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## SCIENCE & POLICY OPINION

### A Prescription for the Pharmaceutical Industry

By Susan D. Ross, MD, FRCPC



*Dr. Susan Ross is the Vice President, Medical Affairs for United BioSource Corporation.*

A recent Harris poll reported that only 13% of Americans consider drug companies to be honest or trustworthy. The industry responsible for so many wonderful contributions to human health now finds itself at the bottom of public approval rankings, next to the tobacco industry. How could this happen? It happened because the pharmaceutical industry — at least the product commercialization side of the industry — has lost touch with the evidence needs of its customers. While doctors, nurses, hospitals, formularies, payers, policy makers, and even patients have

embraced the principles and practices of evidence-based medicine (EBM), many drug companies have not — yet.

The Institute of Medicine definition of EBM is the conscientious and judicious use of current best evidence in patient care. The chief “tools” of EBM are systematic reviews and meta-analyses, and, within the pharmaceutical industry, these tools are applied to answer questions of drug efficacy, safety, and value. The MetaWorks® Method, pioneered by Dr. Thomas Chalmers, the father of meta-analysis in medicine and the co-founder of MetaWorks Inc., follows standard operating procedures and uses a platform database technology called MetaHub™. A systematic review is the best way to identify and synthesize all the current best evidence on a clinical question.

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## FDA Draft Guidance Released

On February 2, the Food and Drug Administration (FDA) released their long-awaited draft document “**Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.**”

This guidance document was released and distributed for comment purposes only, and comments and suggestions regarding this draft document must be submitted within 60 days.

*Look for more information on this topic in the upcoming months, including an article in the May issue of Research News.*

## The Evolution of Large Streamlined Trials

By Annette Stenhagen, DrPH and Gerald Faich, MD, MPH

*Dr. Stenhagen is the Vice President and Dr. Faich is the Senior Vice President of Risk Management and Epidemiology for United BioSource Corporation.*

Regulatory agencies recognize the importance of collecting postmarketing safety data in large numbers of patients, as a supplement to clinical trial data collected pre-marketing, in order to quantify rare serious adverse events (SAEs) and to evaluate a heterogeneous patient population. These objectives can be achieved using a large, streamlined study design (LSS). (Reference is also made to LSS in the

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## Large Streamlined Trials

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March 2005 FDA Risk Management Guidance document, “Pre-marketing Risk Assessment,” as a way to increase knowledge about a new drug or biologic prior to marketing.)

Large streamlined studies have been an essential element of public health research for decades, with designs ranging from community intervention trials to morbidity and mortality “mega trials” to epidemiological observational studies. One landmark early example is the 1954 polio vaccine field trial, which used an “observed” population as the comparison group.<sup>1</sup> All second graders in specified geographic areas were

vaccinated, with first and third graders providing polio incidence rates as a comparison population.

Alternatives of observational studies have been advocated for decades as well.

**Large streamlined studies have been an essential element of public health research for decades, with designs ranging from community intervention trials to morbidity and mortality “mega trials” to epidemiological observational studies.**

Dr. Louis Lasagna in the early 1970’s made a plea for the “naturalistic” study of medicines. His treatise was that only by observing who was prescribing specific medications, how they were being used, and noting the outcomes could we determine the most effective treatments. Many actual use studies and registries are designed to document prescribing behavior without intervention. This is particularly important when evaluating safety risks and estimating incidence of SAEs in the general population using a specific medication.

Large morbidity and mortality studies such as the International Study of Infarct Survival (ISIS) provide contrasting approaches and designs to strictly observational studies.<sup>2,3</sup> ISIS was a randomized controlled study of the effects of intravenous beta blockage on mortality. The first ISIS trial evaluated over 16,000 patients with myocardial infarction to determine “hard” endpoints of 7 day and 30 day mortality and demonstrated the improvement in survival by  $\beta$ -blockade. A premise of this and other LSS is that the study of major endpoints is more important than minor endpoints (that is, focus on SAEs and deaths) and that follow-up of these major “hard” endpoints can be simple since they are documented readily in hospital records.

Another example of an LSS is the assessment of the safety of pediatric ibuprofen.<sup>4</sup> This was a randomized, double-blind acetaminophen controlled trial of 84,192 children. The “hard” endpoints evaluated were hospitalizations for GI bleeding, acute renal failure, and anaphylaxis. Outcome data were collected by mail and phone follow-up with parents at four

weeks. The results of this study supported a label change for the pediatric indication for ibuprofen use.

As analytic and methodological techniques have evolved in recent decades, greater consideration has been given to study designs that differ from the intensive, traditional randomized, double-blind, placebo controlled study of a limited number of patients, allowing for consideration of studies with thousands of patients. Outcomes research within the pharmaceutical and biotechnology industries has also been an evolutionary force to broaden study designs from this traditional model. Technological advances have contributed as well. These technological innovations and the consequent cost savings, particularly in methods of data collection, have brought greater acceptance to these approaches. The total cost of an LSS in cost per subject, cost per data collection page, and total costs are generally less than a very small, traditional randomized controlled trial (RCT).

Whether using a randomized design, being structured as a quasi observational study (patients randomly assigned to treatment and then followed in an observational manner), or as a completely observational study or registry, LSS follow the common tenants of:

- Simple protocol that defines study objective, patient recruitment, and data collection
- Brief data collection form focused on “hard” endpoints
- Limited number of patient visits to mimic usual care as much as possible, with no additional diagnostic testing or other procedures
- Inclusion of many community physicians rather than clinical research sites to reflect usual clinical practice
- Large numbers of patients selected based on broad eligibility criteria to enable a heterogeneous study population

In this era of risk minimization and benefit maximization, the LSS can be a powerful tool in better quantifying risk, identifying areas for risk intervention to minimize risk by appropriate product use, and documenting important patient outcomes and product benefits.

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<sup>1</sup>Francis T, Korns R, Voight R et al. An evaluation of the 1954 poliomyelitis vaccine trials. *Am JPH* 1955; 45:1–50.

<sup>2</sup>Yusuf S, Collins R, Peto R. Why do we need some large simplified randomized trials? *Stat in Med* 1984; 3:409–20.

<sup>3</sup>Peto R, Collins R, Gray R. Large-scale randomized evidence: large simplified trials and an overview of trials. *J Clin Epidemiol* 1995; 48:23–40.

<sup>4</sup>Lesco SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *J Amer Med Assoc* 1996; 275:986–991.

## SCIENCE &amp; POLICY OPINION

## A Prescription for the Pharmaceutical Industry

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A properly done systematic review is reproducible, explicit, objective, and with bias-control procedures built in. Given the sheer volume of disparate and dispersed information that exists for most clinical topics, a systematic review using the MetaWorks Method typically takes a team of four to five people, including a physician and statistician, three to four months to complete. To keep the resulting database current is no small task either. As an example, in the area of bariatric surgery, more than 100 new citations are available every six months.

Our scientists and research staff have used the MetaWorks Method to produce more than 300 systematic literature reviews, publishing scores of them. All of the data extracted from these reviews are also available in the evolving data warehouse, MetaHub™, which currently holds group data from more than 7,000 studies of more than six million patients. This database is an integral component of our review procedures, and it also permits external users to query, export, and analyze clinical trial outcomes by study and patient characteristics, and treatment variables. Most importantly, it facilitates periodic updates of any evidence-base to keep it current.

In a systematic review, data can be synthesized qualitatively or quantitatively. The latter is called meta-analysis, a statistical pooling of data from multiple clinical trials that adjusts for both between- and within-study differences. Meta-analyses can:

- Strengthen the precision of our knowledge because the effect of bias inherent in any one study is reduced and the play of random chance is reduced
- Examine questions no single study can address
- Inform practice guidelines and individual treatment decisions
- Point the way to future research

In conclusion, my prescription for pharma's public relations problem is EBM. I believe that drug companies taking the EBM cure will also boost their product development and commercialization success. Adoption of the principles and tools of EBM by the pharmaceutical industry is the right thing to do ethically (to regain public confidence and respect), and the right thing to do financially. If the industry needs an immediate incentive to take this cure, it should realize that it can use systematic reviews of current knowledge for:

- Messaging (for sales representatives, advocacy groups, consumers, prescribers, and formularies)
- Risk Management (to provide safety benchmarks and to evaluate potential safety signals)
- Competitive Advantage (to compare drugs directly or indirectly, e.g., efficacy or safety)
- Reimbursement (for NICE, Oregon DERP, CMS, payers, formularies)
- Life-Cycle Management (to explore new indications for marketed drugs)

Data currency, accuracy, completeness, and transparency really do matter. The conscientious and judicious use of evidence *matters*.

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## Application of Item Response Theory to Develop Short Form Depression Severity Scales: An Illustration

By Wen-Hung Chen, PhD & Dennis Revicki, PhD

Modern test theory approaches complement and extend classical test theory methods for understanding the psychometric characteristics of clinician rated or patient rated outcome measures. Item response theory (IRT) refers to a set of mathematical models that describe, in probabilistic terms, the relationship between an individual's response to a question and that person's level of the latent variable measured by the scale. The latent variable is usually a hypothetical construct (e.g., depression severity, fatigue, etc.) which cannot be directly assessed but is indirectly measured using multiple questions in an instrument. The value of IRT application is that it can assign an item and a person to places along the same continuum represented by this latent construct.

Because of this property, instruments developed using IRT can be made adaptively to assess around the individual's

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level, rather than the whole instrument, thus reducing the number of items needed to obtain a precise measurement for that person. In addition, while the person measure is the unweighted mean or sum of the

item scores for classical test theory, the person measure is the weighted composite for the IRT. The item weight depends on the degree of association between the item and the latent variable. In other words, for IRT, endorsement of certain items contributes more to the person measure than endorsement of other items of the same instrument.

We developed and evaluated the psychometric characteristics of IRT-based short form depression severity scales based on combinations of the Hamilton Depression Rating Scale (HDRS) and Montgomery-Asberg Depression Rating Scale (MADRS). Three short form depression severity outcome measures were developed based on clinician review and recommendations, as well as exploratory factor analysis and IRT analyses of the HDRS and MADRS items.

First, we interviewed five psychiatrists about the depression-related symptoms that, in their experience, were most responsive to depression treatment. The items selected covered depressed mood, anhedonia, impaired work and other daily activities, suicidal ideation, anxiety/irritability, lassitude/fatigue, feelings of guilt, and general somatic symptoms. Based on these interviews, we identified items within the HDRS and MADRS which reflected these symptoms.

Second, we completed item analyses and an exploratory factor analysis of the HDRS and MADRS items. The item analyses focused on examining response distributions, standard deviations, etc. While the majority of the items demonstrated the entire range of responses and acceptable distributional characteristics, several items proved problematic. The item analysis demonstrated that there was very little variation and extreme skewness for suicide, insight and genital symptoms items. These items were flagged for further consideration since items with little variation might not contribute to differentiating treatment effects. For example, almost all subjects indicated some level of insight into their depression, which makes sense given that these subjects were recruited into a clinical trial of antidepressant therapy and had to have sufficient insight to agree to participate in the study.

Principle axis factor analysis was used to examine the underlying factor structure among the HDRS items and the MADRS items separately. We anticipated that there would be multiple factors within the HDRS, and IRT analysis depends on assumptions of unidimensionality. The factor analysis was used to help select the initial collection of potential depression severity items and to ensure relative unidimensionality of these items. The factor analysis confirmed the multidimensional domain structure of the HDRS items, but did identify a dominant factor that covered mood-related rather than somatic-related items. The remaining factors were represented by combinations of sleep, appetite and other somatic symptoms.

An IRT analysis was completed using all the HDRS and MADRS items. Because the HDRS and MADRS items are Likert scale type items with more than two response options, they were analyzed with a multiple-response category IRT model, that is, Samejima's graded response model. The software Multilog was used to fit the graded response model to the items and to complete the item IRT calibration. These IRT analyses were performed on the entire set of HDRS and MADRS items to guide selection of final items. Finally, IRT analyses using the graded response model were completed separately for the items included in the derived short-form depression severity measures.

In an IRT analysis, the slope indicates the association between the items and the underlying trait. Our results showed that the average slope for HDRS items was relatively smaller than that for MADRS items. This suggested that the MADRS items, in general, were more closely related to the underlying trait, depression severity. In addition, most of the items were sensitive between high and low responders. The small average slope associated with the HDRS items suggested they might be measuring different underlying traits or

that the items were too general and did not discriminate well between high and low responders.

Several of the HDRS items demonstrated good discriminative properties for assessing depression severity, including depressed mood, work/activities, guilt, psychic anxiety and general somatic symptoms. However, there were a number of HDRS items that did not exhibit acceptable item discrimination characteristics, including the insomnia related items, gastrointestinal symptoms, genital symptoms, and hypochondriasis. The insight and suicide items only demonstrated modest item discrimination. In general, the MADRS items had better item discrimination parameters compared with the HDRS items. There are several differences between the two depression severity measures which may have resulted in improved item parameters for the MADRS. First, the MADRS consists of items that were selected to be more unidimensional and responsive to depression treatments. The unidimensionality of the MADRS compared to the evident multidimensionality of the HDRS also contributes to a better IRT model fit (i.e., unidimensionality is a key assumption for IRT). The HDRS items were originally selected for application in hospitalized depression patients and some of these items may be less relevant for patients treated in outpatient settings. Second, the MADRS uses a 7 point response scale, while the HDRS uses 3 to 5 point response scales. In addition, there were fewer items with response categories with missing data for MADRS items (3 of 10) than for HDRS items (6 of 17). The better item discrimination observed for the MADRS items may be attributable to the more homogeneous item content and/or the expanded response scale.

Three short-form versions of the combined HDRS and MADRS items were developed (i.e., DS-1, DS-2, DS-3) based on the result of psychiatrist recommendations, factor analyses, and the exploratory IRT analysis. The short-form depression severity scales, ranging in number of items from 7 to 10, had good internal consistency reliability (0.87 to 0.93), validity, and responsiveness to treatment differences. Reliability and validity of the short-form depression severity scales were comparable to the measurement qualities of the HDRS or MADRS. More important, the short-form depression severity scales demonstrated responsiveness to antidepressant treatment effects. In the two clinical trials included in the current study, one trial showed significant differences between treatment and placebo groups, while the other demonstrated no treatment differences. The three short-form depression severity scales, the HDRS and the MADRS showed similar patterns of treatment effects across the two clinical trials. However, the DS-2 and DS-3 had effect size estimates that were larger than the effect size for the HDRS and slightly larger than the effect sizes for the MADRS. Given these larger effect sizes, it may be possible to reduce sample size without compromising statistical power in clinical trials. These findings support the application of short-form depression severity scales, based on IRT, without any loss of

responsiveness and with the ability to detect antidepressant treatment effects.

An important advantage to IRT-based static short forms or tailored outcome measures, based on computer adaptive testing, is briefer assessments that are as sensitive as the longer form measures. In computer adaptive testing for depression outcomes, different subjects would complete different short-form measures tailored to their level of depression severity, and the items completed could vary over different assessments and across subjects. There are several challenges to the acceptance of IRT-based tailored tests from clinical trial researchers and regulatory authorities. First, the tailored testing approach is unfamiliar, and both clinical researchers and regulatory authorities may be uncomfortable with the idea of different subjects completing different short-form versions over the course of a clinical trial. Depression severity measures, such as the HDRS and MADRS are familiar and known. It will be necessary to complete further research which demonstrates the measurement qualities and responsiveness of IRT-based short-forms to effectively convince clinical researchers and regulatory agencies as to the scientific soundness of this method for assessing depression outcomes. Second, there may be some resistance given difficulty in interpreting the data from studies involving IRT-based short-forms or tailored tests. Therefore, interim steps toward convincing clinical researchers and regulatory agencies as to the value of IRT and tailored testing might involve including these type measures, such as the DS-2 or DS-3, as secondary or exploratory endpoints in antidepressant clinical trials. In addition, secondary analyses of existing PRO data from existing completed clinical trials can be analyzed using IRT to verify these findings. The ability of these IRT-based measures to detect treatment differences can then be compared to the original HDRS or MADRS results.

In summary, we developed three short-form depression severity scales based on combinations of HDRS and MADRS items and psychometric analyses. The new short form measures were similar to other short-forms developed based on the HDRS, and we found that they were reliable and valid for patients with major depressive disorder treated in two clinical trials. More importantly, we demonstrated that the short-form depression severity measures were as responsive as the original HDRS or MADRS in detecting treatment differences between treatment and placebo. It is, however, uncertain whether these findings are generalizable to other clinical trial or community practice populations with outpatient major depressive disorder. Additional research is needed, either as secondary analyses of existing clinical trial data or in future clinical trials, to confirm these results. These short-form depression severity measures may be useful for future clinical trials in depression and may allow more frequent assessment of outcomes to differentiate early effects of antidepressant treatment.

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## DIALOGUE

## An Interview with Terry Wilcox: The Use of Evidence in Formulary Decision Making

### **“What types of evidence are payors looking for in their formulary decision making?”**

First, let me say that I am speaking about non-government payors in this discussion since currently governmental formulary decision makers have their own set of guidelines in this area.

One of the most highly regarded and most used guidelines are those created by the Academy of Managed Care Pharmacy (AMCP). Formulary decision makers often will require that the AMCP guidelines be used for any dossier submission, and they may also require additional information to support the information in that dossier.

Decisions on whether a product is added to a payor's formulary list depends on many things. Payors are looking at clinical safety, efficacy and economic impact, and they would also like to have comparator data if available. The issue with comparator data is that it is not always available, especially if the product is the first compound to market for a specific indication, or in some cases, companies may decide to do these comparator studies after launch. Real world data is also highly valued, but this information requires at least a year of claims data. In most cases, providing analytic models is acceptable with the understanding that real world data is submitted within 12-18 months to support the model conclusions. It is also important to note that some payors in the US will accept modeling work done in Europe as long as it is linked to US data.

### **“Are there different guidelines used for each health plan?”**

Most plans start with the submitted dossier, and then there is often additional criteria they review before making their decision. The pharmacy department or an affiliated Prescription Benefit Manager (PBM) of a health plan will often have separate studies done through an outside contractor to validate the information in the dossier and to see if the submitting company is telling the whole story about their product. Additionally, the pharmacy will identify if there are any guidelines from professional associations or government agencies relating to the class of drug being reviewed. If other guidelines exist, then the pharmacy will look to see if the product is mentioned in those guidelines. This is important for a company to think about strategically. If there are guidelines that have products listed as being preferred for treatment, then a company should be thinking strategically about what types of evidence they need to show to get their product recommended in those guidelines. I highly recommend that companies have a strong and clear dialogue with payors regarding their product and the existing guidelines. There can be ambiguity in some of the guidelines, so understanding on both parties is critical in this process.

### **“Are there other types of information that health plans look at when deciding if a product is added to their formulary?”**

Health care plans are very concerned about their HEDIS scores, so attention is paid to treatments that can have a positive affect on a plan's HEDIS score.

### **“For those who are not familiar with the term, what exactly is a HEDIS score?”**

HEDIS stands for Health Plan Employer Data and Information Set and was created and is maintained by the National Committee for Quality Assurance (NCQA). This is a set of standardized performance measures that was created so purchasers of health plans have some type of system for comparing different health care plans. HEDIS scores are related to major public health issues and also include survey results of consumers' experiences with different plans that include such things as access to care, how their claims were processed, and customer service.

### **“And what relationship exists between the HEDIS score and a payor's decision to include a product on their formulary?”**

If a health plan can show increased quality for its members, then the plan becomes more attractive, and consequently, more people want to use that plan. So, for example, if patients are found to be more compliant with a specific treatment, if a specific product is found to be much more cost-effective, or if a treatment reduces the number of hospitalizations needed, then a health plan will most likely want to add those products to their formulary, hence increasing the quality of care for its members.

This is why it is important for pharmaceutical and device companies to look at the pieces of evidence that make up the value message for their product and concentrate on what factors may impact HEDIS scores. During this process, a company may find that they need to do additional studies (such as Patient Reported Outcome (PRO) or economic studies) that may make their product more attractive to payors. Then, when packaging their product to present to payors, companies should highlight factors that have the greatest impact, such as increased quality of care, economic impact, or improved quality of life.

**“Who is actually making the decision within the health plan on whether a product is added to a formulary?”**

Procedures and cultures vary from payor to payor, however, most payors have experts from different areas that review submissions and then vote on whether a product should be added to the payor’s formulary. There is a pharmacy representative who will look at the submission from a budget perspective, and a medical director who will be concerned with the overall care of the patient — looking at such things as quality, safety, lab results, and PROs. There will also be representatives from disease management, quality management, and clinicians in the community. All of these individuals will be looking at the submission from different, yet sometimes overlapping, perspectives to determine if the product should be added to the formulary.

Submitting companies need to be aware of this process and who is involved so they can appropriately prepare their submissions to meet the needs and perspectives of all reviewers. In some cases, a company will have the opportunity to present their submission to all the voting members in a group setting, which can be very beneficial since each voting member can hear questions and discussions from the other members. However, in some cases, companies may need to present separately to each member, forcing the company to tailor each presentation to the perspective of each member. Again, this is where having an open dialogue with payors is very important and will help you gain a better understanding of what you need to win formulary status.

A submitting company should also be aware of other avenues for promoting their product to the payor’s submission reviewers. For example, if a doctor is a voting member and he/she informs the submitting company (usually by talking to sales representatives) that he/she is reviewing their product, then the sales representative is open to discuss the product to help make the doctor aware of the benefits. However, a company must be careful here and is not allowed to inquire if a doctor is a submission reviewer — this acknowledgement must be initiated by the doctor. There are also government regulations on what type of information can be used and discussed for promotion of products under consideration. For example, it is rare that health economic endpoints can be promotionally discussed since the data is generated by designs other than two well-controlled clinical trials. However, some pharmacoeconomic data can be shared with formulary decision makers (based on FDMA, Section 114).

**“Have you seen a change in types of evidence that are considered for formulary decision making, or do you foresee changes in the near future?”**

In the past, efficacy and safety were the key factors considered by payors, and these will always be the mainstay for decision making. However, the past several years have shown that other factors are being considered as well in decision making, namely cost-effectiveness, and more recently, health outcomes such as patient-reported outcomes.

There is also greater emphasis on safety in lieu of recent events and a demand for more post-marketing evaluation beyond clinical trials. I think that we will continue to see an increase in the demand for real world data, and for some products, formulary access on a preferred tier may be delayed until real world product value is demonstrated.

Formulary decision making has always been, and continues to be, a complicated formula that varies greatly among payors, and I expect that will continue. However, the need for additional evidence beyond what has traditionally been considered will continue to grow, and it will fall on the pharmaceutical and device companies to be more prepared in their planning and submission processes. The more evidence a company can proactively provide to demonstrate their product’s value, the better chance they have for getting approval on a timely basis for formulary access.

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## ISOQOL Publishes New Book on Research Methods and Applications

The International Society for Quality of Life Research is pleased to announce that the book, *Advancing Health Outcome Research Methods and Clinical Applications*, edited by William Lenderking and Dennis Revicki, has been published. The book is based on invited presentations during the ISOQOL meeting held in Boston in June 2004. This book includes a collection of chapters covering a wide range of conceptual and theoretical, methodological, measurement, and statistical topics, and focuses on innovative and sometimes unfamiliar areas of research that might contribute to advancing health outcomes assessment. It is hoped that health outcomes researchers, students, clinical researchers, those involved in drug development, and others interested in patient-reported outcomes and health-related quality-of-life outcomes will find much that is intriguing and stimulating within the book. The first chapter, by Robert Kaplan, focuses on the past, present, and future of quality-of-life assessment for health policy analysis. He provides important background information on some of the early applications of health outcomes research aimed at understanding the outcomes of the health care system and differing health interventions. He also covers more recent research activities and challenges for the future.

The chapters by Chih-Hung Chang and by Ronald Hambleton and Ning Han focus on different aspects of item response theory (IRT). Chang's chapter is a broad overview of IRT models, including the basics of IRT, types of IRT models, how IRT models have been applied to date, and new directions in applying IRT models to patient-reported outcomes assessment (PROs). This chapter is a good introduction to IRT methods for readers interested in understanding more on these psychometric methods. Hambleton and Han point out that although many of the technical challenges of IRT have been resolved, not enough attention has been paid to establishing model fit. They focus their chapter on establishing the validity of model fit, as well as pointing out several graphical approaches to the assessment of model fit.

The chapters by Cindy Chung and James Pennebaker and Arthur Graesser and Sarah Petschonek provide fascinating discussions of the use of computational approaches to text analysis. Chung and Pennebaker describe how computers can be used to link the rich texture and meanings conveyed through natural language use (something that is lost to some extent in standardized surveys) to objective indicators of quality of life. Graesser and Petschonek provide an overview of advanced methods for automated evaluation of the text of questionnaires and surveys as well as presenting an interesting analysis of some health outcome measures.

Different statistical methods applied to health-related quality-of-life outcomes and longitudinal analysis are covered by Max Su and Marcia Testa, Joseph Hogan, Herbert Thijs and colleagues, and Diane Fairclough and Xin Shelley Wang. Su and Testa focus on statistical methodology, with a particular emphasis on applications of structural equation modeling to estimate latent variable growth models using clinical trial data. The chapter by Hogan is an able presentation on the use of generalized estimating equations (GEE) to fit regression models to incomplete longitudinal data. The chapter by Thijs, Geert Molenberghs, Ivy Jansen, Caroline Beunckens, Michael G. Kenward, Craig Mallinckrodt, and Raymond J. Carroll presents a very good overview and summary of methodological and analytic issues associated with handling missing data in clinical trials. The chapter by Fairclough and Wang covers both applied and methodological issues, discussing at the individual rather than group level the analysis of changes in symptoms and biological status in patients with cancer.

The symposium included a plenary session specifically on applications of health outcomes research, reflected in the chapters by Robert Meyer and by Holger Schünemann and Gordon Guyatt. The chapter by Meyer, an FDA official, is an excellent overview of the regulatory perspective on outcomes research. Schünemann and Guyatt provide a very practical discussion and review of the clinical interpretation of quality-of-life data to inform treatment decision making and clinical practice.

Theoretical issues are covered in the chapters by Karen Langsam, Antonio Frietas, and Tory Higgins; Joseph Sirgy; Julia Fox-Rushby and colleagues; and Eve Wittenberg. Langsam, Frietas, and Higgins have prepared a chapter that discusses, from a theoretical perspective, the psychological mechanisms that relate the enjoyment of activities to the pursuit of long-term goals. Sirgy's chapter is a review of several of the key strategies people use to enhance their life satisfaction and well-being. The chapter by Fox-Rushby, Kirstin Johnson, Isaac Mwanzo, Mary Amuyunzu, Tim Allen, and Melissa Parker describes the difficulties of developing truly universal measures of health concepts — challenges that flow from an overly mechanistic approach to the translation process and a failure to appreciate the context in which language is used in different cultures. Wittenberg's contribution is a description of the theory that underlies preference-based measures of health-related quality of life.

Howard Tennen, Glenn Affleck, and Alex Zautra provide a discussion of the application of daily process methodology to problems in health status assessment, and clearly describe how, when, and why this methodology should be used, as well as some findings from their research.

Methodological chapters on preference assessment, Q-TWiST analyses, and Bayesian approaches are provided by Bernard Cole, Shari Gelber, and Richard Gelber; Reed Johnson; David Feeny; and Dennis Fryback and Janel Hanmer. The chapter by Cole, Gelber, and Gelber presents

a welcome and practical summary of the Q-TWiST method for the analysis of quality-adjusted survival data, which includes suggestions for software that can be used to perform a Q-TWiST analysis. Johnson discusses issues related to the development of conjoint analysis-determined preference measures and contrasts them with utilities and quality-adjusted life years. Feeny's chapter describes and contrasts utility and willingness-to-pay methods. Fryback and Hanmer provide an introduction and summary of Bayesian methods applied to health status data, and they provide a useful example on the application of Bayesian methods for estimating quality-of-life-adjusted life expectancy.

In the closing chapter, Peter Fayers provides a very nice summary of the meeting, and his chapter reflects his view of what the assembled contributions say about the future of outcomes research and about some topics that were not covered by the book. He also notes some of the key challenges for health outcomes research in the future.

For more details on the book, please visit [www.isoqol.org](http://www.isoqol.org), call the ISOQOL Executive Office at 703-556-9222, or email [info@isoqol.org](mailto:info@isoqol.org).

For more information on outcomes research methods, please contact [Dennis.Revicki@unitedbiosource.com](mailto:Dennis.Revicki@unitedbiosource.com).

## NEWS BRIEFS

### UBC Center for Pricing & Reimbursement Announces New Managing Director

**Jeannine M. Bender, PhD** is a Managing Director with UBC's Center for Pricing & Reimbursement in Arlington, VA. Dr. Bender brings a strong skill set and 20 years of experience in Federal and State health policy, strategy and government affairs — an area that we hope to develop further. Dr. Bender's capabilities clearly add a new dimension to our offering and will immediately help us expand our potential to work actively with CMS, BIO, PhRMA, and specialty societies on client issues and enhance our role with clients on reimbursement policy.

Much of Dr. Bender's experience in government affairs and policy is in the pharmaceutical and biotechnology industry. Most recently, she was the Director of Government Affairs for Cephalon where she implemented Cephalon's federal legislative and public policy agenda, establishing and managing their corporate Washington DC office, developing policy positions on health care, and distributing PAC funds. In this capacity, her primary issues focus was Medicaid, Medicare (implementation of MMA), drug safety, reimbursement, managed care, DEA regulation of controlled substances, and evidence-based medicine policy. Prior to taking on federal issues, Jeannine is also credited with implementing Cephalon's first state government affairs program with a primary focus on Medicaid, senior pharmaceutical assistance programs, state business taxes and economic development. She also coordinated Cephalon's leadership role in PhRMA and BIO, supporting Cephalon's CEO in his role on the Board of Directors of both of these organizations.

Prior to joining Cephalon, Dr. Bender was Senior Director of Policy for PhRMA where she directed and coordinated the 2001 Strategic Planning Session for the Board of Directors. She also directed state policy development, strategic planning and legislative analysis for the eastern half of the United

States, which included Medicaid policy, structure, and reimbursement issues.

Prior positions included Senior Manager, Merck State Government Affairs; Director of Policy and Legislative Affairs for the Pennsylvania Department of Health; Director of Government Affairs, Mustard Seed, Inc. (Behavioral Health Managed Care Organization); Assistant to the Deputy, Office of Mental Health and Director of Federal & State Relations, Pennsylvania Department of Public Welfare; and Director of Legislation, The Hospital Association of Pennsylvania.

"I am excited to be part of UBC and involved in a company that is part of the leading edge of healthcare delivery. Most of my 20 years in healthcare public policy has focused on fixing some part of this complex system. Today's leaders of U.S. health policy are recognizing that to maintain and afford a high quality, innovative health care system, it **must** be based on solid clinical evidence and patient outcomes. UBC's mission to be in the forefront of establishing evidence-based awareness and design across all phases of clinical trials, through marketing and reimbursement strategy, is both visionary and transformational. I'm proud to be part of this great team."

Dr. Bender received her MA and PhD from The Pennsylvania State University.

For more information, please contact [Jeannine.Bender@unitedbiosource.com](mailto:Jeannine.Bender@unitedbiosource.com).

### UBC Welcomes New Senior Research Scientist

**Teresa (Terry) Wilcox, RPh, PhD** is a Senior Research Scientist with UBC's Center for Health Economics and Policy and is located in Southern California. Dr. Wilcox will be participating in the design, analysis, and interpretation of studies in health economics and outcomes research (HEOR), and she will be interfacing directly with regional HEOR teams to support the dissemination of HEOR information to the

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## NEWS BRIEFS

## New Senior Research Scientist

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healthcare payor and employer segments. She has experience in a variety of therapeutic areas and has done extensive work in the area of respiratory conditions.

Dr. Wilcox is a pharmacist and worked in a 1000-bed teaching hospital pharmacy for 10 years. Her responsibilities included drug usage evaluation, adverse drug event monitoring, formulary assessment and investigational drug service. Her experience in industry includes working for GlaxoSmithKline for 12 years where she initially was part of the International Pharmacoeconomic Group located in London. In this role, she focused on measuring quality of life and economic endpoints in studies. She was promoted to a Senior Pharmacoeconomic Scientist, and most recently, Dr. Wilcox was a Senior Regional Medical Scientist; she provided medical information to clinicians, discussed and developed disease management guidelines/algorithms, and served as a link to research and development initiatives.

Dr. Wilcox is widely published in peer-reviewed journals and has presented her work at major professional clinical conferences. Additionally, she has been an invited lecturer at such institutions as the University of California San Diego, The Ohio State University, Ohio Northern University, and the University of Maryland. Dr. Wilcox is a member of many professional societies, including the International Society

for Pharmacoeconomics and Outcomes Research and the American Thoracic Society, as well as maintaining membership in the Alpha Zeta Omega Pharmaceutical Fraternity. Dr. Wilcox completed her PhD from The Ohio State University with an emphasis in health outcomes and epidemiology.

“I am very pleased to join a company like UBC that provides the opportunity to collaborate with colleagues in a progressive environment for measuring and communicating the value of health care to decision makers,” says Dr. Wilcox.

For more information, please contact Terry.Wilcox@unitedbiosource.com.

## Luce Named Senior Scholar

**Bryan Luce, PhD, MBA**, Senior Vice President, Science Policy for the United BioSource Corporation has been named a Senior Scholar with the Department of Health Policy at Jefferson Medical College in Philadelphia, PA. The department, originally established in 1990 by the leadership of Jefferson Medical College and Thomas Jefferson University Hospital, has evolved into a nationally recognized academic research, education, and consulting group specializing in outcomes, health services research, and customized training programs. Their mission is to conduct research and education programs which will contribute to quality, safety, and cost-effectiveness of health care. The Department's activities are meant to inform decisions made by government policy makers, providers, payers, and other health system stakeholders about how best to deliver and finance care in order to improve the health of the public.

## Senior Staff Promotions Announced

**Rachael Florence, MBA, PhD** has been promoted from Senior Project Manager to Research Scientist for UBC's Center for Health Economics and Policy. Dr. Florence's main areas of interest are economic evaluations, decision-analytic Markov models, including Monte-Carlo simulation techniques, and value of information methodology. She has worked in a number of disease areas including osteoporosis, menopausal conditions, pressure ulcers, rheumatoid arthritis, Crohn's disease, ulcerative colitis, HPV infections, colorectal cancer and sinusitis. She has published in journals such as *Health Policy*, the *International Journal of Technology Assessment in Health Care*, *Osteoporosis International*, and the *Journal of Wound Care* as well as a number of book chapters.

Dr. Florence received her Master's degree and her PhD in Health Economics from the University of York. In addition, she holds an MBA from the Ecole Supérieure des Sciences Economiques et Commerciales (ESSEC, Paris)

and a Bachelor's degree in Social and Political Sciences from the University of Cambridge.

**Miriam Bar-Din Kimel, Ph.D.** has been promoted from Senior Project Manager to Research Scientist with UBC's Center for Health Outcomes Research. Dr. Kimel's responsibilities include planning, designing, and implementing patient outcomes studies, emphasizing patient education and the patient/provider relationship. During her 10-year career as a clinical pharmacist and researcher, Dr. Kimel developed expertise in pediatric medicine, including developing education programs for pediatric asthma and AIDS medications. She has been published in *Arthritis Care and Research*, *Circulation*, and the *American Journal of Health System Pharmacists*.

Dr. Kimel earned her Bachelor's degree in pharmacy from Rutgers University, and she completed her Master's degree in public health and Doctorate degree in social and behavioral sciences at the Johns Hopkins University School of Hygiene and Public Health.

## SPOTLIGHT ON SCIENCE

## Recent Publications

UBC welcomes comments and inquiries about our scientific work. In each issue, we feature a list of current publications and industry presentations. For more information, please call 301-654-9729 or email [analytics@unitedbiosource.com](mailto:analytics@unitedbiosource.com)

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- **Dekoven M, Marlo K, Robinson S.** "Ensuring Access for Specialty Pharmaceuticals through Payer Education." *Specialty Pharma* 2006 Jan/Feb; 2(1):62-65.
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- Niebauer K, **Dewilde S**, Fox-Rushby J, **Revicki DA.** "Impact of Omalizumab on Quality-of-Life Outcomes in Patients with Moderate to Severe Allergic Asthma." *Annals of Allergy, Asthma & Immunology*; In Press.
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- Dale MT, Naik R, Williams JP, **Lloyd AJ**, Thompson JP. "Impairment of Sustained Attention after Major Gynecological surgery." *Eur J Anaesthesiol.* 2005 Nov; 22(11):843-7.
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- **Shikhar R, Flood E**, Siddique R, Howell J, Dodd S. "Development and Validation of the Gastroesophageal Reflux Disease Treatment Satisfaction Questionnaire." *Digestive Diseases and Sciences* 2005; 50(11):2025-2033.

## Upcoming Presentations

### The Medical Device Regulatory and Compliance Congress

March 29-31, 2006, Harvard University, Cambridge, MA, USA

“Doing Double-Duty: Collecting Data for FDA and CMS in the same study” **Gregory de Lissovoy, Ph.D.** Senior Research Scientist, UBC’s Center for Health Economics and Policy

### 16th European Congress of Clinical Microbiology and Infectious Diseases

April 1-4, 2006, Nice, France

“The Economic Impact of Linezolid in the Treatment of Skin and Soft Tissue MRSA Infections in Italy”

Eandi M<sup>1</sup>, Dale P<sup>2</sup>, Sorensen S<sup>3</sup>, Baker T<sup>3</sup>, Proccacini M<sup>4</sup>, Duttagupta S<sup>5</sup>. <sup>1</sup>University of Torino; <sup>2</sup>United BioSource Corporation, London, UK; <sup>3</sup>United BioSource Corporation, Bethesda, MD, USA; <sup>4</sup>Pfizer Italia srl, Rome, Italy; <sup>5</sup>Pfizer Inc., New York, NY, USA

### The Academy of Managed Care Pharmacy’s 18th Educational Program

April 5-8, 2006, Seattle, Washington, USA

Dinner Symposium

“The Health and Economic Burden of Persons with Cardiometabolic Risk Profiles.” Moderator: **Bryan R. Luce, Ph.D., MBA**, Senior Vice President, Science Policy, United BioSource Corporation

### 25th Annual Scientific Meeting of the American Pain Society

May 3-6, 2006, San Antonio, TX, USA

“Efficacy of Alvimopan, a Peripheral Opioid Receptor Antagonist, for the Management of Gastrointestinal Adverse Events (GIAEs) Associated with Opioid Use: Assessment using the PAC-SYM Questionnaire.” Morlions B<sup>1</sup>, Aggarwal N<sup>2</sup>, Frank L<sup>3</sup>, Rentz A<sup>3</sup>, Kleoudis C<sup>4</sup>, Bell T<sup>4</sup>. <sup>1</sup>Fac Geneeskunde; <sup>2</sup>Finchgate Boulevard; <sup>3</sup>UBC’s Center for Health Outcomes Research; <sup>4</sup>GlaxoSmithKline

“Effect of Alvimopan, a Peripheral Opioid Receptor Antagonist, on Health-Related Quality of Life (HRQOL) in Patients who Develop Gastrointestinal Adverse Events (GIAEs) while Taking Opioids for Persistent-non-Cancer Pain: An Assessment using the PAC-QOL Instrument.” Tark M<sup>1</sup>, Sabatowski R<sup>3</sup>, Frank L<sup>3</sup>, Rentz A<sup>3</sup>, Kleoudis C<sup>4</sup>, Bell T<sup>4</sup>. <sup>1</sup>Georgia Medical Research Institute; <sup>2</sup>Department of Anesthesiology, University of Cologne; <sup>3</sup>UBC’s Center for Health Outcomes Research; <sup>4</sup>GlaxoSmithKline

### American Thoracic Society International Conference 2006

May 19-24, 2006, San Diego, CA, USA

“Development of a Needs-Based Quality of Life (QOL) Measure for Asthma” Meads DM<sup>1</sup>, McKenna SP<sup>1</sup>, Beusterien KM<sup>2</sup>, Flood R<sup>2</sup>, Lau H<sup>3</sup>, Glendenning A<sup>4</sup>. <sup>1</sup>Galen Research; <sup>2</sup>UBC’s Center for Health Outcomes Research; <sup>3</sup>Novartis Pharmaceutical Corp, East Hanover, NJ, USA; <sup>4</sup>Novartis Research Centre, Horsham, West Sussex, UK

“Patient Reported Outcomes of Sleep and Fatigue in Asthma and COPD” **Flood R<sup>1</sup>, Revicki DA<sup>1</sup>**, McKenna SP<sup>2</sup>, Meads DM<sup>2</sup>, Lau H<sup>3</sup>, Glendenning A<sup>4</sup> and Sung J<sup>3</sup>. <sup>1</sup>UBC’s Center for Health Outcomes Research; <sup>2</sup>Galen Research; <sup>3</sup>Novartis, East Hanover, NJ, USA; <sup>4</sup>Novartis AG, Horsham, England

“Development of a Patient-Perceived Control Measure for COPD” **Roberts L<sup>1</sup>, Beusterien KM<sup>1</sup>**, McKenna SP<sup>2</sup>, Meads DM<sup>2</sup>, Lau H<sup>3</sup>, Glendenning A<sup>4</sup>, Sung J<sup>3</sup>. <sup>1</sup>UBC’s Center for Health Outcomes Research; <sup>2</sup>Galen Research; <sup>3</sup>Novartis, East Hanover, NJ, USA; <sup>4</sup>Novartis AG, Horsham, England

“What Aspects of Asthma Treatment are Most Important to Patients? A Patient Preference Study.” **Lloyd A<sup>1</sup>**, McIntosh E<sup>2</sup>, Rabe KF<sup>3</sup>, Kaptein A<sup>3</sup>, Williams AE<sup>4</sup>. <sup>1</sup>United BioSource Corporation, London, UK; <sup>2</sup>University of Oxford; <sup>3</sup>Leiden University Medical Centre; <sup>4</sup>GlaxoSmithKline

“Validating a measure of global treatment effectiveness in Asthma” **Lloyd A<sup>1</sup>**, Turk F<sup>2</sup>, Leighton T<sup>2</sup>. <sup>1</sup>United BioSource Corporation; <sup>2</sup>Novartis AG

“Development of a needs-based Quality of life (QoL) measure specific to COPD” McKenna SP<sup>1</sup>, Meads DM<sup>1</sup>, **Beusterien KM<sup>2</sup>, Flood R<sup>2</sup>**, Lau H<sup>3</sup>, Glendenning A<sup>4</sup>. <sup>1</sup>Galen Research; <sup>2</sup>UBC’s Center for Health Outcomes Research; <sup>3</sup>Novartis Pharmaceutical Corp., East Hanover, NJ, USA; <sup>4</sup>Novartis Research Centre, Horsham, West Sussex, UK

### ISPOR 11th Annual International Meeting

May 20-24, 2006. Philadelphia, PA, USA

#### Pre-Meeting Short Courses

Saturday, May 20, 2006, 8:00am-2:00pm

*Modeling Methods*

**Bayesian Analysis: Overview** FACULTY: **Bryan Luce MBA, PhD**, Senior Vice President, Science Policy, United BioSource Corporation; **Christopher S. Hollenbeak PhD**, Surgery and Health Evaluation Sciences, Penn State College of Medicine and Visiting Scientist, UBC’s Center for Health Economics & Policy; David Vanness PhD, University of Wisconsin Medical School

Saturday, May 20, 2006, 1:00pm - 5:00pm

*Modeling Methods*

**Bayesian Analysis: Applications** FACULTY: **Bryan Luce MBA, PhD**, Senior Vice President, Science Policy, United BioSource Corporation; **Christopher S. Hollenbeak PhD**, Surgery and Health Evaluation Sciences, Penn State College of Medicine and Visiting Scientist, UBC’s Center for Health Economics & Policy; David Vanness PhD, University of Wisconsin Medical School

Sunday, May 21, 2006, 8:00am - 12:00pm

*Real World Data Methods*

#### Use of Real World Data in Outcomes Research

FACULTY: **Gregory de Lissovoy, PhD, MPH**, Senior Research Scientist, UBC’s Center for Health Economics & Policy; Diana Brixner, PhD, RPh, Associate Professor and Department Chair, College of Pharmacy, University of Utah; Daniel M. Huse, MA, Practice Leader, Information Products, Thomson Medstat Inc.

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## A Medicare Update

By Diane L. Simison, PhD

As we have learned, every day is a new adventure with the Medicare Modernization Act (MMA) and Medicare Part D implementation, and there is plenty of information for you to prepare your company to support Medicare coverage and appropriate reimbursement for new products. The benefit is a reality for those Medicare beneficiaries who have enrolled in a prescription drug plan. The Centers for Medicare & Medicaid Services (CMS) is reporting more than 11 million Medicare beneficiaries are now enrolled, but only about one million of these have enrolled voluntarily. The remaining ten million are dual-eligible Medicare and Medicaid beneficiaries who are being automatically enrolled as the statute provides. There is still a long way to go to convince most Medicare beneficiaries to sign up for the benefit.

In the meantime, CMS is holding weekly information sessions by phone with providers to answer their questions about Part D. During the first call held on January 4, 2006, over 1300 providers participated and a variety of questions were asked, mostly concerning access issues and coverage for the dual-eligible beneficiaries. You can link into the call every week, and instructions on how to do so are available on the CMS website at [www.cms.hhs.gov](http://www.cms.hhs.gov).

### MMA Section 1013 — Important for every health researcher

In the news, there has been information on the December 15, 2005 release of the first Agency for Healthcare Research & Quality (AHRQ)-sponsored comparative effectiveness review mandated by Section 1013 of the MMA, specifically an evidence-based review of treatments for Gastroesophageal Reflux Disease (GERD). We believe that CMS will be watching these releases closely and will be considering ways of using the findings to benefit Medicare enrollees, which may or may not involve writing coverage policy based on findings from the reviews. The AHRQ report is available on the agency website at [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

### Medicare Data Initiatives

CMS is making other moves that will interest researchers, including building the capability to link Part D data to hospital claims, physician office claims, and Medicaid data to better understand how Medicare beneficiaries receive treatment. This database will not be immediately available, however there is widespread researcher interest in this database, including how it can be linked with other data sets to improve the richness of our research tools. Payers worry that little is known about how new drugs will perform under conditions of actual use, and data tools of this kind will provide the opportunity to learn much more about post-marketing performance. Part D also includes language allowing more widespread consideration of outcomes and economic data in Part D formulary committee decision making.

CMS has issued publicly available information on the kind of data that will be reported for Part D claims, to include a limited subset of data elements on 100 percent of prescription drug “claims” or events. You can find the report titled, *Instructions: requirements for submitting prescription drug event data*, on the CMS website. Data will be submitted per event, and it will be used by CMS to make payments and conduct reconciliations.

### Getting the Medicare coverage decision or formulary position that you want

The coverage and reimbursement future will require that companies prepare product evidence to demonstrate superior outcomes and safety, while differentiating the technology where possible from others that are similar. Evidence will form the basis of the coverage decision, and it will also undoubtedly be used to determine the formulary position. Appeals of claims denials will increasingly be evidence-based, demonstrating the importance and the breadth of the use of the evidence in daily reimbursement decision making.

Preparation of evidence begins with careful design of data collection plans, including measuring payer-valued outcomes. Data collection plans include careful attention to patient inclusion

and exclusion criteria for clinical studies so that data will be available on the key patient groups that payers serve; otherwise coverage can be denied. As you can see, it is vitally important to consider payer needs and requirements as part of your planning process.

For more information, contact [Diane.Simison@unitedbiosource.com](mailto:Diane.Simison@unitedbiosource.com).

**The coverage and reimbursement future will require that companies prepare product evidence to demonstrate superior outcomes and safety, while differentiating the technology where possible from others that are similar.**

## The Dilemma of Single vs. Multiple Cohort Simulation in a Markov Model

By Sarah Dewilde, MSc (Belgium)

Currently, modeling-based economic evaluations are based on single birth cohort simulations. Although this may be appropriate in situations where a one-off choice is modeled — such as the adoption of new sample reading technology — this is not the indicated technique when decisions are being made that have a time dimension. For example, when the policy under evaluation affects a broad age range of people, such as when screening frequencies or screening age ranges

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## Single vs. Multiple Cohort

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are assessed, simulations that include different population subgroups or different birth cohorts are more suitable.

The conventional single cohort approach effectively considers the impact of a policy change only on those who are about to enter the screening age range. It does not take into account the effect of a change in screening policy on the rest of the eligible population. Moreover, when discounting the costs and benefits of the policy for the oldest in the target age range, this group will be severely undervalued. The multiple cohort approach, on the other hand, allows modeling the effect of a policy on the entire population that is affected by that policy, while also incorporating the age distribution of the target population.

Applying the single and the multiple cohort approach on a model of cervical screening (Myers et al., 2000) revealed that the impact on cost-effectiveness estimates could be considerable when using the multiple cohort approach. The incremental cost-effectiveness ratio in an Australian adaptation of this model increased by 30% when including multiple cohorts in the analysis, compared to the single cohort approach. Other sensitivity analyses also demonstrated that the results were insensitive to the age distribution of the population.

The obstacle to the easy implementation of the multiple cohort approach is that age-specific incidences for all health states in the model are needed to have the “starting positions” of these multiple cohorts, and this is not always available. A universal problem is that the cross-sectional data

that are typically available for calibrating even single cohort models already contain cohort effects.

Consequently, the dilemma of choosing between single

and multiple cohort simulations continues and is one aspect of the broader tension that pervades all modeling exercises — that between model sophistication and data availability.

This topic was presented at the annual modeler’s meeting of the National Cancer Institute held in Washington, DC in December, 2005, and a more expansive look at this issue can be found in the article “The Cost-effectiveness of Screening Programs Using Single and Multiple Birth Cohort Simulations: A Comparison Using a Model of Cervical Cancer” found in *Medical Decision Making*, 2004 Sep-Oct; 24(5): 486-492.

For more information, please contact Sarah.Dewilde@unitedbiosource.com.

## Cost-Effectiveness Issues in Central Europe

*By Edit Remák, BSc, MSc (Hungary), Noémi Muszbek, BSc, MSc (UK) and Ágnes Benedict, BSc, MSc (Hungary)*

The share of the Gross Domestic Product (GDP) devoted to health care increased markedly in 2001 for Organisation for Economic Co-operation and Development (OECD) countries on average, after a period of relatively stable health care expenditures ratios.<sup>1</sup> However, Central and Eastern European countries are at the bottom of the list, with the Czech Republic devoting 7.3% of their GDP and the Slovak Republic 5.7% to health care with Hungary and Poland falling somewhere in between. These countries spend a lower proportion on health care out of an already lower GDP. Therefore, differences in health care spending across countries are greater than differences in GDP per capita. For instance, in 2001, GDP per capita in the U.S. was 40% higher than the OECD average, while expenditure on health care was 135% greater. Most of the Central European countries see greater deviations from the OECD average in relation to health care expenditures per capita (converted to US\$ purchasing power parity) than for GDP per capita. With the OECD average being \$2,080, the Czech Republic spent \$1,106, Hungary \$911, the Slovak Republic \$682, and Poland \$629 per capita on health care in 2001.

Given the relative scarcity of resources to be spent on health care in Central Europe, it is even more paramount that these resources are used wisely and cost-effectively. Many of the institutional developments over the past years have been aimed at introducing and/or enforcing the concept of cost-effectiveness in the financing of health care. These changes mostly focus on pharmaceuticals because a relatively large percentage of the total expenditures are for pharmaceutical expenditures. Pharmaceuticals have international market prices while labour costs are usually based on national wage structures. For example, Hungary and the Slovak Republic spent approximately 30% of total health care expenditures on pharmaceuticals, while the US, Germany, and Australia all spent less than 15%.

Four Central and Eastern European countries (Hungary, Latvia, Lithuania and Poland) have implemented pharmaceutical economic guidelines and three additional countries (Czech Republic, Romania and Slovakia) have proposed such guidelines.<sup>2</sup> The published guidelines are in line with guidelines to be found in other parts of the world. Hungary even set up an independent organisation, the Strategic Health Research Institute, in May 2004 to evaluate pharmaceuticals aiming to receive reimbursement. What is the problem then?

First and foremost: the lack of transparency in the decision making. Let us take Hungary as an example. Even though both the laws governing the operation of the social security funds and the government resolution on pharmaceutical reimbursement state that every-day operation and individual decisions on reimbursement should be based on cost-

**...one aspect of the broader tension that pervades all modeling exercises — that between model sophistication and data availability.**

## Recent Presentations

### DIA 17th Annual Workshop for Medical Communications

March 5-8, 2006, Orlando, FL, USA

“Medicare Part D: Communicating Evidence for Informed Decision Making” Session Chaired by **Bryan R. Luze, PhD, MBA**, Senior Vice President, Science Policy, United BioSource Corporation

### Association of European Psychiatrists: 14th European Congress of Psychiatry

March 4-8, 2006, Nice, France

“A new Approach to Assessing Objective Functional Outcomes in Schizophrenia: A Validation Study” Dubé S<sup>1</sup>, Zhao Y<sup>1</sup>, Bowman L<sup>1</sup>, Kinon B<sup>1</sup>, **Kleinman L<sup>2</sup>, Frank L<sup>2</sup>, Revicki DA<sup>2</sup>**, Mohs R<sup>1</sup>. <sup>1</sup>Eli Lilly; <sup>2</sup>UBC's Center for Health Outcomes Research

### 62nd Annual Meeting of the American Academy of Allergy, Asthma, and Immunology

March 3-7, 2006, Miami Beach, FL, USA

“The Impact of Asthma on Quality-of-Life (QoL) and Other Patient-Reported Outcomes: The Patient's Perspective” McKenna SP<sup>1</sup>, Meads DM<sup>1</sup>, **Beusterien K<sup>2</sup>, Flood R<sup>2</sup>**, Lau H<sup>3</sup>, Glendenning A<sup>4</sup>. <sup>1</sup>Galen Research; <sup>2</sup>UBC's Center for Health Outcomes Research; <sup>3</sup>Novartis Pharmaceutical Corp., East Hanover, NJ, USA; <sup>4</sup>Novartis Research Center, Horsham, West Sussex, UK

### Thirteenth Biennial Winter Workshop on Schizophrenia Research

February 4-10 2006, Davos, Switzerland

“An Objective Measure of Daily Functioning in Schizophrenic Patients” Dubé S<sup>1</sup>, Zhao Y<sup>1</sup>, Bowman L<sup>1</sup>, Kinon B<sup>1</sup>, **Kleinman L<sup>2</sup>, Frank L<sup>2</sup>, Revicki D<sup>2</sup>**, Lieberman J<sup>3</sup>, Keefe R<sup>4</sup>, Carpenter W<sup>5</sup>, Mohs R<sup>1</sup>. <sup>1</sup>Eli Lilly; <sup>2</sup>UBC's Center for Health Outcomes Research; <sup>3</sup>Columbia University; <sup>4</sup>Duke University; <sup>5</sup>University of Maryland

### 2006 Health Economics and Outcomes Research Forum

January 30-31, 2006, Amsterdam, The Netherlands

“The Evaluation of NICE Guidance on Cancer Treatments in Response to New Products and New Evidence.” Hutton J, Senior Research Leader, United BioSource Corporation

“Overview of Health Economics and Drug Reimbursement Policy in Hungary.” **Noemi Muszbek, BSc, MSc**, Research Associate, United BioSource Corporation

### Annual CISNET Meeting — 2005

December 12-16, 2005, Bethesda, MD, USA

“Cost Effectiveness Modeling in the Single Hypothetical Cohort vs. Population Multi-Cohort Setting.” **Sarah Dewilde, MSc.**, Senior Research Associate, The MEDTAP Institute at UBC, Belgium

### i3DLN Continuing Medical Education

November 22-22, 2005, Cincinnati, Ohio, USA

“Pharmacoeconomics in Bipolar Disorder and Schizophrenia: Are the Outcomes Worth the Costs?” **Dennis Revicki, PhD**, Director and Sr. Research Leader, The Center for Health Outcomes Research, The MEDTAP Institute at UBC

### 58th Annual Scientific Meeting of the Gerontological Society of America

November 18-22, 2005, Orlando, FL, USA

“Testing the Reciprocal Relationship Between Self-Assessed Global Health and Depression: A Replication.” **Stull D<sup>1</sup>**, Kosloski K<sup>2</sup>, Kercha K<sup>3</sup>, Van Dussen D<sup>4</sup>; <sup>1</sup>The MEDTAP Institute at UBC; <sup>2</sup>University of Nebraska at Omaha; <sup>3</sup>University of Maryland

### American Heart Association (AHA)

#### Scientific Sessions 2005

November 13-16, 2005, Dallas, TX, USA

“The Impact of Atrial Fibrillation Treatment on Cost and Resource Use.” **Coyne KS<sup>1</sup>, Paramore LC<sup>1</sup>**, Grandy S<sup>2</sup>, Mercader M<sup>3</sup>, Reynolds M<sup>4</sup>, Zimetbaum P<sup>4</sup>. <sup>1</sup>The MEDTAP Institute at UBC; <sup>2</sup>AstraZeneca LP; <sup>3</sup>George Washington University; <sup>4</sup>Beth Israel Deaconess Medical Center, Harvard Medical School

### American Society of Nephrology (ASN)

#### 38th Annual Renal Week Meeting

November 8-13, 2005, Philadelphia, PA, USA

“Cost-Effectiveness of Epoetin Alfa in Patients on Chronic Kidney Dialysis.” **Hollenbeak C<sup>1,2</sup>**, Davies A<sup>2</sup>, Russo P<sup>1</sup>, Niebauer K<sup>2</sup>, McClellan W<sup>3</sup>, **de Lissovoy G<sup>2</sup>**. <sup>1</sup>Pennsylvania State University College of Medicine; <sup>2</sup>The MEDTAP Institute at UBC; <sup>3</sup>Emory University School of Medicine

“Economic Impact of Vascular Access Modality in the Medicare End-Stage Renal Disease Program.” **Blume S<sup>1</sup>**, Schon D<sup>2</sup>, Niebauer K<sup>1</sup>, **Hollenbeak C<sup>1,3</sup>**, **de Lissovoy G<sup>1,4</sup>**. <sup>1</sup>The MEDTAP Institute at UBC; <sup>2</sup>University of Arizona; <sup>3</sup>Pennsylvania State University; <sup>4</sup>Johns Hopkins Bloomberg School of Public Health

effectiveness, it is not clear what is to be considered cost-effective. Due to the short history of economic evaluation in Hungary, it is very hard to compare results to “other accepted technologies”, while deriving a cost-effectiveness threshold as a benchmark from other sources proves to be very controversial challenge.

Lack of transparency characterises the evaluation process as well. Although successful efforts have been made to keep the 90 day timeline, the assessment process itself is not clear despite the requirement of the EU Transparency Directive,<sup>3</sup> and the assessment report is not publicly available. Parts of

the assessments have been outsourced without publishing the names of the collaborating organisations.

Second, the issue is further complicated by the lack of skilled staff for authorities. Training in the basic concepts of technology assessment has started, however it is lagging behind the tasks and the requirements. Further and more focused training is urgently needed, not just for those now leaving the university setting, but for all staff in the institutions and regulatory authorities.

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## Upcoming Presentations

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### Academy Health 2006 Annual Research Meeting

Jun 25-27, 2006, Seattle, WA, USA

#### Seminar

June 24, 2006, 10:00am - 5:00pm

“Bayesian Methods” **Bryan R. Luce, PhD, MBA**, Senior Vice President, Science Policy, United BioSource Corporation; **Christopher S. Hollenbeak PhD**, Surgery and Health Evaluation Sciences, Penn State College of Medicine and Visiting Scientist, UBC’s Center for Health Economics & Policy; David Vanness PhD, Assistant Professor of Population Health Sciences, University of Wisconsin Medical School

## Cost-Effectiveness Issues

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Structural characteristics of the region are not acknowledged in the economic evaluation process. As mentioned before, relative price differentials between pharmaceuticals and cost of labour (e.g., cost of hospitalisations, etc.) means that many drugs reducing the need for labour intensive procedures that are highly cost-effective in more developed countries may not be cost-effective in Central and Eastern Europe. The relative price differential, in some cases, also influences the treatment protocols by, for example, including more diagnostic services and changing the structure of the cost-effectiveness models. Furthermore, due to the slower infusion of newer technologies to Central and Eastern Europe (again mainly due to scarcity of resources), the currently available best practice to be used as comparator may be very different from that in the country of origin of the assessment.

Inaccessibility of required data contributes to the difficulties. Although in Hungary inpatient and outpatient resource use and cost data are routinely collected by the National Health Insurance Fund, and the use of these data is required for the evaluations by the pharmacoeconomic guideline,<sup>4</sup> the access to the data is very limited and arbitrary.

As a consequence of the factors listed above, assessments by well-respected health technology assessment centres in

the UK, Canada, Australia, Switzerland and the US are very often accepted for Eastern Europe without much consideration for local circumstances, instead of performing original analyses or adaptations.

There are other obstacles facing the actual application of cost-effectiveness results. Alongside the economic evaluation in the reimbursement submission, a comparison of the cost of the daily dose is required for all drugs in the same therapeutic class (defined by level 4 of the Anatomical Therapeutic Chemical (ATC) classification system for drugs). The decisions are, in many cases, based on this price comparison without any reference to the required cost-effectiveness or efficacy of the different drugs.

Economic evaluation of health technologies is continually becoming more of a standard in Central and Eastern Europe. However, it is not the result of an organic, but rather a top-down, process. As a result, the institutions, regulations, and official requirements are almost all in place, even though the actual manpower and the extensive experience in economic evaluations may yet be missing. Cost-effectiveness results from other parts of the world cannot be simply generalised to Central and Eastern Europe; a complete adaptation to local circumstances should be carried out for the evaluation to be credible and useful for decision-makers in these countries.

Although the application of cost-effectiveness as a criterion in decision-making in Central and Eastern Europe is not without problems and controversies, these are mainly due to the recent development of the field in this region. With more transparency, professional debate, experience, and education in health economics, these issues can, and hopefully will, be overcome.

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<sup>1</sup>Huber M, Orosz E. Health expenditure trends in OECD countries, 1990-2001. *Health Care Financing Review* 2003; 25(1):1-22.

<sup>2</sup>Davey P, Price N, Lees M, et al. Comparison of reimbursement systems of various countries in Central and Eastern Europe, Africa, Middle East and Asia. *ISPOR Connections* 2005; February 15:4-6.

<sup>3</sup>COUNCIL DIRECTIVE of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems, (89/105/EEC).

<sup>4</sup>Szende et al (2002) Methodological guidelines for conducting economic evaluation of healthcare interventions in Hungary: a Hungarian proposal for methodology standards. *The European Journal of Health Economics* 2002; 3(3): 196-205

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