



**PHARMACOECONOMICS:  
IDENTIFYING THE ISSUES  
ADVISORY PANEL REPORTS**

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# EXECUTIVE SUMMARY

Marilyn Dix Smith PhD  
ISPOR Executive Director

Health care administrators, policy makers, and practitioners must balance the needs and desires of individual patients with the needs and desires of society at large, realizing that not all needs and desires can be met. Information comparing the expected gains of a medical intervention against the expected cost of that intervention versus other health care interventions are, many times, difficult to interpret or compare. The mission of the International Society for Pharmacoeconomics and Outcomes Research is to translate pharmacoeconomics and outcomes research into practice to ensure that society allocates scarce health care resources wisely, fairly, and efficiently. Toward this mission, ISPOR, co-sponsored with the U.S. Health and Human Services, Agency for Health Care Policy and Research, and the Health Outcomes Work Group of the Pharmaceutical Research and Manufacturers of America, convened an Advisory Panel Meeting and Conference on Pharmacoeconomic Issues, February, 1998. This conference provided a forum for researchers and practitioners to communicate needs and concerns as consensus is developed on methodology, interpretation, and use of pharmacoeconomic information.

The objective of this interdisciplinary conference was to identify the issues in conducting pharmacoeconomic studies, interpreting the results of these studies, and using pharmacoeconomic information in health care decisions. The specific goals of the conference were to:

1. identify key contentious methodology issues in conducting health care economic evaluations with clinical studies
2. identify key contentious methodology issues in conducting health care economic evaluations using modeling studies
3. identify key contentious methodology issues in conducting health care economic evaluations using databases
4. determine the education and skills needed for conducting pharmacoeconomic evaluations in health care decisions
5. identify the issues in application of economic evaluations in health care intervention protocol development, formulary decisions, and practice guideline development and use
6. identify the issues in addressing bias, credibility, and quality of pharmacoeconomic evaluations
7. identify the issues in communicating and reporting health care economic evaluation information

During this conference, sixty-one pharmacoeconomics and outcomes researchers, clinical practitioners and healthcare decision-makers in the United States met to develop consensus on issues relating to pharmacoeconomic and outcomes research evaluations and the use of these evaluations in healthcare decisions. The results of this deliberation are as follows:

## METHODOLOGICAL ISSUES IN CONDUCTING PHARMACOECONOMIC EVALUATION - CLINICAL STUDIES

Pharmacoeconomic methods used to assess cost alone or other measures of value often fall short of regulatory standards. Conversely, study methods used to demonstrate drug efficacy, such as randomized Clinical studies, are insufficient for addressing the question of value in other applied settings. To overcome the limitations of using clinical studies data for health economic evaluations, researchers, decision-makers, policy-makers and consumers should be well-versed in the appropriate use of clinical studies

There are four key issues are as follows:

1. *When should randomized clinical studies be the primary approach to assessing questions of value?*
2. *What modifications to randomized clinical studies would improve their usefulness as tools for health economic decision-making?*
3. *When should observational studies be used to assess questions of value?*
4. *What modifications to observational studies would improve their usefulness as tools for health economic decision-making?*

The recommendations for these issues are:

1. *Define 'usual care':* As trials adopt more naturalistic designs, the use of "usual care" as comparator will likely increase and comparability will be necessary.
2. *Develop new methods to account for protocol-related costs*
3. *Develop alternative methods for intent-to-treat analyses in usual care trials* Although the intent-to-treat analysis is important, there may be other research questions important to decision-makers that would benefit from alternate or additional analysis.
4. *Address problems of pooling economic data* due to significant differences in clinical practice across settings and sites, especially in international studies.
5. *Establish the range for "acceptable" levels of certainty of study results to inform value-based decision-making.*
6. *Improve statistical methods for adjusting for selection bias*, for example, instrumental variables and propensity scores.
7. *Develop better methods to estimate variance around the components of value*, such as bootstrapping and re-sampling techniques.
8. *Develop systematic comparison of randomized Clinical studies and observational studies* on the same interventions.
9. *Survey other disciplines* (such as psychology, sociology, marketing research) *for new approaches* to methodology, particularly in the areas of data collection, analyses and instrumentation.
10. *Use large, simple trials to measure resource utilization* such as early Phase IV studies,.
11. *Develop better methods to measure direct medical costs not routinely captured*, such as nursing time and telephone care (OMERACT

panel).

12. *Develop better methods to measure relevant indirect costs* such as caregiver time or lost productivity (ARAMIS). As electronic medical records evolve and expand, encourage inclusion of standardized outcome measures.

## **METHODOLOGICAL ISSUES IN CONDUCTING PHARMACOECONOMIC EVALUATION - MODELING STUDIES**

The primary purpose of modeling is to inform the decision-making process. One considerable benefit of model formalization is that the uncertainties and assumptions in this process are made explicit and transparent. Currently there are two major obstacles confronting modeling methodology currently: a) how to optimize the production of useful information for health economic decision-makers and b) how to encourage its acceptance and use of information

There are seven key issues (areas of controversy) in modeling methodology as follows:

1. *Standardization*
2. *Making choices*
3. *Methodological development*
4. *Extending Clinical studies and data issues*
5. *Effectiveness measures*
6. *Model validation*
7. *Peer review.*

The recommendations for these issues are:

1. *Work towards general acceptance that modeling of both costs and effectiveness as a valid and often essential method to inform health care decision-making*
2. *Assemble a consensus of opinion on standardized practices and policies*
3. *Prepare and disseminate a reference text of these practices* once standardization has been achieved.
4. *Permit pharmacoeconomic claims based on these generally accepted modeling approaches 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.
5. *Initiate and assemble* a balanced international panel of thought-leaders and end-users in the field of modeling to develop a package of generally accepted modeling practices
6. *Encourage all stakeholders, professional societies, manufacturing associations, journals, government agencies, regulatory agencies, payers and health care providers, to accept these as standards and to endorse their use once these practices have been documented.*

## **METHODOLOGICAL ISSUES IN CONDUCTING PHARMACOECONOMIC EVALUATIONS - RETROSPECTIVE AND CLAIMS DATA STUDIES**

Health care decision-makers require rapid access to information. The evidence that assists decision-makers to draw conclusions often has not been available. Both RCTs, and retrospective methods using existing databases, provide such information, and typically answer different questions. Most RCTs are designed to measure efficacy, not effectiveness. "Real world" data can be provided by database studies.

Eight key issues were identified as follows:

1. *What research questions can be answered by retrospective analyses?*
2. *What data sources are available to answer these questions?*
3. *How is cost-effectiveness measured using automated databases?*
4. *How can data quality within a database be evaluated?*
5. *What types of statistical methods can be utilized to control for treatment effects?*
6. *What potential types of bias exist in retrospective database analyses?*
7. *What alternative methods for assessing selection bias are available?*
8. *How can transparency be ensured in retrospective database analyses?*

The recommendations for these issues areas follows:

1. *Begin retrospective database analysis studies with a clear question and design, based on guidelines for good epidemiological practices.*
2. *Ensure privacy of individuals at all times in retrospective database analyses.*
3. *Use techniques that exist to address shortcomings of retrospective data sets*
4. *Subject multivariate models to extensive specification testing.*
5. *Examin age- or gender-adjusted utilization rates and annual per capita expense by payer, health plan, geographic region and country*
6. *Augment administrative databases, frequently used for retrospective pharmacoeconomic studies, to include more clinical informa-*

tion

7. *Establish standard measures to deal with all areas of potential bias.*

## **EDUCATION AND SKILLS NEEDED TO CONDUCT, INTERPRET AND USE ECONOMIC EVALUATIONS IN HEALTHCARE**

Like other disciplines, to expand and grow as a mature area of research and application, the field of health economics requires experts and skilled professionals. Unlike many other scientific fields, there is no one background or training that prepares the researcher or the user of health economic information, who currently come from a diversity of educational and experiential backgrounds

The key issues related to education and skills in the field of health economics are as follows:

1. *Multidisciplinary Programs* - The structuring of multidisciplinary programs needs to be defined for people coming from a variety of backgrounds.
2. *“Real-World” Applications* - Training must include “real-world” applications.
3. *Ideal Program*: It is unlikely that an ideal program can be created in any one place within one institution or group without collaboration with others.
4. *Minimal Competencies* - The usefulness of minimal competencies in the field has to be determined. Minimal competencies will be different for current and future practitioners by depth of involvement. For each level of involvement, the type of competencies will have to be defined.
5. *Who should be trained* - Questions pertaining to who should be trained, how should training be performed and what level of training is required need to be answered.
6. *Credentialing* - The necessity of credentialing needs to be assessed.
7. *Training Opportunities* - There is need to improve the way information about training opportunities is disseminated.

The recommendations for these issues are as follows:

1. *Develop three levels of expertise: awareness, application, and conceptualization*
2. *Develop access to detailed information about available educational programs in the field of health economics*
3. *Utilize relevant educational resources outside of health economics to enhance the educational infrastructure*
4. *Accommodate multidisciplinary participants through the availability of prerequisite trainings and flexible core course offerings for degree programs*
5. *Balance didactic and experiential education*
6. *Develop a credentialing process to establish standards for the field*
7. *Standardize training and certification through a three step process: a) develop guidelines for post-professional degree training; b) accredit pharmacoeconomic residencies and fellowships; c) establish collaborations with other organizations to expand accreditation to other relevant residencies*

## **APPLICATION OF HEALTHCARE INTERVENTION ECONOMIC EVALUATIONS IN HEALTHCARE DECISION-MAKING**

Information about the impact of new therapies on costs within a healthcare system should be essential for making better healthcare decisions. However, the relevance of health economic information to decision-makers has not been demonstrated. There is little user-friendliness in the health economic data. There is a lack of consistency of approach and format that would facilitate comparison under review. Finally, much of the information presented lacks the transparency necessary for the user to determine the appropriateness of methods or the soundness of assumptions. A fundamental disconnect exists between a) the way decisions are made by healthcare decision makers, b) type of information presented to healthcare decision makers and c) the type of information required by health economic and outcomes researchers.

There are eleven key issues as follows:

1. *Evaluative criteria are often weighed differently* by potential users of health economic research data for decision-making purposes such as formulary committees, providers, health plan managers, patients or employers.
2. *Language and definitional barriers hinder effective communication* between potential users and producers of the information may exist.
3. *Lack of treatment comparisons*. There is little data on direct product or treatment comparisons that are of greatest interest to potential users.
4. *Lack of communication*. Little dialogue exists between the potential users and the producers of information on what is relevant and what information can be generated by health economic research.
5. *Lack of understanding*. Potential users of health economic research data may be hesitant to include health economic information in their decision-making process because it is different from their established clinical orientation.
6. *Conflicting study design*. To conduct studies which provide health economic information that meets users’ needs, certain research designs for health economic and outcomes research studies may conflict with clinical design, causing regulatory and liability concerns.
7. *Research Funding*. Some sources of research funding may present a barrier to the credibility and application of study results.
8. *Societal perspective vs. individual perspective*. A conflict may exist between recommendations based on population data and the care

of individual patients.

9. *Lack of quality criteria.* When health economic research data is used in the decision-making process, there is no recognized approach for measuring the quality of the decision or the net result.
10. *Lack of experts.* There are few skilled opinion leaders or other resources from which potential users can seek advice and assistance.
11. *Segregation of organizational finances and health outcome decisions.* Decision-maker organizations segregate budgetary decisions for pharmaceuticals from those related to other medical technologies and services.

The recommendations for these issues are:

1. *Recruit a central organizer to coordinate the improvement of the application of healthcare intervention economic evaluations in healthcare decision-making.*
2. *Create focus groups to provide a forum for dialogue* between potential users, producers, and regulators of information. Researchers and suppliers of health economic data must actively engage with decision-makers to determine the key health economic evaluation criteria for decision-making purposes and formulate ways to supply the information consistently.
3. *Determine a set of variables which researchers can supply.* Decisions are seldom made using a single variable.
4. *Develops a set of simple criteria for evaluation of these studies,* agreed upon by consensus of all parties involved and designed to recognize different types of perspectives and research design so that specified research questions and business needs are met.
5. *Seek to bolster the objectivity, reliability, and credibility of the health economic studies* through various mechanisms, including working with sponsors, researchers and journal editors, to adopt protocols that will establish the independence of research and statements for the disclosure of funding sources.
6. *Offer training for decision-makers in using health economic research information for decision-making.* A consortium of managed care and other purchasing organizations, academic researchers and one or more health economic research organizations should be formed to execute this recommendation.
7. *Develop a standard reporting format* to allow flexible weighting of factors based on individual decision-making preferences. The presentation of the results of health economic analyses be modified to show the various components of effectiveness measures, service utilization measures and costs.
8. *Form a committee that would produce a standard format for Data Element Shells (DES).* DES would be in the form of desegregated data from cost-consequence or cost-effectiveness analyses. For each outcome of interest, reference to the data source could be made to allow reviewers to discern the degree of scientific support for each data element. ISPOR, in collaboration with potential users and producers of information, could be responsible for creation and updating of a DES form. The ISPOR committee would decide on the level of specificity of the DES, perhaps either a general format for all drugs or a specific format for individual drug classes.
9. *Support an information clearinghouse* of available thought-leaders and experts in the field. This should include development and maintenance of an Internet WEB site with links to expert's homepages and e-mail addresses. ISPOR as an organization brings together many of the researchers qualified to evaluate health economic research and interpret findings.
10. *Develop rosters of persons qualified to review studies,* similar to editorial boards for journals, where the reviewers would agree to participate in reviewing documents or addressing queries to promote a better understanding of the field of health care economics.

## **ADDRESSING QUESTIONS OF BIAS, CREDIBILITY AND QUALITY IN HEALTH ECONOMIC EVALUATIONS**

Multiple published studies have criticized the rigor, relevance, objectivity, methods, and reports produced within the health economic research domain. Consequently, health economic research findings are not used as extensively as they could be and rational decision processes about the efficient use of health care resources may not be fully informed. Ultimately, care for patients and populations may be adversely affected. In this context, there is a need for continued improvement in the quality of economic research conducted.

There are three key issues as follows:

1. *Quality: are best methods being used?*
2. *Bias: whether real or perceived, how do we deal with it?*
3. *Credibility: do we have a problem with believability or with relevance?*

The recommendations are as follows:

1. *Design and conduct studies using the best available practices consistent with the study objectives*
2. *Disclose any financial relationships which authors and speakers have linking them directly or indirectly to the interventions under study*
3. *Authorship should conform to generally recognized practices among the peer research community.* Research data, given full disclosure, transparency, and sufficient information to replicate the study, should be judged on the merits of its content
4. *Develop a code of ethics for health economic researchers*
5. *Develop study methodology practice standards*
6. *Convene a conference similar to this conference in 2 years to evaluate progress and recommend next steps*

## **COMMUNICATION AND REPORTING HEALTH ECONOMIC INFORMATION**

Users of health economic information represent many different perspectives with various levels of expertise and information needs. To obtain most value from the resources invested in health economic research, how do we optimize the effectiveness of our communicating of health economic information?

There are three key issues as follows:

1. *Relevance: Is it needed?:*
2. *Usefulness: Will the intended audience be able to make use of it?*
3. *Credibility: Is it believable?*

The recommendations are as follows:

1. *Identify the needs of users of health care economic information.* A survey of all users of health economic information, will provide a basis for standardization of communications.
2. *Establish standard communication formats* based on predetermined relevance, information and credibility needs of users and on standard health economic performance standards that should be under development elsewhere. These should eventually include: a) uniform presentation, standard terminology, adequate disclosure; and a basis in previously published guidelines
3. *Adopt a Reporting Guidance (RGs)* and apply to all publicly presented communications, as standardized formats are established
4. *Evaluate the use of Reporting Guidance and the quality of reporting* on a biannual basis.
5. *Establish a principle of publicly accessible reports that adhere to ISPOR RGs.* This would allow access to research reports that is not directly controlled by the researcher or the research organization. Once a report has been “filed” for public accessibility, all subsequent communications could refer to that report
6. *Institute an enhanced mode of peer review* for all forms of health economic communications. This type of review would assure that there was compliance with ISPOR RGs and fair, full and adequate disclosure, allow for review of the underlying data and any model used, and confirm that all other ISPOR standards for the conduct of health economic studies have been met.

### **EXPECTED OUTCOMES OF THIS CONFERENCE**

The following are the expected outcomes (products) of this conference in addition to this report are:

1. **Publication:** This report will be published in VALUE IN HEALTH, Journal of the International Society for Pharmacoeconomics and Outcomes Research
2. **Follow-up Activities:** Conferences are planned based on the recommendations given in this report
3. **ISPOR Policy Statements:** Specific policies of the International Society for Pharmacoeconomics and Outcomes Research will be developed from these recommendations ISPOR, in cooperation with other scientific and practitioner organizations and institutional organizations, will work to implement these policies. Examples of these organizations are the Health Outcomes Work Group of the Pharmaceutical Research Manufacturers of America and the Pharmaceutical Research Standards Committee of the American Managed Care Pharmacy Association.
4. **Agenda for Future Research Activities** The recommendations included in these reports are suggested to be the agenda for future research activities by the Agency for Health Care Policy and Research.

# OVERVIEW

Marilyn Dix Smith PhD  
ISPOR Executive Director

Health care administrators, policy makers, and practitioners must balance the needs and desires of individual patients with the needs and desires of society at large, realizing that not all needs and desires can be met. Information comparing the expected gains of a medical intervention against the expected cost of that intervention versus other health care interventions are, many times, difficult to interpret or compare.

The mission of the International Society for Pharmacoeconomics and Outcomes Research is to translate pharmacoeconomics and outcomes research into practice to ensure that society allocates scarce health care resources wisely, fairly, and efficiently. Toward this mission, ISPOR, supported by grants from the U.S. Department of Health and Human Services, Agency for Health Care Policy and Research, and the Health Outcomes Work Group of the Pharmaceutical Research Manufacturer's Association, convened an Advisory Panel Meeting and Conference on Pharmacoeconomic Issues, February, 1998. This conference provided a forum for researchers and practitioners to communicate needs and concerns as consensus is developed on methodology, interpretation, and use of pharmacoeconomic information.

The objective of this interdisciplinary conference was to identify the issues in conducting pharmacoeconomic studies, interpreting the results of these studies, and using pharmacoeconomic information in health care decisions. The specific goals of the conference were to:

- identify key contentious methodology issues in conducting health care economic evaluations with clinical studies
- identify key contentious methodology issues in conducting health care economic evaluations using modeling studies
- identify key contentious methodology issues in conducting health care economic evaluations using databases
- determine the education and skills needed for conducting and/or using pharmacoeconomic evaluations in health care decisions
- identify the issues in application of economic evaluations in health care intervention protocol development, formulary decisions, and practice guideline development and use
- identify the issues in addressing bias, credibility, and quality of pharmacoeconomic evaluations

- identify the issues in communicating and reporting health care economic evaluation information

During this conference, sixty-one pharmacoeconomics and outcomes researchers, clinical practitioners and healthcare decision-makers in the United States met to develop consensus on issues relating to pharmacoeconomic and outcomes research evaluations and the use of these evaluations in healthcare decisions. The seven Advisory Panels, in closed sessions and then in open sessions with all Advisory Panelists, discussed and debated the issues.

In addition to the Advisory Panel co-chairs and members listed on each report, the following pharmacoeconomic researchers participated in the meeting:

- Daniel Mullins PhD, Assistant Professor, Center on Drugs & Policy, University of Maryland
- Tom Einarson PhD, Associate Professor, Faculty of Pharmacy, University of Toronto
- William McGhan PharmD PhD, Professor, University of the Sciences in Philadelphia
- James Smeeding RPh MBA, Director, Center for Pharmacoeconomic Studies, University of Texas
- Hugh Tilson MD, DrPH, Senior Medical Advisor, Glaxo Welcome
- Yen-Pin Chiang PhD, Agency for Healthcare Policy and Research (observer)

The specific objectives of each Advisory Panel and a report of each Panel's deliberation follow. Each Advisory Panel Report summarizes the scientific and historical context for each of the issues discussed, the numerous points of view expressed and the recommendations of each advisory panel for future directions of research and policy in the field of pharmacoeconomics. These reports are presented as working documents as a basis for standardization of the science of outcomes research and healthcare economics, the development of generally accepted pharmacoeconomic policies and an agenda for future research activities.

## **EXPECTED OUTCOMES OF THIS CONFERENCE**

The following are the expected outcomes (products) of this conference in addition to this report are:

1. **Publication:** This report will be published in VALUE IN HEALTH, Journal of the International Society for Pharmacoeconomics and Outcomes Research
2. **Follow-up Activities:** Conferences are planned based on the recommendations given in this report
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organizations and institutional organizations, will work to implement these policies. Examples of these organizations are the Health Outcomes Work Group of the Pharmaceutical Research Manufacturers of America and the Pharmaceutical Research Standards Committee of the American Managed Care Pharmacy Association.

4. **Agenda for Future Research Activities** The recommendations included in these reports are suggested to be the agenda for future research activities by the Agency for Health Care Policy and Research.

# ISSUE I

## METHODOLOGICAL ISSUES IN CONDUCTING PHARMACOECONOMIC EVALUATION - CLINICAL STUDIES

### **Goal**

Identify key contentious methodology issues in conducting health care pharmacoeconomic evaluations – clinical studies

### **Specific Objectives**

- Identify and prioritize the key issues associated with including pharmacoeconomic and outcomes research projects in clinical studies
- Identify a plan of action to resolve these issues
- Recommend next steps

### **Panel Co-chairs**

- Margaret Healey PhD, Director of Clinical Research at the Institute for Research & Education, HealthSystems Minneapolis
- Patricia Deverka MD MS, Medical Director, Hastings Healthcare Group

### **Panelists**

- Steven Fox MD, Center for Outcomes & Effectiveness Research, Agency for Healthcare Policy & Research
- Kathleen Gondek PhD, Director of Health Care Economics & Managed Care at Boehringer Ingelheim
- Barbara Edelman Lewis PhD, Vice President, Focus Managed Research Inc.
- Eva Lydick PhD, Director of Epidemiology & Applied Health Economics, SmithKline Beecham,
- Gurkupal Singh MD, Clinical Instructor from Stanford University Medical Center
- Robert Temple MD, Associate Director of Medical Policy, Food & Drug Administration
- Jeff Trotter MBA, President, ClinTrials Ovation

### **Background and Context**

The pros and cons of various clinical study designs for economic evaluations have been described elsewhere (O'Brien 409; Haycox 39; Drummond 380; Drummond 379). The weaknesses of controlled Clinical studies that incorporate pharmacoeconomic evaluation include questionable choices of comparator therapies, inadequate sample sizes, limited duration of patient follow-up, the inability to separate protocol-driven costs from actual costs of care, and choice of outcome measures that may not be relevant to standard or usual care. These weaknesses threaten generalization of the results from controlled clinical studies. However, such trials have become the standard for establishing the efficacy and safety of new therapies. Study methods used to demonstrate cost-effectiveness often fall short of satisfying regulatory standards. Conversely, study methods used to demonstrate drug efficacy, such as randomized controlled trials (randomized Clinical studies), have been criticized for not adequately addressing cost-effectiveness issues in applied settings.

Consumers of pharmacoeconomics (in particular managed care decision-makers) are increasingly demanding evidence of the value of new interventions to inform formulary and treatment guideline decision-making. For the purpose of this paper, value is defined as outcome as a function of cost, but the relative importance of “cost” depends on the research question and the perspective of the target audience. Pharmacoeconomic data generated from randomized trials has the advantage of interpretability, statistical rigor, better control of bias and well-established and accepted methodology. Limiting pharmacoeconomic data to that derived from randomized Clinical studies, however, would limit the body of available information resulting in decisions based primarily on price and not value. In addition, relying solely on randomized clinical studies may limit the validity and generalization of the economic impact of a treatment in real world practice. Alternatively, results from studies other than randomized Clinical studies may be difficult to interpret and contain bias. Better understanding of the appropriate use of the different methods will increase the usefulness and validity of resulting pharmacoeconomic data.

### ***Problem Statement***

There is considerable overlap between acceptable methodologies for demonstrating the efficacy of drugs and those sanctioned by health economists for addressing questions of value, but the degree of overlap is a matter of fervent debate. Pharmacoeconomic methods used to assess cost alone or other measures of value often fall short of regulatory standards. Conversely, study methods used to demonstrate drug efficacy, such as randomized Clinical studies, are insufficient for addressing the question of value in other applied settings. To overcome the limitations of using clinical studies data for health economic evaluations, researchers, decision-makers, policy-makers and consumers should be well-versed in the appropriate use of clinical studies (both experimental and observational).

### ***Issues***

Four key issues were identified to be addressed in this document:

1. *When should randomized clinical studies be the primary approach to assessing questions of value?*
2. *What modifications to randomized clinical studies would improve their usefulness as tools for health economic decision-making?*
3. *When should observational studies be used to assess questions of value?*
4. *What modifications to observational studies would improve their usefulness as tools for health economic decision-making?*

**1. When should randomized clinical studies be the primary approach to assessing questions of value?**

Pharmacoeconomic data can be derived from randomized clinical studies, but these are not always first choice for a variety of reasons, both practical and scientific. These studies should be used as the primary approach only when certain criteria are met.

- i. Are the potential results of sufficient importance to justify the expense of a randomized clinical trial? Not every question requires a randomized clinical trial to arrive at a credible answer. The “cost-effectiveness” of the study should be evaluated.
- ii. Is there reasonable likelihood of obtaining outcomes within a relatively short timeframe, or are intermediate end-points acceptable? Principally because of their cost, randomized Clinical studies are best suited to studying acute outcomes or intermediate endpoints with well-established links to long-term outcomes. When intermediate outcome variables are used, the data supporting the level of certainty in the link between the intermediate variable and final outcomes needs to be disclosed.
- iii. Is there consensus about appropriate comparator(s)?
- iv. Are effect sizes predicted to be small (e.g., relative risk less than 2.0)?
- v. Is randomization an acceptable strategy for the patients and the investigators?
- vi. Will compliance issues remain independent of the study outcomes?

**2. What modifications to randomized clinical studies would improve their usefulness as tools for health economic decision-making?**

To increase the overlap between acceptable randomized clinical studies and acceptable health economic assessments, rigorous application of good scientific and clinical practice principles are the foundation (Spilker 481). More specific recommendations include the following.

- i. Conduct more randomized clinical studies within the settings where decisions will be made, such as within managed care organizations.
- ii. Adopt more naturalistic study designs including imitating usual care as much as possible, to increase generalizability of the results.
- iii. Minimize or liberalize randomized clinical trial inclusion and exclusion criteria.
- iv. Use active comparators rather than placebos, which are not usually considered relevant by decision-maker. When less robust measures of effectiveness are anticipated, as in antidepressant trials, a placebo comparator may also

be needed to increase credibility of a cost-effectiveness assessment.

- v. Test multiple doses of comparator.
- vi. Without compromising safety, reduce the burden of adverse event reporting.
- vii. If there is adequate power in sub-populations, design studies to answer secondary questions using nested designs.
- viii. Provide more variance information around economic variables to enhance the usefulness of data to decision-makers.
- ix. Design randomized clinical studies to capture more resource utilization data.

### **3. *When should observational studies be used to assess questions of value?***

Discussion here is limited to those observational studies that make use of primary data sources. Observational studies should be considered for use as a primary approach only under certain conditions. When the cost-effectiveness of performing a randomized Clinical studies questionable, adequate data may be derived from an observational study. In fact, the unacceptable cost of a randomized clinical trial may be created by some of the following conditions.

- When the primary outcome is a rare event.
- When multiple comparators are considered desirable.
- When the primary outcome has a long term horizon.
- When the objective of a study is to evaluate a single intervention, such as the cost of treatment before and after introduction of a new therapy.
- When the intervention in question has been available for a long time.
- When conducting a randomized clinical trial is ethically questionable, such as when the magnitude of effect is very large or in the case of breakthrough treatments of life-threatening diseases.
- When randomization is not an acceptable option for patients, such as surgery versus pharmacotherapy or placebo-controlled trials in life-threatening illnesses.
- When an assessment of practice patterns is part of the evaluation.

### **4. *What modifications to observational studies would improve their usefulness as tools for health economic decision-making?***

While good clinical research practices obviously apply to the conduct of observational studies as well as to randomized clinical studies, observational studies are more frequently criticized for methodological inadequacies. Following good

research practices such as those provided in the International Society for PharmacoEpidemiology recommendations (ISPE 470) are again the foundation. Specifically, the study should be hypothesis-driven, with the research questions specified at the outset, as well as the study design and methodology, analysis plan and how the results will be disseminated. As well, studies should be replicated in several settings to reinforce validity of the findings, and to determine their generalizability.

## ***Recommendations***

The following recommendations address the four issues identified:

1. The definition of usual care requires development. As trials adopt more naturalistic designs, the use of “usual care” as comparator will likely increase and comparability will be necessary.
2. New methods to account for protocol-related costs should be developed, especially for studies where these costs are not balanced across study groups.
3. Alternative methods to intent-to-treat analyses in usual care trials should be explored. Although the intent-to-treat analysis is important, there may be other research questions important to decision-makers that would benefit from alternate or additional analysis.
4. Problems of pooling economic data must be addressed, due to significant differences in clinical practice across settings and sites, especially in international studies.
5. Establish the range for “acceptable” levels of certainty of study results to inform value-based decision-making.
6. There is a need for improvement of statistical methods for adjusting for selection bias, for example, instrumental variables and propensity scores.
7. Better methods can be used to estimate variance around the components of value, such as bootstrapping and resampling techniques.
8. Systematic comparison should be made of randomized Clinical studies and observational studies on the same interventions.
9. Other disciplines (such as psychology, sociology, marketing research) should be delved for new approaches to methodology, particularly in the areas of data collection, analyses and instrumentation.
10. Use large, simple trials such as early Phase IV studies, to measure resource utilization.
11. Develop better methods to measure direct medical costs not routinely captured, such as nursing time and telephone care (OMERACT panel).

12. Develop better methods to measure relevant indirect costs such as caregiver time or lost productivity (ARAMIS).
13. As electronic medical records evolve and expand, encourage inclusion of standardized outcome measures.

The timeliness of these recommendations will be relative to the evolution of the research (user) with respect to pharmacoeconomic measurement and application.

### ***Summary***

There is agreement that useful pharmacoeconomic data can be derived from both randomized Clinical studies and observational studies. The process of randomization does lend some credibility to studies, although this may not always be perceived as necessary by the end user. The most important factors for a researcher to consider in designing a clinical trial are knowing the precise question(s) that the study is required to answer and knowing the informational needs of the target audience. Over the long term, it is recommended that effort be directed towards more consensus and a greater degree of standardization of definitions and methodologies for assessing health economic questions through clinical studies.

# ISSUE II

## METHODOLOGICAL ISSUES IN CONDUCTING PHARMACOECONOMIC EVALUATION - MODELING STUDIES

### **Goal**

Identify key contentious methodology issues in conducting health care pharmacoeconomic evaluations - Modeling Studies

### **Specific Objectives**

- Identify and prioritize the key issues associated with pharmacoeconomic modeling studies
- Identify a plan of action to resolve these issues
- Recommend next steps

### **Co-chairs**

- Joel Hay PhD, Associate Professor, Department of Pharmaceutical Economics & Policy, University of Southern California
- Joseph Jackson PhD, Executive Director, Outcomes Research, Bristol Myers Squibb
- Panelists:
- Bryan Luce PhD MBA, Senior Research Leader & CEO of MEDTAP International
- Jerry Avorn MD, Associate Professor, Harvard Medical School
- Talat Ashraf MD MS, Vice President, PPD Pharmaco & Informatics

### **Background and Context**

The primary purpose of modeling is to inform the decision-making process (Medical Decision Making 473; Clinical Decision Analysis 474). 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 is frequently insufficient to allow optimal health care 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 studies (RCT) 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 (Gold 471). 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 health care 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 currently: a) how to optimize the production of useful information for health economic decision-makers, and b) how to encourage its acceptance and use of information.

### ***Issues***

There are seven key issues (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.

#### ***1. 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 (Weinstein 113) 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 health care, 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 (Weinstein 113) 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.

## **2. *Making Choices***

Beyond standardization, in each study a range 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.

In deciding on perspective, societal perspective is preferable, and the societal perspective includes all relevant cost and outcomes consequences. Certain options in decision-making will be cost-effective from 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 decision on resource allocation is 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 or 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.

### **3. *Methodological Development***

A limitation of decision tree models is that they are not well suited to represent recurrent events over time (Evans 340; Beck 475). 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 equation, deterministic models, and stochastic models or discrete event simulations (O'Brien 476).

### **4. *Extending Clinical studies and Data Issues***

Some degree of modeling is usually necessary to assess clinical outcomes and economic consequences beyond the

necessarily parameters of a clinical trial, and modeling represents the only appropriate analytic approach to estimate health care 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 (Drummond 379).

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.

##### **5. *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 is 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.

## **6. 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.

## **7. 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) and raises questions about the handling of proprietary property and confidentiality.

## **Recommendations**

The following recommendations address the seven issues identified:

- 1 Working towards general acceptance that modeling of both costs and effectiveness is a valid and often essential method to inform health care decision-making will be necessary to establish modeling as an invaluable healthcare decision-making tool.
- 2 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.
- 3 Once standardization has been achieved, a reference text of these practices should be prepared and disseminated.
- 4 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.
- 5 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 published upon previously work.

- 6 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 health care 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.

It is to be hoped 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.

# ISSUE III

## METHODOLOGICAL ISSUES IN CONDUCTING PHARMACOECONOMIC EVALUATIONS - RETROSPECTIVE AND CLAIMS DATA STUDIES

### ***Goal***

Identify key contentious methodology issues in conducting health care pharmacoeconomic evaluations – using retrospective studies and claims data

### ***Specific Objectives***

- Identify and prioritize the key issues associated with pharmacoeconomic and outcomes research studies using retrospective and claims data
- Identify a plan of action to resolve these issues
- Recommend next steps

### ***Co-chairs***

- Renee Goldberg Arnold PharmD, President, Pharmacon International
- James G. Kotsanos MD MS, Director, Division of Global Health Economic Research, Eli Lilly and Company

### ***Panelists***

- Brenda Motheral RPh, PhD MBA, Associate Professor, University of Arizona
- Scott Ramsey MD PhD, Center for Cost & Outcomes Research, University of Washington, Seattle, WA
- William Crown PhD, Economist, MEDSTAT,
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- Mark Hornbrook PhD, Program Director, Kaiser Permanente
- Alan Wright MD MPH, VP & Chief Medical Officer, Advanced Paradigm Inc.
- Michael Murray PharmD MPH, Regenstrief Institute

### ***Background and Context***

Pharmacoeconomic analyses can be conducted within the context of clinical studies or using retrospective databases.

Randomized Clinical studies (RCTs) and observational studies, specifically retrospective database analyses, answer different questions. For example, most randomized Clinical studies are designed to measure efficacy, not effectiveness.

Existing databases can provide effectiveness and “real world” data. Cost-effectiveness analyses utilizing retrospective databases can provide real-time, relevant, and comprehensive decision support.

Retrospective analyses are relatively inexpensive to perform and can be done quickly. They are reflective of specific populations, that cannot be easily studied using RCTs, and for which data may be difficult to obtain. Relative to random-

ized controlled trials, retrospective studies tend to cover more realistic time frames, and are not constrained by the limitations of a set trial period. The perspective of a particular organization's experience can be obtained, and large samples can be surveyed. Usually, the sample sizes of retrospective databases are much larger than RCTs, enhancing their statistical power to detect important differences in outcomes. Retrospective databases encompass a wealth of variables, and analyses of these data can be used for benchmarking purposes, and for capturing real-world prescribing patterns. Notwithstanding the advantages of retrospective database analyses, there are challenges that face these analyses when used for health economic evaluations.

### ***Problem Statement***

Health care decision-makers require rapid access to information. The evidence that assists decision-makers to draw conclusions often has not been available. Both RCTs, and retrospective methods using existing databases, provide such information, and typically answer different questions. Most RCTs are designed to measure efficacy, not effectiveness. "Real world" data can be provided by database studies. The validity of retrospective analyses is often questioned due to the potential for selection bias, confounding factors, sponsorship, data quality and privacy issues. In addition, since there may be a time lag in the availability of information about new therapies and its incorporation into and availability from databases, the timeliness of the economic evaluations resulting from a retrospective analysis can be questioned.

### ***Issues***

Eight key issues were identified which are addressed in this document:

- What research questions can be answered by retrospective analyses?
- What data sources are available to answer these questions?
- How is cost-effectiveness measured using automated databases?
- How can data quality within a database be evaluated?
- What types of statistical methods can be utilized to control for treatment effects?
- What potential types of bias exist in retrospective database analyses?
- What alternative methods for assessing selection bias are available?
- How can transparency be ensured in retrospective database analyses?

#### ***1. What research questions can be answered by retrospective database analyses?***

The types of economic studies that can be conducted using automated databases include cost- consequence, cost-

effectiveness, and cost-of-illness analyses. Currently, cost-utility analyses are rarely addressed due to the lack of utility data captured in databases.

Of paramount importance to utilizing retrospective database analysis for health economic evaluations is the careful crafting of the research question. This question must be derived at the outset from the perspective of the appropriate parties, and such perspective may include society, the provider, the payer or the patient.

Crafting the question is critical to the success of a project since it drives all other aspects of the research project. It dictates:

- how the literature review is performed;
- the study objectives;
- the definitions of health outcomes and variables to be studied;
- the study design, including sample size;
- the time frame to be evaluated;
- data source(s), validation and analyses; and
- the budget.

## ***2. What data sources are available to answer the question?***

The types of data sources that can be utilized for health economic evaluations based on retrospective analysis include:

- electronic medical records (integrated modules of pharmacy, laboratory, and clinical databases),
- claims data such as that from managed care databases, the Health Care Finance Administration (HCFA), the Department of Defense, Veterans Affairs, self-insured employers, pharmacy benefit managers (PBMs);
- encounter data such as that from a staff/group model of health maintenance organizations (HMOs);
- expert opinion;
- results of published literature, such as meta-analyses;
- patient registries; and
- national survey databases, such as the Medical Expenditure Panel Survey (MEPS), formerly the National Medical Expenditure Survey (NMES).

## ***3. How is cost-effectiveness measured using automated databases?***

Cost-effectiveness studies require comparison of two or more competing therapeutic options. It is possible to measure cost-effectiveness using automated databases. First, one must determine if the particular database is appropriate to answer the question. Evaluation depends on the disease in question and availability of the outcome measures of effectiveness. For example, it would be inappropriate to select a hospital discharge database to evaluate lithotripsy use in kidney stones if the procedure is performed on an outpatient basis. Databases containing both outcome and cost information are required to perform cost-effectiveness analyses, including, for example, administrative claims as well as laboratory and prescription data. In some cases, linkage of databases might be appropriate to address some research questions. An example of database linkage for estimating cost of care for patients with cancer has been published (Potosky et al 666). Outcome measures can include, for example, diabetic ketoacidosis episodes or amputations avoided, which are coded using the International Classification of Disease (ICD-9) or Current Procedural Terminology (CPT-4) codes. Intermediate outcome measures can also be used, such as the percentage reduction of low-density lipoprotein-cholesterol rather than occurrence of a major cardiovascular event. Currently, databases do not usually contain quality of life (QoL) or utility data. However, QoL data are beginning to be collected, such as in the Patient Outcomes Research Teams (PORT) databases, in selected managed care databases, and in the managed care Health Plan Employer Data and Information Set (HEDIS) that captures data from questionnaires like the SF-36.

#### ***4. How can data quality within a database be evaluated?***

Assessing the accuracy and completeness of the database (The MEDSTAT Group 94 665; Iezzoni 359) is integral to a research study based on automated database information. Data checks must be performed regularly and consistently. Issues to be considered include the following:

- Are there missing data elements, and if so, what percentage is missing?
- Is the cohort continuously tracked over the period of interest?
- Is it possible to trace services and diagnoses across healthcare settings (e.g. hospitals, nursing homes, and clinics)?
- Were all relevant diagnoses and procedure codes accurately recorded for the visit or episode of care?
- Are data recorded uniformly using widely accepted recording standards?
- Was the accuracy of the diagnostic and utilization records verified with chart reviews or benchmarking?
- Were logical consistency checks performed, such as searching the database for illogical matches, e.g. those between “hysterectomies” and “males”?
- Are there unique identifiers for each family member?

- Were events recorded when they actually occurred?
- Is population-denominator data available? That is, does the database contain enrollment information that enables the identification of individuals without healthcare utilization?

**5. *What types of statistical methods can be utilized to control for treatment effects?***

With retrospective database studies in particular, it is important to control for as many confounding variables as possible. A need exists for statistical methods to control for these effects and implies that multivariate analysis should be performed whenever possible.

**6. *What potential types of bias exist in retrospective database analyses?***

The potential areas for bias (Sackett 655) within retrospective database analyses form a long list, including, but not limited to the following examples.

- **Selection bias.** Individuals are not typically randomly assigned to health plans or treatments. Estimates of the effects and costs can be biased due to a correlation between unobserved factors associated with treatment selection and outcomes, such as baseline health status. Sample selection bias is often referred to by other names. For example, vintage bias, which is due to variation in physician training and practice styles or in availability of technologies resulting in confounding measures of costs and outcomes, is a specific type of selection bias.
- **Bias from censoring of data.** Bias can be introduced when the length of time that individuals are observed is correlated with their outcomes. For example, some studies may impose a minimum eligibility period that leads to the omission of subjects with short-term eligibility. If the reasons for the failure to meet the minimum eligibility criteria are correlated with utilization patterns, such as a death, then biased conclusion will result. Similarly, if the length of the observation period varies for individuals, then bias may be introduced because of failure to observe utilization that occurred after the observation period ended (e.g., There is less opportunity to observe service utilization patterns for patients treated with relatively new drugs.)
- **Measurement error bias.** There are numerous sources of error in measurement of data that can introduce bias. For example, specialists may tend to code diagnoses with more specificity than general practitioners. Similarly, fee-for-service providers may have an incentive to document diagnoses and services relative to at-risk providers who may have an incentive to minimize the burden of documentation. Recall bias is yet another form of measurement error. Recall bias refers to the tendency, on the part of respondents, to recall service utilization that occurred more recently with greater accuracy than service utilization that occurred in the more distant past.

- **Misspecification bias.** As with measurement error, there are a variety of forms of misspecification errors that can lead to biased estimates. These include omitted variables, incorrect function form, and using single equation models when a multi-equation model is more appropriate.
- **Investigator bias/ obsolescence bias.** In addition to the sources of bias just mentioned, there are sources of bias that may be introduced which are not directly a function of retrospective data themselves. These include investigator bias which arises when a researcher interprets findings in the context of preconceived viewpoints or adopts a study design (e.g., exclusion criteria) that biases the study results in the direction of the researcher's preconceived viewpoints. Investigator bias is often unintentional. Similarly, obsolescence bias may occur because medical technology used during the periods covered by a retrospective database is obsolete by the time the study is conducted.

Finally, bias is not the only statistical problem that may undermine the validity of inferences drawn from retrospective studies. Other problems include the correlation of error terms among respondents (autocorrelation), non-constant variance of error terms among respondents (heteroscedasticity), and high correlation among explanatory variables (multicollinearity).

#### 7. *What alternative methods for assessing selection bias are available?*

Perhaps the most fundamental area in which bias occurs in a retrospective database analysis is during selection of study subjects. Whereas RCTs reduce sample selection bias through randomization by evenly distributing subjects among treatment arms, retrospective database analyses are non-randomized. Non-randomized studies that attempt to evaluate treatment outcomes have been widely criticized (CCOHTA Guidelines 94 96; Anderson 368) because unobserved variables might correlate with both treatment selection and outcomes. Such a correlation can result in erroneous inferences about the magnitude and statistical significance of treatment effects.

Alternative methods for assessing selection bias include using propensity scores, instrumental variables (IVs) and sample selection models; however, these methods may fail to fully control for selection bias.

- i. Propensity score analysis has received growing attention as a methodology for reducing the bias due to inherent differences between treatment groups that go unobserved (Rosenbaum 84 659; Robins 92 660; Drake 95 358). Although the propensity score approach is non-parametric, Angrist (Angrist 97 66) has recently shown that propensity score analysis may be more closely related to sample selection models than previously believed.

- ii. The use of Instrumental Variables (IVs), in recent papers by McClellan (McClellan 94 662; McClellan 95 663), has been proposed to control for the confounding effects of unobserved variables. Instrumental variables are widely used by researchers to correct for a variety of statistical problems, most notably, simultaneous equation bias and errors in measurement (Kennedy 92 658; Green 93).
- iii. Sample Selection Models attempt to control the bias introduced by unobserved variables in treatment selection, which are also correlated with the outcome variable of interest. Sample selection models have seen wide use in the econometrics literature to study labor supply decisions, and to model the effectiveness of job training programs, housing programs, welfare experiments, and many others (Heckman 95 664). Very recently, these models have begun to find application in the health economics literature (Dowd 96 657; Hylan 97 656). Selection models are a special case of IVs and may require parameter estimates.

#### 8. ***How can transparency be ensured in retrospective database analyses?***

A great deal of consensus exists among the guidelines about transparency of assumptions and methods (Mullins 98 426). Full disclosure and detailed methodology when reporting study results of health economic evaluations is recommended by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (Uniform Requirements 393), the Task Force on Principles for Economic Analysis of Health Care Technology (Task Force 479), and the Pharmaceutical Research and Manufacturers of America's Methodological and Conduct Principles for Pharmacoeconomic Research (PhRMA principles 423).

One final point is that data privacy has become an increased focus of attention. The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) has recently adopted the data privacy recommendations developed by the International Society for Pharmacoepidemiology (ISPE Data Privacy).

### ***Recommendations and Next Steps***

The credibility of retrospective database analyses in health economic evaluations must be enhanced by good research design, multiple and varied checks on data quality and attention to areas of potential bias in a given study. The following recommendations address the eight issues identified.

- 1 It is recommended that retrospective database analysis studies begin with a clear question and design, based on the

International Society for Pharmacoepidemiology guidelines for good epidemiological practices (ISPE Guidelines 470).

- 2 Privacy of individuals must be ensured at all times in retrospective database analyses.
- 3 Techniques that exist to address shortcomings of retrospective data sets should be used.
- 4 Multivariate models should be subjected to extensive specification testing.
- 5 Examining age- or gender-adjusted utilization rates and annual per capita expense by payer, health plan, geographic region and country is suggested.
- 6 Administrative databases, frequently used for retrospective pharmaco-economic studies, need to be augmented to include more clinical information (e.g., the results of lab tests, not just an indicator that a lab test was conducted).
- 7 Bias is a threat to the validity of inferences drawn from any retrospective and claims database analysis. When bias exists, either real or perceived, standard measures should be established to deal with all areas of potential bias. Ways to address specific biases include:
  - Selection Bias: modeling (e.g., Heckman approach, fixed-effects and random effects models), or propensity scores;
  - Measurement Error and Bias: modeling (e.g., bootstrap estimation), data imputation;
  - Mis-specification Bias and other violations of model assumptions: conduct and report specification error tests, select appropriate model and error distribution, or adjust observations to remove the specification error(s);
  - Investigator Bias: disclosure of conflict of interest, analysis assumptions, and study sponsor for investigator(s) and key staff;
  - Obsolescence Bias: use expert opinion to identify key innovative technologies and model them; look at time trends in key utilization parameters; estimate models for separate time periods;
  - Vintage Bias re: Human & Physical Capital: modeling; link with other data sources such as area resource file (HCFA);

## ***Summary***

Retrospective databases can be useful tools for health economic evaluations. They offer large populations using real-world information within rapid and realistic treatment periods, and can answer questions related to cost-effectiveness. Nevertheless, pharmaco-economic studies based upon retrospective databases face a variety of threats to the validity of the inferences drawn from them. The credibility of retrospective database analyses in health economic evaluations must be enhanced by careful study design, elimination of bias, and reporting the results of these studies in a clear, believable, and transparent fashion.

# ISSUE IV

## EDUCATION AND SKILLS NEEDED TO CONDUCT, INTERPRET AND USE ECONOMIC EVALUATIONS IN HEALTHCARE

### **Goal**

Determine education and skills needed for conducting evaluations, interpreting and using healthcare pharmacoeconomic evaluations in health care decisions.

### **Specific Objectives**

- Describe basic knowledge and skills required for researchers
- Present the appropriate training methods (courses, workshops, academic certification, or in-house programs) for pharmacoeconomic researchers
- Suggest courses for degree programs
- Recommend next steps

### **Co-chairs**

- Katie Copley-Merriman MS MBA, Director, Outcomes Research, Parke-Davis Pharmaceutical Research  
Gordon Vanscoy PharmD MBA, Vice President, Managed Clinical Division Stadtlander Drug Company Inc. and Assistant Dean, University of Pittsburgh

#### Panelists:

- David Angaran RPh MS,
- Sara Beis RPh MS, Medications Use Policy Pharmacist, Center for Drug Policy Analysis University of Wisconsin Hospitals & Clinics
- JoLaine Draugalis RPh PhD, Associate Professor & Assistant Dean, University of Arizona College of Pharmacy
- Deborah Freund PhD MPH, Vice Chancellor for Academic Affairs, Indiana University, James Pellissier PhD, Senior Biometrician, Merck Research Laboratories
- Richard Schulz PhD, Professor, University of North Carolina College of Pharmacy

### **Background and Context**

Like other disciplines, to expand and grow as a mature area of research and application, the field of health economics requires experts and skilled professionals. Previous educational efforts by schools of pharmacy includes the 1993 Invitational Conference, the American College of Clinical Pharmacists Proposed Guidelines for Pharmacoeconomics Fellowships (ACCP) , and International Federation of Pharmaceutical Manufacturer Associations' Survey (IFPMA). Various published surveys have also been produced with respect to the teaching of health economics at the university level.

Unlike many other scientific fields, there is no one background or training that prepares the researcher or the user of health economic information, who currently come from a diversity of educational and experiential backgrounds. Because this can and often does lead to difficulties in attaining consistent and high quality research, and achieving optimal use of health economic information in decision-making, a standardization of the educational and skills requirements for health

economics providers and users need to be determined.

## ***Problem Statement***

At the present time there is a strong demand for, and short supply of, qualified professionals in the field of health economics. The educational infrastructure is inadequate to satisfy the demand. Courses are not standardized and there is a shortage of adequately trained faculty members. Position variability and the multidisciplinary nature of the field make selection of qualified applicants with various backgrounds difficult for employers. Currently, a diversity of training opportunities exists for both decision-makers and researchers but there are few recognized formal programs. There is also a lack of awareness of available training opportunities.

## ***Issues***

The following key issues related to education and skills in the field of health economics were identified:

### ***1. Multidisciplinary Programs***

The structuring of multidisciplinary programs needs to be defined for people coming from a variety of backgrounds.

### ***2. "Real-World" Applications***

Training must include "real-world" applications.

### ***3. Ideal Program***

It is unlikely that an ideal program can be created in any one place within one institution or group without collaboration with others.

### ***4. Minimal Competencies***

The usefulness of minimal competencies in the field has to be determined. Minimal competencies will be different for current and future practitioners by depth of involvement. For each level of involvement, the type of competencies will have to be defined.

### ***5. Who should be trained***

Questions pertaining to who should be trained, how should training be performed and what level of training is required need to be answered.

### ***6. Credentialing***

The necessity of credentialing needs to be assessed.

### ***7. Training Opportunities***

There is need to improve the way information about training opportunities is disseminated.

A number of training opportunities specifically related to economic evaluations in health care already exist, including Self-study Continuing Education (CE) Programs, sponsored workshops and live CE programs. Certificate programs are also available. For example, the American Society of Health-System Pharmacists (ASHP) Competitive Edge Program which is society-sponsored includes self-study (30 hours), lecture and simulation exercises (4.5 days) and a research project (3-4 months). University-based certificate programs, undergraduate major degrees and minor concentrations exist in the field of health economics. Post-doctoral fellowships are also available. Various types of Master's Degrees (MS, MBA, MPH), medical training (MD) and doctoral training (PharmD, PhD) in a number of related disciplines also contribute significantly to existing training opportunities in health economics. Key Disciplines contributing to expertise in health economics are:

- 1 Accounting
- 1 Business
- 2 Economics
- 3 Engineering
- 4 Environmental Forecasting
- 5 Epidemiology
- 6 Finance
- 7 Health Administration
- 8 Management Science
- 9 Marketing
- 10 Medicine
- 11 Nursing
- 12 Pharmacy
- 13 Psychometrics
- 14 Sociology
- 15 Statistics/Biostatistics

### ***Recommendations and Next Steps***

Recommendations are proposed in the following domains:

1. Levels of expertise
2. Educational infrastructure awareness
3. Educational infrastructure enhancement
4. Proper training “match”

5. Balance between didactic and experiential education
6. Credentialing
7. Standardization of training and certification

**1. Levels of Expertise**

Three levels of expertise were identified by the panel including:

- Awareness
- Application
- Conceptualization

Awareness is defined as an exposure to and factual knowledge of the discipline, allowing trained individuals to converse and understand research data in the field. Individuals trained at the “application” level should be able to critically compare, evaluate and make decisions based on health economic research information. In addition, they should have the ability to initiate studies based on standard methodologies. For the conceptualization level of expertise, trained individuals would have the ability to create new methodology, develop theory and assimilate relevant methodologies and theories from related disciplines

Table 2: Levels of Competency and Corresponding Training Needs in Health Economics

Level of Competency	Level of Training			
	Continuing Education	Experiential Training/Certificate	Fellowships	Formal Degree
<b>Awareness</b>				
Industry Field Force	✓			
Healthcare Practitioners	✓			
Healthcare Administrators	✓			
Clinical and Marketing Industry	✓			
Patient Groups	✓			
Benefits Managers	✓			
<b>Application</b>				
Decision Makers for Populations		✓	✓	
Applied Researcher		✓	✓	✓
<b>Conceptualize</b>				
Academic/Faculty			✓	✓
Senior Industry Scientists			✓	✓
Senior Research Consultant			✓	✓

## **2. *Educational infrastructure awareness***

The panel recommends developing access to detailed information about available educational programs in the field of health economics. Identification of relevant educational resources outside of the field should be part of this awareness. A website would be an ideal tool to disseminate information on availability of all existing training programs.

## **3. *Educational infrastructure enhancement***

Relevant educational resources outside of health economics should be utilized to enhance the educational infrastructure. With respect to health economics training, a website and other available communication technologies should be used to offer educational support. This may include question-answer potential on-line and distance courses through a website. Sponsored formal training programs was also proposed. These would be competitively selected and targeted to different levels. The offering of higher level programs should be encouraged as well as short courses at society meetings and one to two-week training programs.

To assure relevance for all stakeholders, a three-way partnership with managed care, industry and academia needs to be established for fellowship and residency programs. There is also a need for official funding and faculty incentives. Nationally known training sites and “Train the trainer” programs would also contribute to the infrastructure.

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has a role to play in enhancing the educational infrastructure for health economics. Through ISPOR, various types of training could be offered, especially for those at higher levels. Faculty trainers should be experts in the field wherever possible. ISPOR may also wish to join forces with other organizations to expand programs.

## **4. *Proper training “match”***

Degree programs should accommodate multidisciplinary participants through the availability of prerequisite trainings and flexible core course offerings. Potential students of programs at the awareness training level should be made aware of their requirements. ISPOR identification of training programs would be helpful.

## **5. *Balance between Didactic and Experiential Education***

Programs, regardless of level, are enhanced by the incorporation of real-world data and exposure. The panel recom-

mends that any training include working in a real-life setting, with case studies and “live” datasets. Establishment of collaborative relationships between academia, industry and managed care organizations would be necessary to allow optimal training experiences.

#### **6. *Credentialing of individuals***

The development of a credentialing process should be a long-term goal of ISPOR to establish standards for the field. In the short term, for those already active in the field, the use of a professional portfolio demonstrating accomplishment in the field is recommended for credentialing of individuals.

#### **7. *Standards of training and certification***

It is recommended that ISPOR plays a leadership role in standardizing training and certification through a three step process.

- Develop guidelines for post-professional degree training
- Accreditate pharmaco-economic residencies and fellowships
- Establish collaborations with other organizations to expand accreditation to other relevant residencies

### ***Summary***

At the present time there is a strong demand for and short supply of qualified professionals in the field of health economics. Although a diversity of training opportunities exists for both decision-makers and researchers, the educational infrastructure is inadequate to satisfy the demand. Recognizing the need for different levels of expertise, the panel recommends an effort be made to increase awareness of currently available training opportunities and to strengthen the number and quality of these programs. Credentialing and standardization of training and certification are proposed as long term goals in which the International Society for Pharmacoeconomics and Outcomes Research has a major role to play.

# ISSUE V

## APPLICATION OF HEALTHCARE INTERVENTION ECONOMIC EVALUATIONS IN HEALTHCARE DECISION-MAKING

### **Goal**

Identify key issues in the application of health care intervention economic evaluations in health care decision-making.

### **Specific Objectives**

- Identify and prioritize the key issues associated with using healthcare economic intervention in healthcare decision making
- Identify a plan of action to resolve these issues
- Recommend next steps
- Suggest courses for degree programs
- Recommend next steps

### **Co-chairs**

- Jon Clouse RPh MS, Vice President, Applied HealthCare Informatics, United HealthCare Corp.
- Jean Paul Gagnon PhD, Director, Health Economics Policy, Hoechst Marion Roussel

### **Panelists**

- Greg Boyer PhD, Senior Head of Global Health Outcomes, Glaxo Wellcome Inc.
- Diana Brixner RPh PhD, Vice President, Novartis Pharmaceuticals
- Carolyn Clancy MD, Director, Center for Primary Care Research, Agency for Healthcare Policy and Research
- Gregory de Lissovoy PhD, MEDTAP Group
- Louis Morris PhD, Senior VP at PRR Inc
- Peter Neumann ScD, Assistant Professor, Harvard School of Public Health
- Ann Robinow, Executive Director of Care Systems & Finance for Buyers Healthcare Action Group
- Sean Sullivan PhD, Associate Professor, University of Washington, Seattle

### **Background and Context**

The last twelve to fifteen years has witnessed the rapid growth of health economics and outcomes research. This growth has been largely propelled by competitive pressures within the healthcare industry which created a need among healthcare decision-makers for methods that would allow them to contrast and compare the costs and consequences of healthcare intervention. Pharmaceutical product selection has become a key area for use of economic studies.

Formulary decision-makers using the results of economic studies and models can be categorized into three groups:

- 1) Healthcare decision-makers in practice settings use health economic and outcomes information in drug selection for formularies. There are currently over 8,000 hospital and managed care organizations in the United States that fre-

quently make drug-selecting decisions for formulary inclusion.

- 2) Policy makers within state and federal agencies are required to assist in evaluating prescription drug coverage decisions for various programs, or use health economic information to construct policy.
- 3) Development managers within the pharmaceutical industry who have a growing need to increase the return on investment in research and development.

In current market dynamics, drug choice decisions are made or driven by various stakeholders including pharmacy and therapeutics (P&T) committees of hospitals and health plans, drug purchasers for large employers or buying groups, government bodies, practicing physicians, retail pharmacists, insurance companies, pharmacy benefit management companies and patients. Drug choice decisions are made most often on the basis of clinical efficacy and safety information, without knowledge of the impact on total cost to a healthcare system. Groups making these decisions generally have little background in the issues of health economics and outcomes research.

Currently, health economic information is often delivered to decision-makers through the pharmaceutical industry or their representatives (i.e. consultants, research organizations and academia) in support of a particular drug therapy or specific drug choices. There is not much consistency in how this information is offered, since each company and each researcher may present a different view of the research and the results. As a result, health economic studies are viewed skeptically and as of limited applicability in the process of drug choice decision-making. Although this has improved recently, surveys of decision-makers and comments by practitioners on the value and relevance of health economic information and reports do not yet indicate a compelling demand from decision-makers for economic and outcome evaluative information (Slogan 477; Grabowski 389; Drummond 249; Luce 398; IMS 490).

### ***Problem Statement***

Information about the impact of new therapies on costs within a healthcare system should be essential for making better healthcare decisions. However, the relevance of health economic information to decision-makers has not been demonstrated. There is little user-friendliness in the health economic data supplied by industry consultants. Moreover, there is a lack of consistency of approach and format that would facilitate comparison of pharmaceuticals under review. Finally, much of the information presented lacks the transparency necessary for the user to determine the appropriateness of methods or the soundness of assumptions.

## ***Issues***

A fundamental disconnect exists between 1) the way decisions are made by healthcare decision makers, 2) type of information presented to healthcare decision makers and 3) the type of information required by health economic and outcomes researchers. Specific issues include:

### **1. Evaluative criteria perspective.**

Evaluative criteria (e.g., efficacy, safety, cost, quality of life) are often weighed differently by potential users of health economic research data for decision-making purposes such as formulary committees, providers, health plan managers, patients or employers.

### **2. Language and definitional barriers**

Language and definitional barriers hinder effective communication between potential users and producers of the information may exist.

### **3. Lack of treatment comparisons**

There is little data on direct product or treatment comparisons that are of greatest interest to potential users.

### **4. Lack of communication**

Little dialogue exists between the potential users and the producers of information on what is relevant and what information can be generated by health economic research.

### **5. Lack of understanding**

Potential users of health economic research data may be hesitant to include health economic information in their decision-making process because it is different from their established clinical orientation.

### **6. Conflicting study design**

To conduct studies which provide health economic information that meets users' needs, certain research designs for health economic and outcomes research studies may conflict with clinical design, causing regulatory and liability concerns.

### **7. Research Funding**

Some sources of research funding may present a barrier to the credibility and application of study results.

### **8. Societal perspective vs. individual perspective**

A conflict may exist between recommendations based on population data and the care of individual patients.

### **9. Lack of quality criteria**

When health economic research data is used in the decision-making process, there is no recognized approach for measuring the quality of the decision or the net result.

#### 10. **Lack of experts**

There are few skilled opinion leaders or other resources from which potential users can seek advice and assistance.

#### 11. **Segregation of organizational finances and health outcome decisions**

Decision-maker organizations segregate budgetary decisions for pharmaceuticals from those related to other medical technologies and services.

##### ***1. Evaluative Criteria Perspective***

Decision-makers often weigh evaluative criteria differently. One barrier to the use of health economic studies is that multiple decision-makers weigh criteria differently. For example, patients may place a different importance on certain quality-of-life attributes of a product than the physicians prescribing it or the managed care decision-makers providing access to the product in their plan. Even within categories of decision-makers, variability in the weight placed on attributes exists. Taking this a step further, decisions that are optimal from society's perspective may be unacceptable from the perspective of an individual plan or patient. As a result, health economic studies that attempt to construct a single metric may encounter resistance from decision-makers. The Panel on Cost-Effectiveness in Health and Medicine (Weinstein 113) has recommended conducting "reference case" cost-effectiveness analysis from the societal perspective as a way of enhancing comparability across studies as well as from other perspectives which are relevant to the decision at hand.

##### ***2. Language and Definitional Barriers***

Language and definitional barriers exist that prevent the effective communication between users and suppliers of health economic information. Scientific jargon may hinder effective communication between the producer and the end-user of health economic information. A major problem is in definition of terms. For example, 'cost-effectiveness analysis' has been confused by some as meaning only 'cost-saving' or 'cost-reducing' whereas in practice, the term describes the jointly-determined relationship between outcomes of competing therapies measured in terms of effectiveness and the costs required to achieve that level of effectiveness. Cost-savings is only one possible result. Other terms such as cost-utility, quality-adjusted survival, healthy-year equivalents, Gompertz functions, bootstrap, and time preference hold very little meaning to the practicing physician, the pharmacist or the health plan manager. Thus, when economic and outcomes data or models are provided to clinically-oriented individuals for the purpose of formulary consideration, some or most of the message may be lost simply because of these language barriers.

Researchers in the field of health economics may propagate some confusion by coining terms in an attempt to clarify methods to peers that generates confusion for those outside the field. This nomenclature distances the field, the publications, and the potential application of results from the user. If it is to be useful, there is a need for education of the user to better understand this information. There is an even greater need on the part of the information producers to provide economic and outcomes messages that are clear, precise, relevant, and containing no unnecessary jargon.

### **3. *Lack of Treatment Comparisons***

Available information fails to provide data on direct product or treatment comparisons that are of greatest interest to potential users. Head to head comparisons of performance in multiple dimensions, not just cost of the product, of competing drugs is information critical to committees making formulary decisions. For this type of user, comparison of one drug to another may be of primary concern; to other users, such as practicing physicians and patients, these comparisons must look at alternatives beyond drug choices. Physicians are making treatment decisions with increasing input from patients. These decisions are not limited to drug choices. They include no treatment, non-pharmaceutical alternatives such as diet changes, therapy or surgery, and other treatment options such as homeopathic remedies.

### **4. *Little Dialogue***

Little dialogue exists between users and suppliers of health economic information on what is relevant and what can be generated. A multitude of guidelines to health economic research, some of which give conflicting guidance, exist in the US and elsewhere. Healthcare decision-makers, or their consultants, may choose any of these guidelines. Inconsistent decision-making within or between organizations may result. In addition, within the timeframe of current decision making, many of these guidelines are too complex and time consuming to be a realistic part of decision-making for either the user or the supplier of the information. The Pharmaceutical industry has provided information in response to a global request for economic data to support healthcare decisions. However the information is not being used or used appropriately. This behavior indicates a need for clarification by the decision-maker about specifically what information is needed and by the research what information can be provided. Conversely, suppliers of information have not been proactive in seeking to assist users in making decisions. For example, market research data developed for internal product decisions could be very helpful to healthcare decision-makers.

### **5. *Lack of Understanding***

Potential users of health economic and outcomes research data may be hesitant to include health economic information in their decision-making process because it is different from their established clinical orientation. Decisions regarding use of and coverage for pharmaceuticals are usually placed with committees of clinically trained professionals, such as physicians, pharmacists, and nurses whose training focuses their attention on pharmacological and therapeutic aspects of treatments. They usually have little background to support the incorporation of different types of valuing schemes, such as health economic research, into their decisions.

Additionally, federal drug approval regulations require that manufacturers generate evidence of product efficacy and safety through the use of specified research methods. Decision-making bodies have readily adopted the use of efficacy and safety data into their deliberations since it coincides with the clinical aspects of their training. Incorporating information from outside a well-developed decision-making paradigm is difficult. When the existing paradigm is complex, the implications for incorrect decisions are significant. Decision-makers may not feel comfortable with changes to an established process.

#### **6. *Conflicting Study Design***

Regulatory and liability concerns may conflict with certain research designs for health economic and outcomes research studies that meet decision-maker needs. An often-noted problem in developing information for formulary decisions is the timing of drug approvals and the need for comparative information. Drug companies have the responsibility of gathering data to support drug approvals. However, companies also want to provide useful outcomes information about their products at the time of product launch, when formularies make initial purchase decisions. Formularies often request comparative information derived from studies in populations and settings with similar characteristics to the purchasing group.

One solution for this dual set of interests would be for drug companies to perform phase III studies that could be used for both regulatory and marketing purposes. Often humanistic and resource utilization data may be gathered as “add-ons” to existing protocols. However, certain regulatory requirements may make it difficult to create valid designs for outcome studies. For example, safety concerns may make it necessary for protocol planners to include physician visits, physical examinations, and laboratory tests at more frequent intervals than would be utilized in routine practice. These planned visits and tests may make it impossible to assess whether study drugs variably caused unscheduled and extra physician visits. Similarly, patient management concerns at managed care organizations may make it difficult to plan valid Clinical studies. They may have policies that prohibit the use of placebos, random assignment of patients to treatment, or other

design features essential to the conduct of a clinical trial. Managed care organizations may also be unwilling to fund certain data collection costs, or their accounting system may require them to charge all of the costs necessary to treat patients enrolled in the trial, even costs not related to the trial, to the funding agent.

## **7. *Research Funding***

The source of research funding may present a barrier to the credibility and application of study results. Many health economic studies are currently funded by the pharmaceutical industry, either directly or indirectly through persons contracted to do such research such as consultants, research organizations or academia. This has led to serious concerns by potential users of the information that it is biased towards the sponsoring company's product and therefore lacks credibility.

In light of the fact that decision-makers at managed care organizations have complained about the lack of independence of health economic research studies, it is curious that they have not funded more studies themselves. Only rarely have some plans paid for studies, directly or indirectly, by sponsoring research conducted by independent groups or consultants. This may reflect their lack of familiarity with health economic research techniques or it may be that plans cannot capture for themselves the full return on investment when sponsoring the information.

## **8. *Societal Perspective vs. Individual Perspective***

A conflict exists between recommendations based on population data and care of individual patients. By definition, health economic analysis is population based. Decisions about drug alternatives using health economic data inherently consider optimization of resource use relative to outcomes across populations. These decisions are made using the values of the decision makers applied to larger groups, which may not coincide with the values of individual patients or physicians, especially when the economic issues considered do not directly apply to them. Patients are generally unmoved by physician or health plan explanations that their drug- or treatment-of-choice is not available to them because it is not "cost effective".

This debate about optimization of health for populations versus individuals is far from resolution in the US. Without an agreed-upon values framework that will stand up to scrutiny by all users, decision-makers will continue to struggle to defend decisions, not just drug choice, that are in any way driven by a trade-off between population health costs against individual outcomes.

### **9. Lack of Quality Criteria**

There is no measurement system to validate decisions. Health economic research is designed to inform choices among alternative medical technologies. In the most complex situation, a study may find that a certain relatively costly new therapeutic product offers more “value” to the adopting organization than the current less expensive therapy. “Value” may be defined using an abstract metric such as quality-adjusted life years.

Once an organization has adopted a new technology, some implications of the decision may be readily visible. For example, pharmacy expenditures may have increased. But whether or not “value” has also increased may not be so readily discernible. While the potential consumers of health economic research, such as managed care organizations, have in place mechanisms to track resource utilization (cost) they generally lack comparable procedures for quantifying outcomes of care (effect).

### **10. Lack of Experts**

There is an inadequate availability of opinion leaders to turn to for assistance. For the end-users of health economic analysis, interpretation of a study can represent a formidable task. Methods and findings are typically described using the jargon that characterizes any specialized field. Analytic methodology may be complex, and is becoming more so as researchers adopt techniques such as calculation of confidence intervals around cost-effectiveness ratios.

The availability of published checklists to evaluate the quality of a study can facilitate review by persons with somewhat limited expertise. However, a study that appears to conform to recognized standards may still be seriously flawed. In part, this is due to the widespread dissemination of guidelines for health economic research. These guidelines are effectively creating templates for study presentation.

Many end-users lack internal expertise to assess the validity and reliability of health economic studies. In such a situation it would be natural to seek outside advice; however, this is not easy to locate. End-users may not be aware of mentors, individuals or organizations such as academic groups or consultants, that could offer guidance, and there is no formal mechanism for identifying such expertise or referring end-users to potential advisors.

### **11. Segregation of Organizational Finances and Health Outcomes Decisions**

Decision-maker organizations segregate budgetary decisions for pharmaceuticals from those related to other medical technologies and services. Managed care organizations and hospitals most often have separate budgets managed by separate departments for pharmaceuticals versus other medical technologies and services. This separation places downward pressure on both budgets separately, and creates difficulty for efforts that attempt to assess the budgetary impact of individual pharmaceutical therapies on the entire medical cost budget. This silo effect is a significant impediment to better utilization of pharmacoeconomic and outcomes information in decision-making.

### ***Recommendations and Next Steps***

For the following recommendations to become a reality, a central organizer must be recruited to coordinate the improvement of the application of healthcare intervention economic evaluations in healthcare decision-making. The International Society for Pharmacoeconomic and Outcomes Research (ISPOR), as a recognized leading international organization in the field of health economics, is proposed as the critical link to implementing these recommendations.

1. To determine the information needs of the community, ISPOR-sponsored focus groups be created to provide a forum for dialogue between potential users, producers, and regulators of information. Researchers and suppliers of health economic data must actively engage with decision-makers to determine the key health economic evaluative criteria for decision-making purposes and formulate ways to supply the information consistently. Because decisions are seldom made using a single variable, determining a set of variables which researchers can supply will move the discipline toward greater relevance. A multivariable approach will allow the decision-makers flexibility to focus on evaluative criteria germane to their population while providing researchers the opportunity to highlight key criteria on which a product excels or falls short. To establish the needed relevance, cooperation among users and researchers, both industry and academic is essential.
2. ISPOR develops a set of simple criteria for evaluation of these studies, agreed upon by consensus of all parties involved and designed to recognize different types of perspectives and research design so that specified research questions and business needs are met. ISPOR should also seek to bolster the objectivity, reliability, and credibility of the health economic studies through various mechanisms, including working with sponsors, researchers and journal editors, to adopt protocols that will establish the independence of research and statements for the disclosure of funding sources.

3. A training initiative for decision-makers in using health economic research information for decision-making can be offered through ISPOR. Educational programs in the area of health economic analyses should be created for clinically trained decision-makers. The focus may be directed towards how health economic information can be incorporated into existing decision-making paradigms and the added value that health economic data can provide in decision-making. A consortium of managed care and other purchasing organizations, academic researchers and one or more health economic research organizations should be formed to execute this recommendation. Funding to support the effort should come from pharmaceutical industry, government, and to the extent possible from managed care and other purchasing organizations that wish to participate. The project should be conducted over a two-year education period with a two-year follow-up evaluation. The education program itself should continue until the results of the two-year evaluation are completed.

Suggested criteria for project evaluation could include:

- a) interviews with decision-makers regarding changes in their decision analysis process;
- b) impressions as to how the decisions have been changed; and
- c) longer term analysis of the impact on health care resource allocation and on patient health within the participating health care systems.

4. A standard reporting format to allow flexible weighting of factors based on individual decision-making preferences should be developed by ISPOR in collaboration with potential users and producers of information. It is suggested that presentation of the results of health economic analyses be modified to show the various components of effectiveness measures, service utilization measures and costs. This way clinically oriented decision-makers can observe similarities of information between what they currently use and that used in health economic analyses. A standard approach to providing clinical, economic and outcomes data to decision-makers should be developed to minimize use of technical jargon and effectively communicate the necessary data and results. Coincident with an effort to train the user community in language and methodology of economic evaluation and outcomes research (as in recommendation 2), this would reduce the language gap between the producer and consumer of healthcare economic information.

5. ISPOR form a committee that would produce a standard format for Data Element Shells (DES). DES would be in the form of desegregated data from cost-consequence or cost-effectiveness analyses. For each outcome of interest, reference to the data source could be made to allow reviewers to discern the degree of scientific support for each data

element. The information presented would be based upon feedback from managed care organization purchasing agents about the types of information needed to make purchasing decisions (as in recommendation 1). This type of cost-consequence information would be provided in addition to full cost-effectiveness analyses. It would permit purchasers to understand the effects of drugs that are being considered on the outcomes of greatest relevance to the individual groups. Drug companies would be free to present additional information on outcomes. Managed care organizations could easily compare the results of several competing CEAs with the use of a standardized format. Areas where data was not available would be evident. ISPOR, in collaboration with potential users and producers of information, could be responsible for creation and updating of a DES form. The ISPOR committee would decide on the level of specificity of the DES, perhaps either a general format for all drugs or a specific format for individual drug classes.

- 6 ISPOR should support an information clearinghouse of available thought-leaders and experts in the field. This should include development and maintenance of an Internet WEB site with links to expert's homepages and e-mail addresses. ISPOR as an organization brings together many of the researchers qualified to evaluate health economic research and interpret findings. ISPOR could develop rosters of persons qualified to review studies, similar to editorial boards for journals, where the reviewers would agree to participate in reviewing documents or addressing queries to promote a better understanding of the field of health care economics.

### ***Summary***

Applying the knowledge provided by health economic studies to health care decisions at all levels can only be an asset to healthcare systems. To achieve this, it is paramount that the information needs of potential users of health economics be determined, that training is provided to facilitate better use of this information, and the results of health economic studies be presented in an easily interpreted and comparable way. Allowing users of this information access to experts in the field when additional support is needed will ensure that the information is not dismissed because it is not understood. A relevant association such as ISPOR has been proposed as a facilitator, bringing representatives of drug companies, managed care organizations and regulatory agencies together to discuss areas of compromise, which will allow performance of more efficient and useful studies. ISPOR should also participate in the design and funding of educational programs and in the development of standardized data reporting formats.

# ISSUE VI

## ADDRESSING QUESTIONS OF BIAS, CREDIBILITY AND QUALITY IN HEALTH ECONOMIC EVALUATIONS

### **Goal**

Identify key issues in addressing bias, credibility, and quality of pharmacoeconomic evaluations.

### **Specific Objectives**

- Identify and prioritize the key issues associated with reducing bias and increasing credibility and quality of pharmacoeconomic evaluations
- Identify a plan of action to resolve these issues
- Recommend next steps

### **Co-chairs**

- Rod Barnes MBA, Director, Health Outcomes, Alcon Laboratories, Inc.
- Alan Heaton PharmD, Pharmacy Gold Inc

### **Panelists**

- Carole Magoffin MS, Senior Advisor, National Pharmaceutical Council
- Jack McMillan PhD, Director & Team Leader, Outcomes Research, Pfizer Inc.
- Tom Taylor PhD, Associate Professor & Co-director of the University of Iowa College of Pharmacy
- Albert Wertheimer PhD MBA, Director, Outcomes Research & Management, Merck & Co Inc

### **Background and Context**

Bias, quality, and credibility are long-term research issues addressed by experts in many fields. Like other disciplines, the field of health economics continues to evolve and challenge itself in this regard. Improvements in this field of research necessitate support and adhesion to the highest quality work and integrity, promotion of continuous quality enhancement and open dialogue.

Definition of bias in the field of health economic research refers to a meaning beyond the Stanley and Campbell (Campbell 63 667; Cook 81 668) statistical concept, i.e., as a threat to validity. Bias is also an ethical issue dealing with disclosure and conflict of interest. The following definition of bias was proposed by The Task on Principles for Economic Analysis of Health Care Technology in 1995 (Task Force 479): as, "A range of factors that systematically influence the measures undertaken independent of the studied intervention; a tendency, intentional or unintentional, to inappropriately or unfairly favor one or more of the interventions being evaluated."

Resolution of bias, quality and credibility issues in health economics is complicated by a host of factors, especially the variety of stakeholders and their unique perspectives and information needs. These stakeholders include users of research such as managed care organizations, governments, payers and providers, and the producers of research such as government agencies, pharmaceutical firms, payers and providers, academics, consultants, and foundations.

The objectives of this panel were to address the issues of bias, quality, and credibility of health economic research from the perspective of both producers and users of these data with patient care as the underlying concern. The scope of the panel's deliberation included public dissemination of research data, methods to improve quality, minimize bias, and thus enhance credibility of health economic studies. Methodology issues are elsewhere. The panel anticipates that as advancements are made over time, concerns over bias, quality, and credibility of health economic research will diminish.

### ***Problem Statement***

Multiple published studies have criticized the rigor, relevance, objectivity, methods, and reports produced within the health economic research domain (Drummond 378; Udvarhelyi 417; Coyle 114; Bradley 30; Balas 363; Iskedjian 394; Hillman 669; Blades 670; Lee 671). Consequently, health economic research findings are not used as extensively as they could be and rational decision processes about the efficient use of health care resources may not be fully informed. Ultimately, care for patients and populations may be adversely affected. In this context, there is a need for continued improvement in the quality of economic research conducted.

### ***Issues***

The panel identified the following key issues surrounding these matters:

1. **Quality:** are best methods being used?
2. **Bias:** whether real or perceived, how do we deal with it?
3. **Credibility:** do we have a problem with believability or with relevance?

#### ***1. Quality***

Health economics is a relatively new science without strong consensus on all methods. There is a need to develop consensus on methodology for quality issues to be resolved. The multidisciplinary nature of this field of research makes

peer identification for manuscript review difficult. In addition, there is a lack of consensus on evaluation criteria, rendering the peer review process difficult.

## 2. ***Bias***

Bias can be divided into “intentional bias” and “unintentional or subtle bias” which includes design flaws and inappropriate conclusions irrespective of the medical interventions under study.

Bias can be related to the underpowered nature of many clinical and database studies which would require much larger samples. There is a perception that financial sponsorship will bias study results. However, despite objectivity problems, industry is still the major funding body for healthcare economic information. Withholding negative findings and failure to submit data to public scrutiny can bias the literature and applications of research data which are disseminated. There are few occasions when circumstances would make the withholding of results acceptable (Yee 97 419).

## 3. ***Credibility***

The relevance of health economic research data is questioned by decision-makers with respect to populations studied and the disconnect between decision makers' criteria (business decisions under risk or uncertainty where majority rules) and methodologists' concerns (scientific standards seeking statistical significance) Stakeholders have different objectives. Methods are geared to societal decision-making but practical applications are at a different level. In addition, decisions have to be made right away and cannot wait for the development of better methods. Some groups and journals such as the New England Journal of Medicine (Kassirer 91) have questioned the credibility of health economic analyses and restricted the dissemination of data. The ownership of health economic data must be defined, as well as access to this information. Health economic tools are expected to be employed to optimize use of the resources of society, but few decision makers use them that way.

## ***Recommendations and Next Steps***

The following recommendations will improve the quality and credibility of health economic research. These recommendations pertain to four major domains:

1. Design and research practices
2. Sponsorship
3. Publication and dissemination

4. Role of professional societies and organizations

5. Follow-up conference

### **1. *Design and research practices***

Researchers should design and conduct studies using the best available practices consistent with the study objectives. Methods should be specified in advance as well as explicitly and transparently reported. Health economic studies should generally follow ethical Good Clinical Practices provisions such as those described by the American Federation of Clinical Research (AFCR Good Clinical Practices) or other authoritative bodies. Prospectively designed pilot studies are essential for the evaluation of feasibility and the planning of future research. In addition, studies should not be terminated early in an attempt to hide unwanted health economic results of potential interest. Base case assumptions should be clear, and the sensitivity analyses should include conservative assumptions for the new technology being assessed.

### **2. *Sponsorship***

Full disclosure of any financial relationships which authors and speakers have linking them directly or indirectly to the interventions under study should be listed. Sponsored research should have a written protocol agreed to by researchers and sponsors in advance. Unanticipated issues should be handled by mutually agreed protocol amendments. Access to relevant documents and data, project control, presentation, and publication rights should be defined in advance in the contract (Schulman 415). The contract would reflect the code of ethics recommended by this panel.

### **3. *Publication and dissemination***

Authorship should conform to generally recognized practices among the peer research community. Research data, given full disclosure, transparency, and sufficient information to replicate the study, should be judged on the merits of its content. One or more authors should be receptive to and available for reader inquiries in those cases where it is clearly not practical or possible to provide all information necessary for replication of the study within a manuscript. Publication decisions by journals should use the same criteria for evaluating merit of health economic studies that are used for other types of manuscripts, and should not preclude publication of health economic work due solely to funding arrangements or author affiliations. Published reports should address the criteria established by experts and be completely transparent to facilitate evaluation, comparison or reproduction.

Mandating full publication rights in a code of ethics for health economic research remains an area of debate among panel

members. Certain members believe that this issue is at the heart of bias and credibility problems and they advocate full publication rights for contractors performing health economic research. Other panel members anticipate that mandatory rights in certain health economic studies could be problematic. Organizations, industries or government bodies using contractors to perform studies are not likely to allow full publication rights for their services.

#### **4. *Role of professional societies and organizations***

A professional society such as the International society for Health economics and Outcomes Research (ISPOR), the Association for Health Services Research (AHSR) or the Society for Medical Decision-making (SMDM) should consider developing a code of ethics for health economic researchers. Those professional societies need to collaborate on education and best practices for the benefit of association members, the journal community and research users, and to improve quality, reduce bias, and enhance credibility of health economic research. Professional societies should also help journal editors identify peer reviewers and advise on their review procedures. A foundation to address these ideas may be in order. ISPOR and similar bodies should also publicize awards for high quality research, including student or fellowship awards.

The concept of an independent body that would provide confidential advice and would certify voluntarily submitted health economic study designs and reports deserves further discussion. This body could be a quasi-public organization that discloses all its financial relationships. Importantly, a similar body might also investigate means of evaluating health economic research for continuous quality improvement and development of the field.

#### **5. *Development of Study Methods and Ethics Standards***

In the near future, clear best methodological and ethical practice statements should be developed and disseminated. Meetings with journal editors and users should be organized to educate and offer assistance to stakeholders. Specific recommendations are:

- i. Researchers should design and conduct studies using the best practices consistent with the study objectives. Methods should be specified in advance, explicitly and transparently reported.
- ii. Health economic studies should generally follow the ethical Good Clinical Practices provisions described by authoritative organizations such as the American Federation of Clinical Research.
- iii. Authorship should conform to generally recognized practices among the peer research community.
- iv. Full disclosure of financial relationships of authors and speakers should be listed.

## **6. Follow-up conference**

A conference similar to this one should be convened in two years to review progress made as a result of these deliberations. ISPOR should work with other societies and organizations to further explore all the other recommendations made by the panel which require additional thought.

In addition to the above recommendations, ISPOR should develop the following activities:

- Establishment of a code of ethics addressing among other issues the use of appropriate methodology, reproducibility, publication rights and disclosure of potential conflicts of interest. Internal distribution and acceptance should be sought in the coming year, with subsequent external promotion.
- Creation of an office to continue work on the issues raised by the panel, to coordinate collaborative efforts with other organizations, to provide regular commentary and input and to facilitate the exchange of ideas in the ISPOR journal.
- Dissemination and high exposure of information related to awards obtained for high quality research including annual meeting presentations, journal articles and student fellowships.
- Establishment of a working relationship and coordination of regular meetings with the Food and Drug Administration (FDA) to develop health economic guidelines to address concerns related to bias, quality, credibility and ethics.

## **Summary**

Criticism of health economic research has resulted in limited utilization of this data by decision-makers and end-users, potentially affecting care for populations. A number of recommendations were proposed by the panel to address the issues of bias, quality, and credibility of health economic research from the perspective of both producers and users of these data with patient care as the underlying concern. Suggestions pertain to four major domains, including design and research practice, sponsorship, publication and dissemination of research data and the role of professional associations and organizations.

# ISSUE VII

## COMMUNICATION AND REPORTING HEALTH ECONOMIC INFORMATION

### **Goal**

Identify key issues in communicating and reporting health care economic evaluation information.

### **Specific Objectives**

- Identify and prioritize key issues
- Describe the mechanisms for putting pharmacoeconomic and outcomes information and data into the same operational format that decision-makers use to make formulary decisions
- Identify the entities, which are conducting/supporting, the research, the purpose of research and their target audiences for communicating research results
- Discuss outlets of communication of research results and advantages and disadvantages of source and ways to improve the effectiveness of the outlet.
- Discuss Optimal Formats for communication of Economic Evaluation Results
- Recommend next steps

### **Co-chairs**

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### **Panelists**

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- Laurie Burke RPh MPH, Senior Regulatory Research Officer, US Food & Drug Administration
- Gloria Governali BA, Phase V Communications
- Eduardo Ortiz MD MPH, Associate Director, Outcomes Research, Merck & Company
- Jane Osterhaus, Director, Pharmacoeconomics, G.D. Searle and Company
- Lisa Sanchez PharmD, President, PE Applications

### **Background and Context**

Although a great deal of time, effort and resources are invested in the performance of health economic evaluations, usually only minimal thought is devoted to most of its communication. This is extraordinary considering that the primary objective of health economic assessment is to provide healthcare stakeholders with useful tools to assist them in decision-making, and that effective communication is of key importance in influencing decision-making.

The audiences at which health economic information is directed are as diverse as the decisions that must be made. From government policy-makers involved in the allocation of federal resources to health care and biomedical research, through

to the patient who needs to play a knowledgeable role in his own health care, each consumer of health economic information has specific needs. The following are target audiences of health economic information:

- 16 Government policy-makers
- 17 Regulatory agencies
- 18 Healthcare providers
- 19 Healthcare professionals
- 20 the healthcare industry
- 21 researchers and educators
- 22 the public (e.g., consumers, patient interest groups)

For a health economic message to be “heard” by its intended audience, certain criteria must be met. The message should be:

There are also usually barriers to acceptance of a message which must be overcome before it can be “heard”. These may be explicit or implicit, rational or emotional, they may be specific to the entire target audience or to a subset of it. To maximize the influence that health economic information may potentially have, these barriers need to be recognized, identified, and disposed of.

### ***Problem Statement***

Users of health economic information represent many different perspectives with various levels of expertise and information needs. To obtain most value from the resources invested in health economic research, how do we optimize the effectiveness of our communicating of health economic information?

### ***Issues***

Three main areas for development have been identified as keys to more effective communication:

1. **Relevance:** *Is it needed?*
2. **Usefulness:** Will the intended audience be able to make use of it?
3. **Credibility:** Is it believable?

## **1. Relevance**

*Is the message relevant for its intended audience?*

How well we meet the needs of the intended audience depends on how well we know them. Who are they? What information do they need to make appropriate choices? What is their decision-making process? What is their level of understanding and expertise?

This information can be obtained from numerous sources. However, the target audience itself should be involved in delineation of its needs and process, although assistance from the producers of health economic information may be needed, according to the degree of experience of the user.

Among the points to be considered when evaluating relevance are:

- the varied information needs of end-users and their magnitude of importance;
- the changing environment or time constraints in which decisions are being made; and
- the predominant influence(s) over those making them, for example, political, social, budgetary, clinical, or logistical.

There is often disagreement between researchers and their audiences concerning relevance of research design to the application its results. Greater awareness of the intended purpose of the research and objectives of the user before study design may help to reduce that conflict.

## **2. Usefulness**

*Will the information be useful to its intended end-user?* Three areas were identified as issues with regard to the usefulness of health economic information, reporting standards, communication formats and content of the information.

### *i. Reporting standards*

*How much standardization is wanted?* There are distinct benefits to having standard formats for health economic reporting structures. They allow for greater clarity and understanding of the content, they create a sense of familiarity with terminology and format that allows faster integration of new information, they promote comparabil-

ity across studies. For educational purposes, they simplify the learning process, and facilitate the work of editors and reviewers in the review and evaluation of health economic documents. Creating standard formats for all types of health economic communications will help end users wade through the overload of information available, more quickly comprehend the message, and be able to compare it for decision-making purposes.

Creation of reporting standards for all types of health economic studies, Clinical studies, modeling, database studies, would necessarily be the first step to standards for publication in peer reviewed journals and elsewhere, and other modes of communication such as public presentations and posters, and formulary submissions.

## *ii. Communication formats*

*What is the most appropriate communication vehicle?* Besides the ones that are most familiar, (abstracts, posters, public presentations, reports and articles, health economic communications), more and more communications are taking place through other forms of written communication such as targeted briefing documents and various types of submissions to healthcare providers, on an interpersonal level, or through the mass media. Consideration should be given to the usefulness of each type of communication, and its potential role in information transfer.

## *iii. Content of Information*

*How useful will the intended audiences find the information content?* Again, the users of health economic information possess a variety of backgrounds and expertise in this multidisciplinary field. The content of any message has to be tempered according to the level of sophistication of the users, as well as knowledge of the needs of the audience. Managed care organizations have different needs than do physicians, who may in turn be looking for something different from consumers. The key is knowing the needs and abilities of an audience.

## **3. Credibility**

*How do we enhance the credibility of health economic communications?* Once a solid base of useful information has been created and focussed to the needs of the target audience, no matter how well presented it may be, unless the audience finds it credible, it will not be used. To enhance the believability factor of health economic information, three areas must be explored, accepted standards of practice, the concept of disclosure, and validation of the information.

*i. Accepted standards of practice*

Establishing standards of health economic performance are the mandates of other panels, with respect to methodologies, ethics, bias and conflict of interest. It is important to note though that without a set of standardized criteria on which to base judgement of health economic information, only the most experienced audience will be able to feel (rationally) confident about its acceptability.

*ii. The concept of disclosure*

The concept of disclosure includes more than simple transparency. While transparency provides that all assumptions and all influences that went into the creation of the health economic information are revealed, disclosure goes beyond. The information provider must furnish sufficient detail to enable the audience to make a relevant decision about the information. The amount and sophistication of the detail disclosed will vary according to the expertise and the skills of intended user. At present this concept is poorly developed; standardization of levels of disclosure is needed.

*iii. Validation of health economic information*

How much protection does the consumer of health economic information want? That will probably depend on the importance of the decision to be made and the discriminatory abilities of the user to determine the quality of an analysis, which will in turn depend on their training and experience. There is no one appropriate level of health economic background needed by all, but clearly there is a need for a basic level of knowledge for all users of health economic information users (see the education and skills panel).

A systematized independent review process of health economic research that provided a measure of validity according to generally accepted standards, would increase the level of credibility associated with that research. It would confirm that a study met acceptable design, methods, conduct, format, disclosure and presentation standards. As a form of accreditation, this review would allow users to be more comfortable with reported results.

## ***Recommendations and Next Steps***

Six areas which require future development have been identified, to strengthen the relevance, usefulness and credibility

of health economic communication.

### **1. Identification of users and their needs**

To extend the relevance of ongoing health economic research, key users of health economic information should be identified, along with their information needs. This should be a three-step process involving all interested stakeholders, but should be coordinated by an independent professional association such as ISPOR.

Step 1: Perform a comprehensive evaluation of the literature to determine what has already been published on the subject

Step 2: Establish working groups that include other interested professional organizations to identify the relevant stakeholders, the types of information needed, and the potential barriers to communication that exist. This may be an iterative process, including other stakeholders at later stages

Step 3: With the information gathered in step two, prepare and conduct a survey of all users of health economic information, to provide a basis for standardization of communications

### **2. Standard communication formats**

To increase usefulness of health economic communications, establish standard communication formats based on predetermined relevance, information and credibility needs of users and on standard health economic performance standards that should be under development elsewhere. These should eventually include: a) Uniform presentation, b) standard terminology, c) adequate disclosure; and d) a basis in previously published guidelines (Uniform requirements 393; Mason 468).

### **3. Reporting guidance**

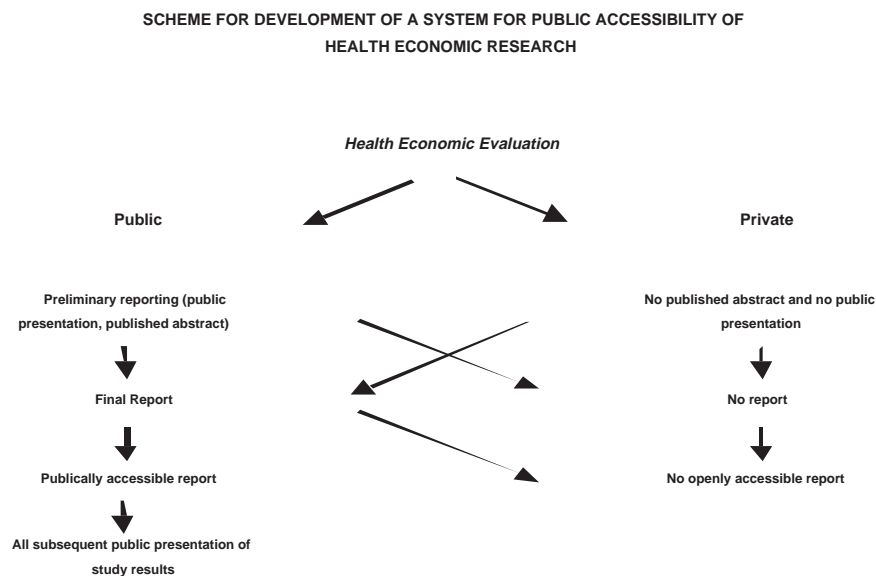
As standardized formats are established, Reporting Guidance (RGs) should be adopted by ISPOR and applied to all publicly presented communications, including ISPOR's journal. Other vehicles of communication, such as other biomedical journals and internet publishers, should also be encouraged to use these standards. ISPOR Reporting Guidance should establish reporting standards for each major study type, and over the long term, tailored to each specific type of audience as well.

#### 4. *Biannual surveys*

Performance surveys to evaluate the use of Reporting Guidance and the quality of reporting should be undertaken on a biannual basis.

#### 5. *Public accessibility*

A principle of publicly accessible reports that adhere to ISPOR RGs should be established. This would allow access to research reports that is not directly controlled by the researcher or the research organization. Once a report has been “filed” for public accessibility, all subsequent communications could refer to that report. The following figure illustrates a scheme for the development of a system for public accessibility.



#### 6. *Enhanced peer review*

An enhanced mode of peer review should be instituted for all forms of health economic communications. This type of review would assure that there was compliance with ISPOR RGs and fair, full and adequate disclosure, allow for review of the underlying data and any model used, and confirm that all other ISPOR standards for the conduct of health economic studies have been met.

## ***Summary***

Pharmacoeconomics has numerous diverse audiences with various perspectives, objectives, backgrounds and skills. To get the most value from health economic research we need to increase the relevance, usefulness and credibility of our communications to these audiences. Only by ensuring that we are aware of our audience's true needs and endeavoring to provide a product they can understand and use, can we have the most impact on decision-making with health economic tools.

# REFERENCES

- Agro KE, Bradley CA, Mittman N, Iskedjian M, Ilersich AL, Einarson TR. Sensitivity analysis in health economic and pharmacoeconomic studies. *Pharmacoeconomics* 1997;11(1):75-88. 115
- Ament A, Baltussen R. The interpretation of results of economic evaluation: explicating the value of health. *Health Economics* 1997;6:625-35. 367
- Andersson F. Why is the pharmaceutical industry investing increasing amounts in health economic evaluations? *International Journal of Technology Assessment in Health Care* 1995;11(4):750-61. 368
- Angrist J. Conditional independence in sample selection models. *Economic Letters* 1997;54:103-12. 661
- Anis AH, Carruthers G, Carter AO, Kierulf J. Variability in prescription drug utilization: issues for research. *Can Med Assoc J* 1996;154(5):635-40. 262
- Anonymous. Wrestling with the issues of economic research. *Managed Care Marketing* 1995;April:32-3.381
- Anonymous. Cost-effectiveness assumptions "reasonable" at "some point"; CE analyses should avoid using assumptions in making major conclusions - FDA's Woodcock. *FDC Reports - The Pink Sheet* 1996;58(49):15-6. 385
- Balas EA, Kretschmer RAC, Gnann W, West DA, Boren SA, Centor RM, Nerlich M, Gupta M, West T, Soderstrom NS. Interpreting cost analyses of clinical interventions. *JAMA* 1998;279(1):54-7. 363
- Beck J, Pauker S. The Markov process in medical diagnosis. *Medical Decision Making* 1983;3:419-58. 475
- Blades C, Culyer A, Walker A. Health service efficiency: Appraising the appraisers -- a critical review of economic appraisal in practice. *Social Science and Medicine* 1981;24:461-72. 670
- Blumstein JF. The Oregon experiment: the role of cost-benefit analysis in the allocation of medicaid funds. *Social Science and Medicine* 1997;45(4):545-54. 369
- Bootman JL; Townsend R; McGhan WF. Principles of pharmacoeconomics. 2nd ed. Cincinnati: Harvey Whitney Books; 1996. 484
- Bootman JL, Harrison DL. Pharmacoeconomics and therapeutic drug monitoring. *Pharmacy World and Science* 1997;19(4):178-81. 459
- Boyer JG, Pathak DS. Establishing value through pharmacoeconomics: the emerging third objective in Clinical studies. *Topics in Hospital Pharmacy Management* 1994;13(4):1-10. 460
- Bradley CA, Iskedjian M, Lanctot KL, Mittman N, Simone C, St.Pierre, Miller E, Blatman B, Chabursky B, Einarson TR. Quality assessment of economic evaluations in selected pharmacy, medical, and health economics journals. *Annals of Pharmacotherapy* 1995;29:681-9. 370
- Buring, J.E. and Jonas, M. Large and simple randomized trials. In, *Tools for Evaluating Health Technologies*. BP-H-142. Washington, DC. Congress, Office of Technology Assessment, U.S. Government Printing Office. 1995; 487
- Cahill NE. Caveats in interpreting and applying pharmacoeconomic data. *American Journal of Health-System Pharmacists* 1995;52(Suppl 4):24-5. 428
- Campbell D, Stanley J. Gage N, editors. *Handbook on Research on Teaching*. Chicago: Rand-McNally; 1963; *Experimental and Quasi-Experimental Designs for Research on Teaching*. p. 171-246. 667
- Canadian Coordinating Office for Health Technology Assessment. *Guidelines for Economic Evaluation of Pharmaceuticals*. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 1994. 96

- Christiansen CL, Morris CN. Improving the statistical approach to health care provider profiling. *Ann Intern Med* 1997;127:764-8. 449
- Clemens K, Townsend R, Luscombe F, Mauskopf J, Osterhaus J, Bobula J. Methodological and conduct principles for pharmaco-economic research. *Pharmacoeconomics* 1995;8(2):169-74. 88
- Clouse JC. Pharmacoeconomics: a managed care perspective. *Topics in Hospital Pharmacy Management* 1994;13(4):54-9. 461
- Cook C; Campbell D. *Quasi-Experimentation: Design and Analysis Issues for Field Settings*. Boston: Houghton-Mifflin; 1981. 668
- Cooke J. The practical impact of pharmaco-economics on institutional managers. *Pharmacoeconomics* 1994;6(4):289-97. 371
- Coyle D. Statistical analysis in pharmaco-economic studies. *Pharmacoeconomics* 1996;9(6):506-16. 114
- Data JL, Wilke RJ, Barnes JR, DiRoma PJ. Re-engineering drug development: integrating pharmaco-economic research into the drug development process. *Psychopharmacology Bulletin* 1995;31:67-73. 362
- Davidoff F. Databases in the next millennium. *Ann Intern Med* 1997;127:770-4. 451
- Detsky A. Using cost-effectiveness analysis for formulary decision making. *Pharmacoeconomics* 1994;6(4):281-8. 373
- Dickersin K, Min Y. NIH Clinical studies and publication bias. *Online Journal of Current Clinical studies* 1993;Document No. 50. 463
- Donaldson, M. and Capron, A. Patient outcomes research teams: managing conflict of interest. Committee on Potential Conflicts of Interest in Patient Outcomes Research Teams, Institute of Medicine, National Academy Press. 1991; 464
- Dowd B, Feldman R, Moscovice I, Wisner C, Bland P, Finch M. An analysis of selectivity bias in the medicare AAPCC. *Health Care Financing Review* 1996;17:35-57. 657
- Drake C, Fisher L. Prognostic models and the propensity score. *International Journal of Epidemiology* 1995;24:183-7. 358
- Draugalis JR. Updating skills: pharmaco-economics as continuing education. *Topics in Hospital Pharmacy Management* 1994;13(4):72-6. 458
- Draugalis JR, Coons SJ. The role of colleges of pharmacy in meeting the pharmaco-economic needs of the pharmaceutical industry: a conference report. *Clinical Therapeutics* 1994;16(3):523-37. 374
- Draugalis JR, Coons SJ. Pharmaco-economic research - facilitating collaboration among academic institutions, managed care organizations, and the pharmaceutical industry: a conference report. *Clinical Therapeutics* 1995;17(1):89-107. 434
- Dreyer EB, Sugar A. Prospective versus retrospective studies. *Ophthalmology* 1992;99(5):646-7. 452
- Drummond M. Current concerns about economic evaluation. *Pharmaceutical Times* 1990;February:18-9.378
- Drummond M, Davies L. Economic analysis alongside Clinical studies – revisiting the methodological issues. *International Journal of Technology Assessment in Health Care* 1991;7(4):561-73. 380
- Drummond M. Cost-effectiveness guidelines for reimbursement of pharmaceuticals: is economic evaluation ready for its enhanced status? *Health Economics* 1992;1:85-92. 377
- Drummond M, Brandt A, Luce BR, Rovira J. Standardizing methodologies for economic evaluation in health care. *International Journal of Technology Assessment in Health Care* 1993;9(1):26-36. 142
- Drummond M. Evaluation of health technology: economic issues for health policy and policy issues for eco-

- conomic appraisal. *Social Science and Medicine* 1994;38(12):1593-600. 376
- Drummond M. Guidelines for pharmacoeconomic studies - the way forward. *Pharmacoeconomics* 1994;6(6):493-7. 375
- Drummond M, Jefferson TO. Guidelines for authors and peer-reviewers of economic submissions to the BMJ. *British Medical Journal* 1996;313:275-83. 138
- Drummond M. The future of pharmacoeconomics: bridging science and practice. *Clinical Therapeutics* 1996;18(5):969-78. 379
- Drummond M, Cooke J, Walley T. Economic evaluation under managed competition: evidence from the U.K. *Social Science and Medicine* 1997;45(4):583-95. 249
- Einarson TR, McGhan WF, Bootman JL. Decision analysis applied to pharmacy practice. *American Journal of Hospital Pharmacy* 1985;42:364-71. 382
- Else BA, Armstrong EP, Cox ER. Data sources for pharmacoeconomic and health services research. *American Journal of Health-System Pharmacists* 1997;54:2601-8. 360
- Evans C. The use of consensus methods and expert panels in pharmacoeconomic studies: practical applications and methodological shortcomings. *Pharmacoeconomics* 1997;12(2 Pt 1):121-9. 340
- Evans RG. Manufacturing consensus, marketing truth: guidelines for economic evaluation. *Ann Intern Med* 1995;123(1):59-60. 383
- Fayers PM, Hand DJ. Generalisation from phase III Clinical studies: survival, quality of life, and health economics. *Lancet* 1997;350:1025-7. 384
- Finder S. Providing cost-effective therapy using pharmacoeconomic evaluations: the public sector approach. *Clinical Therapeutics* 1997;19(1):160-6. 386
- Fowler, F.J. Using patients reports to evaluate medical outcomes. In, *Tools for Evaluating Health Technologies*. BP-H-142. Washington, DC. Congress, Office of Technology Assessment, US Government Printing Office. 1995; . 485
- Freeman RA. Standards for the conduct of industry-sponsored economic and quality of life research. *Journal of Research in Pharmaceutical Economics* 1992;4(2):15-30. 387
- Frenkel M, Farber MD, Lepe I. Teaching health economics in American medical schools. *Journal of Medical Practice Management* 1991;7(2):151-4. 457
- Freund DA, Dittus RS. Principles of pharmacoeconomic analysis of drug therapy. *Pharmacoeconomics* 1992;1(1):20-32. 318
- Gagnon, J.P. What constitutes a useful economic study for the pharmaceutical industry. Presented at the Economics and Cost-effectiveness in Evaluating the Value of Cardiovascular Therapies Meeting. Duke Clinical Research Institute. 1997; 388
- Genduso LA, Kotsanos JG. Review of health economic guidelines in the form of regulations, principles, policies and positions. *Drug Information Journal* 1996;30:1003-16. 167
- Gold MR; Siegel JE; Russell LB, et al. *Cost-effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996. 471
- Gostin L. Health care information and the protection of personal privacy: ethical and legal considerations. *Ann Intern Med* 1997;127:683-90. 437
- Grabowski H, Mullins CD. Pharmacy benefit management, cost-effectiveness analysis and drug formulary decisions. *Social Science and Medicine* 1997;45(4):535-44. 389
- Granados A, Jonsson E, Banta H, et al. EUR-ASSESS project subgroup report on dissemination and impact.

- International Journal of Technology Assessment in Health Care 1997;13(2):220-86. 361
- Hailey D. Australian economic evaluation and government decisions on pharmaceuticals, compared to assessment of other health technologies. *Social Science and Medicine* 1997;45(4):563-81. 390
- Haycox A, Drummond M, Walley T. Pharmacoeconomics: integrating economic evaluation into Clinical studies. *British Journal of Clinical Pharmacology* 1997;43:559-62. 391
- Heckman J, Smith J. Assessing the case for social experiments. *Journal of Economic Perspectives* 1995;9(2):85-110. 664
- Henry D. Australian national drug policy: using cost-effectiveness to gain value for money. Presented at the annual meeting of the International Society of Technology Assessment in Health Care 1996;12:19 392
- Hillman A, Eisenberg J, auly M, et al. Sounding board: Avoiding bias in the conduct and reporting of cost-effectiveness research sponsored by pharmaceutical companies. *New Eng J Med* 1991;324:1362-5. 669
- Hornberger J, Wrone E. When to base clinical policies on observational versus randomized trial data. *Ann Intern Med* 1997;127:697-703. 438
- Hylan T, Kotsanos J, Anderson J, Brown S, Copley-Merriman C, Egbuonu-Davis L, Heiligenstein J, Overhage J, Whiteside R. Comparison of a decision analytic model with results from a naturalistic economic clinical trial: An application to evaluating alternative antidepressants. *The American Journal of Managed Care* 1996;2:1211-23. 656
- Iezzoni LI. Assessing quality using administrative data. *Ann Intern Med* 1997;127( 8 Pt 2):665-74. 359
- IMS Pharma Strategy Group. Health economics in the USA: expectations, applications and future directions. IMS America. 1998; 490
- International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *New Eng J Med* 1997;336(4):309-15. 393
- International Society for Pharmacoepidemiology. Good research practice guidelines. *Pharmacoepidemiology and Drug Safety* 1996;5:333-8. 470
- Ioannides-Demos LL, Eckert GM, McLean AJ. Pharmacoeconomic consequences of measurement and modification of hospital drug use. *Pharmacoeconomics* 1992;2(1):15-33. 465
- Iskedjian M, Trakas K, Bradley CA, Addis A, Lanctot KL, Kruk D, Ilersich AL, Einarson TR. Quality assessment of economic evaluations published in pharmacoeconomics - the first four years (1992 to 1995). *Pharmacoeconomics* 1997;12(6):85-694. 394
- Jacobs P, Bachynsky J, Baladi JF. A comparative review of pharmacoeconomic guidelines. *Pharmacoeconomics* 1995;8(3):182-9. 79
- James S, Waddington C. Capacity building in health economics opportunities for training in developing countries. *Health Economics* 1996;5:473-8. 455
- Kassirer JP, Angel M. The journal's policy on cost-effectiveness analyses. *New Eng J Med* 1994;331(10):669-70. 91
- Kassirer JP, Angell M. Cost-effectiveness analyses - the Journal's policy on cost-effectiveness analyses. *Letters. New Eng J Med* 1995;332(2):123-5. 456
- Katz BP. Biostatistics to improve the power of large databases. *Ann Intern Med* 1997;127:769 450
- Kennedy P. The MIT Press, editors. *A Guide to Econometrics*. 3rd. ed. Cambridge: 1992; 9, Violating Assump-

- tion Four: Measurement Errors and Autoregression. p. 134-50. 658
- Kozma CM, Reeder CE, Schulz R. Economic, clinical, and humanistic outcomes: a planning model for pharmaco-economic research. *Clinical Therapeutics* 1993;15(6):1121-32. 433
- Laine C. Coming to grips with large databases. *Ann Intern Med* 1997;127(number 8 (part 1)):645-7. 627
- Lair TJ. Using retrospective database in the design of prospective clinical and economic studies. *Drug Information Journal* 1996;30:679-91. 395
- Langley PC. Outcomes research and modeling therapeutic interventions for economic evaluations. *Clinical Therapeutics* 1994;16(3):538-53. 397
- Langley PC. Therapy evaluation, patient distribution, and cost-outcomes ratios. *Clinical Therapeutics* 1995;17(2):341-7. 435
- Langley, P.C. and Martin, R.E. Integrated Pharmaceutical Services and Foundation Health Corporation. Guidelines for Formulary Submissions. 1996; 425
- Langley PC. The November 1995 revised Australian guidelines for the economic evaluation of pharmaceuticals. *Pharmacoeconomics* 1996;9(4):341-52. 77
- Langley PC. The future of pharmaco-economics: a commentary. *Clinical Therapeutics* 1997;19(4):762-9. 396
- Langley PC. *Pharmacoeconomics - achieving Gold Standards*. London: Financial Times Healthcare; 1997. 466
- Langsdale T. How do customers judge the quality of pharmaco-economic studies? *Pharmacoeconomics and Outcomes News* 1996;13 January:3-4. 408
- Lazaridis EM. Database standardization, linkage, and the protection of privacy. *Ann Intern Med* 1997;127(8):696 427
- Lee J, Sanchez L. Interpretation of "cost-effectiveness" and soundness of economic evaluations in the pharmacy literature. *American Journal of Hospital Pharmacy* 1991;48:2622-7. 671
- Liang MH, Shadick N. Feasibility and utility of adding disease-specific outcome measures to administrative databases to improve disease management. *Ann Intern Med* 1997;127:739-42. 431
- Lillard LA, Farmer MM. Linking medicare and national survey data. *Ann Intern Med* 1997;127:691-5. 439
- Lock S. Communicating science to practitioners (abstract). Presented at the annual meeting of the International Society of Technology Assessment in Health Care 1993;9:12 467
- Longnecker, M.P. Meta-analysis. In, *Tools for Evaluating Health Technologies*. BP-H-142. Washington, DC. Congress, Office of Technology Assessment, US Government Printing Office. 1995; 488
- Luce BR. Cost-effectiveness analysis - obstacles to standardisation and its use in regulating pharmaceuticals. *Pharmacoeconomics* 1993;3(1):1-9. 400
- Luce BR, Simpson K. Methods of cost-effectiveness analysis: areas of consensus and debate. *Clinical Therapeutics* 1995;17(1):109-25. 401
- Luce BR. Working toward a common currency: is standardization of cost-effectiveness analysis possible? *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 1995;10(Suppl 4):19-22. 57
- Luce BR, Lyles CA, Rentz AM. The view from managed care pharmacy. *Health Affairs* 1996;15(4):1-9. 398
- Luce BR, Hillman AL. When is a cost-effectiveness claim valid? How much should the FDA care? *The American Journal of Managed Care* 1997;3(11):1660-6. 399
- Lyles A, Luce BR, Rentz AM. Managed care pharmacy, socioeconomic assessment and drug adoption decisions. *Social Science and Medicine* 1997;45(4):511-21. 402

- Martin PA. Writing a useful literature review for a quantitative research project. *Applied Nursing Research* 1997;10(3):159-62. 403
- Mason J. Reporting guidelines for economic studies. *Health Economics* 1995;4:85-94. 468
- Mason J. The generalizability of pharmacoeconomic studies. *Pharmacoeconomics* 1997;11(6):503-14. 404
- Matchar DB, Samsa GP, Matthews JR, Ancukiewicz M, Parmigiani G, Hasselblad V, Wolf PA, D'Agostino RB, Lipscomb J. The stroke prevention policy model: linking evidence and clinical decisions. *Ann Intern Med* 1997;127:704-11. 440
- Mauskopf J. Industry responsibility in interactive computer modeling. *Medical Care* 1996;34:165-72. 430
- McClellan M, McNeil B, Newhouse J. Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? Analysis using instrumental variables. *JAMA* 1994;272:859-66. 662
- McClellan M. Uncertainty, health-care technologies, and health-care choices. *The Economics of Health and Health Care* 1995;85(2):38-44. 663
- McDonald CJ, Overhage JM, Dexter P, Takesue BY, Dwyer DM. A framework for capturing clinical data sets from computerized sources. *Ann Intern Med* 1997;127:675-82. 436
- McGhan WF, Lewis NJ. Guidelines for pharmacoeconomic studies. *Clinical Therapeutics* 1992;14(3):486-94; discussion 485. 71
- McGhan WF, Briesacher BA. Implementing pharmacoeconomic outcomes management. *Pharmacoeconomics* 1994;6(5):412-6. 406
- McGhan WF. *Quality of Life Considerations in Clinical studies*, B Spilker, Editor. 2nd ed. Philadelphia: Lippincott-Raven Press; 1996; Using decision analysis approaches to integrate quality of life and cost data in drug therapy selection. 462
- McGhan WF. Pharmacoeconomics and outcomes research - visions for the 21st century. *Clinical Therapeutics* 1996;18:1-4. 405
- McGhan WF. Guidelines and pitfalls in pharmacoeconomics. *The Journal of Management and Economics* 1998;?:3-6. 424
- McHorney CA. Generic health measurement: past accomplishments and a measurement paradigm for the 21st century. *Ann Intern Med* 1997;127:743-50. 446
- Mullins, C.D. An Update of Pharmacoeconomic Guidelines and Principles. Presented at the ISPOR Conference, Issues in Pharmacoeconomics, Crystal City, VA, 18 February. 1998; 426
- Nerenz DR. Measuring plans and measuring health. *Ann Intern Med* 1997;127:751 447
- Neumann P, Zinner D. The FDA's oversight of pharmacoeconomic claims. *Risk in Perspective* 1995;3(7):1-2. 407
- Neumann PJ, Zinner DE, Paltiel AD. The FDA and regulation of cost-effectiveness claims. *Health Affairs* 1996;15(3):54-71. 84
- O'Brien B. Economic evaluation of pharmaceuticals - Frankenstein's monster or vampire of trials? *Medical Care* 1996;34(12):D599-DS108 409
- O'Brien B, Drummond MF, Labelle R, Willan A. In search of power and significance: Issues in design and analysis of stochastic cost-effectiveness studies in healthcare. *Medical Care* 1994;32:150-63. 476
- Oster G, Menzin J, Epstein RS, et al. *Controlled Clinical studies*. New York, NY: Elsevier Science Inc.; 1994; 16, A randomized trial to assess effectiveness and cost in clinical practice: rationale and design of the cholesterol reduction intervention study (CRIS). 365

- Palmer RH. Process-based measures of quality: the need for detailed clinical data in large health care databases. *Ann Intern Med* 1997;127:733-8. 445
- Paltiel AD, Neumann PJ. Why training is the key to successful guideline implementation. *Pharmacoeconomics* 1997;12(3):297-302. 410
- Pharmaceutical Research and Manufacturers of America. Methodological and conduct principles for pharmaco-economic research. 1995; 423
- Potosky A, Riley G, Lubitz J, Mentnech R, Kessler L. Potential for cancer related health services using a linked Medicare tumor registry database. *Medical Care* 1993;31:732-48. 666
- Powe, N.R. and Griffiths, R. Clinical-economic trials. In, *Tools for Evaluating Health Technologies*. BP-H-142. Washington, DC. Congress, Office of Technology Assessment, US Government Printing Office. 1995; 489
- Prevention Effectiveness Technical Work Group. A practical guide to prevention effectiveness: decision and economic analyses. Atlanta, GA. Centers for Disease Control, US Department of Health and Human Services. 1998; 420
- Pringle M, Ward P, Chilvers C. Assessment of the completeness and accuracy of computer medical records in four practices committed to recording data on computer. *British Journal of General Practice* 1995;45:537-41. 429
- Ray WA. Policy and program analysis using administrative databases. *Ann Intern Med* 1997;127:712-8. 441
- Reeder CE. Overview of pharmaco-economics and pharmaceutical outcomes evaluations. *American Journal of Health-System Pharmacists* 1995;52(Suppl 4):5-8. 432
- Reinhardt UE. Making economic evaluations respectable. *Social Science and Medicine* 1997;45(4):555-62. 411
- Robins J, Mark S, Newey W. Estimating exposure effects by modelling the expectation of exposure conditional on confounders. *Biometrics* 1992;48:479-95.660
- Rosenbaum P, Rubin D. Reducing bias in observational studies using subclassification on the propensity score. *Journal of the American Statistical Association* 1984;79(387):516-24. 659
- Rothman KJ. Conflict of interest - the new McCarthyism in science. *JAMA* 1993;269(21):2782-4. 412
- Rovira J, Antonanzas F. Economic analysis of health technologies and programmes - a Spanish proposal for methodological standardisation. *Pharmacoeconomics* 1995;8(3):245-52. 413
- Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997;127(Pt 2):757-63. 366
- Sackett D. Bias in analytic research. *Journal of Chronic Diseases* 1979;32:51-63. 655
- Sacristan JA, Soto J, Galende I. Evaluation of pharmaco-economic studies: utilization of a checklist. *The Annals of Pharmacotherapy* 1993;27:1126-33. 192
- Sanchez LA. Expanding the role of pharmacists in pharmaco-economics - why and how? *Pharmacoeconomics* 1994;5(5):367-75. 414
- Sanchez LA. Pharmaco-economics and formulary decision making. *Pharmacoeconomics* 1996;9 (Suppl 1):16-25. 75
- Schulman KA, Rubinstein LE, Click HA, Eisenberg JM. Relationships between sponsors and investigators in pharmaco-economic and clinical research. *Pharmacoeconomics* 1995;7(3) 415
- Schulman KA, Liana T, Yabroff K. Economic assessment within the clinical development program. *Medical Care* 1996;34(Suppl 129):89-95. 469

- Selby JV. Linking automated databases for research in managed care settings. *Ann Intern Med* 1997;127:719-24. 442
- Simon GE, Vonkorff M, Heiligenstein JH, Revicki DA, Grothaus L, Katon W, Wagner EH. Initial antidepressant choice in primary care. *JAMA* 1996;275(24):1897-902. 364
- Slogan F, Whetten-Goldstein K, Wilson. Hospital pharmacy decisions, cost containment, and the use of cost effectiveness analysis. *Social Science and Medicine* 1997;45(4):523 477
- Smith DM. Database research: is happiness a humongous database? *Ann Intern Med* 1997;127(8 (pt 2)):725-443
- Sox H; Blatt M; Higgins M, et al. *Medical Decision Making*. Butterworths; 1988. 473
- Spilker B. Use and abuse of pharmacoeconomic trials. *Drug News and Perspectives* 1994;7(6):363-9. 481
- Spoeri RK, Ullman R. Measuring and reporting managed care performance: lessons learned and new initiatives. *Ann Intern Med* 1997;127:726-32. 444
- Staquet M, Berzon R, Osoba D, Machin D. Guidelines for reporting results of quality of life assessments in Clinical studies. *Quality of Life Research* 1996;5(5):496-502. 83
- Stergachis, A., Gardner, J.S., Sullivan, S.D. et al. What are the training needs for developing research skills in pharmaceutical outcomes research? Paper presented at invitational conference, Patient Outcomes Interventions: A Scientific Foundation for the Future. American Pharmaceutical Association, November. 1994; 453
- Szczepura A, Kankaanpaa J. Interests in health care technology assessment (HCTA) and HCTA training needs in eight European countries: Comett-Assess. *Soc Sci Med* 1994;38(12):1679-88. 416
- Taskforce on principles for economic analysis of health care technology. Economic analysis of healthcare technology: a report on principles. *Ann Intern Med* 1995;123(1):61-70. 479
- Temple, R. and O'Neill, R. Principles for the review of pharmacoeconomic promotion. Food and Drug Administration. 1995; 421
- Testa M, Lenderking W. Interpreting pharmacoeconomic and quality-of-life clinical trial data for use in therapeutics. *Pharmacoeconomics* 1992;2(2):107-17. 480
- The MEDSTAT Group. A guide for States to assist in the collection and analysis of medicaid managed care data. Prepared for the Health Care Financing Administration. 1997; 500-92-0035. 665
- Thomas N. The role of pharmacoeconomics in disease management. A pharmaceutical benefit management company perspective. *Pharmacoeconomics* 1996;9 (Suppl 1):9-15. 74
- Udvarhelyi S, Colditz GA, Epstein AM. Cost-effectiveness and cost-benefit analyses in the medical literature - are the methods being used correctly? *Ann Intern Med* 1992;116:238-44. 417
- Weinberger M, Hui SL, aine C. Measuring quality, outcomes, and cost of care using large databases. Perspectives from the Sixth Regenstrief Conference. *Ann Intern Med* 1997;127(number 8 (part 2)):665-774. 626
- Weinstein MC; Fineberg H; Frazier A, et al. *Clinical Decision Analysis*. Philadelphia: WB Saunders; 1980. 474
- Weinstein MC. Principles of cost-effective resource allocation in healthcare organisations. *International Journal of Technology Assessment in Health Care* 1990;6:93-103. 472
- Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996;276(15):1253-8. 113
- Wells NEJ. Regulation of the pharmaceutical industry - and now pharmacoeconomic research? *Pharmacoeconomics* 1992;2(6):435-9. 418

- Whittle, J. Large administrative database analysis. In, Tools for Evaluating Health Technologies. BP-H-142. Washington, DC. Congress, Office of Technology Assessment, US Government Printing Office. 1995; 486
- Yee GC, Hillman AL. Applied pharmacoeconomics - when can publication be legitimately withheld? *Pharmacoeconomics* 1997;12(5):511-6. 419
- Zhou X-H, Melfi CA, Hui SL. Methods for comparison of cost data. *Ann Intern Med* 1997;127:752-6. 448