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SCIENCE & POLICY OPINION

Benefit/Risk Evaluation: Use of Simulation to Support Decision Making

By Alex Ward, PhD



Does the value of the expected health benefit from new drug therapies warrant the risk of adverse events? When there is clear-cut evidence of benefit over risk, these decisions are straightforward. But more often, such decisions have to be made in the face of uncertainty. The much tougher judgments arise when the risks vary with patient, treatment regimen, or disease characteristics (e.g., prior medical history, disease severity, prior failed therapies), or when evaluating rates for various types of events that are not life-threatening. In these common situations, it may be better (although not simple or straightforward) to assign a value to each benefit and adverse effect and then determine the net impact of the weighted risks and benefits. Simulation using quantitative disease models is a tool

that can help us make better informed benefit-risk judgments when we are faced with the challenge of making decisions in the context of much ambiguity and complexity.

Even carefully-tested drugs can produce unexpected side effects; they may cause rare events, such as spontaneous liver failure, or more common events, such as heart attacks. While simulations cannot identify completely unanticipated side effects, they can provide for risk-benefit assessments informed by the data collected from a variety of sources, including efficacy trials, meta-analyses,

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A Blended Learning Approach to Training

By Justin Huss, MS

The need for consistent and effective training is a critical component in the success of clinical trials. What is the most efficient way to deliver training while accomplishing educational objectives? Some prefer traditional face-to-face training for the expert instruction and group interaction while others prefer the convenience and self-paced style of e-learning.

Recent research suggests face-to-face training is still the preferred method of delivery for many forms of training because it facilitates live interactive learning while remaining cost-effective by reducing the need for remediation activities.¹ However, some organizations value the business impact and benefits that accompany e-learning, such as workforce effectiveness, reduced travel costs, and improved retention.²

Blended learning is the combination of several approaches to learning. It is a learning method where more than one delivery mode is being used with the objective of optimizing the learning outcome and cost of program delivery.³ The most common types of blended delivery modes include a combination of live face-to-face training, e-learning (CD-ROM, DVD or online), job/study aids and tip sheets. The idea is to use these different mediums in a way which will have the most impact on learners and their learning styles.

Many organizations have begun to adopt this approach and report exceptional results from their initial blended learning initiatives. Learning objectives can be obtained in 50 percent less class time than traditional strategies and costs of travel and time have been reduced by up to 85 percent.⁴

A traditional blended training experience for clinical trial professionals may include e-learning pre-work, a live face-to-face training session (usually at an

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Investigator Meeting [IM]) and an e-learning refresher course which is launched 3 - 6 months later. The required e-learning pre-work typically serves as a fact finding and general introduction into material which will be presented at the IM. The live face-to-face training sessions have experts on hand to present pertinent didactic presentations, answer questions and provide guidance for rater training exercises and various breakout sessions. The refresher e-learning courses reinforce important discussion points and allow raters to receive instant feedback while scoring patient video interviews. Job aids and tip sheets are commonly provided throughout the process to help guide raters and minimize common mistakes.

Blended learning approaches to training have multiple advantages.

- They offer a similar training experience in multiple mediums. This satisfies different learning styles (auditory, tactile and visual).
- They can provide trainees with several practice opportunities. Practice opportunities will result in significantly fewer application errors.⁵
- They allow for more discussion, practice and interaction in the face-to-face setting since trainees are already familiar with the content.
- They help solve the traditional business problems of speed, scale and impact.⁶

As described, a blended learning experience may be the right fit in many situations. Blended learning encompasses the advantages of both e-learning and face-to-face training while proving to be beneficial to both raters and organizations.

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Credential Variability in Global Clinical Trial Raters

By Marian A. Ormont, MD and Adam Butler

The global expansion of phase II and III clinical trials has altered the pool of clinicians participating in any given clinical trial. International trials now employ clinicians at many sites, in many countries, who speak many different languages. Consider the clinical trial which involves sites in the United States, Canada, Latin America, Western Europe, Eastern Europe, and Asia; the potential exists for great variety in credentials, experience and proficiency among the clinical professionals who support it. In addition, the make-up and conduct of both clinical practice and clinical research is very different from region to region.

Inherent in the design of a given clinical trial is the need to specify appropriate efficacy and safety measures. Some measures (such as laboratory tests) have a high degree of objectivity, and apart from the need to perform the procedure correctly, little investigator expertise is required to gain an accurate and reproducible result on such a measure. On the other hand, measures which require investigator assessment and scoring are more subjective and require a different level of experience and education on the part of the clinical researcher. This is true of many of the efficacy measures employed in psychiatry and neurology clinical trials. It could be said that the degree of objectivity of the specified efficacy measure is inversely proportional to the need for investigator proficiency in efficacy measure administration and assessment.

In many trials, raters are frequently required to employ interview-based rating scales to assess subject-reported symptomatic change. Subjective endpoints are included in virtually all central nervous system (CNS) clinical trials, as well as in many trials in such other disease areas as oncology, pulmonology, gastroenterology, dermatology, urology and gynecology. Sponsoring companies rely heavily on these raters to perform sound research interviews, to accurately evaluate the subjects' reported symptoms, and to score the instrument reliably. Raters must be consistent in their administration of the rating scales and in their adherence to scoring conventions—both those that are scale-specific and those that are sponsor-specified. Raters with diverse credentials and experience are likely to approach this task with different skill sets and different levels of rating scale administration and scoring proficiency. Signal detection is clearly linked to inter-rater and intra-rater reliability; thus dissimilar pools of raters may present an obstacle to the ultimate goal of accurate separation of study drug from placebo and/or active comparator.

Pharmaceutical companies frequently require physicians to rate certain scales, most notably Clinical Global Impression scales. However, they are less rigid in their requirements

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epidemiologic studies, registries, and spontaneous reports. Such a simulation provides a structured and quantitative method to support complex assessments and allows us to inform decision making based on all the available evidence. Developing a model provides for characterizing uncertainty and exploring the impact of variability of the inputs. This approach enables the weighted averaging of risks and benefits to suggest whether, on balance, use of the therapy is warranted.

Using sophisticated software and advanced mathematical modeling is essential to creating realistic benefit-risk simulations. Discrete event simulation considers multiple competing risks and benefits by sampling from probability distributions of event times, which are, in turn, dependent on the estimated occurrence functions. Simulating individual patients allows us to combine epidemiologic data and clinical evidence into a single framework, and run scenarios where the medication is prescribed to subgroups carrying differing risk profiles. This approach supports exploring the implications for vulnerable subgroups, such as the frail elderly with multiple risk factors, and allows us to rapidly ask “what if” questions. Simulations may be helpful for determining the potential effectiveness of risk minimization interventions physicians might adopt and any failure points in the process.

To develop such realistic simulations, the design decisions, data inputs, risk functions and value assessments quickly become intricate and multifaceted—and so a multidisciplinary team is essential to conduct these studies successfully. The team members include researchers who ensure we apply

- Epidemiologic principles appropriately,
- Design data analysis projects to develop the required functions and inputs, and
- An in-depth understanding of how to implement these correctly to design and build a sophisticated simulation tool.

Using sophisticated software and advanced mathematical modeling is essential to creating realistic risk-benefit simulations.

Validation also becomes an essential aspect of the project in order for the model to be credible.

Our understanding of the continuous benefit-risk balance for products occurs throughout a product’s lifecycle, as such risk assessments are often made when there is imperfect information on the frequency and severity of the risks. The greatest value of a simulation tool is the development of a systematic quantitative framework that supports our assessment of joint effects, and rapid integration of new data as they become available. Development of realistic simulations helps us obtain a more complete picture of the implications of the information available to support assessments of both the potential benefits and harm.

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for clinical staff rating other scales such as the Hamilton Depression Rating Scale.

For these other scales, which may be primary efficacy variables, sponsors may require a certain number of years of scale experience or of clinical or research experience with the population under study. For some studies, almost no experience or credential limits are defined.

CNS clinical trial raters in the United States are varied in their level of education and have various credentials. UBC has received Rater Experience Surveys from raters around the world. In the US, that pool has included physicians, research scientists, nurses, social workers, dieticians, raters with

Associates Degrees, raters with Bachelors Degrees, college interns, as well as many other credentials. In fact, about half of the raters from the US and Canada in one UBC database are physicians (MD) or physician-equivalents (DO, PhD, PsyD), and about half of raters from the US and Canada have other types of credentials; a ratio of 0.99.

The situation in other countries is significantly different. In Asia and the Middle East, the ratio of physician and physician equivalent raters to other raters is 2.1 (1074/520) and 3.0 (444/146) respectively. The ratio is 6.8 (3005/440) in Western Europe, 37.9 (795/21) in Latin America, and 56.9 (2505/44) in Eastern Europe. These numbers identify a

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significant difference in the CNS clinical trial rater pool between the US and other countries.

Region	Doctor (or equivalent)	Non-Doctor	Ratio
US	3355	3372	0.99
Asia-Pacific	1074	520	2.07
Middle East	444	146	3.04
W. Europe	3005	440	6.83
Latin America	795	21	37.86
E. Europe	2505	44	56.93

Compounding the differences in rater credentials is the great variety of training received by raters in different regions (even those with similar credentials) prior to their clinical trial involvement.

Whether these international differences in physician training and experience translate into rating scale administration and

scoring discrepancies is unclear. Future UBC research will focus on how these differences impact study conduct and outcomes. Separating such effects on ratings from cultural and language effects would be difficult. However, it is worth considering whether the cause of inter-rater reliability would be well-served if site selection were tailored to control first for credentials and then for rater experience.

Not all raters are the same. This is true not only within the US, but across the globe. It would appear that rater credentials and experience should be considered in the site selection process. In addition, rater training goals should be revisited so as to maximize the educational nature of the experience for specific groups of raters. Accurate training is of great importance to the establishment of inter-rater reliability which, in turn, is one of the keys to any clinical trial that relies on a subjective endpoint. The goal for successful clinical trials is to obtain inter-rater reliability across all raters in all countries.

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

SCIENCE POLICY CORNER

- **Comparative Effectiveness Research (CER) is once again *de rigueur* for federal policymakers seeking to improve health care quality, evidence, and decision making.**

In 2007, CER was the focus of a number of Congressional hearings and legislation, IOM workshops, and other stakeholder discussions. Although common ground was not agreed to by the time Congress adjourned in December, momentum continues. Similar proposals are expected to be incorporated into health-related legislation in 2008—beginning with a planned bill to amend physician reimbursements from Medicare—sometime in early spring.

- **Appropriations funding for FY08 underscored the perceived value of the work of the Agency for Healthcare Research and Quality (AHRQ)**

Despite a 1.75 percent across-the-board cut for all programs in the Labor-HHS appropriations bill, AHRQ received \$334 million, a 4.7 percent (\$15 million) increase from FY07, including a doubling in funding for the Effective Health Care Program which undertakes most of the agency's comparative effectiveness research, evidence synthesis, and health technology assessment activities.

- **Despite the increase in AHRQ's funds, a number of unresolved issues remain.**

Will congressional initiatives include an expansion of AHRQ's current authority, or will a new government entity be established with oversight responsibility? To what extent will the funding and governance of any new organizations be public or private? Will new initiatives include enough funding to run comparative clinical trials, or focus on expanding current evidence and literature review activities? CER remains a bipartisan issue with both public and private sector support. The proverbial "policy window" remains wide open and UBC will provide analysis on these changes throughout the year.

Controlling for Selection Bias in Claims Studies of Medication Adherence

By Feng Pan, MA

Administrative claims data has been widely used to study patient adherence to medication treatments. Compared to methods such as patient self-report, clinician perception, pill counts and electronic measurement devices, adherence studies using claims databases are less time consuming and less expensive. More importantly, the large claims databases provide a vast amount of information about the pattern and timing of drug exposure, and they allow us to generalize the findings to large populations.

In evaluating adherence effects across different medical therapies, however, observational studies do present a great challenge. Because drug assignment in observational studies is not randomized, different treatment groups may have large differences on their observed and unobserved characteristics, and these differences can lead to biased estimates of treatment effect. Traditional multivariate adjustments can control for observed variables, but cannot control for unobserved characteristics.

The instrumental variable approach is a common tool to eliminate such selection bias in econometric analysis. An instrumental variable must be correlated with the choice of treatment but uncorrelated with patient adherence. When such an instrument is used in the regression, the effect of unobserved factors on the choice of treatment will be removed, and the estimates of treatment effect will be unbiased. However, as the administrative claims data provides little information that would predict patients' choice of treatment, it is often difficult to find an instrumental variable.

Two other econometric methods are available to minimize the selection bias: propensity scoring and fixed effect modeling. The idea behind the propensity score approach is to first summarize the probability of being assigned to the treatment, given a set of observed covariates. Individuals are then matched or grouped into strata based on their propensity score. Once the propensity scores and covariates are balanced between treatment and control groups within each stratum, the treatment assignment within each stratum can be functionally regarded as random. A limitation of the propensity score method is that it only controls for unobserved factors to the extent that they are correlated with the observed covariates. It cannot fundamentally remove the selection bias. However, compared to single-stage multivariate models, it is more robust with respect to model specification errors since there is no functional form assumed in the propensity score approach.

The fixed effect model, on the other hand, can control for some of the unobserved factors but requires longitudinal panel data. In a fixed effect model, each patient must have at least two periods of observations: one prior to the treatment

assignment in which all patients are subject to the same treatment, and the other after the treatment assignment. Compared to the propensity score method, a fixed effect model can eliminate the selection bias due to time invariant, unobserved patient characteristics or other factors. But it is not able to control for the unobservables that change over time.

We applied both the propensity score method and fixed effect model in our study, *"Impact of Fixed-Dose Combination Drugs on Adherence to Prescription Medications."* Fixed-dose combination drugs are two or more drugs produced in a single tablet to treat one disease with complimentary actions or treat multiple clinical conditions. Using longitudinal data

from a large health insurance claims database, we assess the adherence effect of fixed-dose combination drugs, compared to a multi-pill regimen. Our analyses showed that the two therapies users were significantly different in terms of baseline adherence rates, patient characteristics and many other observed covariates. The analysis results from a propensity score method and a fixed effect model were only slightly different in this case.

In conclusion, three methods are available in observational studies using administrative claims data to control for selection bias. The instrumental variable approach is the most unbiased method, but requires identification of a valid instrument. The fixed effect model is less able to remove bias, but requires longitudinal panel data. The propensity score method, although it cannot control for the unobserved factors, is less sensitive to model misspecification.

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...the large claims databases provide a vast amount of information about the pattern and timing of drug exposure, and they allow us to generalize the findings to large populations.

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Upcoming Presentations

International Stroke Conference 2008 (ISC)

Feb 20–22 2008, New Orleans, LA, USA

“Atorvastatin for Secondary Stroke Prevention: an Economic Evaluation of the SPARCL Trial Using Discrete Event Simulation” **Kongnakorn T¹, Ward A¹, Roberts CS², O’Brien JA¹, Proskorovsky I¹, Caro JJ¹**; ¹United BioSource Corp.; ²Pfizer, Inc.

International Society for the Study of Women’s Sexual Health (ISSWSH) 2008 Annual Meeting

Feb 21–24, 2008, San Diego, CA, USA

“The Impact of Lower Urinary Tract Symptoms on Women’s Sexual Health: Results From the EpiLUTS Study” **Coyne K¹, Sexton C¹, Kopp Z², Thompson C¹, Irwin D³, Milsom I⁴, Chapple C⁵, Tubaro A⁶, Wein A⁷**, and the EpiLUTS Working Group; ¹United BioSource Corp.; ²Pfizer Inc.; ³Univ. of North Carolina; ⁴Göteborg Univ.; ⁵Royal Hallamshire Hospital; ⁶Sant’ Andrea Hospital; ⁷Hospital of the Univ. of Pennsylvania

“The Prevalence of Sexual Activity and Sexual Desire in Women: Results from EpiLUTS” **Coyne K¹, Sexton C¹, Kopp Z², Thompson C¹, Irwin D³, Milsom I⁴, Chapple C⁵, Tubaro A⁶, Wein A⁷**, and the EpiLUTS Working Group; ¹United BioSource Corp.; ²Pfizer Inc.; ³Univ. of North Carolina; ⁴Göteborg Univ.; ⁵Royal Hallamshire Hospital; ⁶Sant’ Andrea Hospital; ⁷Hospital of the Univ. of Pennsylvania

2008 American Association for Geriatric Psychiatry (AAGP) Annual Meeting

Mar 14–17 2008, Orlando, FL, USA

Presented as part of the symposium: Dementia Screening in Clinical and Community Settings

“What to Know When Implementing a Screening Program” **Steffens D¹, Borson S², Ashford W³, Frank L⁴**; ¹Duke Univ. Medical Center; ²Memory Disorders Clinic and the ADRC Satellite Univ. of Washington; ³Stanford/VA Aging Clinical Research Center; ⁴United BioSource Corp.

2008 Annual Meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI)

Mar 14–18 2008, Philadelphia, PA, USA

Oral Presentation

“Use of Fluticasone Propionate/Salmeterol Fixed Combination as Initial Asthma Controller Therapy in Children in a Commercially

Insured Population” **Friedman HS¹, Eid NS², Crespi S³, Wilcox TK⁴, Reardon G⁵**; ¹Analytic Solutions; ²Univ. of Louisville; ³Schering-Plough; ⁴United BioSource Corp.; ⁵Informagenics, LLC

23rd Annual European Association of Urology Congress

Mar 26–29, 2008, Milan, Italy

Poster Presentation

“The Prevalence, Bother, and Overlap of LUTS in the US, UK, and Sweden: EpiLUTS” **Coyne KS¹, Sexton C¹, Kopp Z², Irwin D³, Milsom I⁴, Aiyer L², Tubaro A⁵, Chapple C⁶, Wein A⁷**, on behalf of the EpiLUTS Team; ¹United BioSource Corp.; ²Pfizer Inc.; ³Univ. of North Carolina; ⁴Göteborg Univ.; ⁵Sant’ Andrea Hospital; ⁶Royal Hallamshire Hospital; ⁷Hospital of the Univ. of Pennsylvania

American Thoracic Society (ATS) 2008 International Conference

May 16–21, 2008, Toronto, Ontario, Canada

Poster Presentations

“Attributes of Cough Severity from the Patients’ Perspective” **Vernon MK¹, Leidy NK¹, Nacson A¹, Nelsen LM²**; ¹United Biosource Corp., Bethesda, MD, USA; ²Merck & Co., North Wales, PA, USA

“Measurement of Cough Severity: A Review of the Literature” **Vernon MK¹, Leidy NK¹, Nacson A¹, Nelsen LM²**; ¹United Biosource Corp., Bethesda, MD, USA; ²Merck & Co., North Wales, PA, USA

American Urological Association 2008 (AUA) Annual Meeting

May 17–22, 2008, Orlando, FL, USA

Podium Presentations

“The Impact of Lower Urinary Tract Symptoms on Men’s Sexual Health: Results from EpiLUTS” **Coyne KS¹, Sexton C¹, Kopp Z², Irwin D³, Milsom I⁴, Aiyer L², Wein A⁵, Chapple C⁶, Tubaro A⁶, Wein A⁶**; ¹United BioSource Corp.; ²Pfizer Inc.; ³Univ. of North Carolina; ⁴Göteborg Univ.; ⁵Hospital of the Univ. of Pennsylvania; ⁶Royal Hallamshire Hospital; ⁷Sant’ Andrea Hospital

“The Impact of Lower Urinary Tract Symptoms on Women’s Sexual Health: Results From the EpiLUTS Study” **Coyne KS¹, Sexton C¹, Kopp Z², Thompson C¹, Irwin D³, Milsom I⁴, Chapple C⁵, Tubaro A⁶, Wein A⁷**; ¹United BioSource Corp.; ²Pfizer Inc.; ³Univ. of North Carolina; ⁴Göteborg Univ.; ⁵Royal Hallamshire Hospital; ⁶Sant’ Andrea Hospital; ⁷Hospital of the Univ. of Pennsylvania

Evidence Synthesis for Decision Modelling

April 14-18, Boston, MA

UBC is organizing the *Evidence Synthesis for Decision Modelling Workshop* in collaboration with faculty from the Universities of Leicester and Bristol (UK).

This is the first time the course will be conducted in the United States.

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This course is intended for: (a) Anyone undertaking health technology assessments, including cost-effectiveness analyses, and (b) Statisticians, with or without experience in meta-analysis, who wish to learn about Bayesian methods for evidence synthesis particularly in the context of cost-effectiveness analysis.

The methods taught in the course are designed to be compatible with the recent guidance issued by the National Institute for Clinical Excellence, requiring probabilistic methods on cost-effectiveness models. The course focuses particularly on Bayesian methods for evidence synthesis that can be integrated within a probabilistic modelling framework, and can be used to statistically combine evidence from a range of structures. The course is built around a series of examples using the WinBUGS statistical software.

Recent Changes in the Spanish Health Care System and New Opportunities for Health Technology Assessment *By Yolanda Bravo, MSc, MA*

The Spanish health care system has undergone major changes since the approval of the Constitution (1978), including the transition from a means-tested system of social security to a National Health Service (NHS) with universal coverage, as defined by the 1986 General Health Care Act; the transition from an insurance-oriented system into a tax-funded system (1986 to 1999); the administrative and political decentralization of the health care system to the regional level (1981 to 2002); and finally, the introduction of the principle of regional fiscal co-responsibility (2001 fiscal reform), also applied to the national budget of health care.

The decentralisation of the state in Spain is mainly based on the concept of devolution (i.e., the responsibility for health care is transferred from the central administration to politically elected regions, in line with the quasi-federal constitutional structure of the country).^{1,2} Since 2002, the governance of the health care system has completely devolved to the 17 *Comunidades Autónomas* (autonomous communities, ACs), which hold planning powers, purchasing and provision, as well as the capacity to organise their own regional health services. At the central level, the Spanish Ministry of Health assumes responsibility for certain strategic areas, including general coordination and basic health legislation, definition of a benefits package guaranteed by the NHS to all Spanish citizens, pharmaceutical policy (market authorisation, pricing and reimbursement) and training and research.³

The Pharmaceuticals Department of the Ministry of Health (Dirección General de Farmacia y Productos Sanitarios, MSC) is in charge of determining which pharmaceuticals should be co-financed by the state budget and setting their price. The central government has the right to establish the reference price for all pharmaceutical types (groups or products), whereas over-the-counter products are only regulated based on quality and safety.^{4,5} Since 1999, the Pharmaceuticals Agency (Agencia Española de Medicamentos y Productos Sanitarios) is in charge of evaluating the clinical effectiveness of new brands and authorising their commercial registration. The requirements for submission of Pricing and Reimbursement dossiers (P&R) are not formally established by the MSC, but the standard procedure is to submit a technical report with details on the clinical comparative advantage of the candidate, the burden of disease, and any quality of life evidence and pharmacoeconomic results that can support the producer claims. On the other hand, the regions hold extensive powers over the implementation of centrally issued legislation in the pharmaceutical field (e.g., regional tenders for hospital products and medicines, regional reference pricing systems by active ingredients, establishment of financial incentive schemes such as the 'prescription profiles' sent to physicians, etc.).³

Since the mid-1990s, a number of regional health technology assessment (HTA) agencies have been created in Spain to provide technical support to policy-makers on technology selection and implementation in the Spanish NHS and to offer regional prescribing guidelines. The Institute of Health Carlos III (Madrid) is in charge of, among other responsibilities on training and research, HTA activities at a national level. The institute performs these functions through the Agency for Assessment of Health Technology (Agencia de Evaluación de Tecnologías Sanitarias, AETS). Among other functions, AETS is responsible for the coordination of HTA activities in Spain.³ The list of agencies developed at a regional level and affiliated to the International Network of Agencies for Health Technology Assessment (INAHTA)⁶ is extensive:

OSTEBA	Basque Office for Health Technology Assessment (País Vasco, 1992)
CAHTA	Catalan Agency for Health Technology Assessment & Research (Cataluña, 1994)
AETSA	Andalusian Agency for Health Technology Assessment (Andalucía, 1996)
AVALIA-T	Galician Agency for Health Technology Assessment (Galicia, 1999)
UETS	Unit for Health Technology Assessment (Madrid, 2003)

In 2003, the lead regions in the HTA field created a supra-regional appraisal committee for new pharmaceuticals (el Comité Mixto de Evaluación de Nuevos Medicamentos), setting up common guidelines for the evaluation of new pharmaceuticals based on their degree of innovation, and their clinical and economic comparative advantage *versus* standard treatment(s) to offer regional prescribing guidelines.⁷ However, these guidelines do not allow for the participation of the industry in the appraisal process.

Spain belongs to a group of federal OECD countries with a high number of HTA agencies operating at a national and regional level. This group of countries has three or more HTA agencies registered at INAHTA, with the extreme cases of the UK and Spain, which currently have five and six registered organisations, respectively.⁸ However, in the case of the UK, four out of the five agencies affiliated are academic units based at Universities (Birmingham, Southampton, York) that provide services to the UK NHS via NICE and the HTA programme, carrying out important dissemination activities and serving the whole nation or at least the English and Welsh population. In this sense, the case of Spain is paradoxical, as all the agencies currently operating are non-profit public

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Recent Changes

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agencies affiliated to a regional health service and serving the corresponding population of the AC (with the exception of the national agency AETS).

The *New Medicines Act*⁴, approved in July 2006, has recently replaced the 1990 *Pharmaceuticals Acts*.⁵ The *New Medicines Act* focuses on the principle of selective financing of medicines and specifies the system for public reimbursement of pharmaceuticals and their price-setting (i.e., economic evaluation, reference prices, price controls). In this sense, it enforces some of the principles already stated in the 2004 *Pharmaceutical Policy Strategic Plan*,⁹ stating that the ‘therapeutic utility’ (as well as the degree of innovation) will be key factors taken into consideration to determine whether a new medicine will be publicly reimbursed (art 89.1). The therapeutic utility of new medicines compared to the already available products will be determined based on “...reports on therapeutic utility undertaken by the Inter-Ministerial Pricing Commission Agency, who will work with an external network of independent experts nominated by the ACs” (art 90.3). Although there are still unresolved issues regarding the use of HTA, mainly of organisational and methodological nature, some regions have already published some pharmacoeconomic guidelines and have their own regional agencies evaluating new medicines’ therapeutic utility. At this early stage we can say, at least, that there is a growing relevance of HTA in Spain, that the role of regions is becoming more important—constituting the new ‘clients’ for the pharmaceutical industry—and that the *New Medicines Act* might open new market opportunities in the field of HTA for the private sector.

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Pricing of Pharmaceuticals in the UK: Implications of Reform to the Pharmaceutical Price Regulation Scheme (PPRS)

By Stuart Carroll, BA (Hons), MSc

Spiralling health care costs and tighter budget constraints have impelled modern governments to place additional emphasis on allocating scarce resources efficiently and effectively. The pricing of pharmaceutical drugs is one such area. In the UK, approximately 10% of the entire National Health Service (NHS) budget—roughly £11 billion per year—is spent on drugs and medicines. Of this expenditure, £8 billion is exhausted on branded products alone.¹ It is from this premise that national decision-makers have paid increasing attention to the way in which drugs are reimbursed.

Pricing & Reimbursement in the UK

The *Pharmaceutical Price Regulation Scheme* (PPRS) is the voluntary agreement between the UK Department of Health (DH) and the Association of the British Pharmaceutical Industry (ABPI) whereby companies negotiate profit rates from sales of branded drugs to the NHS every five years. The scheme has been running since 1956 (formerly the *Voluntary Price Regulation Scheme*) but has recently been the subject of growing scrutiny and debate.²

Advocates argue that the PPRS has facilitated the sustained retention of UK-based drug companies, instituting the appropriate mix of incentives between investment in research and development (R&D) and profit-making.³ Opponents contend that the scheme is arcane, serving more the purposes of industry rather than delivering “value for money” to NHS patients.⁴

How Does the PPRS Work?

The workings of the PPRS are complex. However, in broad terms the scheme encompasses two key elements:

- 1) **Profit controls**—
These set a maximum level on company profit earning. Exceeding this ceiling requires repayment of excess profits to the DH. However, the controls also enable companies to increase prices should profits drop below a given minimum.
- 2) **Price controls**—
These provide industry with the freedom to set initial prices for new medicines but with subsequent restrictions. The controls also include price cuts as agreed during scheme renegotiations. Companies enjoy some flexibility in selecting products for targeted price cutting; a system known as “price modulation”.⁵

Objectives of Pricing Systems

The PPRS is unique amongst other pricing systems. Many countries employ reference pricing, but increasingly there has been gravitation towards the use of formal economic evaluation as policy goals have sharpened.

Common objectives of pricing and reimbursement systems include:

- 1) **Delivering value for money:** providing medicines at fair and affordable prices to the health care system, patients and the taxpayer.
- 2) **Encouraging and rewarding innovation:** incentivising research and rewarding innovation to encourage the role of the pharmaceutical industry in the development of health care and medical advances.
- 3) **Assisting the efficient uptake of new medicines:** supporting the introduction of new pharmaceuticals particularly in priority disease areas.
- 4) **Facilitating stability and sustainability in pharmaceutical provision:** fostering a durable and open market that is attractive to investors.^{5,6}

PPRS: The Beginning of the End?

In 2005, the UK Office of Fair Trading (OFT) initiated a market study into the PPRS to evaluate whether the scheme optimises the accomplishment of the above objectives.⁵ The OFT published its findings earlier this year which are now subject to a consultation period between government and industry.

The OFT's key recommendation is to replace the PPRS with *ex ante* value-based pricing (VBP). Prices would be determined during the licensing process following assessment of a new drug's clinical and cost-effectiveness, with periodic review performed as new data becomes available. Bodies such as the National Institute of Health and Clinical Excellence (NICE) would take responsibility for evaluation. The OFT has estimated the move could save the NHS £500 million.⁵

In principle, VBP may foster allocative and dynamic efficiency in the NHS. However, the devil is in the detail. Moving to a VBP system raises fundamental questions about how cost-effectiveness should be measured.⁶ The OFT report is less forthcoming in this regard.

Reaction to the OFT's findings has been largely approving. The UK government has promulgated "support" for the "principle of reform,"^{7,8} whilst a handful of prominent publications have championed the OFT's core recommendation.^{4,6} Although the ABPI has warned that any overhaul could hit investment, it has been suggested that reform of the PPRS could commence in early 2008.⁹

The Road Ahead

Should the OFT's recommendations be accepted, what are the likely implications for industry?

1) The "fourth hurdle" — raising the bar

VBP is likely to tighten the terms of reference governing cost-effectiveness and enhance the scope of NICE. Companies will need to more cogently and completely demonstrate product value to clear an elevated "fourth hurdle". This has implications for the design of clinical trials and the possible employment of subgroup analyses. Companies will need to better handle the reality of incomplete or "missing" data, utilising evidence-based techniques such as meta-analysis where appropriate.

2) Health economics & the product pipeline

Given a stricter definition of cost-effectiveness and the concomitant squeeze on reimbursement, decision-making today will impact evermore on tomorrow. Practical constraints dictate that development of the product pipeline is limited to choices between competing alternatives invariably in the absence of perfect information.

Although health economics has traditionally played an "end game" role, upfront application of basic principles is important for optimal

preference selection. This can focus attention on blockbuster potential, whilst tapering the pursuit of unprofitable "pet products". Better use of health economics on initiation can facilitate better outcomes at fruition, not least when seeking to efficiently utilise scarce resources exhausted during R&D.

3) "Me too" squeeze

A VBP system combined with more rigorous evaluation will likely compress opportunities for extensive "me too" reimbursement. Companies will need to better demonstrate product value at the margin, especially in "flooded" markets.

4) International "spill over" effects

It would be wrong to view any proposed reform of the PPRS as merely a national issue relevant only to UK policy-makers. Although the UK market is small (3% share of the global pharmaceuticals market), it has influence over many other European markets which directly benchmark UK prices (25% of the global market). Thus, the implications of the OFT report confer an international connotation. Monitoring these "spill over" effects is therefore important.

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Pricing & Reimbursement: A “New Order”

The “rules of the game” are changing. This is a philosophical shift by no means exclusive to the UK. Governments are wising up to the real importance of inculcating the shared concepts of “cost-effectiveness” and “value for money” as part of formal pricing and reimbursement decisions. This is not simply the result of rational health economics but also the political imperative.

As health assumes the mantle of the “number one issue,” patient demands for improved health care are at an all time high. Generous pricing arrangements are no longer an option for the modern politician.

Whether the recommendations of the OFT study will be approved after consultation or compromises struck between government and industry, it is clear the findings of this report cannot be shuffled to one side. Early reaction has been positive, making reform of sorts highly likely. The OFT’s report might be a bitter pill for industry to swallow, but it is one companies must line the stomach for as decision-makers become increasingly cost-conscious. Regardless of its virtue, the policy gauntlet has been thrown down. Industry must now prepare its response.

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Setting of Ceiling Prices for Pharmaceuticals

By J. Jaime Caro, MDCM, FRCPC, FACP

A new pharmaceutical product is coming to market. It has been carefully studied for several years and, based on that research, it has met the requirements for efficacy and safety. All that remains is to set a price for it that is reasonable to both the buyers and the manufacturer, in the sense that it fairly rewards the investments made but also reflects the society’s values. This simple question—*what is a fair price?*—is not so easy to answer. But, answer it we must, in a clear, transparent manner that accords with the best available evidence.

This article is based on a presentation made in Cologne, Germany on November 14, 2007 at the fall symposium of Germany’s Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG*). The concepts presented are at the core of the upcoming **Methods for Economic Evaluations for the German Statutory Health Care System**. Three topics are covered:

- What are ceiling prices?
- What are the existing approaches for setting them?
- In the absence of international standards, what approach will IQWiG adopt?

Ceiling Prices

Ceiling prices are the maximum amount that an insurer or health authority will pay for a product. They do not necessarily correspond to the actual amount paid as a company may choose to price below the ceiling or offer rebates. Otherwise, the patient may have to shoulder the extra cost. For example, in Germany, the patient has to cover any excedent. The ceiling ‘price’ may not even be constant as it may depend on such things as the volume of sales and what else happens over time (e.g., arbitrary across the board price cuts).

Setting a ceiling price has become commonplace as health care systems seek to overcome the difficulties that result when the marketplace is not operating normally. Without the market as a price-setting tool, either the manufacturer is allowed to determine the price freely or another mechanism is needed to establish the price. In principle, the approach should yield a price that reflects how much the insured are willing to pay for the (additional) benefit provided by the intervention.

There are several approaches commonly used to set pharmaceutical ceiling prices across the world. In many countries, several techniques are implemented in various combinations depending on the context. These tools can be put into operation before the product reaches the marketplace

(so called *ex ante*) or they can be applied after the drug has been on the market for some time (*ex post*); in some jurisdictions, price-setting activities take place both before and after launch.

The simplest means to set a ceiling price is to do so arbitrarily. This is typically not done for individual products, especially before launch. Instead, the usual approach is to order percentage price cuts for all drugs across the system. Needless to say, this technique does not yield prices that accord with the insured's willingness to pay for a given benefit, nor do they provide for a reasoned, transparent value that can be evaluated and discussed.

A close cousin of arbitrary price setting is reference pricing. The idea here is that the ceiling price in a given jurisdiction should reflect prices for similar products—either in the same place or in other areas. While this approach facilitates setting a ceiling price, it also ignores the local values, deferring instead to whatever basis there was for setting the prices that serve as a reference. Reference pricing could happen *ex ante* or *ex poste* market launch.

A much more indirect way to set ceiling prices is to place controls on the profits that manufacturers can garner. This is done by establishing a “reasonable” maximum level (a minimum is often set as well) of profits that companies can earn. Then at some point, usually the end of the fiscal year, the actual profits are assessed and if they exceed the maximum, the manufacturer is asked to repay the insurer/health authority—in effect, retrospectively lowering prices across the board for those products. Of course, if there happens to be a shortfall, then the insurer must “top up” the payments, leading to a retrospective increase in the ceiling prices.

Although profit controls have been implemented successfully, in the UK for example (*please see article in this issue by Stuart Carroll regarding proposed changes in the UK*), several major problems have been noted. One important issue is that it is hard to measure profit accurately in the pharmaceutical industry. Difficulties arise because operations are usually multinational and thus modifications in transfer pricing provide a means for companies to allocate profits advantageously away from jurisdictions that control them. Even if this is not done, establishing the costs is problematic as many are incurred in other countries and can be hard to verify. Moreover, given the lengthy development process, there is a long lag between investment and return and there is a high rate of unsuccessful investment.

Not only is factoring these aspects into the profit calculations complicated, but controlling profits can provide some perverse incentives. Given that profits perceived to be in excess are taken away, this will undermine any incentive to reduce costs (which would lead to an increase in “profit”). More negative yet is the fact that profit controls treat all companies equally regardless of how innovative they may

be. Thus, a company that does little to advance the field, producing copy-cat drugs, is allowed the same profit as one whose research leads to breakthrough products. There is little incentive for innovation or risk-taking in the investment of research funds. Profit controls may yield predictable budgets but they don't reward benefits to patients.

A more rational approach to setting ceiling prices is to base them on the value provided by each product. With value based pricing, the “value” of the standard of care (i.e., other products already on the market) should be taken into consideration. This

value-based pricing can be implemented before a product is launched or afterward, or in combination. When implemented *ex*

ante, it involves estimating the **potential** value of a product in actual practice based on the results obtained in the artificial environment of clinical trials. The ceiling price is set prior to launch via economic evaluation that models the likely outcomes that will be achieved. If evidence is judged to be insufficient to securely predict the results, a “risk-sharing” arrangement may be agreed to, whereby an initial price is granted, the parties agree on what evidence is to be collected and consent to reconcile the results with the expectations via repayments or other arrangement later on.

Value-based pricing can also be implemented after a product has been launched. In this approach, the company is free to set its price at launch but economic evaluation will be carried out after the product has been on the market for some time. A ceiling price going forward is then determined based on the results of the economic evaluation. This is the approach that will be taken by IQWiG and G-BA (Gemeinsamer Bundesausschuss—the Federal Joint Committee) in Germany.

The key to value-based pricing is, of course, establishing the value of the benefit provided by a product. This is problematic because we do not have a recognized, reliable method for doing so across a population. In individuals, utility theory provides the basis for establishing the **relative** value of one set of consequences by comparison to the best and the worst possibilities **in that context**. This method breaks down when one tries to apply it across contexts because “best” and “worst” consequences become meaningless. In health, for example, this attempt has led to the nonsensical concepts of “perfect health” and “death” as best and worst outcomes. Not only is perfection unfathomable, but it is well known that most people can readily imagine states worse than death. Even if one persists and obtains a utility for each individual, there remains the unsolved—unsolvable

A more rational approach to setting ceiling prices is to base them on the value provided by each product.

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according to Arrow—problem of combining these to arrive at an acceptable utility for the group. Straight averaging (i.e., *utilitarianism*) does not ensure a representative value, and in any case, the mean is no longer a utility.

Recognizing this problem, health economists have proposed abandoning utility theory and reporting outcomes instead as the weighted-average survival with the weights corresponding to an average quality of life. This so-called “quality-adjusted life year” (QALY) does not solve the problem, of course. It no more reflects value than its component parts—it is just an aggregated consequence with the valuation still to be done: what is a QALY worth? This question has proved

intractable so far. Moreover, using weighted-average survival as a proxy for value can lead to very incongruous relative rankings of outcomes.

A new approach focused on individual therapeutic areas may be more tractable than seeking to establish group values across all areas of health. With this approach to value-based pricing, the value of the standard of care (e.g., other products already on the market) is used as the reference for the new product. This is the basis for the new *Methods for Economic Evaluation* that will be implemented by IQWiG.

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SPOTLIGHT ON SCIENCE

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Optimal Recall Period: A Complicated Question

By William R. Lenderking, PhD

I am delighted to join UBC during this time of great ferment and growth in Outcomes Research and the pharmaceutical industry in general. The release of the FDA PRO draft guidance has stimulated many questions regarding how to meet its standards, and it will also improve the quality of the science that our clients bring in support of labeling claims. However, in spite of the fact that the guidance does codify certain standards for the field, some of the recommendations have led to controversy. One of the areas of greatest controversy is around the appropriate recall period for reporting subjective health states, specifically the recommendation that in many cases the most appropriate recall period is the current state. Many well-established measures have been used to support claims and evaluate the effectiveness of treatments with a longer recall period, such as a week or a month. Does this recommendation mean that such well-established scales as the Hamilton Depression Rating Scale (HAM-D) in depression will no longer be accepted in support of claims? Will all new antidepressant treatments need to be approved on the basis of daily data?

Although research has indicated that forgetting increases with the length of the recall period, the optimal recall period for many health outcomes has not been established. For example, although symptoms might be best measured on a daily basis (and this has not been definitively established), bias due to memory loss can take place even across a 24-hour period. Furthermore, some symptoms, such as pain, can fluctuate throughout the day and are influenced by external factors, such as activity level. In the face of this type of variability, what is the most precise way to measure pain? Two studies in pain that have examined recall bias are illustrative. The first study found that average pain ratings over the past 24 hours (daily recall) were influenced by ratings of current pain and the most extreme pain experienced over the same period. However, the authors concluded that the bias was small enough that 24 hour ratings were still valid.¹ A second study reported that a combination of peak and recent pain over seven days was a better predictor of recalled patient pain on the eighth day than was a simple average of all momentary pain reports over the seven days.² Both of these papers observed the importance of peak and end pain ratings in forming average ratings of pain even over relatively short time periods such as a day, but appear to have come to different conclusions regarding the use of momentary ratings. Yet another study of low back pain patients carried out over the course of a year concluded that averaged weekly pain ratings were just as useful as momentary ratings.³ This would suggest that the optimal recall period for pain assessments should be determined in the context of the particular pain condition and based on the

length of the study observation period, and that momentary assessments should not necessarily be the default recall period in every study. Other outcomes less focused on symptoms might simply be better measured over a longer time period, such as health status, physical functioning, or even recalled adherence. A recent study, for example, indicated that longer recall periods can sometimes be more accurate, such as the study which found that one-month recall of adherence to HIV medications was more accurate than three-day or seven-day recall when compared with MEMS (Medication Event Monitoring System or electronic pillboxes) caps results.³ In another study of patients with medically unexplained symptoms, the authors found that the number of symptoms reported actually increased over a one-week recall period when compared with a one-day period,⁴ suggesting that forgetting is not the only operative factor in biasing recall. These few studies suggest that the optimal recall period for various health outcomes can be a complicated question and is worthy of further research.

As a result of this recommendation to capture patient-reported outcomes in real time, many companies are developing diaries that facilitate capturing information from patients on a daily or more frequent basis. This has contributed to the considerable growth in the field of electronic data capture (EDC). Hopefully, the FDA recommendation will also stimulate research into the optimal recall period for various health outcomes, and therefore, the field will have not only better-validated instruments, but also a greater understanding of the disease processes under study and how they affect sufferers.

Ultimately, recall period, like response choices, is an issue of internal validity. Researchers should consider recall period as seriously as they do conceptual definitions and response choices. Different phenomena require different recall periods, and the recall period must be matched to the phenomenon of interest and the purpose of the assessment.

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NEWS BRIEFS



Kelly D. Davis, MD Joins UBC as Vice President, Medical and Safety Solutions

Dr. Davis recently joined the UBC Epidemiology and Risk Management Group with over 23 years experience in medicine as a physician, clinical researcher and pharmaceutical executive. Dr. Davis is an Endocrinologist and received her medical degree from the University of Kansas College of Health Sciences, followed by an Internal Medicine residency at Temple University Hospital and fellowship at the University of Pennsylvania. Subsequently, she spent several years on the medical school faculty at Penn in the Division of Endocrinology, Diabetes & Metabolism.

Kelly brings deep and extensive experience in clinical trial and observational study design, development strategy, and operations to UBC's team of industry-leading risk management and epidemiology experts. She spent the past ten years working in Clinical Research & Development at Wyeth where, most recently, she was Vice President and Therapeutic Area Head for Inflammation, Metabolism, and Gastroenterology. In this role, she was responsible for clinical development strategies and overseeing clinical trials from early development through the postmarketing period for projects in a multitude of indications.

In her role at UBC, Kelly will provide strategic input to clients; research, design, and develop innovative scientific and operational solutions for UBC customers; serve as a medical resource to other UBC safety staff; and provide consulting services to clients in risk management, pharmacovigilance, regulatory agency interactions, study design and protocol development.

Eric Caplan, PhD, Joins UBC as Senior Director, Health Policy

Dr. Caplan joins UBC's Center for Health Economics, Epidemiology, and Science Policy with over 20 years of experience as a leader, manager, and practitioner in the corporate, academic and non-profit arenas. As a Practice Manager/Senior Director for the Advisory Board Company, Dr. Caplan directed major research projects in the health care and higher education sectors, developing Best Practice studies and providing expert advice to Advisory Board members. He also worked for McKinsey & Company providing expertise on enhanced clinical trial design and biomarker development and implementation. He contributed to the Firm's Business and Society initiative defining the pharmaceutical industry's social contract, outlining social and political issues for clients and developing a framework for addressing social and political concerns. For seven years, Dr. Caplan worked for Pfizer's Global Research and Development division in positions of increasing responsibility and global reach leading cross-functional teams on orientation and education programs worldwide.

In his role as Senior Director at UBC, Dr. Caplan will be working closely with colleagues across the organization along with those in academia, industry, regulatory and payers to develop effective, innovative pathways for generating timely, market-relevant evidence about pharmaceutical products and medical devices.

A former William Rainey Harper Fellow at the University of Chicago, Dr. Caplan received his doctorate and masters degrees from the University of Michigan and his bachelor's degree in economics from Wesleyan University. He is the author of *Mind Games: American Culture and the Birth of Psychotherapy* (Los Angeles: University of California Press, 1998).

William R. Lenderking, PhD, Joins UBC as a Senior Research Scientist

Dr. Lenderking, a clinical psychologist, has 17 years experience in the field of outcomes research and joins UBC's Center for Health Outcomes Research as a Senior Research Scientist. During the past seven years he served as a Director and Team Leader with Worldwide Outcomes Research for Pfizer Inc. Prior to joining Pfizer, Dr. Lenderking was a consultant to the pharmaceutical industry with Phase V Technologies, Inc. and Abt Associates, where he worked as a psychometrician. He began his career as a post-doc at Harvard School of Public Health with the AIDS Clinical Trials Group, held a staff position in the Psychiatry Department at Massachusetts General Hospital, and later became an assistant clinical professor at Harvard Medical School.

Bringing his extensive experience to UBC, Dr. Lenderking is leading instrument development and psychometric validation research along with strategic and regulatory consulting with a particular focus on patient-reported outcomes.

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Dr. Lenderking is widely published, including a book he co-edited with Dennis Revicki: *Advancing Health Outcomes Research Methods and Clinical Applications*. He has served as Co-Editor for Quality of Life at *Value in Health* since 1999 and served as Associate Editor of *Quality of Life Research* from 2000 to 2003. Dr. Lenderking contributed to the Pfizer and ISOQOL responses to the FDA PRO draft guidance issued in February 2006; co-led two ISOQOL symposia and a contributed workshop on the draft guidance; and is part of the ISPOR Task Force working on a white paper describing validation issues for e-PRO technology. Dr. Lenderking received his MA and PhD in Clinical Psychology from the University of Connecticut and his B.A. in Anthropology from Dartmouth College.

Mkaya Mwamburi, MD, PhD, Joins UBC as an Associate Medical Director

Dr. Mwamburi is an Associate Medical Director in UBC's Center for Health Economics, Epidemiology, and Science Policy (CHEP). Dr. Mwamburi serves as principal investigator on UBC's systematic review, meta-analysis and cost-effectiveness projects. He has extensive clinical and research experience in conceptualizing and conducting clinical, epidemiological and economic research projects in infectious diseases, psychiatry and pediatrics. Dr. Mwamburi is a clinical research specialist who has practiced medicine and surgery in Kenya and South Africa and has designed and conducted research projects in the United States, Kenya, South Africa, Pakistan and India.

Dr. Mwamburi obtained his PhD in Clinical Research from Tufts University, Boston with a focus on biostatistics, Markov modeling and discrete event modeling of clinical and economic outcomes. Dr. Mwamburi has published in several journals, including *JAMA* and *Clinical Infectious Diseases*. Prior to joining UBC, Dr. Mwamburi was a full-time Assistant Professor in Public Health and Family Medicine at Tufts University School of Medicine where he was the course director for Biostatistics and mentored medical students, infectious diseases fellows and PhD candidates. Dr. Mwamburi continues his professorial duties in a part-time capacity.

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CBI Pharmaceutical Risk Management

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ISPOR 13th Annual International Meeting

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CBI's 11th Registries and Post Approval Studies Congress

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IIR-USA 2008 Fundamentals of Clinical Outsourcing—East Coast

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