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Every Patient a Research Subject

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FOCUS ON: The New Era of Evidence



Soon Every Patient Will be a Research Subject

By Rob Thwaites, MA, Vice President, Value Development, Europe

Supermarkets have for some time been able to track our purchases and target their marketing to each one of us based on their electronic records of our personal expenditures. With advances in information technology, their special offers are now tailored to our own individual spending patterns, making it far more likely that we will take advantage of their offers. This person-based market research by supermarkets, followed with offers that are personalised to our individual needs, is now commonplace. In the retail sector, every consumer has become a market research subject.

A parallel and exciting development for medical research has been the emergence of health care data available electronically. Sources of data such as primary care medical records, originally collected for the purpose of patient management in primary care, and claims data, originally collected for the purpose of making payments for medical services, are increasingly being aggregated, anonymised, and made available to researchers for further study. Research based on electronic health care data, to produce evidence and new approaches to treatment benefiting populations of patients, is now common. In the health care sector, we are entering the era when every patient is also a participant in research.

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A Personalized View on Comparative Effectiveness

By Felix Frueh, PhD, President, Medco Research Institute



Determining the comparative effectiveness of a clinical intervention implies that an option exists to choose one intervention over another one, or over several other interventions. In an era in which making such a decision can be supported by novel tools such as molecular or genetic tests, for example, it is imperative that we expand the idea of comparative effectiveness as a measure of one intervention with another by introducing the question "for whom?" This expanded view is consistent with the rapid increase in our understanding why individual patients have different responses to therapies, in particular when factors such as genetic variability between individuals is considered. The idea is simple:

assume drug A is compared to drug B, further assume 40% of patients respond to drug A and 50% to drug B. Is drug B better? Yes, if the 40% that respond to drug A are a subset of responders to drug B (and not exposed to additional risk). No, if the responders to drug A, or a subset thereof, are a different group of patients than the responders to drug B. The discrimination of these subpopulations is particularly powerful if we have tools that allow us to determine a priori who benefits from drug A versus drug B; a consideration moving us from trial and error towards precision health care and a decision-making process aimed at benefitting individuals rather than populations. Consequently, what comparative effectiveness should assert is the inclusion of an evidentiary framework that allows

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Evidence Matters

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Every Patient a Research Subject

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The Richness of Patient-level Data

Researchers have long understood the potential of electronic health care data. While there were early studies, including drug utilisation reviews, in the 1970s and 1980s, it was the emergence of electronic patient-level data for research in the 1990s that stimulated the rapid growth of research based on these sources. In that period, record linkage work in the Netherlands and the U.K., for example, provided the foundation for the establishment of some of the most well-developed databases based on patient records available today.

Much of the research that has been conducted using these data sources has been in the area of pharmacoepidemiology,

With investments in research infrastructure, advances in analytical methods and technologies, as well as more extensive availability of data, the contribution of patient-level data to medical research is accelerating.

These developments have also helped to further the acceptability of the evidence and, therefore, to increase the impact of the research on health care decisions.

exploring the safety and effectiveness of drugs. With new technologies, such as systems to apply analytical methods to disparate observational databases without requiring custom programming for each data source, the richness of

the data for literally millions of patients can be exploited far more rapidly and cost-effectively than was possible even a few years ago. In this way, insights into drug safety and effectiveness can be captured much earlier.

Increasingly, other types of study questions are being addressed as well. With the growing need for agencies to assess the value of treatments, for example, studies have been done to explore the costs and effectiveness of treatment, and results from these studies can also be used to populate cost-effectiveness models with information on the frequency or concurrence of events that would otherwise be expensive or impractical to obtain.

Take one example from clinical research to highlight the richness of the information now available through these sources: the ability to analyse information at a patient level means that the cumulative impact of multiple eligibility criteria for a clinical trial can now be tested. Whether it will be possible to find

subjects meeting all the strict criteria has always been a big uncertainty facing the sponsor of a clinical trial. Traditionally, disparate pieces of information from reports, tables, expert opinions, and site surveys on each separate criterion would be considered in predicting the feasibility of recruiting patients. Crucially, however, these pieces could not be combined at an individual patient level to give a picture of the cumulative impact of all the criteria. In contrast, today's patient-level data can be broken down and, with the electronic power and sheer size of the databases, can be analysed to assess the cumulative impact of the eligibility criteria and to successfully answer feasibility questions. With up to a third of clinical trial sites failing to recruit a single patient in the past, harnessing electronic patient-level data to help design and plan clinical trials in the future will have a huge impact on recruitment and, therefore, on the success of clinical research.

Turning Data into Acceptable Evidence

To produce relevant and reliable evidence for health care decision making, however, we need not only the data but also the ability to analyse that data and turn it into acceptable evidence. Evidence based on electronic patient-level data is increasingly available. With investments in research infrastructure, advances in analytical methods and technologies, as well as more extensive availability of data, the contribution of patient-level data to medical research is accelerating. These developments have also helped to further the acceptability of the evidence and, therefore, to increase the impact of the research on health care decisions.

Investments in research infrastructure have been expanding over the last few years. In the U.K., for example, a series of initiatives largely publicly funded, are being coordinated to build capabilities and to link databases to provide comprehensive patient-level information, eventually on the majority of people in the country. By including in this the existing detailed historical data (which for many patients stretches back a decade or more), the U.K. hopes to have the richest and most accessible patient data for researchers anywhere in the world.

The acceptability of the evidence is crucial—turning the data into evidence that is credible is essential if the research is to have an impact on health care decision making. The observational nature of patient data is both a strength and a weakness: a strength in that it reflects clinical care in practice, a weakness in that this creates biases for research purposes that can be difficult to address. Decision makers in health care have understandably been reluctant to rely on observational data when so much experimental information, without the same biases, has been available through randomized controlled trials (RCTs).

In the new era of evidence, however, traditional thinking in health care about levels or quality of evidence, with some types of evidence being better than others, is being questioned more widely. Hierarchies of evidence, that have been devised to aid decision making, have typically favoured randomised controlled trials, placing them “on an undeserved pedestal” according to Rawlins,¹ who asserted that “the notion that evidence can be reliably placed in hierarchies is illusory.” There is increasing recognition that evidence from observational data in many ways can complement evidence from RCTs in helping to inform decisions in health care.

As the availability and the quality of the patient data improve, and as methods and technologies advance, the quality of the evidence will improve. As the evidence improves, and becomes more acceptable, health care professionals at all levels will increasingly turn to that evidence to make decisions and improve treatment and care.

From Populations to the Individual

Today’s research using electronic patient-level data typically produces evidence used to determine how populations of patients will be treated. With the granularity of the data, however, sub-groups of patients can be identified and treatments targeted to those with particular characteristics, such as a genetic predisposition to respond to a particular therapy, and, crucially, any mix of particular characteristics. Ultimately, the flexibility inherent in electronic patient-level data provides the means to better understand the individual patient and to target specific treatments based on the known mix of characteristics that make up that individual. The data itself is a central means to personalising the treatment by applying current best knowledge to an assessment of the individual patient.

While supermarkets have progressed from using information with the intention of better understanding market segments to better understanding and responding to individual customers, health care researchers are still largely using data to produce evidence on populations of patients rather than individual patients. Harnessing the data, however, to understand the individual patient and to personalise medicine is already possible. While our experience in doing this is still in its infancy, with the current advances in electronic patient-level data, we are well into the era when every patient is also a participant in medical research.

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¹Rawlins MD. De Testimonio. On the Evidence for Decisions about the Use of Therapeutic Interventions: Harveian Oration Delivered to the Royal College of Physicians, London 16th October 2008.

Comparative Effectiveness

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us to evaluate the effectiveness of a clinical intervention at the level of the individual patient.

There are several instances where such a framework has been translated into clinical practice. Examples can be found in areas where detailed knowledge about subpopulations that are likely to benefit from treatment existed at the earliest stages of drug development and then was used during later development phases (e.g., to stratify a patient population), all the way to discoveries made long after a drug has been approved. It is with this continuum in mind that we have to create scientific, regulatory, and reimbursement strategies that, ultimately, benefit the patients we serve. To illustrate: a monoclonal antibody used in the treatment of breast cancer has been developed after discovering that the antibody only exerts its desired effect in tumors that are overexpressing the Human Epidermal growth factor Receptor 2 (Her2/neu, also known as ErbB-2), a protein giving higher aggressiveness in breast cancers. Consequently, Phase II and III studies were conducted in patients overexpressing this protein in their tumors, which allowed the clinical trials to be of manageable size and cost (only about 25-30% of breast cancers overexpress Her2/neu). Moreover, because this treatment is not without risk (cardiotoxicity can be severe), it would be unethical to expose patients who predictably cannot benefit from treatment to such risk. This example highlights how a scientific discovery early in the development of a new therapy has led to a streamlined development path, resulted in a regulatory decision to indicate the drug’s use only for the treatment of cancers overexpressing Her2/neu, as well as reimbursement decisions based on demonstrating that a patient’s cancer indeed overexpresses this enzyme. The field of oncology has many more examples, e.g., BCR-ABL gene testing for imatinib used for certain types of leukemia, KRAS testing for panitumumab for colorectal cancer, and others, in particular because we have begun to understand a great deal about the molecular mechanism of disease. Therefore, by definition, we are able to identify subpopulations based on the characteristics that are inherent to the form of cancer an individual patient possesses. This situation, unfortunately, is the exception rather than the rule and other chronic and complex diseases, such as cardiovascular disease and diabetes, are less well understood. This does not mean that a more personalized, more precise way of treatment is not possible however. In fact, particularly in the area of cardiovascular disease, significant progress has been made with the identification of genetic variations that are responsible for differences in response to certain medications as well as predicting disease risk or risk for adverse reactions associated with drug therapy. For example, the drug warfarin,

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a difficult to administer anti-coagulant due to its narrow therapeutic window, benefits from assessing a patient's sensitivity to the drug by determining the genetic makeup of the two genes cytochrome P450 2C9 (CYP2C9) and vitamin K oxidoreductase complex 1 (VKORC1). A recent Medco-Mayo collaborative study¹ has shown that by measuring these two genes and providing information about the patient's warfarin sensitivity back to the treating physician, up to 30% of hospitalizations that occur due to complications with warfarin therapy can be prevented. Another relevant example is genetic testing for clopidogrel treatment: clopidogrel is a prodrug that must be activated via CYP2C19, another polymorphic cytochrome P450 enzyme. Depending on the form of this enzyme (extensive, intermediate or poor metabolizer form), a patient can or cannot fully activate clopidogrel. Since 2009, a new drug, prasugrel, is on the market that does

By applying the idea of personalized medicine to comparative effectiveness studies, we will be able to advance our understanding of which treatment works better, and for whom.

not have this activation problem, but appears to have a more significant risk of bleeding compared to clopidogrel. Therefore, the theory is for patients who can fully activate clopidogrel (identified as extensive metabolizers), clopidogrel may be the preferred drug, whereas for individuals who cannot activate clopidogrel (intermediate and poor metabolizers), prasugrel may be the drug of choice. However, so far no study has directly compared the outcomes in extensive metabolizer patients treated with clopidogrel to outcomes in patients treated with prasugrel; this is the goal of a personalized medicine comparative effectiveness study (Genotype-Guided Comparison of Clopidogrel and Prasugrel Outcomes, GeCCO) currently underway at the Medco Research Institute. These latter two examples from the cardiovascular area illustrate the need for comparative effectiveness studies in the post-market environment: neither the markers for warfarin nor the marker for clopidogrel was known at the time of approval of these drugs — they were discovered only recently. However, the Food and Drug Administration (FDA) has already taken important action by updating the labels for both drugs alerting practitioners and patients about the benefit of genetic testing. In fact, in the case of warfarin, the FDA provides specific dose recommendations based on genotype, and in the case of clopidogrel, the FDA has inserted a black box warning as clopidogrel may not be effective in patients who are unable to fully activate the drug.

Comparative effectiveness has many flavors. Highlighted here is the need that no matter what type of comparative effectiveness approach we consider, we must ultimately think about not treating a population but an individual patient. Personalized medicine has made, and will continue to make, a big difference in individual patients' lives. By applying the idea of personalized medicine to comparative effectiveness studies, we will be able to advance our understanding of which treatment works better, and for whom.

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The Cognition Working Group of Critical Path Institute's PRO Consortium: An Update

*By William Lenderking, Senior Research Leader, Outcomes Research, on behalf of the UBC Cognition Initiative Team**

UBC is working with academic researchers and sponsors from the pharmaceutical industry in a pre-competitive environment with the aim of creating new patient- and informant-reported measures for global cognition clinical trials. The Cognition Initiative kicked off in 2008, and we have now completed Phase 1 and the concept elicitation phase of Phase 2, having completed two literature reviews, two Expert Panel meetings, extensive focus groups and individual interviews. Publicly available information on our expert panelists and core advisors along with our sponsors can be found at www.cognitioninitiative.com.

The UBC Cognition Initiative team has partnered with the PRO Consortium's Cognition Working Group to address the need for more sensitive measurement at mild levels of cognitive impairment, and to incorporate both Food and Drug Administration (FDA) and broad industry input at early stages of the measurement development process. The Cognition Working Group is chaired by Chris Leibman of Janssen AI and Usha Mallya of Novartis. By examining experiences and symptoms relevant to patients and confirmed by informants, this research initiative may also expand on the universe of outcomes measured in cognition and could contribute additional patient-based measures to studies of mild-moderate Alzheimer's disease (AD), as well as mild cognitive impairment (MCI).

The goal of the Cognition Working Group is to develop a new patient-reported measure of the consequences of early cognitive impairment, specifically in the areas of Interpersonal Functioning (IF) and Complex Activities of Daily Living (CADLs). Our measures will be relevant for patients across the range of severity from very mild cognitive impairment that can represent an early stage of Alzheimer's disease to moderate probable AD.

No universally accepted diagnostic criteria exist for mild cognitive impairment but consensus is emerging that the amnesic subtype of MCI represents those patients with the highest probability for progression to diagnosable Alzheimer's disease.¹⁻² Accordingly, amnesic MCI is suggested as a suitable target for disease modifying agents.³ Interest in identifying pre-MCI is also growing. Targeting the measure to this segment of the dementia population is a key goal of this Initiative.

A major focus for our group currently is the exploration of the validity of patient self-report. This is important because of the well-documented reduction in insight into symptoms and functioning due to cognitive problems associated with AD. In particular, our qualitative research has been designed in novel ways to hone in on the demonstration of patient insight in those with MCI. This will supplement the findings from our literature review, which suggest that it is feasible to obtain valid patient self-report on symptoms and symptom impact,⁴ and that insight is preserved at least for some domains of functioning. A key feature of our work will be to demonstrate the preservation of insight for the domains we are most interested in measuring.

Improving measurement sensitivity in this patient population is the primary aim of the Working Group. In addition, the patient's perspective on the disorder and treatment benefits may identify aspects of the disease process not accessible through neuropsychological test batteries or even clinical interviews. An early definition of MCI included reference to intact activities of daily living,⁵ a requirement undergoing scrutiny given documentation of functional deficits sometimes present in MCI.⁶⁻⁹ Consensus on the specific functional deficits that characterize MCI has not been reached and this Initiative may provide further relevant data. Several performance-based or informant-reported measures are being used in the field.^{7, 10-12} Diagnostic criteria for AD include reference to functional performance deficits ("significant impairment in social or occupational functioning" per the American Psychiatric Association [DSM-IV-TR])¹³ so a relationship between cognition and functioning might be expected in early cognitive impairment.

This spring and summer, the Cognition Initiative Team will be working on cognitive debriefing of our new instrument and coordinating an Expert Panel meeting to discuss the instrument and how it can best be used in clinical trials. The Cognition Working Group's Scoping Stage Summary

Document was submitted to the FDA, and we are now moving forward into the Consultation and Advise phase. Following the FDA process will help to ensure that we achieve the ultimate goal of qualification of our instrument.

For more information, please contact William.Lenderking@unitedbiosource.com or contact study staff through the project website at www.cognitioninitiative.com.

* *The UBC Cognition Initiative Team: Anne Brooks, Adam Butler, Charlotte Cates, Riane Hoffman, Kellee Howard, Leah Kleinman, William Lenderking, Kelly McDaniel, and David Miller.*

Special acknowledgements to Lori Frank who has left UBC, but remains actively involved in the Cognition Working Group, and to Leah Kleinman and Kellee Howard who provided comments on this article.

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Medicaid: A Market to Watch

By Louisa Hefty, MSc, Managing Director

On March 23, 2010, The Patient Protection and Affordable Care Act (PPACA) was passed by the U.S. Congress and signed into law. Numerous changes to Medicaid, the federal and state-funded health insurance program for low income persons, were included in health care reform (the PPACA), and although these will not be implemented until 2014, this program continues to be an important market to watch.¹ Medicaid covers nearly 60 million Americans and it is the largest source of financing for nursing home and community-based long-term care.^{2,3} Annual expenditures for outpatient prescription drugs through Medicaid were \$23.6 billion in 2008.⁴ This program is an integral part of the U.S. health care system and, with the expansion under the PPACA, Medicaid will significantly increase in size and importance, reducing the number of uninsured with the federal government picking up the vast majority of the cost.⁵

Medicaid's Role in Health Reform

Health reform will provide coverage for low-income Americans, who are currently uninsured, thus extending health insurance coverage to 32 million Americans.⁶ An estimated

16 million more people will receive their coverage through Medicaid programs administered by the states.

Approximately 70% of Medicaid recipients receive care through private managed care plans and this percentage will increase due to cost savings when care for the Medicaid population is

While it is important to watch what happens on the federal level to understand Medicaid, most of the action is on the state level where states have the ability to tailor their programs to their own needs within federal guidelines. States are burdened by the budgetary pressures from their share of costs for Medicaid programs, especially since the enhanced Federal Medical Assistance Percentage provided through the stimulus ends July 1, 2011.

managed.⁷ The PPACA includes a number of other changes to Medicaid including new options to expand community-based long-term care, funding for demonstration programs, opportunities for innovative payment and delivery systems, and the coordination of care for dual eligibles, those covered by both Medicaid and Medicare. These changes could

provide some additional means to achieve cost savings and improve care in the near-term as well as over the long-term, but could have negative implications for pharmaceutical and device manufacturers.⁸

For example, the PPACA provides a new health home initiative to better coordinate care for individuals with chronic conditions with a 90% match rate for these services. The PPACA also allows states to integrate care for dual eligibles, and thereby improve value or efficiency.

Controlling Program Costs

Since 2005, Medicaid has had more authority to control Medicaid drug spending through dispensing limits, preferred drug lists, step therapy, prior authorization, generic substitution, increased cost sharing for non-preferred drugs, and inclusion of authorized generic drugs in the calculation of "best price" for drugs. There have also been changes in the way Medicaid pays pharmacists, allowing pharmacists to refuse prescriptions for beneficiaries who do not pay their co-payment amounts. By 2007, most states had already implemented many of these approaches, so additional measures to control drug spending slowed.

A 2009 survey of 50 states and the District of Columbia found that more than half had implemented Medicaid pharmacy cost containment measures, including preferred drug lists and prior authorization programs (about 45% of states), supplemental rebates from manufacturers, and state Maximum Allowable Cost programs for generic and multi-source brand drugs (44%); smaller proportions of states were members of multi-state purchasing coalitions (26%) or had limits on quantities dispensed per prescription (16%).⁹ Despite these initiatives, states are finding these cost-containment strategies inadequate and there is evidence that these practices are increasing.¹⁰ As noted, many states have implemented policies to expand generic substitution and other cost containment policies in their state Medicaid programs and others are moving towards this policy. For example, legislation has been introduced in South Carolina to create a Pharmacy and Therapeutics Committee, which must recommend "classes of drugs that should be included on a preferred drug list." These cost cutting measures come at a time when Medicaid programs continue to implement additional drug management tools.¹¹

Medicaid Rebates

The PPACA increased the amount of rebates that drug manufacturers would be required to pay under the Medicaid drug rebate program, but the amounts attributable to these increased rebates were initially to be paid to the federal government rather than state Medicaid programs. The potential loss of rebates to the states was a budgetary concern for

the states. Therefore, in September 2010, the Centers for Medicare and Medicaid Services (CMS) revised their policy concerning the federal offset of Medicaid prescription drug rebates and specified that the federal government would not obtain rebate revenues at the expense of states.¹² Specifically, CMS determined that the offset provision would reflect the lesser of the difference between the increased minimum rebate percentage and the average manufacturer price (AMP) minus best price (BP). CMS would offset the amount equal to the increased amount of rebates resulting from the PPACA. The law also requires manufacturers to provide rebates for drugs provided through Medicaid Managed Care Organizations (MCOs). MCOs must also submit utilization data for physician administered drugs for rebate purposes to comply with the same requirements for state Medicaid programs. Finally, the PPACA also exempts discounts under the Medicare Coverage Discount Program from a manufacturer's best price calculation.¹³

Other Initiatives

While it is important to watch what happens on the federal level to understand Medicaid, most of the action is on the state level where states have the ability to tailor their programs to their own needs within federal guidelines. States are burdened by the budgetary pressures from their share of costs for Medicaid programs, especially since the enhanced Federal Medical Assistance Percentage (FMAP) provided through the stimulus ends July 1, 2011. While governors suggesting their states could opt out of the Medicaid program may be hyperbole, state programs and legislatures are seeking methods to contain their Medicaid costs. Other changes to Medicaid will also have an impact on manufacturers. For example, legislation has been introduced to change the reimbursement for Texas hospitals from hospital-specific rates to an average rate that might promote greater hospital efficiencies.¹⁴

There are also opportunities to promote efficiency or enhance value through initiatives in care management, coordination, and payment methods. Significant benefits from some of these opportunities might be achievable over a longer time frame and are often difficult to predict. While not all cost cutting legislation will be signed into law, manufacturers are wise to monitor Medicaid programs for changes in coverage of their products as states continue to balance their budgets. These initiatives could have implications for prescription drug coverage due to increased management.¹⁵

Manufacturers need to be poised to maximize opportunities in this expanding program, and be prepared to address challenges that will come from a dynamic market place. Medicaid is a program to watch.

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Hear UBC Speakers at the Following Presentations during the ISPOR 16th Annual International Meeting

ISPOR Sessions/Presentations

ISPOR SHORT COURSE

Discrete Event Simulation for Economic Analyses

Faculty: **J. Jaime Caro**, MDCM, FRCPC, FACP, McGill University and United BioSource Corporation; **Jörgen Möller**, MSc Mech Eng, United BioSource Corporation

Sunday, May 22, 8:00 am - 5:00 pm

ISPOR FORUM

Career Options in the Wake of Health Care Reform and Recession

Moderators: Zeba M. Khan, RPh, PhD, Celgene Corporation; Urvi Desai, BPharm, Virginia Commonwealth University School of Pharmacy

Speakers: **Chris L. Pashos**, PhD, United BioSource Corporation; C. Daniel Mullins, PhD, University of Maryland School of Pharmacy; Jens Grueger, PhD, Pfizer

Session I, Monday, May 23, 5:30 pm - 6:30 pm

ISPOR PLENARY SESSION

Modeling Task Force Recommendations

Speaker: **J. Jaime Caro**, MDCM, FRCPC, FACP, ISPOR-SMDM Modeling Good Research Practices Task Force and United BioSource Corporation

Wednesday, May 25, 10:00 am - 11:30 am

UBC Contributed Presentations

EDUCATIONAL SYMPOSIA

Navigating the New Comparative Effectiveness Landscape: The Role of HIT

Moderator: **Bryan R. Luce**, PhD, MBA, United BioSource Corporation
Speakers: **Jonathan A. Morris**, MD, United BioSource Corporation; Richard E. Ward, MD, MBA, Reward Health Sciences; Jean Paul Gagnon, MD, Independent Consultant

Monday, May 23, 7:00 am - 8:00 am

Personalized Healthcare and Comparative Effectiveness Research: Realizing the Evidence on "What Works for Whom and When"

Moderator: **Kathleen W. Wyrwich**, PhD, United BioSource Corporation
Speakers: Amy Abernethy, MD, Duke University School of Medicine; Felix Frueh, PhD, Medco Research Institute; Jens Grueger, PhD, Pfizer

Tuesday, May 24, 1:30 pm - 2:30 pm

ISSUE PANELS

IP2: Paying for Value - Which to Go For: The New UK Approach or the New German Law or Neither?

Moderator: **J. Jaime Caro**, MDCM, FRCPC, FAC, United BioSource Corporation

Panelists: Peter L. Kolominsky-Rabas, MD, PhD, MBA, University of Erlangen-Nurnberg; Alistair J. McGuire, PhD, LSE Health and Social Care

Session I, Monday, May 23, 11:00 am - 12:00 pm

IP6: When is the Evidence Adequate: Different Perspectives from Key Health Care Decision-Makers

Moderator: Robert W. Dubois, MD, PhD, National Pharmaceutical Council

Panelists: **Bryan R. Luce**, PhD, MBA, United BioSource Corporation; Steven Pearson, MD, MSc, Institute for Clinical and Economic Review; Robert S. Epstein, MD, MS, Medco Health

Session II, Tuesday, May 24, 2:45 pm - 3:45 pm

WORKSHOPS

W9: Using Comparative Effectiveness Research (CER) to Support a Value Based Health Care System, Examples from the United States and Europe

Discussion Leaders: Rachael Fleurence, PhD; **Feng Pan**, PhD, United BioSource Corporation; Corinna Sorenson, MPH, MHSA, London School of Economics and European Health Technology Institute for Socio-Economic Research

Session II, Monday, May 23, 4:15 pm - 5:15 pm

W13: Use of Simulation to Inform the Design of Pragmatic Comparative Effectiveness Trials

Discussion Leaders: **David Wilson**, MA, United BioSource Corporation; **J. Jaime Caro**, MDCM, FRCPC, FAC, United BioSource Corporation; **K. Jack Ishak**, PhD, MSc, United BioSource Corporation; Myoung Kim, PhD, MA, MBA, Ortho-McNeil Janssen Scientific Affairs

Session III, Tuesday, May 24, 4:00 pm - 5:00 pm

W16: The Evolving Role of the Agency for Healthcare Research and Quality (AHRQ) in Comparative Effectiveness Research (CER)

Discussion Leaders: Jean Slutsky, PA, MSPH, Agency for Healthcare Research and Quality; Nina A. Thomas, MPH, Doctor Evidence, LLC; **Steven Blume**, MS, United BioSource Corporation

Session III, Tuesday, May 24, 4:00 pm - 5:00 pm

W17: Patient-Reported Outcome (PRO) Assessments in Clinical Trials: Navigating the EMA and FDA Regulatory Framework

Discussion Leaders: **Ingela Wiklund**, PhD, United BioSource Corporation; Olivier Chassany, PhD, MD, Assistance Publique-Hopitaux de Paris; **Kathleen W. Wyrwich**, PhD, United BioSource Corporation

Session III, Tuesday, May 24, 4:00 pm - 5:00 pm

W23: Practical Approaches for Systematic Analysis of Observational Data; Real World Case Studies from the Pharmaceutical Industry

Discussion Leaders: **Stephanie Reisinger**, United BioSource Corporation; Gregory E. Powell, PharmD, MBA, GlaxoSmithKline; David Miller, ScD, SM, Schwarz Bioscience; **Jonathan A. Morris**, MD, United BioSource Corporation

Session IV, Wednesday, May 25, 1:45 pm - 2:45 pm

W24: Generalized Evidence Synthesis in Comparative Effectiveness Research: Could the Evidence Base Be Broadened in Mixed Treatment Comparisons?

Discussion Leaders: **Agnes Benedict**, MSc, MA, United BioSource Corporation; **Huseyin Naci**, MHS, United BioSource Corporation; David Vanness, PhD, University of Wisconsin

Session V, Wednesday, May 25, 3:00 pm - 4:00 pm



POSTERS

Session I, Monday, May 23, 8:00 am - 8:30 pm

PCV82: Evaluation of Relationship Between Blood Pressure Control Among Hypertensive Patients and Integration of Services Within Physician Organizations
Smalarz A, Fraser K, Wong K, Wu N, Wogen J, Boulanger L

PSS19: Psychometric Evaluation of the National Eye Institute Visual Function Questionnaire 25 and Visual Function Questionnaire Utility Index in Patients with Non-Infectious Intermediate and Posterior Uveitis
Naik RK, Gries KS, Rentz A, Kowalski JW, Revicki DA

PSY72: Variation by Age in Health-Related Quality of Life of Patients Initiating Treatment for Myelodysplastic Syndromes
Pashos C, Grinblatt DL, Komrokji RS, Sekeres MA, Narang M, Sullivan KA, Street TK, Khan ZM

PUK14: A Markov Model Comparing Sacral Neuromodulation and Botulinum Toxin-A for Medicare Patients with Idiopathic Overactive Bladder Refractory to Conservative Care
Ganz M, Clemens JQ, Anger J, Denevich S, Shah D, Carlson A, Wittek MR, Pashos C

Session II, Tuesday, May 24, 8:00 am - 7:45 pm

PDB65: Economic Burden of Cushing's Disease – A Population Analysis of Direct Medical Costs and Utilization
Swearingen B, Wu N, Chen SY, Pulgar S, Biller B

PIH13: The Cost-Effectiveness of the Levonorgestrel-Releasing Intrauterine System (LNG-IUS, Mirena) for the Treatment of Heavy Menstrual Bleeding in the United States
Ganz M, Shah D, Gidwani R, Filonenko A, Su W, Pocoski J, Law A

PMS44: Assessing Vitality in Patients Undergoing Etanercept Therapy for Rheumatoid Arthritis
Gandra SR, Vernon M, Cole JC, Bitman B, Park GS, Wang B, Chaudhari S, Fleischmann RM

PMS55: Impact of Efficient Practices in the Care of Patients with Fibromyalgia
Chandran A, Brown TM, Garg S, McNett M, Silverman SL, Hadker N

PRS25: Factors Influencing Satisfaction with COPD Maintenance Medication: Concepts Elicited through Qualitative Interviews with Patients
Mocarski M, Palsgrove A, Schaefer M, Setyawan J, Wilcox T

PRS26: Reliability and Validity of the EXACT-Respiratory Symptoms (E-RS) Score to Quantify the Severity of Respiratory Symptoms of COPD
Sexton CC, Leidy NK, Notte S, Jones P, Monz BU, Nelsen L, Ramachandran S, Sethi S

PRS27: The Development of a Patient-Reported Outcome Instrument to Evaluate Nighttime Symptoms of COPD
Palsgrove A, Schaefer M, Hareendran A, Houghton K, Mocarski M, Carson R

PRS45: Modeling the Impact of Multiple Quit Attempts in Smokers Using Discrete Event Simulation (DES)
Marton J, Getsios D, Revankar N, Wilke RJ, Li Q, Ishak KJ, Caro JJ, Zou KH, Xenakis J

Session III, Wednesday, May 25, 8:00 am - 3:00 pm

PCN4: Body Mass Index and Stage of Diagnosis of Ovarian Cancer: A Systematic Review and Meta-Analysis
Blieden MB

PCN33: Cost Savings Associated with Transfusion Independence in Patients with Myelodysplastic Syndrome with a 5Q-Deletion
Bozkaya D, Mahmoud D, Mitsi G, Khan ZM

PCN91: Arthralgia and Patient-Reported Outcomes in Postmenopausal Women with Early Breast Cancer Taking Aromatase Inhibitors: Longitudinal Analyses
Castel LD, Mayer IA, Chen H, McLellan SE, Deppen SA, Abramson VG, Boomershine CS, Friedman DL, Gundy CM, Lenderking WR, Hartmann KE, Johnson DH, Cella DF

PCN117: Association of Health-Related Quality of Life (HRQOL) with ISS Stage and ECOG Status in Multiple Myeloma
Pashos CL, Durie BG, Mehta J, Toomey K, Terebelo HR, Abonour R, Fonseca R, Gasparetto C, Narang M, Rifkin RM, Shah JJ, Sullivan KA, Street TK, Khan ZM

PCN133: Estimating the Epidemiology of Late-Stage Cancers – A Mathematical Approach
Pan F, Sorensen S, Stern S

PMH12: The Profile of Impairments to Attention and Episodic Recognition Memory in Mild Cognitive Impairment and Alzheimer's Disease
Wesnes K, Lenderking WR

PMH28: Real-World Health Care Utilization and Costs in Newly Diagnosed Depression Patients Between 2006 and 2008
Schneider G, Roy A, Busner J, Crean S, Lanes S, Dabbous OH

PMH38: Economic Implications of the Effect of Lurasidone versus Other Selected Atypical Antipsychotics on Cardiometabolic Parameters in Patients with Schizophrenia
Guo S, Hernandez L, Green J, Sarocco P

PMH40: Cost-Effectiveness and Budget Impact of Adjunct Quetiapine Fumarate Extended-Release in Patients with Major Depressive Disorder with an Inadequate Response to Previous Therapy
Svedsater H, Locklear J, Sukhvinder J, Stillman IO

PND10: Budget Impact Analysis of Everolimus for the Treatment of Growing Subependymal Giant Cell Astrocytoma Secondary to Tuberous Sclerosis Complex
Stillman IO, Whalen JD, Sun P, Liu Z

PND19: Humanistic and Economic Burden in Tuberous Sclerosis Complex with Neurological Manifestations: Systematic Review
Hallett L, Foster T, Valentim J, Blieden M, Liu Z

PND63: Little or No Treatment Effect? Application of Growth Mixture Models to Explore Unknown Subgroups of Differential Responders to Treatment
Stull DE, Houghton K, Wesnes K

PRM48: Design and Operational Considerations for Pragmatic Clinical Trials to Support HEOR Evaluations
Ishak KJ, Payne KA, Schrammel P, Caro JJ

FOCUS ON:

The New Era of Evidence

Patient-Reported Outcome (PRO) Assessments in Clinical Trials: Navigating the EMA and FDA Regulatory Framework

By Ingela Wiklund, PhD, Senior Research Leader, United BioSource Corporation; Olivier Chassany, MD, PhD, Professor, Hôpitaux de Paris and Paris Diderot University; Kathy Wyrwich, PhD, Senior Research Leader, United BioSource Corporation

Patient-reported outcomes (PROs) are increasingly being used in clinical trials to support label claims.^{1, 2} In symptomatic conditions, such as pain, migraine, asthma, dermatological conditions (e.g., psoriasis) and urinary incontinence, a PRO is often the primary endpoint or may be included as key secondary endpoint. Claims described in the packet insert have value for the pharmaceutical industry because this information can subsequently be used to educate the prescribing clinicians and patients on the value of pharmaceutical products. Moreover, in the U.S., the PRO label claims granted by the Food and Drug Administration (FDA) can be incorporated into direct-to-consumer (DTC) advertising, which is a powerful tool to bolster sales. In Europe, DTC advertising is not permitted, but PRO label claims granted by the European Medicines Agency (EMA) are used to inform the prescribing clinicians about the added value of pharmaceutical products in medical journals. Table 1 lists the products and their approval dates, indications and PRO instruments that have FDA-approved PRO label claims approved in 2010 (the full list can be found at <http://unitedbiosource.com/pdfs/newsletter/fda-pro-label-claims.pdf>); Table 2 provides the products and relevant information for EMA-granted PRO label claims approved in 2010 (the full list can be found at <http://unitedbiosource.com/pdfs/newsletter/ema-pro-label-claims.pdf>).

To help clarify the regulatory requirements for support of a PRO label claim for medicinal products, the FDA first published its *Draft Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* in 2006 followed by the *Final Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* in 2009.³ A similar need was perceived in Europe, and in 2005 the EMEA (since renamed the EMA) published a *Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products*.⁴

To secure a successful FDA and EMA submission of data generated in international clinical trials using PRO endpoints in support of label claims, a full understanding of the similarities as well as the differences between the two regulatory bodies is required. With increasing collection of patient-based data in international trials, the importance of navigating the requirements on development history and psychometric documentation of PRO data, the analytical approaches, and the format of FDA PRO evidence dossiers and EMA briefing books for submissions have escalated.

A major difference between the FDA and EMA is the terminology used to describe and characterize patient-based endpoints and the implications of these terminology differences. The FDA PRO Guidance coined the concept of patient-reported outcomes, defined as “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.”³ Symptom reports are by far the most frequently used PRO, and therefore, need to meet the criteria outlined in the FDA PRO Guidance for content validity, concept saturation, and psychometric properties (reliability, construct validity and responsiveness). Special consideration is also required regarding the clinical and demographic characteristics of patients included in interviews/cognitive debriefing interviews and focus groups to guarantee the characteristics of the intended trial population are reflected, and additionally to ensure diversity in terms of ethnicity and socioeconomic status is met.

In contrast to the FDA, the EMA shies away from using PROs and confines their guidance to apply to the use of health-related quality of life (HRQL) instruments. Importantly, within the EMA paradigm, symptom endpoints are classified as clinical endpoints, and therefore require no specific documentation on development history or psychometric properties. Indeed, the EMA reflection paper states that: “In addition, HRQL should be clearly differentiated from the core symptoms of a disease (e.g., pain, migraine, pyrosis...) assessed by the patient himself which are well-accepted primary and secondary efficacy endpoints in registration trials.”⁴ Single domain endpoints depicting specific and clearly defined concepts, such as physical functioning, are favored by EMA because they are easier to understand and can be associated more directly to a disease and its symptoms.

Additional differences of note between the FDA and EMA reviews continue to be driven by the more detailed requirements and level of scrutiny by FDA. For example, the FDA has favored 24-48 hour recall periods for symptom endpoints assessed using a daily diary, and preferably an electronic diary to secure a time stamp of completion. EMA for now has no such requirements for this specific recall period or the method of data collection. The FDA also requires that a user manual be presented detailing all information about the PRO, as well as training material for users and standardization of PRO implementation in the trial. In terms of similarities, EMA asks for the same evidence documentation of psychometric properties as FDA. In essence, this means that a relevant and

Table 1 Full table of approvals available at: <http://unitedbiosource.com/pdfs/newsletter/fda-pro-label-claims.pdf>

PRO Label Claims Approved in 2010 – FDA			
Drug	Product Approval Date	Therapeutic Area/Condition	Instrument(s) or PRO Claim
Ampyra	1/22/2010	Multiple Sclerosis	Multiple Sclerosis Walking Scale
Articaine HCL w/ Epinephrine	2/26/2010	Pain Associated with Dental Surgery	Visual Analog Scale
Asclera	3/30/2010	Spider and Reticular Veins	Verbal Satisfaction Scale
Butrans	6/30/2010	Chronic Back Pain	Numerical Rating Scale
Cayston	2/22/2010	Respiratory Symptoms Associated With Cystic Fibrosis	Not Specified
Dulera	6/22/2010	Asthma	Asthma Quality of Life Questionnaire
Egrifta	11/10/2010	Reduction of Abdominal Fat in HIV Patients	Patient Distress Associated with Appearance (Likert Scale)
Exalgo	3/1/2010	Moderate to Severe Pain in Opioid Treatment Patients	Numeric Rating Scale on a Patient Diary
Jalyn	6/14/2010	Benign Prostatic Hyperplasia	International Prostate Symptom Scale
Nuedexta	10/29/2010	Pseudobulbar Effect (PBA) in Multiple Sclerosis and Amyotrophic Lateral Sclerosis	Center for Neurologic Study – Liability Scale
Silenor	3/17/2010	Insomnia	Wake After Sleep Onset (WASO)
Staxyn	6/17/2010	Erectile Dysfunction	Index of Erectile Function (IIEF) Sexual Encounter Profile (SEP)
Vimovo	4/30/2010	Pain Associated with RA, Osteoarthritis, Ankylosing Spondylitis	WOMAC Pain and Physical Function Subscales Patient Global Assessment

Table 2 Full table of approvals available at: <http://unitedbiosource.com/pdfs/newsletter/ema-pro-label-claims.pdf>

PRO Label Claims Approved in 2010 – EMA			
Drug	Product Approval Date	Therapeutic Area/Condition	Instrument(s) or PRO Claim
Leflunomide Winthrop	1/8/2010	Psoriatic and Rheumatoid Arthritis	Western Ontario and McMaster Universities Osteoarthritis Index - Pain Subindex
Silodyx	1/29/2010	Prostatic Hyperplasia	IPSS
Urorec	1/29/2010	Prostatic Hyperplasia	IPSS

Biologics and Biologics License Applications (BLAs) not included. Tables compiled by Andrew Palsgrove (andrew.palsgrove@unitedbiosource.com).

appropriately validated questionnaire is acceptable to EMA, but FDA additionally requests that all details on the qualitative and quantitative development history be outlined. With this in mind, it is not surprising that the EMA recommends many well-known, widely used in previous clinical trials and validated questionnaires for use. In general the EMA tends to rely on efficacy endpoints (including symptoms, when relevant) that have been used in previous briefing book submissions, especially if these submissions were successful. The FDA, on the other hand, considers patient input critical, and recommends starting with the label claim to drive the development of an endpoint model, including both clinical and PRO endpoints to ensure the claim is appropriately reflected in the content of the PRO.

Other similarities between the FDA and EMA include:

1) justification of the relevance of concept studied to the patient population under study, and 2) evidence of validation in the same population provided prior to inclusion of the instrument in Phase III trials. Both agencies ask for evidence

of reliability, construct validity and responsiveness to change over time, as well as information on interpretability. Regarding translations and cultural adaptations of patient completed questionnaires developed in another language and/or culture than where they are used during the clinical trial, both agencies look for a standardized process similar to that outlined in the ISPOR Task Force.⁵

The FDA has produced disease-specific guidance documents for Chronic Obstructive Pulmonary Disease (COPD)⁶ and Irritable Bowel Syndrome (IBS)⁷ where recommendations are described to guide endpoint selection, including PROs. Currently, the FDA finds none of the COPD-specific instruments acceptable to support a PRO label claim, whereas the EMA has accepted claims evidence based on the St. George's Respiratory Questionnaire.⁸ The EMA IBS guidance recommends the use of a global pain assessment using either a numerical rating scale or a visual analogue scale.⁹

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PRO Assessments in Clinical Trials

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The similarities also include trial design and analysis plan, even though some important differences also exist. For instance, generally two successful randomized blinded Phase III trials are required by both agencies for product registrations, with placebo control preferred by both the FDA and EMA. As to trial design considerations, a statistical analysis plan with a hierarchy of predefined endpoints detailing methods for multiplicity adjustment is a standard requirement, and additionally EMA would like Sponsors to present sample-size estimates for PROs used as secondary endpoints.⁴ Both agencies review the amount of missing PRO data; the FDA encourages inclusion of pre-specified procedures in the clinical trial protocol to avoid missing data and requests detailed information on how missing data are handled for the PRO. Interpretability of PRO results is requested by both agencies. The FDA provides several anchor-based and supporting distribution-based methods for demonstrating important change, and has named the “individual PRO score change over time that should be interpreted as a treatment benefit” as the responder definition.³ Moreover, the FDA has also stated a preference for cumulative distribution of response charts for interpreting relevant changes across trial results and sharing this information in approved labels.⁷ Conversely, the EMA is interested in the pre-specified minimal important difference (MID) that is used to power studies, and the MID should be “based on a combination of statistical reasoning and clinical judgment and none of these on its own is sufficient.”⁴ EMA encourages Sponsors to disclose relevant methods to help to interpret the results. For example, several EMA guidelines, like in osteoarthritis, recommend presenting the results in terms of the responder rates, with the definition of responder based on a specified reduction in pain over time.¹⁰

While the FDA requires the submission of a PRO evidence dossier in agreement with the template embedded in the guidance document, EMA is looking for a shorter briefing book version. Both agencies encourage Sponsors to seek their advice early on. EMA and FDA have developed qualification processes, which include PROs. Indeed, a full understanding of the evidentiary requirements, the differences, and their implications is important, especially when PROs are used in global trials. This attention to the requirements will improve efficiency and increase the likelihood of successful trial outcomes and future PRO label claims.

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Value-Based Pricing: What Effect Does It Have on Evidence Generation

By Radoslaw Wasiaik, PhD, Research Scientist

Pricing of medicines in the United Kingdom (U.K.) is about to undergo the biggest set of changes in half a century. The U.K. government intends to introduce a system of value-based pricing when the current Pharmaceutical Price Regulation Scheme (PPRS) expires at the end of 2013, with the aim of giving National Health Service (NHS) patients better access to effective and innovative medicines. The new system will be designed to provide greater access to medicines and better outcomes for patients. Commentators have flagged concerns over the proposals, and the detailed design of the new arrangements will determine the success of the changes.¹⁻⁴ More specifically, issues over the evidence needed for assessment have been identified and companies will need to keep abreast of these issues for products to be launched from 2013.⁵

Current System

Currently, prescription medicines are priced under the regulation known as the PPRS.⁶ First introduced in 1957, and typically renegotiated every five years, the PPRS is a voluntary scheme agreed upon by the Department of Health and the pharmaceutical industry. The main goal of the PPRS is to achieve a balance between reasonable prices for the NHS and a fair return for the pharmaceutical industry from investment in developing new medicines. In the PPRS, a pharmaceutical company is able to set the price of any new active substance, but prices of its medicines have been constrained as the PPRS controls the profits that a pharmaceutical company is allowed to make on its sales to the NHS.

Contrary to popular understanding, the National Institute for Health and Clinical Excellence (NICE) does not have a direct role in pricing decisions under the current system. However, NICE's appraisal process is likely to be a factor in the pricing decisions of pharmaceutical companies as companies aim to set prices that satisfy the cost-effectiveness criteria. This is particularly true in cases where NICE concludes that a drug may offer benefits that are insufficient to justify the price at which the drug is available. In those situations, NICE has to recommend that the NHS restricts its use of that drug.

Why Change?

Recent developments in the U.K. have introduced more flexibility to the existing system. Patient Access Schemes were introduced in an attempt to share the risk associated with outcome of therapy by offering discounts or rebates to reduce the cost of a drug to the NHS (examples include Lucentis® for the treatment of macular degeneration, Sutent® for renal cell carcinoma and gastrointestinal stromal tumour

and Velcade® for multiple myeloma). In addition, following a public media campaign, NICE introduced explicit rules aiming to provide additional flexibility during the appraisal of drugs for less common conditions and for end of life conditions.

Nevertheless, the new U.K. government did not see these changes as sufficient to achieve the goal of ensuring optimal pricing of branded drugs for NHS, increasing patient access to innovative drugs, or clearly linking the price the NHS pays and the benefits that a medicine delivers.⁷ The U.K. government hopes that the new system will provide a pricing scheme that improves patients' access to the most effective medicines, is more predictable, and can reward innovation through clear investment signals for pharmaceutical companies.

The New Value-Based Pricing System and Key Considerations in Demonstrating Value

The key principle of the proposed system would be to ensure NHS funds are used to gain the greatest possible value for patients. In order to do so, a range of thresholds or maximum prices would be set based on the differences in values offered by medicines. Under the government's proposals, the value of new products would still be assessed using a cost-effectiveness threshold. However, new weights would be applied to the benefits provided by new medicines, which would imply a range of price thresholds reflecting the maximum price acceptable.⁷ These thresholds would be explicitly adjusted to reflect a broader range of relevant factors so they could be used to calculate the full value of a new product; the current proposal includes higher thresholds due to high burden of disease, high level of innovation, and demonstrated societal benefits. Explicit statement of different thresholds is likely to have an impact on evidence generation, as manufacturers will need to evaluate if a new medicine would qualify for a higher threshold. For example, transparency in the definition of what is considered "demonstrated societal benefit" will be required for this process to work efficiently.

The new system is to be introduced on January 1, 2014. One of the key questions is whether medicines on the market before that date should also be subject to the new arrangement. In theory, applying the value-based pricing criteria to all medicines would create a more efficient allocation of resources at a point in time, and would offer a transparent model to patients, decision makers, and companies. In practice, however, the sheer volume of work is likely to preclude this, and in many cases, the likelihood and value of any changes in prices would simply not be worth the effort. Given the expected challenges during what is expected to be a lengthy transition, the key to any process developed will be its transparency, particularly regarding the evidence needed to support products prior to, and immediately after, January 1, 2014.

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Value-Based Pricing

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Another key consideration is how to deal with situations where there is insufficient evidence to allow full assessment of value. There will be some medicines where the data to confidently assess the value of a medicine are not available at time of launch; for example, where for ethical or practical reasons such evidence cannot be produced. In such cases, the decision regarding public funding could be accompanied by a price reflecting the distribution of risk between the manufacturer and payer. There is a growing body of experience with allowing patients access to medicines while the evidence on value is further developed and a subsequent reappraisal of the medicines (and possible renegotiation of the price) are completed.⁸

This in turn would help overcome one of the issues in the U.K.: the relatively slow uptake of new medicines. In its consultation document, however, the government does not see a need to continue the current patient access scheme arrangements for new medicines assessed under value-based pricing. It is not clear, however, why the introduction of value-based pricing will in itself guarantee improvements in access to, and uptake of, medicines (and therefore improvement in patient outcomes). As the details of the new system are further developed, information on how the objective of ensuring faster uptake of new medicines will be achieved should be provided. In particular, this should include a detailed description of the requirements for evidence in manufacturers' submissions so that companies can plan for and conduct the studies to produce the appropriate evidence in good time.

A core principle of the new system should be to evaluate the entire body of evidence available at the time and to provide sufficient flexibility to deal with cases that are not standard. A pragmatic approach is also desirable; the system does not need to create evidence requirements that are cost-prohibitive or impossible to meet by manufacturers. In particular, this needs to be very specific regarding how to treat generation of evidence for products launching at the time of the system change. The system should also allow for use of the most appropriate methodologies for evidence generation and not create rigidities in the process by mandating approaches unnecessarily.

Although the new policies will not be implemented for more than two years, there is a long way to go to design the new system and to address the many views and concerns of the different stakeholders. While the intent of this new process is focused on showing value, it is important that the new system does indeed include improvements without losing the positive features of the PPRS. Specifically, this is an opportunity to clarify the evidence requirements needed

from companies and build an approach that is pragmatic, cost-efficient, and in the end, ensures patients are receiving better access to effective and innovative treatments.

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References

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Monitoring Product Safety

*By Robert Sharrar, MD, Executive Director,
Safety and Risk Management*

Product safety is a public health issue because sooner or later we, or our loved ones, will be taking these medicines to improve our quality of life. Most drugs, if not all drugs, have harmful side effects, but in almost all instances, the benefits are greater than the risks. Adverse experiences happen to people while they are taking these medicinal products. The question then becomes “Are these adverse experiences related to the drug, to the disease process being treated, to a concomitant illness or concomitant medications, or are they just unrelated background events that would occur in any population under observation?” It is important to answer this question because health care providers and patients need to know the safety profile of a product so that they know how to use the product and what to expect from it.

Pharmacovigilance is the process of monitoring the safety profile of medicinal products as they are used in a population. The World Health Organization defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding, and prevention of adverse drug effects or any other drug related problems. Since the safety profile of

a product can only be determined by examining its effect on a population of individuals taking the product, various epidemiologic methods have been developed to monitor product safety. They include clinical trials, post-marketing surveillance, case series analyses, various methods of signal detection, registries, and observational (and by observational we mean non-randomized) post-approval scientific and data gathering activities following the use of drugs in a population.

Pharmaceutical companies and regulators have always been concerned about product safety. This is not a new concept. However, the world of pharmacovigilance has changed dramatically since 2005 because of the new regulations and guidelines established by regulatory agencies and because of increased public interest in product safety. These regulations and guidance documents include ICH E2E¹ Pharmacovigilance Planning; the three FDA guidance documents on Good Risk Management Practices: 1) Premarketing Risk Assessment, 2) Development and Use of Risk Minimization Action Plans (RiskMAPS),³ and 3) Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment;⁴ and the FDA Amendment Act of 2007.⁵ The EMA guidelines and regulations are described in the European Medicines Agency CHMP Guideline on Risk Management Systems for Medicinal Products for Human Use⁶ and in Volume 9A of the rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use.⁷ Although these guidelines are extensive, they can be summarized in three words. Regulatory agencies want pharmaceutical companies to be *proactive*, *focused*, and *transparent* about their activities concerning product safety.

Why should there be all of these regulations concerning pharmacovigilance when clinical trials have been performed to demonstrate that the product is both effective and safe before the drug gets approved for distribution? Clinical trials are designed primarily to demonstrate efficacy because you know what you are trying to prove and you can design a clinical study to demonstrate efficacy. However, clinical trials are not very good at determining the safety profile of the product for many reasons. Clinical trials are too small numerically to identify rare adverse events which may occur at a rate of 1:10,000 or less. Secondly, clinical trials, which normally last for less than a year, are too short to identify any safety issues from long term use of the product. Third, clinical trials, because of exclusion criteria, involve a homogeneous population which means that many people not included in clinical trials will end up using the product. Finally, everything is done correctly in clinical trials, which may not happen when the drug is used by physicians in the real world. It is not possible to determine the complete safety profile of a product until it is used by a large number of health care practitioners on many patients, many of whom have concomitant illnesses and are taking concomitant medications.

The purpose of these regulatory and guidance documents is to aid pharmaceutical companies in planning risk management activities. They do this by describing a method for

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Using Metrics to Measure Success in Publications Programs

By Michelle Seymour, Client Solutions, and Russell Traynor, Client Solutions, UBC-Envision Group

Effective dissemination of clinical trial data via a well-planned publications program is one of the most important elements in the ultimate success of a product. Metrics can be useful tools for providing the information by which the performance of a program, against its predetermined objectives, can be measured and improved upon — but metrics must be accurate, appropriate, available, and in context.

Identify the metrics that will have the greatest impact, which will vary depending on:

- The stage in a product's life cycle
- The market in which the product is competing
- Their applicability for measuring success across products in pre-, peri-, and post-launch stages as mature products or orphan/niche drugs, as well as those in highly competitive environments

Metrics that should be assessed include:

- Publication quality
- Audiences/journals targeted
- Time to submission/publication
- Acceptance rate, citation rate
- Timeliness of review completion
- Support of communication objectives

As the program's objectives vary by lifecycle and competitive environment, so should the selection and weighting given to specific metrics at defined time periods. The metrics for measuring performance against objectives should be selected, recorded, interpreted, and modified appropriately to allow teams to maximize the success of their programs. In order for metrics to be used effectively to improve the management of a publications plan, details should be communicated clearly to all stakeholders outlining which metrics have been selected and how they will be used.

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summarizing important safety information and by proposing a structure for a pharmacovigilance plan. The ICH E2E document used four guiding principles in its development. It first recommended that planning of pharmacovigilance activities take place throughout drug development and that company pharmacovigilance experts get involved early in product development. Secondly, it recommended that effective collaboration should take place between regulators and industry and that planning and dialogue with regulators should start early in drug development. A Risk Evaluation and Mitigation Strategy (REMS) and a Risk Management Program (RMP) should be a negotiated document between pharmaceutical companies and regulators so that all concerns can be appropriately addressed. The document also recommended a science-based approach to risk documentation. Although we like to think that we are scientific about all that we do, it is a bit more difficult to be completely scientific about product safety issues. We simply do not always have enough information to know for sure. Consequently, we have to make the best subjective decisions that we can based on the available objective information. It also means that any study that is proposed should be able to provide interpretable data. Studies that generate data that are not interpretable only make the situation worse. Finally, it stated that pharmacovigilance activities should be applicable across the three ICH regions which are the United States, Europe, and Japan.

Risk management is defined as risk assessment plus risk minimization, and risk assessment consists of identifying and characterizing the nature, frequency, and severity of the risks associated with the use of a product. It is no longer sufficient simply to say that an adverse reaction is associated with the use of a product. Regulatory agencies now expect pharmaceutical companies to quantify the risk in terms of rates, and they also expect pharmaceutical companies to identify risk factors as to why certain individuals developed the adverse reaction in question. The second part of risk management is called risk minimization, which means to minimize a product's risk while preserving its benefits. Risk minimization activities can be difficult to design because they have to be applicable in different populations in different geographical areas without interfering with the delivery of health care.

It is clear that regulatory agencies want pharmaceutical companies to not only collect more information about product safety, but they also want pharmaceutical companies to better analyze the data that they already collect. Furthermore, regulatory agencies want pharmaceutical companies to be more proactive when it comes to identifying and evaluating safety signals. They also want pharmaceutical companies to focus their pharmacovigilance activities

on important identified and potential risks and missing populations identified in clinical development. It is not possible, nor is it necessary, to follow up every potential safety signal. Finally, pharmaceutical companies should be transparent about the safety issues that they are evaluating.

This increased demand for safety information is basically good for everyone. It benefits the patient and the physicians because they know how to use the product and what to expect from its use. It benefits the pharmaceutical companies because proper use of the drug and minimizing its risk helps keep the drug on the market. The main disadvantage is that these activities are costly and will increase the price of drugs. This means that all parties concerned should make certain that the proposed pharmacovigilance studies make epidemiologic sense. Careful thought has to be given to the proper interpretation of spontaneous post-marketing safety reports, to safety signals identified by a disproportionality analysis, and to the design of registries and observational studies to evaluate important identified safety issues. This requires an understanding of clinical medicine, of the natural history of disease processes, and of the basic principles of statistics and epidemiologic analysis.

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Upcoming Presentations

ATS 2011 International Conference

May 13 - May 18, 2011, Denver, CO, USA

Poster Presentation

Patients' Experience of Nighttime COPD Symptoms: Results from Qualitative Research **Schaefer M, Palsgrove A, Hareendran A**, Houghton K, Mocarski M, Carson R, Setyawan J, Make B

Quantifying the Severity of Respiratory Symptoms of COPD: Reliability and Validity of a Patient Diary **Sexton CC, Leidy NK, Notte SM**, Jones P, Monz BJ, Nelsen L, Ramachandran S, Sethi S

AUA 2011 Annual Meeting

May 14 - May 19, 2011, Washington, DC, USA

Podium Presentation

Development of the Hypogonadal Impact of Symptoms Questionnaire (HIS-Q): A Patient-Reported Outcome Measure to Evaluate Symptoms of Hypogonadism **Gelhorn HL, Vernon MK**, Miller MG, Brod M, Althof SE, DeRogatis LR, Dobs A, Seftel AD, Revicki DA

The Impact of OAB on Work Productivity in the US: Results from OAB-POLL **Sexton CC, Coyne KS, Bell JA**, Clemens JQ, Dmochowski R, Chen C-I, Bavendam T, Kopp Z

Poster Presentation

The Prevalence of Overactive Bladder (OAB) by Race: Results from the OAB-POLL Study **Coyne KS, Sexton CC, Thompson CL**, Dmochowski R, Clemens JQ, Chen C-I, Bavendam T, Kopp Z

164th Annual Meeting American Psychiatric Association (APA)

May 14 - May 18, 2011, Honolulu, HI, USA

Poster Presentation

Surveillance Strategies for Enhancing Data Quality in Adjunctive Psychopharmacotherapy Trials **Busner J, McNamara C, Oakley M, Platko K**, Montgomery S

11th International Symposium on Myelodysplastic Syndromes

May 18 - May 21, 2011, Edinburgh, UK

Presentation

Health-Related Quality of Life by RBC Transfusion Dependence or Independence of Patients Initiating Treatment for MDS **Pashos CL**, Grinblatt DL, Sekeres MA, Komrokji RS, Narang M, Street TK, Sullivan K, Harding G, Khan ZM

ASCO 2011 Annual Meeting

June 3 - June 7, 2011, Chicago, IL, USA

Poster Presentation

Exploring the Relation Between Overall Survival (OS) and Progression-Free Survival (PFS) in Gastrointestinal Stromal Tumor (GIST) via Meta-Analysis **Keyser RL**, Tranbarger Freier KE, Hoaglin DC, Tziveleki S, Ozer-Stillman I

AHRQ's Third Symposium on Comparative Effectiveness Research Methods

June 6 - June 7, 2011, Rockville, MD, USA

Presentation

Development of Algorithms to Identify Metastatic Cancer in Claims Data, Using Oncology EMR Data **Nordstrom B**, Whyte JL, Stolar M, Mercaldi C, Kallich JD

13th World Congress on Menopause

June 8 - June 11, 2011, Rome, Italy

Poster Presentation

The Burden of Overactive Bladder in Menopausal and Post-Menopausal Women: Results from OAB-Poll **Lodowski N**, Chen C, Bavendam T, **Bell J, Coyne K**

NCDEU 2011 New Clinical Drug Evaluation Unit

June 13 - June 16, 2011, Boca Raton, FL, USA

Panel Presentation

The Automation of Cognitive Testing in Clinical Trials **Chairs: Keith Wesnes**, PhD, Practice Leader, United BioSource Corp. and Amy Veroff, PhD, Medical and Scientific Affairs, i3 **Panelists:** Alan Boyd, PharmD, CNS Vital Signs; Andrew Blackwell, PhD, Cambridge Cognition; Paul Maruff, PhD, CogState

Poster Presentations

Attention Deficits Play a Major Role in the Profile of Cognitive Dysfunction in Parkinson's Disease **Wesnes K, Miller D**, Allcock LM, Eccles M, Robinson L, Stutt A, Burn DJ

Comparing Measures of Negative Symptoms of Schizophrenia in Clinical Trials: The Investigators' View **Daniel D, Dries J**, Velligan D, Greco N, Bartko JJ

Improvement of Clinicians' Assessments of Patients at Inclusion Visits in an MDD Clinical Trial **Busner J**, Montgomery SA, **Daniel D, Sachs G**

Understanding of Influence on Placebo Response by Investigators and Site Staff in CNS Clinical Trials **Daniel D, Dries J**, Loebel A, Cucchiaro J

DIA 2011 - 47th Annual Meeting

June 19 - June 23, 2011, Chicago, IL, USA

Symposium Chair

Critical Issues Related to Evidence Generation, Evaluation, and Standards for Comparative Effectiveness Research **Chair:** Bryan R. Luce, PhD, MBA, Director, Pragmatic Approaches to Comparative Effectiveness (PACE)

Symposium Speakers

Gaining Efficiency, Flexibility and Applicability for CER Trials: The READAPT (REsearch in ADaptive Methods for Pragmatic Trials) Study Design **Jack Ishak**, PhD, Director, Biostatistics and Data Analysis, United BioSource Corp.

Are Any Data Better Than No Data? Considerations for Use of Mixed Methods of Data Collection of Patient-reported Outcomes in Clinical Trials **Sonya Eremenco**, MA, e-PRO Manager, United BioSource Corp.

Session Chairs

Natural History of Disease: An Often Overlooked Study Concept **Annette Stenhagen**, DrPH, FISPE, SVP Safety, Epidemiology, Registries & Risk Management, United BioSource Corp.

Risk Management Assessment Reports: The New Medical Writing Challenge **Michael D. Hoffman**, MS, Senior Director, Medical Writing and Regulatory Operations, United BioSource Corp.

Session Speakers

Can Pharmaceutical Companies Successfully Outsource Regulatory Strategy? Critical Success Factors and Case Studies **Mark Ammann**, PharmD, VP, Regulatory Affairs, United BioSource Corp.

Trends in REMS Evaluations **Kelly D. Davis**, MD, VP, Safety, Epidemiology, Registries & Risk Management, United BioSource Corp.

MASCC/ISOO 2011 International Symposium

June 23 - June 25, 2011, Athens, Greece

Poster Presentation

Retrospective Study to Evaluate the Patient Time Burden Associated with Outpatient Red Blood Cell Transfusions in Cancer Patients Receiving Chemotherapy **Corey-Lisle P**, Shrey S, Collins H, **Payne K, Desrosiers M-P**, Freier K

FOCUS ON:

The New Era of Evidence

The Importance of Planning Ahead For Indirect and Mixed Treatment Comparisons Analyses

By Kyle Fahrbach, PhD, Senior Biostatistician and Risha Gidwani, DrPH, Stanford Hospital

Authors' note: The purpose of this article is to introduce the concept of indirect and mixed treatment comparisons and communicate recommended practices for the pharmaceutical industry to follow when setting up clinical trials. The design and execution of clinical trials have a substantial bearing on the credibility of indirect and mixed treatment comparisons analyses.

Overview

Imagine this scenario: You have just invested millions of dollars in a Phase III trial of a new treatment. In the trial, you have compared your new treatment with placebo. The drug is approved, and there is much rejoicing.

Soon thereafter, a major regulatory agency or insurer requests a health economic analysis comparing your treatment against other active therapies approved for the same indication. “No problem!” you say, as you are aware that mixed treatment comparison (MTC) methodologies allow you to draw conclusions about the relative efficacy of therapies that have not been directly compared in a single randomized controlled trial (RCT). Specifically, MTC methods allow you to compare your treatment to other treatments that also compared themselves to your comparator treatment (in this example, placebo).

Sadly, soon thereafter, you find that “No problem!” has turned into “Big problem!”, as the active comparators of greatest interest have no trials comparing themselves to placebo. Other problems arise when you realize studies of other relevant comparators have defined response differently than you did in your Phase III clinical trial, or measured their outcomes at a different timepoint, or looked at a substantially different patient population. In these situations, a mixed treatment comparisons analysis is either infeasible, or requires major assumptions to be made that undermine the credibility of the enterprise.

This scenario is far from theoretical; UBC has seen multiple clients experience exactly this sort of pain. In this article we briefly review the theory behind mixed treatment comparison meta-analyses and provide a list of items that should be strongly considered when constructing a Phase III trial, if trustworthy comparative health economic analyses are desired after the drug is approved.

Mixed Treatment Comparisons: Introduction

At the heart of mixed treatment comparisons are indirect comparisons — comparison of two treatments (Figure 1, A and B) through a common comparator. If one trial examines Treatment A vs. Placebo, and another, Treatment B vs. Placebo, after one makes some (generally reasonable) assumptions, one can estimate the effect of Treatment A vs. Treatment B.

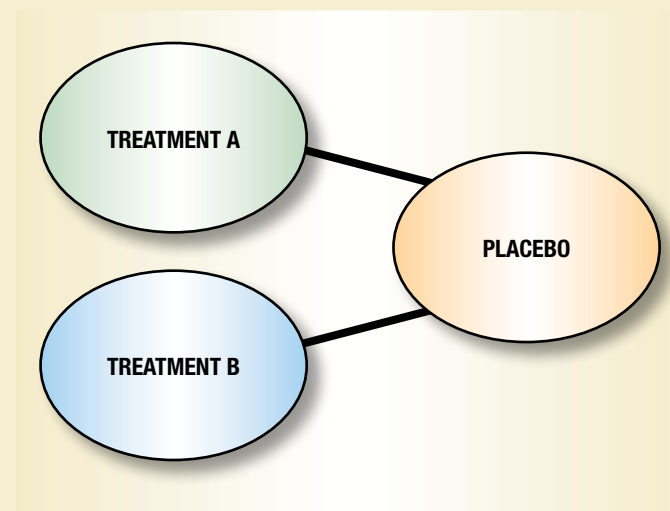


Figure 1: An Indirect Treatment Comparison

Complex statistical methods are not necessary to do this comparison; indeed, there is a long history of conducting indirect comparisons using classical methods. However, consider an evidence network, like that in Figure 2, which has multiple treatments and many relationships are examined through a mix of direct and indirect evidence.

Estimation of relative treatment efficacy through mixed treatment comparisons requires more advanced statistical techniques; in particular, Bayesian Markov Chain Monte Carlo (MCMC) models that have been developed over the last ten years. These models provide both estimates of absolute efficacy and relative effects, simultaneously, for all possible treatments and treatment comparisons. These estimates can be used as inputs into health-economic models evaluating the relative cost-effectiveness of Treatment A vs. Treatment B vs. Treatment C, etc. However, there are a host of assumptions necessary to conduct indirect treatment comparisons (ITCs) and MTCs, and the more studies included, the less reasonable the assumptions may be.

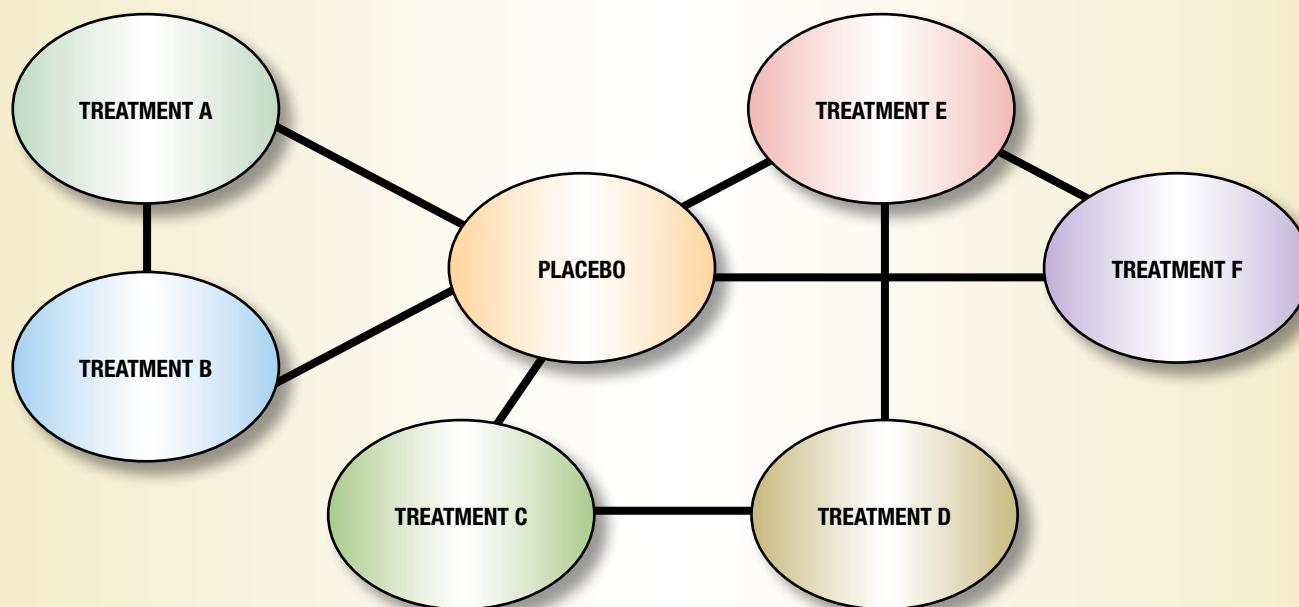


Figure 2: A Mixed Treatment Comparison

Assumptions

Indirect and mixed treatment comparisons rest on three main assumptions: heterogeneity, similarity, and consistency. In essence, these assumptions reduce to the following:

- We assume that any given underlying relationship is relatively consistent across the patient populations examined
- We assume that the patient populations and outcome definitions are similar in different studies
- We assume that the direct evidence is estimating the same underlying relationship as the indirect evidence

Taken as a whole, we are assuming that in any given study of A vs. B, if treatment “C” were added to the trial, we could predict what the A vs. C and B vs. C results would have been in that trial.

While ITCs and MTCs provide a useful statistical technique for evaluating therapies that have not been directly compared, one major limitation is that patients have not been randomized to one of the treatments in the evidence network (but rather have been randomized to one of the treatments within an individual study). Thus, MTCs suffer from the same potential biases as observational studies, are inferior to randomized trials, and are, consequently, treated as such by regulatory agencies. Of course, it is rare for a randomized trial to investigate every treatment of interest for a given indication, so MTCs will continue to play an important role in the evaluation of relative treatment efficacy and safety.

Planning for an MTC

Companies interested in comparing the efficacy and safety of their products to others must generally consider the MTC

approach in lieu of personally conducting RCTs against any and all other active treatments. However, an MTC will be difficult to conduct unless there is similarity (or, preferably, absolute equivalence) on the following factors:

- **Treatment choice.** If your trial compares your treatment to a drug that no one else has compared themselves to, in your patient population of interest, an MTC is impossible without making some very strong (and questionable) assumptions. This can happen when conducting subgroup MTCs, in which a trial looks at both treatment naïve and non-naïve subjects and uses a comparator drug that is only employed in a treatment naïve population. An MTC connecting that treatment to others, in the non-naïve population, may not be possible.
- **Treatment delivery.** If one trial uses 100mg daily of Treatment C as the comparator, and another examines 250mg daily of Treatment C, then unless one assumes there is no dose effect, Treatment C cannot be used as a common comparator for indirect comparisons.
- **Patient population.** The greater the difference between the patient population in one company’s trials and other trials, the less reasonable it is to assume that the relative efficacy found between two treatments in one trial would be the same as in the other, if it had investigated the same treatments.
- **Outcome definition.** If one company’s trials define response in a way markedly different than other trials, an MTC may very well be impossible. The justification that “We are measuring response better in our trial.” may be true; however, if that choice prevents the ability to make indirect comparisons, it needs to be reconsidered, and

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perhaps multiple definitions of response should be used.

- **Timepoints.** If one trial stops at three months, and all others report data at six months, the MTC is difficult to conduct unless one makes the (possibly unreasonable) assumption that relative efficacies do not differ between those time points.

When these assumptions are violated, MTCs become difficult to conduct without making additional assumptions — assumptions that will often be questioned by key opinion leaders and the agencies evaluating the conclusions of the analysis.

Conclusion

Mixed treatment comparisons are becoming increasingly important as they provide regulatory agencies with an indication of the relative value of treatments within a therapeutic indication and as the need for high-quality inputs for health-economic analyses continues to grow. The success and validity of any mixed treatment comparisons meta-analysis depend on the extent to which the assumptions are met,

especially the degree to which there is similarity or equivalence in study design, patient populations, comparator treatments, outcome definitions, and time points measured. Pharmaceutical companies designing new

Mixed treatment comparisons are becoming increasingly important as they provide regulatory agencies with an indication of the relative value of treatments within a therapeutic indication and as the need for high-quality inputs for health-economic analyses continues to grow.

clinical trials have a responsibility to both themselves and the greater scientific community to set up studies to maximize the opportunity to compare their treatments with other treatments in a way that makes the fewest possible assumptions. In the absence of some standardization of analysis and reporting within therapeutic area, the ability to conduct MTCs is severely limited without making strong assumptions that may be challenged by regulatory agencies and others.

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Using Social Media to Enhance Patient Recruitment

By Abbe Steel, Executive Director of Trial Enhancement

With increasing numbers of people seeking health information online, Sponsors and contract research organizations (CROs) are using additional avenues of outreach to widen the recruitment funnel. Every unique online communication platform offers another way to reach and interact with potential patients, to support and inform patients, identify influencers who help inform patients, and make study information easily accessible.

Social networks can provide an excellent forum to generate awareness and drive potential patients to a study. With 152 million blogs on the Internet, 25 billion tweets sent in 2010,¹ and 1,200 Facebook communities that have been set up around chronic illnesses, the absence of an online presence can limit visibility and awareness for companies seeking to enroll patients in a study. Yet 38% of life sciences companies do not currently use social networks and have no plans to do so.²

The Internet has been an important source of medical information for multiple stakeholders (physicians, nurses, patients, caregivers, etc.). But interactive social media has changed the landscape for sharing and accessing medical information online. Not only that, but it has changed patient expectations — they want information quickly, and they want to be a part of the conversation.

Social Media in Action

What is social media? It's an umbrella term for media sharing, sociability, and dialogue. Social media includes blogs, podcasts, social networking sites, wikis, and media sharing platforms. Social media can be categorized into two types of outreach: user generated and paid. User generated content includes functionality to support user editing and contributions, rating or voting, and user comments. This type of forum can be an important part of a comprehensive media campaign by providing information on peer-to-peer forums. Paid social media includes banner ads on health websites, text advertisements, and search engine AdWords.

All social media tactics about a program or study should use the study name and brand to promote credibility and general awareness and to direct patients to a study website with an online screener. Examples of social media tactics to support clinical trials include:

- **Facebook:** U.S. hospitals have set up Facebook accounts that provide information about their services. Facebook offers multiple methods of outreach:

- Facebook study page
- Facebook advertising
- Study website links from advocacy group Facebook pages

- **YouTube:** Video overview of your program (i.e., upload 60-second TV spot to YouTube)
- **Twitter:** Have investigative sites create a study account and provide study updates.

Know Your Patients

The first step to determining if and how social media tactics may play a role in a patient recruitment program is an assessment of the target population. This involves analyzing how similar populations are engaging online — what information is being exchanged and how it is being communicated. For example, the Multiple Sclerosis community is widely known for its active social networks, which use online communities to share information on a wide range of topics, from comparing side effects to lifestyle tips. It is important to determine which groups, forums and networks matter most to your study's target population. For example, does your patient population belong to a Facebook page? Are they active in a patient advocacy group? Are they looking for a new treatment or drug delivery system?

One way to use social networks is to develop partnerships with top bloggers, social networkers, and forum moderators. There are individuals and companies that are seen over and over again talking about certain topics. They can have many followers and be quite influential. You want to know who they are and follow what they are saying. Placing advertising or content on a website with information that the potential patient is actively seeking can greatly impact awareness, credibility and recall association. An example of an advertisement that could be used on a blogger's site is a banner ad. A banner ad is an image that includes a short call to action and is linked to the study website.

Online Advertising

When creating content for online advertisements, consider the call to action, value proposition, and how to engage the Internet user. Here are some pointers for creating online advertisements to promote a study:

- Utilize a good set of keywords (medical and lifestyle) and compelling text
- Remember that clinical trials are not known to everyone
- People generally need to hear messages at least eight times to take action
- People browse the Internet — it takes many more ad impressions to get someone's attention
- If an ad is less "flashy" but more credible, medical and provides useful information, it will have a better response rate

FDA Guidelines

There are no current Food and Drug Administration (FDA), guidelines on the use of social media. The FDA has convened public hearings to collect information to begin crafting regulatory guidelines for the use of social media. Absent these guidelines, it is important for drug companies to follow the standard regulatory and legal approaches they use for other media. Because some social media limits Sponsor control over content, Sponsors should take into consideration the limitations of social networks, including the challenge of monitoring content for adverse events, the possibility of unbalanced information around risks and benefits, and avoiding information exchanges among trial participants. These challenges should not dissuade companies from implementing a social media campaign. If executed correctly, risks can be minimized and there is much to be gained.

Conclusion

Social media is only part of a widespread online media campaign. Tools like study websites, online screeners, and referral tracking software are essential to ensuring the success of any patient recruitment campaign. For all online media tactics, consistent monitoring and iterative adjustments will lead to optimized spending and results. Social media requires some initial investment and monitoring, but it offers an effective tool for Sponsors, CROs and patients to exchange and share information that will enhance recruitment, and, in the end, provide better care and access to patients.

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Retrospective Database Research and the Advent of the "Rolling Retrospective Study"

By Matthew W. Reynolds, PhD, Vice President, Epidemiology and Database Analytics and Beth Nordstrom, PhD, MPH, Director and Senior Epidemiologist

Regulatory agencies historically have relied heavily on 5bscientific evidence from randomized controlled trials to drive decisions, but in recent years, database studies have begun to have increasing influence in regulatory decision-making. The term "database" is a generic term that can refer to many different sources and types of data. In the area of pharmaceutical research, these could include medical claims databases, electronic medical records (EMRs), surveys,

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prescription databases, as well as others, including datasets that combine multiple data types such as medical claims data linked to EMR data.

The importance of employing retrospective database research has never been more clearly relevant in pharmaceutical research as it is in today's environment. Database publications continue to increase markedly over time for both claims database and EMR database research (yields from recent PubMed searches by five-year publication intervals are shown in Table 1). In addition to the increase in usage of these database resources, we have seen a tremendous effort in the incorporation of high quality methods to support these initiatives. Regulatory-based research initiatives such as the U.S. Food and Drug Administration's (FDA) Sentinel Initiative¹

Table 1

Year	Claims Database Publications (% increase/decrease from previous 5 years)	EMR Database Publications (% increase/decrease from previous 5 years)
2006–2010	8,962 (47%)	4,401 (152%)
2001–2005	6,102 (61%)	1,749 (171%)
1996–2000	3,787 (55%)	646 (145%)
1991–1995	2,442 (124%)	264 (230%)
1986–1990	1,090 (102%)	80 (-16%)
1981–1985	538 (38%)	95 (-55%)
Pre-1981	390	209

and The European Network of Centres for Pharmacoeconomics and Pharmacovigilance (ENCePP[®])² led by the European Medicines Agency (EMA), as well as groups like the Observational Medical Outcomes Partnership (OMOP)³ have been created to focus their efforts in the area of epidemiological and safety-based database research methods and study conduct.

Pharmaceutical researchers in the areas of epidemiology, drug safety, health economics, and outcomes research have increasingly leveraged retrospective database studies as efficient ways to confirm research hypotheses, document treatment patterns, examine clinical outcomes, and understand economic outcomes in real-world data via observational methodologies. The number of available databases has also increased over time, and the variety and complexity of observational methods has expanded and become more acceptable as a companion, and for some purposes even a replacement, for evidence from randomized controlled trials.

One of these notable changes in the approach to retrospective database research has been an increasing practice of using these data in a prospective manner. It is true that the overwhelming use of these databases, historically, has been to conduct purely retrospective studies (e.g., retrospective cohort studies, cross-sectional studies, and/or case-control studies), where the data are already existing and the information on clinical events, exposures, and follow-up time is already determined and existing in the data. Prospective studies, on the other hand, enroll patients, collect new data, and then follow the patients over time, examining the data for occurrences of outcomes of interest. Prospective studies allow novel data collection and use of current and future data, while retrospective studies require the use of already collected data but are significantly quicker and less expensive to conduct.

A hybrid approach has now become an increasingly more prevalent and attractive option as researchers attempt to leverage retrospective data as part of prospective scientific endeavors. Since there is no industry accepted term for this type of study approach, nor any results from a search of the medical literature via MedLine or a similar search of the Internet, we refer to it as a "Rolling Retrospective Study." The aim of a rolling retrospective study (RRS) is to use retrospective databases for prospective studies

of future treatment patterns and risk of clinical outcomes. Using databases that already exist (e.g., a medical claims database), scientists design a protocol to examine a particular research question such as whether Drug A is associated with an increased risk of Safety Event X. The protocol is designed to be implemented in the retrospective database, but then is also employed at pre-specified future time points (e.g., every six months) as new data are accrued in the database of interest. Hence, the analyses are planned to be conducted in the future on data that do not currently exist, but that are retrospective data at the time of each analysis.

During the first round of analysis in an RRS, the programming for data management and analysis is developed. This first round may occur either after accrual of some minimum number of patients of interest in the database or, in the case of a newly approved drug where insufficient users have accrued, using similar patients such as those treated with similar drugs for the same indication as the drug of interest.

For all future rounds of analysis, given that the analysis plans and programming have already been completed, results can typically be produced very quickly after each data update (outside of the time often needed to clean and finalize the data in these databases). Additionally, the advent of analytical tools like SAEftyworks®, UBC's web-based software that allows rapid investigation and understanding of observational databases, allow for efficient real-time analytics in a matter of hours or days after the data are available.

As the quantity and quality of available data sources increase, and methods are developed and implemented to improve study quality (e.g., database coding algorithm validation via OMOP and mini-sentinel initiative), we anticipate that the RRS will continue to gain in both acceptability and frequency of usage for post-launch activities such as

pharmacovigilance safety studies, comparative effectiveness, and cost-effectiveness studies.

For more information, please contact
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References

¹U.S. Food and Drug Administration's Sentinel Initiative — Transforming How We Monitor the Safety of FDA-Regulated Products. <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm>. Accessed on April 18, 2011.

²The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®). <http://www.encepp.eu/>. Accessed on April 18, 2011.

³<http://omop.fnih.org/>

Observational Medical Outcomes Partnership (OMOP): A Platform to Advance the Methods for Safety Signal Assessment

By Jon Morris, MD, Vice President, Evidence Development

The next generation of safety signal refinement, performed in the assessment period prior to the definition and launch of confirmatory studies, will be analyses performed on observational databases, such as those composed of administrative claims and electronic health records. There are many reasons that these types of data will be increasingly utilized for safety research, including the fact that the data is “real world” and not as confounded by selection bias (as in randomized controlled clinical trials), the large patient population (usually measured in millions of patients), the geographic and demographic diversity represented in the data, and the opportunity to analyze patients through a series of healthcare settings over time.

However, there are many challenges in the utilization of observational data for drug safety analysis, most of which relate to the fact that the data is being repurposed for safety analyses. Specific challenges include data volume/size, privacy and confidentiality, medical concept codings and mappings (i.e., translating from “charge capture” language to “drug safety” language), and the need for a thorough understanding of the inherent strengths and limitations of the data source itself. In addition, unlike previous generations of drug safety data where there is an explicit drug-event association recorded for a given patient, observational databases capture the totality of healthcare encounters independent of any particular product-adverse event designation. As an example, in spontaneous reporting safety systems, a patient that receives a vaccine and develops a seizure within four hours will likely have a specific adverse event report that identifies the biopharmaceutical agent involved (in this case, the vaccine), a specific term for the adverse event term from an industry accepted adverse event dictionary (MedDRA),

the timing of the adverse event (AE) with the administration of the agent, an assessment of the severity of the AE, and an attempt to identify other potential causal or contributing events or agents that may have influenced the AE, among other things. Administrative claims data, captured on that same vaccine-seizure encounter, will likely show that a vaccine was administered in an office setting (CPT code for injection), and another charge was generated that day from an emergency room (ER) visit (there is a clue), an ICD-9 code for seizure was assigned to the ER visit (second clue), and anti-epileptic medication was administered in the ER setting (third clue).

What is OMOP?

The Observational Medical Outcomes Partnership (OMOP)¹ is a public-private partnership consisting of resources from the pharmaceutical industry, academic institutions, non-profit organizations, the Food and Drug Administration (FDA), and other federal agencies, which serves public health by testing whether multi-source observational data can improve our ability to assess drug safety and benefits.

Specific OMOP research objectives include the following:

- A systematic approach to objectively assess the coverage of certain healthcare conditions in different observational databases
- The creation and testing of common definitions for specified Health Outcomes of Interest
- The development of a common data model as a foundation for observational database transformation prior to data analysis

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FOCUS ON:

The New Era of Evidence

Observational Medical Outcomes Partnership (OMOP)

continued from page 23

- A systematic assessment of various analytic methods which may be used to better detect drug-outcome pairs of interest when they are represented in observational data

Multiple methods for signal assessment have been identified and have undergone empirical testing to measure performance with respect to their ability to detect “safety signals” in various observational data sets (See Table 1). OMOP research has also benefited greatly from the initial and ongoing development of a high fidelity simulator (developed by United Biosource Corporation) to test and assess the performance of various analytic methods.

The various analytic methods identified in Table 1 employ different inherent mechanisms to control for confounding, or to take into account other parameters that may be reflected in the data which could, in part, explain observed differences in the population exposed to the drug. As a humorous example, one could observe (hypothetically) in a healthcare database that contains nutrition and disease, that there is a positive association of ingestion of peanut butter & jelly (PB&J) sandwiches with freedom from Alzheimer’s disease, because an analyst notes that as patients decrease their ingestion of peanut butter and jelly sandwiches, the

likelihood of Alzheimer’s disease increases. In fact, an enthusiastic analyst could attempt to calculate the protective index and “freedom from Alzheimer’s disease” conferred by PB&J sandwiches. The major confounding variable omitted from that analysis is patient age – young patients eat lots of PB&J sandwiches, but young patients are less likely to develop Alzheimer’s disease.

While the previous example is extreme and designed to illustrate a point, in reality, confounding by age, disease state, temporal relationship (the timing and sequencing of drug and condition occurrence), and other biases reflected in healthcare data (insurance coverage, regional variation, physician and patient preferences) may be critical elements that influence and are reflected in the distribution of drug and medical condition relationships within observational data. These underlying biases can influence the subsequent calculation of an association or a relationship between a drug safety product-outcome pair of interest, and must be taken into account as a known limitation of the analyses being performed.

There is some significant disagreement as to the manner of analysis and the weight of evidence generated by these analytic routines in observational data. Data analysis with no control for confounding and all by all comparisons (“data mining” or “signal detection”) runs the risk of the greatest number of evaluable drug-outcome pairs of interest identified in the course of an analysis, due to the potential inclusion of large numbers of false positives in the results of a given study. While interesting from a theoretical research standpoint,

Table 1 From <http://omop.fnih.org/MethodsLibrary>

Method Name	Parameter Combinations	Release Date
Disproportionality Analysis (DP)	112	15-Mar-10
Univariate Self-controlled Case Series (USCCS)	64	2-Apr-10
Observational Screening (OS)	162	8-Apr-10
Multi-set Case Control Estimation (MSCCE)	32	16-Apr-10
Bayesian Logistic Regression (BLR)	24	21-Apr-10
Case-control Surveillance (CCS)	48	2-May-10
IC Temporal Pattern Discovery (ICTPD)	84	23-May-10
Case-crossover (CCO)	48	1-Jun-10
HSIU Cohort Method (HSIU)	6	8-June-10
Maximized Sequential Probability Ratio Test (MSPRT)	144	25-Jul-10
High-dimensional Propensity Score (HDPS)	144	6-Aug-10
Conditional Sequential Sampling Procedure (CSSP)	144	30-Aug-10
Statistical Relational Learning (SRL)		
Incident User Design (IUD-HOI)		

this approach is not always practical from an operational standpoint, where hundreds of false positive product-outcome pairs could create an alarming amount of evaluation work and quickly overwhelm a drug safety team.

At the other extreme, observational data has long been used by the pharmacoepidemiology community to perform various types of studies comparing treatments and treatment outcomes. These approaches, usually driven by a formal study protocol, assess a particular drug-outcome relationship, and usually include some attempt to control for confounding. This approach requires more time and effort, and usually requires custom analytic coding to capture all of the subtleties and nuances of the data. Controlling for confounding requires medical drug and disease knowledge, as well as the introduction of subtleties of epidemiological methods which can influence the results obtained in a signal confirmation activity.

In between “signal detection” and a formal pharmacoepidemiology study is signal assessment (also called “signal evaluation” or “signal refinement”). These activities are intended to provide additional evidence for a product-outcome pair of interest, including:

- Baseline and natural history of the population of interest
- Information about a comparator population of interest
- Incidence and prevalence of conditions of interest in the population

Historically observational data was not used for this kind of activity, as it was too unwieldy or took too long to perform studies. With the advances in clinical informatics in the last 10 years, combined with the some of the principles being evaluated and implemented within OMOP environment, computer systems that perform database automation analytics can now bring the timely utilization of observational data into the signal refinement phase of drug safety.

Why do we need OMOP?

Prior to OMOP, safety scientists and the pharmacoepidemiology community disagreed on the relative merits of various observational databases, the need to transform observational data prior to analysis, how to best define common Health Outcomes of Interest, how to best approach the taxonomy mapping and coding issues, and fundamentally which analytic methods (and what parameters for each of those methods) yielded the “best” results. OMOP has systematically assessed each of these parameters in isolation, attempting to remove the bias and confusion created when one tackles a problem as inherently complex as “drug safety in observational data.”

The combined expertise of industry, the FDA, and collaborating organizations, including UBC, has brought a diverse set of stakeholders to the table and crafted a research agenda that informs our use of these incredibly valuable and

complex resources. OMOP promotes transparency by placing all information of interest in the public domain as quickly as possible. A publicly accessible website is utilized to communicate the research and maintain awareness for consumers, patients, and providers.

Conclusion

The Observational Medical Outcomes Partnership is a public-private partnership designed to identify, study, measure, and compare many of the essential analytic components necessary for the systematic use of observational databases applied in the

context of a drug safety system. Utilized in the right way with the right tools and the right framework, observational data can be rapidly and systematically used to generate additional evidence which furthers our understanding of biopharmaceutical product safety.

At this time, United BioSource Corporation is the only company with both a commercially marketed software product (SAEfetyWorks®) consistent with the OMOP common data model, and a full-service team of epidemiologists and database analysts to execute these types of projects and analyses for our clients.

For more information, please contact
Jon.Morris@unitedbiosource.com.

Additional Resources on OMOP

- Common Data Model
 - <http://omop.fnih.org/CDMandTerminologies>
- Standardized Terminology
 - <http://omop.fnih.org/Vocabularies>
- Data Characteristics Tools
 - OSCAR — <http://omop.fnih.org/OSCAR>
 - NATHAN — <http://omop.fnih.org/NATHAN>
- Health Outcomes of Interest Library
 - <http://omop.fnih.org/HOI>
- Methods Library
 - <http://omop.fnih.org/MethodsLibrary>
- Simulated Data
 - <http://omop.fnih.org/OSIM>

OMOP promotes transparency by placing all information of interest in the public domain as quickly as possible.

References

¹<http://omop.fnih.org/>

Recent Presentations

PharmaSUG 2011

May 8 - May 11, 2011, Nashville, TN, USA

Oral Presentations

Analytical Methods for Health Outcomes and Safety Surveillance

Juliane Mills, Project Manager, Safety, Epidemiology, Registries & Risk Management, United BioSource Corp.

Epidemiology and Risk Management and its Impact on Pharmaceutical Analysis **Annette Stenhagen**, DrPH, FISPE, Sr. Vice President, Safety, Epidemiology, Registries & Risk Management, United BioSource Corp.

From SAP to BDS: The Nuts and Bolts Nancy Brucken, Principal Statistical Programmer, i3 Statprobe; **Paul Slagle**, Manager, Clinical Programming, United BioSource Corp.

Keeping Patients on Schedule, the Art of Visit Windows and Cycle Slotting **Paul Slagle**, Manager, Clinical Programming, United BioSource Corp.

Programmer's Introduction to Survival Analysis Using Kaplan Meier Methods **John Ventre**, Principal Programmer, United BioSource Corp.; **Lisa Fine**, Sr. Clinical Programmer / Analyst, United BioSource Corp.

Quick - Ready Set Retain, and Maybe Reset **Lisa Fine**, Sr. Clinical Programmer / Analyst, United BioSource Corp.

13th International Myeloma Workshop

May 3 - May 6, 2011, Paris, France

Poster Presentation

Association of Health-Related Quality of Life (HRQOL) with Bone Disease in Multiple Myeloma **Pashos CL**, Durie BG, Rifkin RM, Terebello HR, Abonour R, Toomey K, Mehta J, Shah JJ, Fonseca R, Narang M, Casparetto C, Sullivan KA, Street TK, Khan AM

ARVO 2011

May 1 - May 5, 2011, Fort Lauderdale, FL, USA

Poster Presentation

Normative Comparison of Patient-Reported Outcomes in Noninfectious Intermediate or Posterior Uveitis Lightman S, Lowder C, Naik R, **Rentz A**, Kowalski J, Foster S, Belfort R, **Revicki D**, Whitcup S

CBI's 3rd Annual Bio/Pharmaceutical Drug Safety Forum

April 27 - April 28, 2011, Philadelphia, PA, USA

Oral Presentation

A Proactive, Focused and Transparent Approach to Overcome Risks Associated with Missing Data **Robert Sharrar**, Executive Director, Safety and Risk Management, United BioSource Corp.; **Jon Morris**, MD, Vice President, United BioSource Corp.

IAGG's VII European Region International Congress (International Association of Gerontology and Geriatrics)

April 14 - April 17, 2011, Bologna, Italy

Symposium

Computerized Programs for the Diagnosis and Improvement of MCI: From Feasibility to Reality **Keith Wesnes**, PhD, Practice Leader, United BioSource Corp.

2011 ACCA Cardiovascular Administrators' Leadership Conference

April 13 - April 15, 2011, Chicago, IL, USA

Poster Presentations

Economic Modeling of New Stent Platforms to Evaluate Cost Effectiveness: Analysis of the TAXUS Liberté versus TAXUS Express Stents in Small Vessel Coronary Stenting Turco MA, **Kansal AR**, **Stern S**, Amorosi, SL, Underwood PL, **de Lissovoy G**, Dawkins KD

Evaluating Cost Effectiveness Using an Economic Model: Analysis from the TAXUS ATLAS Long Lesion Trial Turco MA, **Kansal AR**, **Stern S**, Amorosi SL, Underwood PL, **de Lissovoy G**, Dawkins KD

World Drug Safety Congress America 2011

April 12 - April 15, 2011, Boston, MA, USA

Speaker

A Proactive, Focused and Transparent Approach to Overcome Risks Associated with Missing Data **Jon Morris**, Vice President, United BioSource Corp.

AAN 2011 Annual Meeting

April 9 - April 16, 2011, Honolulu, HI, USA

Poster Presentations

Costs Associated with Lost Productive Time Among Working Adults with Chronic and Episodic Migraine in the United States and Canada Maglinter GA, Bloudek LM, **Stokes ME**, Wells L, Blumenfeld AM, Lipton RB, Buse DC, Becker WJ, **Wilcox TK**

Healthcare Resource Use and Costs Among Patients with Chronic and Episodic Migraine in the United States **Stokes ME**, Varon SF, Sullivan SD, Blumenfeld AM, Lipton RB, Goadsby PJ, **Wilcox TK**

SAS Global Forum 2011

April 4 - April 7, 2011, Las Vegas, NV, USA

Oral Presentations

Order, Order Please: Sorting Data Using PROC REPORT **Lisa Fine**, Sr. Clinical Programmer / Analyst, United BioSource Corp

Ready Set Retain, and Then Maybe Reset **Lisa Fine**, Sr. Clinical Programmer / Analyst, United BioSource Corp.

ACC.11 - 60th Annual Scientific Session & Expo

April 2 - April 5, 2011, New Orleans, LA, USA

Poster Presentation

Economic Modeling of Cost-Effectiveness for New Stent Platform Designs: The TAXUS Element (ION) Stent Compared to the Bare Metal Express Stent in Small Vessels Modeled to Determine Cost Efficacy Turco MA, Cannon LA, Amorosi SL, **Stern S**, Stivland T, Underwood P, **de Lissovoy G**, **Kansal AR**

2011 13th International Congress on Schizophrenia Research (ICOSR)

April 2 - April 6, 2011, Colorado Springs, CO, USA

Workshop Presentation

What are the Best Approaches for Achieving Accurate and Reliable Ratings in International Schizophrenia Clinical Trials? **Daniel D**, Lindenmayer J-P, Opler M, Williams J, Alphas L, Loebel A

Poster Presentation

Internal Consistency of Ratings Improve and Error Rates Decrease with Ongoing Monitoring and Feedback in an International Schizophrenia Clinical Trial **Daniel D**

Harvard University Program in Ethics & Health

March 29 - March 29, 2011, Boston, MA, USA

Guest Speaker

Allocating Resources Under Extreme Scarcity: A Cure for QALYphilia **J. Jaime Caro**, MDCM, FRCP, FACP, Senior Vice President, United BioSource Corp.

DIA 23rd Annual EuroMeeting

March 28 - March 30, 2011, Geneva, Switzerland

Oral Presentations

Harmonising the Final FDA Patient-Reported Outcomes Guidance and the EMA "Points to Consider" Document - What is the Best Way Forward? **Ingela Wiklund**, PhD, Senior Research Leader, United BioSource Corp.

Collaborative Efforts for Developing Patient-Reported Outcome Tools - Examples, Opportunities, Challenges **Asha Hareendran**, PhD, Senior Research Scientist, United BioSource Corp.

26th International Conference of Alzheimer's Disease International

March 26 - March 29, 2011, Toronto, Canada

Poster Presentation

Regional Estimates for Prevalence of Apolipoprotein e (APOE) e4 Carrier (Heterozygotes and Homozygotes) Among Patients Diagnosed with Alzheimer's Disease: a Meta-Analysis **Ward A**, **Crean SM**, **Mercaldi CJ**, **Collins JM**, Boyd D, Cook MC, Arrighi HM

Alliance for Aging Research Educational Lunch Briefing — The Silver Book: Thrombosis Briefing

March 23, 2011, Washington, DC, USA

Speaker

Cost Implications of Atrial Fibrillation, Stroke and VTE **J. Jaime Caro**, MDCM, FRCP, FACP, Senior Vice President, United BioSource Corp.

26th Annual EAU Congress

March 18 - March 22, 2011, Vienna, Austria

Poster Presentation

The Burden of Urinary Urgency Incontinence (UUI): Results from EpiLUTS
Coyne KS, Kvasz M, **Ireland A**, Milsom I, Chapple C, Kopp ZS

Visiongain's 6th Annual Pharmacovigilance

March 16 - March 17, 2011, London, UK

Oral Presentations

Pharmacovigilance During the Pre-Approval Phases: An Evolving Pharmaceutical Industry Model and Key Transition Between Pre and Post Marketing Safety in the EU **Veronique Basch**, PharmD, Executive Director Safety, Europe

2nd Annual PRO Consortium Workshop

March 15, 2011, Silver Spring, MD, USA

Panel Discussion

Responder Definition and Interpretation of Scores Using Cumulative Distribution Functions **Panelists: Kathleen W. Wyrwich**, PhD, Sr. Research Leader, United BioSource Corp.; Lisa A. Kammerman, PhD, Office of Biostatistics, CDER, FDA; Joseph C. Cappelleri, PhD, MPH, Sr. Director, Biostatistics, Pfizer

Oral Presentation

Selection and Implications of Different Recall Periods for PRO Endpoints
Dennis A. Revicki, PhD, Senior VP, Scientific Affairs and Sr. Research Leader, United BioSource Corp.

DIA / FDA CDER / CBER Computational Science Annual Meeting

March 14 - March 15, 2011, Arlington, VA, USA

Oral Presentation

Innovative Methods in Comparative Effectiveness Research **Jon Morris**, MD, Vice President, United BioSource Corp.

10th International Conference on Alzheimer's & Parkinson's Diseases (AD/PD)

March 9 - March 13, 2011, Barcelona, Spain

Oral Presentation

Attention Deficits Play a Major Role in the Profile of Cognitive Dysfunction in Parkinson's Disease **Wesnes K**, **Miller D**, Allcock L, Stutt A, Eccles M, Robinson L, Burn D

Poster Presentations

Country Differences in Assessing UPDRS Part III **Kott A**, **Swartz J**

Use of Biomarkers to Identify Prodromal Alzheimer's Disease: The Role of Cognitive Function Assessment **Wesnes K**

The Aging Cognition Evaluation (ACE) CSF Registry; 2011 Update **Flax J**, Lotzof P, Harper M, Marks C, **Wesnes K**

In-Study Ratings Surveillance: Its Impact on Data Quality in Global AD Trials
Miller D, **Samuelson P**, **McNamara C**, **Young A**

8th Annual ENETS Conference

March 9 - March 11, 2011, Lisbon, Portugal

Poster Presentation

Overall Survival (OS) Analysis of Sunitinib (SU) After Adjustment for Crossover (CO) in Patients with Pancreatic Neuroendocrine Tumors (NET)
Ishak J, Valle J, Van Cutsem E, Lombard-Bohas C, Ruzniewski P, Sandin R, Korytowsky B, **Proskorovsky I**, Chao R, Raymond E

CRT 2011

February 27 - March 1, 2011, Washington, DC, USA

Poster Presentations

Evaluating Cost Effectiveness Using an Economic Model: Analysis from the TAXUS ATLAS Long Lesion Trial **Turco MA**, **Kansal AR**, **Stern S**, Amorosi SL, Underwood PL, **de Lissovoy G**, Dawkins KD

Economic Modeling of New Stent Platforms to Evaluate Cost Effectiveness: Analysis of the TAXUS Liberte versus TAXUS Express Stents in Small Vessel Coronary Stenting **Turco MA**, **Kansal AR**, **Stern S**, Amorosi SL, Underwood PL, **de Lissovoy G**, Dawkins KD

CBI's 7th Annual Summit on Late Phase Research

February 23 - February 24, 2011, London, UK

Opening Address

The Increasingly Global Reach of Late Phase Studies — What Does it Mean for Sponsors and CROs? **Hazel Wohlfahrt**, Executive Director, EU Site Management & Monitoring, United BioSource Corp.

ISCTM 7th Annual Scientific Meeting and 2011 National Mental Health Research-to-Policy Forum

February 21 - February 23, 2011, Washington, DC, USA

Working Group Sessions

Suicidality Assessment **Co-Chairs: Adam Butler**, AVP, Client Services, United BioSource Corp.; **Michelle Stewart**, PhD, Director, Pfizer

Negative Symptoms **Co-Chairs: Stephen Marder**, MD, Director, Dept. of Veterans Affairs; **David Daniel**, MD, SVP, Chief Medical Officer, United BioSource Corp.

Poster Presentations

Comparing Measures of Negative Symptoms in Clinical Trials: The Investigators View **Daniel D**, Velligan D, Greco N, Bartko J

Is An In-Study Surveillance Program Effective at Reducing Error Rates for Both Experienced and Novice Raters? **Miller D**, **McNamara C**, **Samuelson P**, **Mulder D**, **Young A**

A Comparison of the Performance of Japanese and English Volunteers on the CDR System **Wesnes K**

2011 SRNT 17th Annual Meeting

February 16 - February 19, 2011, Toronto, Canada

Oral Presentation

Using Discrete Event Simulation (DES) to Evaluate the Long-Term Impact of Smoking Cessation Interventions **Xenakis J**, **Marton JP**, **Revankar N**, **Getsios D**, **Willke RJ**, **Li Q**, **Ishak KJ**, **Caro JJ**, **Zou KH**

6th Annual Pricing, Reimbursement & Market Access in Pharma

January 19 - January 20, 2011, Barcelona, Spain

Speaker

HTA Evaluations - Understand Fully the System of Funding **Floortje van Nooten**, MSc, Research Scientist

DIA's Pharmacovigilance and Risk Management Strategies 2011

January 9 - January 12, 2011, Washington, DC, USA

Program Chairpersons & Session Facilitators

Annette Stemhagen, DrPH, FISPE, Senior Vice President, Safety, Epidemiology, Registries and Risk Management, United BioSource Corp. and **Wenda K. Brennan**, RPh, Director, Pharmacovigilance, United BioSource Corp.

Welcome and Opening Remarks

Wenda K. Brennan, RPh, Director, Pharmacovigilance, United BioSource Corp.

Sessions

Analysis of Health Care Data **Session Chairperson: Wenda K. Brennan**, RPh

Industry Perspective - Observational Medical Outcomes Partnership
Speaker: Jon Morris, MD, Vice President, United BioSource Corp.

Ask the Experts — Question and Answer Panel **Moderator: Wenda K. Brennan**, RPh

What Are REMS and RMPs - The Differences Between the Requirements for REMS and RMPs **Speaker: Robert Sharrar**, MD, MS, Exec. Dir., Safety, Epidemiology, Registries and Risk Management, United BioSource Corp.

Beyond Spontaneous Reporting **Session Chairperson: Annette Stemhagen**, DrPH, FISPE

Maximizing the Utility of Observational Studies **Speaker: Kelly D. Davis**, MD, Vice President, Safety, Epidemiology, Registries and Risk Management, United BioSource Corp.

NEWS BRIEFS

UBC Welcomes New Visiting Scientists

The UBC Visiting Scientist program was developed to encourage collaboration between UBC scientific staff and methodological or therapeutic area experts in the design and execution of studies. The goal is to enhance our value and better serve client needs. The following experts have recently joined the program.

■ **Olivier Chassany, MD, PhD**, is a Professor of Medicine and Medical Head of the Department of Clinical Research and Development of Parisian Hospitals. He has developed patient-reported outcomes (PRO) measures in irritable bowel syndrome and dyspepsia and quality of life questionnaires for individuals living with HIV. He is involved in international working groups on PROs: European Regulatory Issues on Quality of Life Assessment and COCHRANE Quality of Life Methods Group. Dr. Chassany is the Associate Editor of the journal *Health Outcomes Research in Medicine* and active in ISOQOL, ISPOR and DIA.

■ **Trevor Gibbs, FRCB, MRCGP, DCH, FFMP**, has extensive experience in the development of medicines, formerly holding positions of responsibility from early clinical activities to in-market management at GlaxoSmithKline. Dr. Gibbs led global clinical programs in a wide range of disease areas, responsible for health outcomes, epidemiology and health economics functions. He was a member of the Appraisals Committee for the National Institute of Health and Clinical Excellence (NICE) for seven years. He continues to be active in the field through his academic position at the University of London and his membership in the External Scientific Advisory Board of “Protect,” the first funded pharmacovigilance project from the European Innovative Medicines Initiative (IMI). Dr. Gibbs received his medical degree from Kings College Hospital School of Medicine in the United Kingdom. He is a Fellow of the Royal College of Physicians and a visiting Professor at the London School of Hygiene and Tropical Medicine.

■ **Joseph D. Jackson, PhD**, worked primarily on the clinical side of the pharmaceutical industry from the 1980s, but also has experience in sales and marketing. His work has involved many facets of outcomes research, including the translation of clinical evidence into user-friendly cost-effectiveness models in a variety of therapeutic areas. He has generated quality of life evidence and obtained a listing in the package insert for a patient-reported outcomes claim for a medication in the U.S. and Europe, and has been associated with numerous market access filings for health technology assessment reviews. Currently, Dr. Jackson is the Program Director, Applied Health Economics and Outcomes Research, at the Jefferson School of Population Health,

Thomas Jefferson University in Philadelphia, PA, and holds an adjunct faculty appointments at the University of Mississippi (School of Pharmacy), Rutgers University (School of Pharmacy), and Robert Wood Johnson Medical School (Department of Medicine).

For more information on UBC’s Visiting Scientist program, please contact Ruth.Brown@unitedbiosource.com.

Dr. Jaime Caro Published in *Disaster Medicine and Public Health Preparedness Journal*

■ **Dr. J. Jaime Caro**, Senior Vice President of Health Economics at United BioSource Corporation recently chaired the ethics subcommittee of a Health and Human Services task force convened to produce guidelines on how to deal with the catastrophic terrorist explosion of an improvised nuclear device. This work resulted in two articles published in the Nuclear Preparedness issue of *Disaster Medicine and Public Health Preparedness*. Dr. Caro was lead author on “Resource Allocation after a Nuclear Detonation Incident: Unaltered Standards of Ethical Decision Making” (found at http://www.dmph.org/cgi/reprint/5/Supplement_1/S46) which focused on providing ethical guidance for clinicians making decisions after a nuclear detonation. In this article, the philosophical position was taken that utilitarian efficiency should be tempered by the principle of fairness in making decisions about providing lifesaving interventions and palliation, and that the most practical way to achieve these goals is to mirror the ethical precepts of routine clinical practice, in which three factors govern resource allocation: order of presentation, patient’s medical need, and effectiveness of an intervention.

The second article, “Scarce Resources for Nuclear Detonation: Project Overview and Challenges” (found at http://www.dmph.org/cgi/reprint/5/Supplement_1/S13) discusses the need for careful planning and a clear understanding of how best to allocate scarce resources, triage and evaluate patients, and implement crisis standards of care after a nuclear incident.

A full listing of authors and the full text for these articles can be found in the March 2011, Volume 5, Issue Supplement available at http://www.dmph.org/content/vol5/Supplement_1/index.dtl.

McGill University Offers Summer Course in Pharmacoeconomics June 20-23, 2011

Faculty: J. Jaime Caro, MDCM, FCRPC, FACP, Adjunct Prof. of Medicine, Adjunct Prof. of Epidemiology & Biostatistics, McGill Univ. & Sr. Vice President of Health Economics, United BioSource Corp.

This course provides a detailed introduction to the key concepts of this field, including those providing the foundation for the new Economic Evaluation Guidelines of IQWiG in Germany. After defining the basic economic problem, study types (cost-benefit, cost-utility, cost-effectiveness) and corresponding decision rules are examined. An example is

presented in detail to demonstrate how simulation models are developed, and the advantages of using discrete event simulation instead of Markov models or decision trees. Students are shown approaches to populating the models — the determination of costs and parameterization of effectiveness — and how to analyze the model results, including how to deal with all levels of uncertainty. The course presents techniques for presentation of results to decision makers in the public and private health care systems, including the efficiency frontier approach.

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