

New Report Available: Health-Related Quality of Life (HRQL) Data in Drug Regulatory and Reimbursement Processes in Europe

By Agota Szende, Ph.D. (c)

MEDTAP's scientists have reviewed and reported on the recommendations on — and the actual use of — HRQL data in drug regulatory and reimbursement processes in Europe. In the regulatory part of the study, the research focused on the centralized regulatory approval process in the EU, while in the review of recommendations related to the reimbursement of pharmaceuticals, the research focused on recommendations published in individual countries.

This approach reflected the current situation that while the centralized process is becoming increasingly important in drug regulatory processes in Europe, the

public reimbursement of pharmaceuticals still falls under the responsibility of individual member states.

In addition to the general review, the report includes the description and synthesis discussion of:

- ▶ Nineteen disease group-related recommendations on HRQL and other PRO research in clinical trials for regulatory purposes
- ▶ Review of the actual use of HRQL and PRO data in 45 centrally registered drugs
- ▶ More detailed description of 10 selected cases where HRQL and other PRO data were used in the regulatory process

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SCIENCE AND POLICY OPINION

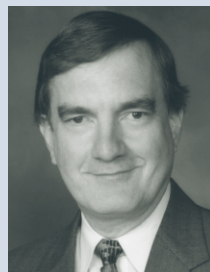
A Dialogue Between Biostatisticians and Health Economists

By Ya-Chen Tina Shih, Ph.D. and Chris Barker, Ph.D.



TINA SHIH

Dr. Shih: Chris, it is exciting to have a senior biostatistician with your level of expertise as a colleague. Researchers trained in biostatistics and econometrics tend to approach analytical issues somewhat differently, even though both disciplines are rooted in statistics. Some of the differences involve terminology — for example, what I know as “simultaneous equation models” you might describe as “systems of equations” — but there are also some fundamental differences between our other academic roots — economics and biological science.



CHRIS BARKER

Dr. Barker: I'm very glad to be at MEDTAP, and looking forward to collaboration with such a diverse group of scientists. My own education included both

economics and biostatistics. The benefit is that I can identify those statistical methodologies that are applied the same way in both disciplines (e.g. a t-test), and those important areas where there are no immediate common statistical equivalents. For example, while economists

may discuss behavioral or policy models, there is no equivalent in biostatistics.

Conversely, the mainstay of most clinical trial statisticians is the designed experiment, exemplified by the randomized clinical trial. The tools and techniques for analyzing and interpreting randomized clinical trial data are simply not applicable when the data arise in a non-randomized or non-experimental design setting. In my personal experience, the “bridge” between biostatistics and econometrics occurs in health outcomes research, where it is necessary to apply clinical trial results to a “real world” environment.

Dr. Shih: I agree with your observation that outcomes research “bridges” econometrics and biostatistics. However, I have occasionally seen researchers use observational data, such as administrative claims data, to develop parameters for decision analytic models that compare the clinical course with alternative treatment interventions. While the model implicitly assumes random assignment to treatment, treatment assignment in observational data is largely systematic. In fact, for many economic studies, whether or not patients receive any treatment is, by itself, an important selection issue.

Chris, as we prepared our Bayesian statistics short course for the upcoming ISPOR meeting, I found that we view the application value of Bayesian statistics somewhat differently.

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HRQL

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- ▶ Review of recommendations on HRQL/utility data in official and academic pharmacoeconomic guidelines in 14 European countries
- ▶ Comparative analysis of recommendations and the actual use of HRQL data at the EMEA and the FDA
- ▶ Comparative analysis of recommendations on HRQL/utility data between European and 4 non-European countries

MEDTAP scientists are following closely any centralized European or national developments that could affect the use of HRQL research in clinical trials that are conducted for regulatory purposes or in health economic evaluation studies that are submitted for reimbursement.

For more information or to order the report, please contact Agota Szende at +31-75-642-9463 or email szende@MEDTAP.nl. ■

The Use and Value of the AMCP Format for Pharmaceutical Dossier Submissions

By L. Clark Paramore, M.S.P.H.

In Fall 2001, the Academy of Managed Care Pharmacy (AMCP) in the U.S. issued the *Format for Submission of Clinical and Economic Data in Support of Formulary Consideration by Managed Health Care Systems in the United States*. The AMCP guidelines (herein the AMCP Format) were intended to aid managed care organizations (MCOs) in the decision-making process for adding prescription drugs to formulary. As of March, 2002, 8 MCOs and 3 state agencies have either adopted or announced plans to adopt the AMCP Format, accounting for as many as 100 million lives. Many of these decision makers are requiring pharmaceutical manufacturers to conform to the AMCP Format for formulary consideration. Today, virtually all major manufacturers are submitting formulary submission documents (i.e. dossiers) which adhere to the AMCP Format.

The development and adoption of the AMCP Format are important for the pharmaceutical industry, not only because it may be required for formulary consideration but also because it appears to provide a safe harbor for the industry to communicate the value message of their products to managed care. The value message cannot normally be communicated to managed care through traditional promotional vehicles because the evidentiary requirements by the Food and Drug Administration's (FDA) Division of Drug Marketing, Advertising and Communications (DDMAC) often cannot be met using

traditional pharmacoeconomic techniques. However, as long as an MCO requires a manufacturer to submit a dossier conforming to the AMCP Format, the information is believed to constitute an "unsolicited request" and, thus, is permissible by DDMAC. Although as of this writing DDMAC has not formally issued guidance to the industry relative to the Format, we believe guidance is forthcoming. We have no reason to believe that adherence to a requirement to submit a dossier conforming to the AMCP Format will be problematic.

As the AMCP Format becomes a standard requirement across managed care, pharmaceutical manufacturers can expect to have fairly rigorous demands for pharmacoeconomic information placed upon them. Of course, the clinical evidence will not change from what is generally now required, but the economic and possibly patient-reported-outcomes (PRO) data expectations are substantially increased. Therefore, it is even more vital than before that pharmaceutical manufacturers begin the planning process for drug dossiers (i.e., formulary submission documents) in the early stages of their Phase III programs. This early planning will help to ensure that the value message for a new drug is supported by credible evidence. In addition, having a dossier ready for submission to MCOs at market launch increases the likelihood of reaching maximum market penetration. Of course, since the AMCP Format requirements are similar to that experienced in Canada, Australia, the UK (NICE) and other European countries, the effort envisioned here can be amortized over much of the Western world markets.

For more information on dossier preparation, contact Clark Paramore at 301-664-7277 or email paramore@MEDTAP.com. ■

Budget Impact Models: A Powerful Tool for Managed Care Decision Making

By Sonja Sorensen, M.P.H.

In the United States, using models to determine the budget impact of the adoption of new pharmaceuticals has become increasingly accepted as a tool for helping managed care organizations and other payers make formulary decisions.

Section IV of the recently released AMCP format provides guidance on developing impact models, including budget impact models. Although, the specific model design (e.g. decision tree or Markov model or other) is not specified in the Format, good modeling practices are strongly recommended. Guidelines for good modeling practices published by Drummond and

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International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

SEVENTH ANNUAL INTERNATIONAL MEETING — ARLINGTON, VA, USA — MAY 19-22, 2002

SHORT COURSE

- **Introduction to Bayesian Approaches to Health Economics and Outcomes Research.** Bryan Luce¹, Ya-Chen Tina Shih¹, Chris Barker¹, Frank E. Harrell², ¹MEDTAP International, Inc., Bethesda, MD, USA; ²University of Virginia School of Medicine, VA, USA

PANEL SESSION

- **Standards of Evidence: What is Appropriate?** Bryan Luce, MEDTAP International, Inc., MD, USA

WORKSHOP PRESENTATIONS

- **The SEER-MEDICARE Database: A unique Resource for Pharmacoeconomic Research in Oncology.** de Lissovoy G¹, Warren JL², ¹MEDTAP International, Inc., Bethesda, MD, USA; ²National Cancer Institute, Bethesda, MD, USA
- **Methodological and Practical Issues in Developing and Analyzing Oncology Models.** Shih YCT¹, Sorensen S¹, Nuijten M², ¹MEDTAP International, Inc., MD, USA; ²MEDTAP International, Jisp, Netherlands

PODIUM PRESENTATION

- **Psychometric Properties of the Acute Bronchitis Symptom Severity Scale in an International Sample.** Margolis MK¹, Frank L¹, Leidy NK¹, Duprat-Lomon F¹, Amiot N², Sagnier PP³, ¹MEDTAP International, Inc., Bethesda, MD, USA ²Bayer Pharma, Puteaux, France ³Bayer Plc, Stoke Court, UK

POSTER PRESENTATIONS

- **Blood Pressure Reduction and Gains in Life Expectancy Based upon a Markov Model of Primary and Secondary Cardiovascular Events.** Sesso HD¹, Chen RS², L'Italien GJ³, Lapuerta P², Lee WC⁴, Paramore C⁵, Glynn RJ⁶, ¹Brigham and Women's Hospital, Boston, MA, USA; ²Bristol-Myers Squibb, Princeton, NJ, USA; ³Bristol-Myers Squibb, Wallingford, CT, USA; ⁴MEDTAP International, Inc., Bethesda, MD, USA
- **Clinical, Public Health, and Economic Issues Associated with Switching Second-Generation Antihistamines from Prescription to Over-the-Counter.** Prasad M, Shih YCT, Luce BR, MEDTAP International, Inc., Bethesda, MD, USA
- **From Health-Related QOL to Utility — Is There a Way?** Svensson K¹, Szende A², Stahl E¹, Lundback B³, ¹AstraZeneca R&D Lund, Sweden; ²MEDTAP International, Jisp, Netherlands; ³University Hospital, Umea, Sweden
- **Modeling on the Stochastic Frontier: Cost of Treatment for Acute Decompensated Heart Failure.** de Lissovoy G¹, Stier DM², Ciesla G³, Strausser B³, Burger AJ⁴, ¹MEDTAP International, Inc., Bethesda, MD, USA; ²Eureka Research Inc., San Francisco, CA, USA; ³Scios Inc., Sunnyvale, CA, USA; ⁴Beth Israel Deaconess Medical Center, Boston, MA, USA
- **Electronic Data Collection of Patient-Reported Outcomes.** Schmier JK¹, Rentz AM¹, Dennison CR¹, Jones R², Rothman³, ¹MEDTAP International, Inc., Bethesda, MD, USA; ²Health Economics, Johnson & Johnson, Raritan, NJ, USA
- **Psychometric Evaluation of the Modified Strain in Nursing Care Assessment Scale.** Ciesla G¹, Frank L¹, Kleinman L¹, Brodaty HF², Rupnow M³, ¹MEDTAP International, Inc., Bethesda, MD, USA; ²University of New South Wales, Sydney, Australia; ³Janssen Pharmaceutical Products, L.P., Titusville, NJ, USA
- **Informal Caregivers Costs in the Elderly US Population: A Multivariate Regression Model of the Visually Impaired Versus Unimpaired.** Shih YCT¹, Lustig SP², ¹MEDTAP International, Inc., Bethesda, MD, USA; ²Pfizer Inc., Groton, CT, USA
- **Functional Limitations in the US Elderly Population with Varying Levels of Visual Impairment.** Susan LP¹, Shih YCT², Prasad M³, ¹Pfizer Inc., Groton, CT, USA; ²MEDTAP International, Inc., Bethesda, MD, USA
- **Economic Impact of Respiratory Syncytial Virus Infection on Healthcare Resource Utilization and Costs in the United States.** Paramore C¹, Ciuryla V², Ciesla G³, Liu Z⁴, ¹MEDTAP International, Inc., Bethesda, MD, USA; ²Wyeth-Ayerst Research, Philadelphia, PA, USA
- **Preliminary Results of a U.S.-Based Study to Validate the Acute Bronchitis Symptom Severity Scale.** Leidy NK¹, Margolis MK¹, Merchant S², Gondek K², Li-McLeod J³, Kiskien A⁴, Choudhri S⁵, Church D⁶, ¹MEDTAP International, Inc., Bethesda, MD, ²Bayer Corporation, West Haven, CT
- **The Association between Health Related Quality of Life and Adherence to Therapy in Hepatitis C.** Green J¹, Wintfeld N¹, Barker C², Revicki D³, Bernstein D⁴, ¹Hoffman LaRoche Inc., Nutley, NJ, USA; ²MEDTAP International, Inc., Seattle, WA, USA; ³MEDTAP International, Inc., Bethesda, MD, USA; ⁴North Shore University Hospital, Manhasset, NY, USA
- **A Budget Impact Analysis of Early Referral to a Nephrologist for Elderly Medicare Patients with End-Stage Renal Disease.** Shih YCT¹, Guo AM², Prasad M³, Just PM⁴, ¹MEDTAP International, Inc., Bethesda, MD, USA; ²Baxter Healthcare Corporation, Deerfield, IL, USA
- **Validation of the Perception of Bladder Condition Measure in Overactive Bladder.** Coyne K, Matza LS, MEDTAP International, Inc., Bethesda, MD, USA
- **Validation of the Urgency Perception Scale.** Cardozo L¹, Coyne KS², Versi E³, ¹Kings College Hospital, London, UK; ²MEDTAP International, Inc., Bethesda, MD, USA; ³Pharmacia Corporation, Peapack, NJ, USA
- **How Responsive is the Overactive Bladder Questionnaire (OAB-Q) to Changes in Urgency, Frequency, and Incontinence?** Tomera KM¹, Coyne K², Matza LS³, Corey R⁴, ¹Alaska Clinical Research Center, Anchorage, AK, USA; ²MEDTAP International, Inc., Bethesda, MD, USA; ³University of the Sciences in Philadelphia, Pharmacia Corporation, Peapack, NJ, USA

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for the Exhibitor's Open House Reception, Monday, May 20, 6-8pm.
We also invite you to visit MEDTAP's exhibit during the conference to meet our scientists.

RECENT PUBLICATIONS

MEDTAP welcomes comments and inquiries about our scientific work. Each issue, we feature a list of current publications and industry presentations. If you wish to obtain reprints of papers or a complete publication list, please call 301-654-9729.

BROWN RE, HENDERSON RA, KOSTER D, HUTTON J, SIMOONS ML. "Cost-Effectiveness of Eptifibatide in acute coronary syndromes: An economic analysis of western European patients enrolled in the PURSUIT trial." *European Heart Journal*; 2002; 23:50-58.

COYNE K, DAVIS D, FRECH F, HILL M. "Health-Related Quality of Life in Patients Treated for Hypertension: A Review of the Literature from 1990 to 2000." *Clinical Therapeutics* 2002; 24:142-169.

NUIJTEN MC, BERTO P, BERDEAUX G, HUTTON J, FRICKE F-U, VILLAR FA. "Trends in decision-making process for pharmaceuticals in Western European countries: A focus on emerging hurdles for obtaining reimbursement and a price." *HEPAC 2* 2001; 4:162-169.

NUIJTEN MC, HUTTON J. "Cost-Effectiveness analysis of interferon beta in multiple sclerosis: A Markov process analysis." *Value in Health*; January/February 2002; 5(1:44-54).

SPIES J, COYNE K, GUAOU N, BOYLE D, SKYRNARZ-MURPHY K, GONZALVES, S "The UFS-QOL, a New Disease-Specific Symptom and Health-Related Quality of Life Questionnaire for Leiomyomata." *Obstetrics & Gynecology* 2002; 99(2):290-300.

RECENT PRESENTATIONS

DIA'S 9th Annual Symposium for Quality of Life Evaluation

HILTON HEAD ISLAND, SC — MARCH 24-26, 2002

- "Patient Reported Outcomes (PROs): Their Impact on Future Studies". Leidy NK¹, "Assessment of QoL in Children: Methodological Issues". Matza LS¹, "Impact of Development Approaches on Instrument Psychometrics and Equivalence". Flood E¹, "Evaluating the Symptom Experience of Patients with Type II Diabetes". Jones TL¹. ¹MEDTAP International, Inc., Bethesda, MD USA.

Mayo Clinic Meeting: Assessing Clinical Significance for Quality of Live Measures in Oncology Research

ROCHESTER, MN — APRIL 5-6, 2002

- "Interpretation of Quality of Life Data from a Clinician's Point of View: Getting to the Clinical in Clinically Meaningful Change". Dennison CR¹, Leidy NK¹, Silberman C², Heyes A³.

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- "What Does it all Mean? Using Health-Related Quality of Life Data to Interpret Treatment Outcomes". Leidy NK¹, Jonas D¹, Silberman C², Margolis MK¹, Heyes A³. ¹MEDTAP International, Inc., Bethesda, MD, USA; ²AstraZeneca, Wilmington, DE USA; and ³AstraZeneca, Macclesfield, UK.

UPCOMING PRESENTATIONS

2002 Pediatric Academic Society Annual Meeting

BALTIMORE, MARYLAND — MAY 4-7, 2002

- "Patient, Caregiver, and Family Distress During Hospitalization for Respiratory Syncytial Virus (RSV)". Leidy NK¹, Margolis MK¹. ¹ MEDTAP International, Inc., Bethesda, MD USA.

American Society of Hypertension Annual Meeting

NEW YORK, NY — MAY 14-18, 2002

- "Modeling Clinical and Economic Outcomes of Antihypertensive Treatment Alternatives". Sonja V Sorensen¹, Ruth E Brown², Timothy M Baker¹, Feride Frech² and Krista Yokoyama². ¹MEDTAP International, Inc., Bethesda, MD, USA; ²MEDTAP International, Inc., London, UK; and ³Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

American Nephrology Nurses' Association, 33rd Annual National Symposium

ORLANDO, FL — MAY 23-26, 2002

- "Impacts of rHuEPO Injections on the Daily Routines of CRI Patients". Jill Lindberg¹, Jamie Foret, Lynn Pitts¹, Jon Ford², Ruth Brown³, and John Lu². ¹Ochsner Medical Clinic, New Orleans, LA, USA; ²Amgen Inc, Thousand Oaks, CA, USA; ³MEDTAP International, Inc., Bethesda, MD, USA.

Annual European Congress of Rheumatology "EULAR 2002,"

STOCKHOLM, SWEDEN — JUNE 12-15, 2002

- "Evaluation of Outcome Measures in Assessing Productivity Loss in Patients with Rheumatoid Arthritis". A. Lloyd¹, G. Lawless², J. Hutton¹, R. Brown¹. ¹MEDTAP International, London, United Kingdom; ²Amgen Inc., Thousand Oaks, CA, USA.

Budget Impact Models

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Jefferson (1996) are included in Appendix A of the Format; also see Halpern et al (*Value in Health*, 1998 and the recent ISPOR Task Force Report on Good Modeling Practices, www.ispor.org). The model should be developed to depict the natural history of disease and the clinical pathways. For example, an oncology model examining a new chemotherapy should consider disease progression or recurrence, treatment-related toxicities and switches to different therapies. The choice of specific

comparators included in the model will depend on existing clinical practice patterns which optimally will include persistence/compliance rates for different clinical pathways. The comparators need to include all primary treatments used in the plan. For example, in the case of antidepressants, it would be important to include generic fluoxetine (since this agent has a large market share) for the validity of the model. For a budget impact model to have relevance to a plan, plan-specific information such as the size of the plan, prevalence of disease and current

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Budget Impact Models

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treatments about the health plan should be included. In addition, since treatment patterns and costs vary from plan to plan, these parameters should be specific to the plan to the extent possible. Unfortunately, it is often difficult to obtain these specifics. Since the target audience is the managed care plan, the perspective of the model should be from the third party payer. The time horizon for these models may vary depending on whether the new treatment is for an acute or chronic condition. It is important to follow patients long enough to capture the health benefit and potential cost offsets, however, managed care plans are generally interested in models that follow patients over one to three years, since patients do not remain in the plan much longer than that.

According to the AMCP format, the outcomes should be presented as cost/consequences. Outputs of interest include cost per member per month or cost per treated member per month. Costs of care should be broken down by medical resource utilization and drug costs. Sensitivity analyses should be conducted to assess the robustness of the key assumptions on the results.

In addition to reporting the results of the model, the manufacturer should provide a copy of the model to the health plan for the plan to conduct exploratory analyses. For this reason and for the user to make well informed decisions, the model should be transparent so a user understands assumptions (such as how switching is handled) and the calculations. Data for these models can come from various sources, however, this should be well documented in the model. Carefully designed and executed budget impact models continue to demonstrate their value in the health care decision-making process.

Finally, although the budget-impact model is of key interest to health plans, the AMCP Format also envisions a decision-analytic model which permits a manufacturer to position its products in terms of cost-effectiveness relative to other courses of therapy.

For more information, contact Sonja Sorensen at 301-654-9729 or email sorensen@MEDTAP.com. ■

Financial Analysis in Health Care Financing

By Mark Nuijten, M.D., M.B.A., and John Hutton, B.Sc. Econ, B.Phil.

Health care financing has been a topic high on the political agenda in Western Europe in recent times. Every government is eager to control the increase of expenses by the implementation of central cost containment policies, and pharmaceuticals are a principal focus. Pharmaceutical expenditures increased in Europe and the US during the 1990's. In most countries, pharmaceutical spending has reached 10-15% of the total health care budget (in some countries such as Greece, Portugal and Spain this proportion is higher than 20%).¹

For the most part, "top-down" cost containment measures have relied on budgeting or price controls, including negotiated prospective budgets for hospitals, centralized negotiated budgets for ambulatory physicians including drug prescriptions, and limitations on payments for particular medications. Because those traditional centralized mechanisms have been only partially successful, the health authorities in Europe are adopting new strategies for decentralizing health care decision-making and implementing market mechanisms, and creating incentives for efficient health care delivery.

There are three parallel trends that demonstrate increasing data requirements at a central level, more decentralization of the responsibilities and decision-making processes, and restrictions on prescribing. In Sweden, there is a plan to transfer the responsibility for financing prescription medicines in ambulatory care from the RFV to the county councils, over a three-year period. The Dutch government is considering giving the local health insurers responsibility for the purchasing process for drugs, which means that they will directly bargain and negotiate with pharmaceutical companies.

Expanding Data Requirements

Pricing and reimbursement have been based, until recently, on the traditional clinical trial outcomes (efficacy, safety and quality parameters) used for registration. Now we can distinguish various extra data requirements which all relate to the use of the drug in real daily practice, while the traditional clinical trial outcomes are only derived from randomized clinical trials.

Effectiveness: There is an increasing demand for effectiveness data. While efficacy and effectiveness are two different concepts, both have something to say about the effect of a drug. In the case of efficacy, the effect is

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**Meet Chris Barker,
Director of Statistical Research**

MEDTAP is pleased to announce that Chris Barker, Ph.D., joined our staff as Director of Statistical Research on January 2. Dr. Barker’s position creates a new satellite office in Redwood City, located in the Bay Area/Silicon Valley section of California.

With 22 years of experience conducting statistical analyses (14 of those years with major pharmaceutical manufacturers), a master’s in economics, and another master’s and a Ph.D. in biostatistics, Dr. Barker adds a new skill set to MEDTAP’s illustrious staff of scientists. He’s worked for both the economic and clinical trial sides of health care research. He bridges the gap between statisticians and economists. Dr. Barker has been widely published and has made numerous presentations around the world.

Dr. Barker is currently working on a MEDTAP project for a breast cancer drug, but as word of his cutting-edge statistical expertise spreads, he is getting more requests to pitch in on other MEDTAP projects.

“I anticipate providing my statistical expertise in projects involving both quality of life and economic modeling. In addition, I bring to MEDTAP a unique background in design conduct and reporting of Phase II and III clinical trials, with the accompanying statistical-regulatory experience in dossier submissions and successful registrations with U.S. (FDA), European, Australian, and Japanese regulatory agencies” says Barker. His therapeutic clinical trial background is extensive and includes an immunologic agent for solid organ transplantation, a sleep hypnotic, anxiolytic, cardiovascular, antibiotics, anti-inflammatory, and breast and colon cancer.

Dr. Barker’s collaborative work with economists and his familiarity in biometrics and econometrics has paved the way for his effective use of clinical trial data. This work provides data and statistical analyses used in economic modeling and assessments of cost effectiveness. His collaborative work has also resulted in submission to agencies such as National Institute for Clinical Excellence (NICE).

According to Bryan Luce, CEO, “There just aren’t many statisticians working in the health economics field, and certainly not people with the education and regulatory experience that Chris has. He’s providing a skill that we were lacking, and his location will be an added

advantage in pursuing some of the biotech business out on the West coast.”

When asked why he chose to join MEDTAP, Barker responded, “Namely because of the tremendous scientific integrity for which MEDTAP is known. I’m intimately familiar with the regulatory side of this business — I know how clinical trial databases are built...I’ve prepared dossiers for successful drug registration and formulary approval...I’ve worked with the economists at Roche — I’m interested in the kind of work that MEDTAP does. It is especially exciting to be involved in Bayesian analyses for Health Economic evaluations — in collaboration with MEDTAP scientists.”

Andrew Lloyd, D.Phil., Joins MEDTAP London

MEDTAP is pleased to announce that Dr. Andrew Lloyd has joined our London research staff. He is a senior research associate charged with strengthening MEDTAP’s portfolio in health-related quality of life and other areas of outcomes research.



ANDREW LLOYD

As a research psychologist, Dr. Lloyd’s primary interests are in assessing outcomes from medical treatments and medical decision making, as well as assessing quality of life and cognitive function. He is a member of the EuroQol group. More recently Dr. Lloyd has examined the strengths and weaknesses of different preference elicitation methods such as conjoint analysis and willingness-to-pay from a psychological perspective. Dr. Lloyd is currently looking at the measurement of productivity decline in rheumatoid arthritis. He has been published in *Medical Decision Making*, *Quality in Health Care*, *British Journal of Surgery*, and *Lancet*, among others. Dr. Lloyd received his B.Sc. in psychology from the University of Hull and his D.Phil. from the University of York.

MEDTAP Scientist Rentz on Temporary Assignment to Germany

Anne Rentz, M.S.P.H. has begun a three-year assignment in Stuttgart, Germany. In addition to providing research planning services to clients in the U.S., Anne will be working with MEDTAP staff in both the U.K. and Amsterdam offices, with an emphasis on outcomes research projects. Anne can be reached by email at rentz@MEDTAP.com. ■



Science and Policy Opinion...

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You seem especially interested in confidence intervals. We both agree that an acceptability curve analysis based on net health benefit may be more informative to decision-makers than the arbitrarily pre-determined 0.05 P-value typical of the frequentist approach. Until I read the excellent review article by Spiegelhalter et al¹ (2000), I have to say that I haven't paid much attention to Bayesian methods for meta-analysis or Bayesian hierarchical models.

Dr. Barker: Your comments about treatment assignment and selection issues in observational databases are very interesting. A number of interesting statistical developments have occurred in both statistics and economics. For the frequentist this is called "propensity scoring" and the economic counterpart is "instrumental variables."

I believe there will be an important Bayesian impact on a common problem in the interpretation of both clinical trial and observational data — the problem of missing data. Noted Bayesian, Don Rubin has suggested using imputation or multiple imputation of missing data as a way to examine the uncertainty with traditional imputation methods, such as the "last observation carried forward." Last observation carried forward is often applied to clinical trial data, and now there are many better methods of imputation, including software available to study the uncertainty associated with this type of imputation. Bayesian methods also provide a natural framework for describing uncertainty.

Confidence intervals present a somewhat special problem. The strict frequentist interpretation is that the C.I. covers the true value 95% of the time, or some other arbitrary interval. However, the C.I. is rarely interpreted this way. When paired with an estimate, then the C.I. is typically interpreted as the upper and lower limit of possible values. That's not wrong, but it is a different way of thinking.

I find the Bayesian interpretation of a C.I. very useful and frankly, I'm surprised it isn't used more often in patient prognosis. Specifically, the Bayesian interpretation allows one to place a probability distribution on treatment effects and to describe the probability of a treatment effect of a certain size. I think that kind of interpretation is more useful to both patients and decision makers (e.g. treating physicians) than the conventional C.I.

For example, suppose the clinical trial for a new cancer treatment demonstrated improved survival (vs. placebo) of 6 months with a 90% C.I. of 4 to 8 months. That's the frequentist CI. From the patient's point of view, I'd prefer to know that I had a 20% probability of either a 4 or 8 month improvement effect, a 50% probability of 6 month improvement and perhaps a 5% chance of a 1 month or 12 month improvement. That's a Bayesian interpretation. Frequentist C.I.s are often interpreted in this manner, but that is not at all appropriate.

Dr. Shih: The Bayesian Initiative was instituted to explore the value of the Bayesian approach in cost-effectiveness

analysis. But one challenge for our sponsors is to convince their in-house biostatisticians of the value of this approach. Chris, as a biostatistician who previously worked in a pharmaceutical company, do you feel that there's resistance in using the Bayesian approach among biostatisticians in pharmaceutical companies?

Dr. Barker: Based on informal discussions at a recent meeting of industry and FDA statisticians that I attended, my sense is that while the FDA is quite open to Bayesian methods, industry is reluctant to change. This reflects the very conservative and cautious approach that typifies industry approach to trial design and analysis: "if it worked last time, then do it again" at times is the prevailing attitude in industry. However, I rarely find my statistical colleagues approach statistical problems in this way. Many of my colleagues are very receptive to new and innovative approaches. I believe more Bayes success stories in the analysis and interpretation of randomized clinical trials would be useful to my colleagues.

I am also certain there are very pragmatic reasons why Bayes methods are not used more frequently, and one reason is the lack of good software. For example, the statistical theory for "mixed models" in clinical trial statistics has been available since the early 1900s. However, the computational task is extremely challenging and only in the last 10-15 years has readily available statistical software made such complex methods feasible. Of course, access to software packages does not mean that the methods are applied correctly!

Publicly available software for Bayes analyses has only been available to the statisticians with the advent of BUGS. Soon there will be an S-PLUS Bayes function library and I presume Bayesian software is in the works at SAS and the other major software companies. As David Draper and others have observed, Bayes computing methods such as Metropolis Hastings, Gibbs Sampling, and Markov Chain Monte Carlo (MCMC) simulation are only now possible because the enormous power in modern chip sets means that computations can be carried out in a few hours or less, rather than days.

Even software for multiple imputation of missing data, has only been commercially available within the last 10 years.

I would select the area of patient prognosis and outcomes as a promising area to demonstrate the explanatory power of a Bayes analysis. A starting point would be to apply a Bayes analysis to an existing frequentist analysis. Certainly having the two side by side would highlight the "value added" by the Bayes analysis.

¹Spiegelhalter DJ, Myles JP, Jones DR, and Abrams KR. "Bayesian methods in health technology assessment: a review." *Health Technology Assessment* 2000; 4(38). ■

Financial Analysis

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examined under ideal conditions in a homogeneous group of patients, and usually with the assistance of intermediate end-points. Effectiveness data, on the other hand, offer a clearer picture of the actual value of a drug because the effect is examined under more realistic conditions using a more heterogeneous group of patients. This information about use in common practice also provides more insight into whether the aim of the treatment will ultimately be achieved.

Cost-effectiveness data from a health economic

analysis: The fourth hurdle in drug development in many countries is the requirement for manufacturers to demonstrate the cost-effectiveness of their products before acceptance for reimbursement or, less frequently, agreement on a price. Health economic data should permit reliable, reproducible and verifiable insight into the effectiveness 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. There is currently an increasing demand for health economic data in the decision-making process in Europe. Several countries now have formal reporting requirements (the UK, Finland and Portugal) or will have in the near future (The Netherlands, Norway and Italy).² In France, health economic data are used to help support a premium price, as part of the negotiations.

“Health economic data should permit reliable, reproducible and verifiable insight into the effectiveness of a drug...”

Budgetary impact data from a financial analysis: Besides the cost-effectiveness of a new drug, reimbursement decisions will also be based on its impact on the annual national health care budget. For the financial analysis, data on the following subjects will be required: descriptive epidemiology (data on incidence and prevalence); the patient group that is indicated for the drug and the anticipated substitution effects (i.e. the extent to which the existing treatment will be replaced); the use of the drug (posology, length of the treatment, etc.), the price of the drug; the expected market share (plus the variables that would facilitate or slow down drug sales) and the total treatment costs. On the basis of the cost-effectiveness analysis and the financial analysis (and other policy factors), a decision can be made as to whether the drug should be reimbursed. Examples of this process can be seen in The Netherlands, UK and Italy.²

There are differences between an economic evaluation (EE) and a budgetary impact analysis (BIA).³

- ▶ An EE follows a patient cohort over time while a BIA looks at the costs of all treated patients in a fixed period, usually a year. An EE measures all costs and outcomes; a BIA looks at financial costs.
- ▶ An EE usually takes a societal perspective; a BIA takes the payer's perspective.
- ▶ An EE uses opportunity costs while a BIA uses market prices.
- ▶ There are many guidelines for EE but none for BIA.

If reimbursement of pharmaceuticals is going to be based in part on data derived from a financial analysis, it is vital to scrutinize and refine this type of analysis. In a new paper, we have presented a modeling technique (methodology) for an appropriate assessment of the budgetary impact of a new drug, which simultaneously can be used for traditional cost-effectiveness analysis. To illustrate the methodology, a model was constructed for a new drug in Parkinson's disease from the social perspective in The Netherlands⁴.

In summary, financing prescription medicines in ambulatory care has been a central responsibility, which was based on the traditional clinical trial outcomes (efficacy/safety parameters) used for registration. Although there is large variation between countries, there are three common and related trends: decentralization of the health care decision-making process, prescription restrictions, and extra data requirements. At a central level the demand for cost-effectiveness and budgetary impact data is increasing, which has already resulted in some countries having formal reporting requirements. Although the most evident impact of health economic and budgetary impact studies is expected to affect central reimbursement audiences, evidence for the use of health economic studies by other audiences is expected to increase (e.g. patients, hospitals, insurers, formulary committees)³.

¹OECD Health Data, 1999. ²Nuijten MJ, et al, “Trends in decision-making processes for pharmaceuticals in Western European countries.” *European Journal of Health Economics*, 2002; -03-26. ³Trueman P, Drummond MF, Hutton J, “Developing guidance for budget impact analysis.” *PharmacoEconomics*, 2001; 19: 609-621. ⁴Nuijten M, Rutten F. “Combining a budgetary impact analysis and a cost-effectiveness analysis using decision analytic modeling techniques.” Accepted by *PharmacoEconomics*. ■

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