Current Issues in Pharmacoeconomic Modeling

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The Editor of the Journal of Health Technology Assessment invited me to comment on some current issues in pharmacoeconomic modeling. Most of these relate to how pharmacoeconomic models should be constructed and how health care policy decision-makers should interpret model results when important clinical or other drug profile information is incomplete, unavailable or must be projected from dissimilar patient populations or treatment scenarios.

Generally speaking, if important drug characteristics (e.g., safety, efficacy, long-term outcomes, etc.) are unknown for a particular target patient category, then pharmacoeconomic modeling cannot replace this fundamentally missing information. On the other hand, health care decision makers still have to develop drug usage guidelines when drug or treatment information is uncertain, incomplete or otherwise unavailable for all patient categories. There are few, if any, situations where complete information, particularly head-to-head randomized clinical trials (RCTs), exists for all possible drug or treatment comparators for all patient sub-groups. But even when clinical knowledge is uncertain or incomplete, pharmacoeconomic models, when well-constructed, transparent and clear, can provide useful information; particularly regarding how treatment decisions would change with alternative model parameter assumptions or treatment scenarios.1,2)

Question 1. How do you choose the right alternatives to be compared when there are no alternatives in the target patient group for the new drug? What evidence do you use when one of the alternatives has no clinical trial information for that target patient group?

The comparison of alternative treatments in situations where at least one of the comparators has not been evaluated in head-to-head comparisons against other alternatives for one or more population sub-groups falls into the general category of Indirect Treatment Comparisons (ITCs).3) There is now a large literature on how to conduct ITCs.4) Typically, if one only has clinical trial evidence on Drug A vs. placebo from one RCT and Drug B vs. placebo from a separate RCT, then one would have to infer the benefits of Drug A vs. Drug B by looking at each drug’s relative performance compared to the placebo groups even though the studies were conducted separately and independently of each other. Similarly if one has evidence on Drug A vs. placebo for an RCT in a target patient group, and evidence on Drug A vs. Drug B in another patient group one would use ITC methods to infer the benefits of Drug B relative to Drug A in the target patient group.

In making these indirect treatment comparisons one would have to carefully consider how closely the comparator groups (e.g., the placebo/control groups) resemble each other in the two (or more) separate studies of Drug A and Drug B. For example, a placebo-controlled clinical trial of etanercept in treating psoriasis patients found a 45% improvement in the psoriasis area-and-severity index (PASI) efficacy score,5) while a placebo-controlled trial of ustekinumab found a PASI improvement of only 35%.6) Based on only these clinical trials one would infer that etanercept had a clinical advantage over ustekinumab. Nevertheless, when etanercept and ustekinumab were compared against each other in a head-to-head clinical trial ustekinumab was found to have a 27% higher PASI improvement than etanercept.7) In this case the indirect treatment comparisons would give a totally different answer than the head-to-head comparative efficacy trial.

One way to adjust for potential confounders that may alter outcome differences for ITCs, particularly when one has access to the individual subject clinical trial data is to use multiple regression, propensity scores or other statistical methods to match treatment effects in the two separate clinical trials on observable confounders. For example if Drug A is tested against placebo in a group of mostly older males, while Drug B is tested in mostly younger females one may be able to adjust for such observable confounders in the ITC. Nevertheless, there is always a possibility that there will be unobserv-
able confounders that bias the ITC results.

Song et al.\textsuperscript{8} reviewed a number of indirect treatment comparison studies compared to subsequent direct comparison studies and concluded that significant inconsistencies between the results of direct and indirect treatment comparisons are not infrequent. They caution that one needs to carefully consider whether it is reasonable that the direct and indirect treatment comparisons would yield consistent results. The problem is that when no directly comparable treatment effect evidence exists, one is forced to rely on ITC results. The researcher should never assume that complex or mathematically sophisticated methods for combining indirect treatment evidence (e.g., network meta-analysis or hierarchical Bayesian analysis) will everfully compensate for potential bias in ITC results.\textsuperscript{9,10} Lacking actual head-to-head RCT evidence for the comparator treatments in the relevant target patient groups, one can only make the best projections possible based on reasonable interpretations of existing data.

**Question 2.** It is difficult to quantify the clinical value of treatments that improve patient convenience (e.g., three pills per day vs. once daily, self injector vs. intravenous administration), and to reflect this clinical value in the economic assessment. How can we show the value of this benefit of the new drug?

Certainly one important way of quantifying the value of improved treatment convenience is the extent to which it will be reflected in patient treatment adherence and persistence measures. All else equal, a medication that requires three pills a day vs. one pill a day will demonstrate relatively poor adherence and persistence and this will likely be reflected in the pharmacoeconomic model of treatment costs, efficacy and clinical outcomes.

Beyond this, there is an important additional preference assessment methodology that is gaining popularity in evaluating the strength and importance of patient preferences for alternative treatment characteristics such as route and frequency of dose administration, adverse events, drug interactions and efficacy. This is the use of the Discrete Choice Experiment (DCE) version of conjoint analysis to systematically evaluate patient preferences. As Louviere et al.\textsuperscript{11} indicate DCE survey methods capture the strength of subject preferences for alternative treatment attributes using a methodology that is rigorously grounded in an economic theory of behavior (i.e., random utility maximization) and that leads to specific testable empirical models of choice (i.e., multinomial logit and its extensions such as nested logit and mixed logit).\textsuperscript{12,13}

As reviewed by Ryan and Gerard\textsuperscript{14} and de Bekker-Grob et al.\textsuperscript{15} hundreds of discrete choice experiments have been reported in the scientific literature addressing the relative preference weights that patients place on alternative treatment attributes. Since many of these DCEs include some measure of treatment price or cost as an independent attribute, these studies can also be analyzed to estimate the subject’s willingness to pay for each of the assessed treatment attributes in terms of the estimated ratio of any other treatment attribute preference weight to the preference weight for the price or cost attribute. This method can be used to assess the value, in monetary terms, that patients place on alternative drug dosing options (e.g., once daily pill vs. three times daily) or any other treatment attribute. Since DCE surveys are applicable to any subject population in addition to patients, one can also use this method to assess the value of alternative treatment attributes to physicians, other health care providers, government program or insurance program decision-makers, or representatives of the general community.

DCE patient surveys are a useful alternative to standard health-related quality of life (HRQOL) assessment instruments such as the SF-12, EQSD or HUI for assessing the utilities of patient quality of life changes with alternative treatments, since they can be adapted to capture the full range of variation in subject strength of preference for treatment attributes. HRQOL instruments, by necessity, mask the individual variation in utility assessment by imposing a reference group formula to each subject’s preference responses. Moreover, DCEs are designed to efficiently assess subject preferences without allowing the subjects to “game” their responses to exaggerate the importance of specific treatment attributes or attribute levels.

**Question 3.** There are increasing numbers of new drugs developed for rare diseases. However, it is difficult to show the efficacy/effectiveness of these drugs due to small patient sample sizes in available clinical trials. Moreover, clinical trial results often report non-inferiority results rather than demonstrating which treatment is significantly better. How should we deal with these issues in terms of pharmacoeconomic modeling and reimbursement decision-making?

Pharmacoeconomic models, no matter how sophisticated or complex, cannot resolve clinical issues that are still uncertain or incompletely known based on the best available evidence. Unfortunately one still sees pharmaceutical companies inappropriately using pharmacoeconomic models to hide or obfuscate the fact that there aren’t meaningful clinical differences between their products and those of their competitors.\textsuperscript{16,17} Such misuse of economic models is not consistent with good modeling practice guidelines for pharmacoeconomics.\textsuperscript{18}

Nevertheless, pharmacoeconomic models can still be help-
ful even when clinical differences are uncertain or not fully demonstrated for the target patient group. For example, if one only knew that Drug A was non-inferior to Drug B in terms of safety and efficacy, it could still be the case that Drug A was significantly lower than Drug B in terms of total treatment costs and thus preferable on a pharmacoeconomic basis using a cost minimization analysis. Moreover, even with clinical uncertainty the pharmacoeconomic modeling of Drug A vs. Drug B could help to define the extent of precision regarding the differences between Drug A and Drug B necessary to make a reimbursement decision between the two drugs. This “value of information” analysis would be very helpful in determining sample sizes and other study design characteristics for additional clinical trials that would adequately resolve the outstanding clinical issues.19)

Conclusions

Rising health care costs are a challenge to government health care programs and health insurance organizations around the world. Pharmacoeconomic models can assist in the fair and efficient allocation of limited health care resources to patients given existing budget limits. While pharmacoeconomic models cannot resolve existing clinical uncertainties and will never be the sole basis for health care decision-making, when carefully constructed these models can assist in making better, more-informed policy decisions and in setting the agenda for generating new research.

REFERENCES

Professional Biography:

Joel W. Hay is Professor and Founding Chair in the Department of Pharmaceutical Economics and Policy in the School of Pharmacy and a Professor of Health Policy and Economics in the Leonard Schaeffer Center for Health Policy and Economics, with a joint appointment in the Department of Economics at the University of Southern California. He also serves as the USC Project Coordinator for the Rand Evidence-Based Medicine Practice Centers of Southern California funded by the US Agency for Health Research and Quality (AHRQ). He is a Health Economics Research Scholar at the UCLA Center for Vaccine Research. He is a founding member and founding Executive Board member of the American Society for Health Economics (ASHEcon) and of the International Society for Pharmaceutical Economics and Outcomes Research (ISPOR).


Dr. Hay has served as a consultant to U.S. Centers for Medicare and Medicaid Services, U.S. Agency for Healthcare Research and Quality, U.S. Centers for Disease Control and Prevention, U.S. Public Health Service, U.S. Food and Drug Administration, U.S. Environmental Protection Agency, Government of Hungary, Hong Kong Centre for Economic Research, Hong Kong Medical Executives Association, World Bank, California AIDS Commission, California Medi-Cal Drug Advisory Board, County of San Diego Medically Indigent Adult program, and County of Sacramento Homeless Program. Dr. Hay has also written numerous health-related editorials published in papers such as Los Angeles Times, New York Times, Wall Street Journal, Orange County Register, San Francisco Chronicle, San Diego Union, Sacramento Bee and Newsday.

Dr. Hay served as Health Economics Expert Consultant to the State Attorneys General Working Group on Pharmaceutical Benefits Management (PBM) Market Competition Issues. He has served as a Member of the Expert Advisory Panel on Drug Utilization Review, United States Pharmacopeial Convention; an Executive Committee member for the federally-sponsored Southern California Evidence-Based Medicine Practice Center; and a member of the JAMA Web Site HIV/AIDS Editorial Review Panel. Dr. Hay is a founding member of the Board of Directors of the International Society for Pharmacoeconomics and Outcomes Research. He completed a study of hospital and pharmaceutical costs for the national Blue Cross Blue Shield Association. This report has been published in two peer-reviewed scientific publications and discussed in several national media, including NPR, CSPAN, USA Today, US News and World Report.

Dr. Hay currently holds a three-year appointment as an Extramural Grant Reviewer, Healthcare Systems & Value Research Study Section Review Panel, AHRQ, U.S. Dept. of Health & Human Services. He has previously served on the AHRQ Health Services Research Study Section and twice served as an External Reviewer for the AHRQ Developing Evidence to Inform Decisions about Effectiveness: The DEcIDE Network. He has also served as an External Reviewer for the U.S. National Institutes of Health, the U.S. National Science Foundation and the Netherlands Health Technology Assessment Methodology Programme (ZonMw).

Joel Hay was Founding Editor-in-Chief of Value in Health the peer-reviewed scientific journal of the International Society for Pharmacoeconomics and Outcomes Research until 2003. This journal, started in 1998, became Medline-listed in 2002. In its first impact factor, Value in Health was ranked #1 in two categories for the year 2004, by the ISI Journal Citation Reports® (JCR) with an impact factor of 3.657. Value in Health led all other journals listed both in the Health Care Sciences and Services category in the JCR Science Edition and in the Health Policy & Services category in the JCR Social Sciences Edition.

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