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SCIENCE & POLICY OPINION



Accounting for Productivity Losses in Health Technology Assessments

By Radoslaw Wasiak, PhD, MA, MSc, Research Scientist

Health technology assessment (HTA) plays an essential role in modern health care by supporting evidence-based decision making in health care policy and practice. Although it has been recommended that both direct and indirect costs be accounted for in HTAs,¹ most only take direct medical costs into consideration (the two notable exceptions are Sweden and the Netherlands). In particular, indirect costs, such as those due to productivity loss associated with a health condition, are typically not included in cost-effectiveness calculations. This omission occurs despite the fact that indirect costs can constitute a large proportion of the economic impact of illness, particularly for chronic or recurrent conditions in younger people. A recent study of back pain-related costs in Germany reported that associated productivity losses accounted, on average, for 54 percent of total costs.² Similarly, two recent studies of the costs associated with cancer found that lost productivity and loss of earnings due to premature death resulted in a higher proportion of total costs than direct medical resource use.^{3,4}

What is the rationale for not including indirect costs, and productivity losses in particular? One argument is that not all productivity loss can be attributed to a health condition. Other factors such as type of work, attitude toward employer/supervisor, or job satisfaction have been shown to relate to the duration of time off work, creating uncertainty about appropriate attribution of productivity loss to health-related factors.

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United States to Adopt ICD-10 Changing Landscape for the Researcher's Navigation Tools

By Carol Ware, Certified Professional Coder

Researchers use claims databases to provide information about treatment options, trends, and costs. Claims databases rely on the accepted coding classifications to identify diagnoses, procedures, drugs, and supplies used in treatment. Coding, therefore, is a means of classifying clinical data and assigning a numeric or alphanumeric representation to that data to describe diseases, injuries, problems, reasons for visit or encounters, illnesses, procedures, and supplies used in the delivery of health care services. Coded data are:

- Uniform
- Standardized
- Reproducible

Rarely, do physicians assign codes to claims. Generally, physicians dictate operative reports or chart the details of the clinical encounter, which

he or she then gives to another individual to code for claims submission and payment. The other individual, preferably a certified coder, assigns the codes that identify the clinical data, seeking clarification or additional specificity from the physician to code the data accurately.

Diagnosis Coding: Current and Future

One essential coding classification is that which identifies diagnoses. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), currently used in the United States, is a coding classification that classifies morbidity and mortality data for statistical purposes, medical care and basic health statistics. In the clinical and coding communities, the long-held belief, however, is that ICD-9-CM has outlived its usefulness.

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United BioSource Corporation

United States to Adopt ICD-10

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“ICD-9-CM is 30 years old, has outdated and obsolete terminology, uses outdated codes that produce inaccurate and limited data, and is inconsistent with current medical practice. It cannot accurately describe the diagnoses and inpatient procedures of care delivered in the 21st century.”¹

The successor to ICD-9, the International Classification of Diseases, Tenth Revision (ICD-10) system, including Clinical Modification (CM) and Procedure Coding System (PCS), was developed more than a decade ago and continues to be

Coders and researchers also must be prepared to work within the system. Coding accreditation organizations (e.g., American Health Information Management Association [AHIMA]) suggest a phased approach in preparation for the change to include assessment, implementation, and “go live” (www.ahima.org). Coders have embraced ICD-10-CM/PCS as a more comprehensive and accurate classification system to identify diagnoses and inpatient procedures. Research projects will benefit from the improved accuracy and specificity afforded by ICD-10-CM/PCS.

Implications of ICD-10-CM/PCS for Health Care Researchers

Converting to ICD-10-CM/PCS will be exciting, yet there will be challenges as researchers should be aware when accessing datasets; they may be based on the older ICD-9-CM coding, the new ICD-10-CM, or a combination of both, depending on dates. Synchronizing the data may require developing or purchasing a mechanism that provides a systematic crosswalk between old and new. Despite the challenges, an advantage with ICD-10-CM/PCS is that, ultimately, U.S. researchers may more easily combine U.S. and ex-U.S. data. Nevertheless, the promise that ICD-10-CM/PCS holds for U.S. researchers immediately upon adoption is data that more accurately represents U.S. medical utilization—a clear benefit for the entire U.S. research community.

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¹ Centers for Medicare and Medicaid Services. ICD-10 Clinical Modification/Procedure Coding System Fact Sheet. Accessible at: www.cms.hhs.gov.

Table 1
Coding Comparison between ICD-9-CM and ICD-10-CM for Pressure Ulcer Codes

ICD-9-CM	ICD-10-CM
9 location codes (707.00-707.09)	125 codes
Show broad location, but not depth (stage)	Show more specific location as well as depth including: L89132—Pressure ulcer of right lower back, stage II L89134—Pressure ulcer of right lower back, stage IV L89141—Pressure ulcer of left lower back, stage I L89143—Pressure ulcer of left lower back, stage III

updated annually. It is only recently (August 22, 2008) that the U.S. Department of Health and Human Services (HHS) formally proposed to adopt ICD-10-CM and ICD-10-PCS as the standard diagnosis and inpatient procedure code | set effective October 1, 2013 (FY 2014). Doing so would align the U.S. with many other countries, including the United Kingdom, France, Australia, Germany, and Canada, which have adopted ICD-10 within the past 15 years. The proposed date of adoption is October 1, 2013, following a public review and comment period to the Centers for Medicare and Medicaid (CMS). The implementation date is subject to change based on public input.

Anticipating Implementation of ICD-10

ICD-10-CM will allow for greater specificity in coding diagnoses and inpatient procedures (please see the example shown in Table 1). It is expandable and flexible to recognize health conditions and incorporate new diagnoses and procedures. With only two years until expected implementation, health care providers must prepare for the change from ICD-9-CM to ICD-10-CM and PCS. Software changes will be required, as well as updates to physician offices' super bills (list of commonly used codes) and modifications to claim forms to accommodate the new systems. Many disciplines in the health care setting can expect an impact, including Health Information Management (HIM), Patient Financial Services, Information Systems, Clinical Services, and Executive Management. Information Systems will play a crucial role in database design, data storage, and data retrieval systems.

Patient Channeling

By Stephan Lanes, PhD, Senior Research Scientist

Commercial success of therapies has become increasingly dependent on reliable knowledge about rare, unintended effects. As concerns about drug safety shape public confidence and redefine the regulatory environment, there is a growing emphasis on nonrandomized studies using administrative databases that enable researchers to efficiently harvest information from thousands, or even tens of thousands, of patients in a matter of months instead of years. Like randomized trials, nonrandomized studies can be designed to compare incidence rates of various outcomes between different medications. In nonrandomized studies, treatments are not randomly assigned by investigators but, instead, physicians decide what to prescribe and to whom.

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SCIENCE & POLICY OPINION

Accounting for Productivity Losses continued from front page

It is also argued that the causal relationship between work, health, and well-being is not well understood.⁵ Traditionally, work was viewed as a hazard, so time away from work when ill was expected and early return to productivity was viewed as detrimental to one's health and well-being. If the only benefit of a medical intervention is a reduction in productivity loss, such an outcome may not be viewed as desired under this traditional paradigm and inclusion of productivity loss in HTAs not necessary.

There is growing evidence, however, suggesting that long-term worklessness is harmful to physical and mental health.⁶ Work can be therapeutic, with the evidence particularly strong that those on sick leave or disability—if their condition permits—should be encouraged and supported to remain at work. Therefore, reduction of productivity loss could be associated with better health outcomes and inclusion of such indirect costs in HTAs particularly appropriate for medical interventions providing such potential cost offsets. This has to be viewed in light of the fact that—as mentioned earlier—other, non-health related factors may lead to absenteeism and productivity loss.

Another argument made for not including indirect costs is that cost offsets due to a reduction in productivity losses are included in the effectiveness calculations that use the QALY, a commonly used measure in these analyses. However, a closer inspection reveals that currently used and recommended instruments cannot properly capture the extent of potential gains, as they have not been designed to measure the degree of productivity loss or, in more general terms, work disability. In the two measures found in HTAs, EQ-5D and SF-36, responders are asked to rate their associated participation restriction (as defined by the International Classification of Functioning, Disability, and Health) when performing their usual activities, but are not asked to quantify the amount of said restriction. More specific research instruments exist (e.g., Work Limitations Questionnaire)⁷, but they are rarely, if at all, used in cost-effectiveness studies.

Finally, HTAs evaluate cost-effectiveness of a technology with a particular payer in mind. Therefore, the perspective should be that of the payer and not of society, and thus, indirect costs should not be included. However, in those settings where HTAs are used for reimbursement purposes, the payer is typically the government, rendering the distinction between payer and societal perspective rather unclear and making the case for inclusion of indirect costs stronger.⁸ Even in those settings where payer and societal perspectives can be clearly differentiated (e.g., in the United States), incorporating indirect costs can be of use from more than a payer perspective, as many health care plans are employer-sponsored, generating interest among non-payer stakeholders about potential cost offsets for increased medical costs.

In light of the above arguments, what is the case for incorporating productivity losses into HTAs? Work remains a major activity of people's life and methodologically-sound and transparent accounting of the complex dynamic between health, work, and well-being should at least be attempted. This is not to say that this has to be done for all health conditions and medical interventions, but for those where the possibility exists that the inclusion of indirect costs may substantially impact the findings of cost-effectiveness analyses. Furthermore, capturing effects that are important to the society that ultimately bears the burden of any illness should be one of the goals for HTAs. Therefore, omitting costs and benefits that at times are greater than direct medical costs is difficult to defend, even if some of the absenteeism is due to other factors than ill health or medical intervention and exact proportion may have to be estimated. After all, economic models allow for explicit treatment of uncertainties about the relationships between variables and their distribution, and thus, the appropriate sensitivity analyses can be performed.

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Patient Channeling

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“Patient channeling” occurs when the decision to prescribe a particular medication is related to the risk of a particular outcome. For instance, patients prescribed lipid-lowering medications may be at increased risk of dying from cardiovascular causes owing to risk factors present before the drug was prescribed. This particular form of channeling, where the endpoint of interest is related to the indication for treatment, can give rise to an especially tenacious bias known as confounding by indication.

Patient channeling can arise for various reasons and depends on the medication, the endpoint of interest, and other factors. A new therapy about which little is known may initially be used among patients for whom previous therapies were deemed unsatisfactory. To the extent that past treatment failure predicts future treatment failures, the new therapy is at a disadvantage. If a medication is the first in its class to offer a preferred dosing regimen, it might be prescribed preferentially to noncompliant patients who tend to have poorer outcomes. In addition, patients who received higher doses of a medication may be the sickest patients. Prescribing patterns in the real world are the product of human decisions, influenced by individual and group preferences, perceptions, and habits. It becomes the job of the epidemiologist to understand and unravel the channeling process in order to make appropriate inferences about the relations between therapies and outcomes.

Controlling for bias introduced by channeling of therapies to certain types of patients is perhaps the most renowned challenge of nonrandomized studies. Bias due to channeling can impact the design, analysis, and interpretation of

Controlling for bias introduced by channeling of therapies to certain types of patients is perhaps the most renowned challenge of nonrandomized studies.

studies, but channeling does not necessarily invalidate such studies. Consider that the newer non-steroidal anti-inflammatory drugs (NSAIDs), also known as COXIBs, were developed to reduce the risk of gastrointestinal bleeding and have been prescribed preferentially to patients who were at increased risk of bleeding, either because they were elderly or because they had a bleeding history. Nevertheless, despite the fact that the newer drugs were prescribed to high risk patients, an epidemiologic database study demonstrated a lower risk of gastrointestinal complications with COXIBs than with traditional NSAIDs.¹

There are many tools available to deal with the influence of patient channeling. In study design, the choice of study population using inclusion and exclusion criteria as well as the selection of comparators can ameliorate both the likelihood and extent of channeling. No matter how carefully the study population and comparison is crafted, however, it will always be important to assess and, usually, to enhance comparability in the analysis. This need implies that availability of information pertaining to factors that influence prescribing decisions (e.g., medical history) be anticipated in the design of the study.

In nonrandomized studies, large imbalances between treatment groups with regard to important baseline risk factors are sometimes presumed to imply irrevocably biased results. If the variables that predict channeling are measured comprehensively and without error, however, analytic control of confounding can effectively remove the bias and yield a valid result. For example, restricting the study population to patients at increased risk of the endpoint will reduce the magnitude of differences between treatment groups with regard to baseline risk. Alternatively, when baseline risk can be characterized accurately, statistical methods are available that make comparisons within homogeneous subgroups and produce summary effect estimates that are corrected for baseline differences. Hence, the presence of baseline differences should not be taken to imply an invalid result.

Of course, knowledge of predictors of channeling is often murky, and data on predictive factors may be incomplete or measured with error. Even in these situations, all is not lost. Assessment of validity can benefit from sensitivity analyses that involve postulating plausible error rates and determining the likely direction and magnitude of biases compatible with such rates. The position of the observed result in relation to this compatibility range can inform the discussion about the role of channeling.

The use of sophisticated analytic procedures makes the interpretation of nonrandomized studies with channeling less straightforward than that of a typical randomized trial, and leans more heavily on epidemiologic training and experience. No matter how carefully the data are analyzed, certain hurdles defy analytic solutions. For example, random allocation will tend to balance unmeasured risk factors as well as measured risk factors. The impact of bias due to confounding can then be assessed probabilistically using conventional statistical analyses. In contrast, in nonrandomized studies, only measured risk factors can be controlled. While conventional statistical analyses used in random studies are also applied to nonrandomized studies, a crucial assumption (random allocation) no longer holds and needs to be considered in the interpretation.²

With renewed emphasis on post-marketing risk assessment, nonrandomized studies will be an increasingly important

source of information about drug safety, and patient channeling will take on a new importance. By tackling the challenges of patient channeling head-on, we may find that the rumors of an incorrigible monster have been greatly exaggerated.

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Mixed Treatment Comparisons

By Steven Blume, MS, Senior Research Associate

Decision-makers often need to draw conclusions about the relative efficacy of treatments that have not been compared head-to-head in a randomized clinical trial. If two such treatments have been in trials with a common comparator (typically a placebo), analysts can make indirect comparisons between them, assuming similar study designs and populations. The concept is illustrated in Figure 1, where treatments are nodes (A,B,C), and a trial comparing two treatments is indicated by a connecting link. Treatments of most interest for decision-making are indicated by the dark shading. The effects relative to the common comparator d_{AC} and d_{BC} are used to compute the indirect comparison d_{AB} , preserving the randomization of the trials.

The approach can be extended to a meta-analysis of several trials (where in the Figure each link could represent more than one trial) and to the inclusion of both indirect and direct evidence in a "mixed treatment comparison" (MTC), also known as a network meta-analysis or multiple treatment comparison. Compared to Figure 1, Figure 2 adds trials that directly compared A to B head-to-head, as well as trials of two other treatments D and E.

Even when there are direct trials available, it is still valuable to consider the other trials as they provide information on the mean and variability of treatment effect, as well as the consistency of the evidence. When multiple comparisons are of interest (e.g., it is desirable to know how A compares to C and D), having one set of evidence for estimating all effects simultaneously and consistently is obviously desirable.¹

Since 2006, the National Institute for Clinical Excellence (NICE) has been requiring that in submissions where no

direct trials exist for the treatments of interest, a meta-analysis of indirect comparisons be performed. Where there are direct trials, they added language in 2008 stating that mixed treatment comparison analyses could be submitted in addition to the required meta-analyses of the direct trials.²

Methods for performing meta-analyses of mixed direct and indirect evidence have been developed from both Bayesian³ and classical perspectives.⁴ The Bayesian approach, frequently used with non-informative priors, has proven especially popular, partly due to ease of implementation with the simulation tool WinBUGS.⁵

With more trials and comparators, the issues in conducting any proper meta-analysis, such as population and outcome comparability, become even more critical. Several such considerations are discussed by Sutton, et al.¹ For example, expansions to the network of trials to be analyzed can appear to add more information, but trials more distant from the comparison of interest may offer diminishing returns

Figure 1

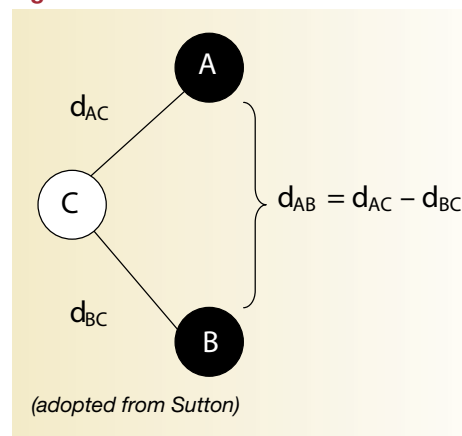
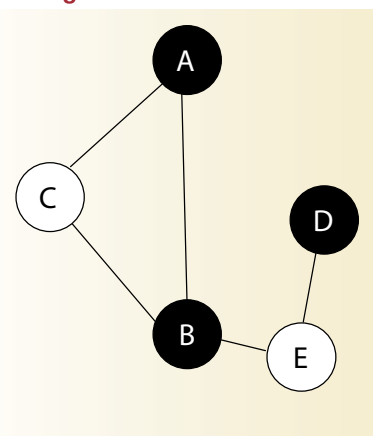


Figure 2



or even represent subtly heterogeneous populations or practice patterns. Also, as there are more trials from which to choose, selectivity of results is more possible, so a transparent protocol for inclusion/exclusion must be constructed.

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Upcoming Presentations

American Association for Geriatric Psychiatry (AAGP) 2009 Annual Meeting

Mar 5–Mar 8 2009, Honolulu, HI, USA

Poster Presentation

Administration and Scoring Variability Among ADAS-Cog Raters **Miller D**, Bartko J, Connor D

Joint Conference—49th Cardiovascular Disease Epidemiology and Prevention Annual Conference and Nutrition, Physical Activity and Metabolism Conference

Mar 10–Mar 14 2009, Palm Harbor, FL, USA

Poster Presentation

The Impact of Drug-Related Side-Effects on Persistence with Amiodarone or Sotalol in the Management of Atrial Fibrillation: An Exploratory Analysis **Ishak KJ**, Proskorovsky I, Guo S, Lin J, Caro JJ

International Congress on Schizophrenia Research (ICOSR)

Mar 29–Apr 1 2009, San Diego, CA, USA

Poster Presentation

Contrasting Scoring Patterns of Japanese and Rest of World Investigators on the PANSS **Daniel D**, Bartko J, Davis J

Pharma Pricing & Market Access Outlook Europe 2009

Apr 28–May 1 2009, London, UK

The Patient's Perspective in Reimbursement Assessments **Asha Hareendran, PhD**, Senior Research Scientist, UBC

Using Health Economic Data for Evidence Based Decision Making **Ruth Brown**, Director, Scientific Operations Support, Senior Scientist, UBC

American Thoracic Society International Conference

May 15–20, 2009 San Diego, CA, USA

Poster Presentations

How Stable is Stable in COPD: An Analysis of Day-to-Day EXACT Score Variability in Acute and Stable Patients with COPD **Leidy NK**, **Wilcox TK**, Sethi S, Jones PW and the EXACT-PRO Study Group

Patient Perceptions of COPD: Development of the COPD Assessment Test **Harding G**, **Robert L**, **Gavriel S**, **Murray L**, Jones P, Berry P, Wiklund I, **Leidy NK**

Oral Presentation

Patterns of Recovery from Exacerbations of COPD: EXACT Change Scores Days 1 – 14 **Wilcox TK**, **Leidy NK**, Sethi S, Jones PW and the EXACT-PRO Study Group

ISPOR 14th Annual International Meeting

May 16–May 20 2009, Orlando, FL, USA

Short Courses

Saturday, May 16, 2009

Bayesian Analysis: Overview and Applications **Faculty: David Vanness, PhD**, Research Scientist, Center for Health Economics & Science Policy, UBC; **Christopher S. Hollenbeak, PhD**, Asst. Professor, Surgery and Health Evaluation Sciences, Penn State College of Medicine

Finding and Extracting Cost Data **Faculty: L. Clark Paramore, MSPH**, Exec. Director and Research Scientist, Center for Health Economics & Science Policy, UBC; **Denise Boudreau, RPh, PhD**, Research Scientist, Center for Health Economics & Science Policy, UBC

Sunday, May 17, 2009

Bayesian Analysis: Advanced **Faculty: David Vanness, PhD**, Research Scientist, Center for Health Economics & Science Policy, UBC; **Keith R. Abrams, PhD**, Prof. of Medical Statistics, Dept. of Health Sciences, Univ. of Leicester; **Christopher S. Hollenbeak, PhD**, Asst. Prof., Surgery and Health Evaluation Sciences, Penn State College of Medicine

Discrete Event Simulation for Economic Analyses **Faculty: J. Jaime Caro, MDCM, FRCPC, FACP**, Adjunct Prof. of Medicine, Adjunct Prof. of Epidemiology and Biostatistics, McGill Univ., and Senior Vice President of Health Economics, UBC; **Jörgen Möller, MSc Mech Eng**, Vice President, Modeling, UBC

American Psychiatric Association (APA) Annual Meeting 2009

May 16–May 24 2009, San Francisco, CA, USA

Workshop

The Use of Research Measures In Clinical Practice **Moderator: J. Busner, PhD**, Practice Leader, Specialty Clinical Services, UBC

Recent Presentations

50th American Society of Hematology (ASH) Annual Meeting and Exposition

Dec 6–Dec 9, 2008, San Francisco, CA, USA

Poster Presentation

Impact of Management of Iron Overload in Patients with Myelodysplastic Syndrome **Bozkaya D**, **Migliaccio-Walle K**, Baladi JF

CBI's 3rd Forum on Patient Reported Outcomes (PRO)

Nov 19–Nov 20, 2008, King of Prussia, PA, USA

Session

Analyze FDA Requirements for PRO Studies and Discuss Next Steps if FDA Rejects a PRO Claim **William R. Lenderking, PhD**, Senior Research Scientist, UBC; Jeff Sloan, PhD, Lead Statistician, Mayo Clinic

Analyze Industry Experience with the FDA and Discuss Anticipated Changes from the Revised Guidance **William R. Lenderking, PhD**, Senior Research Scientist, UBC; Jeff Sloan, PhD, Lead Statistician, Mayo Clinic

2008 NPC Annual Forum

Nov 13–Nov 14, 2008, Alexandria, VA, USA

Session

What Evidence Do Payers Need? **Moderator: Bryan R. Luce, PhD, MBA**, Senior Vice President, Science Policy, UBC

2008 Annual Meeting of the American College of Allergy, Asthma & Immunology

Nov 6–Nov 11, 2008, Seattle, WA, USA

Presentations

Can Patients with Asthma Feel Inhaler Therapy Working Right Away? A Clinical Trial Testing the Influence of Daily Versus Weekly Assessment on Patient Perception **Leidy NK**, Gutierrez B, Lampl K, Uryniak T, O'Brien C

Can Patients with Asthma Feel Inhaler Therapy Working Right Away? A Clinical Trial Testing the Influence of Predose Versus Postdose Assessment on Patient Perception **Leidy NK**, Gutierrez B, Lampl K, Uryniak T, O'Brien C

Patient Perception of Onset of Effect: Results of Exit Interviews from Two Clinical Trials in Patients with Asthma **Petrillo J**, Walter K, **Harding G**, **Leidy NK**, Gutierrez B, O'Brien C

Relationship of Nasal Congestion and Ocular Symptoms with Patient-Reported Sleep, Mood and Productivity **Stull DE**, Schaefer M, Sandor D, Crespi S

Assessing Cognitive Change in Clinical Research Through the Use of Computerized Test Batteries

By Paul Maruff, PhD, Chief Scientific Officer, CogState Ltd.,
Cynthia McNamara, PhD, Clinical Manager, UBC

Cognitive impairment, associated with psychiatric and neurological diseases, can have a significant impact on daily function and quality of life for both patients and caregivers. Pharmaceutical companies are focusing significant resources on the development of compounds that act to improve cognition. This shift in treatment strategy in neurology and psychiatry is a direct result from a change in the interest in cognitive improvement with drug trials, not just measuring toxicity.¹ This also means that there is a need for systems that can be used to guide decision making about the effects of novel and licensed drugs on cognitive function.

Historically, the effect of drugs on cognitive function has been measured using paper-and-pencil measures of functions such as attention and memory. However, the globalization of pharmaceutical clinical trials has magnified the limitations of these instruments, which may include variability in administration among raters, lack of cultural neutrality, and costly monitoring and translation of instruments.

On July 28, 2008, United BioSource Corporation entered into a partnership with CogState, Ltd., a cognitive testing company headquartered in Melbourne, Australia, with additional locations in the United Kingdom and the United States.

Since their founding in 1999, the computerized cognitive testing solutions developed by CogState have demonstrated effective utilization in various cultures, standardized administration, adaptability based upon sponsor needs, and cost-effectiveness.

The inclusion of computerized cognitive testing in clinical trials allows for detection of subtle cognitive changes that a subject may either be unaware of or unable to report accurately. These changes may also go unnoticed in the course of clinical observation. Detection of these changes may be particularly beneficial during the course of early phase trials to assist in determination of whether to proceed with development of a compound.

In clinical trials, cognitive tests must be given repeatedly, at least before and after administration of the drug. Consequently, it is important that the tests are standardized so that performance can be compared meaningfully, can be repeated without giving rise to learning effects, and are relatively brief so that patients do not lose motivation or become fatigued when doing the tests. Computerized cognitive tests serve to minimize rater variability associated with administration of the instrument. The computer software is able to

present test items consistently and determine the speed and accuracy of responses to those items. The software can then generate randomized forms of the same tests so that previous assessments do not influence current performance (i.e., a practice effect) and can rapidly perform complex calculations which allow for more in-depth analysis of data.²

Past research indicates that computerized cognitive tests are appropriate for use in clinical trials covering a broad group of diseases, including Alzheimer's disease, schizophrenia, depression, HIV, hepatitis C, insomnia, ADHD, Parkinson's disease, pain and traumatic brain injury. Each indication may be tested with a specific set of tasks which are administered electronically. Each task is presented in a similar format with easy to read instructions for the subject.

One example is the Groton Maze Learning Task. This measurement of executive function asks the subject to move through the maze

by clicking on the squares while also adhering to a specific set of rules (Fig.1). The computer administration of this test allows for consistency in the test environment. Other examples include the Social-Emotional Cognition task (Fig. 2) where the subject is asked to click on the face that is most different from the others.

These tests demonstrate consistency in delivery, and thereby, eliminate variance in cognitive abilities for repeat testing.

This unique factor also has shown tests to be unaffected by language and cultural variances.³

By creating a standard form of administration for new and widely used tests, the computerized batteries are able to establish a firm baseline for each patient and then rate them in a consistent manner in subsequent tests.

The changing landscape of cognitive measurement has introduced a number of new considerations to clinical research. More accurate and sensitive tools to measure

Figure 1

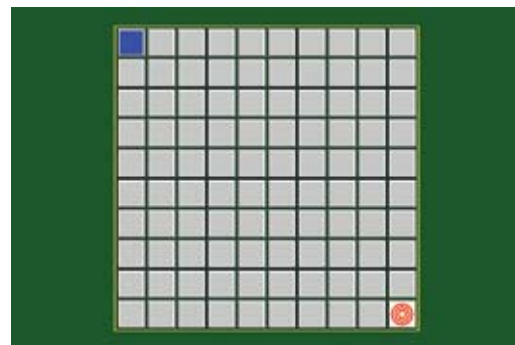


Figure 2



Assessing Cognitive Change

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cognitive changes are critical, and computerized cognitive tests are one method researchers are employing to achieve this end.

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Limited Clinical Trial Participation of African Americans: Are We a Part of the Problem?

By Andrea M. Ireland, PhD, MPH, Senior Research Associate

Background

In 1998, the Food and Drug Administration disseminated the Demographic Rule requiring investigational new drug applications to provide safety and effectiveness data by subjects' age, gender, and race. Almost a decade later, the FDA encouraged racial categorization in the United States using the revised, standardized Office of Management and Budget (OMB) Federal Standards for Racial and Ethnic Data. Briefly, individuals self-reported their ethnicity and race with standard response options. A minimum of five categories of race include white, black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and their ethnicity as Hispanic or Latino or not Hispanic or Latino.¹ Moreover, biracial and multiracial individuals could select more than one racial category for the first time.

As a result of these data collection activities, it has become increasingly evident that while African Americans bear the disproportionate disease burden for conditions such as asthma,^{2,3} cancer,^{4,5} diabetes,⁶ and cardiovascular disease,^{7,8} they are less likely than their white counterparts to participate in clinical trials of investigational drugs from which they or future generations could greatly benefit.⁹⁻¹¹ Moreover, the absence of subjects from diverse racial and ethnic groups in clinical trials is a significant threat to the generalizability of results to larger patient populations.

Racial differences in treatment responses have been noted in the literature.¹²⁻¹⁴ For example, one study found that angiotensin-converting enzyme (ACE) inhibitors may be less effective in the treatment of African Americans with heart failure compared to whites due to decreased availability of nitric oxide.¹²⁻¹⁴ However, it is important to note that race is a social construct.¹⁵ An individual's race is antecedent of the proximal factors which may affect his or her disease state and/or treatment response, such as household and neighborhood exposures to environmental triggers, financial and geographic access to medical care, beliefs about disease etiology, and adherence to medication regimens.¹⁵ As such, race should be considered when designing and implementing clinical trials.

One reason for limited clinical trial participation among African Americans is the Tuskegee Syphilis Study which engendered much distrust of clinical research among African Americans.¹⁶ Briefly, the United States Public Health Service commissioned the Tuskegee Syphilis Study in 1932. Its primary objective was to study the natural history of untreated syphilis among African American men residing in Macon County, Alabama, a rural, poor, and politically disadvantaged community of sharecroppers. The men were left untreated, even after awareness of penicillin as an effective treatment for syphilis. Furthermore, study administrators limited patients' ability to receive medical care from local physicians not affiliated with the Tuskegee study by using "blacklists." The study continued until 1972 when news of the study was leaked to the press.

To illustrate the ramifications of Tuskegee, a recent study by Katz, et al.¹⁷ found that compared to whites, African Americans had four times greater odds of being familiar with the Tuskegee study, controlling for age, gender, education, and income. Additionally, using focus group interviews with African Americans residing in four major cities in the United States, Freimuth and colleagues found that participants were familiar with this notorious study but could not recall accurate facts of this event; a common misperception was that the Tuskegee participants were injected with the syphilis virus.¹⁸

A Proactive Approach

While we must acknowledge the role of historically-based fears of clinical research among African Americans, our efforts to encourage greater participation of African Americans will be stagnant unless we are willing to take a more action-oriented, proactive approach. First, it is imperative that we invest adequate time and resources to understand the cultural values, community assets, and socioeconomic backdrop of African Americans, while recognizing the considerable heterogeneity within this group. To ensure that our understanding of this context is accurate, greater participation from African American physicians and health outcomes researchers is vital.

Second, it is critical that African Americans participate in qualitative research for the development and validation of patient-reported outcomes (PRO) instruments. An exploration of the language used to describe salient symptoms and their perceived impact on PROs will ensure that new instruments adequately capture the disease experience from a wider range of patients. Importantly, the content validity of existing PRO instruments should be assessed among minority groups if not previously documented.

We must consider how elements within the clinical trial study design unintentionally restrict eligibility for subgroups of African Americans. For example in asthma, a common exclusion criterion is emergency department utilization within a pre-specified period of time. Arguably, many assert that this type of health services use is a proxy of disease severity. However, the decision to seek care from an emergency department may not reflect the need for urgent care but may more accurately represent limited availability in light of the substantial geographic and financial access barriers encountered by African Americans. Similarly, we should consider the time and economic costs of trial participation from the subject's perspective. Individuals who do not receive paid time-off from employers may be reluctant to enroll in clinical trials with frequent study visits.

Careful attention must be given to the selection of investigational sites. Ideally, study sponsors should strive to enroll sites in close proximity to geographic communities where African Americans reside. More importantly, an evaluation of the cultural competence of physicians and other site personnel is imperative as these individuals will present the background of the clinical trial, describe the informed consent process, and allay any fears of scientific misconduct to prospective African American subjects.

One strategy to enhance the recruitment and retention of African American patients in clinical trials is the development of culturally sensitive recruitment materials. Prospective African American subjects are more likely to perceive pamphlets, posters, and mailers as culturally appropriate when the images, layout, and content of these materials encompass beliefs, values, lifestyle factors, and the social landscape within the African American community.¹³ These recruitment strategies have been found to increase the rates of participation in public health intervention studies and may represent an avenue to achieve racial diversity in health outcomes studies.

Conclusion

In summary, while historical-based fears to clinical participation remain a significant challenge to clinical trial participation in African Americans, there are numerous barriers that have been given far less attention. Health outcomes researchers have an important part to play in reversing this trend by considering the socio-cultural landscape of African Americans in

their clinical study design, expanding the rubric for investigational sites to include geographic accessibility and cultural competence of staff, ensuring culturally relevant PROs, and eliciting feedback from representative patients.

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FEDERAL POLICY UPDATES ON WHAT IS IMPACTING *OUR* RESEARCH AND *YOUR* BUSINESS

SCIENCE POLICY CORNER

Comparative Effectiveness Research (CER) will play a strategic role in health care reform as federal policymakers seek to improve health care quality, evidence, and decision making.

On January 21, the House Appropriations Committee passed an economic stimulus bill (H.R. 598) worth \$825 billion by a 35-22 vote. It is likely that these funds are infusing recipients with some breathing room and increased responsibility. What may remain unclear, however, is how, where, why, and when the government will pursue its apparently ambitious comparative effectiveness research agenda.

Astronomical numbers with no crystal ball

The economic stimulus bill earmarks \$1.1 billion for CER, more than has been previously proposed. The language, however, lacks transparency, governance, structure, methodology, priority, or other provisions that would give direction and focus to the intent of the funds. The appropriations language stands in stark contrast to the balanced and thorough proposal from Sen. Max Baucus, D-Mont., and Sen. Kent Conrad, D-N.D., in the Comparative Effectiveness Research Act of 2008 (S. 3408 in the 110th Congress).

In the economic stimulus bill, \$700 million is earmarked for the Agency for Healthcare Research and Quality (which in FY09 received \$30 million for its entire Effective Health Care Program), \$400 million of which would be transferred to the National Institute of Health (NIH). Additionally, \$400 million is earmarked for the Department of Health and Human Services in order to establish the Federal Coordinating Council for Comparative Effectiveness Research (which will be made up entirely of government agency officials). The language in the bill is silent on certain contentious issues such as the extent to which cost-effectiveness research will be conducted, as well as the direct impact the research may have on coverage or other medical policy decisions. In past proposals, both of these issues have been resolved temporarily by specifying that the research scope must not include cost effectiveness and preventing the research reports from making coverage or policy recommendations.

And yet, the story continues its trajectory...

It is clear that further health care reform is on the horizon, particularly as policymakers vie for expanded government-run insurance programs, Medicare reform, and many other cost-driven system adjustments. However, many questions remain: Will health care reform packages build on the money distributed from the economic stimulus package, or was the economic stimulus bill a way of dismissing a first round of issues? Will specific congressional proposals (such as Sen. Baucus's legislation) regain traction in order to provide direction for CER funds, or will we see a primarily agency-driven and designed CER strategy? The proverbial "policy window" remains wide open and UBC will provide analysis on these changes throughout the year.

Demystifying the Expected Value of Perfect Information (EVPI)

By David Vanness, PhD, Research Scientist and Peter Quon, MPH, Research Associate

As pharmacoeconomists, we help decision-makers determine which treatment is best. We rely on evidence such as clinical trial data, resource cost-estimates and elicited utilities. Uncertainty in evidence translates to uncertainty in the adoption decision. The best way to resolve this uncertainty is to gather more information, but this may be costly and time consuming so careful consideration must be taken. This is where value of information (VOI) analysis comes in. NICE Appraisal Committee member Karl Claxton summarized: "VOI analysis evaluates the extent to which new evidence might improve expected benefits by reducing the chance for error and compares that improvement with the cost of the information."¹ He and other leading pharmacoeconomists have published extensively on VOI, however, the explanation

of the math behind VOI is fairly complicated. The purpose of this article is to illustrate VOI using a simple numerical example so there's no need to dig out your old calculus textbook.

Expected value of perfect information (EVPI) and expected value of partial perfect information (EVVPI) are two commonly-encountered VOI analyses.²⁻⁴ EVPI answers the question: What is the maximum amount society can pay for additional research before it is no longer beneficial to society? EVVPI answers the question: Which factors should be prioritized for further research? This article focuses on EVPI, and a future article will address EVVPI.

VOI analysis is based on the assumption that every decision has an economic value. In business, every decision

has costs and benefits, and the best decision is one that maximizes net benefits (benefits minus costs). In pharmacoeconomics, our benefits are health outcomes such as quality adjusted life years (QALYs). We apply an economic value to QALYs (i.e., willingness-to-pay per QALY), thereby permitting comparison with costs of a decision.

For example, consider a health authority deciding whether to treat atrial fibrillation patients with a new antiarrhythmic drug. The new drug results in expected lifetime costs of \$95,000 over standard care and the patient living an expected additional 1.6 QALYs. If the decision-maker values each additional QALY at \$50,000, then the value of the decision to use the antiarrhythmic drug over standard care, or in other words the expected net benefit (ENB) is $1.6 \times \$50,000 - \$95,000$. Because ENB is negative, the decision-maker rejects the new drug.

But “expected” values are not certain. Suppose that the authority’s decision was based on a review of two trials, and the review panel concluded that there was a 40 percent chance that patients gain one QALY and a 60 percent chance they gain two QALYs (expected QALYs = $1.6 = .4 \times 1 + .6 \times 2$). Suppose there was also uncertainty about costs—a 25 percent chance that additional costs over standard care are \$50,000 and 75 percent chance they are \$110,000 (expected cost = $\$95,000 = .25 \times \$50,000 + .75 \times \$110,000$). The information on which the authority based their decision is called *current information*.

The downside of current information is that it is uncertain and may lead to the wrong decision! Suppose the review panel could learn the complete truth, and it turned out to be that the new drug actually results in lifetime costs of \$50,000 and the patient living two additional QALYs. This is *perfect information*. With perfect information the authority realizes it would have made the wrong choice to reject the new drug under current information. Using the value per QALY of \$50,000 the net benefit (NB) is $\$50,000 = 2 \times \$50,000 - \$50,000$. Having perfect information would have saved the authority from mistakenly rejecting a new treatment with a \$50,000 net benefit. If this were the true state of the world, how much would a decision maker be willing to pay to have that information? Well, anything up to and including \$50,000!

But now suppose instead that the new drug actually results in additional lifetime costs of \$110,000 and the patient living two additional QALYs. This is also perfect information, but reflecting a different “state of the world.” Now, the true net benefit, $NB = -\$10,000 = 2 \times \$50,000 - \$110,000$. How much would it be worth to the decision-maker to know that information? The answer may surprise you. It’s worth \$0. Nothing. Why? Because having this set of perfect information would have led to the same decision (reject the new drug) as having current information (reject the new drug). The decision maker would be willing to pay \$0 for the perfect information because they would gain nothing from having it. Perfect information only has value if it changes the decision made under current information.

There are two other possible sets of perfect information besides the two already described: 1) \$50,000 in additional costs and one additional QALY ($NB = \$0 = 1 \times \$50,000 - \$50,000$); and 2) \$110,000 in additional costs and one additional QALY ($NB = -\$60,000 = 1 \times \$50,000 - \$110,000$). In both cases, the decision-maker would be unwilling to pay anything to learn this information, because both would have led to the same decision as current information: do not adopt the new drug.

So, what is the *expected* value of perfect information? It’s the sum of the probabilities that each set of perfect information is actually true (given current information) times the willingness to pay to know each set of perfect information. There is only one state of the world where having perfect information is worth anything to the decision-maker: if costs were \$50,000 and QALY gains were two, where having the information would prevent a \$50,000 mistaken rejection of the drug. Given our current information, that state of the world has a 15 percent chance of being true.

True State of the World	Probability True	Value of Perfect Info
\$50,000 and 1 QALY	$0.25 \times 0.4 = 0.1$	* \$0 = \$0
\$50,000 and 2 QALY	$0.25 \times 0.6 = 0.15$	* \$50,000 = \$7,500
\$110,000 and 1 QALY	$0.75 \times 0.4 = 0.3$	* \$0 = \$0
\$110,000 and 2 QALY	$0.75 \times 0.6 = 0.45$	* \$0 = \$0
		EVPI: = \$7,500

Hence, the expected value of perfect information, EVPI, is $\$7,500 = .15 \times \$50,000 + .85 \times \$0$. The decision-maker should be willing to pay \$7,500 to know the truth about cost and QALYs, given their current information.

Pharmacoeconomists should consider conducting VOI analyses along with cost-effectiveness analyses. In addition to informing decision makers on how to invest in research, VOI analyses assess the accuracy of cost-effectiveness analyses by identifying limitations in current information.

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The PACE Initiative Picks Up the Pace: First Annual Update

One year ago this month, UBC launched an ambitious effort that we termed the PACE Initiative (**P**ragmatic **A**pproaches to **C**omparative **E**ffectiveness). The PACE Initiative is intended to be a collaborative effort to improve the practicality and efficiency of comparative clinical studies to address mounting “real-world” evidentiary demands by payers, clinicians, and policy makers. It was created in the belief that whereas the comparative effectiveness national agenda must include comparative and pragmatic trials, traditional approaches to designing and conducting such trials are too costly, take too much time and are commonly not answering real-world needs. PACE investigators are exploring the challenges and opportunities, in particular, of Bayesian and adaptive trial techniques as applied in real- world applications and to improve efficiency.

2008 was a foundational year. We successfully:

- recruited a diverse and impressive senior advisory board;
- raised funds from a growing list of, mainly, corporate sponsors;
- launched a website (www.PACEInitiative.org) which soon will be interactive;
- developed collaborative relationships with key, innovative organizations that have similar or related objectives;
- sponsored, or participated in, several seminars and forums, one of which was a privately funded forum to explore Bayesian adaptive comparative trial designs for a novel drug soon to be launched;
- welcomed David Vanness, PhD, as scientific director for the PACE Initiative.

In 2009, we are embarking on two major efforts to further explore the scientific and policy questions inherent in the mission of the PACE Initiative.

National Forum: This coming spring, the PACE Initiative will host a national invitational forum co-organized by three related groups: The PACE Initiative, the Center for Medical Technology Policy (CMTP) and the Clinical Trial Transformation Initiative (CTTI). The theme of this invitational forum will be pragmatism and efficiency for comparative trials.

Working Paper Series: Under Dr. Vanness’s leadership, we have initiated several working papers, initially to include:

1. The landscape of real-world comparative effectiveness clinical trials. PI: Bryan R. Luce, PhD, Senior Vice President of Science Policy, UBC
2. Building off the existing evidence in comparative effectiveness (aka The world may be flat, but is the prior?). PI: David J. Vanness, PhD, Research Scientist, UBC
3. Thresholds to invest: manufacturers’ elasticities for sponsoring real-world comparative trials (aka Just how much does cost, time, risk need to be decreased for a manufacturer to be willing to fund a CE trial of its product?). PI: Anirban Basu, PhD, Asst. Professor, Hospital Medicine, Dept. of Medicine, University of Chicago
4. Getting to “Yes” (aka When do we know [what is the minimal threshold] when we have “just enough” evidence for a real-world [read, coverage decision maker; clinical guideline committee] decision?). PI: TBA
5. The role of dynamic predictive simulation in guiding the pragmatic, adaptive trial. PI: J. Jaime Caro, MDCM, FRCPC, FACP, Senior Vice President & Senior Research Scientist, Health Economics, UBC

Collaborative Relations: The PACE Initiative has established collaborative relations with the following organizations: The Center for Medical Technology Policy (CMTP); the Clinical Trial Transformation Initiative (CTTI); Friends of Cancer; and the **EX**cellence in **P**ragmatic and **O**bs**ER**vational **S**Tudies (**EXPERT**) Research Design Network of Eli Lilly. We perceive such strategic relationships to be crucial in order to realistically and creatively address the questions of pragmatism, efficiency, and innovation in clinical trials. We thank these organizations for undertaking this monumental task with us and encourage others who share our objectives to contact us.

For more information, please contact PACEInitiative@unitedbiosource.com.

SPOTLIGHT ON SCIENCE

Recent Publications

- Andrade SE, McPhillips H, Loren D, Raebel MA, Lane K, Livingston J, **Boudreau DM**, Smith DH, Davis RL, Willy ME, Platt R. "Antidepressant Medication Use and Risk of Persistent Pulmonary Hypertension of the Newborn." *Pharmacoepidemiol Drug Saf* 2009 Jan 15 [Epub ahead of print]
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NEWS BRIEFS

UBC Launches Safety, Epidemiology, Registries and Risk Management Group

The passage of the FDA Amendments Act of 2007 (FDAAA) has created monumental change in many aspects of the drug development lifecycle. Two key areas affected by this legislation are post-marketing surveillance and risk management. To augment our ability to assist Sponsors in complying with these increased safety challenges, UBC has assembled a cohesive team of scientific and operational experts dedicated to the delivery of postmarketing safety surveillance, epidemiology, registries and risk management services. UBC's Safety, Epidemiology, Registries and Risk Management team of experts in pharmacovigilance, risk management and post-marketing research work together interpreting FDA regulation and guidance and predicting post-marketing commitments and risk management requirements. This team applies their knowledge in the design and development of proactive solutions. Our clients can, with confidence, count on innovative solutions to support their clinical and commercial development needs.

According to Patrick Lindsay, UBC's Executive Vice President, "the recent promotions of Chad Clark to General Manager and Annette Stemhagen to Senior Vice President to lead UBC's Safety, Epidemiology, Registries and Risk Management group forms the industry's most experienced team. Under the direction of Chad and Annette, this team enhances and reinforces UBC's position as the industry's recognized leader in safety surveillance and pharmacovigilance; the design and conduct of registries and observational studies, and the development and successful implementation of risk assessment and risk mitigation strategies."

UBC believes that addressing issues of product risk early and comprehensively offers our customers additional value within their development efforts. Never before has the domain expertise around the U.S. and European regulatory and approval frameworks been more critical. The scale of programs under management at UBC from design through implementation offers us tremendous insight into the risk-propensity, approval requirements and design needs of our customers' portfolios. UBC's investment in specialized technology and the development of its Safety, Epidemiology, Registries and Risk Management team formalizes the people, processes and structure of this approach, and enables UBC to strategically package its unique solutions in a way that demonstrates immediate value for its customers.



Chad Clark
General Manager
Safety, Epidemiology, Registries
and Risk Management

Chad.Clark@unitedbiosource.com

Mr. Clark brings expertise in multi-national research to his leadership role. For over the past decade, he has led global project teams in the development, implementation and management of some of the most stringent, regulatory-mandated risk assessment, risk minimization, and evaluation programs in the world. Mr. Clark maintains a hands-on role in all aspects of registry programs, including design, operational and software implementation and budgeting. He has also implemented large, complex global observational programs and led the creation of performance-linked access systems and restricted distribution programs, critical to some risk minimization programs.

In addition, Mr. Clark oversees strategic business management and strategic growth through acquisitions—further building our operational delivery and service lines.



Annette Stemhagen, DrPH, FISPE
Senior Vice President
Epidemiology, Registries
and Risk Management

Annette.Stemhagen@unitedbiosource.com

Dr. Stemhagen assumes her role at a time when epidemiology and real-world safety data are in demand at an unprecedented level by global regulatory authorities. With more than 25 years of public health/epidemiological research experience (including 15 years in safety surveillance of pharmaceutical, biotech and vaccine products), Dr. Stemhagen is successfully leading and working with an already seasoned team to continue the growth of UBC's strategic consultative and program design services. In the growth of this team, Dr. Stemhagen continues to focus on safety surveillance, design, implementation, and analysis of epidemiologic studies, registries, pregnancy exposure registries, large streamlined safety studies, actual use programs and observational studies for products in Phase IIIb and post-approval.

Dr. Stemhagen has designed and evaluated risk assessment studies, including more than 15 regulatory-mandated, long-term safety studies. She has also developed risk intervention programs, risk management evaluation studies and risk minimization action plans (RiskMAPs)/REMs for more than 40 products.

Dr. Stemhagen was the first Industry Representative on the FDA Drug Safety and Risk Management Advisory Committee, and remains focused on the design, implementation and evaluation of risk evaluation and mitigation strategies (REMS) for pharmaceutical and biotechnology sponsors. Her leadership in this area is critical, not only for the growth of our company, but for the success of our clients.

Gerald Faich, MD, MPH, FISPE
Senior Vice President
Epidemiology, Registries and Risk Management
 Gerald.Faich@unitedbiosource.com

Dr. Faich is a recognized leader in drug safety and pharmaco-epidemiology with research focused in risk assessment, pharmacoepidemiology and the design and conduct of registries and streamlined trials for Phase IIIb and IV.

Currently a visiting scholar at the University of Pennsylvania and a past President of the International Society for Pharmaco-epidemiology, he is also a Fellow of the American Colleges of Physicians, Preventive Medicine and Pharmacoepidemiology. Dr. Faich has authored over 90 scientific papers and received numerous awards, including FDA's Outstanding Service Award for contributions to Post-Marketing Surveillance and Public Health.

Kelly Davis, MD
Vice President, Medical and Scientific Solutions
Epidemiology, Registries and Risk Management
 Kelly.Davis@unitedbiosource.com

Dr. Davis provides clinical expertise to assist clients in clinical trial and observational study design, operations and development strategy, as well as support for REMS and safety aspects of studies and projects, including client drug safety monitoring boards (DSMB) and endpoint adjudication committees.

Dr. Davis brings over 23 years of experience in medicine, as an endocrinologist, clinical researcher and pharmaceutical executive. She spent several years on the medical school faculty at the University of Pennsylvania in the Division of Endocrinology, Diabetes & Metabolism. Prior to joining UBC, Dr. Davis was Vice President and Therapeutic Area Head for Inflammation, Metabolism and Gastroenterology in Clinical Research and Development at Wyeth Pharmaceuticals.

Peggy Schrammel, MPA
Vice President
Registries and Post-Approval Development
 Peggy.Schrammel@unitedbiosource.com

Peggy Schrammel brings over 16 years of experience designing and executing post-approval clinical trials and patient registries across multiple therapeutic areas, with specific expertise in pharmacoconomics and outcomes research.

Ms. Schrammel has directed large global operational divisions, launched various corporate initiatives in the medical device and endpoint adjudication areas, and been responsible for strategic marketing and business development in the post-approval arena. She is a respected and a frequent speaker at national and international conferences on various subjects pertinent to post-approval research.

Her research focus includes community-based research, psychiatric and mental health research, and post-approval risk management strategies.

Catherine Sigler, DVM, MPH, PhD
Senior Epidemiologist
Epidemiology and Risk Management
 Catherine.Sigler@unitedbiosource.com

Dr. Sigler provides technical expertise in pharmaceutical safety issues related to epidemiologic or large streamlined clinical trial approaches and RiskMAPs. She has broad therapeutic experience and direct expertise in risk management strategies, including signal evaluation and the design, conduct and analysis of case-control, cohort, registries and large streamlined clinical trials. As a Senior Epidemiologist with UBC, Dr. Sigler has been primary author of, and leads teams in the creation of, RiskMAPs and REMS. Prior to her career at UBC, Dr. Sigler worked for Parke-Davis Research/Pfizer, focusing on risk management, epidemiology and pharmacovigilance.

Robert Gene Sharrar, MD, MSc
Executive Director
Epidemiology and Risk Management
 Robert.Sharrar@unitedbiosource.com

Dr. Sharrar has a long and distinguished career in public health and in pharmacovigilance. He spent 17 years as the city's epidemiologist for the Philadelphia Department of Public Health where he was responsible for monitoring the surveillance of communicable diseases, managing the various diseases control programs and conducting outbreak investigations of acute communicable diseases, including the investigation of Legionnaire's disease.

Additionally, he has 17 years experience with the pharmaceutical industry, monitoring the safety profile of products primarily in the post-marketing environment and developing, writing, implementing and monitoring risk management plans for newly marketed products.

Dr. Sharrar has authored many scholarly publications, been a Lecturer and Clinical Assistant Professor at prominent universities and received numerous academic and professional honors.

Wenda Brennan, RPh
Director, Pharmacovigilance
 Wenda.Brennan@unitedbiosource.com

Wenda Brennan directs the safety staff at UBC, manages the safety department, and provides input into pharmacovigilance plans and risk management plans.

Ms. Brennan brings over 20 years of pharmaceutical industry experience to UBC. Ms. Brennan has worked on clinical trial design, project management and data collection. With expertise in safety monitoring and risk management across a variety of therapeutic areas, Ms. Brennan has implemented key risk management plans. In addition, she has directed the safety reporting activities for two major product recalls, overseeing clinical and post-marketing safety reporting departments.

NEWS BRIEFS

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Janet Pientka, RN, BSN
Epidemiology and Risk Management Associate
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Ms. Pientka is a Project Manager with responsibility for project management activities related to risk management programs and epidemiologic and observational studies. Ms. Pientka tracks and coordinates activities as they pertain to project management milestones, deliverables, contracts and budget expectations. Her clinical research experience has included therapeutic areas such as in HIV/infectious disease, cardiology, pulmonary, neuroscience and oncology.

Ms. Pientka began her career as a nurse in medical surgical nursing and coronary critical care. She then served as a Clinical Research Coordinator in both hospital and outpatient settings identifying and enrolling patients and coordinating the operational aspects of NIH funded trials, industry sponsored trials and investigator-initiated trials. Subsequently, Ms. Pientka worked at a large, global pharmaceutical organization for 11 years in the areas of Clinical Research and Clinical Research Operations managing the scientific and operational aspects of clinical trials.

Matthew W. Reynolds, PhD
Executive Director
Epidemiology & Database Analytics
 Matthew.Reynolds@unitedbiosource.com

Dr. Reynolds directs the Epidemiology and Database Analytic services within UBC. This group uses the power of individual patient databases and electronic medical records for a broad array of epidemiologic studies, including those for natural history of disease, practice pattern assessment and safety surveillance.

Prior to joining UBC, Dr. Reynolds was the Senior Director of Risk Management and Safety Services at MetaWorks, Inc., which merged with UBC in January 2006. His extensive background in epidemiology also includes positions with AstraZeneca and Pharmacia Corporation (formerly Searle Pharmaceutical). He has led and published many evidence-based medicine projects, including full systematic literature reviews, meta-analyses and individual patient database analyses.

UBC LOCATIONS

UBC has offices, staff and/or resources in the following countries:

- **Belgium**
- **Canada**
- **Colombia**
- **Czech Republic**
- **Germany**
- **Hungary**
- **Russia**
- **Spain**
- **Sweden**
- **Ukraine**
- **United Kingdom**
- **United States**

Please visit our website, www.unitedbiosource.com, for a detailed list of all locations and contact information.

UBC Announces New Scientific Center

UBC is proud to announce the formation of the Center for Epidemiology and Database Analytics (CEDA). Formerly part of the Center for Health Economics, Epidemiology & Science Policy, UBC's epidemiology and database expertise has grown into its own Center, adding senior staff to both North America and Europe. The new Center will continue to focus on the high quality design and analysis of observational databases, including medical claims, electronic medical records, registries, safety databases, and other prospective data collection databases. CEDA researchers will also continue to employ a variety of other epidemiological and analytical tools in their work, including the conduct of focused literature reviews, design of observational and retrospective studies, as well as providing epidemiological support for the other scientific divisions within UBC.

Dr. Matthew Reynolds, who has worked on epidemiology, database and safety issues for over 10 years, will act as the Executive Director for CEDA. Dr. Beth Nordstrom, who has been a Senior Research Scientist in this area for several years with UBC, and Mr. Andrew Maguire, a new addition to UBC's office in London, will act as the Directors of CEDA for the U.S. and Europe, respectively.



Andrew Maguire Joins UBC as European Director, CEDA

Andrew R. Maguire, BSc (HONS), MSc has joined UBC's London office as the European Director of the Center for Epidemiology & Database Analytics (CEDA). Andy will oversee and lead

epidemiology, database, and safety-related projects in Europe, such as individual patient database analyses, prospective epidemiology and drug safety studies, and systematic literature reviews and meta-analyses.

Andy was most recently a Medical Research Manager at EPIC in London, a company dedicated to the use of longitudinal UK patient data for pharmaco-epidemiological, health economics and drug safety studies. As head of the Medical Research group at EPIC in the UK, he was responsible for epidemiological studies in several European countries and coordinated work to evaluate the importance of data quality.

He has held several posts in local government and university-based research organizations in Barcelona, principally in the areas of AIDS and cancer research. In 2000, he moved to the area of pharmaco-epidemiology and drug safety and worked for several major pharmaceutical companies. One of his key focus areas was the methodological development for the population risk-benefit of therapies, specifically Cox-2 vs. NSAIDs, which was used by European and U.S. regulatory authorities after the withdrawal of a popular NSAID due to risk factors.

Andy received his BSc (Hons) degree in applied science from the University of Kingston, England. He received his MS degree

in medical statistics, and is currently working on his PhD on risk benefit quantification of medical therapy in the general population, from the London School of Hygiene and Tropical Medicine, University of London.

Mike Page Joins UBC as Senior Director, Regulatory Affairs

Mr. Mike Page, BS, has joined UBC's Regulatory Affairs division to support our existing regulatory strategy services and to expand opportunities in this area. Mike was formerly with Pfizer Inc. where he was Director, Oncology in Worldwide Regulatory Strategy in New London, Conn. He has been involved in drug discovery and development for over 19 years. Mike has more than 12 years experience in regulatory affairs, providing strategic regulatory input to development programs in a number of therapeutic areas including oncology, urology, sexual medicine, neuroscience, rheumatology and cardiovascular medicine.

With extensive knowledge and experience in a variety of geographic regions, including the U.S., European Union and Japan, Mike's strategic leadership has resulted in positive outcomes in a number of critical regulatory authority interactions. He has provided regulatory input at all stages of product lifecycle from pre-clinical development through in-line product support. Mike led the regulatory team which obtained marketing authorizations for a novel atypical antipsychotic via the EU mutual recognition procedure; he also led the worldwide submission and approval activities for a major smoking cessation product. Most recently, Mike was Regulatory Lead for the immuno-oncology product portfolio. He has experience with both small molecule and biologic drug development.

Mr. Page graduated with honours with a Bachelor of Science degree in Biochemistry from the University of Hull, United Kingdom.

Dr. Asha Hareendran Joins UBC's London Office as Senior Research Scientist

Asha Hareendran, PhD, MPhil, MA, has joined UBC as a Senior Research Scientist. She brings extensive knowledge in research design and methodology in the area of health outcomes and has over 15 years of experience in the health care industry.

Dr. Hareendran's responsibilities include instrument development and validation and the design and management of research studies focused on patient-reported outcomes (PROs). She has worked in a variety of disease areas, including coronary artery disease, venous leg ulcers, benign prostatic hypertrophy, COPD and restless leg syndrome, among others. In addition, Dr. Hareendran has experience with the use of electronic PROs and the incorporation of translations into clinical trials. Prior to joining UBC, Dr. Hareendran was the Senior Director of Global Outcomes Research at Pfizer Inc. in Sandwich, UK.

Dr. Hareendran received her doctorate from the Postgraduate Institute of Medical Education & Research in Chandigarh, India, and her masters of philosophy in clinical social work from the National Institute of Mental Health and Neurosciences in Bangalore, India. She also has a master's degree in clinical medical and psychiatric social work from the Tata Institute of Social Sciences, Bombay, India, and a bachelor's degree in psychology from the University of Kerala, Trivandrum, India.

Dr. Stephan Lanes Joins UBC as Senior Research Scientist

Stephen Lanes, PhD, MPH, has joined UBC's Center for Epidemiology & Database Analytics as a Senior Research Scientist. Dr. Lanes focuses on projects using claims and electronic medical record databases, as well as projects supporting risk management activities.

Previously, Dr. Lanes spent 10 years at Boehringer Ingelheim Pharmaceuticals, where he most recently held the position of Distinguished Clinical Scientist. At Boehringer Ingelheim, he developed and applied epidemiologic methods to address effects of medications. Specifically, Dr. Lanes designed, conducted, and managed epidemiologic and clinical studies pertaining to drug safety and health outcomes in various therapeutic areas, including respiratory, cardiovascular, HIV and CNS.

Dr. Lanes is a member of the International Society of Pharmacoepidemiology, where he has served on the Board of Directors and Chaired the Committee on Good Pharmacoepidemiology Practices. Previously, he was Principal Epidemiologist at Epidemiology Resources Inc. in Boston. Dr. Lanes has published many papers on epidemiologic studies and epidemiologic methods in the peer-reviewed medical literature and presented his work at scientific meetings and to regulatory authorities worldwide.

Dr. Lanes received his doctorate in epidemiology and Masters of Public Health from the University of Pittsburgh.

Dr. David Vanness Joins UBC as Research Scientist

David J. Vanness, PhD, has joined UBC's Center for Health Economics and Science Policy as a Research Scientist. Dr. Vanness has over 10 years of experience in health economics,

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SPOTLIGHT ON SCIENCE

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Yu O, **Boudreau DM**, Buist DS, Miglioretti DL. "Statin Use and Female Reproductive Organ Cancer Risk in a Large Population-Based Setting." *Cancer Causes Control* 2008 Nov 30; [Epub ahead of print]

McGill University Offers Summer Course in Pharmacoeconomics

JUNE 1 - 4, 2009

Faculty: **J. Jaime Caro MDCM, FCRPC, FACP**, Adjunct Prof. of Medicine, Adjunct Prof. of Epidemiology & Biostatistics, McGill Univ. & Senior Vice President of Health Economics, United BioSource Corp.; **L. Clark Paramore, MSPH**, Executive Director, Center for Health Economics & Health Policy, United BioSource Corp.; **Jörgen Möller, MSc**, Vice President of Modeling, United BioSource Corp.; **Elizabeth Merikle, PhD**, Research Scientist, Center for Health Outcomes Research, United BioSource Corp.

The assessment of pharmaceuticals has expanded beyond efficacy and safety to cover economic implications and other consequences. This course provides a detailed introduction to the key concepts of this field. Following the methodological guidelines recently issued by IQWiG for Germany, the course details the use of efficiency to inform pricing decisions and contrasts this with the cost/QALY approach that prevails elsewhere. Budget impact analysis is also covered. An example is presented in detail to demonstrate how simulation models are developed and their advantages relative to 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 ends with techniques for presentation of results to decision makers in the public and private health care systems.

For more information, please visit the website (<http://www.mcgill.ca/epi-biostat-occh/summer/coursestimetables/>) or email Diane Gaudreau (diane.gaudreau@clinepi.mcgill.ca).

UBC is seeking highly qualified and motivated researchers to join our expanding international team.



At the
convergence of
science, technology
and innovation

UBC offers a flexible, stimulating and collegial environment where everyone is dedicated to conducting the highest quality research in the industry. Positions are available across the **UNITED STATES, CANADA AND EUROPE.**

We are looking for INNOVATIVE RESEARCHERS with experience in the following areas:

- Pharmacoeconomics
- Econometrics
- Decision analytic and/or simulation modeling
- Patient-reported outcomes
- Instrument development & psychometric evaluation
- Biostatistics
- Data analysis
- Epidemiology
- Systematic literature reviews
- Pricing & Reimbursement

Who excel at:

- Strategic consultation
- Project management
- Data interpretation & dissemination
- Research presentations
- Publication development
- Effective communication skills
- Global knowledge and management

For more information and consideration, please visit our website at www.unitedbiosource.com/careers.



Evidence Matters.

UBC Would Like Your FEEDBACK on *EvidenceMatters*

UBC produces our newsletter, *EvidenceMatters*, three times a year to provide our clients and colleagues with informative and useful articles on issues facing our industry, including the increasing need for evidence to support product development and marketing.

To ensure that we are providing you with the information that you seek, and in the format that you prefer, we will be sending our readers a short survey via email regarding our newsletter. We would greatly appreciate you taking a few minutes of your time to complete this survey so that we may continue to improve our newsletter to meet your needs.

If you do not currently receive the newsletter via email, you can take the survey on the UBC website at <http://unitedbiosource.com/survey>.

We appreciate your feedback!

NEWS BRIEFS

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econometrics, and health services research in both clinical and academic research environments.

Dr. Vanness was on the consulting staff of the Mayo Clinic, including two years as Asst. Professor of Health Services Research at the Mayo Clinic College of Medicine. During that time, Dr. Vanness focused on the development of microsimulation and Bayesian methods for cost-effectiveness analysis and participated in applied health economics research in several clinical areas. He also served as an internal consultant on pricing strategy, managed care contracting, and strategic operations.

Previously, Dr. Vanness served as an Asst. Professor in the Department of Population Health Sciences at the University of Wisconsin (UW) School of Medicine and Public Health. He was a member of the UW Paul P. Carbone Comprehensive Cancer Center and an affiliate member of the NIH-funded Cancer Intervention and Surveillance Modeling Network

(CISNET) Colorectal Cancer Working Group. He served as the economics investigator for the National CT Colonography Trial, in which he coordinated the simultaneous application of all three CISNET colorectal cancer microsimulations to the economic evaluation of screening with “virtual” colonoscopy compared to current screening guidelines.

Dr. Vanness has taught several graduate-level courses in health economics and the economic assessment of medical technologies at the UW School of Medicine and Public Health, and in cost-benefit analysis at the LaFollette School of Public Affairs. He has served as a contributor, co-organizer, and co-chair of methodological workshops and sessions at several industry conferences and serves as a referee for numerous industry journals, including the *Journal of the American Medical Association*.

Dr. Vanness earned a bachelor's degree in economics and government, *summa cum laude*, from Georgetown University, and his master's and doctoral degrees in economics from the University of Wisconsin, Madison.

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EvidenceMatters is a publication of United BioSource Corporation, providing evidence-based solutions that enhance patient care and help people live longer, healthier lives.

