

**SCIENCE AND POLICY**

*Opinion*



NANCY KLINE LEIDY, Ph.D.

**Interpreting Health-Related Quality of Life Outcomes**

Determining the value of a drug, device or other clinical intervention often includes an evaluation of its

impact on patients' physical, psychological and social functioning and well-being—that is—their health-related quality of life (HRQL). This information can complement and extend clinical efficacy, safety, and cost data, helping consumers and their health-care providers/payers make informed treatment choices.

Among the interesting discussions in the HRQL field is the interpretation of clinical trial results and the effective translation and communication of empirical data to end users, including regulatory bodies, clinicians, and, ultimately, the patients themselves. Unlike many traditional clinical indicators for which evaluation criteria are based on years of accumulated scientific and clinical evidence, HRQL is a relatively new field with a more limited interpretation context. To complicate matters, there is no single metric for summarizing HRQL outcomes; scale scores vary from instrument to instrument and can range from 4 points to over 100 points. Under these circumstances, how is a statistically significant difference score interpreted? To what extent is the observed difference "meaningful"?

A number of approaches have been proposed for interpreting HRQL effects, beyond the traditional statistical significance criterion. One of the most frequently cited approaches is an instrument-specific numeric threshold or cut-off value, often referred to as the "minimal clinically important difference (MCID)." The MCID has been defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's

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**Halpern Briefs Pennsylvania Government on Smoking Cessation**

MEDTAP International vice president Michael Halpern, M.D., Ph.D., briefed representatives of the Pennsylvania state government on the economic impact of covering prescription smoking cessation aids under the state's Medicaid program. Smoking cessation aids are currently not covered for the approximately 1,000,000 people throughout the state receiving Medicaid benefits.

Using advanced computer modeling, Dr. Halpern was able to demonstrate the economic effects of smoking cessation programs, calculating not only the incremental costs of the program each year, but also how long before the savings in decreased healthcare utilization matched the cost for covering cessation activities. "Computer modeling allows us to examine cost issues in decision making from a variety of perspectives and for multiple populations," said Dr. Halpern. "For example, we were able to plug in demographic data on the Pennsylvania Medicaid population, such as age and gender. In addition, we were able to use information on rates of smoking among a northeastern U.S. Medicaid population based on national survey data. Based on the model projections, by year four of covering prescription smoking cessation aids, Pennsylvania stands to realize approximately \$500,000 in net savings of healthcare costs."

Smoking cessation programs tend to be organized in a variety of permutations: prescription drugs alone, drugs coupled with counseling either by physicians or by telephone counseling services; counseling services alone. The computer model was used to compare a combination of counseling and drugs as well as counseling alone.

MEDTAP International provides a range of health economics and health outcomes research, enabling decision makers to make informed judgements about the efficient and equitable allocation of health resources. ■

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## MEDTAP Furthers Evidence-Based Research for Healthcare Decision Making with Shih Appointment

**M**EDTAP International, which has long been committed to providing its clients with high-quality research that demonstrates the economic value of medical interventions, has further extended its capabilities with the appointment of Ya-Chen Tina Shih, Ph.D. to the position of Research Scientist. As part of MEDTAP's Center for Healthcare Decision making, Dr. Shih is responsible for design and implementation of health outcomes modeling studies that project the impact of new drug therapies and technology on healthcare outcomes and costs. She also performs retrospective and prospective clinical trial economic analysis, naturalistic trial design and analysis, and multi-country economic studies based on clinical trials and models.



YA-CHEN TINA SHIH, Ph.D.

Dr. Shih earned her Ph.D. in Economics at Stanford University, California, with an emphasis in health economics. Stanford University is well known for economics, and its faculty members have frequently served as information resources in healthcare policy making in the United States. "I feel fortunate to have studied in an organization that would enable me to develop skills in applying the tools of economic decision making in the healthcare arena," commented Dr. Shih. Her dissertation "Evaluation of the Cost Effectiveness of Medicare's End Stage Renal Disease Program" was based on analysis of a large database of Medicare claims.

Dr. Shih was formerly assistant professor at the University of North Carolina School of Pharmacy, Division of Pharmaceutical Policy and Evaluative Sciences. As the former director of the Pharmacoeconomics Modeling Laboratory at the School of Pharmacy at UNC, Chapel Hill, Dr. Shih was responsible for conceptualizing and organizing the lab, procuring hardware and software, and developing the modeling program for use by pharmacy and public health students.

Dr. Shih is in charge of the day-to-day coordination of the Bayesian initiative, a multi-industry sponsored research project in health economics. The Bayesian approach to health economics is based on the treatment of each problem to be researched as a decision problem—

with key elements being resources to be invested and losses and gains to be realized—rather than purely a statistical problem. In order to make health economic analysis more useful to decision makers, Bayesian theory makes room for qualitative factors such as intuition, prior experience, perception of utility on the part of the decision maker.

In addition to her duties at MEDTAP, Dr. Shih holds the positions of adjunct assistant professor of health policy and administration at the School of Public Health, research fellow at the Cecil G. Sheps Center, and core staff member of the Center for Pharmaceutical Outcomes Research (CePOR), all at the University of North Carolina (UNC), Chapel Hill.

"Companies developing healthcare interventions such as drugs, devices, and other technologies are increasingly challenged to provide scientific evidence of value—not just from a clinical efficacy point of view, but also from an economic standpoint," said Bryan R. Luce, Ph.D. and CEO of MEDTAP International. "Dr. Shih's expertise and experience in health economics research make her a welcome addition to our scientific staff, and will offer a valuable resource to our clients in developing economic evidence." ■

## EDITORIAL

### Time to Reconsider the Hierarchy of Evidence?

**H**ealth care payers—insurers, self-funded plans, managed care organizations—are developing complex processes for evaluating new technology and procedures. Coverage decisions are increasingly based on consideration of "evidence"—credible information about the effect of using the new technology relative to established alternatives.



GREGORY DE LISSOVOY, Ph.D.

In the USA, one important body now grappling with the issue of appropriate evidence is the HCFA Medicare Coverage Advisory Committee (MCAC). At its December 8 meeting, the MCAC executive committee rejected coverage recommendation reports from subcommittees due to concern about inadequate and inconsistent weighting of evidence concerning specific technologies.\*

What constitutes valid and reliable evidence for coverage decisions? The randomized controlled clinical trial (RCT) is invariably put forth as the “gold standard”—the highest form of evidence. Lower in the hierarchy are observational studies, such as retrospective database analysis. Models, which draw on sources of data within the hierarchy, occupy an uncertain role as tools for manipulating data. That is the traditional view. But strict adherence to this hierarchy may lead to sub-optimal decisions.

Clinical trials conducted as part of the registration process, although important, offer only limited insight on the potential effectiveness of a technology in actual practice. Trial duration is rarely sufficient to capture all important outcomes. Pharmaceutical trials may compare a new compound against placebo rather than best current therapy, while the significance of placebo effects is rarely fully examined in subsequent analysis. True head-to-head trials are typically powered to show equivalence rather than superiority. Device trials are often uncontrolled case series where the procedure is performed by pioneers of the technology. In short, evidence from clinical trials does not always deserve a place at the top of the hierarchy.

Retrospective studies are suspect because of potential selection bias. Frequently absent from the most accessible databases are variables needed to establish the clinical status of patients at study entry and their eventual outcomes. Selection bias can be addressed using new analytical methods based on instrumental variables and generalized estimating equations. The increasing availability of electronic medical records will facilitate retrospective measurement of numerous clinical parameters. With appropriate software, managed care organizations could use their administrative data systems to follow selected patient cohorts in near real time. Provisional coverage decisions could be reconsidered after only a few months, before a technology becomes firmly entrenched.

Modeling the impact of new medical technology is increasingly popular, due in large measure to exceptional software such as Excel® and DATA®. But constructing good models is not an easy task. Complex models often suffer from lack of transparency while simple models ignore the often convoluted pathways in an episode of care. Models often draw on multiple types of data, including non-experimental sources. Consequently, results from models are often suspect. That is unfortunate because, used appropriately, models provide a mechanism for integrating all relevant information about a new therapy and projecting its true effectiveness. Models play a critical role in every other high technology sector. For example, every modern airplane begins its life as a computer model. Once in production, proposed

modifications are first tested by adapting the model. Should an accident occur, computer simulations attempt to recreate circumstances surrounding the event.

A well-constructed model, grounded in data from randomized clinical trials, supplemented by retrospective data and expert opinion, may yield more valid insight on the effectiveness and cost-effectiveness of a new technology than rigid adherence to a hierarchy of evidence. Medical technology development is increasingly based on modeling and computer simulation instead of in vitro studies. Coverage decision making should be moving in the same direction.

\* See the *Gray Sheet* (Dec. 13, 1999) for an excellent report of this meeting. For deeper insight, download the meeting transcript ([www.hcfa.gov/quality/8b1-i3.htm](http://www.hcfa.gov/quality/8b1-i3.htm)). ■

## MEDTAP Scientist Wins Distinguished Author Award

Ya-Chen Tina Shih, Ph.D. has been named recipient of the J. Warren Perry Distinguished Author Award from the Journal Of Allied Health. Dr. Shih's article, "Growth and Geographical Distribution of Selected Health Professions, 1971-1996", was published in the *Journal of Allied Health*, Vol. 28, No. 2, Summer 1999, pp. 61-70. ■

### COMING EVENTS

#### FEBRUARY 29, 2000

- Drug Information Association Workshop "Marketing Pharmaceuticals in the New Millennium", New York, New York. "Promoting Products Based on Quality of Life and Health Economic Evidence of Effectiveness." By Bryan R. Luce, Ph.D.

#### APRIL 5-8, 2000

- Academy of Managed Care Pharmacy, Phoenix, Arizona—Poster presentation by L. Clark Paramore, M.S.P.H.

#### MAY 5-10, 2000

- American Thoracic Society, Toronto, Canada—MEDTAP exhibit #840.

#### MAY 21-24, 2000

- International Society for Pharmacoeconomics and Outcomes Research, Arlington, Virginia. MEDTAP exhibit ■



## RECENT PUBLICATIONS

**MEDTAP** International welcomes comments and inquiries about our scientific work. Each issue, we feature one or more abstracts and a list of current publications. If you wish to obtain reprints of papers or a complete publication list, please contact Rebecca Sergi at 301 654-9729.

### **Memory Performance, Perceived Cognitive Function, and Mood— The Need for Separate Assessment.**

LEIDY NK, ELIXHAUSER A, MEADOW K, MEANS E, WILLIAN MK. "The relationship between memory performance, perceived cognitive function, and mood in patients with epilepsy." *Epilepsy Research* 1999; 37:13-24.

The low correlations between memory performance and subjective memory may be attributable to disparities between tasks in neuropsychological tests and cognitive experiences of day-to-day living. This study evaluated the relationship between everyday memory performance, perceived cognitive functioning, and mood among patients with epilepsy. Conclusion: memory performance tests provide qualitatively different information than patients' self-reported cognitive difficulties, thus it is important to assess memory performance, perceived cognitive function, and mood separately because the constructs are related but not redundant.

### **Multichannel Cochlear Implant – An Analysis of Cost and Benefit.**

PALMER CS, NIPARKO JK, WYATT JR, ROTHMAN M, DE LISSOVOY G. "A prospective study of the cost-utility of the multichannel cochlear implant." *Archives of Otolaryngology—Head and Neck Surgery* 1999; 125:1221-1228.

Multichannel cochlear implants have been found to benefit individuals with advanced sensorineural hearing loss who are unable to gain effective speech recognition with hearing aids. This prospective study was designed to measure the cost per quality-adjusted life-year (QALY) for adults receiving implants. Conclusions: overall, multichannel cochlear implants significantly improved recipients' performance on measures of speech understanding and ratings of health-utility within 6 months of implantation. In addition, implants yielded a very favorable cost per QALY.

CHAMBERS M, HUTTON J, GLADMAN J. "Cost-Effectiveness Analysis of Antiplatelet therapy in the Prevention of Recurrent Stroke in the UK. Aspirin, Dipyridamole and Aspirin-Dipyridamole." *Pharmacoeconomics* 1999; 16(5pt2): 577-93

FRANK L, KLEINMAN L, FARUP C, TAYLOR L, MINER P, JR. "Psychometric validation of constipation symptom assessment questionnaire." *Scandinavian Journal of Gastroenterology* 1999; 9:870-877.

HUTTON J, BERRY E, KELLY S, HARRIS KM, RODERICK P, BOYCE JC, ET AL. "A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease." *Health Technology Assessment* 1999; 3(18).

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NUIJTEN M, MEESTER L, WAIBEL F, WAIT S. "Cost effectiveness of letrozole in the treatment of breast cancer in post-menopausal women in the UK." *Pharmacoeconomics* 1999; 16(4): 379-397.

NUIJTEN MJC. "Pharmacoeconomics in European Decision-Making." *Value in Health*. 2 (5): 319-322. 1999

NUIJTEN MJC. "Farmacoeconomische gegevens binnenkort verplicht." Interview in *Transmitter*. 32- 35. 1999.

REVICKI DA, SMITH RA, SORENSEN SV. "Evaluating the cost-effectiveness of antidepressant therapies: decision analysis modeling vs. randomized clinical trials." *The Economics of Neuroscience* 1999; 1(2): 45-51.

REVICKI DA. "The new atypical antipsychotics: a review of pharmacoeconomic studies." *Expert Opinion in Pharmacotherapy* 2000; 1(2): 249-260.

REVICKI DA, KAPLAN-MACHLIS B, SPIEGLER GE. "Health-related quality of life in primary care patients with gastroesophageal reflux disease." *The Annals of Pharmacotherapy* 1999; 33:1032-1036.

REVICKI DA, CRAWLEY JA, ZODET MW, LEVINE DS, JOELSSON BO. "Complete resolution of heartburn symptoms and health-related quality of life in patients with gastroesophageal reflux disease." *Alimentary Pharmacology and Therapeutics* 1999; 13(12): 1621-1630.

YABROFF RK, MANDELBLATT JS. "Interventions targeted toward patients to increase mammography use." *Cancer Epidemiology, Biomarkers & Prevention* 1999; 8:749-757.

YABROFF, RK, MANDELBLATT JS. Effectiveness of interventions designed to increase mammography use: a meta-analysis of provider strategies. *Cancer Epidemiology, Biomarkers & Prevention* 1999; 8:759-767.

## Health Economic Data Requirements in European Drug Policy

By MARK NUIJTEN, M.D., M.B.A.

How should economic information be used to influence drug usage and reimbursement in Europe? While health economic data has increased in importance over the last few years, its use in decision making by regulatory authorities is seldom clearly defined. Authorities are hesitant to disclose the rationale for their decisions for both technical and political reasons. A manufacturer submitting health economic data may claim confidentiality of pricing and drug profile characteristics. Further, most European countries do not have official requirements for submitting health economic data, so when it is included in pricing/reimbursement submissions, authorities are not obligated to publicize their judgements on the data or its weight in the decision-making process.

One exception was the official report by the Dutch Health Care Council on the rationale for a positive reimbursement decision in 1996 for mycophenolate, an anti-rejection drug used after renal transplantation. The report refers to a health economic study and states that reimbursement of this more expensive drug may be justified due to a reduction of other direct medical costs as a result of fewer rejections, fewer other medications, and less dialysis and hospitalization. This is probably the first hard evidence in Europe of the added value of health economic evaluation contributing to the reimbursement success.

A recent survey by MEDTAP indicated that published evidence for the impact of health economic data in the decision-making process is only the tip of the iceberg. Interviews were conducted with many national decision makers in Europe who are involved in pricing and reimbursement decisions. When asked about requirements for health economic data to support pricing and reimbursement decisions, they indicated a trend towards an increasing demand for this type of information, and in several countries, formal reporting requirements in the near future.

Our recent overview of Europe clearly indicated that reimbursement and pricing may be considered as two separate procedures: decisions are made by different bodies, different laws apply, different reporting data are required, and reimbursement and pricing are sequential decisions. Reimbursement decisions are often made by first clustering a new drug in an existing drug group, then pricing the drug, often based on a reference price basket for neighboring countries.

The growing burden on manufacturers to demonstrate the cost-effectiveness of their products before acceptance

for reimbursement may have considerable consequences for all players involved. For example, in the Netherlands, new pharmacoeconomic research guidelines that have been approved but not yet implemented state that pharmacoeconomic studies should permit reliable, reproducible, and verifiable insight into the therapeutic value of a drug, the costs that will result from its use, and the possible savings that will be made compared with other drugs and/or treatments.

The Dutch guidelines emphasize that evaluations should focus on the registered indication of drugs and consider both efficacy and effectiveness. The ideal design to demonstrate effectiveness and costs is a naturalistic prospective study. However since study drugs are usually not approved for registration at the time economic studies are performed, the use of prospective naturalistic trials is limited, making submission of data on effectiveness and expected costs at the time of reimbursement not feasible. On the other hand, projections about a drug's effectiveness and expected costs can be modeled using realistic and explicit assumptions based on data from clinical studies.

If reimbursement of pharmaceuticals will be based predominantly on economic data derived from modeling studies, it is vital to scrutinize and refine this approach carefully. Data sources for the variables in a model may be clinical trials, literature (e.g., meta-analysis), databases, medical records, and official tariff lists. The use of Delphi (expert) panels to establish information that could not be derived from existing data sources raises questions concerning the validity of that information, and calls for caution.

Even when guidelines adequately address the methodological issues, there are other dimensions, often political, to be considered. First, guidelines prescribe proper execution of health economic evaluations but not cut-off points for approving reimbursement. Researchers may advise on interpretation of a cost per QALY, but the decision about how much society will pay for increased effectiveness is political. Next, the weight of health economic evaluation versus that of financial impact analysis (used to assess the macro costs for the national health-care budget) should be defined before formal requirements are implemented.

Formal economic reporting requirements should also describe the procedural framework within which the pharmacoeconomic evaluation takes place. It should be made clear, in advance, which bodies are going to evaluate the pharmacoeconomic analysis, whether there is an appeals procedure and what arrangements would be followed for subsequent drugs within a therapeutic cluster compared with the innovator.

The matter discussed will have far-reaching consequences, both near-term and long-term. ■

## Science and Policy Opinion...

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management" (Jaeschke et al., p. 408). Methods underlying the MCID appear to be gaining momentum, despite the fact that they have been challenged forcefully on a number of grounds.

Perhaps the appeal of an MCID-type threshold approach is the apparent ease with which HRQL outcomes can be interpreted. It leaves no "gray area"; results either exceed the threshold, or do not. By definition, statistically significant HRQL differences that fail to cross a given threshold are interpreted as "no HRQL effect", i.e., as though they were not statistically significant. The clear disadvantage of using a threshold approach in isolation, however, is that it effectively discards potentially very useful information. One would conclude, for example, that an intervention has no impact on HRQL, regardless of the effect size observed or the potentially substantial proportion of patients who did, in fact, experience improvements in HRQL. This problem is even more disconcerting when one considers the logical and analytical limitations of the MCID itself. Is it reasonable to assume, for example, that a given MCID is consistent across patients with different levels of disease severity, sociodemographic characteristics (e.g., age, ethnicity), or even diseases. In the latter case, is it reasonable to assume that the MCID for a given generic measure is the same for patients with epilepsy, congestive heart failure, and depression?

Although the simplicity of using an MCID to interpret statistically significant outcomes may be appealing, it should not be used in isolation. Until we have scientific and clinical track records through which to intuitively gauge the magnitude of HRQL differences, we should use the full arsenal of analytical and interpretive tools currently available. At the same time, we should be developing new and better methods for understanding patient and clinician perspectives of clinically meaningful change in health-related quality of life.

*For a bibliography on interpreting HRQL outcomes, visit MEDTAP's web site at [www.medtap.com/contact.us.html](http://www.medtap.com/contact.us.html) and request it.*

### REFERENCES:

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## MEDTAP International Welcomes Sasane for Health Economics and Quality-of-Life Project Management

MEDTAP International welcomes Medha Sasane, M.S. to the position of project manager. Ms. Sasane is responsible for planning and coordination of health economic and quality-of-life research activities, including large database studies, retrospective database analysis, and other modeling-based decision-analytic studies.



MEDHA SASANE

Formerly at Provantage Health Services, Ms. Sasane was involved in several clinical and cost (economic) outcomes studies in the areas of infectious diseases and cardiovascular disease. In addition, she

combined her expertise in pharmacology and database studies to provide assistance in developing drug utilization review software. The software is a tool that uses patient population information such as age, gender, number of drugs being taken, utilization patterns, and morbidity to calculate the potential for hospitalization due to adverse effects in drug therapies.

While an intern with the United States Pharmacopoeia, Ms. Sasane conducted an extensive review and annotated bibliography of published economic and quality-of-life literature on congestive heart failure. Her work was used to generate disease-based criteria for drug utilization review, a study that analyzed drug and disease data to evaluate the entire disease state for use in publishing disease-based treatment monographs.

Ms. Sasane holds a master of science degree in pharmaceutical policy from the University of North Carolina, Chapel Hill, School of Pharmacy. Her thesis is entitled "The estimated feasibility of retrospective drug utilization review in outpatient clinics." ■

EDITOR:  
Wendy Schneider-Levinson  
MEDTAP INTERNATIONAL  
7101 Wisconsin Avenue  
Suite 600  
Bethesda, MD 20814  
TEL: 301-654-9729

EMAIL:  
[schneider@medtap.com](mailto:schneider@medtap.com)

WEB SITE:  
[www.medtap.com](http://www.medtap.com)

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