

Inside this Issue

Cover Story:
Individual-Level Simulation

Health Technology Assessment:
Impact in Europe 1

Planning Late Stage Studies 2

Site Selection for a
Successful Study 6

Exploring the Ceiling Ratio for
Health Technologies in Spain 7

Use of the SEER-Medicare
Database 9

FOCUS ON: e-Evidence

Cognitive Debriefing...of
Electronic PRO Measures..... 11

Advance of "e-Learning"
in Clinical Trials 12

Electronic Health
Economics Data Capture 12

The Importance of a
Good User Interface..... 13

Evidence-Based Research
from EMRs 15

A Web-Based Portal for Evidence-
Based Decision Making..... 16

EXACT-PRO Initiative Update..... 17

Using IT Tools to Increase
In-Study Ratings Reliability..... 18

Using e-PROs to Facilitate
Enrollment in Clinical Trials..... 19

Upcoming Presentations 20

Recent Publications 21

UBC at ISPOR..... 22

New Briefs..... 23

SCIENCE & POLICY OPINION



Individual-Level Simulation is Here: Can You Afford to be Without It?

By Jaime Caro, MDCM, FRCPC, FACP

The new product has been shown to provide some advantages, including a favourable tolerability profile that may enhance compliance. It is not a breakthrough therapy, however. Several good treatment alternatives exist, including non-pharmacological options, and doctors can sequence them to suit their patients and their responses. Moreover, the clinical trials have focused on intermediate endpoints, with the studies of ultimate outcomes

still years away. There will likely be some savings—still unproven—from additional events that are prevented by the new product but the company wants a premium price that will outweigh these.

This scenario has become familiar to those labouring to bring drugs, biotech agents, devices, and other products to market. The evidence of a favourable benefit to risk is there but its translation to value is uncertain. By now, it is widely accepted that this key piece cannot be provided by clinical trials—it must be achieved via modeling of the disease and its management. These models are

continued on page 3

Health Technology Assessment: Impact in Europe

By Laura Horsfall, MSc, Floortje van Nooten, MSc and Ruth Brown, MS, MHSA

Health technology assessment (HTA) is generally defined as the process of synthesizing the best scientific evidence on the medical, social, economic, ethical and legal implications of all kinds of health care interventions. These interventions include drugs, devices, medical and surgical procedures, as well as measures for diagnosis, prevention and rehabilitation of disease. Over the past decade, HTA has gradually become more important among European countries leading to the emergence of various agencies. The best known agency is the National Institute for Health and Clinical Excellence (NICE), covering England and Wales, which was founded in 1999 with the aim of identifying cost-effective treatments and reducing regional inequalities in prescribing practices.

The NICE HTA framework takes both clinical effectiveness and cost-effectiveness into consideration and the organization has met with considerable approval from external institutions including the World Health Organization.¹ Since its inception, NICE has published 119 HTA reports, of which 38 recommended the technology for the licensed

indication, 69 were recommended for selective use, 8 for research use only, and 4 were not recommended.² But what is the evidence that these recommendations are having the desired effect on prescribing practices? This is a hard question to address due to the lack of data, however, a growing number of independent reports available through the Evaluation and Review of NICE Implementation Evidence (ERNIE) database suggest NICE HTAs are working. For example, in 2006 the National Cancer Director conducted a large updated review into the prescribing of cancer drugs.³ The results indicated that cancer drugs with a positive recommendation had increased usage by a median of 47% (a range from 11% increase for vinorelbine and fludarabine to 120% for temozolomide). Although there are relatively few technologies that have received a definitive 'no' from NICE, the small amount of data that exists does suggest the decision can impact prescribing rates. In 2003, NICE recommended that anakinra should not normally be used as a treatment for rheumatoid arthritis, and by 2005 the amount spent on the therapy by the National Health

continued on page 2

Health Technology Assessment

continued from front page

Service reduced from £200,000 to £70,000.⁴ There is also evidence that NICE is reducing the disparities of post-code prescribing. For instance, the same report by the National Cancer Director found there had been a reduction in variation in the prescribing of cancer drugs that had undergone HTA. For example, trastuzumab saw a 4.2 fold variation in use in 2003 reduced to a 2.8 fold variation in use in January to June 2005.³

Many variations in HTA are used by other European agencies. Other agencies include the Scottish Medicines Consortium (SMC), the German Institute for Quality and Efficiency in Health Care (IQWiG), the Haute Autorité de santé (HAS) in France, the Pharmaceutical Benefits Board (LFN) in Sweden, the National Centre for Pharmacoeconomics (NCPE) in Ireland and the Danish Centre for Evaluation for Health Technology Assessment (DACEHTA). Like NICE, the SMC, the LFN, the NCPE and the DACEHTA also incorporate cost-effectiveness in their assessments. The HAS only includes clinical considerations in their appraisal process. IQWiG only focused on clinical effectiveness previously, but from May 2007 onwards, cost-effectiveness is also taken into account. NICE guidance is based on the ratio between costs and quality adjusted life years (QALYs). Not all agencies use this outcome measure, but the SMC, LFN and the NCPE do consider QALYs.

Undertaking a rigorous HTA is extremely complex, time consuming and uses considerable resources. As such, it might be tempting for European countries with less rigorous HTA methods or with limited resources to simply use the decisions of agencies such as NICE for their own local decisions. Early this year, UBC staff in Europe undertook a comprehensive review of the decisions and processes in other European HTA agencies in an attempt to identify the impact of published NICE recommendations on other agencies' decisions. Evidence of NICE influence was difficult to detect. Whereas the recommendations are widely read and provide a basis of information, other country-specific criteria (e.g., treatment patterns, health care system, budgets, government initiatives) come into play. Thus, a negative (or positive) recommendation by NICE does not necessarily lead to negative (or positive) decisions elsewhere. For example, in 2006 NICE issued new guidance on donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease that restricted their previously broad use to just the moderately severe stage. The guidance was contested in court by the manufacturers and patient groups but the decision by NICE was upheld. Currently, these treatments are not similarly restricted by other European health authorities, thus not following the NICE guidance.

Countries from the former "Eastern bloc," like Hungary, appear to rely heavily on NICE in determining their guidelines for incorporating HTA into health care decision making.⁵ Setting up and subsequently reforming the Hungarian HTA

process included review of assessment practices in different countries. However, NICE and SMC were considered gold standards and the Hungarian system is currently modeled on the SMC type of organization, mainly due to the wider scope but less comprehensive and shorter appraisal process.

It appears that European countries are moving towards more rigorous HTA methodologies like those used by NICE aided by initiatives such as the European network for Health Technology (EUNetHTA) and International Network of Agencies for Health Technology Assessment (INAHTA). While these initiatives are useful for informing methodologies and collating international outcomes, it is important that all European countries make local decisions on health technologies and do not simply copy other countries HTA recommendations to save time and resources.

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Planning Late Stage Studies

By Sean L. Hart, MBA

With the recent intense scrutiny by worldwide regulatory and government bodies of the long-term safety of medicines, there is a growing call for post-approval drug monitoring, bringing with it the potential for delayed decisions for approval. In parallel, physicians, payer/formulary committees and consumers are all more likely to scrutinize the benefit-to-risk ratio of new products. These increasing demands are causing a shift in the industry's post-approval strategies away from purely commercially focused studies and toward increased post-approval monitoring of real-world utilization.

Pharmaceutical and biotechnology companies now see these post-monitoring studies as drivers of evidence collection, resulting in fundamental changes in how late-stage trials are designed. Where once it was adequate to prove that your drug was safe and effective in well-controlled trials, sponsors now feel pressure to implement studies with endpoints that:

continued on page 4

SCIENCE & POLICY OPINION

Individual-Level Simulation is Here *continued from front page*

analytic tools that are used to understand the system and estimate outcomes for a given scenario of care. It is understood that models cannot represent reality perfectly; they are based on a reduced set of components and require simplifying assumptions. Nevertheless, it is crucial that the model be valid in the sense that it sufficiently reflects the system it represents.¹

Although a number of modeling techniques are available,^{2,3,4} it is for the most part today taken for granted that a cohort model using state-transition (“Markov”) techniques is the way to go.^{5,6} And, indeed, decision makers have been content so far with this approach. As they, and their questions, become more sophisticated, however, the severe weaknesses of the technique are becoming obvious.^{7,8} To properly convey the value of products, we need to be much more realistic in our modeling. Fortunately, the solution is at hand.

Cohort Markov models address a population in the aggregate⁹ while *individual* simulations derive the impact on the group by considering the individuals that constitute it. Each individual has a unique set of characteristics and is modeled over the time horizon with his or her events and experiences recorded and used to predict the subsequent course. Events can reflect changes in clinical conditions, medical procedures and visits, the use of other resources, patient behaviour such as compliance, clinical decision points, and even changes to the system as a whole (e.g., the introduction of a new treatment, or a change in reimbursement). This turns out to be a very flexible concept that allows for natural representation of the disease process, treatment patterns, compliance, and other relevant factors. As time is explicit and continuous and events can be anything that happens in reality, they can occur in whatever order makes sense, capturing the experience of patients very accurately. Furthermore, as there are no cycles in a discrete event simulation, there is also no restriction on the number of events that can occur within any given time interval. For example, an individual can experience an adverse event, be admitted to a hospital, and die, all in the same day. This allows for a more natural accounting of time and for accurate application of costs and discounting. In addition, individuals not only have their own characteristics but “carry” their personal histories. This permits the model to keep track of medical history and give it its proper due. Thus, time since onset of some condition, duration of treatment, response to treatment, prior events and decisions, and any other relevant past occurrences can affect the subsequent course, as appropriate.

By far the most commonly used technique for these individual models is discrete event simulation⁷ and related techniques.¹⁰ Although there continues to be resistance to its use,¹¹ it is widely accepted that individual-level simulation is a more flexible and accurate approach that provides information to a much wider range of health care problems.^{12,13} The technique’s flexibility also allows for the simultaneous specification of multiple levels of complexity within the same model. In cases where data are highly limited, the same model can be run with a simple set of inputs (e.g., use average treatment effect instead of sampling from a distribution of treatment effects), but also under more sophisticated scenarios. This allows the analyst to address how the results change if richer data is available from the decision maker.

As discrete event simulation provides a framework for very natural representation of disease and resource use, it is well-suited to modeling the economic impact of health care interventions. Furthermore, modern software such as Arena® allows for a very transparent representation of the relationships in the model and possible patient flows through the simulation. As discrete-event simulations can produce a wide range of intermediate and final results, assessing the outcomes at numerous levels is possible. This provides a much more comprehensive set of results that can address the concerns of different decision-makers and analysts.

While the commonly asserted guidance that one should use the simplest modelling technique that answers the research question¹⁴ is inarguable, for most problems in health care, sophisticated approaches are required. The broad simplifying assumptions adopted in many commonly used modeling techniques today will not only render the models of very limited utility, but more importantly, are likely to produce misleading results that underestimate the value of new products. Models that are forced to be simple on principle leave considerable doubt about their suitability—how can one know if the model is indeed “accurate enough”?

Thus although cohort models are supposed to be simpler and easier to understand², they are in fact confusing, unrealistic, and cumbersome. Using them leads us into the strange universe where we tell the decision makers what

continued on page 4

SCIENCE & POLICY OPINION

Individual-Level Simulation is Here continued from page 3

questions they can ask rather than providing them answers to the ones they actually have. As it turns out, individual models do require more data and computing power, but they can actually be much simpler to specify and understand. More importantly, they readily provide the answers decision-makers are seeking. With them, a product's value can be fully extracted and communicated!

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Planning Late Stage Studies

continued from page 2

- Collect evidence on how products work (in terms of safety and effectiveness) in the “real world,”
- Demonstrate risk-benefit and cost effectiveness,
- Test physician and patient-training strategies on products,
- Supply physicians with patient feedback on the products they prescribe, and
- Provide patient-reported outcomes and pharmacoeconomic data.

According to a *CenterWatch* (April 2006), “the development spend for phase IIIB/IV is projected to leap from \$9.2 billion in 2005 to \$15.4 billion in 2009, or about a 60% jump.” Studies in this category include patient or disease registries, large streamlined studies (LSTs), expanded access programs, outcomes studies and additional randomized clinical trials (RCTs).

Beyond strategic considerations, the need for logistical expertise far exceeds what traditional studies require, due primarily to the sheer size of many late-stage studies. In a traditional study, for example, you might have up to 100 sites with approximately 500 to 1,000 patients. By contrast, a large, streamlined study or patient registry might include up to 8,000 sites and 60,000 patients.

As a result, important differences to consider in the logistical launch and conduct of these studies include regulatory

continued on page 5

document strategy, monitoring and these three areas that we explore in this article:

- Site recruitment and management
- Simplifying protocols and CRF materials
- Endpoint capture and design

Site Recruitment & Management

During the planning process of late-stage studies, a significant challenge is to decide how many community-based physicians (both generalists and specialists) will be targeted as investigators. Just as important is what percentage of these target sites will be research-naïve sites—that is, sites with minimal or no previous clinical trial research experience. Logistically, working with these sites (where the majority of all patients are treated) requires an aggressive training plan, detailed study processes and increased mechanisms for communication with the investigators. For the success of the program, it is equally essential to ease the burden of work on the investigators through all means necessary by simplifying processes wherever possible.

Simplifying Protocols & CRFs

Another great challenge in late-stage programs is streamlining complex protocols. This involves simplifying more than just the protocol itself; it involves streamlining data collection forms, regulatory documents, safety information collection and all study processes—including site training—in order to gather the information necessary to answer the endpoints of the study. For late-stage studies to be completed efficiently, it is imperative to have late-stage SOPs that allow for the appropriate logistical processes to successfully launch and manage the variety of programs available, such as patient registries, LSTs, expanded access programs and outcome studies. These SOPs need to cover the range of options in the areas of training, technology, data collection, monitoring, safety, statistical analysis and report generation.

For example, even if you decide to collect responses to only four additional questions, but your late-stage safety trial sample size is 30,000 patients, that's a total of 120,000 questions. This volume will lead to additional burden on the investigators, increased data entry (EDC, paper or hybrid system) and more queries. It is always important to ask these two questions continually throughout the planning process: "Do we need to collect these data? What do we plan to do with them?"

Endpoint Capture & Design

This case study demonstrates how one late-stage, streamlined program looked at different endpoints than a traditional study might:

In a traditional Phase II or III study, a sponsor might collect efficacy and safety data on a metabolic product. This late-stage study focused, instead, on how the product worked in the "real world" and on specific safety events (i.e., events of special interest). The product under study had a new delivery mechanism that cost more, but was hypothesized

to be easier for patients to use. The study collected patient-reported outcomes and data on whether the new delivery system was quantifiably simpler for the patient to use and transport, as compared to traditional treatment.

Since the delivery system was new to this therapeutic area, there were safety events of special interest that had to be studied. The collection of these events required a sample size involving more than 3,000 patients at over 200 community-based sites. By increasing the number of patients and gathering more data about their actual use with the product, we were able to build a robust database that gave the sponsor a better understanding of long-term compliance and its impact on control of the clinical endpoint in the real world. That is, we were able to include in the program patients who would typically be excluded, such as those with extensive medical histories (e.g., with multiple co-morbidities), patients taking a variety of medications, or people who were older or younger than might be admitted to a controlled study.

Given the large cohort of patients enrolled in this program, we collected specific safety events that needed to be reviewed by a specialty adjudication board. As part of this procedure, we eliminated thousands of adverse events that were not related to the safety endpoint, enabling us to focus, instead, on the hundreds of events determined to need the maximum amount of follow-up information collection for further adjudicated processing.

At the end of this program, we were able to arm our sponsor with outcomes, effectiveness and safety evidence that will truly aid payers in determining whether or not this product should be placed onto their formulary.

In beginning to plan a late-stage study, therefore, it is critical to ask first, "What are the precise endpoints you are seeking?"

While it is intriguing to imagine how much can be learned in these real-world trials, the financial burden—based on their size—requires that sponsors determine exactly which questions need to be answered.

Value of Late-Stage Studies

In summary, the momentum to collect evidence in the late-stage research area continues to grow each day because the advantages are so important, allowing:

- Significant expansion of a product's safety and effectiveness database
- Better understanding of product use and training in real-world use
- Collection of patient-reported outcomes (PROs)
- Feedback loop directly from the patient to the physician investigators

continued on page 6

Planning Late Stage Studies

continued from page 5

- Greater clarity of physician practice patterns
- Entry into many new community-based physician practices
- Ability to track healthcare utilization data for future use
- Information about comparator products in head-to-head studies

With the recent evolution of late-stage studies, the opportunity exists for sponsors and pharmaceutical service organizations to gather and analyze real-world data and use them to support the quest for real-world evidence in decision-making.

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Site Selection for a Successful Study

By Abbe Steel

Site selection is an important component for the success of any study. The recruitment of investigators should involve a well-defined process for site selection through the use of comprehensive study-specific questionnaires, feasibility assessments and expert evaluation of the potential sites to ensure a high probability of success for each study. Understanding how sites perform and selecting sites based on their patient population, prescribing patterns and enrollment capabilities can ensure a successful and cost-effective patient recruitment program. Site selection can be thought of as a four step process:

- Step 1: Designing a Well Thought Out Feasibility Questionnaire
- Step 2: Selecting Your Preliminary Site List
- Step 3: Executing the Site Feasibility
- Step 4: Evaluating the Feasibility Results and Selecting the Sites

Step 1: Designing a Well Thought-Out Feasibility Questionnaire

Typically, if the feasibility questionnaire is more than two pages long, the likelihood of a study site responding is very low. It is essential to include the most important questions in your feasibility questionnaire and keep it concise and easy to complete. In addition to study site contact and demographic information, the questionnaire should include the most important and relevant topics related to the protocol. If the survey includes multiple choice questions rather than open ended questions, it will help ensure a high response rate. The information collected from the feasibility questionnaire

is crucial in identifying a preliminary list of the most feasible sites for a particular study.

For any given study, it is important to define the characteristics of the ideal site for the given study. These criteria need to be defined and ranked based on importance. Following are criteria we examine as part of site selection and should help shape the feasibility questions:

- Previous experience in studies or registries of patients with particular disorder/disease/condition
- Sufficient patient base to achieve enrollment goals
- Interest in participating in the study
- History of above average enrollment (in past trials they provide 60-75% of promised enrollment)
- Type of practice
- Use of local/central IRB
- Competing studies
- Experience when recruitment is driven by an integrated marketing campaign
- Location of practice

In addition to these criteria, additional characteristics that are important to site selection that can directly impact overall patient recruitment include:

- Ability to screen patient within 48 hours of referrals being sent to the site
- Some type of electronic database to keep track of potential patients for the study
- Dedicated Research Coordinator and/or dedicated patient recruiter or clinic staff available to answer or make return calls from potential patients during some period of the day
- History of independent advertising
- Flexible screening hours 7-9am or 5-9pm in addition to the traditional core clinic hours
- 75% internal patient pool lives within 0-30 minute driving range or close to public transport
- If clinic can not perform basic labs, a lab option within 0-30 minute driving range

Step 2: Selecting Your Preliminary Site List

Developing a feasibility survey is really just the first step in understanding site selection. It is absolutely critical that the types of sites that are asked to complete the feasibility questionnaire are carefully considered in the first place. In developing the preliminary list of sites, useful resources include: key opinion leaders, investigators the sponsor has worked with, and investigators the CRO (if applicable) has worked with. This ensures that these sites have some type of validity in participating in research studies. Other sources for sites include high prescriber lists of the studied medication

or a competitor's medication (procured from IMS or NDC), professional societies, and Site Management Organizations (SMOs).

Including investigators that the sponsor/CRO has worked with in the past is important but it is also essential to consider the type of study the site was enrolled in. For example, a community-based, multi-physician practice may have been ideal for a Phase IV observational study, but may not be appropriate for a Phase III, double blind, placebo-controlled study.

Even the best feasibility would not predict successful enrollment if the sites asked to complete the questionnaire were not carefully selected to begin with. In order to develop an effective site selection strategy it is very important to consider all the ways in which a potential patient may enter the health care provider system. This is especially important when a specialist is involved and a patient may first present at a PCP/internist. Therefore, sometimes it is just as important to include study sites that may not be the first, most obvious site for a particular study. For example, recently, UBC was awarded a Phase IV cardiovascular study that from initial protocol review, one would assume that cardiology sites would make the best sites to participate in the study. This conclusion was based on the fact that cardiologists are the high prescribers for the studied medication. The sponsor provided UBC with the site list which included all of their high prescribers for this medication. Shortly after the study was initiated, it was clear that these high prescribers were not as effective for study execution, because the study called for an undiagnosed patient population. In this case, these patients would first present at their primary care physicians and not initially see a cardiologist. We found that PCPs would have been better suited to see the most qualified patients based on the inclusion/exclusion criteria. The cardiologists enrolled in this study were only seeing patients previously diagnosed and on treatment. Using this example, one can see, that a more thoughtful site evaluation and feasibility would have lead the sponsor to selecting different sites for this study which would have resulted in faster patient recruitment.

Step 3: Executing the Site Feasibility

There are multiple approaches to site feasibility. The fastest and most cost-effective way is typically via blast fax. UBC has also found great success utilizing a web-based portal approach for sites as a method for entering their responses to the feasibility questionnaire. This allows the more Electronic Data Capture (EDC) proficient sites to utilize their preferred mode of communication and ensures a better response rate. In terms of numbers, usually 10% of the sites will respond to the feasibility questionnaire. Therefore, if 100 study sites are required for a study, we recommend sending out 1,000 feasibility questionnaire to sites. Increasing the number of questionnaires sent out will ensure a better response rate.

Step 4: Evaluating the Feasibility Results and Selecting the Sites

Based on results from the feasibility questionnaires, site responses must be carefully analyzed to determine a site's potential success for the study. A scoring algorithm should

be assigned to each question based on what is most important in selecting the most ideal site for a particular protocol. We also recommend that a sub-set of sites be contacted via phone for further, more in-depth evaluation of their potential success. UBC has had great success in discovering inconsistencies in a site's response to a questionnaire as well as validation of the responses to a questionnaire during this phone call. Often study sites overestimate their capabilities and their expected patient recruitment potential. It is essential to have an individual that is very familiar with the protocol and study design to make these follow-up phone calls.

Based on the site's responses to the questionnaire and the follow-up phone calls, sites should be ranked and tiered (A list, B list, etc.) for formal invitation into the study.

RapidRecruit™

UBC takes a multi-pronged approach for identifying and evaluating sites for studies and registries. We have developed a proprietary system called the RapidRecruit™ enrollment process which allows for a streamlined and efficient site selection and enrollment process that targets the most appropriate and qualified sites for a given study. UBC has applied the above steps to site selection and these steps have led to successful site identification. We have found that when sponsors invest time and resources upfront, the studies ultimately complete faster and meeting target timelines.

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Exploring the Ceiling Ratio for Recommending the Adoption of Health Technologies in Spain—Evidence from a Literature Review

By Erwin De Cock, MSc

Health care systems across Europe have developed different measures to help in cost containment. In the UK, Sweden, and The Netherlands, new drugs have to pass the hurdle of showing cost-effectiveness in addition to clinical efficacy and safety. In Spain, drugs represent the biggest share in health expenditure, accounting for more than 50% of the primary care budget and between 15 and 20% of the hospital budget.¹ In response, there is growing debate in Spain on establishing a formal system of health technology assessment with the creation of a national "Commission for the Evaluation of Comparative Therapeutic Use."

Other European countries requiring cost-effectiveness evaluations have established formal or informal estimates of how much the health care system is willing to pay for an additional unit of effect. The value of willingness to pay (per Quality-adjusted Life Years [QALY]), also termed the threshold or cut-off value,² used implicitly in the UK is £30,000/QALY.³

continued on page 8

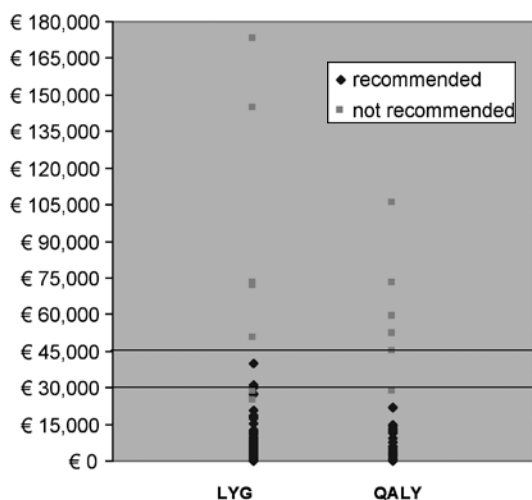
Exploring the Ceiling Ratio

continued from page 7

Values quoted for The Netherlands and Sweden are £20,000/Life Years Gained (LYG)⁴ and 500,000 kr,⁵ respectively.

With the addition of economic evaluation to the drug hurdles in Spain, there is a need for an explicit cost-effectiveness (CE) threshold. A review of published economic evaluations between 1991 and 2001 in Spain showed that all interventions with an Incremental Cost Effectiveness Ratio (ICER) below

Figure 1: Cost/LYG and cost/QALY results being recommended vs. not recommended



threshold could be obtained, based upon recommendations of authors of more recent economic evaluations, and (2) to reflect on the appropriateness of a literature review to try and estimate a likely level of ceiling ratio.

We searched PubMed/Medline, Embase, IME (Indice Medico Español) and NHS EED (NHS Economic Evaluations Database, University of York) and selected complete economic evaluations for drugs or vaccines in Spain published from 2001 to April 2005. The following information was abstracted into an Excel spreadsheet: technology evaluated and comparator(s), cost-effectiveness outcome (LYG, QALY, LS [life saved]), cost-effectiveness results, recommendation of author on adoption of technology, and information on ceiling ratio and value, amongst others. Mean and median ICERs were calculated for recommended versus non-recommended results. For different ranges of the ceiling ratio, the number of recommended versus non-recommended results was explored.

Of 344 titles selected, 22 studies fulfilled the selection criteria. 18 studies used cost/LYG and included 65 CE results, while 7 studies included 31 cost/QALY results (4 studies included both cost/LYG and cost/QALY results). One study presenting results as cost per life saved was not considered further. Recommendations about the adoption or rejection of the intervention were established in all studies

but one. Thirteen studies referred to a threshold value: 3 studies referred to the £30,000 value by Sacristan et al,⁶ 3 studies referred to \$50,000 which likely refers to the annual cost of haemodialysis as mentioned in a 1973 US Congress ruling, 2 studies referred to a value of £26,000, 1 study referred to C\$55,000 proposed by Laupacis et al,⁸ and 4 other studies referred to threshold values between £24,040 and £126,500 based on economic evaluations of mainly cholesterol-lowering treatments and cardiovascular prevention that are being reimbursed in Spain.

Figure 1 shows the distribution of recommended vs. non-recommended interventions for both cost/LYG and cost/QALY and indicates at which range of the cost-effectiveness limit the decision shifts from interventions being recommended to not being recommended. For cost/LYG, 13/15 results were considered cost-effective below £45,000. Above £45,000, all results were considered cost-ineffective. For cost/QALY, 4/5 results below £30,000 were considered cost-effective. Above the £30,000 threshold, all results were considered cost-ineffective. Overall, results suggest a likely ceiling ratio in the range of £30,000 to £45,000.

The ceiling ratio is a criterion for prioritization by health care decision makers. The objectives of this review were to inform on a likely range of ceiling ratio in Spain and to compare with results obtained from a similar review conducted in 2002.⁶ When making recommendations about the adoption or rejection of a health technology, many authors (9/22) did not give an explicit value of ceiling ratio. The others (13/22) referred to previously published ceiling ratio estimates, or previously published studies reporting ICERs for drugs which are being financed by the Spanish NHS. The main limitation of informing a likely CE threshold from published literature is that many authors refer to arbitrary threshold values in a circular way without empirical foundation. Also, those thresholds may not be in accordance with the societal willingness to pay per unit of benefit in Spain. Contrary to the previous review,⁶ we do not present a range within which results are unclear (£30,000-£120,000), but suggest a wider range for a likely ceiling ratio between £30,000 and £45,000.

In agreement with other Spanish health economists,¹ we argue that cost-effectiveness should be used in decision-making for drugs in order to produce maximum social benefit. As long as there is no such explicit value, there is the risk that every decision-maker adopts a different (arbitrary) level of ceiling ratio, which might lead to important differences in equity and accessibility of drugs across Autonomous Regions in Spain. Soto Álvarez¹ suggested ceiling ratios of £24,000-£36,000 for diseases with a low treatment cost and of £36,000-£42,000 for diseases with a high treatment cost (and for which society may be willing to pay more). Considerations such as the size and type of the patient population, the disease area and the level of unmet medical need, may all affect the societal willingness to pay and hence the assessment of the cost-effectiveness ratio.

This review suggests a likely ceiling ratio in the range of £30,000 to £45,000. However, explicit elicitation of a societal

willingness to pay would be preferred through a broad consensus of all society stakeholders in Spain.

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information including primary cancer incidence and survival from 18 cancer registries representing approximately 26% of the United States (US) population.¹ Data elements include patient demographics, primary tumor site, tumor morphology, cancer stage at diagnosis, and survival status. The Medicare administrative database contains files of health care utilization and costs for hospital inpatient and outpatient care, physician services, hospice care, home health care, and skilled nursing facility care. The linkage between these data sources provides a unique opportunity to follow cohorts of cancer patients aged ≥ 65 years from cancer diagnosis until death while tracking cancer and non-cancer treatment, health outcomes, and medical costs. Data on Medicare beneficiaries without cancer are also provided so that researchers may compare differences in costs and outcomes between cancer cases and non-cancer controls.

The linkage between these data sources provides a unique opportunity to follow cohorts of cancer patients aged ≥ 65 years from cancer diagnosis until death while tracking cancer and non-cancer treatment, health outcomes, and medical costs.

Advantages & Limitations

Advantages of using the SEER-Medicare data for cancer research include the detail of the clinical information that is recorded at the time of primary cancer diagnosis and the long-term survival data that is also available. This information cannot be readily obtained using a commercially available managed care database making analyses that stratify by initial cancer stage or morphology type difficult to perform. Data on survival (date of death) are also usually not available. As a result, information on terminal care costs and utilization are not easily obtained from commercial data sources. The costs of acquiring the SEER-Medicare database are only around \$5,000, much less than the price of other competing sources.

Before using these data, researchers need to consider the following limitations. The Medicare data only contains claims for services covered by Medicare during the study time period of interest; oral prescription drugs are not in the currently available database. There are no claims when a Medicare beneficiary receives care covered by Medicare but not billed to Medicare.²

The SEER-Medicare Data in Action

Many types of studies have been conducted using the SEER-Medicare data studying different aspects of cancer care. These have included the study of the patterns of initial treatment associated with a specific type of cancer and the influence of patient characteristics (race, gender, comorbidity, geographic region) on the likelihood of receiving various therapies. The longitudinal nature of the Medicare claims and the years of data available (1991-2005) also make it ideal

continued on page 10

Use of the SEER-Medicare Database for Studying the Economics and Outcomes of Cancer in the United States

By Michael E. Stokes, MPH

The Surveillance, Epidemiology, and End Results (SEER)-Medicare database links clinical data from cancer registries with administrative claims from the Medicare program. The combination of these data sources provides researchers with a powerful tool for conducting large-scale retrospective studies examining health care utilization, costs, and outcomes for cancer patients throughout all phases of their disease (e.g., prior to cancer diagnosis, during diagnosis and initial treatment, during cancer remission, and finally, terminal care).

SEER-Medicare Overview

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database currently collects clinical

SEER

continued from page 9

for the study of long-term costs and outcomes. Researchers have used the control (non-cancer) data to examine the costs attributable to specific cancers by using this group to estimate routine medical costs unrelated to cancer treatment. Costs attributable to a specific cancer are then obtained by subtracting this estimate from total costs calculated from cancer cases in SEER. Studies have also compared long-term costs among patients receiving competing cancer therapies. Table 1 is a sampling of published studies that illustrate some of the specific uses of this database.³⁻⁸

A variety of therapies are either currently available or in development for the prevention of cancer recurrence. Although SEER only collects data on primary cancers (data on recurrence is not available), researchers have begun to develop algorithms using the Medicare claims to identify patients that experience cancer recurrence (relapse). Work has already been completed with acute myelogenous leukemia and breast cancer.^{6,7} Specific algorithms have been tested by linking Medicare claims with gold-standard clinical trial or medical records data. Researchers are just starting to utilize these algorithms to estimate long term survival and costs following cancer recurrence.⁸

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Table 1. Sampling of Published Studies Using SEER-Medicare Data

Reference	Study Title	Cancer Cohort	Study Objectives	Research Contributions
(3) Earle et al.	Who gets chemotherapy for metastatic lung cancer?	Stage IV NSCLC patients diagnosed between 1991 and 1993 (N=6,308)	Identify patient characteristics associated with chemotherapy use.	Showed that non-medical factors such as nonblack race and higher socioeconomic status increased a patient's likelihood of receiving chemotherapy.
(4) Ramsey et al.	Chemotherapy use, outcomes, and costs for older persons with non-small cell lung cancer.	Advanced NSCLC patients diagnosed between 1994 and 1999 (N=14,875)	Examined community patterns of care with a focus on chemotherapy.	Concluded that chemotherapy prolongs survival for persons with NSCLC. Found lower utilization in minorities and certain geographic regions.
(5) Etzioni et al.	Estimating the costs attributable to a disease with application to ovarian cancer.	Ovarian cancer patients	Examined methodological issues in estimating costs attributable to cancer with censored cost data	Investigation of the statistical properties of the Kaplan-Meier Sample Average (KMSA) estimator and comparison to others commonly used. Showed how certain methods for discounting costs may introduce bias.
(7) Lamont et al.	Measuring disease-free survival and cancer relapse using Medicare claims from CALGB breast cancer trial participants.	Breast cancer patients (N=45)	Creation of algorithm to detect recurrence and comparison with CALGB trial disease-free survival information.	Showed that an algorithm for identifying breast cancer recurrence and the calculation of disease-free survival using Medicare claims had good sensitivity (100%) and specificity (97%).
(8) Stokes et al. (in press)	Ten-year survival and cost following breast cancer recurrence: Estimates from SEER-Medicare data.	Breast cancer patients with recurrence (N=1,833)	Creation of algorithm to detect patients with specific types of breast cancer events (local and distant recurrence, contralateral).	Shed light on the economic and survival consequences of developing breast cancer recurrence with 10-year estimates of cost and survival.

FOCUS ON:

e-EVIDENCE

Cognitive Debriefing for Content Validity and User Acceptance of Electronic Patient-Reported Outcome Measures

By Makiko Meguro, MPhil and Jennifer Petrillo, BS

In recent years, the data collection method for patient-reported outcome (PRO) measures has changed rapidly from traditional “paper and pencil” to electronic formats. PRO measures originally developed in the paper and pencil format are being modified to an electronic platform for various studies, including clinical trials. Generally, having electronic PRO measures (ePROs), in a clinical trial setting in particular, enhances the integration of data collected with other commonly used electronic platforms for collecting clinical data such as Personal Digital Assistants (PDAs), Interactive Voice Response systems (IVRS), interactive web-based systems (IWRs), and tablet PCs.

In circumstances where a PRO measure presented for data collection uses an interface varying from the originally developed format, the equivalence to the original format should be demonstrated. Newly developed instruments designed as ePRO tools are no exception, and further consideration to the impact of technology on patients should be given when an alternative user interface is used. Careful considerations should be given for the length of the questions, the time to completion, and the frequency of administration, particularly when multiple ePRO measures are used. Factors such as these can increase the burden of the instrument completion and potentially affect the reliability of the data.

Cognitive debriefing (CD) interviews can be used to evaluate the content validity and user acceptance of an ePRO measure with the study population. CD with ePRO measures is a new development area and one in which few public or regulatory guidelines are published. CD does not offer the evidence for quantitative or statistical validation; however it provides qualitative data contributing confidence in the instrument content and format and its use in the study population.

CDs allow ePRO measures to be assessed in a given clinical population prior to the deployment into the main study. Patients similar to the clinical study population respond to the instrument on an electronic platform and provide a verbal description of their cognitive processes. Questions generally relate to their comprehension of the question, including how they made the decisions to answer questions and how their internal response matches the given response options, thereby ensuring consistency with the intent of the instrument. Instructions for instrument device use may also be tested for completeness and understanding by the patient. Overall, CD examines the concordance of the intended purpose of the instrument and establishes the content validity of the outcome measure, accounting for the use of technology in the study population.

The CD process should be documented in the same manner for ePRO measures as paper-and-pencil PRO measures. To start, a description of the purpose of the study, respondent population, recruitment methods, and method of the interview should be made, while additionally documenting the resulting patient comments on the ePRO items. Any adaptation made specifically to the ePRO measure should also be discussed.

Another technique to evaluate the adequacy and ease of administering an ePRO measure in a trial population is user acceptance testing (UAT). UAT

is a term historically used in the information technology (IT) and engineering industries where a client or a customer tests the functionality of a system. In ePRO measure evaluation however, it refers to the acceptance of a typical user, the patient, to the usability of the interface. The UAT assesses the patient’s ability to handle and maintain the device and to navigate between screens, in addition to the technical implementation, which could include the font size, ease to enter the data (using a touch screen, stylus, or mouse) or to evaluate the most appropriate selection of the interface in a given disease group. The burden of the instrument completion is an important element that should be minimized. The extent of user burden as well as possible solutions can be assessed during UAT.

With the recent advances in technology comes the opportunity to redesign data collection measures for efficiency. Careful consideration should be given to deciding on the proper data collection platform, with recognition that the best solution may be a combination of electronic platforms including PDA, IVRS, IWR, and tablet PC. In the event that an existing paper-and-pen measure is converted to an electronic platform, proper steps should be in place to ensure it maintains its intent. When used properly, the potential for improved data collection efficiencies is limitless.

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The UAT assesses the patient’s ability to handle and maintain the device and to navigate between screens, in addition to the technical implementation...or to evaluate the most appropriate selection of the interface in a given disease group.

FOCUS ON:

e-EVIDENCE

The Advance of “e-Learning” in Clinical Trials

By Adam Butler

Effective and consistent training is one of the hallmarks of good clinical practice. While live training is still the most common venue for training in a clinical trial, e-learning is being utilized in more and more situations.

In May of 2007, the FDA reiterated this position in a draft guidance titled “Guidance for Industry—Protecting the Rights, Safety, and Welfare of Study Subjects—Supervisory Responsibilities of Investigators.” The guidance is broad, but contains specific sections that impact how sponsors and sites consider training issues, including a focus on **“whether study staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study.”**¹

In many clinical trials, this training is conducted in face-to-face, live venues, typically at an Investigator Meeting or during a site initiation visit. Increasing pressure to manage study costs and the difficulty of convening in-person meetings for global trials are growing challenges. For example, in some situations where a live, large-group gathering such as an Investigator Meeting is the primary training event, the turnover rate of site staff can be more than 50%.²

Although previous research indicates that live, face-to-face training may often be a more effective forum for adult learning,³ e-learning is now commonly utilized in clinical trials. E-learning can refer to any number of computer-based venues for delivering training. These can include interactive CD-ROM, video delivered by DVD or videotape, web-based self-paced training, and web-based virtual meetings.

Virtual meetings—made popular by software like the Microsoft Live Meeting platform or WebEx—are distinct from other computer-based mechanisms as they occur synchronously, with all trainees participating at once, live but not in-person.

Self-paced interactive CD-ROMs or web-based tools can include traditional slide presentations, and can include audio and video; however, they can also include supporting presentation documentation such as PDF files and transcripts, as well as the ability to search presentations for specific topics. These tools may also be programmed to collect information from users, including demographic information, quiz and assessment results. For studies conducted in more than one language, subtitling, voice-overs, and translated documents may also be included.

In addition, the use of a web-based Learning Management System (LMS) allows for management and delivery of more complex training programs. UBC’s proprietary LMS allows for creation and storage of electronic records in compliance

with 21 CFR Part 11, ensuring the availability of a consistent training record that satisfies existing regulations.

E-learning has become necessary to ensure education and training efforts are keeping up with the needs of clinical trials, particularly for time-sensitive issues to avoid any potential delays. Additional e-learning benefits include:

- Providing training and assessment for clinical trial participants who were unable to attend the live meetings or are new to the study,
- Training investigators on study protocols and study execution to promote standardization during the trial process, and
- Educating study participants about critical study functions, such as Adverse Events, Data Collection, Good Clinical Practices, regulatory issues, study drugs, and unique procedures or assessments.

While live training is still preferred in many cases, e-learning has become crucial in providing effective and consistent training in many different areas and continues to grow as a valuable tool for clinical trials.

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Electronic Health Economics Data Capture

By Krista Payne, MSc, Steve Blume, MS, and Meghan Werner, MPP

The appeal of the electronic data capture (EDC) tools described in this e-Evidence Focus Section—interactive voice response (IVR), mobile devices, etc.—extends to the collection of economic outcomes. As with clinical and patient-reported outcomes, EDC offers opportunities to design and implement innovative methodologies while improving efficiency.

EDC streamlines the data collection and data and site management processes by eliminating the need to enter the data twice, first on paper, and then later into a database (often using double-entry methods). Simultaneously it reduces errors and increases compliance compared to paper-based collection. For example, EDC can implement logic at the point of data entry that notifies the user if the response is not

valid and prevents them from proceeding until a valid answer is entered.

EDC also offers study staff immediate reports to monitor compliance and study completion, thus making remote site and data management feasible without the need for expensive and time-consuming monitoring visits. The result is cleaner, more complete data in less time. The EDC infrastructure can also be complemented by trained call center staff who can resolve user support issues and thus contribute to higher rates of patient compliance.

Increasingly, country-specific economic evaluations in support of pricing and reimbursement submissions are required. As pharmacoeconomic modeling methods evolve, there is a growing need for tailored (and often multi-national) data gathering approaches. The challenges to collecting these data under time and resource constraints while maintaining quality control are formidable. EDC methodologies can help provide solutions to these challenges.

Web-based data collection and remote study monitoring has been successful in recent health economics studies of the burden of iron chelation therapy in US and UK patients with thalassemia and sickle cell disease,¹ as well as the impact of disability post acute ischaemic stroke in patients from the UK, Germany, Australia, and Greece.² In these studies, resource utilization, lost productivity, and quality of life data were collected. Using another EDC paradigm, health economic data have also been collected successfully in patient populations ranging from a few hundred to thousands of patients using toll-free telephone-based interactive voice response systems (IVRS).^{3,4,5} Resource utilization data capture via an IVRS has been shown to be feasible even in elderly patients.

The advantages of EDC for health economic data collection may be most pronounced when frequent patient diary entries would be the best way to measure resource use, treatment compliance, or productivity.⁶ Often, paper diaries are judged to be too burdensome, error-prone, and expensive for this purpose. A possible alternative is to use handheld computers (PDAs) to issue an alert to the patient and ask a simple question: “Did you work a full day today?” or “Did you go to the doctor this week?” Further, with the now high prevalence of cell phones (and relatively low cost of issuing them to patients), this process can also be handled via text messages and avoid custom PDA application development. Techniques can also be combined, such as sending alerts via cell phone for patients to call into an IVRS system.

EDC lends itself to other creative measurement approaches as well. Researchers can randomly sample slices of patient time—e.g., “Are you working right now?”—reducing both reliance on patient recall and survey burden on the patient. Automatic time-stamping on a mobile device enables new measures of treatment compliance, such as when the patient is instructed to make an entry immediately after taking medication. Another promising area for EDC is time and motion studies, where use of a tablet-PC could strengthen

data quality by time-stamping observations and ensuring that required fields (e.g., staff or supplies) are filled out. For one-time or infrequent surveys, handheld or laptop computers, (especially tablet touch-screen computers), have increased the options for EDC at the clinician office.

In summary, EDC offers several opportunities for capturing health economic variables. As researchers and sponsors are considering the use of EDC for the collection of clinical data and patient-reported outcomes, they should also consider the ability of EDC to benefit economic study design and data collection.

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Conveying Complex Information: The Importance of a Good User Interface

By Bernardo Duran

Market forces and public opinion have intensified the need for pharmaceutical and life sciences companies to deliver credible evidence supporting the use of their products. For such evidence to be useful, it must be delivered in a way that

continued on page 14

FOCUS ON:

e-EVIDENCE

Conveying Complex Information...

continued from page 13

facilitates its utilization, understanding, and dissemination. Otherwise, it is unlikely that it will be used in the decision making process. As evidence has gained in complexity, health economic models being a case in point, this has become even more important. Thus, user interfaces have become an indispensable tool. What makes a good interface?

Three common principles often touted for software development are **Simplicity**, **Intuitiveness**, and **Consistency**. These concepts do not necessarily lead to a good user interface, however. They must be modified to produce interfaces that help understand and use health economic models.

First Principle: Clear Instead of Simple

Rather than simplicity, an interface should provide a **clear** exposition of the subject. Simplifying, as a principle, exposes the designer to the danger of eliminating key elements that in some cases may be a fundamental part of the economic model. "What is to be sought in design for the display of information is the clear portrayal of complexity. Not the complication of the simple; rather the task of the designer is to give visual access to the subtle and the difficult—that is, the revelation of the complex."¹

Figure 1

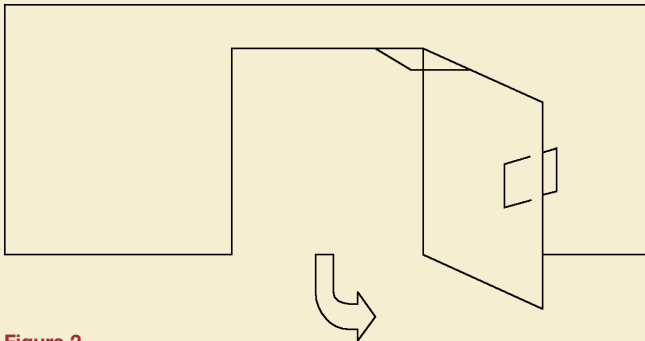
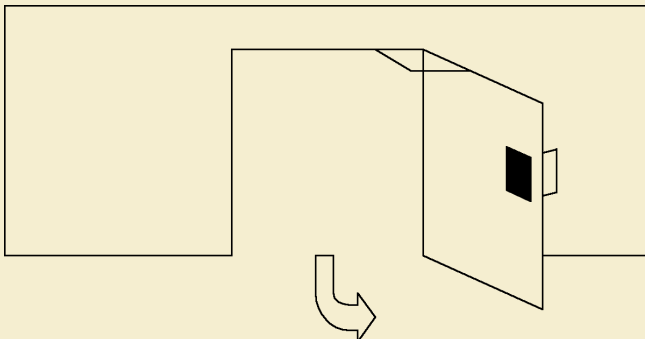


Figure 2



Second Principle: Familiar Instead of Intuitive

By the same token, there is a danger in applying the principle of "intuitive design" to interface development. In reality, what is intended is not to make an interface intuitive, that is, to be understood without any kind of training, but to make it easy to learn, or if this is not possible due to the complexity of the model, make it look **familiar** once it is learned. Someone who has never seen a computer mouse would not be able to tell its purpose nor how to use it just from looking at it. Nevertheless, we all understand and accept it immediately after its functionality is learned. The mouse is a tool that appears to us to be very familiar.

Third Principle: Guarantee Veracity Not Just Consistency

Although interfaces must certainly be consistent, this principle is not enough by itself, because one can be consistently wrong! Thus, **protecting graphical integrity**, or in other words, **guaranteeing the veracity of the information** being presented, must be a priority in order to avoid incorrect interpretations. Additionally, the concept of consistency is relative to a frame of reference which must be made explicit. The design of one of the door handles in Figure 1 is consistent in relation to the other handle. One side of the door is exactly the same as the other side. But a person trying to come in would try to pull the door, when in reality he should try to push. In this case, the design is inconsistent with the way the door is opened. A better design of the door handles which does not generate difficulties nor is ambiguous, and that complies with all the principles discussed above, is indicated in Figure 2.

And last, even though it is important to consider the nature of the model and its characteristics in the design of an interface, it is even more important to give a higher priority to the final user of the tool. After all, a GUI means "graphical USER interface" and it is for the user that we are designing the interface. Fundamental to the success of the interface is taking into consideration the user's audience and the purpose and required functionality. Without taking these into account, you may build a flashy and simple interface for a researcher in need of a scientific look who requires a high degree of functionality from the tool. Or conversely, you can design a complex interface for a decision maker whose main purpose is to provide only an overview of the model and being able to present its results. In either case, you have not met the need of the user because that was not taken into account during the design phase.

The design of an interface that clearly explains the model, soon looks familiar to the user, and protects the integrity of the information, is key for a successful implementation of a project of this nature. It is also very important that the design of the tool bear in mind the audience and the user's required functionality and expectations.

Throughout the years, we have developed specialized techniques to ensure that our interfaces are clear, familiar and valid.

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Evidence-Based Research from Electronic Medical Records (EMRs)

By Kathy H. Fraeman, SM, and Beth L. Nordstrom, PhD, MPH

What are EMRs?

Electronic medical records (EMRs) are paperless digital versions of physicians' paper charts. EMRs can contain a myriad of health care information, including medical histories, details of diagnoses and treatments, clinical laboratory test results and treatment responses, and visit scheduling and billing information.

Medical data are entered into EMR systems in a variety of ways. Data can be manually entered into EMRs with a mouse and keyboard at a computer workstation. EMR data can also be entered through smaller portable devices, like a tablet PC or a handheld personal digital assistant (PDA) palmtop computer. Clinical data generated in digital format—including automated laboratory test results and digital medical images—can be directly downloaded into EMRs. Some EMR systems incorporate voice recognition technology to enable physicians to quickly dictate notes, although these notes result in unstructured, free-format text. Finally, some EMR systems permit direct patient-entered data.

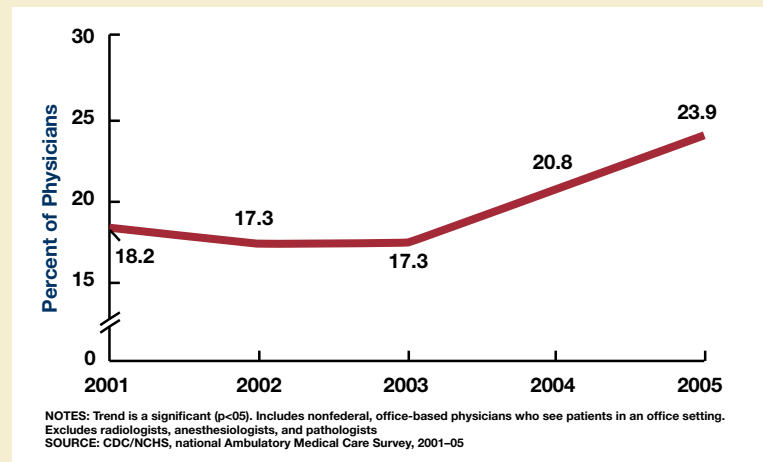
Numerous studies have touted the advantages for physicians using EMR systems. EMRs have the potential to improve the quality of patient care while substantially reducing medical costs. When patient EMR data are shared among multiple health care providers, these providers can more effectively coordinate patient care.

Trends in EMR Use by Office-Based Physicians

Even with the many recent advances in information technology, and with the promise of their potential benefits, EMRs have not gained widespread acceptance in the medical community. Problems with EMR use include installation and maintenance costs, patient privacy concerns, data entry difficulties, and reluctance of physicians to either disrupt or alter their existing medical records systems.

Although EMRs are not yet widely used in a majority of physician offices, their use is increasing. A survey conducted by the CDC's National Center for Health Statistics found that almost one in four physicians (23.9%) reported using either full or partial EMR systems in their office-based practices in 2005, representing a 32% increase since 2001.¹

Figure 1. Percentage of office-based physicians who report using electronic medical records: United States 2001-5



The CDC report noted that EMR use did not vary by physician age, gender, or specialty type, although physicians in group practices are more likely to use EMR systems than solo practitioners.

Evidence-Based Research from EMR Data

While physicians use EMRs to improve the quality of medical care and efficiency of their practices, scientists and medical researchers see the enormous research potential in de-identified EMR data. Not only do EMR data provide a wealth of information about real-world medical practices, they also include laboratory results and patient treatment response assessments not found in insurance claims databases. EMR data further provide important patient demographics not available in claims databases, such as patient height and weight, and smoking status and alcohol use.

Using EMR data for research does present some limitations. EMR databases don't typically cover multiple sites of care for a patient, and data entered into EMR systems are not always complete or standardized.

UBC Research with an Outpatient Oncology EMR

For over two years UBC has had access to an outpatient oncology EMR database which is refreshed monthly. This EMR database includes medical and treatment information for more than 150,000 cancer patients from 17 outpatient oncology provider organizations comprising 71 clinic locations across the United States. All of the data are de-identified, as required by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations.

A major strength of this oncology EMR database is its ability to link patterns of treatment for cancer patients with clinical laboratory data. One UBC research study used these data to examine the effect of zoledronic acid on renal function.² Zoledronic acid is a bisphosphonate that reduces skeletal-related events in cancer patients with bone metastases, but that may sometimes impact renal function. This research effort studied serum creatinine elevations and subsequent

continued on page 16

FOCUS ON:

e-EVIDENCE

Evidence-Based Research...

continued from page 15

treatment changes among patients in the EMR identified as receiving zoledronic acid.

Additional UBC research with the outpatient oncology EMR examined adherence to guidelines for use of erythropoiesis stimulating agents (ESAs) in patients with chemotherapy-induced anemia.³ Treatment of chemotherapy-induced anemia with ESAs has been shown to improve the quality of life and decrease the need for red blood cell transfusions. National guides for supportive care in oncology have specified hemoglobin levels at which ESAs should be initiated, maintained, and withheld. Using these EMR data, we tracked across time the real-world patterns of ESA use in chemotherapy patients, relative to hemoglobin levels during each cycle of chemotherapy.

Analysis of EMR data requires expertise in data management and programming techniques, in addition to knowledge of study design and analytic methodologies. UBC is currently standardizing the content of the outpatient oncology EMR across the various outpatient oncology practices for ongoing research efforts.

The Future of EMR-Based Research

UBC is also employing additional EMR databases, such as the General Practice Research Database (GPRD) and the GE Medical EMR database, to conduct research. The GPRD is a well documented general practice EMR database from the United Kingdom. The GE general practitioner EMR contains patient and treatment information and laboratory results on over six million patients from a group of over 2,600 general practitioners, in more than 25 different states.

As the use of EMR systems in medical practices continues to increase, we anticipate the number of patients, different specialties represented, and total length of follow-up available on each patient will rise. As the medical and scientific communities realize the value of EMR data for health-related research, we hope EMR systems will be designed to generate more standardized data entry, thus reducing errors in patient records and allowing more easily accessible data. Further, if standards for the interoperability of EMR systems are developed, data across multiple sites of care for a single patient can be combined. Interoperability between EMR systems will not only improve patient care by allowing shared information among different providers but will also provide a more complete view of de-identified medical events for research.

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A Web-Based Portal for Evidence-Based Decision Making

By Isabella Sledge, MD

As expenditures for health care consume an increasingly large share of individual, employer, and governmental budgets, the pressure to both control costs and to show value for health care interventions has escalated. The impact of increasing expenditures has been magnified by the convergence of three trends:

- The increasing proportion of health care costs born by individuals.
- The shift in decision making away from individual physicians and toward multiple stakeholders
- The ease of medical information through the internet

The impact of these changes has been a 'higher bar' for the demonstration of value for costly health care interventions. In addition, as certain stakeholders become more sophisticated in their interpretation of evidence so have they also become more skeptical of evidence put forth by manufacturers. Developers of new drugs and technologies must communicate this evidence of value through information that is unbiased, credible, and accessible.

Disseminating Evidence Through a Web Portal

Different decision makers may consider disparate types of evidence when evaluating a health care intervention. For example, payers may be most interested in health technology assessments and data from randomized controlled trials. Providers may be searching for review articles or other literature syntheses such as meta-analyses or practice guidelines. Patients may prefer less technical summaries found on professional society websites. Collating and presenting this disparate information can be accomplished through a web portal.

Suitability of a Web Portal to Address a Wide Range of Evidence Needs

A web portal offers the following attributes that make it an especially suitable solution for housing and organizing information:

- Access through the internet. Permission-specific access limits various users to different areas in the portal.
- *Specificity of information* achieved through customization of modules for different users.
- *Searchability* through an interface that can be queried and filtered.
- *Currency*. Unlike written material, the portal information can easily be updated.

The Creation of a Web Portal for Information on Bariatric Surgery

One medical device company with multiple products of use in bariatric surgery partnered with UBC to create a web portal that allows multiple stakeholders to access a single comprehensive evidence base derived from a systematic review of the literature as a way of promoting evidence-based decision making. This web portal offers access to a relational database with information extracted from over 1000 studies. The methodology used to obtain the studies is described in a detailed protocol available on the site. The intent of the portal is to discourage ‘cherry picking’ of studies by allowing decision makers to examine all published literature relevant to a particular question. The bariatric surgery portal was presented at the Cochrane Collaboration North American conference in May 2006 in an abstract titled, *“Integrating a Systematic Review of the Bariatric Surgery Literature into a Web-Based Portal to Facilitate Evidence-Based Decisions in the Surgical Management of Morbid Obesity.”*

How the Portal is Being Utilized

Currently the bariatric portal has been accessed by a variety of payer and provider groups. Frequent demonstrations of the information housed in the portal are conducted via WebEx. Most of these demos have been presented to medical directors making decisions about the appropriateness of bariatric surgery for certain patient sub-groups. For example, payers making decisions about safety and efficacy of bariatric surgery for adolescents and for super obese patients have accessed the portal to obtain information on the evidence available for these patient groups. Because the information in the portal has been collected systematically via methodology that is transparent, non-industry stakeholders have not been skeptical of information presented. The sponsor is also able to track the number of visits for each user to understand how often different stakeholders access the site. The response to the site has been overwhelmingly positive and the portal has been influential in expanding the range of evidence considered by payers in their decision making about access of various subscribers to bariatric surgery.

Who Should Consider a Web Portal

A web portal is an effective means of harnessing evidence from a variety of sources in an area with rapidly developing clinical literature and where treatment and reimbursement patterns are evolving quickly. Disease areas such as diabetes, treatment of cancer-related anemia, and treatment of cardiovascular disease with stents are examples of other clinical areas with exploding information. A web portal can be a resource for a variety of stakeholders who seek to make evidence-based decisions in a clinical area where the evidence landscape is shifting rapidly.

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EXACT-PRO Initiative Update

By Nancy Kline Leidy, PhD, Teresa Wilcox, RPh, PhD, Kellee Howard, MA, MSc, Jennifer Petrillo, BS, and Randall Winnette, BS for the EXACT-PRO Team

The EXACT-PRO (EXAcerbations of Chronic pulmonary disease Tool—Patient Reported Outcome) initiative is a unique, multi-sponsor project bringing together experts in instrument development and validation, specialists in clinical practice and research, and experts from the U.S. Food and Drug Administration (FDA) to develop a single, validated, patient-reported outcome (PRO) measure to evaluate exacerbation-related outcomes of treatment in drug development trials of chronic obstructive pulmonary disease. A key element of the project has been the interest and enthusiasm of the pharmaceutical sponsors, the FDA, and the content experts committed to improving PRO evaluation in chronic pulmonary disease through this innovative, cooperative program.

Phase I of the project involved a literature summary which continues to be updated monthly, patient focus groups and individual interviews, and two expert panels to inform instrument content and item structure. Focus groups and one-to-one interviews involved over 70 patients with COPD who had undergone an exacerbation within the previous 6 months (8 within the last 10 days). These patients described their exacerbation experiences, including key components such as cues for self-diagnosis, care-seeking, progression, and recovery. Themes and concepts were identified in the qualitative data and organized for analyses using Atlas.ti™. This comprehensive assessment of the patient’s perspective and discussion with experts formed the basis of the EXACT. Methods and results of this qualitative work were presented at the American Thoracic Society Annual Meeting in San Francisco in May 2007.¹

Reliability and validity of the instrument are being examined during Phase II of the project. The prospective, two-group observational study enrolled both acute and stable patients. Patients experiencing a clinician-confirmed exacerbation completed the EXACT daily via PDA during the first 28 days of their exacerbation and again from days 60 to 67. Stable

continued on page 18

FOCUS ON:

e-EVIDENCE

EXACT-PRO Initiative Update

continued from page 17

patients completed the EXACT daily over a seven day period. Data will be used to evaluate the performance characteristics of the items comprising the EXACT item pool, determine the final items and scoring of the instrument, test its reliability and validity, and assess its responsiveness to change in patients recovering from an acute exacerbation.

Data collection for the prospective validation study is now complete and data analyses are underway. Over 400 patients were enrolled in the study, including 222 acute and 189 stable patients with 16 patients from the stable group crossing over to the acute when they experienced an exacerbation. An “analytical summit” was held in UBC’s Bethesda office in mid-August with the project’s senior research consultants, Dr. Paul Jones and Dr. Sanjay Sethi to review the EXACT data and begin the process of item evaluation and reduction. Final analyses of the dataset, including full validity and reliability testing, will commence the last week of September. The third expert panel meeting will convene in late fall to review the final instrument and its empirical performance properties and discuss next steps.

To make certain sponsors, experts, and the FDA have access to comprehensive, up-to-the minute information from and about the project, the EXACT-PRO initiative includes a limited access web site (www.exactproinitiative.com). Log-in passwords give sponsors, experts, and the FDA access to the project’s comprehensive bibliography on acute exacerbations of chronic bronchitis and COPD, literature summary tables, study protocols and interview guides, and updates on study progress and results. A dialogue page serves as a medium for asking questions and sharing ideas about the PRO instrument development process.

UBC’s EXACT-PRO team includes Nancy Kline Leidy, PhD, Director and Principal Investigator of the project, Teresa Wilcox, PhD, Wen-Hung Chen, PhD, Kellee Howard, MA, MSc, Jennifer Petrillo, BS, Charlotte Cates, MA, Randall Winnette, BS and Lindsey Murray, BA with support from many other members of the UBC staff. Drs. Paul Jones and Sanjay Sethi serve as Senior Clinical Research Consultants. EXACT-PRO expert panelists include experts in PROs, pulmonary research, and members of the FDA.

The EXACT-PRO Initiative is possible through the commitment of the following Phase II sponsors: Adams Respiratory, Altana, Astra-Zeneca, Boehringer-Ingelheim, Forest Laboratories, GlaxoSmithKline, Merck, Novartis, Ortho-McNeil, Pfizer, Schering-Plough, and Sepracor.

For more information, please contact Kellee.Howard@unitedbiosource.com, Randall.Winnette@unitedbiosource.com, or any member of UBC’s EXACT-PRO team.

Reference

¹ Leidy NK, Howard K, Petrillo J, Wilcox T, Sethi S, Jones PW, & the EXACT-PRO Study Group. (May 2007). The EXAcerbation of Chronic Pulmonary Disease Tool (EXACT): A Patient-Reported Outcome, Phase I. Poster presented at the American Thoracic Society International Conference, San Francisco, CA.

Using IT Tools to Increase In-Study Ratings Reliability

By Joan Busner, PhD

Clinical trials frequently rely on subjective Clinician Rated Outcomes as pivotal endpoints. Often these scale ratings are based on clinical subjectivity and individual interpretation, which can increase variability across sites and raters that is unrelated to patient presentation, potentially contributing to failed or inconclusive studies. These endpoints are included in nearly all CNS clinical trials and are also widely included in trials in many other disease areas, such as oncology, pulmonology, gastroenterology, dermatology, urology and gynecology.

Improving the competency of the data collection “vehicle” (in this case, the clinician-rater) may reduce rater noise, thereby increasing the likelihood that drug signals—if they exist—will be detected. Certainly Rater Training and Certification (RTC) is an essential component in developing the “best raters” for a study as it provides the basis for obtaining initial inter-rater reliability across raters and intra-rater reliability within raters. However, rater training prior to study initiation does not guarantee sustained ratings quality and reliability in-study.

The use of electronic tools can assist in reinforcing the continued reliability of data collected using Clinician-Rated Outcomes (CROs). Real-time Ratings Surveillance Systems are an important new tool for monitoring these data. At the core of a typical surveillance system are a series of protocol-specific numeric data edits used as a flagging device. The edits highlight differences from *expected thresholds of normative activity so as to detect potentially ‘deviant’ ratings or data*. To eliminate execution bias, data edits are developed and set during protocol development and prior to initiating the surveillance program and *uniformly applied to all raters and all patient visits*.

Although rater training and certification is an effective and reliable method of increasing understanding of rating scales and their anchors,¹ it does not ensure that the scale will be utilized without error. One retrospective review found nearly three-quarters of the patient interviews conducted in a clinical trial to be unsatisfactory.²

In data presented at the 2007 Mid-Year Conference of the International Society for CNS Clinical Trials and Methodology, it was demonstrated that use of a ratings surveillance

system resulted in a statistically significant decrease in ratings errors between the initial and final study visits.³ The surveillance system was carefully designed to apply high level clinical monitoring of ratings in near real-time. The surveillance system, proprietary to UBC, worked by identifying and “flagging” instances in which Clinician-Rated Outcomes appeared to have been rated in an erratic or invalid fashion. By utilizing existing Case Report Form (CRF) data capture systems, and designing customized tools to view, process, and flag the data, observing clinicians were able to identify potentially problematic ratings. Clinicians then were able to provide tutorials to raters before the study subject returned for a consecutive visit, preventing an existing problem from being compounded. The errors would not have been detected by traditional monitoring processes, both because interval monitoring visits often occur weeks or months from the time of the error, and because monitors typically do not have the advanced clinical background required to evaluate ratings and remediate raters.

In recent talks, FDA representatives have encouraged pharmaceutical sponsors to explore innovative solutions to the issue of poor ratings and outcomes in clinical trials utilizing subjective outcomes. Continued research of surveillance systems is an important part of this process.

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Using e-PROs to Facilitate Enrollment in Clinical Trials

By Margaret Vernon, PhD

Technological advances are creating more options for capturing clinical data effectively and efficiently, with trials moving towards paperless modes of administration through electronic data capture (EDC). Electronic patient-reported outcomes measures (e-PROs) are becoming part of this movement. There are many advantages to administering PRO instruments electronically, including the potential for increased data precision and options for new measurement methods or trial designs.

Electronic modes of data capture can be programmed to upload data to a secure database in real time. One of the many advantages of this is that data for each participant can be made available immediately, facilitating patient enrollment based on e-PRO score during study run-in.

For example, clinical trials that include PROs as endpoints often use PRO scores (e.g., above or below a certain score) as eligibility criteria. PRO instruments can consist of multiple items which need to be calculated to determine a patient's score. For a clinician or study coordinator involved in screening potential participants, managing a screening script, a screening form, and all of the eligibility criteria, including a potentially lengthy PRO assessment that involves a scoring algorithm to determine eligibility, can be complex.

To make matters more complex, required scores for eligibility might vary depending on target recruitment goals. For example, recruitment might target the enrollment of equal numbers of participants with different scores on a given PRO instrument (e.g., higher and lower severity groups). Hence, target recruitment goals that group patients based on PRO scores increases the complexity of the enrollment task both within and between sites. Traditionally, sites would keep a weekly recruitment tracking log and send this via fax once a week to keep the study sponsor updated on screening successes and failures as well as participants enrolled and which target enrollment group they fall into.

Using electronic data capture methods, PRO data collected during patient screening can be entered into an electronic data capture instrument and scores calculated in real time. When eligibility criteria require that a participant have a certain score on a PRO for inclusion, this decreases the complexity of the screening task for the study coordinator as well as reduces time to determine eligibility status of the potential participant. The electronic data capture device can provide the screener with a ‘decision’ about whether the patient is eligible in real time. Hence, e-PROs used during screening both reduces the potential for human error as well as increases efficiency in the screening and enrollment process.

Furthermore, as patients are screened, eligibility data are entered into a database immediately, allowing sponsors to have automatic updates of number of patients screened, eligibility successes and failures, and descriptive information on enrolled patients on a rolling basis. This automatic feedback loop can further increase efficiency. Study coordinators do not need to spend time providing the sponsor with enrollment updates each week. Since the data are available almost immediately, this automation may further facilitate meeting recruitment goals by providing sites and the sponsors with updates on moving recruitment targets. For example, the immediate updates take into account enrollment at all study sites, so this should help sponsors and sites to rapidly adjust recruitment goals when target enrollment is fulfilled for a certain group of participants based on PRO scores and other eligibility criteria.

E-PROs provide an opportunity to decrease the complexity and increase the efficiency of participant recruitment and enrollment for clinical trials by providing immediate ‘decisions’ about eligibility based on PRO scores and by providing automatic updates about enrollment to sites and the study sponsor. This is only one of the many advantages of e-PROs.

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Upcoming Presentations

14th Annual Conference of ISOQOL: Health Related QOL Research: From Measurement to Understanding

Oct 10–13, Toronto, Ontario, Canada

Symposium

“New Perspectives on How Preference-Based Indexes (EQ-5D, HUI2, HUI3, QWB-SA, and SF-6D) Scale Summary Health-Related Quality-of-Life” Fryback DG¹, Kim JS², Palta M³, **Revicki DA**⁴; ¹Population Health Sciences, Univ. of Wisconsin; ²Educational Psychology, Univ. of Wisconsin; ³Population Health Sciences, Univ. of Wisconsin; ⁴Center for Health Outcomes Research, United BioSource Corp.

Workshop Presentations

“Advanced Psychometric Methods, Part 1: Use of Exploratory and Confirmatory Factor Analyses in PRO Instrument Development and Evaluation” **Don Stull, PhD, Dennis Revicki, PhD**; Center for Health Outcomes Research, United BioSource Corp.

“Advanced Psychometric Methods, Part 2: Executing and Interpreting Exploratory and Confirmatory Factor Analyses in PRO Instrument Development and Evaluation” **Don Stull, PhD, Dennis Revicki, PhD**; Center for Health Outcomes Research, United BioSource Corp.

“Capturing Patient-Reported Outcomes Electronically: From e-PRO Design to Implementation” **Nancy Kline Leidy, PhD, Kellee Howard, MSc, Meghan Werner, MPP**; Center for Health Outcomes Research, United BioSource Corp.

Poster Presentations

“Psychometric Characteristics of the Daily Sleep Interference Scale Among Diabetic Peripheral Neuropathy and Postherpetic Neuralgia Patients” **Vernon MK**¹, Brandenburg NA², Alvir JMJ², **Revicki DA**¹; ¹United BioSource Corp.; ²Pfizer, Inc.

“Content Validity and Usability of the Treatment Outcome Score and Mean Complex Severity Score: New Electronic PROs to Assess Symptom Severity and Improvement in Hereditary Angioedema” **Vernon MK**¹, **Rentz A**¹, White M², Schmalbach T³; ¹United BioSource Corp.; ²Institute for Asthma & Allergy; ³Dyax, Corp.

“Estimating Utility Values for Symptom Control in Metastatic Non-Small Cell Lung Cancer (NSCLC)” **Doyle S**¹, Lloyd A², **Gavriel S**¹, Lewis G³; ¹United BioSource Corp.; ²Formerly of United BioSource Corp.; ³Roche Products Ltd.

“COPD and Asthma Fatigue Scale (CAFS): Development and Psychometric Properties” **Flood R**¹, **Revicki DA**¹, Meads DM², Glendenning GA³, Gale R³, McKenna SP²; ¹United BioSource Corp.; ²Galen Research; ³Novartis Research Center

“COPD and Asthma Sleep Impact Scale (CASIS): Development and Psychometric Properties” **Revicki DA**¹, **Flood R**¹, Meads DM², Glendenning GA³, Gale R³, McKenna SP²; ¹United BioSource Corp.; ²Galen Research; ³Novartis Research Center

“Development and Validation of the Asthma Life Impact Scale (ALIS)” Meads DM², McKenna S¹, **Revicki D**², **Flood R**², Glendenning GA³, Hunter C⁴; ¹Galen Research; ²United BioSource Corp.; ³Novartis Research Center; ⁴Peterborough District Hospital NHS Trust

“Development and Validation of the Living with COPD (LCOPD) Quality of Life (QoL) Measure” McKenna S¹, Meads DM², **Revicki D**², **Flood R**², Glendenning GA³, Hunter C⁴; ¹Galen Research; ²United BioSource Corp.; ³Novartis Research Center; ⁴Peterborough District Hospital NHS Trust

“Preliminary Psychometric Analysis of the PROMIS Pain Behavior Item Bank” **Chen WH**¹, Cook KF², Amtmann D², **Revicki DA**¹; ¹United BioSource Corp.; ²Rehabilitation Medicine, Univ. of Washington

“Factor Structure of the QOL-AD” **Frank LB**¹, **Kleinman L**¹, Zhao Y²; ¹United BioSource Corp.; ²Eli Lilly and Company

“Developing a Tool to Assess Depression and Remission: Focus Group Results” **Frank LB**¹, Morlock R², **Mannix S**¹, Feltner D², **Matza L**¹, **Werner M**¹, Hanlon J³, **Revicki DA**¹; ¹United BioSource Corp.; ²Pfizer, Inc.; ³QualityMetric

“Development of a Nocturnal Gastroesophageal Reflux Disease (GERD) Symptom Severity and Impact Instrument” **Roberts L**¹, Spiegel BM², Kothari-Talwar S³, Reema Mody³, **Revicki DA**¹, Kahrilas PJ⁴, Camilleri ML⁵, **Walter K**¹; ¹United BioSource Corp.; ²Internal Medicine and Digestive Diseases, VA Greater Los Angeles Healthcare System David Geffen School of Medicine; ³TAP Pharmaceutical Products, Inc.; ⁴Gastroenterology, Northwestern Univ.; ⁵Medicine, Mayo Clinic

“Assessing Symptoms and Health-Related Quality of Life (HRQL) in Pediatric Gastroesophageal Reflux Disease (GERD)” **Kleinman L**¹, Kothari-Talwar S², **Roberts L**¹; ¹United BioSource Corp.; ²TAP Pharmaceutical Products, Inc.

ECNP 20th Annual Congress Oct 13–17, Vienna, Austria
“Effect of Comorbidities and Adverse Events on Clinical Global Impressions Ratings” **Busner J**^{1,3}, **Targum SD**^{1,2}, **Miller DS**¹; ¹United BioSource Corp.; ²Massachusetts General Hospital; ³Penn State College of Medicine

“Determination of Hamilton Anxiety Rating Scale Severity Gradation in Generalized Anxiety Disorder” **Kott A**¹, **Friedmann**², **Miller DS**²; ¹United BioSource Corp. s.r.o., Prague, Czech Republic; ²United BioSource Corp., Wayne, PA

American Academy of Pediatrics' (AAP) 2007 National Conference & Exhibition

Oct 27–30, San Francisco, CA, USA

“Cost-effectiveness of Respiratory Syncytial Virus Prophylaxis with Palivizumab Among Preterm Infants After Valuing a Reduction in Persistent Wheezing” Polak MJ¹, **Crugin LS**², Groothuis JR³, McLaurin KK³, **Sorensen SV**², Mahadevia PJ³; ¹Dept. of Pediatrics, West Virginia Univ. School of Medicine; ²United BioSource Corp.; ³MedImmune, Inc.

15th UEGW 2007 (United European Gastroenterology Week)

Oct 27–31, Paris, France
“Reduction in Health Resource Utilization with Cyclooxygenase-2 Inhibitor Parecoxib Compared to Opioids after Noncardiac Surgery in the UK” **Remak E**¹, **Muszbeq N**¹, **Manson S**¹, Zlateva G², Chen C²; ¹United BioSource Corp.; ²Pfizer Inc.

CHI: Drug Safety Strategies: Best Practices to Mitigate Risks Throughout the Product's Life Cycle

Nov 13–14, Philadelphia, PA, USA
“Leveraging Drug Registry Tools to Assess Safety and Performance” **Annette Stenhagen, DrPH FISPE**, Vice President, Epidemiology & Risk Management, United BioSource Corp.

“Costs and Opportunities of Phase IV Risk Management Programs” **Gerald A. Faich, MD**, Sr. Vice President, Epidemiology & Risk Management, United BioSource Corp.

The Gerontological Society of America's 60th Annual Scientific Meeting

Nov 16–20, San Francisco, CA, USA
Ethics of Dementia Screening
“Whether and Where to Screen for Dementia” **Frank L**¹, Khachaturian Z², Borson S³, Boustani M⁴, Dash P⁵, Ashford W⁶; ¹United BioSource Corp.; ²Alzheimer's Association's Ronald & Nancy Reagan Research Institute; ³Memory Disorders Clinic and the ADRC Satellite Univ. of Washington; ⁴Indianapolis Discovery Network for Dementia Scientist, Regenstrief Institute, Inc. Center Scientist, Indiana Univ. Center for Aging Research; ⁵Dept. of Neurology, Johns Hopkins; ⁶Stanford/VA Aging Clinical Research Center

Research Directions to Support Global Dementia Screening
“Capturing Comprehensive Outcomes through Study Design” Ashford W¹, Mendiondo M², Shankle W³, **Frank L**⁴, Khachaturian Z⁵; ¹Stanford/VA Aging Clinical Research Center; ²Univ. of Kentucky; ³Univ. of California; ⁴United BioSource Corp.; ⁵Alzheimer's Association's Ronald & Nancy Reagan Research Institute

2008 AAGP Annual Meeting

Mar 14–17 2008, Orlando, FL, USA
Dementia Screening in Clinical and Community Settings
“What to Know When Implementing a Screening Program” Steffens D¹, Borson S², Ashford W³, **Frank L**⁴; ¹Duke Univ. Medical Center; ²Memory Disorders Clinic and the ADRC Satellite Univ. of Washington; ³Stanford/VA Aging Clinical Research Center; ⁴United BioSource Corp.

SPOTLIGHT ON SCIENCE

Recent Publications

- Beusterien K, Dziekan K, Schrader S, Flood E, **Flood R**, Shearer A, Davis EA. "Patient Preferences among Third Agent HIV Medications: A U.S. and Germany Perspective." *Aids Care*; [In Press]
- Bravo Vergel Y**. "Explorando la Caja Negra: la Implementación de las NICE Guidances." *Revista Española de Economía de la Salud (ReES)* 2007; 6(2): 93-7.
- Buchwald H, **Estok R**, **Fahrbach K**, Banel D, **Sledge I**. "Trends in Mortality in Bariatric Surgery: A Systematic Review and Meta-Analysis." *Surgery* 2007; [In Press]
- Caro JJ**, **O'Brien JA**, **Hollenbeak CS**, **Spackman E**, Ben-Joseph R, **Okamoto LJ**, **Paramore LC**. "Economic Burden and Risk of Cardiovascular Disease and Diabetes in Patients with Different Cardiometabolic Risk Profiles." *Value in Health* 2007; 10(s1):S12-S20.
- Caro JJ**, **Ward A**, Deniz HB, **O'Brien JA**, Ehreth JL. "Cost-Benefit Analysis of Preventing Sudden Cardiac Deaths with an Implantable Cardioverter Defibrillator versus Amiodarone." *Value in Health* 2007; 10(1):13-22.
- Coyne KS**, **Margolis MK**, Jumadilova Z, Bavendam T, Mueller E, Rogers R. "Overactive Bladder and Women's Sexual Health: What is the Impact?" *International Society for Sexual Medicine* 2007; 4:656-666.
- Daniel DG**, Currier GW, Zimbrow DL, **Allen MH**, Oren D, Maos G, McQuade R, Pikalov AA 3rd, Crandall DT. "Efficacy and Safety of Oral Aripiprazole Compared with Haloperidol in Patients Transitioning from Acute Treatment with Intramuscular Formulations." *J Psychiatr Pract*. 2007 May; 13(3):170-7.
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- Fleurence RL**, Chatterton ML, **Dixon JM**, Rajagopalan K. "Economic Outcomes Associated with Atypical Antipsychotics in Bipolar Disorder: A Systematic Review." *Prim Care Companion J Clin Psychiatry* 2007; [In Press]
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UBC Presents at the ISPOR 10th Annual European Congress

OCTOBER 20-23, 2007, DUBLIN, IRELAND

Short Courses

SATURDAY, OCT 20, 2007

"Discrete Event Simulation for Economic Analyses"

Faculty: **J. Jaime Caro MDCM, FCRPC, FACP**, Adjunct Professor of Medicine, Adjunct Professor of Epidemiology and Biostatistics, McGill University and Sr. Vice President, Health Economics, United BioSource Corp.; **Jörgen Möller MSc Mech Eng**, Simulation Specialist, United BioSource Corp.

"Instrument Development & Evaluation for Patient-Reported Outcomes Assessment"

Faculty: Andrew Lloyd M. Phil, Director, Oxford Outcomes; **Patricia van Hanswijck de Jonge PhD, MSc**; Senior Research Associate, Health Care Analytics, United BioSource Corp.

"Cost-Utility Analysis of Oxaliplatin in the Adjuvant Treatment of Colon Cancer in Hungary" **Muszbek N¹**, Odhiambó R²; ¹United Biosource Corp.; ²sanofi-aventis Zrt

"Cost-Effectiveness Analyses of Rufinamide vs. Topiramate and Lamotrigine as Adjunctive Therapies in the Treatment of Lennox-Gastaut Syndrome (LSG) in the UK" **Benedict A¹, Dale PL¹**, MacLaine G², Verdian L²; ¹United BioSource Corp.; ²Eisai Europe Limited

"UK Cost-Effectiveness Analyses of Docetaxel Versus Generic Paclitaxel Once Weekly and Nab-Paclitaxel in Patients With Locally Advanced or Metastatic Breast Cancer (MBC) Progressed After Anthracycline Chemotherapy" **Benedict A¹**, Cameron D², Corson H³, Jones S⁴; ¹United BioSource Corp.; ²Univ. of Leeds; ³sanofi-aventis; ⁴US Oncology Research

"Modeling the Clinical and Economic Consequences of Treating Relapsing Form of Multiple Sclerosis with Subcutaneous Versus Intramuscular Interferon-Beta-1A" **Guo S¹, Copur D¹, Ward A¹, O'Brien JA¹, Ishak KJ¹**, Bennett R², Al-Sabbah A², Meletiche DM², **Caro JJ¹**; ¹United BioSource Corp.; ²EMD Serono, Inc.

Workshop Presentations

Oct 21 – Workshops Session I

"Risk Factors That Change Over Time: How to Estimate Their Impact on the Occurrence of Health Outcomes" **Ishak I, PhD, Huybrechts KF, MS, Caro JJ, MDCM, FRCPC, FAC**, United BioSource Corp.

Podium Presentations

Oct 22 – Podium Session II: Surgery

"Cost-Effectiveness of Cyclooxygenase-2 Inhibitor Parecoxib Compared to Opioids After Noncardiac Surgery in the UK" **Remák E¹, Muszbek¹, Manson SC¹**, Zlateva² Chen C²; ¹United Biosource Corp., ²Pfizer Inc.

"Micro-Costing of Surgical Procedures Related to Intracerebral Haemorrhage in a UK Health Care Setting" **Manson SC¹, De Cock E¹** Jenkins AJ², Twena N³; ¹United BioSource Corp.; ²Newcastle General Hospital; ³Novo Nordisk Ltd.

Oct 22 – Podium Session IV: Economics of Neurological Disease

"Modeling Treating Multiple Sclerosis with Disease Modifying Drugs Using Discrete Event Simulation" **Guo S¹, Copur D¹, Ward A¹**, Bennett R², Al-Sabbah A², Meletiche DM², **Caro JJ¹**; ¹United BioSource Corp.; ²EMD Serono, Inc.

Poster Presentations

SESSION I: Oct 21, 2007

"Switching from Branded to Generic Risperidone in Patients with Schizophrenia: An Estimation of Potential Economic Consequences in the Netherlands" **Van Nooten F¹**, Rijnders C², **Brown R¹**, Van Agthoven M³; ¹United BioSource Corp.; ²Institute for Mental Health Care Midden Brabant; ³Janssen-Cilag BV

"Time Spent on Anaemia Management with Erythropoietin Stimulating Agents (ESA) in Haemodialysis Centres: A Cross-Countries Perspective" **De Cock E¹, Van Nooten F¹**, Sapède C², **Dale P¹, Petrillo J¹, Werner M¹**; ¹United BioSource Corp.; ²F. Hoffmann-La Roche Ltd.

"Selection of Utility Instruments for Asthma and Chronic Obstructive Pulmonary Disease (COPD)" **Lloyd A, Meguro M**, United BioSource Corp.

"Cost-Effectiveness of Duloxetine vs. Venlafaxine XR and SSRIS in Patients with Major Depressive Disorder in Primary and Secondary Care in Spain" **De Cock E¹, Benedict A¹**, Le TK², Sacristán del Castillo JA³, Dilla T⁴; ¹United BioSource Corp.; ²Eli Lilly and Company; ³Lilly S.A.; ⁴Eli Lilly Spain

"Simulation of Long-Term Costs of Complications in Type II Diabetes in the United States" **Ward A, Kongnakorn T, Moller J, O'Brien JA, Caro JJ**; United BioSource Corp.

"Potential Drug-Drug Interactions with Risperidone and the Risk of Discontinuation: A Retrospective Analysis of Patients in Quebec, Canada" **Ishak KJ¹**, Glass JR², **Tan Y¹**, Luong D², **Caro JJ³**; ¹United BioSource Corp., Montreal; ²Janssen-Ortho Inc.; ³United BioSource Corp., Concord

SESSION II: Oct 22, 2007

"Sunitinib vs. Interferon-A (IFN-A) in First-Line Metastatic Renal Cell Carcinoma (MRC): An Economic Evaluation" **Remák E¹, Brown R¹**, Negrer S², Motzer RJ³, Kim ST⁴, Charbonneau C⁴; ¹United Biosource Corp.; ²Centre Leron Berard; ³Memorial Sloan Kettering Cancer Center; ⁴Pfizer Inc.

"Cost-Effectiveness of Sunitinib as Second Line Treatment in Patients with Metastatic Renal Cancer in Belgium" **Van Nooten F¹, Dewilde S¹**, Van Belle S², Marbaix S³; ¹United BioSource Corp.; ²Univ. Hospital Ghent; ³Pfizer

SESSION III: Oct 23, 2007

"Hospital Costs for Treatment of Acute Heart Failure: Economic Analysis of the REVIVE II Study" **De Lissovoy G¹, Fraeman K¹**, Mullahy J², Durtschi A³, Sterz R⁴, Salon J⁵; ¹United BioSource Corp.; ²Univ. of Wisconsin; ³Abbott Laboratories; ⁴Abbott GmbH & Co. KG; ⁵Abbott Laboratories

"Resource Use and Treatment Costs for Acute Decompensated Heart Failure: Economic Analysis of the SURVIVE Trial" **De Lissovoy G¹, Fraeman K¹**, Sterz R², Salon J³; ¹United BioSource Corp.; ²Abbott GmbH & Co. KG; ³Abbott Laboratories

"Eliciting Utility Scores for Health States Associated with Severe Chronic Pain" **Lloyd A¹, Meguro M¹, Dewilde S¹**, MacLaine G³, Verdian L³; ¹United BioSource Corp.; ²Eisai Europe Limited

"Major Bleed Resource Use and Costs for Patients Hospitalized with Acute Coronary Syndrome in France, Italy and Spain" **Brown R¹**, Parnaby A², Guijarro P³, Nachit-Ouinekh F², Bamfi F⁴; ¹United BioSource Corp.; ²GlaxoSmithKline, Paris; ³GlaxoSmithKline, Madrid; ⁴GlaxoSmithKline Spa, Verona

"Costs of Major Bleeds in Acute Coronary Syndrome Patients" **Brown R¹**, Ferrari E², Drogoul L², Nachit-Ouinekh F³, **De Cock E⁴**; ¹United BioSource Corp., UK ²Hopital Pasteur; ³GlaxoSmithKline; ⁴United BioSource Corp., Spain.

"Cost-Effectiveness of Linezolid vs. Vancomycin in Nosocomial Pneumonia Due to Suspected Methicillin-Resistant Staphylococcus Aureus in France" **De Cock E¹**, Timsit JF², Carlet J³, Leroy O⁴, Wolff M⁵, Levrat F⁶; ¹United BioSource Corp.; ²Hôpital Albert Michallon; ³Groupe Hospitalier Paris Saint Joseph; ⁴Hôpital Guy Chatiliez, Tourcoing; ⁵Hôpital Bichat Claude Bernard; ⁶Pfizer

"Cost-Effectiveness of Linezolid vs. Vancomycin in Complicated Skin and Soft-Tissue Infection Due to Suspected Methicillin-Resistant Staphylococcus Aureus in France" **De Cock E¹**, Besnier JM², Dupon M³, Guéry B⁴, Levrat F⁵; ¹United BioSource Corp.; ²CHRU Bretonneau; ³Hôpital Pellegrin; ⁴Hôpital Calmette, CHRU Lille; ⁵Pfizer

"Retrospective Study of Complications and Resource Use in Endovascular Management of AAA" **Muszbek N¹**, Van Sambeek MR², Soong CV³, Thompson MM⁴, Gavriel S¹, Hutton J⁵, Brasseur P⁶; ¹United BioSource Corp.; ²Erasmus Univ. Medical Center; ³Belfast City Hospital; ⁴St. George's Hospital NHS Trust; ⁵Univ. of York; ⁶Medtronic International SA

"Adult Asthma: A Cohort Analysis of Use and Cost of Hospital and Emergency Department Care by Location of Residence Over Twelve Months" **O'Brien JA, Duran PA, Caro JJ**; United BioSource Corp.

"Probabilistic Sensitivity Analysis in Health Economic Modeling Studies: A Quality Assessment" **Getsios D¹, Ishak KJ², Finnegan S³, Caro JJ³**; ¹United BioSource Corp., Halifax; ²United BioSource Corp., Montreal; ³United BioSource Corp., Concord

"Reducing Global Cardiometabolic Risk in Overweight or Obese Individuals with Dyslipidemia: Projected Benefits of Rimonabant in A Real World Population" **Getsios D¹, Moller J²**, McEwan P³, Danel A⁴, **Ishak KJ⁵, Caro JJ²**; ¹United BioSource Corp., Halifax; ²United BioSource Corp., Concord; ³Cardiff Research Consortium; ⁴Sanofi-Aventis; ⁵United BioSource Corp., Montreal

"Simple Sensitivity Analysis to Assess the Impact of Rounding on Blood Pressure Measurements on Estimates of Control Rates" **Ishak KJ¹, Payne K¹, Caro JJ²**, Khan ZM³, Daley WM³, Califf R⁴; ¹United BioSource Corp., Montreal; ²United BioSource Corp., Concord; ³Novartis Pharmaceuticals Corporation; ⁴Duke Clinical Research Institute

NEWS BRIEFS

Dr. Dennis Revicki Honored with ISOQOL President's Award

Dennis A. Revicki, PhD will be honored by the International Society for Quality of Life Research at their 14th Annual Scientific Meeting, October 10-13, as the recipient of their President's Award. The goal of this award is to recognize outstanding contributions to the advancement of the quality of life (QOL) field in one or more of the following areas: "education of professionals, patients or lay individuals about the value of quality of life assessment as related to health"; "promotion or execution of quality of life research or other scholarly activities"; and "facilitating or furthering policy initiatives that impact upon health-related quality of life." Dr. Revicki is Senior Vice President for Health Outcomes Research at UBC in Bethesda, MD, and Scientific Director of the Center for Health Outcomes Research, with over 25 years experience in designing and conducting studies involving health-related quality of life assessment, health services research, psychometrics and primary care research. He has over 260 journal publications and 25 book chapters and has held leadership positions and memberships in industry associations, as well as faculty positions at the University of North Carolina at Chapel Hill and Georgetown University Medical Center. Receipt of this award acknowledges the substantial contributions that Dr. Revicki has made in the area of health-related quality of life assessment.

UBC Welcomes New Staff

Sandra R. Lottes, PharmD has joined UBC as the **Vice President of Clinical Development**, with overall responsibility for the strategic growth, development and implementation of UBC's Clinical and Emerging Company Strategy. Dr. Lottes comes to UBC with deep and extensive experience in pharmaceutical research (pre-clinical, phase I through phase IV and marketing launch), clinical operations, biostatistics, data management and regulatory affairs. She has served on advisory boards in Cardiology, Gastroenterology and Nephrology. In her former position as Head of Development, R&D Salix Pharmaceuticals, she was directly responsible for all Biostatistics, Data Management and Clinical Programming (BDMP), Clinical Research/Operations and Regulatory Affairs. Sandi held a leadership role in FDA negotiations and approvals of two novel purgatives in 2006 as well as support of the training and launch of the franchise. Dr. Lottes has collaborated on and authored manuscripts in numerous peer-reviewed journals such as *New England Journal of Medicine*, *American Journal of Cardiology*, and the *American Journal of Gastroenterology*. She holds a Doctor of Pharmacy degree from the Philadelphia College of Pharmacy and Science, where she has also served as a Clinical Assistant Professor of Pharmacy and a Bachelor of Arts in Biological Sciences from the University of Delaware. She was awarded a post-doctorate fellowship in Cardiovascular Pharmacology at Hahnemann University Medical School.

Oto Markovič, MD has joined UBC as the **Regional Manager of its Prague, Czech Republic office**, focused on training and education services. Dr. Markovič's responsibilities include the management of client projects, clinical consultant research, business development, and staff and office management. Dr. Markovič is originally from Slovakia where he completed his medical training at the Medical Faculty University Komeniana in 1994. He worked as a psychiatrist at the Army Hospital, Ružomberok in the Slovak Republic; and later as the Deputy Chief of Psychiatry at the Psychiatric Hospital Horní Beřkovice in the Czech Republic. In 1998, Dr. Markovič began his first position in industry working as a CRA with Eli Lilly ČR s.r.o. in Prague and later moved to BMS s.r.o where he held several increasingly senior roles including Senior CRA, Senior Medical Advisor, and Disease Area Head Neuroscience EU Markets Region. In his last role at BMS s.r.o. as *European Medical Communication Lead—EMEA— Global Medical Affairs*, he led a medical team that covered 16 different countries. In addition to his successful track record as a business leader, Dr. Markovič has also published multiple scientific articles.

Krista A. Payne, BA (Hons), MEd is a **Research Scientist and the recently appointed Director of Health Care Data Capture at UBC**, responsible for the design and implementation of health economic related prospective and observational data collection studies. After joining Caro Research in January 1996 as a Project Manager, her pharmacoeconomic research and management efforts have included projects in a variety of therapeutic areas including Alzheimer's disease, stroke, COPD and many others. Ms. Payne has planned and coordinated a number of international health economic assessments as well as implemented international surveys of epidemiological and health and social service resources. She has a keen interest in observational studies of actual practice and has designed and overseen prospective and retrospective data collection projects in more than 8 countries around the world. The results of Ms. Payne's work have been presented at various scientific meetings and she has authored and co-authored several published manuscripts in a variety of peer-reviewed journals.

K. Jack Ishak, PhD is a **Research Scientist and has been appointed Director of Biostatistics for UBC**, responsible for overseeing the planning and execution of statistical analyses for health economics, pharmacoepidemiology and outcomes research studies. Dr. Ishak's methodological expertise covers survival analysis techniques involving time-dependent variables, meta-analysis models, mixed models for longitudinal and correlated data, analyses of compliance and persistence with treatment. He has worked in several disease areas including cardiovascular disease, osteoporosis, hypertension, diabetes, Alzheimer's disease, schizophrenia, depression, hepatitis and multiple myeloma. Dr. Ishak received his undergraduate degree in Statistics from Concordia University and obtained his Masters and Doctoral degrees in Biostatistics and Epidemiology from McGill University. Dr. Ishak has co-authored a number of methodological and substantive papers in peer-reviewed journals.

NEWS BRIEFS

*continued from page 23***Bernardo Duran, BS has been appointed Director of Data Management & Custom Software Solutions for UBC,**

responsible for the management and quality control of all project-related databases and the design and implementation of project-related electronic data capture and health economic modeling. Mr. Duran has approximately 25 years of experience in the fields of software design for health economics modeling, Electronic Data Collection, Marketing Intelligence systems, database management, and Informatics. Prior to UBC, he was the head of Interfaces and IT with Caro Research since 1997. Mr. Duran has extensive experience in the design and programming of user-friendly interfaces for databases and health economic models in numerous disease areas and extensive experience in several programming environments and databases, having designed nearly 100 interface projects. He holds a degree in Civil Engineering from Los Andes University in Bogota, Colombia.

Senior Staff Promotions Announced**Ágnes Benedict, BSc, MSc** has been promoted to **Research Scientist** in UBC's Budapest, Hungary location.

She conducts decision-analyses, cost-of-illness studies, physician and patient surveys, burden of illness studies and cost-effectiveness modeling in a wide variety of therapeutic areas. Ms. Benedict has advanced modeling training and is experienced in stochastic and probabilistic modeling. Ms. Benedict holds a Bachelor of Science degree in Economics, a Master's degree in Public Economics from the Budapest University of Economic Sciences, Hungary and a Master's in Health Economics from the University of York, UK.

Sarah Dewilde, MSc has been promoted to **Research Scientist** and is located in Brussels, Belgium. Ms. Dewilde develops cost-effectiveness models using decision-analytical techniques (including Markov models, cohort or simulation models, and probabilistic sensitivity analysis). She is also involved in data analysis of quality-of-life data and resource use data; her skills in this domain include discrete choice analysis, repeated measurement analysis, survival analysis, missing data analysis and propensity scores adjustment for non-randomisation, all programmed in SAS. Ms. Dewilde holds Masters degrees in Economics and in Statistics from the Katholieke Universiteit Leuven, Belgium, and a Masters in Health Economics from the University of York, UK (1st prize).

Karin Coyne, PhD, MPH has been promoted to **Senior Research Leader** with UBC's Center for Health Outcomes Research. Dr. Coyne's responsibilities include instrument development and validation as well as design and management of research studies focused on patient-reported outcomes.

Her areas of expertise include cardiovascular, urology, gastrointestinal, diabetes, and women's health. Dr. Coyne has extensive experience in all phases of instrument validation and development. Dr. Coyne earned her Bachelor's degree in Nursing from Xavier University, her Master's degree in Public Health from San Diego State University, and her Doctorate in Nursing with a specialization in clinical research from the Johns Hopkins University.

Rhonda P. Estok, RN, BSN has been promoted to **Assistant Clinical Director** in UBC's Boston office. Ms. Estok has been involved in UBC's systematic review and meta-analysis projects for more than 7 years. She currently serves as co-principal investigator for all medical/surgical device projects. Ms. Estok has more than 25 years of experience in perioperative nursing with specific expertise in Orthopaedic Surgery and management. Prior to joining UBC in 1998, she was Director of Perioperative Services at Newton-Wellesley Hospital and Assistant Director of Operating Room Nursing at Duke University Medical Center where she gained comprehensive knowledge of clinical patient care and regulatory agency requirements. Ms. Estok earned her Bachelor of Science in Nursing from the University of North Carolina at Greensboro and is currently a Master's in Public Health Candidate.

United BioSource Acquires Interest in Leading Adaptive Design Technology Service Provider

UBC ClinResearch to Expand Global Reach in Pioneering Field. UBC has acquired ownership interest in ClinResearch GmbH, a global leader in technology solutions and services for flexible, or adaptive, clinical trials. Headquartered in Cologne, Germany, with more than 100 employees, ClinResearch has designed and implemented 80 adaptive programs over the past 7 years. ClinResearch, which will now operate under the name UBC ClinResearch, will be the centerpiece of UBC's adaptive design clinical trial offering, which will deliver a full service, global solution for pharmaceutical, biotechnology and medical device companies seeking to capitalize on the benefits of adaptive design in their clinical development strategy. **Dr. Michael Fischer** and **Mr. Reinhard Eisebitt** are the **Managing Directors of UBC ClinResearch**, both with degrees from the University of Cologne and extensive experience in statistics, biometrics, and clinical trial operations.

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