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Model Parameter Estimation and Uncertainty: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6

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A B S T R A C T

A model's purpose is to inform medical decisions and health care resource allocation. Modelers employ quantitative methods to structure the clinical, epidemiological, and economic evidence base and gain qualitative insight to assist decision makers in making better decisions. From a policy perspective, the value of a model-based analysis lies not simply in its ability to generate a precise point estimate for a specific outcome but also in the systematic examination and responsible reporting of uncertainty surrounding this outcome and the ultimate decision being addressed. Different concepts relating to uncertainty in decision modeling are explored. Stochastic (first-order) uncertainty is distinguished from both parameter (second-order) uncertainty and from heterogeneity, with structural uncertainty relating to the model itself forming another level of uncertainty to consider. The article argues that the estimation of point estimates and uncertainty in parameters is part of a single process and explores the link between parameter uncertainty through to decision uncertainty and the relationship to value of information analysis. The article also makes extensive recommendations around the reporting of uncertainty, in terms of both deterministic sensitivity analysis techniques and probabilistic methods. Expected value of perfect information is argued to be the most appropriate presentational technique, alongside cost-effectiveness acceptability curves, for representing decision uncertainty from probabilistic analysis.

Keywords: best practices, heterogeneity, sensitivity analysis, uncertainty analysis, value of information.

Background to the Task Force

A new Good Research Practices in Modeling Task Force was approved by the International Society for Pharmacoeconomics and Outcomes Research Board of Directors in 2010, and the Society for Medical Decision Making was invited to join the effort. The Task Force cochairs and members are expert developers and experienced model users from academia, industry, and government, with representation from many countries. Several teleconferences and hosted information sessions during scientific meetings of the Societies culminated in an in-person meeting of the Task Force as a whole, held in Boston in March 2011. Draft recommendations were discussed and subsequently edited and circulated to the Task Force members in the form of a survey where each one was asked to agree or disagree with each recommendation, and if the latter, to provide the reasons. Each group received the results of the survey and endeavored to address all issues. The final drafts of the articles were available on the ISPOR and Society for Medical Decision Making Web sites for general comment. A second group of experts was invited to formally review the articles. The comments received were addressed, and the final version of each article was prepared. (A copy of the original draft article, as well as the reviewer comments and author responses, is available at the ISPOR Web site: http://www.ispor.org/workpaper/Model-Parameter-Estimation-and-Uncertainty-Analysis.asp). A summary of these articles was presented at a plenary session at the ISPOR 16th Annual International Meeting in Baltimore, MD, in May 2011, and again at the 33rd Annual Meeting of the Society for Medical Decision Making in Chicago, IL, in October 2011. These articles are jointly published in the Societies' respective journals, *Value in Health* and *Medical Decision Making*. Other articles in this series [1–6] describe best practices for conceptualizing models, building and applying particular types of models, and transparency and validation. This article addresses best practices for parameter estimation and uncertainty analysis and is intended to apply to all types of models. Examples are cited throughout, without implying endorsement or preeminence of the articles referenced.

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Introduction

This report adopts the Task Force's view that a model's purpose is to inform medical decisions and health care resource allocation. Modelers employ quantitative methods to structure the clinical, epidemiological, and economic evidence base and gain qualitative insight to assist decision makers in making better decisions. From a policy perspective, a model-based analysis's value lies not simply in its ability to generate a precise point estimate for a specific outcome but also in the systematic examination and responsible reporting of uncertainty surrounding this outcome and the ultimate decision being addressed. These are the hallmarks of good modeling practice.

The extent to which an uncertainty analysis can be considered "fit for purpose" in part depends on the decision(s) the modeling seeks to support. Uncertainty analysis can serve two main purposes: assess confidence in a chosen course of action and ascertain the value of collecting additional information to better inform the decision.

Many models are designed to help decision makers maximize a given outcome (e.g., cases identified in a screening model or quality-adjusted life-years in a cost-effectiveness model), subject, perhaps, to one or more limiting constraints (such as a fixed budget). The model generates point estimates of the outcome for each possible course of action; the "best" choice is the one that maximizes the outcome subject to the constraint. If the decision maker has to make a resource allocation decision now, has no role in commissioning or mandating further research, and cannot delay the decision or review it in the future, then the role of uncertainty analysis is limited and the decision should be based only on expected values (although some commentators have argued that for nonlinear models, probabilistic sensitivity analysis (PSA) is required to generate appropriate expected values [7]). Nevertheless, decision makers may want to gauge confidence in the "best choice's" appropriateness by exploring its robustness to changes in the model's inputs.

Increasingly, models are developed to guide decisions of particular bodies (e.g., organizations responsible for deciding whether to reimburse a new pharmaceutical). Such decision makers who have the authority to delay decisions or review them later, based on research they commission or mandate, should be interested not just in expected cost-effectiveness but also in a thorough uncertainty analysis and the value of additional research. Such information, as well as assessments of factors such as the costs of reversing a decision shown to be suboptimal as further information emerges, and the cost of research and the likelihood of undertaking it, can influence the array of decisions available. Thus, uncertainty analysis conveys not only qualitative information about the critical uncertainties surrounding a decision but also quantitative information about the decision maker's priorities in allocating resources to further research.

Many models are developed for general dissemination, without a specific decision maker in mind. Such models could inform a range of decision makers with varying responsibilities. Here, there is a case for undertaking a full uncertainty analysis, thus allowing different decision makers to take from the analysis what they require given the decisions with which they are charged.

Best practices

VI-1 The systematic examination and responsible reporting of uncertainty are hallmarks of good modeling practice. All modeling studies should include an uncertainty assessment as it pertains to the decision problem being addressed.

VI-2 The decision-maker's role should be considered when presenting uncertainty analyses. The analytic perspective description should include an explicit statement regarding what is assumed about the decision-makers' power to delay or review decisions and to commission or mandate further research.

Background and Terminology

It is important to be precise concerning the terminology used in this article, which is sometimes confused in the literature (reflecting the multidisciplinary nature of decision modeling in health care). In particular, stochastic (first-order) uncertainty is distinguished from both parameter (second-order) uncertainty and from heterogeneity. Furthermore, each concept is argued to have an analogous form within a "regression-type" model in statistics. As in regression analysis, the structural uncertainty associated with the model itself must also be considered. Table 1 summarizes the concepts used here and preferred terminology, lists other terms used, and provides the link to statistical regression.

The term "parameter uncertainty" is not the same as the uncertainty around the realization of individual events or outcomes. This "stochastic uncertainty" relates to the fact that individuals facing the same probabilities and outcomes will experience the effects of a disease or intervention differently, just as a fair coin might come up heads or tails on any given toss (e.g., the first patient in a sample might respond to a treatment but the next may not; the first may not experience an adverse effect but the second may; the first may stay in hospital for 2 days and the second for 3 days). Parameter uncertainty ("second-order uncertainty") relates to the fact that the probabilities that govern outcomes are themselves uncertain, because they are estimated quantities (e.g., 100 tosses of a fair coin will not always lead to 50 realizations of "heads" and fifty "tails"). Estimates of the probability of "heads" based on 100 observations are uncertain. The sample size informing that estimate and variance in the data contribute to determining the parameter uncertainty. Parameter uncertainty also arises

Table 1 – Uncertainty for decision modeling: Concepts and terminology.

Preferred term	Concept	Other terms sometimes employed	Analogous concept in regression
Stochastic uncertainty	Random variability in outcomes between identical patients	Variability Monte Carlo error First-order uncertainty	Error term
Parameter uncertainty	The uncertainty in estimation of the parameter of interest	Second-order uncertainty	Standard error of the estimate
Heterogeneity	The variability between patients that can be attributed to characteristics of those patients	Variability Observed or explained heterogeneity	Beta coefficients (or the extent to which the dependent variable varies by patient characteristics)
Structural uncertainty	The assumptions inherent in the decision model	Model uncertainty	The form of the regression model (e.g., linear, log-linear)