the other therapy. If there is no trade-off between costs and effects, that is, when one therapy is significantly more effective and less costly when compared with the other therapy, this decision tool may not be necessary because that therapy is unambiguously dominant over its alternative. A third possibility occurs when the two treatments have the same effect. In this case, some authors have interpreted textbooks and guidelines on health economic evaluations to suggest that a cost minimization approach is sufficient (i.e., the lowest cost treatment is the treatment of choice) and there is no need to perform a joint comparison of costs and effects [61–64]. Nevertheless, as our understanding of sampling uncertainty for the comparison of costs and effects has grown, the cases where this interpretation is appropriate is not as common as previously thought. Because cost-effectiveness ratios and net monetary benefit estimated from trial data are the result of samples drawn from the population, one should report the uncertainty in this outcome that derives from such sampling. Identification of methods such as confidence intervals for cost-effectiveness ratios [65–68], acceptability curves [69], and confidence intervals for net monetary benefit [70] for the measurement of this uncertainty have been important methodologic developments in the economic evaluation of medical therapies [71,72]. As a result of uncertainty, the cost-minimization approach has been shown to be rarely appropriate as a method of analysis and the need for a joint comparison still remains under most circumstances [73]. Alternatively, observing no significant difference in costs and effects alone need not rule out that one can still be confident that one of the two therapies is good value because it is possible to have more confidence in the combined outcome of differences in costs and effects than in either outcome alone. In these cases, one should jointly compare costs and effects, and one should report on their sampling uncertainty.

Analysis of cost data. For all economic analysis calculations, costs and cost differences between treatment groups should be expressed by the use of the arithmetic mean, and not medians, because this summary measure permits a budgetary assessment of treatment ($N \times$ arithmetic mean = total cost) and is the statistic of interest for health-care policy decisions [58]. Because of the often highly skewed distribution of cost data, the normality assumption underlying the parametric *t* test is often called into question and standard nonparametric tests (e.g., Mann-Whitney U-test or Wilcoxon rank-sum test), or parametric tests on normalizing transformations (e.g., log transformation) are often

used as a substitute. Yet these popular alternatives are not appropriate for drawing statistical inferences on differences in arithmetic mean costs [74–76]. For example, when one uses a *t* test to evaluate the log of costs, the resulting *P*-value has direct applicability to the difference in the log of costs and to the difference in the geometric mean of costs. It may or may not be directly applicable to the arithmetic mean costs. A Mann-Whitney U-test tests differences in the median of costs. Thus, statistical inferences about these other statistics may not be representative of inferences about the differences in arithmetic mean, which is the statistic of interest. If one does not want to adopt a parametric *t* test to directly test for differences in arithmetic mean costs, one can compare the arithmetic means by using a nonparametric bootstrap. This procedure has the added advantage of avoiding a parametric assumption about the distribution of costs. As a result, the nonparametric bootstrap has increasingly been recommended either as a check on the robustness of standard parametric *t* tests, or as the primary statistical test for making inferences about arithmetic means for moderately sized samples of highly skewed cost data [76–78].

Many clinical trial-based economic evaluations are limited to univariate analyses of costs. Even if treatment is assigned in a randomized setting, there are advantages to using multivariable techniques to analyze costs. Multivariable analysis of costs may be superior to univariate analysis because it improves the power for tests of differences between groups (by explaining variation due to other causes). It also facilitates subgroup analyses for cost-effectiveness, for example, more and less severe; different countries/centers, etc. Finally, it accounts for potentially large and influential variations in economic conditions and practice patterns by provider, center, or country that may not be balanced by randomization. Adoption of multivariable analysis does not, however, avoid the issues that arise in the univariate analysis of cost. For example, regressions on the logarithmic transformation of costs were previously considered an ideal remedy to the violation of the assumption of normally distributed error term that underlies ordinary least squares regression. Nevertheless, as the shortcomings of multiple regression models of log transformed costs became more widely publicized [75], the use of the generalized linear models have become the more acceptable alternative [79–81].

Handling of censored cost data. Incomplete or censored cost data occur in most randomized trials that follow participants for clinically meaningful lengths of time; yet they are often not addressed in the analysis. The ISPOR RCT-CEA taskforce recommended that "ignoring small amounts of missing data is acceptable if a reasonable case can be made that doing so is unlikely to bias treatment group comparisons [58]. However, no clear guidance exists for how much censoring is too much. Hence, whether or not cost data were incomplete, the amount of incomplete data and the statistical method adopted to address any problems posed by incomplete data should routinely be reported in trial-based analyses [58] Many studies in the literature have adopted naïve approaches wherein censored observations are either excluded from analysis (i.e., complete-case analysis) or included as though they were complete observations, (i.e., full sample analysis). In the first naïve approach, only the uncensored cases are used in the estimation of mean cost and this method is biased toward the costs of the patients with shorter survival times because patients with larger survival times are more likely to be censored [82,83] Also, completely discarding patients with censored data can lead to the loss of information and statistical power, which can be problematic if the percentage of censored cases is high. The second naive approach that uses all cases without differentiating between censored and uncensored observations is always biased downward, because the costs incurred after censoring times are not accounted for [83]. Although there exists a mix of approaches to impute the cost data, recent statistical interest in addressing censored cost data has led to the proposal of several methods of estimation that explicitly account for incomplete cost data due to loss-to-follow-up [82,84–95] It is well established that these methods are prone to less bias and return a better estimate of sampling variance than other naive estimation methods [82,83,87,89,96–98].

Sample size and power. Prior to the development of methods for assessing sampling uncertainty for the joint comparison of cost and effect, health economists commonly attempted to estimate sample size based on the larger of the sample sizes needed for estimating prespecified cost and effect differences—i.e., what sample size was required to identify a $1000 difference in costs, and what was required to identify a 10% reduction in mortality. With the development of methods for assessing uncertainty, sample size calculations should now be based on the sample size needed to rule out that the net monetary benefits of the intervention are less than zero [99–102]. Often economic evaluations are piggy-backed on clinical trials with a prespecified sample size. In such instances, researchers should estimate and report the power available to rule out cost-effectiveness ratios that exceed the maximum willingness to pay.

Evaluating transferability (generalizability) of trial results. Multinational clinical trials are the norm for the evaluation of new medical therapies. However, the presence of between-country heterogeneity in trials has led to a growing concern that the pooled or average economic results from multinational trials may not be reflective of the results that would be observed in individual countries that participated in the trial [103]. Common sources for concern about the representativeness of data from multinational trials include transnational differences in morbidity/mortality patterns; practice patterns (i.e., medical service use); and absolute and relative prices for medical service use (i.e., price weights). The use of trial-wide clinical results, trial-wide medical service use, and price weights from a single country has been one of the commonly proposed, potentially inadequate solutions to the problem of transferability (e.g., to tailor the results to the UK, simply use UK price weights, and conduct the analysis as if all participants were treated in the UK). A second potentially inadequate solution has been to use trial-wide clinical results, and country-specific medical service use and price weights. Both approaches have the failing that they ignore the fact that clinical and economic outcomes may influence one another. That is, differences in cost may affect practice patterns, which in turn may affect outcome; differences in practice pattern may affect outcome, which in turn may affect cost. The ISPOR Good Research Practices task force on Economic Data Transferability has recently recommended good research practices for dealing with aspects of transferability including three proposed statistical methods that use patient-level data to address transferability: detection of heterogeneity [104,105], fixed effects models [106,107] and multilevel, or hierarchical models [108–115].

Decision Models

The estimation of the full economic effects of health technologies generally requires the extrapolation of clinical trial evidence beyond the follow-up period through the use of decision modeling techniques to synthesize data from various sources. The aim

of the modeling study is to aid decision-makers in making decisions under uncertainty. Obviously, the results of modeling studies will only be helpful to decision-makers if the study is performed according to current standards. While the quality of cost-effectiveness analyses has improved over time, still current studies do not address all issues appropriately [5,113]. It is clear that guidance is important for those performing modeling studies. In several countries, authorities have formulated guidelines, and ISPOR has also published guidelines through the task force on Good Research Practice in Modeling Studies [116]. Some of the most important issues where quality might be improved, and some new methodological topics that have emerged in the past few years, are discussed.

Methods for evidence synthesis. The ISPOR task force on Good Research Practice in Modeling Studies suggested in their report that systematic review should be conducted on key model inputs. There are various ways of synthesizing the evidence found in various studies (e.g., fixed or random effects meta-analysis, either frequentist or Bayesian), but there is not one optimal method of synthesizing data currently available [117], and the typical meta-analyses cannot straightforwardly be applied to synthesize data for cost-effectiveness models.

One reason is that meta-analysis has been developed to combine quantitative results of several similar studies into a pooled estimate of the treatment effect (e.g., odds ratio, relative risk, difference in change from baseline). It uses the magnitude of the treatment effect and its uncertainty from each individual study to produce a weighted mean of the treatment effect [118,119]. However, in modeling studies, the parameter to be estimated is not only a treatment effect like the odds ratio of having an event. Typically, models contain parameters like transition probabilities between disease states, event probabilities, rate ratios of treatment effects, quality of life or utility values, and costs. These parameters have different distributions which need to be combined. Moreover, the comparator needs to be modeled too, meaning that we are dealing with more heterogeneity than usually remains after the variance in treatment effect has been corrected for the variance in comparator-effect.

Second, meta-analyses have traditionally been performed on studies that compare the same intervention with the same comparator. However, comprehensive decision analytic models aim to identify the most cost-effective treatment among the entire spectrum of all relevant treatment options. This issue may be dealt with through so-called mixed treatment comparisons, which combine multiple different pairwise comparisons across a range of different interventions [120–123]. In mixed treatment comparisons, the relative effect of a treatment compared to a range of alternatives is estimated by including indirect comparisons of two interventions through a common comparator. Evidence from direct and indirect comparisons are analyzed simultaneously, which allows estimates of treatment effects in the absence of head-to-head comparisons. Such mixed treatment comparisons are inevitable in modeling cost-effectiveness.

The fact that the choice between fixed and random effects model and between a Bayesian and a frequentist approach can have a large impact on the outcome of the model underlines the need for complete transparency in the reporting of a modeling study.

Probabilistic sensitivity analysis. Sensitivity analysis should always be an integral part of a modeling study: input parameters of the model are varied to see if and how the outcome changes.

For a long time, the common type of sensitivity analysis was a deterministic one-way or multi-way analysis, in which one or more (usually not more than three) parameters are varied between certain limits. In the last few years, however, more and more studies include a probabilistic sensitivity analysis, in which (ideally) all input variables are varied simultaneously, according to probability distributions [124]. Such an analysis presents information on all possible outcomes, as well as on the likelihood of these outcomes.

In their report, the ISPOR task force on Good Research Practice in Modeling Studies stresses the need to include a sensitivity analysis as part of the modeling study. While those task force guidelines mentions that deterministic and probabilistic analyses are equally appropriate, other guidelines such as the UK and Dutch guidelines strongly prefer a probabilistic sensitivity analysis as a way to correctly represent parameter uncertainty. However, there are still good reasons to also include deterministic sensitivity analysis in a modeling study, such as to account for other types of uncertainty such as uncertainty relating to the structure and assumption of decision models [125]. Series of sensitivity analyses may be done to look at the consequence of changing different assumptions and scenarios in a model. Recently, however, an article was published exploring the option of explicitly incorporating structural uncertainties into the model [126].

Value-of-information. In the last few years, much attention has been given to Value-of-Information (VOI) analysis [127,128]. This type of analysis addresses the question of what the value is of collecting additional information to eliminate or reduce uncertainty, since making the wrong decision comes with a cost that is equal to the benefits forgone because of the wrong decision. These expected costs of uncertainty can be determined by 1) the probability that a decision based on the current ICER is wrong; and 2) the size of the opportunity loss if the wrong decision is made.

The first step in a VOI analysis is the estimation of the expected value of perfect information, which is the maximum amount the decision-maker should be willing to pay to eliminate all uncertainty in the decision. The next step is to calculate the expected value of partial perfect information, which is the maximum amount the decision-maker should be willing to pay to eliminate all uncertainty on one parameter or subset of parameters [129], Based on the latter analyses, priorities may be set for further research. The final part of the VOI is to calculate the expected value of sampling information, which is the maximum amount the decision-maker should be willing to pay to reduce uncertainty through a sample of a certain size and to set this against the costs of obtaining that sample [130].

VOI analysis is important in situations where a decision-maker might prefer to postpone making a decision to collect more information. Basing that decision merely on the outcomes of sensitivity analyses would lead to suboptimal decision-making. As suggested by the ISPOR task force on Good Research Practice in Modeling Studies "The decision to obtain additional data to inform a model should be based on a balance between the expected value of the additional information and the cost of the information."

Model validation. The final part of any model development should concern validation. Several types of validation may be distinguished, among which are: face validity, internal validation, between-model validation, predictive (or prospective) validation, and external validation [116,131].

Face validity means that the results produced by a model look valid at first inspection. If for example a model for pneumococcal vaccination results in so many cases of otitis media that every

child under four would have at least four episodes per year, one might question this result. Such unexpected results are always reason to thoroughly check the model and the inputs.

Internal validation concerns the comparison of model outputs with data used in the model development. While this type of validation is straightforward if the model is based on one source of data, it becomes more complicated if the model is based on a synthesis from various sources of data. It is possible that no model input can be chosen so that the model validates well against each separate data source. However, good effort should at least be made to describe the deviations from the data sources and possible explanations.

Between-model validation involves comparison of the current model and published or publicly available models. If the results differ, an attempt should be made to clarify whether these discrepancies are because of difference in model structure or model input.

Predictive validation aims to compare model results to newly available data from the same data source that was used as model input. On the other hand, external validation concerns the comparison of model results to data from studies not used in the model development. These types of validation are not always possible; if a model contains all data currently available, there is no data source for external validation. As the ISPOR task force on Good Research Practice in Modeling Studies remarks, ". . . it is not necessary that every data estimate or structural assumption be tested in prospective studies, in advance of model use." However, they also stress that models should never be regarded as immutable. They should be updated and possible abandoned as new evidence becomes available to inform structure or input values. If models are inconsistent with the new evidence but have not been amended to calibrate against this evidence, the model should be abandoned until such recalibration has been finished.

The validation phase of model development should be seen as important as all other phases. Researchers should document their validation procedure, and report it in their publications.

How Can We Make the Science Better?

The International Society for Pharmacoeconomics and Outcomes Research has published best practices document for the design, conduct, and reporting of economic analyses alongside clinical trials as well as decision modeling studies [58,116]. Whether explicit guidelines alone will foster improvements in the quality of future studies remains a question, given evidence that such guidelines have had minimal or slow impact in improving the quality of subsequent studies [3,64,132,133].

Part of this problem may be that most of the advances in the statistical techniques for analyzing cost data have been published in highly technical economic or biostatistics journals. Although some applied researchers may not be reading such literature, many may have difficulty understanding the rationale for and implementation of these technical methods. There is clear need for publication in more applied journals that focus on explaining these technical advances in an easily understandable format to support knowledge transfer to researchers who need to apply these newer methods. In addition, there is an equally clear need for better training and education so that researchers can understand more sophisticated techniques. Another problem in raising the quality of studies is space. Transparency of a model is of utmost importance for modeling studies to be taken seriously, both within the health economics community and among clinicians and decision-makers. To achieve full transparency, the model or detailed model description should be made available in electronic format, since it is often not possible to describe every detail of the model sufficiently in an article because of space restrictions.

Additional efforts to improve the quality of future studies may involve providing tools to peer reviewers for both funding agencies and journals so as to identify studies that fail to apply best practices. For example, peer reviewers might be provided with a clear check list of all requirements. Thus, all studies are reviewed consistently, hopefully leading to an increased quality. Regulatory and reimbursement authorities should also explicitly adopt best practices guidelines and uphold all economic data submissions to these high standards while making reimbursement decisions.

Journals and Publication Quality

Journal publication plays a critical role in quality improvement of CER research. This can be done by establishing requirements and guidelines for the conduct and reporting of the various types of studies that comprise the field, through the peer-review process, by dissemination of studies, by peer feedback, and as an ongoing learning process for researchers. Although published work may include abstracts, posters and podium presentations, newsletters and other non peer-reviewed publications (such as educational texts, patient information and marketing materials), for the purposes of this first report the focus has been on peer-reviewed journal publications because these are most accessible and easiest to track.

There are a great many journals globally. To determine how many of these routinely accept and publish articles relevant to HEOR, and how many of these provide or require guidelines for the conduct and reporting of these studies, a survey of the World Association of Medical Editors (WAME; http://www.wame.org) was carried out. This organization represents more than 965 biomedical journals, from more than 91 countries, from all geographic regions of the world. As such, WAME was an ideal source of information relevant to quality improvement in HEOR publication. In the survey which all WAME members were invited to participate, they were asked about journal type, location, scope, circulation, whether they accepted HEOR articles and which types of studies, and how they found reviewers for this type of work. They were also asked whether any HEOR or CER guidelines were recommended or mandatory for authors or reviewers, and if so, which ones.

Of the 965 journals represented in WAME, 55 (6%) responded to the survey. These came from 29 countries and all continents, with 45% representation for North America and Europe. Almost all (98%) were peer reviewed, and the majority (72%) international in readership. Most respondents (83%) were high-level editorial staff. Journal readerships encompassed clinical and academic health-care researchers (76% of respondents), health-care decision-makers, health service researchers, and medical generalists, and specialists (50–67%), health-care policymakers (40%), and other types of readers (37%) (students, patients, or the general public, the paramedical professions, other areas of academia).

The vast majority (92%) of journals accepted all or some types of HEOR work. Of the 10 categories of HEOR research published by respondents (Fig. 2), epidemiological burden of illness studies, database analyses and systematic reviews or meta-analyses were most commonly reported (77–79%), registry studies, clinical trials with economic or resource utilization data, economic burden of illness studies and epidemiological modeling studies were reported by about half the respondents (46–62%), and economic modeling, naturalistic clinical trials were least frequently reported (37–40%).

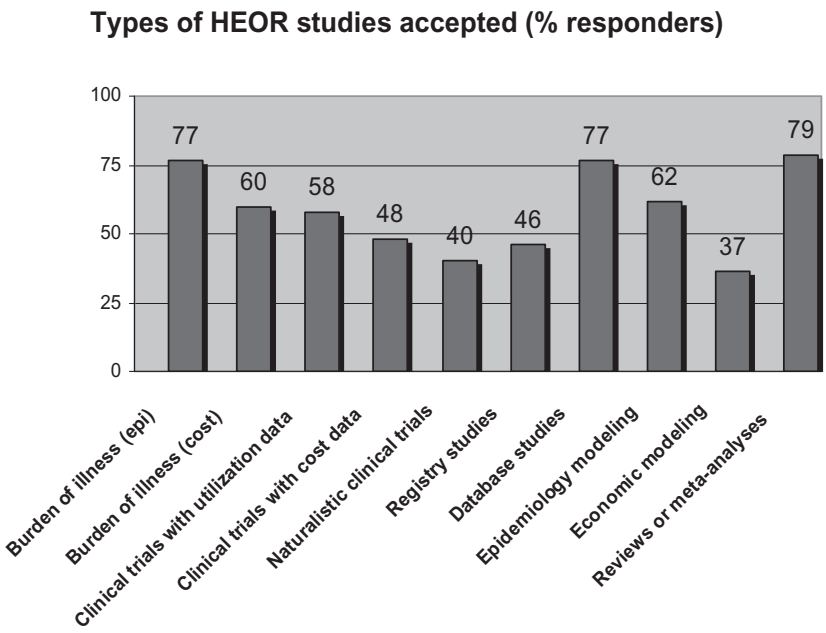

Figure 2 Types of Health Economic and Outcomes Research (HEOR) articles accepted for publication by journals responding to the QICER survey.

Although most journals recommended directly in their Author Instructions the International Committee of Medical Journal Editors (ICMJE) requirements (which includes references to no economic guidelines but some HEOR-relevant guidances [MOOSE (meta-analysis of observational studies in epidemiology), CONSORT (RCTs), STARD (studies of diagnostic accuracy), QUORUM (systematic reviews and meta-analyses) and STROBE (observational epidemiology studies)] or other specialized guidances (QUORUM, STROBE, CONSORT, STARD, and two references for basic statistics), none of the journals provided their own HEOR guidance, and only 4 of the 54 responding journals recommended the BMJ health economic study guidelines [64]. The Cochrane Web site did, however, have links to some PRO and HEOR guidances.

About 58% of journals did not provide their reviewers with any guidelines for evaluating HEOR studies. For the 42% who said they did, in all cases, these were the same as author guidelines (e.g., instructions to authors, ICJME) and only rarely specific to HEOR.

Journals were asked if they would consider using a standard set of HEOR guidances from a recognized professional body to enhance the quality of published HEOR research in their journal; 91% said they would if these were made available.

When asked about the ease with which they found reviewers for HEOR articles, 27% of journals had great difficulty, 60% said it was difficult for some types of articles, and 6% had no difficulty. Almost 90% of respondents felt it would be useful if they had a pool of expertise available to perform reviews of HEOR for their journal. The areas of expertise specifically mentioned covered the spectrum of HEOR research: policy analysis, economic outcomes, resource utilization, clinical epidemiology, public health, preventive medicine, mental health (and other specialties), statistics, and methodologies.

Although this survey sample size was small, a fairly representative range of journals responded and several clear messages were heard. 1) Many biomedical journals accept and publish HEOR research; 2) Almost all do so without giving clear guidance to either authors or reviewers about quality standards for this type of research so discussion of quality control at either the article production stage or the peer-review stage is currently moot. HEOR quality is currently left entirely up to the skill, knowledge and experience of each author and reviewer; 3) Most respondents expressed interest in clear guidances to which they could refer; and 4) many of the respondents reported difficulty finding expert reviewers for HEOR, and almost all were interested in having a larger pool of reviewers.

Future Plans

First steps in improving the quality of HEOR research in publications would be to: 1) develop standard guidances to which journals are able to refer their authors and their reviewers; 2) lobby to establish these guidances within the ICJME Requirements to which most journals refer in their Author Instructions; 3) provide some form of support in terms of additional expertise to those journals without appropriate reviewers. Finally, 4) it would be worthwhile to resurvey WAME members to gauge change over time.

There are also a few research groups who from time to time perform evaluations of HEOR research quality in the published literature [4,6,8,134]. It would perhaps be more useful for these evaluations to use quantitative quality measures that might be compared across evaluations, and follow the evolution of these over time. This might be an ISPOR sponsored initiative, or one undertaken by one or more of the groups currently involved in such evaluations. Rather than reinventing the wheel, it would be worthwhile to examine possible quantitative measures already established, such as the QHES (Quality of Health Economic Studies) instrument [1,7]. A search for other instruments already in development is recommended.

Finally, once standardized, quantitative quality measures have been established, we recommend ongoing assessment of the quality of published HEOR and its reporting through longitudinal sampling of the literature and other publications, perhaps with annual or biannual reports.

Decision-Makers, Practitioners and Evidence-Based Medicine

The Simplest Scheme Model (SSM)

The process of health care decision-making in the era of evidence-based medicine (EBM) can be described by the simplest scheme model (SSM) with three steps:

1. generating evidence by researchers and compiling this evidence in databases;
2. extracting and interpreting evidence from these databases by decision-makers or EBM practitioners; and
3. applying this evidence in health care settings at local levels.

The three-step scheme (SSM) is a clue to the barriers to use and application of cost-effectiveness results faced by decision-makers and clinical practitioners. The second step might result in some information loss or inappropriate interpretation, an evidence gap. Since decision-makers rarely access the full range of evidence from databases, there could be gaps between stored evidence and that extracted in forms such as partial evidence, abstracts, conclusions, executive summaries, commentaries, translations, etc.

In general, practitioners of EBM and decision-makers in health care tend to regard CER as of limited use, even though it must be considered for rational resource allocation in health care. Some obstacles result from insufficient knowledge or skills in cost-effectiveness analysis. Such insufficiencies are related to the "evidence gap" mentioned above, and may lead to skepticism about cost-effectiveness research, often bringing decision-makers to doubt the quality of the studies and the data.

One classic finding on limitations comes from a study [63] which surveyed almost 800 UK decision-makers. The authors concluded that the use of health economic evidence at the local level was not extensive. The major reasons for such a limited use were the inflexibility of budgets, limiting movement of resources between primary and secondary care, and the inability to free resources to adopt new interventions. These issues are related to the third step in the SSM. It was also reported that decision-makers were concerned about the credibility of the studies themselves, specifically with respect to large numbers of assumptions and industry funding. These are validity or credibility issues associated with the first step in the SSM.

Another limitation was reported by a survey [135] which conducted interviews with 17 pairs of UK NHS decision-makers. It raised the issue of technical terms employed in pharmacoeconomics. Some of key words in health economic outcomes research, such as incremental cost-effectiveness ratios, quality-adjusted life years, and willingness to pay, were either not understood or considered irrelevant by decision-makers surveyed. This issue is related to an evidence gap at the second step of the SSM. These studies shed light on key barriers to the use of CER in health care decision-making: validity, generalizability, and local level decision-making.

Some of treatments to overcome such limitations observed in the SSM were investigated by Crump et al. [136] who undertook interviews with12 medical decision-makers in the UK Leicestershire Health Authority, part of the European Network on Methodology and Application of Economic Evaluation Techniques project [137]. Factors identified that encouraged decision-makers to make more use of economic evaluations were: appraisal of studies by a trusted source; increasing flexibility in health care budgets; and better explanation of the practical relevance of study results.

The Evidence and Value: Impact on Decision-Making (EVIDEM) Model

The EVIDEM [56,57,138–142] model is somewhat more detailed than SSM. The basic framework from evidence to decision-maker is similar to that of SSM, but EVIDEM deals with more sophisticated subprocesses in the decision-making scheme, which includes:

1. Providing relevant evidence;
2. Assessing evidence for HTA report;
   a. Synthesizing evidence with weights; and
   b. Quantifying quality of evidence with quality matrix resulting in scores.
3. Evaluating intrinsic values based on Multicriteria Decision Analysis with weights and scores; and
4. Evaluating extrinsic values leading to decisions.

Given any intervention setting in health care, the EVIDEM team clarifies the practical framework for decision-making, provides relevant evidence, supports the deliberative process, and shares the decisions transparently. One of the advantages for the EVIDEM model is to bridge health technology assessment and multi-criteria decision analysis in a transparent and quantifiable approach.

Discussion

As for economic evaluations and decision-making framework, one study [143] was conducted by drawing on decision-makers from two UK health authorities, Leicestershire and North Yorkshire, employing the National Health Service Economic Evaluation Database (NHS EED) [144] as a research vehicle. It confirmed that decision-makers generally recognize the usefulness and necessity of published cost-effective evidence in informing their decision-making processes. However, they often regarded the value of studies limited because of poor generalizability, narrowness of research questions, and lack of methodological rigor, all of which are common seen in published articles. As reported previously [136], using trusted sources to appraise studies encouraged decision-makers to use CER studies, as well as having a quality-scoring system for published studies and not just the critical summaries from NHS EED.

The same research group [143,145] argued that there could be two approaches to addressing the problem: changes to the performance of economic evaluation and changes to the process of decision-making in the NHS. However, they continue to concentrate on one side of the problem, exploring ways to make economic studies more accessible without losing the key elements of critical appraisal. Nevertheless, they also state that: 1) it would be productive to examine some of the potential flaws in health care decision-making; 2) they share concern about requests for quality scores which might lead to even less critical assessment of findings; and 3) cost-effectiveness analysis makes the shortcomings of the clinical data much more apparent. Regarding the quality of clinical effectiveness data in economic studies, we need to find out whether the problem is: the lack of good-quality data for economic evaluations or the lack of available good clinical data for economic studies performed in time of need. There is often a problem of a long and inexplicable lag between the publication of the first clinical data and the subsequent publication of the first cost-effectiveness study [146]; it was suggested that there should be better strategic planning connecting clinical and economic research plans.

The other study [145] pointed out the general assumption has been that if decision-makers do not find economic evaluations useful, then the way the evaluations are conducted or presented

must be changed. Also if an economic decision framework is not satisfactory for decision-makers, it must be assumed there is a different and superior model for decision-making. In addition, they questioned how decisions are made by health authorities for service planning and resource allocation without substantive economic input. To promote better use of cost-effective evidence among NHS decision-makers, it was suggested:

- changing the process for NHS decision-making;
- changing policies on funding local economic studies and expertise; and
- using decision-makers with a better grasp of economics.

They insisted that the changes above might be more appropriate than modifying economic methods to inform unclear decision process.

In an effort to better understand HEOR researchers and decision-makers, a Web-based survey was conducted of all ISPOR members, to which 122 responded. The aim of the survey was to understand the degree of incorporation of HEOR in decision-making [147].

Thirty-four percent (n = 42) of respondents identified themselves as a drug, medical device or diagnostic treatment decision-makers. Years of experience as a decision-maker were categorized as: less than one year, 1–5 years, 6–10 years, 16–20 years, or greater than 20 years. The majority of respondents had between one and five years of experience. Approximately a quarter of the respondents were members of a Pharmacy & Therapeutics Committees, and a fifth were practicing pharmacists. The majority resided in the US, followed by the United Kingdom, Germany, Canada, and Japan.

All respondents had read articles containing HE information; the majority had read articles related to other common terms in HEOR. Overall, 95% of reported receiving formal training; 90% had some training in pharmacoeconomics, and only 40% formal training regarding burden of illness and patient-reported outcomes. The term training here referred to "formal schooling, attended courses, worked with an expert or read extensively." Ninety-five percent of decision-makers believed the training helped them in selecting appropriate interventions, 86% used some form of HE analysis to make decisions. Cost-effectiveness and cost-minimization analyses were the most common analyses used. Seventy-nine percent of respondents had conducted some type of HE analysis. Again, cost-effectiveness and cost minimization analyses were the most common. Seventy-five percent of decision-makers considered HE and/or outcomes research in their last intervention decision.

In reaching out to decision-makers and practitioners, a sophisticated decision-making model such as EVIDEM should be considered. An advantage of the EVIDEM model is its inner structure that separates intrinsic and extrinsic values.

Recommendations

To recognize true value of CER and to establish evidence-based decisions, the QICER task force recommends that ISPOR implement the following:

- Promote comparative effectiveness and outcomes research to generate evidence hierarchy;
- Develop, validate, and revise a decision-making model to fill the gap between health care researchers and practitioners (or decision-makers) associated with the concept of continuous quality improvement;
- Establish the science, from generating evidence to making an evidence-based policy, taking into account how to integrate intrinsic and extrinsic values with multi-criteria decisions;
- Provide the right information at the right time in health care delivery;
- Translate clinical research into clinical decisions and actions; and
- Promote communications with practitioners and decision-makers who are faced with the challenges as how to better understand complex socioeconomic evaluations, how to improve the decisions, and how to seek the rationality of reasoning.

QICER Final Report Recommendations

The QICER Task Force recommends that ISPOR implement the following:

Guidelines

- Promote harmonization of CER guidelines, allowing for differences in application, regional needs and politics;
- Evaluate available instruments or promote development of one to quantify the impact of CER guidelines on the quality of CER studies;
- Report periodically on available guidelines;
- Evaluate periodically the quality of studies submitted to decision-making bodies (as public transparency increases) and journals (preferably with standardized CER guidelines); and
- Develop trainings for researchers and others using CER guidelines, and promote effective mechanisms of continuous knowledge transfer.

Methodologies

- Promote publication of methodological guidelines in more applied journals in more easily understandable format to transfer knowledge to researchers who need to apply more rigorous methods;
- Promote full availability of models in electronic format to combat space restrictions in hardcopy publications;
- Promote consistency of methodological review for all CER studies;
- Promote adoption of explicit best practices guidelines among regulatory and reimbursement authorities;
- Periodically update all ISPOR Task Force reports;
- Periodically review use of ISPOR Task Force guidelines and their impact on CER quality; and
- Periodically report on statistical and methodological challenges in CER.

Publications

- Develop standard HEOR conduct and reporting guidance (beginning with CER) to which journals may refer their authors and their reviewers;
- Lobby to establish these guidances within the ICMJE Requirements to which most journals refer in their Author Instructions;
- Provide support in terms of additional reviewer expertise to those journals without appropriate reviewers;
- Periodically report on journals publishing CER; and
- Periodically report on the quality of CER publications.

Decision-making

- Recognize those countries/agencies/practitioners/ private companies using CER well at least annually;
- Recognize those practitioners/researchers supporting patient use of CER in decision-making at least annually; and
- Promote frequent presentation of case studies of the applied use of CER concepts or guidelines.

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