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## How to be Successful in the New Comparative Effectiveness Landscape

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### A Brave New World

It is not news that manufacturers are currently faced with a rapidly changing external environment. The American Recovery and Reinvestment Act of 2009 allocated \$1.1 billion to support comparative effectiveness research (CER) in the United States, reflecting the paradigm shift that is occurring in financially over-stretched health systems. The promise of CER in the U.S. is to provide evidence on the comparative clinical effectiveness of multiple interventions that should allow patients, providers, payers, and policy makers to distinguish between healthcare interventions in terms of their relative therapeutic value. In Europe, similar trends are at play. Comparative effectiveness (or “relative effectiveness,” as it is referred to in Europe) is emerging as an interface between regulatory agencies and payers, as both market entry and reimbursement are increasingly required for a new product to reach patients.



What CER will mean exactly in practice, and when new standards will come into effect, is still the subject of much uncertainty. Specifically, we do not know yet which evidence standards for generating comparative effectiveness research will be deemed acceptable by various stakeholders. In the U.S., current discussions are focused on the types of study designs that will be used to generate comparative effectiveness evidence, with heated debates occurring between “trialists” who will only consider randomized clinical trial evidence and proponents of observational research. Leading this effort, the methods committee of the Patient-Centered Outcomes Research Institute (PCORI) will play a critical role in shaping

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## Safety at Peri-Approval Time in the EU: Strategic and Operational Considerations

By Veronique Basch, PharmD  
Executive Director Safety, Europe

Drug safety surveillance in the EU has changed significantly in the past several years with the introduction of risk management plans, and stringent safety surveillance regulations. Often, the most challenging period for a new product is transition from pre-authorization to post-authorization. Any mistakes could create costly delays and frustration. Organizing safety activities and the transition process can be particularly challenging for a small

company since they may not have the needed systems in place, including standards and procedures across multiple business units. It is important to involve the right people, to develop processes and timelines, to acknowledge and understand the links among the different documents, and maybe most importantly, to seek help from safety experts when unsure.

### Basics: Integrating a PV System

Integration of a Pharmacovigilance (PV) system includes ensuring many different moving parts are in sync, including:

- Management of the safety profile of the product (medical)

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## Comparative Effectiveness Landscape

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the agenda around various study designs and their relevance for CER. In Europe, the current debate is focused on addressing methodological challenges as well as identifying the potential synergies between the evidence needs of regulators and payer/health technology assessment (HTA) bodies.

Some key trends are already apparent in the U.S. One hallmark of the expanded CER agenda is its increased focus on patients, and specifically on patient-centered outcomes (PCOs). Patient centered outcomes are not always the same as patient-reported outcomes (PROs). For example, five year survival from breast cancer is a clinical outcome which is also a patient-centered outcome that is of value to the patient, provider, payer, and manufacturer.<sup>1</sup> Relief of pain and improved

**One hallmark of the expanded CER agenda is its increased focus on patients, and specifically on patient-centered outcomes (PCOs).**

functioning, however, are PROs that are of great importance to these audiences for acute knee osteoarthritis

requiring knee replacement. Another focus of CER is to help identify the relative responses of different patient subpopulations to therapies in real-world settings. Thus, it will be crucial to identify patient heterogeneity by studying subgroups of patients who may benefit based on personal characteristics. In the U.S., there is also a significant focus on health information technologies (HIT). With increased funding of HIT, the amount of comparative data available and the potential for data sharing will increase significantly over the next few years.

The challenge of meeting future, and to some degree, unknown evidence requirements is high. Manufacturers are finding themselves in the challenging position of having to prepare evidence generation strategies for their product pipeline to meet standards that are not yet clear. At the same time, most manufacturers have generally considered engaging in significant comparative prospective studies fraught with risk and will likely not do so unless there are clear evidentiary requirements for market access that compel them to. Increasingly, however, appropriate comparative evidence will be necessary for successful market access, and we expect this trend to accelerate over the coming years. Some private payers are already making use of this type of information. For manufacturers, the time to prepare for the changing evidence requirements is now, and while there remains uncertainty in the specifics of the evidence standards that will be accepted by payors, there is a robust arsenal of tools at the manufacturers' disposal to start planning for the generation of comparative evidence where deemed necessary.

### Start Planning Now

This is the right time for manufacturers to identify the products in their pipelines that will be the most likely candidates for comparative evidence requirements. In this environment, manufacturers are advised to systematically evaluate their current portfolio to identify products that will likely face the greatest scrutiny. We expect product classes with numerous, comparable alternative therapies and high budget impact to be affected by CER requirements. For example, it should be no surprise that biologic treatments for rheumatoid arthritis and oral anti-diabetics will likely be high on the list, while orphan drugs for rare diseases will have lesser CER scrutiny. Identifying metrics (and sometimes developing these if they do not yet exist) that will have the ability to demonstrate product value in the new CER environment should also be a key component of any manufacturer's CER strategy. These "value metrics" can be thought of as patient-centered endpoints that will adequately capture the value of a technology in a comparative environment.

The good news is that despite uncertainty on the specific evidentiary standards, there are a number of innovative study designs that can support planning robust comparative evidence generation. Retrospective studies, such as database analyses and systematic literature reviews, are relatively fast and inexpensive and can help inform the decision to move to more expensive and time consuming comparative prospective evidence collection. We review some of these study designs below.

**Database analyses** The HIT infrastructure being developed in the U.S. is a key factor in moving retrospective database analyses from being a valued supplement within drug development to a critical element in the lifecycle management of medicinal products. Systematic analytic approaches, beyond the current time-consuming model of one constituent performing one analysis on one data source, are being developed to provide efficient and cost-effective access to evidence contained within disparate observational data. There is much potential in linking together data sets—including those from electronic health records—that offer a wealth of information about real-world interventions and health outcomes. New, promising ways of linking data from multiple databases are also emerging. Retrospective analyses that link process data sets, such as administrative claims data, to outcomes data sets, such as national death records, can provide excellent opportunities to explore the relationship between processes and health outcomes. Within this context, analytical innovations are also emerging. For example, ProSanos, a company recently acquired by UBC, has developed a unique suite of software products that enable systematic analyses of disparate observational databases to be performed rapidly, utilizing a library of standardized analytic routines.<sup>2</sup>

**Systematic reviews and meta-analyses** These are rapid and cost-efficient ways to identify and synthesize existing

information on relevant comparators. These studies also help identify the current gaps in evidence and can guide future research directions. Innovative methods in this area allow us to now simultaneously make comparisons between multiple treatments using indirect evidence. That is, by identifying a network of evidence that includes both direct evidence (when treatments are compared to each other within a trial) and indirect evidence (when treatments are compared to each other between trials using a common comparator treatment), we can produce estimates of relative effectiveness. One limitation of this approach is that the relevance of the evidence is limited by the set of existing trials. If the latter are not externally valid or do not measure relevant patient-centered outcomes, the meta-analysis cannot itself overcome these limitations.

**Trial simulations** In cases where decision-makers need to weigh the relative value of conducting a costly and lengthy prospective trial, a valuable alternative is constructing a trial simulation to predict trial outcomes and possibly to add the “missing” arms to an existing trial. This fairly recent approach yields a simulated head-to-head trial. A major advantage of this approach is that it allows the analyst to simulate a trial and examine what would have happened had all the relevant comparators been included. By closely paralleling the design of existing trials, the trial simulation approach minimizes the impact of discrepancies in baseline characteristics such as differences in study design and enrolled populations. Trial simulations can also minimize follow-up related aspects that may differ among the trials, while leveraging as much of the existing data as possible. UBC scientists have piloted three such projects this year, and while trial simulation is still in its infancy, it is a promising approach to consider.

**Outcome registries** Should it be decided to move ahead with prospective data collection, outcome registries offer many advantages for better understanding patient-centered outcomes. Indeed, investment in registries is gaining momentum as they may simultaneously provide a real-world view of clinical practice, patient outcomes, safety, and comparative effectiveness of interventions of interest. Registries are powerful tools to understand variations in treatment and outcomes; to examine factors that influence prognosis and quality of life; to describe care patterns; to assess effectiveness comparing several interventions of interest; to monitor safety; and to change prescribing behavior through feedback of data. Properly designed registries collect outcomes that may be generalizable to a wide range of patients as the outcomes reported are more representative of what is achieved in real-world practice. Depending on the volume and quality of data collected, they can also provide the opportunity to drill into subgroups and explore issues of patient heterogeneity.

**Adaptive randomized controlled trials** Randomized controlled trials (RCTs) are the “gold-standard” of determining whether or not an intervention works and are required by regulatory authorities such as the Food and

Drug Administration (FDA). However, as currently designed and conducted, RCTs may be inadequate to meet the evidentiary needs of an expanded CER agenda. There are operational and structural inefficiencies inherent in traditional RCTs as they are complex, time consuming, and expensive. Additionally, in some cases they may only be relevant for a narrowly selected population and not reflect real-world practice. There are also analytical inefficiencies: it is difficult to make optimal use of relevant existing or new evidence as it becomes available during the course of a trial. For example, how would we account for a new comparator coming to market after a trial has been started?

Innovative methods exist for exploring ways to make RCTs more flexible in terms of their design, conduct, and implementation. Designs that use features that change or “adapt” in response to information generated during the trial are more efficient than standard approaches. For example, researchers have proposed Bayesian adaptive analytical approaches, which allow for modifying the trial in midstream after rigorous upfront planning.<sup>3</sup> By incorporating existing high-quality, external evidence (such as information from other trials, systematic reviews, and observational studies) into trial design, adaptive designs hold the promise to reduce the sample size, time, and cost required to obtain decision-relevant information. Along with colleagues from the University of Maryland and Berry Consultants, UBC scientists have recently been awarded a 3-year NIH grant to explore the feasibility of applying such adaptive designs.

## Conclusion

The new CER landscape poses many challenges for manufacturers who have to make decisions on whether to generate comparative evidence on their products, and if so, how to do it. This is further complicated by the uncertainty around the evidentiary thresholds and when these thresholds will be applied. Despite the rapidly changing external environment, success in this new landscape will require manufacturers to start planning for CER now. This means assessing the existing evidence and evidence gaps, as well as planning for studies that will fill these gaps. The use of innovative, cost-efficient, and time-saving methods in this field will be critical to meet this challenge.

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## Safety at Peri-Approval Time in the EU

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- Development of processes to ensure information is received, analyzed, and reported appropriately (regulatory, quality)
- Validated systems and tools to ensure accurate recording of information (technology)

In addition, the following are required:

- Detailed Description of Pharmacovigilance System (DDPS) and a Qualified Person for Pharmacovigilance (QPPV) (one for all products)
- Risk Management Program (RMP)
- Company Core Data Sheet (CDDS) (product-specific needs)

In the EU, a DDPS and RMP are mandatory elements of the application for market authorization. The underlying efforts

**The RMP is a living document designed to identify known, potential and unknown risks. Regulatory bodies have accepted the creation of subcategories in these three areas: important identified risks, important potential risks, and missing information—these are mandatory and cannot be customized.**

during the preparation of these documents are enormous. To compile the RMP, a good overview of the risk analysis of the product is needed; for the DDPS, thorough understanding of the safety system structure

and supporting standard operating procedures (SOPs) is required, along with the need to identify a QPPV. Based on the list presented in volume 9A of Eudralex (“The rules governing medicinal products in the European Union”),<sup>1</sup> the number of SOPs necessary can reach up to 10 or more.

An efficient transition period requires the development of a comprehensive, proactive plan and supporting processes and systems in order to facilitate faster document delivery and submission.

### The RMP

One of the first safety documents prepared at the time of application is the RMP. Ideally, preparation of this living document begins during Phase II. During this stage, the RMP will be for internal use only, and many sections will be incomplete or empty, however, these sections will be populated with time after the completion of each key study or in synchronisation with the update of the Investigator’s

Brochure (IB). Preparation of a strong RMP necessitates the participation of all relevant departments, and external experts if necessary. This multidisciplinary team ensures that all appropriate information is collected for the risk-benefit assessment, and that all departments are aware of the safety profile, and the identified and potential risks, as these will be presented in other documents, including the CCDS and Summary of Product Characteristics (SPC). This team should include preclinical, clinical development, pharmacology, medical safety, epidemiology, and safety writing, and should also obtain opinions regarding sensitive therapeutic areas, unclear benefit-risk ratio, etc., from relevant internal or external experts.

The RMP is a living document designed to identify known, potential and unknown risks. Regulatory bodies have accepted the creation of subcategories in these three areas: important identified risks, important potential risks, and missing information—these are mandatory and cannot be customized. The RMP also needs to contain QPPV contact details and a section on routine PV practices that are, of course, in line with the DDPS.

The RMP also contains a plan for risk minimization activities (as appropriate for the defined risks) that includes timing, budget, and organizational aspects of the company. This plan may be discussed with regulatory authorities or ad hoc experts. Making the right assumptions and decisions at this stage may save time and energy later in the process.

### DDPS, the System Before the Document

The second mandatory safety document to complete the application dossier is the DDPS. In preparing the DDPS, the following structural points need to be included:

- Internal/external organisation structure (safety, quality, territory)
- Countries in which the product will be launched and the coordinated distribution/licensing system and partnerships the existing PV system/process
- Details regarding the QPPV and an appropriate backup

For a smaller company’s first approval, a network of affiliates may not be structured and additional questions may not be answered, however, it is important to include as much as possible and describe the system, even if it is still virtual. The DDPS needs to include contact information for identified partners and consultants, demonstrate a strong quality assurance (QA) process, and include supporting SOPs. Although not everything needs to be in place at the time of submission, the plan needs to show what is clear and what is unclear.

### The CCSI and Its Interdependence to Other Safety Documents

In parallel with the preparation of the RMP, the QPPV will liaise with the regulatory and safety team to complete the

contents of the Company Core Safety Information (CCSI). Information originating from the RMP and all important identified and potential risks should be included in the section “warnings and precautions” of the CCSI. All of these will also be presented as adverse events of interest in the Periodic Safety Update Report (PSUR). Lastly, the adverse reactions presented in the undesirable effects section originate from statistical analysis and from individual case medical analysis. In this section, a focus on diagnosis versus symptoms is important for a meaningful medical analysis.

### The Post-Marketing Safety Operations

A good time to start getting ready for daily post-marketing activities (case reception and processing) is to start building the system in parallel with the preparation of the RMP and DDPS. The safety database used during the clinical trials period will be the same for the post-marketing activities. However, there are significant differences between serious adverse events (SAE) originating from clinical trials and post-marketing serious and non-serious cases.

During development, the clinical research associate (CRA) or investigator sends the pre-market reports containing controlled data in English. In comparison, post-marketing cases originate from many different sources and are provided in the local language. The safety system needs to be organized to ensure a complete data collection, which includes literature, consumer and health professionals, affiliates/local contacts, competent authorities, etc., and accounts for issues such as multiple languages. The data collected during the first months after product launch is key, as this is when issues or signals may arise. These signals may of course be detected on a single case level or through regulation signal detection activities (on cluster of cases), but they can also be commented and analyzed at the time of aggregate report preparation.

Addressing the safety issues and requirements early in drug development, and thinking about the post-authorization safety process at the same time, can ultimately save precious time and cost down the road. Consulting safety professionals, especially for smaller companies new to the process, can be a smart step in ensuring a seamless transition from development to approval to post-authorization monitoring. In the end, product safety is crucial for any medical treatment, and knowing the process, engaging the right teams and stakeholders, and identifying and following necessary and planned timelines will ultimately provide for a product's success.

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## Prospective Payment Systems: Challenges and Opportunities for Manufacturers Seeking Market Access

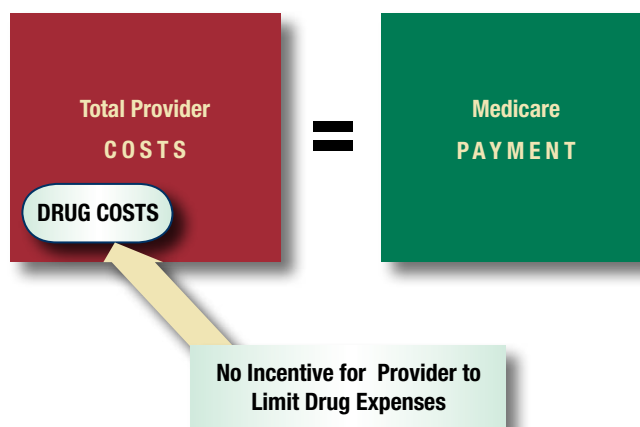
By Daniel Fantore, MHA, Senior Research Manager and Sara Sullivan, BS, Senior Research Manager

On January 1, 2011, Medicare implemented a prospective payment system (PPS) for dialysis providers.<sup>1</sup> Most End Stage Renal Disease (ESRD) drugs used by dialysis patients were previously “separately billable” (and paid), but under the PPS they are folded into the composite rate to create a fully prospective payment system. The ESRD PPS is noteworthy because the Centers for Medicare and Medicaid Services (CMS), the administrator of the Medicare program, specifically cited a drug as the impetus for implementation of this payment system. CMS stated,<sup>1</sup>

“Aside from resulting in a single comprehensive payment for all services included in the bundle, we believe the ESRD PPS would meet several objectives. These include:

- Reducing incentives to overuse profitable separately billable drugs, particularly EPO [Epoetin Alfa],
- The targeting of greater payments to ESRD facilities with more costly patients to promote both equitable payment and access to services, and
- The promotion of operational efficiency.”

Historically, from 1965 to 1983 Medicare used a cost-based reimbursement system—i.e., hospitals and other providers were paid what it cost them to provide care. If a hospital used a new drug that cost more than the standard of care, Medicare paid the hospital for the costs of the drug. Medicare found cost-based reimbursement highly inflationary as providers had financial incentives to provide more care and more expensive care.



**Figure 1: Incentives Under Cost-Based Reimbursement**

Source: United BioSource Corporation, 2011

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## Prospective Payment Systems

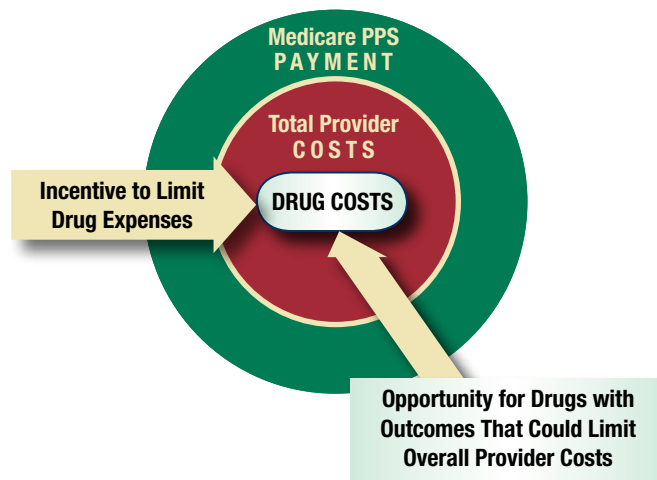
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Since 1983, Medicare legislation/regulation moved from paying providers their costs to a prospective payment, a fixed amount regardless of additional services or products supplied. See Table 1 for a history of some of Medicare's prospective payment systems. This progression to prospective payment signals Medicare's increasing interest in cost containment and is a challenge to pharmaceutical and device manufacturers as a new service, supply, or drug is not paid specifically. Under most prospective payment systems, Medicare uses increased costs to update future prospective payments, but increases are indirect, delayed, and subject to limits. Providers typically believe these updates are too little, too late.

Providers paid on a prospective basis have a financial incentive to provide care in an efficient manner. Under PPS, if a hospital wants to use a new, more costly drug, they must balance the efficacy of the drug, its safety, and the direct cost of purchasing the drug. All things being equal, providers have an incentive to select lower cost products.

### Determining Value

With regard to drugs, all things are not equal and providers consider more than cost. Institutional providers, such as hospitals and dialysis centers, look for advantages and disadvantages of using new technologies and products. Is efficacy better with the new, more expensive drug? Does the new drug have any advantages that have an impact on length of



**Figure 2: Incentives Under Prospective Payment Systems**

Source: United BioSource Corporation, 2011

stay or resource utilization? If a new, expensive drug allows patients to leave the hospital sooner than if they were treated with the standard of care, hospitals will be interested. Creating evidence that will help PPS providers understand the value of new products is central to the commercialization of a new therapy.

One of the concerns with prospective payment systems is they sacrifice quality of care in favor of cost savings, and that may offer an opportunity for manufacturers. Under retrospective

**Table 1: History of Medicare's Prospective Payment Systems**

Site of Care / Provider	Implementation Year	Medicare Payment Methodology
Hospital Inpatient Stays <sup>2</sup>	1983	Medicare Severity Diagnosis-Related Groups
Dialysis Facilities <sup>3</sup>	1983 - Composite Rate 2011 - Fully Bundled PPS	ESRD PPS per dialysis treatment
Hospice <sup>4</sup>	1986	1 of 4 Daily Rates (per diem)
Home Health Services <sup>5</sup>	1997	Home Health Resource Groups
Skilled Nursing Facilities <sup>6</sup>	1998	Daily base rates: Resource Utilization Groups (RUGs)
Long-Term Care Hospitals <sup>7</sup>	1999 and 2000	Medicare severity long-term care diagnosis-related groups
Hospital Outpatient Services <sup>8</sup>	2000	Ambulatory Payment Classifications
Inpatient Rehabilitation Services <sup>9</sup>	2002	Inpatient Rehabilitation Facility (IRF) PPS—per discharge rates
Specialty Psychiatric Inpatient Hospitals <sup>10</sup>	2005	Per diem PPS
Part D (outpatient) Plans <sup>11</sup>	2006	Plans paid an adjusted monthly prospective payment for each enrollee

cost-based reimbursement systems, the concern was overtreatment, the use of expensive drugs or technologies beyond clinical need. One concern with PPS is that patients may be undertreated, leading to increased mortality, morbidity, or other indications of poor quality care. Most prospective payment systems are paired with a quality measure so that the provider is also paid on the basis of quality results. Medicare has also used quality incentives: for example, not paying for readmissions or for some hospital-acquired conditions. Because of the concerns with the quality of care provided under prospective payment, providers are open to products that, even though they may be more expensive, offer an improvement in the quality of care they provide.

Understanding how one's customers are paid can provide the insight necessary for successful market access. Drugs and products used in institutions that are paid on a prospective basis face special challenges, and price is not the only factor considered by providers. Manufacturers are wise to consider the value that their products bring to institutions as well as how price affects that value.

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## Literature Reviews: Facilitating Evidence-Based Decision Making

By Elisabeth Stahl, PhD, Senior Research Scientist and Randall Winnette, BS, Research Associate

### Background/Evidence

Literature reviews play an important role in decision making for clinical development by providing evidence-based health care information. Systematic and targeted or narrative reviews are the most commonly used methodologies with each one providing a different level of evidence. Each of these types of reviews provides information to understand disease and treatment and inform decision making. They vary in their comprehensiveness, analysis, and the form of the results. As such, they address different and potentially complementary information. The effective use of literature is a function of its purpose, the clarity of the questions asked, and matching this information with the methodology to yield the most useful, cost-effective information.

### Types of Reviews

A **systematic literature review** involves a comprehensive review of all information available to address a specific research question.<sup>1-4</sup> The information gathered in such a review may be synthesized as a meta-analysis if the review offers sufficiently homogeneous data. A number of electronic databases can be used to facilitate such a review, including EMBASE and MEDLINE.

**The effective use of literature is a function of its purpose, the clarity of the questions asked, and matching this information with the methodology to yield the most useful, cost-effective information.**

The results of this type of literature review can provide an early understanding of disease and its treatment in order to inform clinical trial design, determine literature gaps for a product, or to identify future therapeutic areas for new indications. Data gathered through a systematic literature review can also be used for evaluation and quantification of efficacy and safety outcomes and to determine optimal dosing or to compare products for efficacy and safety when head-to-head studies do not exist.

A **targeted or narrative literature review** can provide an in-depth review of all relevant studies answering a specific research question with the results used to summarize the current state of the field, identify trends, and formulate hypotheses for future research. Findings can be presented as a narrative overview, summary tables of key information, recommendations, such as a measurement approach or trial

## Facilitating Evidence-Based Decision Making

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design for evaluating treatment efficacy, or study designs for further research. A targeted or narrative literature review can also be a focused literature review covering a smaller amount of recently published studies (e.g., 20-40 compared to potentially hundreds) selected for optimal utility in decision making. This type of review can be used to quickly respond to regulatory inquiries or safety and pharmacoepidemiology issues. It can also be used as a means to provide current, targeted information for internal evidence-based decision making within a product team.

### Key Issues

Gaining an understanding of what has been published in a specific disease or treatment area is essential when making decisions regarding the design of new clinical programs, risk management policies, regulatory submissions, and when planning for commercial and reimbursement support. However, there are several issues to be considered when preparing and interpreting such evidence, and these are presented below.

### Focus/Planning

It is important to decide early what question or questions you want answered through your review. It is also key to understand the purpose and intended audience for the

results of the review. The number of studies published per year has been increasing extensively in the last decade, and therefore, prioritization to help narrow the pool of articles to be reviewed is of the utmost importance. For example, if the initial goal of the study is to obtain information on patient-reported outcome (PRO) instruments that are suitable for use in a clinical drug program for Rheumatoid Arthritis (RA), it may be wise to evaluate the mechanism of the drug in order to understand how the drug may change the patient's subjective experience. Such understanding can assist with narrowing the scope of your search. If, in the case of a search for PRO instruments related to RA, the drug affects a specific symptom (e.g., pain or stiffness), it may be advantageous to narrow the focus of the literature review to instruments that specifically assess that symptom alone or as a subscale.

Another issue that should be clarified early is the time frame of interest for the review. Are you interested in data from as far back as 10 to 20 years or is it recent data that is relevant to your search? If you are searching for PRO instruments to use in a clinical drug program, the release of the Food and Drug Administration (FDA) PRO draft<sup>5</sup> and final guidance<sup>6</sup> may be time points to consider. In these cases, the original development or seminal papers are included to cover appropriate development content as well as for historical context. In other cases, such as a review of epidemiological data, information published more recently, i.e., within the past 3 to 5 years may be the best option, with plans to update the review periodically throughout the development program. In summary, it is of high importance to be focused and very clear of your needs before the literature review is initiated.

**Table 1. Sample Literature Review Entry: Measures of Functional Performance**

*Adapted from: Stull, et al., 2007<sup>8</sup>*

Instrument	Subjective measures of functional performance (daily activity)		
	Citation	Number of items	Subscales/dimensions
<b>GENERIC MEASURES</b>			
SF-36	32-34	36	Physical functioning; role limitations due to physical health; role limitations due to emotional health; social functioning; bodily pain; general health; vitality; mental health
Duke Activity Status Index (DASI)	35,36	12	Personal care; ambulation; household tasks; sexual function; recreation
Functional Status Questionnaire (FSQ)	37,38	34	Physical function; psychological function; role function; social function; 6 single items asking about sick days, interpersonal relationships, and feelings about health
<b>COPD-SPECIFIC MEASURES</b>			
Clinical COPD Questionnaire (CCQ)	39	10	Functional state; symptoms; mental state
Functional Performance Inventory (FPI); FPI Short Form; FPI-Mini	40-43	65; FPI Short-Form: 32 items/6 dimensions or subscales; FPI Mini: 12 items, total score only 21	Body care; maintaining the household; physical exercise; recreation—activities for personal pleasure; spiritual activities; social interaction

## Performance/Quality/Interpretation

Once your research goals have been clearly defined, a research plan or protocol for the review should be developed. This plan may include the following components, depending on the type of review you are planning:

- A detailed description of the study objectives
- A list of search terms
- Inclusion and exclusion criteria to be used during article review
- A list of all target data sources (i.e., databases such as EMBASE/MEDLINE; relevant conference abstracts; product labels)
- Format for data management, including any data spreadsheets and data extraction categories
- Format for presentation of results, such as draft table shells

At this stage, it is helpful to run a test search in order to assess the number of candidate articles to be considered. Certain searches may result in several hundred, or even several thousand, candidate articles. In such cases, the search criteria should be refined in order to increase the accuracy of the search.

When reviewing publications, the quality of the article should also be taken into consideration before including it in the review. There have been attempts to assess and document methodological quality. One scale frequently used for this purpose is using a 3-item scale by Jaded.<sup>7</sup> The criteria used are:

1. Is the study described as randomized?
2. Is the study described as double-blind?
3. Does the study provide a description of withdrawals and drop-outs?

These criteria are particularly useful in systematic reviews that include meta-analyses of randomized trials; they will not be useful in reviews of patient-reported outcome instruments and/or instrument development literature.

The outcome of a literature review should include a detailed summary report outlining methods, findings with concise data tables, and interpretation of the results. The analysis should offer insight into the meaning of the findings relative to the purpose of the review, from strategic implications concerning potential outcome advantages or disadvantages of the product under consideration to recommendations for clinical trial measurement or design.

The data tables presented in the final report should be tailored to the aims of the study. Below is a sample table from a review of measures used to assess functional performance states. Based on the aims of this study, the table was crafted in such a way that it provided key information about the identified instruments which were grouped into one of two categories: generic or COPD-specific. A reference list

with numbered citations was provided with this table so that relevant publications could be easily identified and studied further if additional information on a specific instrument was necessary.

## Organization

For pharmaceutical companies, the need for evidence from the literature can vary throughout the lifecycle of a drug. Early in drug development, empirical evidence is needed for scientific purposes, including selection of study endpoints (measures and timing), power estimation, and possibly strategic insight, e.g., competitive advantages or go/no-go decision making in early phase trials. Later in the cycle, the literature can inform discussions related to reimbursement or marketing of the drug. In this case, consideration should be given to gathering and organizing country-specific evidence.

## Summary

Literature reviews are valuable to develop and document disease processes and the effects of treatment and can enhance the effectiveness and efficiency of decision making in drug development throughout all stages. It is of utmost importance to be focused and to specify the research questions in detail. Systematic literature reviews are most comprehensive and selections are identified by inclusion/exclusion criteria, while targeted/narrative reviews provide an in-depth review of a specific number of articles if a less comprehensive or fast review is needed of recent published literature.

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Randall.Winnette@unitedbiosource.com.

## References

- <sup>1</sup>Lipp A. A Guide to Developing a Systematic Review. *AORN J*. 2003; 78(1):90-94.
- <sup>2</sup>Wrights RW, Brand RA, et al. How to Write a Systematic Review. *Clin Orthop Relat Res*. 2007; 455:23-29.
- <sup>3</sup>Ressing M, Blettner M, et al. Systematic Literature Reviews and Meta-Analysis: Part 6 of a Series on Evaluation of Scientific Publications. *Dtsch Arztebl Int*. 2009; 106(27):456-463.
- <sup>4</sup>Jones T, Evans D. Conducting a Systematic Review. *Aust Crit Care*. 2000; 13(2):66-71.
- <sup>5</sup>Draft Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. FDA 2006. <http://www.fda.gov/ohrms/DOCKETS/98fr/06d-0044-gdl0001.pdf>. Accessed January 25, 2011.
- <sup>6</sup>Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. FDA 2009. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>. Accessed January 25, 2011.
- <sup>7</sup>Jaded AR, Moore RA, Carroll D, et al. Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? *Control Clin Trials*. 1996; 17:1-12.
- <sup>8</sup>Stull D, Leidy NK, Jones PW, Stahl E. How Are We Measuring Functional Performance in Patients with COPD? A Discussion of Patient-Reported Outcome (PRO) Measures. *Curr Med Res Opin*. 2007; 23(11):2655-2665.

## Upcoming Presentations

### 10th International Conference on Alzheimer's & Parkinson's Diseases

March 9 – March 13, 2011, Barcelona, Spain

#### Oral Presentation

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

#### Poster Presentations

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

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

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

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

### 2nd Annual PRO Consortium Workshop

March 15, 2011, Silver Spring, MD, USA

#### Panel Discussion

*Responder Definition and Interpretation of Scores Using Cumulative Distribution Functions* **Panelists: Kathleen W.**

**Wyrwich**, PhD, Sr. Research Leader, United BioSource Corp., Lisa A. Kammerman, PhD, Office of Biostatistics, CDER, FDA; Joseph C. Cappelleri, PhD, MPH, Sr. Director, Biostatistics, Pfizer

#### Oral Presentation

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

### Visiongain's 6th Annual Pharmacovigilance

March 16 – March 17, 2011, London, UK

#### Oral Presentations

*Pharmacovigilance During the Pre-Approval Phases: An Evolving Pharmaceutical Industry Model* **Veronique Basch**, PharmD, Executive Director Safety, Europe

*Executive Director Safety, Europe Key Transition Between Pre and Post Marketing Safety in the EU* **Veronique Basch**, PharmD, Executive Director Safety, Europe

### 26th Annual EAU Congress

March 18 – March 22, 2011, Vienna, Austria

#### Poster Presentation

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

### Late Phase Drug Development World Americas 2011

March 22 – March 25, 2011, Boston, MA, USA

#### Opening Remarks and Oral Presentation

*Optimizing Communications on Late Phase Global Programs* **Peggy Schrammel**, MPA, VP, Registries and Post Approval Development

### 26th International Conference of Alzheimer's Disease International

March 26 – March 29, 2011, Toronto, Canada

#### Poster Presentation

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

### DIA 23rd Annual EuroMeeting

March 28 – March 30, 2011, Geneva, Switzerland

#### Oral Presentations

*Harmonising the Final FDA Patient-Reported Outcomes Guidance and the EMA "Points to Consider" Document—What is the Best*

*Way Forward?* **Ingela Wiklund**, PhD, Senior Research Leader, United BioSource Corp.

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

### ACC.11—60th Annual Scientific Session & Expo

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

#### Poster Presentation

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

### 13th International Congress on Schizophrenia Research

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

#### Workshop Presentation

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

#### Poster Presentation

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

### SAS Global Forum 2011

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

#### Oral Presentations

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

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

### AAN 2011 Annual Meeting

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

#### Poster Presentations

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

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

### World Drug Safety Congress America 2011

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

#### Oral Presentation

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

### 2011 ACCA Cardiovascular Administrators' Leadership Conference

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

#### Poster Presentations

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

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

**IAGG's VII European Region International Congress**

April 14 – April 17, 2011, Bologna, Italy

**Symposium**

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

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

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

**Oral Presentation**

*A Proactive, Focused and Transparent Approach to Overcome Risks Associated with Missing Data* **Robert Sharrar**, Exec. Dir., Safety and Risk Management, United BioSource Corp.; **Jon Morris**, VP, United BioSource Corp.

**PharmaSUG 2011**

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

**Oral Presentations**

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

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

**ATS 2011 International Conference**

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

**Poster Presentation**

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

**AUA 2011 Annual Meeting**

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

**Podium Presentation**

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

**164th Annual Meeting American Psychiatric Association (APA)**

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

**Poster Presentation**

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

**ISPOR 16th Annual International Meeting**

May 21 - May 25, 2011, Baltimore, MD, USA

**EDUCATIONAL SYMPOSIA**

*Navigating the New Comparative Effectiveness Landscape*

**Moderator: Rachael Fleurence**, PhD, Exec. Dir. United BioSource Corp.

*Supporting Personalized Medicine Through a Comparative Effectiveness Perspective* **Moderator: Kathleen W. Wywrich**, PhD, Sr. Research Leader, United BioSource Corp.

**SHORT COURSES**

*Bayesian Analysis: Overview and Applications* **Faculty: David Vanness**, PhD, Visiting Scientist, United BioSource Corp. & Asst. Prof., Univ. of Wisconsin School of Medicine and Public Health; **Christopher S. Hollenbeak**, PhD, Assoc. Prof., Penn State College of Medicine & Visiting Scientist, United BioSource Corp.

*Discrete Event Simulation for Economic Analyses* **Faculty: J. Jaime Caro**, MDCM, FRCPC, FACP, Adjunct Prof. Medicine, Adjunct Prof. of Epidemiology and Biostatistics, McGill Univ., Montreal PQ & Sr. VP Health Economics, United BioSource Corp.; **Jorgen Moller**, MSc Mech Eng, VP Modeling, United BioSource Corp.

**NCDEU 2011**

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

**Panel Presentation**

*The Automation of Cognitive Testing in Clinical Trials* **Chairs: Keith Wesnes**, PhD, Practice Leader, United BioSource Corp. and Amy Veroff, PhD, Medical and Scientific Affairs, i3

**Poster Presentations**

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

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

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

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

**DIA 2011 – 47th Annual Meeting**

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

**Session & Symposium Chairs**

*Critical Issues Related to Evidence Generation, Evaluation, and Standards for Comparative Effectiveness Research*

**Bryan R. Luce**, PhD, MBA, Director, Pragmatic Approaches to Comparative Effectiveness (PACE)

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

*Risk Management Assessment Reports: The New Medical Writing Challenge* **Michael D. Hoffman**, MS, Sr. Dir., Medical Writing & Regulatory Operations, United BioSource Corp.

**Session and Symposium Speakers**

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

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

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

**PLENARY SESSION**

*Modeling Task Force Recommendations* **Speaker: J. Jaime Caro**, MDCM, FRCPC, FACP, Chair, ISPOR-SMDM Modeling Good Research Practices Task Force and Sr. VP Health Economics, United BioSource Corp.

**ISPOR FORUM**

*Career Options in the Wake of Health Care Reform and Recession* **Speakers: Chris L. Pashos**, PhD, VP, United BioSource Corp.; C. Daniel Mullins, PhD, Prof. Pharmacoeconomics and Assoc. Dir. of Center on Drugs and Public Policy, Univ. of Maryland School of Pharmacy; Jens Grueger, PhD, VP and Head of Global Market Access, Pfizer

**ISSUE PANELS**

*IP2: Paying for Value—Which to Go For: The New UK Approach or the New German Law or Neither?* **Moderator: J. Jaime Caro**, MDCM, FRCPC, FAC, Sr. VP Health Economics, United BioSource Corp.

*IP6: When is the Evidence Adequate: Different Perspectives from Key Health Care Decision-Makers* **Panelists: Bryan R. Luce**, PhD, MBA, Sr. VP, Science Policy, United BioSource Corp.;

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## Evaluating Pregnancy Outcomes: Prospective Pregnancy Registries vs. Administrative Database Analyses

By Stephan Lanes, PhD, Senior Epidemiologist; Matthew W. Reynolds, PhD, Vice President, Epidemiology and Database Analytics; Peggy Schrammel, MPA, Vice President, Registries and Post Approval Development; Cathy Sigler, PhD, Senior Director, Epidemiology and Risk Management

### Introduction

Women of childbearing age are susceptible to a wide range of medical conditions (e.g., diabetes, depression, epilepsy, asthma, etc.) that require chronic therapy, and if they become pregnant, they must also face questions regarding the potential impact their medication could have on the health of their child. Those who research the potential risk factors of these medications are often disappointed by the lack of specific information available. While useful observational data have been systematically collected for some drug classes, such as the antiretroviral<sup>1</sup> and antiepileptic medications,<sup>2,3</sup> many important drugs and biologics have very limited available information. The U.S. Food and Drug Administration (FDA)<sup>4,5</sup> and European Medicines Agency (EMA)<sup>6</sup> have issued valuable guidance on relevant topics. Even with guidance from regulatory agencies, the design, conduct, and interpretation of observational studies of birth outcomes following prescription drug use is a challenging venture. In addition to the challenges inherent in observational studies (e.g., non-randomized, potential confounding, no ideal comparison group), the exposure of interest, prescription drug use, brings its own set of issues (e.g., not always collected, same drug called multiple names, confounding by indication, small sample size). The outcome of interest, typically rates of major malformations, also has inherent methodological challenges (e.g., lack of standardization in collection and categorization, high rates of minor malformations). Learning from the experiences of prior work is critical to the success of these important studies.

To address the issue of limited available information, researchers and pharmaceutical companies must initiate studies to gather and assess the relationship between medication use and clinical outcomes in pregnant women, either by beginning a new registry study or using large administrative databases that have both prescription drug use and birth outcome information. The strengths and weaknesses of these approaches are reviewed below.

### Pregnancy Registries

A pregnancy registry is an organized, prospective, observational, longitudinal study designed to estimate the overall risk of birth defects, and potentially infant developmental delays, associated with a particular drug. Pregnancy registries exist

both for specific medical conditions, such as HIV/AIDS, cancer, and epilepsy, as well as for specific products used to treat these and other common conditions, such as type 2 diabetes, multiple sclerosis, and rheumatoid arthritis. Both the EMA and the FDA have issued guidelines on when it is appropriate to conduct a pregnancy registry.

#### Guidelines on When to Establish a Pregnancy Registry<sup>7</sup>

- When the medication has a high likelihood of being used in women of childbearing age
- When the medication is for chronic therapy use and it is unadvisable to discontinue the therapy during pregnancy
- The medication has special circumstances, such as the potential for fetal infection through administration of live, attenuated vaccines
- Animal studies or human case reports have shown the potential for fetal harm
- When the medication belongs to a drug class or has similar components or mechanisms of action (e.g., teratogenic effects)

While many design issues inherent in typical registries hold true for pregnancy registries, there are special elements unique to pregnancy registries that must be addressed. Sample size in a typical, non-safety registry is often determined by the commercial goals for the product, rather than power to detect events of interest. In a pregnancy registry, sample size is dictated by the frequency of the outcome of interest in both the registry (exposed) group and the comparator group.

The selection of an appropriate comparator group in a pregnancy registry is essential and can be accomplished by directly enrolling a non-exposed cohort or, more commonly, by looking to external sources of comparable cohorts and associated outcomes, most often found in hospital, state, or nationwide surveillance systems and databases. Regardless, care must be taken to ensure that the cohort is as generalizable as possible with complete reporting of all pregnancy outcomes.

Finally, successful patient recruitment and retention is dependent on a multi-faceted outreach program to health-care providers and patients. (See *complementary article by Steel on enrollment of patients on page 15.*)

#### Collecting data in a prospective manner allows for:

- *A priori* specification of required data elements, rather than “making do” with available data found in automated databases.
- The inclusion of vital lifestyle data, such as socioeconomic status, smoking status, and drinking habits, which may not always be found in an automated database.
- The fostering of goodwill on the part of the sponsor among prescribers and patients, which supports the registry and the commercial goals of the product.

**Table 1. Strengths and Limitations of Registries and Database Studies for Pregnancy Outcomes**

	Registry	Database Study
<b>Identification of Exposed Population</b>	Referral by healthcare practitioner or self-referred.	Identifiable via pregnancy diagnosis/billing codes.
<b>Identification of Pregnancy Outcomes</b>	Routine follow-up with patient and health-care provider throughout the pregnancy with documentation of final birth outcome.	Identifiable via diagnosis/procedure codes. Validity of coding varies by clinical event of interest.
<b>Comparator Group</b>	Generally derived from an enrolled comparator cohort within the registry or, most often, from external surveillance sources.	Easily identifiable and matchable.
<b>Detail on Risk Factors</b>	Captured <i>a priori</i> on data collection forms.	Limited to those identifiable via diagnosis codes, procedure codes, prescriptions, and other variable database elements (e.g., laboratory values).
<b>Generalizability</b>	May be biased due to lack of complete pregnant population enrolled in the pregnancy registry.	Generalizable to population represented by database (e.g., managed care, Medicaid, etc.).
<b>Timeline for Results</b>	Results compiled on a periodic basis but dependent on enrollment rates and pregnancy status.	3-4 months
<b>Budget (US Dollars)</b>	\$1.0M+	\$125,000-\$250,000

**Conversely, prospective pregnancy registries have the following downsides:**

- **Cost**—The cost of program outreach, call-center maintenance, and data collection is high, compared to the small number of expected pregnancies.
- **Image**—Publicizing a pregnancy registry may lead some patients to believe that the drug is unsafe and must be discontinued.
- **Analytical challenges**—Again, finding a suitable comparator cohort that is generalizable and complete enough to support analyses can be challenging.

**Automated Databases**

Whether a drug has been on the market for many years or is not yet approved, automated databases can serve a useful role in planning and executing risk assessment strategies. To conduct meaningful studies of pregnancy outcomes, at a minimum, we need to identify the occurrence of a pregnancy, approximate date of conception or last menstrual period (LMP), pregnancy outcome occurrence and details by date, and medication exposures by date. This information is usually either contained in, or can be derived from, most administrative databases.

The best database for a particular study depends on the details of the situation. For example, the choice of database is notably different when the drug of interest is prescribed on an outpatient basis rather than for use primarily in the hospital. Most databases capture pharmacy prescriptions, but only a subset of databases capture inpatient data with sufficient detail to identify exposure to specific medications. With regard to the endpoint(s) of interest, the choice of data

source may depend on whether there is broad examination of many pregnancy outcomes or whether there is a focus on a particular type of birth defect. If the aim of the study is to identify a small number of specific defects, it would need to be determined whether those outcomes are identifiable with sufficient accuracy through the coding systems of the various databases. For example, Medicaid inpatient claims coded to ICD-9 codes have been found to provide good positive predictive value (PPV) (>70%) for cardiac, gastrointestinal, and orofacial defects, but were less accurate for defects of the central nervous system.<sup>8</sup> In the General Practice Research Database (GPRD) database in the United Kingdom, however, there was good PPV for neural tube defects as a group, although codes were less accurate for spina bifida, specifically.<sup>9</sup> It is possible though to identify databases that allow for details around the pregnancy outcomes through text in an electronic medical record (EMR) or via a manual chart review to confirm events; the number of databases that allow for this capability is growing in both the U.S. and Europe. In addition, certain defects, such as cleft palate, are easily identified at birth, while others, such as some heart defects or developmental delays, may become apparent only later in life. To identify defects that come to attention after birth, a database must be able to link the mother (and her exposures) with the child. A growing number of databases now offer this capability.

In general, database studies bear no cost of patient enrollment or data collection, so obtaining information rapidly and at relatively low cost are strengths of this approach. On the other hand, databases do not necessarily include all of the

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## Evaluating Pregnancy Outcomes

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data of interest for particular research objectives. Categories of data that are sometimes absent in databases include lifestyle factors, such as smoking, diet, and use of over-the-counter and herbal medications. For studies where the potential influence of these factors is large, certain databases offer the opportunity to augment the automated data with additional data collected from questionnaires. Often, the additional data is minimal and can be efficiently and effectively collected for a sample of the study population.

Database studies may not be well suited to new products for which information is needed urgently because product uptake is not immediate (hence, sample size is small in the beginning) and most databases have a lag-time of three to six months until the data can be analyzed. Finally, database studies are not necessarily an alternative to prospective studies, but are often complementary. For example, prospective pregnancy registries are often uncontrolled. While uncontrolled studies can be useful in identifying strong teratogenic effects or unique types of birth defects, weak, moderate or common birth defects may not be apparent without a control group. In many situations, a suitable comparison group can be developed using automated databases.

### Conclusions

The choice of study approach (registry vs. database) will depend heavily on the primary pregnancy research objectives. While both study designs are viable methods to

answering questions of pregnancy outcomes associated with pharmaceutical exposures, each type of study has its own strengths and limitations. Given the restraints on timing of study conduct, clinical outcomes of interest, and available resources, these strengths and limitations should be carefully considered before deciding which approach to employ. Some of the major strengths and limitations associated with registries and database studies in pregnancy outcomes research are noted in Table 1.

While the research question may often identify a clear choice of study design, it is potentially beneficial to conduct both a database study and registry in parallel. This approach could provide immediate evidence via a database study and more clinically detailed information via the registry study.

As regulatory agencies require increased vigilance regarding pharmaceutical risk management, it is important to understand the various options for identifying valid answers to important safety research questions. Both pregnancy registries and analysis of large individual patient databases provide viable and high quality research approaches to gaining insight into the effects of pharmaceutical products on pregnancy outcomes.

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## Registries & Observational Research — What Are Your Needs?

In an effort to better understand your needs and enhance our registry and observational study services, UBC would like to ask you to complete a short survey on this topic.

The survey should only take a few minutes, and to thank you for your time, we are offering a small token of thanks (go to the survey to see your thank you options). To take the survey, enter this website into your browser (<http://www.surveymonkey.com/s/UBCsurvey1104>). Your response is greatly appreciated and completely confidential.

### References

- <sup>1</sup>Watts DH, Covington DL, Beckerman K, et al. Assessing the Risk of Birth Defects Associated with Antiretroviral Exposure During Pregnancy. *Am J Obstet Gynecol*. 2004; 191:985-992.
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## Effective Outreach to Ensure Successful Enrollment of Patients in Pregnancy Registries

By Abbe Steel, Vice President, Patient and Physician Services

When planning a Pregnancy Exposure Registry (PER), sponsors should develop a proactive and detailed plan for outreach to physicians and patients to ensure enrollment goals are met. The objectives of an outreach plan are to communicate the registry to all healthcare providers (HCPs) involved in patient care, to ensure that all patients of child bearing potential are aware of and educated about the PER, and to garner and sustain commitment among HCPs and patients. The way registry promotion is planned, managed, and delivered to key stakeholders is critical and should include distinct strategies targeted at each key audience and utilize multiple communication pathways to ensure proper dissemination of the registry.

### Outreach to Physicians

IMS data is an excellent source to identify key physician audiences to receive outbound communication about the PER. A broad, direct mail distribution can be the first step for physician outreach. Additionally, an often effective communication vehicle is a simple Registry Resource Kit that can be sent to all high prescribers (top decile prescribers), obstetricians and any prescriber that has written a prescription for the drug within the last 24 months. Healthcare providers should also be directed to a PER website or call center to be able to order additional kits. This Resource Kit can include information for patients as well as a Pregnancy Registry Healthcare Providers FAQ Booklet, which should provide answers to healthcare providers' most frequently asked questions about the pregnancy registry. Topics covered can include a brief overview of the registry and why it was created, information on how healthcare providers and patients can report pregnancies, and guidance on patients' responsibilities after pregnancies are reported.

Professional society meetings, journals, and website links can serve as valuable avenues to promote and disseminate a company's pregnancy registry messages. An aggressive and more frequent advertising campaign may be necessary for the first couple of years following drug launch, and thereafter, a maintenance advertising program should be sufficient. Specific journals should be identified based on publication frequency, circulation, and society affiliation. A sponsor may want to develop upgraded advertising packages that would include online outreach for electronic versions of the journals, as well as advertising on the WebMD network (which includes both consumer and professional network audiences).

For those journals that do not allow advertising, a sponsor should seek other promotion opportunities, such as providing content for the website, panel/poster displays and

printed material distribution at relevant scientific meetings where the drug company has a sponsored booth.

### Outreach to Pharmacists

Outreach to pharmacists is also a way to encourage pregnant patients to contact the registry. To provide outreach to chain store headquarters and mail order/specialty pharmacies, direct mail communication can educate these stakeholders about the PER and provide website and call center information, as well as a sample of the Medication Guide. Electronic communication to the National Association of Chain Drug Stores (NACDS) and National Community Pharmacist Association (NCPA) membership is an effective vehicle to supplement the hard copy direct mail campaign.

### Communication with Patients

In addition to promotion to healthcare providers, there are multiple opportunities to communicate the PER to patients. Tactics such as patient educational materials, outreach to patients through pharmacies, and prescription savings vouchers or cards can raise awareness to promote enrollment at a patient level.

In order to support enrolled patients, it is important to incorporate a high level of personal contact with patients and to assign resources appropriately in order to provide consistency in that contact. Enrolled patients should receive reminders via text message and/or email to go to the registry website and answer questions regarding their pregnancy. Alternative communication methods can include phone calls with a trained interviewer.

#### Sponsors can overcome potential patient attrition with:

- Automated and centralized processes for recovering dropouts and communicating with patients on an ongoing basis. It is important to utilize multiple communication media (text messages, email, phone) in order to ensure continued contact.
- Monetary or other compensation (e.g., a book on infant care or other pre-natal educational item) for completing surveys or phone calls.

### Loss to Follow-up

For purposes of safety evaluation, it is important to minimize the number of subjects lost to follow-up. A contact follow-up plan should be completed at the time of patient enrollment, which would include details such as full address/phone numbers/email address, information on other customary healthcare providers and treating hospitals/clinics, and information on secondary contacts both within and outside the patient's household.

### A Note about Patient Health Literacy

Whenever communications are directed at patients, it is important that all materials are written for a low literacy population (sixth grade reading level). Patient materials should be written by a patient health literacy expert to ensure there are no areas of confusion or formatting issues that could

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## Pregnancy Registries

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obscure the clarity or impact of the key messages. Simple language and illustrations should be used, when appropriate, and presentation and format should always be considered and incorporated into all patient communications.

### The Registry Website

PER websites play an important role in providing credibility and value to potential stakeholders in the enrollment process. A PER website should include an overview of the registry for both patients and healthcare providers and answer frequently asked questions about registry requirements and enrollment information. Targeted Google AdWords, Facebook campaigns, and a keyword search engine optimization (SEO) program will help ensure appropriate promotion of the website. The PER should also be listed on the FDA's Office of Women's Health website<sup>1</sup> which keeps a list of all active pregnancy exposure registries.

### In Conclusion

Many registries fall short of enrollment goals because of the lack of awareness among key audiences. It is essential that a proactive, comprehensive outreach and communication plan is directed at potential patients and likely healthcare providers. The ultimate goal is to ensure that all healthcare providers that have direct patient contact are completely familiar with the PER and are able to properly educate and communicate the registry to appropriate patients. Proactive planning, leveraging multiple communication media, and utilizing an on-going promotion stream can help ensure that planned enrollment targets are met.

For more information, please contact  
Abbe.Steel@unitedbiosource.com.

### References

<sup>1</sup> U.S. Food and Drug Administration (FDA) Science & Research web page. <http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm>. Accessed January 31, 2011.

communications in Phase III research, which means planning for them in Phase II, can increase the likelihood of product success. Although product teams have been reluctant to restrict a product's population, and REMS have been perceived as punitive, REMS, and their alternatives, can be an opportunity to drive a product's success. If the product is safe for the patient, barriers are then removed for patients, healthcare providers, and payers.

Any occasion to communicate directly with a patient, caregiver, or healthcare provider is a good opportunity to reinforce a medication's benefits and risks in the interest of patient safety. Whether through REMS or other channels, proactive planning, an appropriate communication strategy, and a post-approval safety monitoring plan all align to drive a product's success. Pharmaceutical manufacturers are responsible for product safety through the identification and prevention of both known, and the potential for, adverse events. Whether through REMS or an alternative avenue, appropriate messaging, and how and when that messaging is communicated, can lead to safer product use.

Planning for product safety must be done by a cross-functional team early in the drug development process—well before New Drug Application (NDA) planning—to increase safety and product performance. Some manufacturers have a separate risk management team comprised of clinical, commercial, legal, regulatory, and medical representation, among others, that oversees multiple products, while other companies deploy shared personnel to sit directly on product teams. These teams must not only evaluate the data available to them, but they must also anticipate potential risks based on therapeutic class and the patient population and their treatment demographics, including age, economics, education, concomitant illnesses, lifestyle, and the potential for other resulting risk factors.

Regulatory agencies will want to understand the proactive approach to be employed post-launch. Taking advantage of testing the approach and communications in Phase III clinical trials gives companies an opportunity to know and understand in advance what will work, hence saving time and resources in post-marketing. In other words, going to market with a proven safety plan decreases patient risk and can thereby increase market potential for a product. Additionally, proactive knowledge and communications enable a company to control their messaging. Once a product is deemed unsafe or experiences adverse events, the Sponsor is no longer in control of the message patients are receiving—the news media takes over. Moreover, an unanticipated safety problem could result if patients stop taking their medication in response to news reports. Knowledge is power, and from every aspect, it makes sense for a company, when possible, to take the lead in directing information and how it is disseminated.

Phase III research can be leveraged in several ways to help a company understand education needs so they can be

## Leveraging Phase III Research to Plan for Patient Safety and Improve Product Market Performance

*By Gretchen S. Dieck, MPhil, PhD, Vice President, Safety, Epidemiology, and Risk Management*

Proactive planning for patient safety is key to market adoption, whether utilizing Risk Evaluation and Mitigation Strategies (REMS) or other mechanisms, a strong post-approval safety strategy is good insurance for a product. Beginning the testing of post-approval safety tools and

addressed early in the process. Who needs to be educated about particular aspects of the medication? For example, does the product need to be administered in a sterile environment? If not administered in a sterile environment, can infection result? If a sterile environment is needed, the inclusion of physician training, at a minimum, should be included as part of the post-approval plan. Is there a complicated titration? Perhaps packaging that explains each dose can be implemented outside of REMS. Results from Phase III research testing of Knowledge, Attitudes and Behavior (KABs) can be used to determine if a parent or caregiver understands their education on suicidality or the potential for product abuse. Agreements and reminders can be incorporated into study documents, and physician documents can help determine if certain requirements, such as special office/lab monitoring, infusion checklists, patient observation, post treatment, etc., are necessary for safe use.

One important aspect to consider when assessing potential risk is the dependence on others for safe use; treatments that require assistance from someone other than the patient often have an increased safety risk. While no product team wants to consider limited populations or restricted distribution, these mechanisms can increase product safety and improve patient access to the product. Lowered risk of product use decreases the burden on the patient and healthcare provider, and reducing burden can help increase both use and adherence. Risk interventions and adherence to risk management plans can be measured and adjusted prior to market launch, and throughout a product's lifecycle, for increased success in a wider market. Unforeseen issues identified after approval, which could have been avoided with a REMS, such as restricted distribution or caregiver certification, can lead to increased time and resources being spent to address the problem, and can also cause the product to be temporarily unavailable while these issues are addressed.

While it is acknowledged that the Phase III environment is artificial and incomplete, information gained during Phase III can help eliminate the "obvious" issues, anticipate potential questions or concerns, and allow companies to proactively address solutions. Are there barriers to correct usage, such as a unique dosage form or device? Can special packaging create a place for important messages? Clinical development also allows for careful research into therapy discontinuation reasons for both patient safety and marketing research.

Though no one can fully anticipate a REMS requirement, knowledge of the drug class, data from pre-clinical and pharmacology studies, mechanism of action, and epidemiology of the possible adverse events can predict potential risks. Risk minimization actions, including labeling and development and testing of a mitigation plan, could reduce regulatory delays; however, REMS planning should not be overlooked as a key factor in clinical drug development.

Sponsors should consider developing a flexible plan that will allow for management of identified and potential risks,

but also address the potential for an increased regulatory requirement if needed. In the current regulatory environment, taking the approach of "What is the minimum we need to do?" or asking the question "Can we just have a REMS in our back pocket if we need it during negotiations?" is not enough. While there are options to minimize or even avoid REMS, this may not strategically be the best decision. REMS are an opportunity to improve patient safety and product performance, and the thinking needs to shift so that they are no longer seen as a burden. An early start in planning your safety strategy and Phase III testing can drive the most complete and effective communication tools, and ultimately, position a product for the most efficient uptake in the marketplace.

For more information, please contact Gretchen.Dieck@unitedbiosource.com.

## The Use of Patient-Reported Outcomes in Product Labels: An Update of FDA-Approved Products for 2010

By Sajjad Khan, PhD, Senior Research Associate and Andrew Palsgrove, BA, Research Associate

### Background

Patient-reported outcomes (PROs) data in medical product development provide information on treatment efficacy and can offer a patient perspective of treatment benefit and risks to inform treatment-based decision making. Well before the release of the final Food and Drug Administration (FDA) PRO guidance in 2009 (Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims<sup>1</sup>), PRO data were important to the value-based differentiation for new products. The availability of generic drugs and numerous choices of branded agents within therapeutic classes have created additional demand for data, including PROs, that can help differentiate similar products and guide decision making by key stakeholders.

In 2009, UBC published a discussion in its newsletter, *Evidence Matters*, that focused on the FDA's interest in the use of rigorous patient-reported outcome data for new compounds seeking approval.<sup>2</sup> The piece included a review of PRO information in product labels from 2006

**The availability of generic drugs and numerous choices of branded agents within therapeutic classes have created additional demand for data, including PROs, that can help differentiate similar products and guide decision making by key stakeholders.**

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## The Use of Patient-Reported Outcomes in Product Labels

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through 2009; 23 labels and 18 products (2 with multiple indications) were summarized. Last year, in 2010, the table was updated to provide summary data on a total of 37 labels and 31 products from 2006 through 2009.

### 2010 Update

UBC performed a review of the FDA website ([www.fda.gov](http://www.fda.gov)) to identify the presence and use of PROs in new molecular

reported as endpoints. Examples include rating scales, such as the International Prostate Symptom Score (IPSS), the 12-item Multiple Sclerosis Walking Scale (MSWS-12), and the Center for Neurologic Study-Lability Scale (CNS-LS). The label for Asclera, indicated for treatment of spider veins and reticular veins, referenced the use of a verbal satisfaction scale, in which the patient was shown digital images of their skin and rated their satisfaction with treatment on a 5-point Likert scale.

It is possible that the products approved in 2010 were in clinical development before the release of the FDA draft (2006<sup>3</sup>) and final (2009<sup>1</sup>) PRO guidance, so the extent to which the PROs were held to the guidance is unknown. To date, UBC has identified 46 products that include PRO language in their

**Table 1. Medical Products Approved by the FDA in 2010 with PRO Information in the Label<sup>a</sup>**

Product Name Disease Area			
<b>Ampyra</b> <i>Multiple Sclerosis (MS)</i>	<b>Articaine HCL w/ Epinephrine</b> <i>Pain Associated with Dental Surgery</i>	<b>Asclera</b> <i>Spider &amp; Reticular Veins</i>	<b>Butrans</b> <i>Chronic Back Pain</i>
<b>Cayston</b> <i>Respiratory Symptoms Associated with Cystic Fibrosis</i>	<b>Dulera</b> <i>Asthma</i>	<b>Egrifta</b> <i>Reduction of Abdominal Fat in HIV patients</i>	<b>Exalgo</b> <i>Pain</i>
<b>Jalyn</b> <i>Benign Prostatic Hyperplasia (BPH)</i>	<b>Nuedexta</b> <i>Pseudobulbar Effect in MS and Amyotrophic Lateral Sclerosis</i>	<b>Silenor</b> <i>Insomnia</i>	<b>Staxyn</b> <i>Erectile Dysfunction</i>
<b>Vimovo</b> <i>Pain Associated with RA, Osteoarthritis, Ankylosing Spondylitis</i>			

<sup>a</sup>Representing 13 of the 29 New Drug Applications (NDAs) approved in 2010, based on a review of [www.fda.gov](http://www.fda.gov).

entities and new combination products approved by the FDA in 2010, excluding generic agents, biologics, and existing compounds with new manufacturers. Of the 29 products identified, 13 (44.8%) included PRO label language. It is important to note that all of the 29 products did not necessarily warrant a PRO. Table 1 provides a list of the 13 products approved in 2010 with PRO labeling.

The PRO summary table has been updated to include these products, with information on approval dates and verbatim label language related to PROs, and can be found at <http://unitedbiosource.com/pdfs/pro-label-information.pdf>

The 2010 compounds represent a wide range of therapeutic areas, indicating involvement of different reviewing divisions within the FDA. Therapeutic areas included, but were not limited to, cancer, women's health, central nervous system (CNS), endocrinology, and respiratory medicine. PRO instruments used to support labeling claims for these products varied and exemplified the diversity with which patient reports of their treatment experience can be captured and

FDA-approved labels since January 2006. UBC continues to monitor and collect information pertaining to the use of PRO measures in clinical trials and ultimately, in FDA-approved labels. In 2011 and beyond, we would expect to see products emerging that clearly utilized the FDA PRO guidance within their clinical development programs.

For more information, please contact Sajjad.Khan@unitedbiosource.com or Andrew.Palsgrove@unitedbiosource.com.

### References

- <sup>1</sup>Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *Federal Register*. 2009; 74(235):65132-65133.
- <sup>2</sup>Khan S, Palsgrove AC. "Patient-Reported Outcomes (PROs) in Product Labeling, 2006 to Present—An Update." *EvidenceMatters*. 2010 Mar; 16(1):25.
- <sup>3</sup>Draft Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *Federal Register*. February 3, 2006; 71(23):5862-5863.

## Recent Presentations

### CRT 2011

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

#### Poster Presentations

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

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

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

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

#### Working Group Sessions

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

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

#### Poster Presentations

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

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

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

### 2011 SRNT 17th Annual Meeting

February 16 – February 19, 2011, Toronto, Canada

#### Oral Presentation

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

### 6th Annual Pricing, Reimbursement & Market Access in Pharma

January 19 – January 20, 2011, Barcelona, Spain

#### Presentation

*HTA Evaluations – Understand Fully the System of Funding* **Floortje van Nooten**, MSc, Research Scientist, United BioSource Corp.

### 52nd American Society of Hematology Meeting and Exposition

December 4 – December 7, 2010, Orlando, FL, USA

#### Presentation

*Variation in Health-Related Quality of Life (HRQOL) by ISS Stage and ECOG Status Among Multiple Myeloma Patients* **Pashos CL**, Durie BGM, Rifkin R, Shah J, Street T, Sullivan K, Khan ZM

### Late Phase Drug Development World 2010

November 30 – December 3, 2010, London, UK

#### Pre-Conference Workshop

*Management of Differences (or Variations) within the EU Guidelines for Non-Interventional Studies* **Hazel Wohlfahrt**, Exec. Director, EU Clinical Operations, United BioSource Corp.; **Jess Sohal**, Exec. Director, EU Clinical Operations, United BioSource Corp.

#### Presentation

*The Right Evidence, Using the Right Decision, and the Right Tools* **Krista Payne**, MEd, Director and Research Scientist, Health Care Data Capture, United BioSource Corp.

### Gerontological Society of America's 63rd Annual Scientific Meeting

November 19 – November 23, 2010, New Orleans, LA, USA

#### Poster Presentation

*The Prevalence and HRQL Impact of OAB in Older Adults: Results from EpiLUTS* Markland A, **Sexton CC**, **Coyne KS**, **Thompson C**, Bavendam T, Chen C-I

### 7th Forum on Patient Reported Outcomes (PRO)

November 17 – November 18, 2010, Philadelphia, PA, USA

#### Pre-Conference Workshop

*Use Responder Analysis to Support Label Claims for Patient Reported Outcomes* Joseph C. Cappelleri, PhD, MPH, Sr. Dir., Biostatistics, Pfizer; **Kathleen W. Wyrwich**, PhD, Sr. Research Scientist, Center for Health Outcomes Research, United BioSource Corp.

### American Heart Association (AHA) Scientific Sessions 2010

November 13 – November 17, 2010, Chicago, IL, USA

#### Poster Presentation

*Is There an Association Between Aspirin Dosing and Cardiac and Bleeding Events in Acute Coronary Syndrome After Stent Placement? A Systematic Review of the Literature* Berger JS, **Sallum RH**, Katona B, Maya J, **Ranganathan G**, Mwamburi M

### The American College of Allergy, Asthma & Immunology (ACAAI) Annual Scientific Meeting 2010

November 11 – November 16, 2010, Phoenix, AZ, USA

#### Poster Presentation

*An Assessment of Change in Quality of Life Among Patients 12 Years and Older with Persistent Asthma in Mometasone Furoate/Formoterol Fumarate Clinical Trials* **Wyrwich K**

*An Assessment of Change in Asthma Control Among Patients 12 Years and Older With Persistent Asthma in Mometasone Furoate/Formoterol Fumarate Clinical Trials* **Wyrwich K**

### 2010 RAPS Annual Conference & Exhibition

October 24 – October 27, 2010, San Jose, CA, USA

#### Presentation

*REMS: Theory, Practice, Evolution* **Kelly Davis**, MD, Vice President, Safety Epidemiology and Risk Management, United BioSource Corp.; David Feigl Jr., MD, MPH, Principal, NDA Partners LLP; Florence Houn, MPH, MD, Vice President, Regulatory Policy and Strategy, Celgene Corp.; Raj Kishore, PhD, Principal, Regulatory Strategy, Quintiles Consulting

### American Society for Reproductive Medicine (ASRM) 66th Annual Meeting

October 23 – October 27, 2010, Denver, CO, USA

#### Poster Presentation

*Impact of Estradiol Valerate / Dienogest (E2V / DNG) on Work Productivity (WP) and Activities of Daily Living (ADL) Impairment in North American Women with Heavy and / or Prolonged Menstrual Bleeding (HPMP)* **Wasiak R**, Filonenko A, Jensen JT, Law AW, Jeddi M, **Stull DE**

### 48th Annual Meeting of the Infectious Disease Society of America (IDSA)

October 21 – October 24, 2010, Vancouver, Canada

#### Presentation

*Complicated Skin and Soft Tissue Infections (cSSTI) in Hospitalized Patients – a Prospective Multi-Center Observational Study of Clinical Characteristics and Medical Treatment* Lipsky BA, Napolitano L, Moran GJ, Vo L, Nicholson S, **Freier K**, **Boulanger L**, Kim M

### AdvaMed 2010

October 18 – October 20, 2010, Washington, DC, USA

#### Educational Panel Discussion

*Adding Value in Today's Global Medical Devices Industry*

**Moderator:** Ross Segan, MD, FACS, VP, Global Medical Affairs, Deputy Chief Medical Officer, Covidien

**Panelists:** Peter Heeckt, MD, Chief Medical Officer, Smith & Nephew Orthopaedics; **Greg de Lissovoy**, PhD, MPH, Vice President for Health Technology, United BioSource Corp.

## NEWS BRIEFS

## UBC Expands Global Capabilities with Acquisition of Total Healthcare Group

On December 13, United BioSource Corporation (UBC), a wholly owned subsidiary of Medco Health Solutions, Inc., acquired Total Healthcare Group (THG), a London-based international consultancy serving clients in the biopharmaceutical industry. THG, founded in 1966 by Dr. Robert Hollamby, provides global payer research, strategic planning, and global value dossiers for biopharmaceutical products. THG, together with UBC's existing value strategy and research services, will be led by Dr. Hollamby, who has been appointed Senior Vice President at UBC.

"Demonstrating value and providing evidence-based research that allows stakeholders in the health care market to make important economic decisions surrounding biopharmaceuticals and devices is crucial in the market place," said UBC President Mark Clein. "UBC helps clients respond effectively to the evolving health care environment by researching, communicating, and demonstrating value in medicines. The addition of THG significantly expands our capabilities and geographic reach and allows us to launch a comprehensive practice that we expect to be a leader in the global biopharmaceutical industry."

"By combining THG's global payer expertise and research with UBC's scale and its unique portfolio of scientific and late stage research capabilities, we have strengthened our ability to deliver significant value and provide exciting new opportunities for clients throughout our industry," said Dr. Hollamby. "We believe our ability to deliver comprehensive and relevant scientific evidence to payers on a global basis will firmly establish UBC as an industry leader in a discipline that has become crucial to the delivery of high quality health care to patients."

## UBC Introduces Expanded Software Portfolio to Aid Pharmacovigilance and Comparative Effectiveness

In January, UBC began offering an expanded portfolio of proprietary software platforms focused on delivering relevant evidence to assist pharmacovigilance, drug safety, and evaluate comparative effectiveness for biopharmaceuticals and other life science products. The company's new software platforms stem from the November 2010 acquisition of ProSanos Corporation, a Harrisburg, Pennsylvania-based

scientific technology company. The software platforms are capable of rapidly accessing and analyzing information from diverse data sources, including spontaneous adverse event reporting systems and observational databases such as health insurance claims and electronic health records. The expanded UBC software portfolio now includes:

- SÆfetyWorks® Award winning software that helps epidemiologists and product safety scientists analyze separate and distinct observational claims and medical records databases;
- CLÆRITY® Easy-to-use web-based software for investigation and management of potential safety signals in adverse event data;
- CEWorks™ An analytic application that enables rapid generation and synthesis of real world evidence from claims and electronic medical records databases.

"By combining these unique pharmacovigilance and comparative effectiveness software platforms with UBC's well known scientific expertise in product safety, health outcomes, and comparative effectiveness, we are able to significantly increase the quality and efficiency of our clients' product development and commercialization operations," said ProSanos founder Jon Morris, MD. "With this technology, our clients are able to work more efficiently to deliver relevant product evidence and disease analytics." ProSanos software and services have been integrated into UBC's existing product safety and comparative effectiveness practices. Morris will continue to lead the group's business development efforts in close collaboration with senior scientists at UBC and Stephanie Reisinger will continue to lead technology development and operations.

## Proherant Joins UBC

In January 2011, Proherant Health, Inc., joined the UBC organization. Proherant offers a unique portfolio of integrated patient and health care provider support services for manufacturers of biopharmaceuticals and medical devices. The company's services are focused on helping manufacturers guide the safe and effective use of specialty drugs and devices, manage access and reimbursement, and facilitate clinical research. Proherant's key capabilities include coordination services for in-home and alternate site nursing, nursing call centers, clinical liaison programs, clinical research support, reimbursement services, and patient assistance program administration.

"By integrating the capabilities of Proherant into UBC, we are significantly enhancing our ability to deliver complete, end-to-end "hub" solutions that encompass reimbursement management, clinical coordination, clinical call center services, and REMS," said Chad Clark, General Manager of Comprehensive Access and Patient Support at UBC. "This all contributes to an enhanced portfolio of services for our clients

and more robust patient and provider support systems to guide the safe and effective use of drugs and devices.”

Proherant became a part of the Medco Health Solutions, Inc., family of companies in 2005. The company has facilities in Memphis, Tennessee, and Overland Park, Kansas.

## New Research Scientists Join UBC



■ **Kamal Desai, PhD**, has joined UBC as a Research Scientist in Health Economic Modeling and Simulation in our London, UK, office and has a diverse background in epidemiology, biostatistics, and health economic modeling. In particular, Dr. Desai has advanced modeling training and is experienced in Markov, Monte-Carlo

and discrete event simulation modeling. He has worked extensively in the area of infectious and vaccine-preventable diseases in both developed and developing country settings. Before joining UBC, Dr. Desai served as Senior Manager of Epidemiology and Modeling for three years in the vaccine industry where his responsibilities included the development of epidemiological field studies for vaccine-preventable diseases as well as modeling for products in late-stage clinical development and for licensed vaccines. Prior to this, he was a research fellow for six years at Imperial College London where he worked on economic evaluations for HIV/AIDS prevention approaches in collaboration with the Centers for Disease Control and on assessments of the economic impact of HIV/AIDS on education systems in sub-Saharan Africa for the World Bank. Additionally, he was involved as a biostatistician and mathematical modeler in several randomized clinical trials, with tasks ranging from defining statistical analysis plans, modeling the impacts for new prevention interventions, and clinical trial simulation.

Dr. Desai received a Bachelor of Science degree in Mathematics from McGill University, Montreal, and a Master of Science in Statistics and a Doctorate in Mathematical Epidemiology from Laval University, Quebec. He then obtained a Wellcome Trust Fellowship to develop his skills in economic evaluation at Imperial College London. He has co-authored papers in a number of journals including the *Lancet Infectious Diseases*, *AIDS*, and *Emerging Themes in Epidemiology*.



■ **Elisabeth Stahl, PhD**, has joined UBC as a Senior Research Scientist in Health Outcomes Research and is based in our London, UK, office. Prior to joining UBC, Dr. Stahl spent 28 years at AstraZeneca in Sweden and was a Value Demonstration Leader and

Principal Scientist in AstraZeneca's Global Health Economic and Outcomes Research group, providing strategic direction and implementing outcomes research activities in various therapeutic areas, especially in respiratory and diabetes. Dr. Stahl holds a doctorate degree from Lund University, Sweden, where her thesis covered the use of health-related quality of life instruments in asthma and COPD, and she also holds an Honorary Senior Lecturer position at the University of Aberdeen in the UK. Dr. Stahl has presented her PRO research at several European Respiratory Society (ERS) congresses and various other international conferences. She has published more than 55 full-length papers in peer-reviewed journals.



## UBC Adds New Safety Physicians in Europe

■ **Fabio De Gregorio, MD, PhD**, has joined UBC as a Safety Physician in our Geneva, Switzerland office. He brings over 11 years of experience in the clinical research arena. Prior to UBC, Dr. De Gregorio worked at

Tubilux Pharma S.p.A. in Italy as a Qualified Person for Pharmacovigilance (QPPV) where he established and managed the pharmacovigilance service in compliance with the current law requirements. As a medical director in outsourcing, Dr. De Gregorio supported the regulatory department in registering generic ophthalmic products, as well as designed and supervised Phase II and III clinical trials for marketing authorization applications. Additionally, Dr. De Gregorio worked in the Glaucoma Division of La Sapienza University in Rome, Italy, where he was responsible for follow-up of approximately 2,000 patients per year, and more recently, he collaborated with the university on the development, planning and conducting of clinical research activities on various ocular diseases.

Dr. De Gregorio received his medical degree in medicine and surgery and his doctorate degree in patho-physiology of ocular microcirculation from La Sapienza University in Rome, Italy. He has authored over 80 scientific articles published in international peer-reviewed journals and has presented and won awards at various international conferences.

■ **Ruben Miguel Ayzin Rosoky, MD, PhD**, has joined UBC as a Safety Physician in our Geneva, Switzerland, office. Dr. Rosoky has 19 years of experience in clinical research, and prior to joining UBC, he worked for private industry in the health care arena in various capacities. Dr. Rosoky has planned and designed clinical research protocols, as well as medically monitored the conduct of many other trials. As a clinical research physician, he was involved in the processing of individual case reports from clinical trials and providing

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## NEWS BRIEFS

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medical input in the preparation of regulatory mandated documents and bid processes. In his position as a medical monitor, Dr. Rosoky ensured the safety of subjects participating in clinical trials under his responsibility, interacted with the sponsor's Medical personnel, and provided medical support to CRAs, project managers and investigational site staff in medical inquiries arising during these investigations. He has experience working with sponsors and sites from all over the world, as well as in participating in large international multidisciplinary teams conducting clinical trials.

Dr. Rosoky is a board certified angiologist and vascular surgeon and received his medical and doctorate degrees from the University of Sao Paulo in Brazil. He has a Diploma in Pharmaceutical Medicine from the Free University of Brussels, and is a member of the Faculty of Pharmaceutical Medicine of the UK. He has experience in a multitude of therapeutic areas and has many publications in peer-reviewed, international medical journals.

## UBC Outcomes Research Experts Contribute to New Book



Two senior UBC staff members, **Sonya Eremenco, MA, ePRO** Manager, and **Dennis A. Revicki, PhD**, Senior Research Leader, have authored a chapter on "Regulation and Compliance: Scientific and Technical Regulatory Issues Associated with Electronic Capture of Patient-Reported Outcome Data" in a new book on electronic patient-reported outcomes (ePROs), *ePRO: Electronic Solutions for Patient-Reported Data*. This contemporary industry book, edited by Bill Byrom and Brian Tiplady, contains contributions from thought leaders across the ePRO community and provides valuable perspective and experience on the development and



implementation of ePRO instruments in light of the FDA guidance on PRO measures published at the end of 2009. Copies of the book are available from the publisher at <http://www.gowerpublishing.com/isbn/9780566087714>.

## UBC Announces Senior Level Promotions

UBC is proud to announce the following UBC senior staff members who have recently been recognized for exemplary performance with promotions in their respective areas.

<b>Luke Boulanger, MA</b>	Senior Research Scientist, Database Solutions
<b>Lael Cragin, MPH</b>	Director, Comparative Effectiveness Research
<b>Mike Epstein, MS</b>	Director, Market Access
<b>Denis Getsios, BA</b>	Senior Research Scientist, Health Economics Modeling
<b>Jack Ishak, PhD</b>	Director & Senior Research Scientist, Biostatistics
<b>Anuraag Kansal, PhD</b>	Research Scientist, Health Economics Modeling
<b>Huseyin Naci, MHS</b>	Associate Director, Comparative Effectiveness Research
<b>Krista Payne, MEd</b>	Senior Research Scientist, Health Care Data Capture
<b>Matt Reynolds, PhD</b>	Vice President, Epidemiology and Database Analytics
<b>Amy Smalarz, PhD</b>	Research Scientist, Health Economics
<b>Sonja Sorensen, MPH</b>	Senior Research Scientist, Health Economics
<b>Stephanie Van Norman</b>	Senior Director, Coordinating Center
<b>Jeffrey Wehmeyer</b>	Executive Director, Data Management
<b>Ning Wu, PhD</b>	Research Scientist, Health Economics

## McGill University Offers Summer Course in Pharmacoeconomics

**J. Jaime Caro** MDCM, FCRPC, FACP, Adjunct Prof. of Medicine, Adjunct Prof. of Epidemiology & Biostatistics, McGill Univ. & Sr. Vice President of Health Economics, United BioSource Corp., will lead a course on pharmacoeconomics at McGill University on June 20-23, 2011. This course provides a detailed introduction to the key concepts of this field, including the examination of study types (cost-benefit, cost-utility, cost-effectiveness) and corresponding decision rules.

For more information, please visit <http://www.mcgill.ca/epi-biostat-occh/summer> or contact Jaime Caro at [Jaime.Caro@unitedbiosource.com](mailto:Jaime.Caro@unitedbiosource.com).

## SPOTLIGHT ON SCIENCE

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## ISPOR 16th Annual International Meeting

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Steven Pearson, MD, MSc, President, Inst. for Clinical and Economic Review; Robert S. Epstein, MD, MS, Chief Medical Officer, Sr. VP, Medical Affairs, Medco Health

*IP12: Experimental vs. Observational Studies: Which Should Have a Higher Rank in Health Care Decisions?* **Panelists:** C. Daniel Mullins, PhD, Prof., Pharm. Health Services Research Dept., Univ. of Maryland School of Pharmacy; **Rachael Fleurence**, PhD, Exec. Dir., United BioSource Corp.; Winston Wong, PharmD, Assoc. VP, Pharmacy Management, CareFirst BlueCross BlueShield

### WORKSHOPS

*W1: Conducting & Interpreting Indirect Treatment Comparison and Network Meta-Analysis: Learning the Basics* **Discussion Leaders:** Jeroen P. Jansen, PhD, MSc, Research Dir., Mapi Values; Neil Hawkins, PhD, Dir., Oxford Outcomes; Joseph C. Cappelleri, PhD, MPH, Pfizer; **Rachael Fleurence**, Exec. Dir., United BioSource Corp.

*W9: Using Comparative Effectiveness Research (CER) to Support a Value Based Health Care System, Examples from the United States and Europe* **Discussion Leaders:** **Rachael Fleurence**, PhD, Exec. Dir., United BioSource Corp.; **Feng Pan, PhD**, Sr. Research Assoc., United BioSource Corp.; Corinna Sorenson, MPH, MHSA, Research Officer, London School of Economics and European Health Technology Inst. for Socio-Economic Research

*W13: Use of Simulation to Inform the Design of Pragmatic Comparative Effectiveness Trials* **Discussion Leaders:** **David Wilson**, MA, Research Scientist, United BioSource Corp.; **J.**

**Jaime Caro**, MDCM, FRCPC, FAC, Sr. VP Health Economics, United BioSource Corp.; **K. Jack Ishak**, PhD, MSc, Dir. & Research Scientist Biostatistics, United BioSource Corp.; Myoung Kim, PhD, MA, MBA, Dir., HEOR, Ortho-McNeil Janssen Scientific Affairs

*W16: The Evolving Role of the Agency for Healthcare Research and Quality (AHRQ) in Comparative Effectiveness Research (CER)* **Discussion Leaders:** Jean Slutsky, PA, MSPH, Dir., AHRQ; Nina A. Thomas, MPH, VP, Doctor Evidence, LLC; **Steven Blume**, MS, Research Scientist, United BioSource Corp.

*W17: Patient-Reported Outcome (PRO) Assessments in Clinical Trials: Navigating the EMA and FDA Regulatory Framework* **Discussion Leaders:** **Ingela Wiklund**, PhD, Sr. Research Leader, United BioSource Corp.; Olivier Chassany, PhD, MD, Medical Mgr., Assistance Publique-Hopitaux de Paris; **Kathleen W. Wyrwich**, PhD, Sr. Research Leader, United BioSource Corp.

*W23: Practical Approaches for Systematic Analysis of Observational Data; Real World Case Studies from the Pharmaceutical Industry* **Discussion Leaders:** **Stephanie Reisinger**, Sr. Dir., United BioSource Corp.; Gregory E. Powell, PharmD, MBA, Mgr., GlaxoSmithKline; David Miller, ScD, SM, Dir. of Risk Management and Pharmacoepidemiology, Schwarz Bioscience; **Jonathan A. Morris**, MD, Sr. VP, United BioSource Corp.

*W24: Generalized Evidence Synthesis in Comparative Effectiveness Research: Could the Evidence Base Be Broadened in Mixed Treatment Comparisons?* **Discussion Leaders:** **Agnes Benedict**, MSc, MA, Research Scientist, United BioSource Corp.; **Huseyin Naci**, MHS, Research Associate III, United BioSource Corp.; David Vanness, PhD, Asst. Prof. Univ. of Wisconsin



## *join UBC's international team*

UBC is experiencing strong demand for our services and the individuals who join us will have significant opportunity to shape the growth of our international organization. We are currently looking for experienced professionals for two of our most senior positions: Head of Outcomes Research in London and elsewhere in Europe, and Senior Research Scientist Health Economics also in London and elsewhere in Europe.

### **Head of Outcomes Research / Senior Research Leader**

- Recognised expert in the field of health outcomes
- Brings many years of experience in Outcomes Research, with a track record of publications and contributions in the field
- Lead the growth of the outcomes research practice in Europe, with the aim of establishing it as the leading consulting team in the field in London and throughout Europe
- Lead the growth of their area of responsibility
- Act as Principal Investigator or senior consultant on projects
- Lead interactions with clients in the pharmaceutical and medical devices industries
- Act as a guide and mentor to the staff in the London office

### **Senior Research Scientist Health Economics**

- Broad experience in health economics and an expert in economic modelling
- Help successfully establish the health economics-related practice as the leading consulting team in the field in London and throughout Europe
- Lead the growth of their area of responsibility
- Act as Principal Investigator or senior consultant on projects
- Lead interactions with clients in the pharmaceutical and medical devices industries
- Act as a guide and mentor to the staff in the London office

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## Advanced Economic Modeling for Health Care Decision Making: A CASE STUDY

### SITUATION:

#### **NICE Rejection of Products Would Leave Patients Without Optimal Treatment**

Expert teams from United BioSource Corporation (UBC) were commissioned by separate pharmaceutical companies to help them address an adverse draft guidance from the National Institute for Health and Clinical Excellence (NICE) regarding their products. UBC was approached because of:

- Extensive experience and reputation in the disease area,
- In-depth understanding of NICE submissions and processes, and
- Advanced capabilities in modeling techniques, such as discrete event simulation

### CHALLENGE:

#### **Address an Adverse NICE Guidance**

In an earlier assessment of treatments for Alzheimer's disease (AD), NICE concluded the treatments were not sufficiently cost-effective in mild AD, and only some were marginally cost-effective in moderate AD. A legal challenge resulted in a reassessment by NICE, but despite clear errors identified in its economic model, NICE proposed to maintain its original conclusions. The challenge now was to demonstrate that the interpretation of the evidence used by NICE was incorrect and that the model being used to estimate cost-effectiveness did not properly account for key aspects of the disease and treatments.

### SOLUTION:

#### **Demonstrate that an Appropriate Interpretation of the Evidence Showed Value**

To address the challenges, two separate, multi-disciplinary teams comprised of health economists, advanced modelers, epidemiologists, biostatisticians, clinicians, and evidence synthesis experts were created. A key part of this process was the development of a "state of the art" AD economic model. This sophisticated model was able to accurately capture the benefits of treatment over the entire course of the disease and provide powerful justification to counter the negative reimbursement recommendations.

NICE acknowledged the errors found in its models and, most importantly, accepted that the approach and methods used in the discrete event simulation were a valid representation of the disease and the impact of treatments on outcomes. The new model, based on a thorough review of the literature and solid clinical and economic interpretation, provided an accurate description of the disease and a solid basis on which to evaluate the cost-effectiveness of treatments in AD. The cumulative impact of the experts' work was instrumental in reversing the provisional recommendations, and in a final guidance, the recommendations were favorable to these treatments for AD.

UBC's efforts, together with those of the manufacturers, patient associations, and others, reversed the earlier sub-optimal decision regarding the two AD treatments. Most significantly, these efforts helped secure an appropriate decision that supports optimal care and outcomes for patients with AD, their caregivers, and the medical community concerned.

## Internal Audits—A Must, Not an Option

By Leo Tysak, BS, MBA, Director, Regulatory Compliance & Process Implementation

While keeping costs down is important to all companies, rework and poor quality increase costs and delays to any project. Insanity is frequently defined as doing the same thing over and over but expecting different results. If a service provider doesn't have a strong history of performance, would it be reasonable to expect different results?

Investment firms note that past trends do not predict future performance; however, one would not eagerly invest in a fund that performed poorly or had no history. Also, performance of one fund cannot be completely extrapolated to another fund's performance due to the many variables impacting each individual sector. Such is the case with service providers for biopharmaceutical sponsors.

Internal audits by service providers can produce surrogate results to predict operational performance. A service provider should be forthcoming with blinded audit results to demonstrate past and future ability to execute according to a Sponsor's and Regulator's requirements. Repeated findings, regardless of their severity, can signal the inability to share information and adjust processes.

Internal, project-specific, proactive audits are often an optional service proposed to Sponsors. Even with the additional cost, the investment in audits creates insurance against missed targets or the need to redo work for both the Sponsor and provider. Building audits into every project thereby helps eliminate surprises. Additionally, the proactive identification of issues, no matter how small, can help identify a root cause, which can then be corrected before any major impact is made to the project.

This also builds trust between the Sponsor and the provider by showing a proactive attitude in reviewing internal processes and addressing concerns early on.

**...the investment in audits creates insurance against missed targets or the need to redo work for both the Sponsor and provider. Building audits into every project thereby helps eliminate surprises.**

Rigorous new hire and project-specific training increases a project team's ability to pass an audit. One opportunity to strengthen these areas is during the Quality Assurance (QA) process where QA auditors question team members for both understanding and compliance with project plans. During this process, new hires can be more easily integrated into teams and additional training needs can be quality identified and addressed early, thereby avoiding potential problems and keeping projects on the appropriate track and timeline.

Lastly, process audits can only be applied to a mass-production approach; they must be reproduced over and over again for each relevant study. Attempting to extrapolate results from how a process works during one type of study, in a certain indication, and/or within different countries will not produce repeatable findings. Long-term studies, such as observational studies or registries, require their own audits, as each study or project is unique. While lessons should be learned from one study to another, each will still have their own challenges to be uncovered and should be addressed sooner rather than later.

Internal audits are not an option; they are a requirement for a successful, proactive issue identification and resolution plan. Attempting to extrapolate findings from previous studies to prevent issues on a current study is a risk that could lead to lost time, duplication of efforts, increased costs, and potentially a negative effect on your reputation. Taking a chance to cut costs can very likely lead to spending even more down the road. Are you willing to take that gamble?

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

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