Panel 2: Methodological Issues in Conducting Pharmacoeconomic Evaluations—Modeling Studies

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The goal of this panel was to identify key contentious methodology issues in conducting healthcare pharmacoeconomic evaluations in the context of modeling studies. Its specific objectives were to:

• identify and prioritize the key issues associated with pharmacoeconomic modeling studies;
• identify a plan of action to resolve these issues;
• recommend next steps.

Background and Context

The primary purpose of modeling is to inform the decision-making process [1,2]. One considerable benefit of model formalization is that the uncertainties and assumptions in this process are made explicit and transparent.

To estimate costs and outcomes, existing data are frequently insufficient to allow optimal healthcare decision-making. Each type of data (retrospective, prospective, meta-analysis, expert opinion) has inherent strengths and weaknesses. Good modeling practice incorporates the best available evidence from all possible sources into a set of explicit parameters.

Although randomized clinical trials (RCTs) are the gold standard for clinical research, they are not always the best source of pharmacoeconomic and outcomes data. RCT-based data collection is often too costly, too time-consuming, or otherwise not feasible. Sometimes modeling is the only accessible means to inform the clinical and healthcare decision-making process [3]. Although useful for determining efficacy, data from RCTs have significant limitations that sharply reduce their usefulness for measuring the clinical outcomes and economic consequences of drug use in actual populations, including:

• limited duration of follow-up, often only weeks or months;
• exclusion or under-representation of many types of patients, especially the vulnerable;
• sample sizes too small to detect infrequent events;
• atypical treatment settings, providers, and subjects, which may influence compliance, event rates, and costs;
• no assessment of healthcare utilization in routine care.

Mathematical modeling allows a rational and scientific approach to overcoming these inherent limitations of RCTs, using the best available evidence.

Problem Statement

Currently there are two major obstacles confronting modeling methodology. How do we optimize the production of useful information for health economic decision-makers, and how do we encourage its acceptance and use?

Issues

There are seven key areas of controversy in modeling methodology:

1. standardization;
2. making choices;
3. methodological development;
4. extending clinical studies and data issues;
5. effectiveness measures;
6. model validation;
7. peer review.
Standardization

Comparability is the essence that determines the preference of one intervention among alternatives; differences in cost-effectiveness should reflect true differences and not unnecessary differences in method. This panel is not the first to recognize the need for consensus on a set of standards that will promote comparability of studies.

When resources are limited, how are they allocated to programs important to the respective segments of society? The Panel on Cost-effectiveness in Health and Medicine [4] recommended cost-effectiveness analysis (CEA) from a societal perspective for policy decision-making on healthcare resource allocation. They recommended a standardized reference case analysis across all CEAs regardless of the intervention or outcome to provide the methodological uniformity that supports comparability.

Besides health, real-world decisions include other considerations such as access to services, helping the most vulnerable, and other values impacted by health decisions. Economic assessment is only one of the tools decision-makers must use, and the information it provides must be weighed within the context of these other criteria. Values outside of healthcare, which often influence choices about health services, cannot be quantified in CEA. Cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), and cost-consequence analysis (CCA) are complementary and the use of one does not preclude the use of others in a study. Although quality-adjusted life-years (QALYs) have the advantage that they measure changes in quality as well as quantity of life, as currently defined, they do not reflect perfectly everything about health that matters to people, and perhaps never can.

The Panel on Cost-effectiveness in Health and Medicine [4] made recommendations concerning items of intervention and outcome to be included in the numerator and the items for the denominator for a reference case scenario. Most are based on reasonable facts, but some are arbitrarily chosen and recommended for a reference case to maintain consistency across studies. At present, there is still no standard guide to good modeling practices that can be used as a teaching or reference tool. No clear taxonomy of modeling techniques has been documented, and there are no standardized presentation formats.

Making Choices

Beyond standardization, in each study a number of choices are made to fit the model to the research question. Wherever choices are made, conservative values of all parameters should be chosen, and the base case should represent the most plausible assumptions.

When deciding on perspective, societal perspective, which includes all relevant cost and outcomes consequences, is preferable. Certain options in decision-making will be cost-effective from the societal perspective and not from the patient’s perspective. Resource allocation decisions are based on cost-effectiveness evaluated at a specific level. Decisions made at a higher level will affect the resource availability at lower levels. For example, at the societal (governmental) level, policy decisions on resource allocation are made based on the largest proportion of the public affected. When individual perspective is examined, that segment of the population afflicted with a condition evaluated as secondary for resource allocation purposes would need to seek resources elsewhere, and their cost-effectiveness model would have to take this into account. Many healthcare providers find the societal perspective irrelevant for their purposes; a great deal of controversy continues concerning the use of a narrower perspective and whether it should only be presented accompanied by the societal perspective.

Choice of the costs of an intervention from the governmental or societal perspective will take into account the actual wholesale price (AWP) or discounted wholesale price (DWP). From the patient perspective there is a question of which price to use. Are cost and price the same? Should the actual price paid be used, or should the discounted retail price, the brand-name drug prices, or generic drug prices be used? Each decision should be transparent and based on sound rationale.

Choice of assumptions should be realistic, reflecting available data. No model perfectly represents reality; its validity rests on whether its assumptions are reasonable in light of the needs and purposes of the decision-maker and whether after close examination its implications make sense. In making discounting decisions, both costs and benefits should be done at the same rate, a standard of care should be used as the appropriate comparator, and the time horizon should be the duration of time a drug can be expected to meaningfully impact the patient’s health.

Methodological Development

A limitation of decision-tree models is that they are not well suited to represent recurrent events over time [5,6]. In chronic diseases, outcome
events such as complications of the disease or its treatment, recurrence of disease, and mortality, are confounded frequently during a lifetime, with probabilities that change with time, age, and health status. Rather than model each event as a separate branch of a complex decision tree, health economic modeling methodology has room for maturation and refinement to allow more efficient mathematical representations of such events. Current alternatives in development include state-transition models, difference equations, deterministic models, and stochastic models, or discrete event simulations [7].

**Extending Clinical Studies and Data Issues**

Some degree of modeling is usually necessary to assess clinical outcomes and economic consequences beyond the necessarily limited parameters of a clinical trial, and modeling represents the only appropriate analytic approach to estimate healthcare utilization, practice patterns, and other costs associated with observations across defined geographic areas or treatment settings, such as from country to country, health management organization to fee-for-service, or government to private [8].

Many cost and outcomes distributions violate standard normality assumptions, and outliers can have a major impact on results. There are substantial problems with aggregation bias when costs and outcomes are averaged or combined for large groups such as disease related group (DRG) reimbursement levels or average length of stay. As far as possible, data should be analyzed at the individual level for both costs and outcomes. Many still question whether RCT data should be made available to support individual-level analyses.

Analysis of data from all study subjects is necessary to support interpretation of clinical trial data for pharmacoeconomic modeling. However, although intent-to-treat analysis is important, it is not necessarily the only way to analyze RCT data for modeling.

**Effectiveness Measures**

Several other issues arise in the estimation of effectiveness for modeling methodology: specification of survival parameters; use of disease-specific or total mortality data; modeling patient characteristics; using models to vary program parameters; use of modeling to address lead-time and length biases; estimating uncertainties. The techniques that exist to deal with these issues are serviceable, but have not yet achieved state-of-the-art status or standardization.

Parameter uncertainty is generally handled on a qualitative basis with either univariate or multivariate sensitivity analysis or max-min analysis, or quantified using statistical approaches such as the Delta method, joint confidence intervals, bootstrapped estimates, or Monte Carlo simulation. No proven method exists to validate structure uncertainty in a model due to either the parameter values assigned or to the mathematical form in which the parameter values are combined, except to compute C/E ratio estimates for each alternative structural assumption and examine appropriateness of the results. Even process uncertainty is an unknown. Would any two analysts follow the same model, or if the same problem were posed to an analyst a second time (without awareness of the first result), would the same model be followed?

While it is generally agreed that proper application of multivariate sensitivity analysis is necessary, there is ongoing controversy over its value.

**Model Validation**

As a mathematical device, and as a potentially important component of healthcare decision-making, credibility of a pharmacoeconomic model rests on its validity. Besides an estimate of the range of uncertainty of its parameters, each model should be shown to demonstrate face validity and predictive validity. Wherever possible, models should be validated against other data sets.

**Peer Review of Models**

To ensure the quality and enhance the acceptability of pharmacoeconomic modeling, all models should undergo systematic peer review before presentation. This could be a standardized audit of the structure, process, and validity of the model and would ensure that all salient model results are transparent. A technical peer review would necessitate passing an electronic copy of the computer model to the reviewer(s), which raises questions about the handling of proprietary property and confidentiality.

**Recommendations and Next Steps**

The following recommendations address the seven issues identified:

- Working towards general acceptance that modeling of both costs and effectiveness is a valid and often essential method to inform healthcare decision-making will be necessary to es-
establish modeling as an invaluable healthcare decision-making tool.

- Because the usefulness of modeling studies is necessarily based on comparability, it is important to assemble a consensus of opinion on standardized practices and policies.
- Once standardization has been achieved, a reference text of these practices should be prepared and disseminated.
- Pharmacoeconomic claims based on these generally accepted modeling approaches should be permitted by regulatory agencies, and should always include transparency and appropriate disclaimers such as: “This economic analysis is based on assumptions and simulations concerning the efficacy of [drug name] that meet FDA criteria for claims of efficacy.” Any model that relies on assumptions about a drug’s efficacy that are not based on data from RCTs must prominently disclose such limitation in any promotion.
- We recommend that as an independent professional association of pharmacoeconomic and outcomes researchers, ISPOR take the initiative of assembling a balanced international panel of thought-leaders and end-users in the field of modeling to develop a package of generally accepted modeling practices, building upon previously published work.
- Once these practices have been documented, the goal of ISPOR should be to encourage all stakeholders (professional societies, manufacturing associations, journals, government agencies, regulatory agencies, payers, and healthcare providers) to accept these as standards and to endorse their use.

Summary

Mathematical modeling is a potentially invaluable tool to assist the health economic decision-making process. It serves a unique methodological function. However, its practical value is currently limited by:

- insufficient standardization;
- meager documentation of practices and policies;
- no systematic quality surveillance;
- a low level of acceptance by regulatory agencies and end users.

We hope that by supporting the development of standard practices, policy consensus, and a peer review process, the use and acceptability of health economic modeling will be potentiated.

References