

Inside this Issue

Cover Story:

Health Care Reform is Dead!

FDA Final Guidance
Summary of Changes..... 1

Why U.S. Reimbursement Won't
Work for Europe..... 2

Payer and Provider Views on
Health Care Reform 4

The Growing Importance of HTAs... 8

Quantitative Risk-Benefit 9

Upcoming Presentations 11

FOCUS SECTION

The Value of Endpoint Models
and Conceptual Frameworks
to PROs..... 12

Common Ground –
Defining Content Validity..... 13

The MID is Dead..... 15

The Consortia Approach to
Developing PRO Instruments 16

The Cognition Initiative Becomes
Cognition Working Group 18

Other Measurement Properties
of PRO Instruments 20

EXACT-PRO Initiative Update 21

Patient Compliance with
eDiary Completion..... 23

PROs in Product Labeling:
An Update 25

Limitations of the EQ5D and
a Possible Solution for COPD
Exacerbations 25

News Briefs 27

Health Policy Corner 28

Recent Presentations..... 29

Recent Publications 30

SCIENCE & POLICY OPINION

HEALTH CARE REFORM

Health Care Reform is Dead! (Or is It?)— Two Key Provisions That Survived



By Craig A. Hunter, MPP, PGDP, Senior Science Policy Analyst and Senior Manager, Science Policy, Center for Epidemiology & Database Analytics

When I first set out to write this article, health reform seemed to be inevitable. The Democrats' control of the House and super majority in the Senate appeared to give Congress and President Obama the strength needed to pass some of the most sweeping and aggressive health reforms seen in the history of the U.S. health care system. Then came Senator Scott Brown's election in Massachusetts (filling the seat formerly held by the late Senator Ted Kennedy) and both health reform, and this article, became far more difficult to envision. Despite still holding a 59-vote majority in the Senate, the threat of Republican filibusters on key reform topics has forced the majority Democrats to reconsider their far-reaching efforts

continued on page 3

FOCUS ON: Patient-Reported Outcomes

FDA Final Guidance on PRO Measures: Summary of Changes

By Karin Coyne, PhD, Senior Research Leader; Sonya Eremenco, MA, ePRO Manager; Elizabeth Merikle, PhD, Research Scientist, Center for Health Outcomes Research

Summary of Changes from the Draft to the Final Version

Since the 2006 release of the FDA Draft Guidance for Industry on Patient-Reported Outcomes (PROs), the field has been looking forward to the release of the final version. On December 8, 2009, the FDA released the Final Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. This guidance represents the FDA's current thinking on use of PROs to support labeling claims.

Key highlights of the Final Guidance document are:

- Inclusion of endpoint model definition and examples
- Heavy emphasis on content validity with recommendations on required documentation and item tracking matrix

- Removal of reference to minimal importance difference (MID)
- Inclusion of cumulative distribution function for score interpretation
- Inclusion of Appendix to outline requirements for FDA PRO review

UBC health outcomes researchers have reviewed and compared this final guidance with the draft version and have compiled a summary of the differences. We hope you find this comparison useful.

To view the summary of changes, visit www.unitedbiosource.com/pdfs/final-pro-guidance-summary-of-changes-20091211.pdf.

For more information, please contact Karin.Coyne@unitedbiosource.com, Sonya.Eremenco@unitedbiosource.com, or Elizabeth.Merikle@unitedbiosource.com.



United BioSource Corporation

Evidence Matters®

Why a U.S. Reimbursement Strategy Won't Work for Europe

By Beth Hahn, PhD, and Louisa Hefty, MS, Managing Directors, Reimbursement Strategies, Center for Pricing & Reimbursement, and Adam Barak, Head, International Pricing and Reimbursement

Manufacturers generally acknowledge that the data needed to support reimbursement for a new drug, biologic, or device is more than the two well-controlled randomized studies required by the Food and Drug Administration (FDA), and they are aware that submission in Europe will entail some type of an economic analysis in addition to the clinical data. Beyond that, little emphasis in early development is given to the requirements within a specific country. Why bother with a detailed reimbursement strategy by country when a drug's largest market is the United States? What is the downside of evaluating the market opportunity versus the cost of market entry for launch in Europe after the U.S. launch?

The answers to those questions are best addressed by examining the differences between the U.S. and European reimbursement environments in four areas:

- Reimbursement objectives,
- General marketing strategy versus reimbursement strategy,
- Emphasis on Health Technology Assessments, and
- Use of cost-effectiveness/budget impact models for reimbursement decisions.

Reimbursement Objectives

Currently, reimbursement is relatively open in the U.S. compared with Europe. Although large managed care organizations and public payers, such as Medicare and Medicaid,

Increasingly, U.S. payers are reviewing European HTAs as a source of clinical and economic information regarding a specific drug or technology; yet, the purpose for U.S. payers is to feed into formulary placement decisions and not to serve as the primary rationale for reimbursement or market access at this time.

are the dominate payers in the U.S., the approach is at best to show superiority versus therapies currently on the market, and at the very least to be comparable with existing therapies in order to expand the options available to

treat a disease state. Contrast this approach with reimbursement objectives in countries such as the UK, Germany, Italy, and France where the focus is on showing superiority, but at a minimum to provide a better option and to replace a current therapy (with few exceptions for novel therapies that respond to an unmet market need). The relevance of the U.S.

model of “adding to” and the European model of “replacing one” impacts development costs for designing trials to enter the market, but also impacts marketing forecasts that must be predicated on realistic differences that cannot be addressed using the same tools to allocate market share.

Marketing Strategy

Typically, marketing strategies focus on the use of the new therapy in the largest possible market segment. For the U.S., the concern is in narrowing the use beyond that defined by the indication and having the therapy limited to use in a niche that never expands. Clearly, use is restricted by other factors in the U.S., including the physician's willingness to prescribe and the patient's willingness to pay the drug price or insurance copayment; however, the primary concern initially is with defining the market segment as broadly as the indication.

For countries with reimbursement controlled largely by single payers, such as Germany and the UK, the focus is not on the indicated use of the therapy, but a narrower target population within that indication that will benefit the most from the use of the drug/device. Use can broaden after the benefit has been established in a target population, but it must first be proven or established for a defined market segment. To gain market entry in these countries, it is essential to develop an entry-level approach to obtain reimbursement for a targeted subpopulation that would most benefit from the drug. Once the drug is used and gains acceptance, there would be an opportunity to expand this use to a broader group of patients.

Health Technology Assessments (HTAs)

HTAs vary greatly in the level of influence they wield for payers in each environment. For the U.S., the impact of HTAs, with few exceptions (i.e., National Coverage Determinations by Medicare), is limited and may serve to impose restrictions on therapies that should be used prior to the use of a new medication/device, but largely do not restrict access in the same way as European HTAs, particularly from bodies such as the UK's National Institute for Clinical Excellence (NICE) that have nearly closed access. HTAs in Europe are also the source of reference material regarding reimbursement for many countries. Increasingly, U.S. payers are reviewing European HTAs as a source of clinical and economic information regarding a specific drug or technology; yet, the purpose for U.S. payers is to feed into formulary placement decisions and not to serve as the primary rationale for reimbursement or market access at this time.

continued on page 7

Health Care Reform is Dead! (Or is It?) *continued from front page*

and instead refocus on smaller, more limited legislative goals where either cooperation is possible, or the two sides are at least close enough to prevent the extreme option of a filibuster. Additionally, it has become clear in the weeks following Sen. Brown's election, that President Obama intends to continue to push key aspects of reform through a combination of recommended budgeting and political pressure. The result will likely be an end to the sweeping reforms that dominated media attention in 2009 and instead the passage of several key aspects from that legislation in other forms.

Comparative Effectiveness Research

Each of the past four years has seen legislation introduced in Congress with the intent to increase the creation and/or utilization of comparative effectiveness research (CER) in health care decision-making. The health reform bills, as passed by both the House and Senate, contained strikingly similar language in their creation and support of a "Patient-Centered Outcomes Research Institute" to facilitate this evidence development. However, despite bipartisan support for the idea, neither the Democrats nor Republicans have had success finalizing a new direction; instead falling back to a position of increased funding for the Agency for Healthcare Research and Quality's (AHRQ) CER activities. Despite the most recent setback in this area, it appears the president is still very interested in continuing to push for additional CER funding, even if it means doing so by leading the Congress instead of following their lead.

In 2009, President Obama pushed for, and signed, the American Recovery and Reinvestment Act (ARRA). Among other things, this Act earmarked \$1.1 billion for increased CER research and support. This money was intended to serve as a jumping-off point, an initial push that could demonstrate the usefulness of increased CER-derived evidence and thereby provide justification for even larger efforts in the future. While it is still too early to tell whether this will be the case, President Obama made it clear within his recently proposed fiscal year 2011 budget that he intends to continue this push for greater CER:

The Budget includes \$286 million in the Agency for Healthcare Research and Quality for research that compares the effectiveness of different medical options, building on the expansion of this research begun under ARRA. The dissemination of this research is expected to lead to higher quality, evidence-based medicine, arming patients and physicians with the best available information to allow them to choose the medical option that will work the best for them.¹

While \$286 million is most likely not enough money to undertake many large scale CER studies and/or trials, this request represents a notable increase in the Agency's funding and an intention by the Administration to not let the work initiated under the ARRA be a one-time show of support. If passed at this level, AHRQ's 2011 budget would be more than 1.5 times that of 2010, with much of the new money intended to support and expand on the Agency's CER activities. Even if eventually cut down to a more modest level of increase, it's a telling effort by the Administration that during difficult economic times, the continued push for better evidence for health care decision-making is seen as a budgetary priority.

National Medical Device Registry

When the House of Representatives passed its version of a health reform bill, it contained a provision for the creation of a National Medical Device Registry with the purpose of "...facilitate[ing] analysis of post-market safety and outcomes data..."² in order to better understand safety, efficacy, and comparative effectiveness profiles for Class II and III medical devices. While the Senate never adopted matching language within its own health reform bill, the topic was actively discussed for potential inclusion within the combined legislation that would have been considered.

While it seems unlikely that Congress would push this legislation forward with more pressing aspects of reform still being discussed, the Obama Administration has included funding for this same effort within its proposed FY 2011 budget. The Food and Drug Administration (FDA) believes a National Medical Device Registry could "...dramatically enhance [the agency's] ability to understand and respond to device safety, effectiveness, and comparative effectiveness issues."³ Though this ultimate larger goal is still intact, many observers believe that the current iteration will most likely begin with a sole focus on safety surveillance⁴ and then develop over time into the more far-reaching registry that was originally conceived of within the Affordable Health Care for America Act in the U.S. House of Representatives.

continued on page 4

Health Care Reform is Dead! (Or is It?) *continued from page 3*

The Way Forward

In 2009 it seemed a certainty that the U.S. health care system was braced for sweeping change. The failure to realize that change has resulted in an unclear 2010 that has left many wondering what, if any, change will still be realized. There is no certainty in predicting the future of these changes, but clear indications have come from the Obama Administration that there are key aspects of evidence development and support that appear to have the support necessary to make an impact in 2010.

What does seem clear is that the increasing interest in (and importance of) evidence of comparative effectiveness is continuing to garner federal support at an increasing rate. Whether manifested by an increasing number of AHRQ reviews and assessments of pharmaceutical treatments or through the FDA's construction of a mandatory national medical device registry, the federal push for centralized evidence development and application continues despite its temporary inclusion in failed health care reform attempts. These efforts will continue to put additional pressure on manufacturers to produce clear evidence of their products' value, and those that proactively do so seem likely to find the greatest success in 2010 and beyond.

For more information, please contact Craig.Hunter@unitedbiosource.com.

References

¹Office of Management and Budget. Proposed Budget of the United States, Fiscal Year 2011. Available online: <http://www.whitehouse.gov/omb/budget/fy2011/assets/budget.pdf>

²H.R. 3962, Affordable Health Care For America Act, 2009.

³Department of Health and Human Services. Fiscal Year 2011, Food and Drug Administration Justification of Estimates for Appropriations Committees. Available online: <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM199447.pdf>

⁴*The Gray Sheet*, Jan. 18, 2010.

Payer and Provider Stakeholder Views on Health Care Reform

By Sandy W. Robinson, MPA, Executive Director, and Kristen McGowan, CPC, Research Manager, Center for Pricing & Reimbursement

Most would agree that one of the most politically-charged issues in today's current environment is health care reform—but that is where the “agreement” ends. Despite the passage of health care reform bills by both the House and Senate, we remain (at the writing of this article) without a reconciled and merged bill. The architects of reform on both sides of our congressional aisles continue to have much to debate while American citizens are becoming more actively involved in the issue. The outcome of the January 19, 2010, special election in Massachusetts served to further complicate the issue by “tipping” the perceived balance of power (votes) needed to move any current version of the legislation forward.

Since before his election, President Obama made passing health care reform a focus. On November 7 of last year, after less than a year in office, the House gave their approval for an overhaul of the U.S. health care system. Following this, the Senate passed their version of a health care bill on December 24th. At this time, it is likely that neither bill will pass in its current form. Some of the key revisions of the House and Senate bills are compared in the chart below (this is excerpted from a side-by-side comparison completed by the Kaiser Family Foundation).¹

In the early stages of reform, payers were overwhelmingly ready for some sort of overhaul. Today, payers vary on how reform will ultimately impact the way they conduct business. In fact, most payers United BioSource Corporation (UBC) contacted as part of the research for this article remain in a “wait and see” mode. For example, a medical director with a Blue Cross Blue Shield plan stated, “Unfortunately, with so much still up in the air, it is difficult to tell what will happen. If the past is any indication, it will almost be business as usual, although we will likely see rate increases and other taxes.”

Associations and organizations representing payer constituencies such as the American Health Insurance Plans (AHIP), the National Association of Insurance Commissioners (NAIC), and the Blue Cross Blue Shield (BCBS) Association have

continued on page 6

SCIENCE & POLICY OPINION

HEALTH CARE REFORM

A Comparison of the House and Senate Bills

| Topic | House | Senate |
|---|--|--|
| Bill Name | Affordable Health Care for America Act (H.R. 3962) | Patient Protection and Affordable Care Act (H.R. 3590) |
| Timeframe | Effective in 2013 | Effective in 2014 |
| Overall Approach to Expanding Access to Coverage | <p>Require most U.S. citizens and legal residents to have health insurance.</p> <p>Create state-based American Health Benefit Exchanges through which individuals can purchase coverage, with premium and cost-sharing credits available to individuals/families with income between 100-400% of the federal poverty level (the poverty level is \$18,310 for a family of three in 2009).</p> <p>Create separate Exchanges through which small businesses can purchase coverage.</p> <p>Require employers to pay penalties for employees who receive tax credits for health insurance through an Exchange, with exceptions for small employers. Impose new regulations on health plans in the Exchanges and in the individual and small group markets.</p> <p>People who opt not to get coverage will have to pay a penalty fee of 2.5% of adjusted gross income (AGI) over a certain level.</p> | <p>Require most individuals to have health insurance.</p> <p>Create a Health Insurance Exchange through which individuals and smaller employers can purchase health coverage, with premium and cost-sharing credits available to individuals/families with incomes up to 400% of the federal poverty level (the poverty level is \$18,310 for a family of three in 2009).</p> <p>Require employers to provide coverage to employees or pay into a Health Insurance Exchange Trust Fund, with exceptions for certain small employers, and provide certain small employers a credit to offset the costs of providing coverage.</p> <p>Impose new regulations on plans participating in the Exchange and in the small group insurance market.</p> <p>People who opt not to get coverage will have to pay a fine of \$95 in 2014, which will then rise to \$750 or 2% of income, whichever is higher, by 2016.</p> |
| New Taxes | <p>5.4% surtax to be levied on individuals who earn more than \$500,000 per year and families that earn more than \$1 million.</p> <p>New 2.5% excise tax levied on medical devices.</p> | <p>Medicare payroll tax would increase from 1.45% to 2.35% for individuals making more than \$200,000 per year and families making more than \$250,000.</p> <p>New tax levied on high-value insurance plans worth more than \$8,500 for individuals and \$23,000 for families.</p> <p>New annual fees levied on health care companies, including drug makers, medical device manufacturers and insurance companies allocated by market share.</p> |
| Cost | \$1.05 trillion over 10 years | \$871 billion over 10 years |
| Medicare Changes | <p>Reduction in spending on Medicare and other federal programs over 10 years. Reductions would be from changes to Medicare provider payment rates and federal subsidies for privately-run Medicare Advantage plans.</p> <p>Government negotiation of Medicare Part D drug prices Part D plans may offer generic drugs to enrollees with zero copayment to encourage use of lower-cost generic drugs.</p> | <p>Legislation would create an Independent Medicare Advisory Board to make recommendations to reduce Medicare spending, if that spending exceeds targets.</p> <p>Reduced spending on Medicare and other federal programs over 10 years.</p> <p>Reductions would be from changes to Medicare provider payment rates and federal subsidies for privately-run Medicare Advantage plans.</p> |
| Medicaid Expansion | Medicaid would be expanded to cover everyone who earns up to 150% of the federal poverty level. | Medicaid would be expanded to cover everyone who earns up to 133% of the federal poverty level. |
| Comparative Effectiveness | Support comparative effectiveness research by establishing Patient-Centered Outcomes Research Institute. | Support comparative effectiveness research by establishing Patient-Centered Outcomes Research Institute. |
| Follow-On-Biological | Create FDA pathway for quick approval for biologics. | Create FDA pathway for quick approval for biologics. |

Payer and Provider Stakeholder Views continued from page 5

Payer and Provider Organizations' Positions on Reform

| | |
|-------------------------------|--|
| AHIP ² | <p>AHIP supports strong support for comprehensive, bipartisan health care reform that covers all Americans, improves quality, and makes care more affordable. AHIP has encouraged Congress to make a renewed, system-wide effort to hold down the rising cost of medical care to put the health care system on an affordable, sustainable path. AHIP has called for bending the health care cost curve by 1.5 percentage points annually by rewarding best practices, shrinking the wide variation in care, expanding care coordination, and equipping doctors and patients to make decisions based on what works.</p> |
| NAIC ³ | <p>The NAIC recognizes that the nation's health care crisis is beyond the capacity of the states to solve independent of federal reforms. NAIC asked Congress to consider five keys for successful transformation.</p> <ul style="list-style-type: none"> ■ Protect the rights of consumers ■ Address health care spending ■ Promote state innovation ■ Stop cost shifting ■ Avoid adverse selection |
| BCBS Association ⁴ | <p>BCBSA supports reforms that make the market work for everyone by bringing more people in rather than creating a new government-run health plan that would cause millions of Americans to lose their private coverage. BCBSA's position indicates that for health care reform to work, it must include more than insurance reforms. Comprehensive reform also must improve quality, rein in rising costs and ensure everyone has coverage. This is the only way health care reform will be sustainable in the future.</p> |
| AMA ⁵ | <p>The AMA has defined seven items that reform should accomplish.</p> <ul style="list-style-type: none"> ■ Health insurance coverage for all Americans ■ Insurance market reforms that expand choice of affordable coverage and eliminate denials for pre-existing conditions ■ Assurance that health care decisions will remain in the hands of patients and their physicians, not insurance companies or government officials ■ Investments and incentives for quality improvement, prevention and wellness initiatives ■ Repeal of the Medicare physician payment formula that would trigger steep cuts and threaten seniors' access to care ■ Implementation of medical liability reforms to reduce the cost of defensive medicine ■ Streamlining and standardizing of insurance claims processing requirements to eliminate unnecessary costs and administrative burdens |
| AMCP ⁶ | <p>AMCP supports the efforts to enact comprehensive health care legislation and lists several issues of importance to AMCP members and the patients they serve, including:</p> <ul style="list-style-type: none"> ■ Follow-on-Biologics—creation of a regulatory pathway for expedited approval by the Food and Drug Administration (FDA) and either a 5- or 7-year period of data exclusivity instead of the proposed 12-year period. ■ Comparative Effectiveness Research—Patient treatment decisions should take into account clinical effectiveness and safety of prescription drugs, and a decision to utilize these drugs must be based upon the strength of credible scientific evidence and best practice. ■ Generic Exclusion Agreements—AMCP urges acceptance of the House language with regard to prohibiting generic exclusion agreements so that more generic drugs are readily available on the market. |

all commented on health care reform. Provider constituencies, such as, the American Medical Association (AMA) and the Academy of Managed Care Pharmacy (AMCP), have also submitted “wish lists” of what health care reform should entail.

The calendar flipped over to February at the writing of this article and a merged and reconciled health care reform bill remains “in progress.” All agree that the U.S. system needs revamping, but the debate on how it should be revamped continues. The main challenge is that this system is wrought with multiple contributing factors all interconnected, none of them easily unwoven or fixed with a simple solution.

SCIENCE & POLICY OPINION

HEALTH CARE REFORM

For more information, please contact Sandy.Robinson@unitedbiosource.com or Kristen.McGowan@unitedbiosource.com.

References

- ¹Kaiser Family Foundation. Side-by-Side Comparison of Major Health Care Reform Proposals. Kaiser Family Foundation website. 2010. Available at: <http://www.kff.org/healthreform/sidebyside.cfm>. Accessed January 22, 2010.
- ²American Health Insurance Plans. Speech to AHIP's Annual State Issues Conference. American Health Insurance Plans website. 2010. Available at: <http://www.ahip.org/content/pressrelease.aspx?docid=28624>. Accessed January 21, 2010.
- ³National Association of Insurance Commissioners. Health Care Reform Principles. National Association of Insurance Commissioners website. 2010. Available at: http://www.naic.org/topics/topic_health_care_reform_principles.htm. Accessed January 21, 2010.
- ⁴Blue Cross Blue Shield Association. Healthcare Reform. Blue Cross Blue Shield Association website. 2010. Available at: <http://www.bcbs.com/issues/uninsured/>. Accessed January 21, 2010.
- ⁵American Medical Association. The AMA Vision For Health System Reform. American Medical Association website. 2010. Available at: <http://www.ama-assn.org/ama/pub/health-system-reform/resources/resources-archives/our-vision.shtml>. Accessed January 22, 2010.
- ⁶Academy of Managed Care Pharmacy. Letter to Congressional Leaders Addressing Health Care Reform. Academy of Managed Care Pharmacy website. 2010. Available at: <http://www.amcp.org/amcp.ark?c=news&type=splashpage&id=674>. Accessed February 1, 2010.

Why a U.S. Reimbursement Strategy Won't Work for Europe

continued from page 2

Use of Cost-Effectiveness or Budget Impact Models

Cost-effectiveness models are used in Europe to establish the value of a new drug compared with therapies currently on the market. A reimbursement dossier is required by all European countries and a typical component of the dossier is an economic model; yet not all countries require the submission of a cost-effective and/or budget impact model. The UK does require that a model be submitted as part of the dossier and can serve as a general template or basis for other countries that require or prefer that models be included as part of the reimbursement submission.

Conversely, these types of models have been given considerable attention in academic circles in the U.S., but very little attention from payers. Large payers maintain their own models, typically focused on the pharmacy budget, populated with plan-specific utilization data as well as reflecting full knowledge of contracting and rebating agreements—resulting in a model that allows a payer to determine the financial impact of adding a new drug to formulary with a great deal of specificity.

In addition to these issues, each country has different requirements which may or may not have ramifications for other countries. Moreover, each situation is dynamic and depends on the economic or political situation of the country. Therefore, each target country with a substantial market share should be monitored closely throughout the new product's development.

The Way Forward in Developing Global Reimbursement Strategy

The solution to a comprehensive global strategy lies in developing country-specific reimbursement strategies that identify the commonalities across Europe, but also recognize the unique country reimbursement requirements. This document should be developed prior to the decision to move an asset to full commercialization and at minimum should include the following:

- Competitive landscape—including current market volume and pricing
- HTAs—the decisions for related therapies or proxies
- Potential Clinical Scenarios—identify potential sub-populations likely to benefit from the use of a new therapy
- Potential Economic and Political Situations—identify likely situations that will have an impact on reimbursement as well as a response to the threat or benefit that it poses for a new therapy

To be successful, reimbursement strategies must be constantly evaluated and augmented—much like clinical development—with the most current research to develop the most accurate launch scenario to support the product.

For more information, please contact Beth.Hahn@unitedbiosource.com, Louisa.Hefty@unitedbiosource.com, or Adam.Barak@unitedbiosource.com.

The Growing Importance of Health Technology Assessments (HTAs) in Reimbursement Decision-Making

By Julia Green, BS, Research Associate; Floortje van Nooten, MSc, Senior Research Associate and European Manager; and Robert M.A. Thwaites, MA, MCom, Senior Executive Director, Europe and Senior Scientist, Center for Health Economics and Science Policy; and William Lenderking, PhD, Senior Research Leader, Center for Health Outcomes Research

In order to decide whether a new drug or medical technology should be funded, a wide-ranging evaluation is typically needed. A formal health technology assessment (HTA)—the systematic evaluation of evidence gathered to consider the medical, social, economic, and ethical implications of the development, diffusion, and use of medicines, devices, and other

Governments and payers are increasingly relying on HTAs to help with funding and reimbursement decisions.

health-related technologies—can help structure and facilitate this evaluation. Governments and payers are increasingly relying on HTAs to help with funding and reimbursement decisions.

This development has provided significant challenges for companies, particularly pharmaceutical companies. Not only is the use of HTAs expanding rapidly (there are now over 40 national agencies globally, each with its own standards and procedures for HTA evaluation), but evaluation methods are continually evolving as technologies advance and health care structures and organizations change. HTA considerations are assuming an increasingly important role in the process of drug development, with pharmaceutical companies being required to produce evidence of effectiveness and cost-effectiveness in order to gain market access and reimbursement in a number of markets.

In order to understand the landscape for HTAs across the world, United BioSource Corporation (UBC) conducted a review of HTA requirements in 10 markets. Three key issues were examined for each country: initial market access (including market authorization and reimbursement), pricing, and continued market access. The use of HTAs and the typical process of market access are different across countries.

Achieving market access for a new product typically involves a number of steps. In all countries, approval by a regulatory body is required before a product is authorized for use. This approval depends on the safety, efficacy, and quality data for a new product or indication. If a product is to be funded or reimbursed, additional conditions must be fulfilled before

a product can be launched or marketed. These criteria vary among countries but can include effectiveness, safety, drug price, budget impact, and cost-effectiveness, and can be assessed at a national level, sub-national or regional level, or in the case of the United States, by the payers. For pricing, the most common alternatives are that either the manufacturer has discretion in setting the price of the product or the manufacturer negotiates with the appropriate department within the ministry of interest to determine the price. Continued approval for a certain price or expanded or continued access to the market may require additional post-marketing evidence from the sponsors. Below, we provide three short examples of how HTA is conducted in the United Kingdom (UK), Japan, and the United States (U.S.). These countries were selected as case studies because they represent both the broad variability in HTA processes globally and also reveal similarities.

The National Institute for Health and Clinical Excellence (NICE) in the UK is well established and arguably the most stringent HTA body in the world. Both cost-effectiveness and clinical evidence are important factors in the Institute's reviews and recommendations, with clear requirements for literature review and epidemiological information, and set standards for complex, indirect comparison analyses and economic evaluations. Reviews are conducted by a large committee of academics and researchers drawn from universities in the UK and can take six to nine months to complete. Reviews can entail independent reconstruction of economic models submitted by sponsors, among other steps. Recommendations are then made based on explicit thresholds for cost-effectiveness.

In contrast, HTAs have not yet played a major role in Japan or the U.S. Japan's primary criterion for obtaining favorable reimbursement is clinical benefit. Health economic data may be filed along with clinical data, although this is not listed as an essential component of the submission. Once marketing approval has been granted, application for reimbursement must be filed with the Ministry of Health, Labor and Welfare (MHLW) in order to be listed on the National Health Insurance reimbursement list (i.e., a national formulary). The reimbursement price for new treatments is usually determined on the basis of comparison with existing drugs from the same category in Japan and other markets, although new drugs can receive premiums for innovation, usefulness, and market size. If no comparable price is available for a new drug, the price calculation is based on cost-plus methodology, whereby production/import costs, promotion expenses, general administrative expenses, distribution expenses, operative profit, and consumption tax are summed in order to determine pricing. In 2007, the MHLW; the Education, Culture, Sports, Science and Technology (MEXT); and the Economy, Trade and Industry (METI) passed a "5-Year Strategy for the Creation of Innovative Pharmaceuticals and Medical Devices" with the aim of boosting the Japanese pharmaceutical/medical devices industry and streamlining

review processes. Their goals included an accelerated review process, higher standards for clinical trials, and the expansion and improvement of review staff. Although these strategies mark modifications in the Japanese health care system, change is expected to be slow.

Unlike the UK or Japan (and many other countries), the U.S. has no central authority or consortium of ministries responsible for formal assessments of new therapies. A product can be marketed with FDA approval alone, although comparative effectiveness evaluations are beginning to assume greater importance. Payers control access through formulary listings on different tiers, usually with generic medications on Tier 1, preferred branded products on Tier 2, and other branded products on Tier 3. Each tier is associated with different co-payments, with Tier 3 requiring the greatest contribution from the patient. Currently, the most important private organizations involved in HTA-like evaluations are large health plans such as Wellpoint, with cost-effectiveness analyses and budget impact models often included in these HTAs. There is no formal requirement for demonstration of cost-effectiveness for public insurers (Medicare and state Medicaid). Although the U.S. health care system is likely to change over the next few years, the initial focus may be more related to coverage expansion than methods of decision making for new treatments.

Similarities across countries in how HTA is applied seem to be related to general methodological considerations (e.g., the use of cost-effectiveness data, the acceptability of modeling), whereas the differences reflect both national and cultural values around health care and some of the details around assumptions and the type of evidence required (e.g., discount rates applied, cost-effectiveness threshold, economic perspective adopted). Given the nature of decision making in health care systems, these detailed differences will continue to reflect the local diversities that are present for each country.

An important focus of HTA will continue to be geared towards supporting countries' efforts to contain health care costs. Next to price cuts, clawback systems (i.e., repayments to the government when financial gain arises from unforeseen trading benefits, discounts or parallel trade) and rebates, other measures will be put in place. For example, some risk-sharing schemes (where the drug manufacturer shares some financial responsibility for the health outcomes produced) have already been created in the UK, and it is expected that patient access schemes, risk-sharing schemes, and co-pays will continue to expand as a way for payers or agencies to shift the cost burden (and also the risk burden) on to other parties.

Furthermore, the evidence to justify the value of a product will become increasingly important, with stricter requirements for initial market access as well as continued reimbursement for the product after market launch. HTA studies may need

to be completed earlier in the drug development lifecycle; a number of countries (Australia, for example) are exploring how to bring the timing of reimbursement decisions in line with the timing of decisions on market approval. Transparency in the HTA process across markets will also assume increased importance, allowing for greater accountability in the use of HTAs in decision making.

Finally, greater collaboration and discussions among the health authorities of different countries are expected. NICE, for example, is passing on advice to an increasing number of developed, as well as developing, countries interested in health care reform. For the foreseeable future, HTAs are likely to play an increased role in the adoption and reimbursement of new products around the globe. Sponsors will need to consider HTA requirements as another important factor in drug development programs in order to ensure market access.

For more information, please contact
Julia.Green@unitedbiosource.com,
Floortje.Vannooten@unitedbiosource.com,
Rob.Thwaites@unitedbiosource.com, or
William.Lenderking@unitedbiosource.com.

Quantitative Risk-Benefit: A Case Study of Glaucoma Treatments

By Andrew Maguire, BSc, MSc, FSS, Director, Europe, Center for Epidemiology & Database Analysis; Gerald Faich, MD, MPH, Senior Vice President, Risk Management and Epidemiology

The aim of risk management for pharmaceuticals is to minimize the harmful effects of therapies and thereby improve the benefit-to-risk balance. However, the evidence on either side of this balance varies in availability and quality. Benefit and risk may be implied from clinical trials, measured as efficacy and safety, which are conducted prior to drug licensing. However, it has become evident that more post-approval data, often from observational studies conducted in large populations following the drug launch, are needed to define risk and benefit.

Clinical trials, while often considered the keystone for medical evidence, are subject to important limitations when translating efficacy to real-world effectiveness as the experimental conditions may not reflect the use of the drug in clinical practice. Although safety events are recorded, clinical trials are not usually designed or powered to detect low incidence outcomes or outcomes that may occur after long-term exposure beyond the duration of the trial. Furthermore, susceptible patients are often excluded from the trials and protocol-induced effects likely occur. For these reasons, observational studies are needed to complement evidence on benefits and especially risks.

continued on page 10

Quantitative Risk-Benefit: A Case Study of Glaucoma Treatments

continued from page 9

When considering risk benefit balance, there are two types of balance to consider; first, where both harm and benefit are considered together, and, secondly, where only the relative impact of different safety profiles of therapeutic options are compared. This latter scenario can also be termed as Comparative Harm. Such an evaluation is relevant if the drugs have similar effectiveness or if the benefit affects quality of life and the key concerns reside on life-threatening adverse events. Furthermore, these evaluations can be used to examine the likely impact of risk minimization strategies, such as, labeling effects and expanded risk communication programs.

An illustrative example is the study of glaucoma therapy and risks of congestive heart failure (CHF) and pulmonary effects.^{1,2} These risks were examined because one of the

When considering risk benefit balance, there are two types of balance to consider; first, where both harm and benefit are considered together, and, secondly, where only the relative impact of different safety profiles of therapeutic options are compared.

first line therapies, timolol maleate, has been associated with these outcomes.³ The target patient population treated was glaucoma patients obtained from The Health

Improvement Network, "THIN", a UK longitudinal primary care patient database. These patients were characterized according to the risk factors for the outcomes. The next step was to obtain risks of the outcomes from the general population according to the same set of risk factors as the patient population. The entire adult population in the database was followed for 12 months and provided 1.53 million person years from which the incidence and recurrence rates were calculated for each outcome. The resulting risks were assigned to each patient according to the levels of the risk factors.

The expected number of events was then calculated by simply summing the risks for the entire patient group. However, this number represents events in an untreated patient group as the risks are those of the reference population. Therefore, we created scenarios of exposure to timolol by multiplying the risks by published relative risks; the increased risk of incident asthma/chronic obstructive pulmonary disorder (COPD) was 20% and for exacerbation was 47%, and the increased risk of CHF was 20%.⁴⁻⁶ The comparator, latanoprost, was deemed to have no increased risk as it has no systemic

absorption. The number of events is the total expected over one year, and for clarity they were adjusted to a population of 10,000 patients.

For timolol, the expected asthma and COPD events were 212 compared to 145 for latanoprost patients. Similarly, the number of CHF events was 113 for timolol compared with 94 for latanoprost. Subtracting the latanoprost numbers from those for timolol provided the comparative harm estimates.

To examine the theoretical effect of labeling for timolol which contraindicates its use in CHF, asthma and COPD, we modeled the data as follows. From the patient characteristics, we knew that 19% would be contraindicated for timolol. If we then give latanoprost to these patients and timolol to the other 81%, we are essentially modeling a scenario of perfect adherence to the contraindication. We estimated that contraindication would remove a majority of the excess cases as there would be 66 fewer asthma/COPD events and 10 fewer CHF events among the 10,000 glaucoma patients.

This example would indicate that while timolol is potentially more harmful, from a public health perspective, this is minimized if the product contraindications are actually followed.

The glaucoma example has shown that we can use a medical database to provide input parameters for models. However, the described study has limitations in that it does not account for overall mortality or case-fatality and assumes full exposure for one year. Furthermore, it has not accounted for uncertainty in the risk estimates or the relative risk estimates. These issues can be addressed by Discrete Event Simulation (DES), which also offers a natural framework for the synthesis of evidence from medical databases, registries, published observational studies and clinical trials.²

For more information, please contact
Andrew.Maguire@unitedbiosource.com or
Gerald.Faich@unitedbiosource.com.

References

- ¹Maguire A, MacLachlan S. Quantification of Patient Population Impact of Contra-indications: Glaucoma Therapy. *Pharmacoepidemiology and Drug Safety*. 2009; 18:S1-S274(234).
- ²Maguire A, Douglas I, Blak BT. The Application of Discrete Event Simulation to Quantitative Risk Benefit Analysis. *Value in Health*. 2009; 12(7):A453.
- ³Stewart WC, Garrison PM. B-Blocker-Induced Complications and the Patient with Glaucoma, Newer Treatment to Help Reduce Systemic Adverse Events. *Archives of Internal Medicines*. 1998; 158:221-226.
- ⁴Hugues F, et al. Effects of Beta-Adrenoreceptors Blocking Eye Drops in Patients with Chronic Bronchitis. *Therapie*. 1992; 47:211-215.
- ⁵Confalonieri M, et al. Severe Bronchial Spasm Crises Induced by Topical Administration of Eyedrops with Timolol Bas, a Non-Selective Beta Blocking Agent. *Recenti Prog Med*. 1991; 82:402-404.
- ⁶Huerta C, et al. The Risk of Obstructive Airways Disease in a Glaucoma Population. *Pharmacoepidemiology and Drug Safety*. 2001; 10:157-163.

Upcoming Presentations

European Pharmaceutical Reimbursement & Market Access Conference

Mar 8 – Mar 9, 2010, London, UK

Session Presentation

Pricing, Reimbursement and Market Access Strategies for Orphan Medicines **Adam Barak**, Head, International Pricing and Reimbursement, United BioSource Corporation

DIA Evidence-Based Medicine and Health Technology Assessment: Moving from Separate Appraisals to Synergistic Communications

Mar 23, 2010, Washington, DC, USA

Panel Session

Designing Studies for Better Evidence **Bryan Luce**, PhD, Senior Vice President, Science Policy, United BioSource Corporation

Poster Presentation

Do Comparative Effectiveness Reviews Make an Impact? A Case Study of AHRQ Effective Health Care Program Reports **Hunter C, Singer Cohen R**

2010 American Academy of Neurology (AAN) Annual Meeting

April 10 – April 17, 2010, Toronto, ON, Canada

Poster Presentations

Determinants of Migraine-Related Disability Lipton RB, Blumenfeld A, **Ishak KJ**, Varon SF, **Kawata AK**, Manack A, Buse DC, Goadsby PJ

Relationship Between Headache Frequency and Migraine-Related Disability in the International Burden of Migraine Study (IBMS) **Wilcox TK**, Blumenfeld A, Varon SF, **Payne KA**, Manack A, Buse DC, Goadsby PJ, Lipton RB

Digestive Disease Week 2010

May 1 – May 5, 2010, New Orleans, LA, USA

Poster Presentation

Prevalence of Constipation and Fecal Incontinence in Men and Women with Overactive Bladder and Lower Urinary Tract Symptoms Cash BD, **Coyne KS**, Kopp ZS, **Gelhorn H**, Berriman S, Khullar V

19th Annual Partnerships in Clinical Trials

Apr 12 – Apr 14, 2010, Orlando, FL, USA

Presentation

RiskMaps, Registries and REMS: Next Generation PMR and Obligations to Meet Regulatory Standards and Enhance Patient Safety **Annette Stenhagen**, DrPH, FISPE, Senior Vice President, Epidemiology, Registries and Risk Management, United BioSource Corporation

2010 American Thoracic Society (ATS) International Conference

May 14 – May 19, 2010, New Orleans, LA, USA

Poster Presentations

Patient Willingness To Pay For Specific Attributes Of Maintenance Medication For COPD **Kleinman L, Kawata AK, Harding G, Ramachandran S**

Reliability And Validity of The Shortness of Breath With Daily Activity (SOBDA) Questionnaire: A New Outcome Measure For Evaluating Dyspnea In COPD **Wilcox T, Chen WH, Howard KA, Cates CE, Wiklund I**, Watkins ML, Brooks J, Tabberer M, Crim C

Oral Presentations

Session: Celebrating the 25th Anniversary of the National Institute of Nursing Research (NINR)

Intramural Research: Improving Functional Outcomes in COPD **Nancy K. Leidy**, PhD, Senior Vice President, Scientific Affairs, United BioSource Corporation

Session: Meet the Professor

Objective Measurement of Subjective Phenomena: Patient-Reported Outcome Measurement in Clinical Studies **Nancy K. Leidy**, PhD, Senior Vice President, Scientific Affairs, United BioSource Corporation

Statisticians in the Pharmaceutical Industry (PSI) Meeting on Patient Reported Outcomes

June 2, 2010, London, UK

Oral Presentation

Interpreting Change Over Time in Patient-Reported Outcomes **Kathy Wyrwich**, PhD, Senior Research Leader, Center for Health Outcomes, United BioSource Corporation

ASCO 2010 Annual Meeting

June 4 – June 8, 2010, Chicago, IL, USA

Presentation

Economic Analysis of Decitabine Versus Best Supportive Care in the Treatment of Intermediate and High Risk Myelodysplastic Syndromes (MDS) Kim E, **Pan F, Peng S, Fleurence R**

DIA 46th Annual Meeting

June 13 – June 17, 2010, Washington, DC, USA

Panel Sessions

Can a Risk Management Program Save a Product from Withdrawal? **Gerald Faich**, MD, MPH, FISPE, Senior Vice President, Epidemiology, Registries and Risk Management, United BioSource Corporation

Document Preparation When You're Short on Time **Michael Hoffman**, Senior Director, Medical Writing and Regulatory Operations, United BioSource Corporation

Incorporating Risk Management Strategies Into Premarketing Clinical Trials **Annette Stenhagen**, DrPH, FISPE, Senior Vice President, Epidemiology, Registries and Risk Management, United BioSource Corporation

Innovations in Combining Patient-Reported Outcomes with Physiologic Measurements to Leverage Real-Time Access to Data **Sonya Eremenco**, MA, Senior Research Associate, ePRO Manager, United BioSource Corporation

Patient Recruitment in a Technological Era **Abbe Steel**, Executive Director, Trial Enhancement, United BioSource Corporation

Payer Perspectives of Evidence-based Medicine and Comparative Effectiveness: Making Evidence Matter in the Marketplace **Craig A. Hunter**, MPP, PGDP, Senior Science Policy Analyst & Senior Manager, Science Policy, United BioSource Corporation

Personalized Medicine: Are We There Yet? **Georgia Mitsi**, PhD, Manager – Executive Scientific Support, Health Economics, United BioSource Corporation

Qualification of Patient-reported Outcome (PRO) Tools to Support Labeling Claims: Development, Evaluation, and a Consortium Approach **Nancy Kline Leidy**, PhD, Senior Vice President, Scientific Affairs, United BioSource Corporation

REMS Evaluations: What Have We Learned? **Kelly Davis**, MD, Vice President, Medical and Scientific Solutions, Epidemiology, Registries and Risk Management, United BioSource Corporation

What Deliverable? Importance of Close Collaboration between Data Management and Other Functions **Carol Matthews**, Senior Director, Clinical Programming, United BioSource Corporation

FOCUS ON:

Patient-Reported Outcomes

The Value of Endpoint Models and Conceptual Frameworks to PROs



*By Karin S. Coyne, PhD,
Senior Research Leader, Center
for Health Outcomes Research*

The inclusion of endpoint models and conceptual frameworks into clinical trial planning provides the opportunity for Sponsors to clearly plan their goals for including patient-reported outcomes (PROs) into a clinical trial—to begin with the end in mind. As a component of the FDA Final Guidance document,¹ the importance of an endpoint model cannot be understated as the endpoint model outlines how the product will impact the PRO and provide clear communication of the health outcome benefit. It answers the question of how a Sponsor expects its compound, biologic or device to affect the disease pathology to ultimately impact patient outcomes.

PROs can be primary, secondary, tertiary, or exploratory endpoints. The FDA guidance provides two examples of PRO endpoints. Figure 1 depicts a PRO symptom assessment as a secondary endpoint with a physiologic measure as the primary endpoint. As such, the physiologic endpoint would need to meet success before success could be attained on the secondary endpoints. The clinical trial objectives, design, sample size and statistical analysis are all based on the primary endpoint.

Figure 1. Endpoint Model: Treatment of Disease X¹

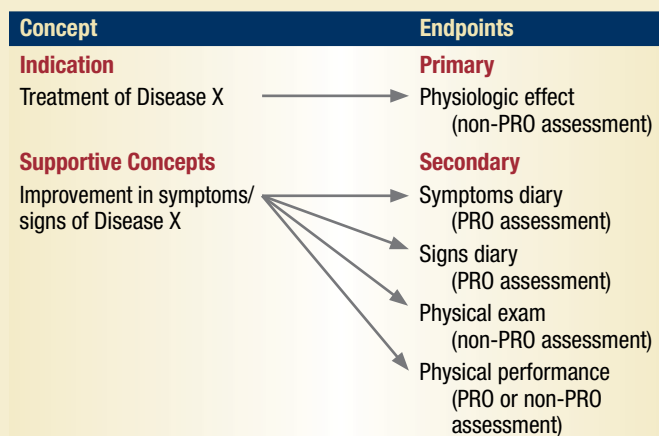


Figure 2 depicts a PRO symptoms assessment as the primary endpoint with physical limitations and physical performance as secondary endpoints. Again, the clinical trial objectives and design are based on the primary endpoint, which in this case is the PRO.

Endpoint models are essential to clearly dispelling ambiguity regarding physiologic impact and patient outcome—particularly when the outcome is distal to the disease. As noted in Figure 3,

outcomes that are more distal to the condition or disease (e.g., emotional well-being or distress related to urinary incontinence) are more difficult and complex to demonstrate than outcomes that are more proximal to the condition or disease (e.g., pain related to migraine). An endpoint model maps the connection of disease to outcome and ultimately supports targeted claims of the concepts being measured.

Figure 2. Endpoint Model: Treatment of Symptoms Associated with Disease Y

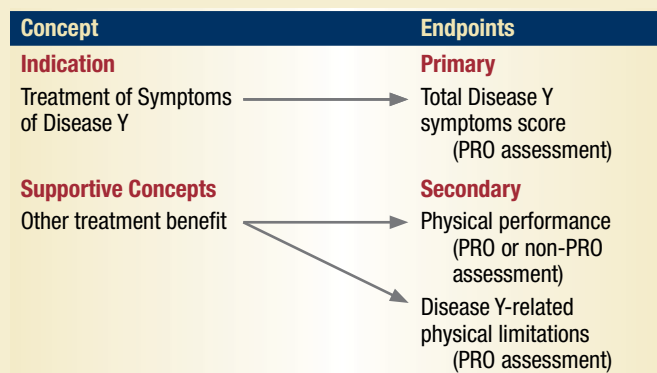
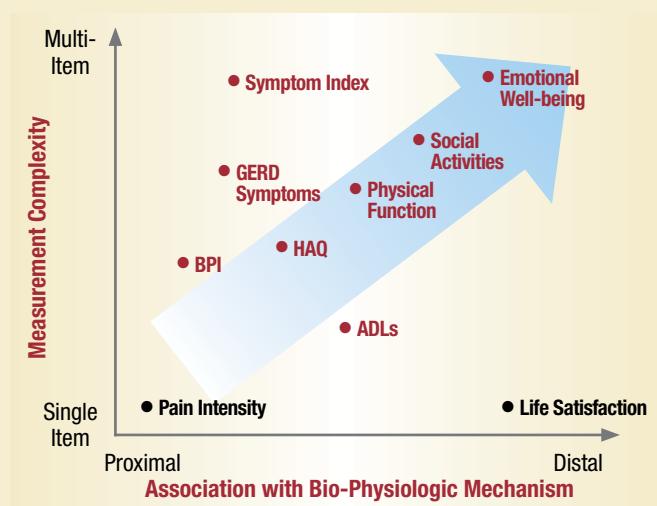
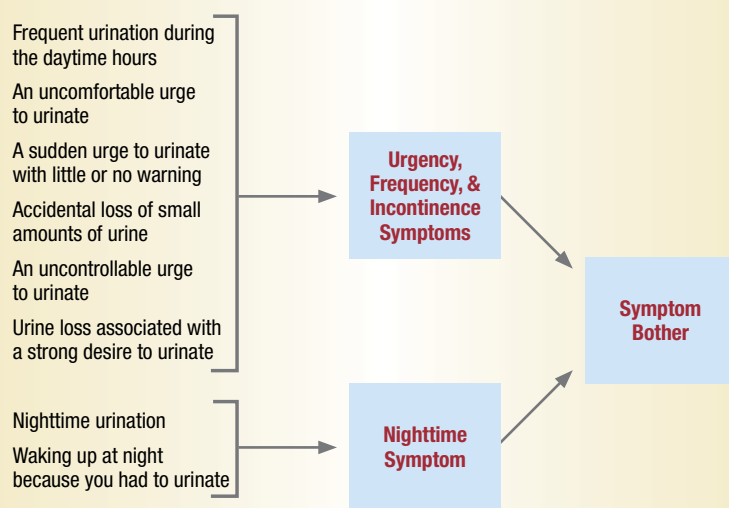


Figure 3. Relationship of Disease to Outcome (aka Index of Regulatory Concern and PRO Evidence)²



Thinking this pathway through is critical in developing not only the endpoint model, but conceptual frameworks as well. The conceptual framework outlines each individual question within the PRO to the concept being measured. In Figure 4, a conceptual framework of Symptom Bother related to overactive bladder (OAB) is displayed. This is an 8-item symptom bother scale which focuses on the cardinal symptoms of OAB; thus being a condition- and concept-specific PRO. Empirical evidence is available to support this PRO as an outcome in terms of content validity³, psychometric validity³ and responsiveness⁴ among OAB patients. Such evidence is needed to support item grouping, scoring, and use in clinical trials.

Figure 4. Diagram of the Conceptual Framework of a PRO Instrument



The inclusion of endpoint models and conceptual frameworks facilitates FDA review of PROs as endpoints in clinical trials as well as providing a foundational road map of the relevance and measurement of the PRO in the clinical trial. The time spent developing, planning, and refining endpoint models and conceptual frameworks is time well spent to ensuring a successful outcome during FDA review.

For more information, please contact
Karin.Coyne@unitedbiosource.com.

References

- ¹Food and Drug Administration. Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *Federal Register*. 2009;1-39.
- ²Revicki D, Cella D, et al. Conceptual Frameworks and Guidance on Statements about PRO Findings in Product Labels and Promotional Materials. ISOQOL Patient-Reported Outcomes and Global Regulatory Environment, Lisbon, Portugal, 2006.
- ³Coyne K, Revicki D, et al. Psychometric Validation of an Overactive Bladder Symptom and Health-Related Quality of Life Questionnaire: The OAB-q. *Qual Life Res*. 2002; 11(6): 563-574.
- ⁴Coyne KS, Matza LS, et al. The Responsiveness of the Overactive Bladder Questionnaire (OAB-q). *Qual Life Res*. 2005; 14(3): 849-855.



Common Ground— Defining Content Validity

By William R. Lenderking, PhD, Senior
Research Leader, Center for Health
Outcomes Research

The measurement of subjective variables has a long history. Codifying rules for evaluating the reliability and validity of these measurements also has a long history, developed in parallel. After all, according to the Standards for Educational

and Psychological Testing,¹ the standard manual developed by the American Psychological Association, National Education Research Association, and National Council on Measurement in Education (NCME), “Validity refers to the degree to which evidence and theory support the interpretations of test scores entailed by the proposed tests.” (p 9).¹ In outcomes research, a relatively young field, there has been varying levels of awareness and adherence to the standards established in other fields. This created a lot of inconsistency in how measures were developed, validated, and interpreted in the decade leading up to 2006. This, of course, was part of the impetus for the Food and Drug Administration (FDA) to develop its Draft Guidance for Patient Reported Outcomes (PROs),² released in 2006, and now the Final Guidance for Patient Reported Outcomes³ released in December 2009. Ambitiously, the first guidance tried to identify best practices for the field, whereas the final guidance retreated somewhat to identify the criteria by which PROs submitted to the

FDA for labeling indications would be evaluated. Prior to the release of these guidances, instrument developers lacked clear instructions from regulators by which they could develop a PRO for the purposes of a label claim, resulting from inconsistent requirements across different disease areas, and confusion by sponsors about expectations for submissions. The guidances were designed to reduce ambiguity and increase the efficiency of review, at least partly, but they have generated both light and heat. One key area of continued emphasis, not without controversy (at least in application), is content validity.

The purpose of this paper is to explicitly review some of the standards of instrument development and validation put forward by the American Psychological Association, National Education Research Association, and NCME in their manual *Standards for Educational and Psychological Testing*,¹ to look for points of agreement and departure, and in particular, to see what their current standards are on content validity. Standards have been evolving for many years; standards regarding the definitions of reliability and validity were first written down in a manual back in 1954, with a number of revisions and iterations put forward subsequently, culminating in the revised manual in 1999. The term “content validity” has changed over time, and was defined in the 1974 manual as an “aspect of validity that was ‘required when the test user wishes to estimate how an individual performs in the universe of situations the test is intended to represent.’” In 1985, the term was changed to “content-related evidence” and now is characterized as “evidence based on test content.” (p 174).¹ Interestingly, the term “content validity” hardly appears in the current manual at all. Secondly, there is a general move away from parsing validity into different subtypes. For example, concurrent validity, criterion validity, known groups validity, etc., should not be considered different things, but rather simply examples of the types of evidence needed to support the interpretations of scores. Furthermore, the term “construct validity” is now

continued on page 14

FOCUS ON:

Patient-Reported Outcomes

Defining Content Validity

continued from page 13

deemed redundant, since all validity refers to the validity of constructs.

Third, the acceptability of a test does not depend upon satisfaction of every single standard in a literal manner, but should rest upon professional judgment, the degree to which standards have been met, the availability of alternatives, and the feasibility of satisfying the standards. Furthermore, blanket claims that tests meet standards should not be made, and since the field is evolving, standards need to be continuously re-evaluated. Finally, construct under-representation and construct-irrelevant variance are two of the most important threats to validity. Construct under-representation is exemplified when the FDA says they are not sure that all aspects of the domain of interest have been captured in the PRO measure. Construct-irrelevant variance occurs when items are included that are not central to the concept being measured. The emphasis on content validity as assessed by capturing the patient's voice is designed to address these threats to validity. It is important to remember, however, that "nearly all tests leave out elements that some potential users believe should be measured and include some elements that some potential users consider inappropriate." (p 10)¹ This is another way of saying that nearly anyone can find fault with a test, whether they be a patient, an outcomes researcher, or a regulator. I make these points to assert that nowhere in the Standards manual does it suggest that content validity is the most important aspect of validity, but that evidence based upon test content is only part of an overall set of evidence to support the interpretation of a particular test score for a certain purpose. Theory and empirical evidence must always be combined to make a valid instrument.

So what defines content validity in the regulatory context? Clearly, qualitative research that links questionnaire items back to patient reports is critical. Saturation, which occurs when successive groups of study participants are providing no new information about a concept under discussion, must be documented as well. But what happens when a symptom is only mentioned by one out of 16 patients in two groups. How can the risk of introducing construct-irrelevant variance be avoided? Consider also the Patient-Reported Outcomes Measurement Information System (PROMIS) initiative, a major National Institute of Health (NIH)-funded initiative to develop new measures of health outcomes using cutting-edge statistical and psychometric technology. During the same time period in which the FDA PRO guidances were being developed, the PROMIS initiative was seeking to move measurement forward through an entirely different approach based on item response theory, item banks, and computer adaptive testing (CAT). Without overlooking the issue of content validity, PROMIS

instruments are designed to cross illnesses, ages, sex, and lifestyles, measuring concepts like pain, sleep, psychological well-being, and social functioning. It is not, however, feasible to test every possible combination of demographic and disease-related factors qualitatively, given the large number of items and domains being evaluated. It is not feasible, and it may be not necessary, simply because interviewing the hundreds of individuals that would be required to fulfill all the demographic combinations would simply not yield enough unique information to make it worth the effort. It is clear that some qualitative research is necessary in order to inform content validity, but how much is enough? How will the FDA evaluate the content validity of the PROMIS item banks?

Generalizability is another critical question: will the content validity of a scale in one population generalize to another? How about a disease syndrome across different demographics, or a symptom across different diseases (e.g., is fatigue in diabetes different from fatigue in AIDS, and if so, how)?

Establishing the validity and reliability of a test score for a particular purpose (such as the measurement of depressed mood as a method for evaluating the efficacy of an antidepressant) is an ongoing process, requiring both qualitative and quantitative approaches. It is not possible to arrive at the level of 100% certainty, but it is possible to estimate the probability of having a valid instrument. It is useful to consider the current guidelines from the FDA in light of standards that have evolved over a 100-year time period in other fields. There is much in the way of agreement between the two sets of guidelines, but the agreement is not complete. In particular, the emphasis on content validity as the most important form of validity is not present in the Standards for Educational and Psychological Testing. Elevating content validity to pre-eminent status in the process of evaluating the reliability and validity of instruments is therefore a) not consistent with well-accepted standards in the field of psychometrics, and b) ironically may increase the risk of evaluating instruments based on subjective opinions, which both the emphasis on the voice of the patient and many years of quantitative methodological development were designed to avoid.

For more information, please contact
William.Lenderking@unitedbiosource.com.

References

- ¹American Psychological Association, National Council on Measurement in Education, American Educational Research Association. Standards for Educational and Psychological Testing. Washington DC: American Educational Research Association 1999.
- ²Food and Drug Administration. Draft Guidance for Industry on Patient-Reported Outcomes Measures: Use in Medical Product Development to Support Labeling Claims. *Federal Register*. 2006.
- ³Food and Drug Administration. Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *Federal Register*. 2009; 74(235):65132-65133.

The MID is Dead. Long Live the MID.



By Kathy Wyrwich, PhD, Senior Research Leader and Louis Matza, PhD, Research Scientist, Center for Health Outcomes Research



As if announcing the death of one king while trumpeting a successor to the throne, the 2009 FDA PRO Guidance has eliminated the term minimum important difference (MID) in their directives for patient-reported outcomes (PROs) label claims.¹ However, given the role that the MID concept has played in the development and understanding of PROs over the past 30 years, the use of this term is likely to continue when discussing the interpretation of PRO change over time.

The reason for the demise of the MID is presumably its frequent misuse. The MID is a threshold for an individual's change over time. However, the MID has often been applied when interpreting the magnitude of differences between active treatment and placebo groups' mean changes in clinical trials. Hopefully, the use of an individual-based change threshold to inform interpretation of meaningful group changes for PRO labeling claims has ended with the elimination of the MID terminology in the 2009 PRO Guidance.

The Food and Drug Administration (FDA) has named the responder definition as a successor to the MID. The responder definition is a minimum important change threshold for identifying meaningful PRO improvement, defined in the 2009 PRO Guidance as "the individual patient PRO score change over a predetermined time period that should be interpreted as a treatment benefit."¹ The FDA wants the responder definition to be determined empirically through anchor-based methods using the targeted population, and this key threshold will be evaluated by the FDA within the context of each specific clinical trial. Once a responder definition is ascertained, the percentage of responders in each treatment arm achieving change at or beyond this threshold can be compared to facilitate the evaluation and communication of PRO results to patients, physicians, and providers.

Two examples of anchor-based methods are provided in the 2009 PRO Guidance: 1) a 50% reduction in incontinence episodes; and 2) patient ratings of change at different time periods or upon exit from a clinical trial. Distribution-based methods, like the standard deviation and the standard error of measurement are also mentioned, but the distribution-based methods are recommended only as supportive evidence to the anchor-based results, and not for use as the sole basis for the responder definition.

The responder definition, however, is not the only named successor to the MID. In the 2009 PRO Guidance, the

FDA recognizes that selecting a threshold for a meaningful response to treatment can be subjective. Therefore, the Guidance offers sponsors the option of presenting PRO change results in terms of a cumulative distribution function. This two-dimensional graph includes separate curves for treatment and placebo groups, with x-axis coordinates conveying PRO change from baseline and y-axis coordinates indicating the proportion of patients achieving these levels of change. With this diagram, the percentage of patients in each treatment group achieving a spectrum of change thresholds can be easily compared, eliminating the need for a specific responder definition to interpret the PRO changes in each group.

Two examples of cumulative distribution functions are provided below. Figure 1, adapted from a 2006 FDA labeling guidance,² depicts two drugs that have relatively similar PRO improvement (i.e., score decreases indicating improvement). When a 2 point reduction is examined ($x = -2$), approximately 54% of patients in both Drug A and Drug B treatment groups had a change score less than or equal to -2 . When there is no change ($x = 0$), which could be a responder definition for a deteriorating disease, there are approximately 85% responders in both treatment groups. In Figure 1, there are few places along the change score continuum (ranging from -8 to $+3$) where Drug A and Drug B differentiate in the cumulative percentage of responders.

Figure 1

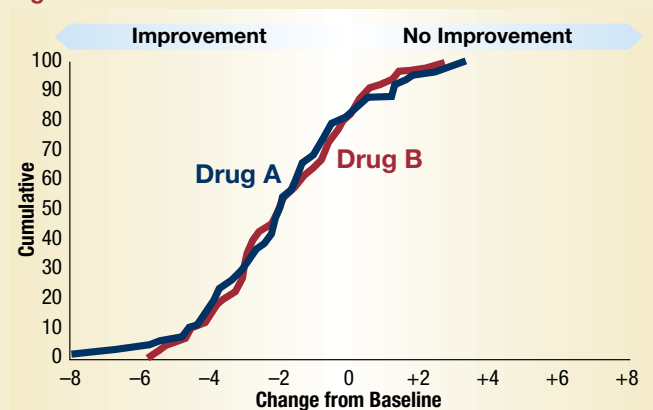
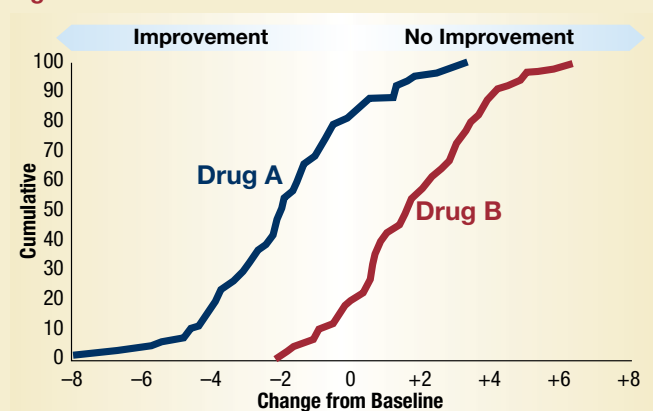


Figure 2



continued on page 16

FOCUS ON:

Patient-Reported Outcomes

The MID is Dead.

continued from page 15

In contrast, the cumulative distribution function in Figure 2 demonstrates a separation between the two treatment groups throughout the range of change scores, with a stronger PRO effect for Drug A than for Drug B. Whether the responder threshold is set at -2 points (55% vs. 3%) or 0 points (85% vs. 20%) or any other possible change score along the x-axis, Drug A outperforms Drug B with regard to the cumulative percentage of responders.

The 2009 FDA Guidance represents another step in the evolution of terminology we use to describe PRO change. The MID term originally emerged because of this need to compare and interpret change over time in PRO scores. Jaeschke, Singer and Guyatt realized that with very little change, the Chronic Heart Failure Questionnaire could demonstrate statistically significant results (e.g., $p < 0.05$) that may not be meaningful to patients.³ As a result, they conducted an anchor-based study using patient ratings of change, and they named the resulting responder threshold the minimal clinically important difference or the MCID. The “clinically” part of this term was later dropped because there were only patient-reported anchors and outcomes used in the process, yielding the simpler term “MID.”⁴ In due course, ascertaining this MID for interpreting change over time has become an essential responsibility in PRO instrument development and use. The 2009 PRO Guidance may have extinguished the term in PRO label claim documentation for the good reason described above, but the need to determine whether PRO changes are truly important to patients clearly endures. Long live the MID, regardless of its current name.

For more information, please contact
Kathy.Wyrwich@unitedbiosource.com, or
Louis.Matza@unitedbiosource.com.

References

- ¹Food and Drug Administration. Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *Federal Register*. 2009; 74(235):65132-65133.
- ²Food and Drug Administration. Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products—Content and Format. *Federal Register*. 2006; 71(15):3999-4000.
- ³Jaeschke R, Singer J, Guyatt GH. Measurement Of Health Status. Ascertaining the Minimal Clinically Important Difference. *Control Clin Trials*. 1989; 10(4):407-415.
- ⁴Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining A Minimal Important Change In A Disease-Specific Quality Of Life Instrument. *J Clin Epidemiol*. 1994; 47: 81-87.



The Consortia Approach to Developing PRO Instruments: Realizing the Potential of Collaborative Efforts

By Asha Hareendran, PhD, Senior Research Scientist and Nancy Kline Leidy, PhD, Senior Vice President, Scientific Affairs, Center for Health Outcomes Research



Recognition that the patients' point of view can play a key role in understanding the benefits and risks of

health care interventions is reflected in the increased use of patient-reported outcomes (PROs) in pharmaceutical and device trials. This, in turn, has led to the development of regulatory guidance documents outlining the empirical evidence required to support “claims” related to labeling and promotion of pharmaceutical and device products. The European Medicines Agency (EMA) health-related quality of life (HRQL) reflection paper¹ came into effect in January 2006 offering guidance in study requirements for these endpoints. In February 2006, the U.S. Food and Drug Administration (FDA) released their PRO Draft Guidance² outlining the agency's view of the necessary performance properties of PROs used to support labeling claims, with the final version of this document released in December 2009.³

The development and validation of PRO instruments to evaluate treatment outcomes is often lengthy and resource intensive, including substantial investments of time and financial support. Regulatory guidance documents make it clear that the concept to be evaluated needs to be relevant to the patient experience and useful for clinical decision-making. Scores from the instrument must be reliable, valid, responsive to changes resulting from treatments, and interpretable. Regulatory agencies require empirical evidence supporting all of these dimensions of PRO measurement together with evidence of sound clinical trial design, execution, and analyses and significant, interpretable study results before a PRO will be approved for labeling or promotional purposes.

The Time is Right for Collaboration: Sharing Expertise and Resources

Recognition of the value of PRO data, and the increasing demand for rigorous evidence to support the use of these

tools to support treatment benefit claims, have led to various forms of collaboration to pool knowledge and resources. Through scientific organizations like the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the International Society for Quality of Life Research (ISO-QOL), and the Drug Information Association (DIA), experts from academia, regulatory agencies, and industry are sharing their knowledge through special interest groups and task forces dedicated to the development of good research practices for generating PRO evidence supporting the value of medical treatments.

Over the past several years, interest has also grown in the development of consortia of pharmaceutical sponsors to share knowledge and resources in the pre-competitive context for the development of standardized outcome measures for use in clinical trials. UBC is leading two of these new consortia initiatives, the EXAcerbations of Chronic pulmonary disease Tool—Patient Reported Outcome (EXACT-PRO) Initiative (www.exactproinitiative.com) and the Cognition Initiative (www.cognitioninitiative.com). These projects bring together pharmaceutical sponsors with common therapeutic and outcome interests, academic researchers, clinical research and psychometric experts, and representatives from regulatory agencies to develop two new, standardized PRO instruments. The intent is to increase efficiencies by combining expertise and resources in the instrument development, validation, and regulatory review process through collaboration, and to advance the science through the use of common metrics to evaluate treatment effects across clinical trials. The EXACT-PRO Initiative was launched in 2006, with an instrument ready for further testing in clinical trials in the fourth quarter of 2007, user manual with additional analyses and interpretation guidelines in 2008, and a PRO evidence dossier submitted to the FDA in 2009 (see EXACT-PRO Initiative article within this issue of *EvidenceMatters*). With the initial expert panel meeting completed and a scoping document in place, The Cognition Initiative has joined forces with the Critical Path Institute's PRO Consortium to move the development process forward. The qualitative research phase is currently underway (see the Cognition Initiative article within this issue of *EvidenceMatters*).

Collaborative Bodies in the U.S. and Europe: C-Path and IMI

Plans for collaborative efforts are growing through the efforts of the PRO Consortium at the Critical Path Institute (C-Path). C-Path is an independent, non-profit organization whose mission is to facilitate collaborations among regulators (scientists from the FDA) and the regulated (medical product industry) to accelerate the development of safe and effective medical products. The PRO Consortium (<http://www.c-path.org/PRO.cfm>) initially targeted some specific therapeutic areas for the development of new PRO tools, including asthma, depression, diabetes, irritable bowel syndrome (IBS)

and oncology. In a recent communication with the director of C-Path's PRO Consortium, Stephen Joel Coons, he asserted that "Harnessing the intellectual and financial resources of multiple stakeholders in a pre-competitive environment for the common purpose of PRO instrument development has the potential to significantly advance our ability to measure PRO endpoints in a scientifically rigorous way." At the same time, The European Innovative Medicines Initiative (IMI) of the European Federation of Pharmaceutical Industries and Associations (EFPIA) has initiated PROactive (<http://www.proactivecopd.com>), a multi-sponsor project to develop, validate and use PRO instruments for assessing physical activity in patients with Chronic Obstructive Pulmonary Disease (COPD). The consortium consists of the 19 partners from academic institutions, subject matter experts, patient organizations and eight major pharmaceutical companies. Both of these approaches and organizations offer opportunities for collaboration. In addition to these formal organizations, there are also opportunities for two or more companies to collaborate on instrument development or validation outside of these organizations, forming their own consortia to help move specific outcomes forward efficiently and effectively.

The development of standardized measures through consortia may reduce regulatory agency review burden by reducing the number of submissions for a target outcome from multiple, different yet related, measures to one instrument designed for a specific, targeted purpose.

Next Step: Review and Qualification of PRO Instruments by Regulatory Agencies

The development of standardized measures through consortia may reduce regulatory agency review burden by reducing the number of submissions for a target outcome from multiple, different yet related, measures to one instrument designed for a specific, targeted purpose.

The EMEA finalized a guidance document in January 2009 outlining a voluntary, scientific pathway leading to either a Committee for Medicinal Products for Human Use (CHMP) opinion or a Scientific Advice on innovative methods for drug development.⁴ This process could potentially be used to obtain "qualification" of a PRO tool in terms of its acceptance for use to collect evidence for a treatment outcome claim. In the U.S., the FDA Center for Drug Evaluation and Research (CDER) is in the process of drafting a guidance that will describe the process of how PROs, as well as

continued on page 18

FOCUS ON:

Patient-Reported Outcomes

The Consortia Approach to Developing PRO Instruments

continued from page 17

certain other drug development, can be formally reviewed in advance of use in a drug evaluation clinical trial.⁵

The Outcome of Collaboration: Facilitating Interpretation and Health Care Decision Making

The use of the same tool and similar responder definitions, across clinical trials of compounds developed by various Pharma companies, will facilitate interpretation and evaluation of treatment benefits using a common “denominator.” Clinicians could be more familiar with the information collected using the PRO tool and rules for interpreting outcomes, so that they can use it for discussions with patients for clinical decision making. Regulatory agencies and payers would also find it easier to review and “value” various health care interventions if the data being provided to them was consistent, to help make these decisions. The use of the same tools across clinical trials of various products could also facilitate meta-analyses and inform health care decision making in other contexts.

The Way Forward?

PRO consortia can be challenging and may be not appropriate in all cases. However, with the right target outcome, good leadership, multiple sponsor interests, dedicated time and effort, a team of multi-disciplinary experts, and a keen commitment to consensus and for improving outcome measurement, the PRO consortia is an idea whose time has come.

For more information, please contact
Asha.Hareendran@unitedbiosource.com or
Nancy.Leidy@unitedbiosource.com.

References

- ¹European Medicines Agency (EMA). Reflection Paper on the Regulatory Guidance For The Use of Health-Related Quality Of Life (HRQL) Measures In The Evaluation Of Medicinal Products, July 2005. <http://www.ema.europa.eu/pdfs/human/ewp/13939104en.pdf>
- ²Food and Drug Administration (FDA). Draft Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *Federal Register*. February 3, 2006; 71(23):5862-5863.
- ³Food and Drug Administration (FDA). Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *Federal Register*. 2009; 74(235):65132-65133.
- ⁴European Medicines Agency website. Human Medicines—Application Procedures; Scientific Advice and Protocol Assistance. <http://www.ema.europa.eu/htms/human/sciadvic/biomarkers.htm>
- ⁵*The Pink Sheet Daily*; 25th January 2010. FDC Reports Inc.

The Cognition Initiative Becomes Cognition Working Group of Critical Path Institute’s PRO Consortium



By Lori Frank, Executive Director and Senior Research Scientist, Center for Health Outcomes Research

UBC is working with academic researchers and sponsors from the pharmaceutical industry on a new pre-competitive sharing consortium with the aim of creating new patient-

and informant-reported measures for global cognition clinical trials. The Cognition Initiative kicked off in 2008 and Phase 1 was completed in 2009. Details on expert panelists and advisors along with Phase 1 sponsors can be found at www.cognitioninitiative.com.

Using the UBC EXACT-PRO as a model, the Cognition Initiative was formed as a collaborative consortium to address the need for more sensitive measurement at mild levels of cognitive impairment, and to incorporate both FDA and broad industry input at early stages of the measurement development process. By examining outcomes relevant to patients and informants, this research initiative may also expand on the universe of outcomes measured in cognition and could contribute additional measures to studies of Alzheimer’s disease (AD), as well as mild cognitive impairment (MCI).

The goal of the Cognition Working Group is to develop new patient- and informant-reported measures of the symptoms of cognitive impairment and the consequences of those cognitive impairment symptoms. Our measures will be relevant for patients across the range of severity from very mild cognitive impairment that can represent an early stage of Alzheimer’s disease to moderate probable AD.

No universally accepted diagnostic criteria exist for mild cognitive impairment, but consensus is emerging that the amnesic subtype of mild cognitive impairment (MCI) represents those patients with the highest probability for progression to diagnosable Alzheimer’s disease.^{1,2} Accordingly, amnesic MCI is suggested as a suitable target for disease modifying agents.³ Interest in identifying pre-MCI is also growing.

By expanding measurement to include both patient and informant, measurement precision may be improved and a set of concepts relevant to treatment response different from those obtained from clinicians may be identified. A key activity for the group will be the exploration of the validity of

patient self-report, given documented reduction in insight and problems with reading and understanding material associated with AD. Although limited work has been completed using patient self-report in MCI, earlier work indicates the feasibility of obtaining valid patient self-report on symptoms and symptom impact.⁴

Improving measurement sensitivity is the key aim of the Working Group. Capture of patient- and informant-reports may aid with establishing the clinical significance of other measures used in cognition trials. In addition, the consumer perspective on the disorder and treatment benefits may identify aspects of the disease process not accessible through neuropsychological test batteries or even clinical interviews. The sometimes subtle impairment noticed by very mildly cognitively impaired individuals—and their families and friends—suggest that complex activities of daily living and aspects of social functioning may be fruitful measurement targets. Of particular interest is the opportunity to push the current limits of diagnostic criteria. An early definition of MCI included reference to intact activities of daily living,⁵ a requirement undergoing scrutiny given documentation of functional deficits present in MCI.⁶⁻⁹ Consensus on the specific functional deficits that characterize MCI has not been reached and this Initiative may provide further relevant data. Several performance-based or informant-reported measures are being used in the field.^{7, 10-12} Diagnostic criteria for AD include reference to functional performance deficits (“significant impairment in social or occupational functioning” per the American Psychiatric Association [DSM-IV-TR])¹³ so a relationship between cognition and functioning can be expected in early cognitive impairment.

In addition, no existing measures provide patient- and informant-reports that correspond to AD diagnostic criteria in the DSM-IV: key memory impairments associated with AD (ability to learn new information or recall previously learned information), or disturbances in executive functioning (planning, organizing, sequencing, abstracting, switching and navigating multiple sensory inputs); agnosia (object recognition), apraxia (motor activity impairment), or aphasia (language impairment). This Initiative will provide measures that align with diagnostic criteria and provide the patient and informant perspective.

This fall, Cognition Initiative sponsors voted to request formal Working Group status from the PRO Consortium of the Critical Path Institute (C-Path). The Coordinating Committee for the PRO Consortium accepted the request in October. In a recent communication with Stephen Joel Coons, the director of C-Path’s PRO Consortium, he noted “UBC’s Cognition Initiative is an extremely important and timely endeavor. I am very pleased that as a Working Group within the PRO Consortium we are able to leverage the resources of additional member firms to contribute to the Initiative’s success.” The Cognition Working Group’s Scoping Stage Summary Docu-

ment was submitted to the FDA for review as the first step in a three-stage qualification process set up by the Critical Path Institute to ensure high quality measure development and to enable input into the process by the FDA.

Phase 2 of the project covers qualitative research through draft measure construction and this phase has just started.

“UBC’s Cognition Initiative is an extremely important and timely endeavor. I am very pleased that as a Working Group within the PRO Consortium we are able to leverage the resources of additional member firms to contribute to the Initiative’s success.”

Stephen Joel Coons
Director of C-Path’s PRO Consortium

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

References

- ¹Gauthier S, et al. Mild Cognitive Impairment. *Lancet*. 2006; 367:1262-1270.
- ²Petersen RC, O’Brien J. Mild Cognitive Impairment Should be Considered for DSM-V. *J Geriatr Psychiatry Neurol*. 2006 Sep; 19(3):147-154.
- ³Vellas B, Andrieu S, Sampaio C, Wilcock G for the European Task Force group. Disease-Modifying Trials in Alzheimer’s Disease: A European Task Force Consensus. *Lancet Neurol*. 2007; 6:56-62.
- ⁴Frank L, Flynn J, Kleinman L, Margolis MK, Matza L, Beck C, Bowman L. Validation of a New Symptom Impact Questionnaire for Mild to Moderate Cognitive Impairment. *Internat Psychogeriatr*. 2006; 18(1):135-149.
- ⁵Petersen RC, Stevens JC, Ganguli M, et al. Practice Parameter: Early Detection of Dementia: Mild Cognitive Impairment (an Evidence-based Review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001 May 8; 56(9):1133-1142.
- ⁶Pernecky R, Pohl C, Sorg C, et al. Impairment of Activities of Daily Living Requiring Memory or Complex Reasoning as Part of the MCI Syndrome. *Int J Geriatr Psychiatry*. 2006 Feb; 21(2):158-162.
- ⁷Peres K, et al. Restriction in Complex Activities of Daily Living in MCI. Impact on Outcome. *Neurology*. 2006; 67:461-466.
- ⁸Reisberg B, Ferris SH, Kluger A, et al. Mild Cognitive Impairment (MCI): A Historical Perspective. *Int Psychogeriatr*. 2008 Feb; 20(1):18-31.
- ⁹Winblad B, Palmer K, Kivipelto M, et al. Mild Cognitive Impairment - Beyond Controversies, Towards a Consensus: Report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004 Sep; 256(3):240-246.
- ¹⁰Farias ST, Mungas D, Reed BR, et al. MCI is Associated with Deficits in Everyday Functioning. *Alzheimer Dis Assoc Disord*. 2006 Oct-Dec; 20(4):217-223.
- ¹¹Farias ST, Mungas D, Reed BR, et al. The Measurement of Everyday Cognition (ECog): Scale Development and Psychometric Properties. *Neuropsychology*. 2008 Jul; 22(4):531-544.
- ¹²Giovannetti T, et al. Characterization of Everyday Functioning in Mild Cognitive Impairment: A Direct Assessment Approach. *Dement Geriatr Cogn Disord*. 2008; 25:359-365.
- ¹³American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (Revised 4th ed.). Washington, DC: APA; 2000.

FOCUS ON:

Patient-Reported Outcomes

Other Measurement Properties of PRO Instruments



By Dennis Revicki, PhD, Senior Vice President, Center for Health Outcomes Research

The final FDA guidance on patient-reported outcomes (PROs) for labeling or promotional purposes emphasizes the assessment of content validity.¹

The FDA focuses attention on the results of qualitative research designed to identify health concepts that are important and relevant to patients, and to evaluate whether PRO instrument instructions, items, response scales and recall period are understandable, comprehensive, and relevant to patients. Qualitative and quantitative methods are complementary, and provide different, yet meaningful, information about content and construct validity. Quantitative methods can be used to explore, and more importantly, confirm the dimensionality and structure of multi-item scales; evaluate item bias across demographic groups; and examine the relationships among health outcomes.

Psychometric analyses are important for understanding the reliability and validity of PRO instruments.² Accumulating evidence supporting the measurement properties of instruments gives us more confidence that these instruments may

Reliability is a necessary attribute in a PRO instrument. There are several approaches for understanding reliability...

meanfully detect changes in a patient's symptom and health status.

Reliability is a necessary attribute in a PRO instrument. There are several approaches for understanding reliability, including internal consistency, test-retest, inter- and intra-rater, and IRT-based methods. Internal consistency reliability, often assessed by Cronbach's alpha coefficient, evaluates how well a group of items, in multi-item scales, hold together in measuring a single construct. Larger reliability coefficients indicate that the items are closely related and share a common source of variance (i.e., single concept). Test-retest reliability, most often assessed using intraclass correlation coefficients (ICCs), measures the stability of PRO instruments in patients who are not changing in their clinical status over a one-two week period. Large ICCs indicate that the PRO instrument is stable and not overly affected by measurement error. Inter-rater and intra-rater reliability are also evaluated using ICCs and are needed when there are multiple different raters of ratings over time, for example when parent proxy and teenage

children are completing outcome scales. Finally, modern measurement theory and item response theory (IRT) analyses have changed how we view reliability. In IRT, it is possible to get reliability assessments across the continuum of the concept being measured. This approach recognizes the fact that measurement precision may vary from the mild to more severe areas of the assessment of a construct. These different approaches to measuring reliability all provide different but useful information on measurement error.

Validity is the degree to which the PRO instrument reflects what it is intended to measure.² Content validity is the extent to which a PRO instrument samples a representative range of the content under study (i.e., fatigue, physical function, etc.). Evaluations of content validity are often subjective and based on qualitative data or expert reviews. Validity testing involves examining evidence supporting the criterion-related and construct (i.e., known groups, convergent, discriminant) validity. Criterion validity is where there are hypotheses about the relationship between the PRO instrument and a criterion or "gold standard". In PRO research there are few gold standards and most validity testing involves assessing construct validity.

Evidence of construct validity is generated by evaluating a series of hypotheses about how the PRO measure should behave. To the extent that these hypotheses are confirmed, we have greater confidence that the instrument is measuring what it is intended to measure. For example, in evaluating the validity of a new patient-reported measure of fatigue, we might hypothesize that the new instrument would be moderately to strongly related to other existing fatigue scales, and moderately related to hemoglobin levels and measures of physical functioning. For known groups' validity, the focus is on identifying groups of participants who are hypothesized to vary on the target construct. For example, for depression, the mean scores on the new PRO instrument might be compared by depression severity groups based on a clinician rating scale, such as the Montgomery-Asberg Depression Rating scale.

Confirmatory factor analysis is used in PRO instrument development to evaluate items for fit within a hypothesized domain by demonstrating that items with a specified domain scale load onto the factors.² Items that cross load on multiple factors may be removed from an instrument. Factor analysis allows us to understand the internal structure of a PRO measure and to evaluate the factor structure across different samples. Confirmatory factor analysis within the context of construct validity allows for the evaluation of specific hypotheses about factor structures and content and can be used to hierarchically test for invariance in factor structure across groups.^{3,4}

Structural equation modeling (SEM) can be used to examine the relationships among PROs and clinical variables.⁵ SEM

is used to evaluate the construct validity of PRO measures by confirming specified relationships between the PROs and antecedents and consequences of interest. SEM allows researchers to assess multiple domains simultaneously and examine the longitudinal relationships among clinical and PRO endpoints. Finally, SEM can be used to cross-validate PROs across sub-groups (i.e., gender, language versions, etc.). SEM allows for the evaluation of complex interactions/relationships among clinical and patient-reported outcomes.⁶ For example, these models can examine the longitudinal relationships between treatment-related impact on hemoglobin in patients with chemotherapy induced anemia and the effect of changes in hemoglobin on changes on patient-reported fatigue. In addition, SEMs can be used to evaluate and confirm PRO endpoint models.

IRT analyses can be used to evaluate the fit of a set of items intended to measure a uni-dimensional concept using a series of mathematical models. IRT analysis focuses on understanding how items and item responses fit a specified model, and how well the items assess the construct across the range of the construct. The item parameter data assist in identifying items at measure mild or severe ends of the continuum and in selecting a smaller set of items that adequately capture the range of experience. Differential item functioning (DIF) examines the relationship among item responses, levels of a trait (construct) being measured, and subgroup membership.⁷ For any given level of a trait, the probability of endorsing a specific item response should be independent of group membership. There are two kinds of DIF. Uniform DIF is consistent across the range of the trait being measured, and non-uniform DIF varies depending on the trait level. DIF testing can be done with ordinal logistic regression. DIF is identified as a significant effect of subgroup membership on item score after controlling for the level of the trait. The trait level is approximated by summing across items or estimating IRT trait scores. These methods are most useful for evaluating large item banks and for multi-item scales. In addition, IRT information curves allow the investigator to know where an item bank or instrument is covering the continuum of severity or impairment.⁸ This information is useful in targeting when additional development work and domain content coverage is needed.

Psychometric analysis can provide insight into content and construct validity of multi-item and multi-dimensional PRO instruments. The generated information complements the qualitative research findings on respondent experiences and understanding of PRO concepts. The results of psychometric analyses confirm and extend the findings of qualitative research studies. Confirmation of content and construct validity is dependent on the accumulation of research evidence. However, once sufficient evidence from multiple sources is demonstrated, it might be reasonable to conclude that there is enough information on content and construct validity of the targeted PRO.

For more information, please contact
Dennis.Revicki@unitedbiosource.com.

References

- ¹Food and Drug Administration. Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *Federal Register*. 2009; 71(23): 5862-5863.
- ²Hays RD, Revicki DA. Reliability And Validity, Including Responsiveness. In Fayers P, Hays RD (eds.). *Assessing Quality of Life in Clinical Trials*, Second Edition. New York: Oxford University Press, 2005.
- ³Joreskog KG. Simultaneous Factor Analysis in Several Populations. *Psychometrika*. 1971; 36:409-426.
- ⁴Revicki DA, Sorensen S, Wu AW. Reliability And Validity Of Physical And Mental Health Summary Scores From The Medical Outcomes Study HIV Health Survey. *Medical Care*. 1998; 36:126-137.
- ⁵Kline R. *Principles and Practice of Structural Equation Modeling*, Second Edition. New York: Guilford Press, 2005.
- ⁶Stull DE. Analyzing Growth And Change: Latent Variable Growth Curve Modeling With An Application To Clinical Trials. *Quality of Life Research*. 2008; 17(1):47-59.
- ⁷Reeve BB, Hays RD, Bjorner JB, Cook KF, Crane PK, Teresi JA, Thissen D, Revicki DA, Weiss DJ, Hambleton RK, Honghu L, Gershon R, Reise SP, Lai J, Cella D. Psychometric Evaluation And Calibration Of Health-Related Quality Of Life Items Banks: Plans For The Patient-Reported Outcome Measurement Information System (PROMIS). *Medical Care*. 2007; 45 (5 Suppl 1):S22-31.
- ⁸Embretson SE, Reise SP. *Item Response Theory for Psychologists*. Mahmah, NJ: Lawrence Erlbaum, 2000.

EXACT-PRO Initiative: Update from a Multi-Sponsor Instrument Development Consortium

By Laurie Roberts, MPH, Senior Research Associate, Nancy Leidy, PhD, Senior Vice President, Scientific Affairs and Senior Research Leader, and Asha Hareendran, PhD, Senior Research Scientist, Center for Health Outcomes Research

The EXACT-PRO (EXAcerbations of Chronic pulmonary disease Tool—Patient-Reported Outcome) Initiative is the first multi-sponsor PRO instrument development consortium project. Initiated in fall 2005, the Initiative is now approaching the end its third phase and is focusing on tasks to maintain the success and ensure the integrity of the new instrument as it is implemented in multinational clinical trials. This article provides a brief overview of the consortium, followed by an update of the project in three areas that are important to the success of new instruments: development of a PRO evidence dossier, scientific dissemination, and standardizing implementation in multinational trials.

Background

The EXACT-PRO Initiative brought together international experts in instrument development, validation, and translation; specialists in clinical practice and research; and

continued on page 22

FOCUS ON:

Patient-Reported Outcomes

EXACT-PRO Initiative

continued from page 21

members of the U.S. Food and Drug Administration (FDA) to inform the development of a single, validated PRO measure to evaluate exacerbations in chronic obstructive pulmonary disease (COPD). The instrument, called the EXACT, was designed for use in clinical trials evaluating the effect of treatment on frequency, severity, and/or duration of exacerbations of COPD in two areas: acute anti-infective treatment and maintenance therapies. To date, the initiative has involved three phases, including a literature review and qualitative research involving elicitation focus groups and interviews and evaluative cognitive debriefing interviews (Phase I); an item reduction and instrument validation study of over 400 patients (Phase II); and the compilation of information and preparation of a PRO evidence dossier for FDA submission and abstracts, presentations, and manuscripts for scientific dissemination (Phase III). The final measure, available for use during Phase II of the Initiative, is a 14-item electronic diary completed by subjects on a daily basis during the course of a clinical study.

The PRO Evidence Dossier

When new instruments are being developed to collect data to support label claims, it is recommended that feedback from regulatory agencies be sought as early as possible. The

U.S. FDA was kept informed throughout the Initiative and members of the FDA participated in periodic panel meetings involving experts in pulmonary

When new instruments are being developed to collect data to support label claims, it is recommended that feedback from regulatory agencies be sought as early as possible.

disease, clinical research, and instrument development that played a central role in the instrument development and validation process. Throughout the dossier development process, United BioSource Corporation (UBC) project staff shared information with sponsors and key opinion leaders involved in the Initiative, and invited feedback and comments that were incorporated into the PRO Evidence Dossier submitted to the FDA for qualification review. The final dossier was submitted to FDA for review at the end of 2009.

Scientific Dissemination

In addition to regulatory review, it is important to disseminate information about scientific methods used to develop

and validate a new PRO instrument, to enable peer-review and ensure that the scientific and clinical communities are familiar with the measure, its intended use, and its measurement properties. UBC's EXACT-PRO team developed a strategy for dissemination which included two posters that were presented at the American Thoracic Society (ATS) and a third that was presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) meetings in May 2009. Methods and results of the qualitative methods that underlie the content validity of the instrument were also presented at the U.S. Drug Information Association (DIA) meeting in June 2009. Three manuscripts are in various stages of development and journal review: one describing the qualitative methods used in the instrument development process, a second detailing the item-reduction process, including classical test theory and Rasch methodologies, and a third outlining the methods and results of the initial tests of reliability, validity, and responsiveness of the new measure.

Standardizing Implementation of the EXACT in Multinational Trials

When a new PRO instrument is developed for use by multiple stakeholders and across multinational clinical trials, it is important to take steps to ensure that 1) changes are not made to the original, validated version; 2) the translation process is sound and the same language versions are used across studies; and 3) the instrument is administered in a consistent way based on lessons learned during the initial validation work.

Implementing the EXACT on Electronic Devices

The EXACT was developed with the electronic age in mind, with the first validation study involving data collection on a Tungsten E2 personal digital assistant (PDA). With the rapid growth in electronic communication devices, the number and type of methods available to administer electronic PROs (ePROs) has blossomed and multiple companies are available to provide ePRO-related services in clinical studies. The EXACT Certification Program was developed to help protect the integrity of the EXACT while offering the flexibility users need to select devices and eDiary vendors based on a programmatic needs and resources. The certification program prepares interested eDiary vendors to implement the EXACT in clinical trials by providing them with guidance on how to set up the items on the device, compliance-enhancing features for the instrument, and specific training information to provide clinical sites and patients when administering the EXACT in clinical trials. In addition, UBC team members review screen shots of the English version of the instrument programmed into the selected device(s) to make certain the vendor has the correct and accurate version and that the layout of this version is as consistent as possible across devices. Certified vendors are not authorized

to license the instrument, but do have the instrument readily available for licensed use. The program does not constitute endorsement of devices or companies, but is designed to optimize choice, efficiency, and consistency of instrument administration across users and over time as ePRO options continue to expand.

Translations of the EXACT

To date, the EXACT has been translated into 25 languages and cognitively debriefed with COPD patients in 34 different target countries. Translation methods have followed the Principles of Good Practice for the Translation and Cultural Adaptation of PRO measures as suggested by the ISPOR Task Force for Translation and Cultural Adaptation.¹ To assure consistency in methodology and version control across users, UBC selects and works directly with the translation vendor. An important step in the translation process was the development of a detailed item definition document that described the intent of each EXACT item and specific guidance for translation. This document is used in the development of each translation. The purpose of following a formal translation methodology, including linguistic validation, is to derive translated versions of the EXACT that are conceptually equivalent to the English source version. Those interested in using an existing or new translation of the instrument should contact a member of the UBC staff for assistance.

Planned Next Steps

UBC continues to provide scientific support to the EXACT-PRO Initiative sponsors and licensed users of the instrument regarding the implementation of the measure in clinical studies and scoring algorithms to assess frequency, severity, and duration of exacerbations. In 2010/2011 we look forward to seeing how the EXACT performs in prospective studies and clinical trials.

UBC's EXACT-PRO team includes Nancy Kline Leidy, PhD, Director and Principal Investigator; Terry Wilcox, PhD, Co-Investigator; Laurie Roberts, MPH, Senior Research Associate; Asha Hareendran, PhD, Senior Research Scientist; Ingela Wiklund, PhD, Senior Research Leader; Sonya Eremenco, MA, ePRO Manager; Wen-Hung Chen, PhD, Statistical Analyst; Ren Yu, MA, Statistical Programmer; and Research Associates Lindsey Murray, BA; Randall Winnette, BS; and Sherilyn Notte, with support from other members of the UBC staff.

The EXACT-PRO Initiative is possible through the commitment of the following Phase III sponsors: AstraZeneca, Boehringer-Ingelheim, Forest Laboratories, GlaxoSmithKline, Merck, MPex, Novartis, Pfizer, Schering-Plough, Sepracor, Almirall and DEY Pharmaceuticals.

For more information, please contact Laurie.Roberts@unitedbiosource.com, Nancy.Leidy@unitedbiosource.com, or Asha.Hareendran@unitedbiosource.com.

Reference

¹Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: Report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value in Health*. 2005 Mar-Apr; 8(2):94-104.

Patient Compliance with eDiary Completion in Clinical Trials

By Lindsey Murray, BA, Research Associate; Charlotte Cates, MA, Research Associate; and Sonya Eremenco, MA, ePRO Manager, Center for Health Outcomes Research

Collecting complete and accurate patient-reported outcomes (PRO) data is a critical component of a successful clinical trial, particularly when the PRO instrument is the primary or key secondary endpoint. Electronic capture of PRO data (ePRO) is an efficient way to collect such data from patients in unsupervised settings and has become the industry norm for daily diary data collection. The increased reliability of eDiary data may lead to a reduction in missing data as well as reduced variability, resulting in the need to recruit fewer patients and a significant cost-savings to the sponsor. However, ensuring patient compliance to eDiary completion per protocol is an ongoing concern.

There are several questions to consider when developing a compliance-enhancing strategy tailored to the context of a clinical trial:

- How can high levels of patient compliance be achieved?
- In which phases of the study should these strategies be implemented?

One approach to achieving high levels of patient compliance with eDiaries is through the use of features available on ePRO devices, including: reminder alarms, restricted completion windows, and required completion of all items in the diary. Such strategies were used successfully in studies with chronic pain and overactive bladder (OAB) patients.¹⁻⁵ Compliance levels ranged from 87% in the OAB study over 14 weeks⁵ to 94% in pain studies lasting up to 3 weeks and maintained at approximately 90% over one year.^{1,4} Of note, both the OAB study and one of the pain studies reported reductions in compliance rates over the course of the study (14 weeks and 3 weeks, respectively).^{4,5} Programming features of electronic diaries, however, are not in themselves a guarantee of high compliance because patients may simply not complete the diary. To address this limitation, one chronic

continued on page 24

FOCUS ON:

Patient-Reported Outcomes

Patient Compliance with eDiary

continued from page 23

obstructive pulmonary disease (COPD) study paired these strategies with daily monitoring of patient diary completion by site coordinators. Site monitors contacted patients directly when their compliance fell below a specified cut-off point after a certain number of days. This combined strategy achieved very high levels of compliance (96% and 94%) in stable and acute COPD populations over 7 and 28 days, respectively.⁶ Published eDiary review studies point to the fact that these strategies are consistent predictors of high patient diary compliance.^{7,8}

Strategies to obtain high levels of compliance, therefore, should be considered from the initial study planning stages of any clinical trial so that practical, compliance-enhancing strategies can be optimally integrated into the study design. It is also important that these strategies be relevant to the therapeutic area, outcome and design of the trial. Compliance should be addressed as part of the eDiary programming requirements, site contracts, site and participant training materials, and the study protocol. Specific examples of each strategy are discussed below. These strategies are not exhaustive and are meant to highlight the wide variety of options available to sponsors.

Electronic Diary Programming Strategies

- Daily alarms, preferably customized for the individual patient so that the diary fits into the patient's life.
- Data entry windows that allow for flexibility and accommodate each patient's lifestyle. Examples include: + 3 hours around "bedtime" or a data entry window that is open from 3 p.m.-midnight for an evening diary.

■ Provide real-time compliance feedback to the patient at the conclusion of each diary entry. An example of a potential screenshot is shown on left.

**You have completed X %
of your diary entries
for the last X day(s).**



NICE!

Site Payment

- Base sites per patient payments on the participants' diary compliance, using a tiered payment structure for compliance levels.
- Terminate patients who drop below a pre-specified minimum compliance rate for reasons other than health or eDiary device problems.

Site Training

- Provide real-time compliance monitoring via web portal or data monitoring systems using customized

reports to easily flag non-compliant subjects, and/or automatic e-mail notifications to site coordinators and/or the CRO when a patient's compliance drops below a specified level. These efforts will reduce the time needed to monitor patient compliance.

- If sites will be receiving the compliance reports, set clear expectations and provide detailed instruction on patient monitoring, as well as the site's responsibility for monitoring patient compliance.
- Sponsors (or designees) monitor sites' overall compliance, as it often is the case that poor patient compliance is localized to a few sites. Quick intervention, such as retraining the site or providing training to a newly hired site coordinator, can lead to better overall site compliance.

Study Protocol—Initial Patient Compliance

- Set a minimum compliance rate during the run-in portion of a trial for a patient to be eligible for the study. This strategy is particularly appealing for more common disease and therapeutic areas where recruitment goals are easier to achieve.

While compliance enhancement strategies are important to consider, limitations do exist. Few studies have compared compliance rates achieved with and without the use of the compliance enhancement strategies mentioned above. Another complicating factor is that there is little empirical evidence that successful strategies employed in an adult chronic pain population, for example, will work equally well for adolescent cystic fibrosis patients, or that the strategies employed early in a trial will continue to work over a long-term study. Additionally, there are often high costs associated with implementing many of these compliance enhancing strategies, which makes determining which strategies best achieve the goal important for sponsors to consider.

Practical experience and anecdotal data suggest improvement in patient diary compliance can be achieved using compliance enhancing strategies, but there are limited data available to guide sponsors in what the precise return on investment to their trial program would be. Further research is needed to determine the most effective compliance enhancement strategies for specific patient populations. In the meantime, Sponsors must strategically analyze their needs and use their best judgment when determining which compliance enhancement strategies will achieve a compliance rate that will meet their study's objectives.

For more information, please contact
Lindsey.Murray@unitedbiosource.com,
Charlotte.Cates@unitedbiosource.com, or
Sonya.Eremenco@unitedbiosource.com.

References

- ¹Jamison RN, Raymond SA, Levine JG, Slawsby EA, Nedeljkovic SS, Katz NP. Electronic Diaries For Monitoring Chronic Pain: 1-Year Validation Study. *Pain*. Apr 2001; 91(3):277-285.
- ²Stone AA, Broderick JE, Schwartz JE, Shiffman S, Litcher-Kelly L, Calvanese P. Intensive Momentary Reporting Of Pain With An Electronic Diary: Reactivity, Compliance, And Patient Satisfaction. *Pain*. Jul 2003; 104(1-2):343-351a.
- ³Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient Compliance With Paper And Electronic Diaries. *Controlled Clinical Trials*. 2003; 24(2):182-199b.
- ⁴Broderick JE, Schwartz JE, Shiffman S, Hufford MR, Stone AA. Signaling Does Not Adequately Improve Diary Compliance. *Ann Behav Med*. Oct 2003; 26(2):139-148.
- ⁵McKenzie S, Paty J, Grogan D, et al. Proving the eDiary Dividend. *Applied Clinical Trials*. 2004; 13(6):54-69.
- ⁶Cates C, Roberts L, Eremenco S, Wilcox TK, Leidy NK. Can Older, Chronically Ill Adults Use Electronic Diaries? Compliance Rates in a Prospective Study of Patients with COPD. Poster presented at ISPOR 14th Annual International Meeting; May 16-20, 2009; Orlando, FL, USA.
- ⁷Hufford M, Shields A. Electronic Diaries: Applications And What Works In The Field. *Applied Clinical Trials*. April 2002:47-55.
- ⁸Hufford M, Shiffman S. Assessment Methods for Patient-Reported Outcomes. *Disease Management & Health Outcomes*. 2003; 11(2):77-86.

inclusion criteria described in our October 2009 article. This brings the total to 31 different drugs with PRO labeling.

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

Limitations of the EQ5D and a Possible Solution for COPD Exacerbations

By Jennifer Petrillo, BSc, Research Associate,
Center for Health Outcomes Research

The EQ5D has been supported as the multi-attribute utility measure of choice for a variety of conditions by reimbursement agencies.¹ The five dimensions covering Anxiety/Depression, Mobility, Pain/Discomfort, Self Care, and Usual Activities over three levels each enable the instrument to broadly measure HRQL impact.² It is with this broad focus that questions regarding the responsiveness, or the ability to detect change, are raised with regards to certain conditions.

continued on page 26

Patient-Reported Outcomes (PROs) in Product Labeling, 2006 to Present—An Update

By Sajjad Khan, PhD, MSW, LCSW-C,
Senior Research Associate and Andrew C.
Palsgrove, BA, Research Associate, Center
for Health Outcomes Research

In the October 2009 issue of *EvidenceMatters*, we presented a short paper on PROs in product labeling with a summary table showing examples of drugs that were granted PRO label language after the release of the FDA Draft Guidance on PROs was published in 2006. A detailed table with specific labeling language was also provided on-line. We hope you have found these tables helpful.

We are pleased to provide you with updated tables that include 13 additional products with PRO labeling, approved from 2006 - 2009. These additions to the tables follow the same

| Product Name (Year of PRO Inclusion) Disease Area | | | |
|--|---|---|---|
| Alvesco (2008) <i>Asthma</i> | Cymbalta (2009) <i>(multiple disease areas^a)</i> | Omnaris (2006) <i>Seasonal and Allergic Rhinitis</i> | Symbicort (2006) <i>Asthma</i> |
| Amitiza (2006) <i>(multiple disease areas^a)</i> | Durezol (2008) <i>Ocular Surgery Pain</i> | OraVerse (2008) <i>Soft Tissue Anesthesia</i> | Thyrogen (2006) <i>Thyroid Cancer Diagnostic</i> |
| Arcalyst (2008) <i>Cryopyrin-Associated Periodic Syndromes</i> | Entereg (2008) <i>Recovery Following Bowel Resection</i> | Qutenza (2009) <i>Postherpetic Neuralgia</i> | Toviaz (2008) <i>Overactive Bladder</i> |
| Azilect (2006) <i>Parkinson's Disease</i> | Kalbitor (2009) <i>Hereditary Angioedema</i> | Rapaflo (2008) <i>Benign Prostatic Hyperplasia</i> | Veramyst (2008) <i>Seasonal and Perennial Allergic Rhinitis</i> |
| Banzel (2008) <i>Lennox-Gastaut Syndrome Seizures</i> | Kapidex (2009) <i>GERD</i> | Relistor (2008) <i>Opioid-Induced Constipation</i> | Vimpat (2008) <i>Partial-Onset Seizures</i> |
| Chantix (2006) <i>Smoking Cessation</i> | Letairis (2007) <i>Pulmonary Hypertension</i> | Savella (2009) <i>Fibromyalgia</i> | Vivitrol (2006) <i>Alcohol Dependence</i> |
| Cimzia (2008) <i>Crohn's Disease</i> | Lyrica (2007) <i>Fibromyalgia</i> | Seroquel (2006) <i>Major Depressive Disorder</i> | Voltaren Gel (2007) <i>Osteoarthritis Pain</i> |
| Clinoril (2006) <i>(multiple disease areas^a)</i> | Nucynta (2008) <i>Pain</i> | Soliris (2007) <i>Paroxysmal Nocturnal Hemoglobinuria</i> | |

Table 1. Examples of Pharmaceutical Products with PRO Label Information, 2006 to Present*

^aChronic Idiopathic Constipation and Irritable Bowel Syndrome

^bOsteoarthritis, Rheumatoid Arthritis, Ankylosing Spondylitis, Acute Painful Shoulder, and Acute Gouty Arthritis

^cFibromyalgia and Generalized Anxiety Disorder

*A comprehensive table with verbatim PRO language is available on-line at <http://unitedbiosource.com/pdfs/pro-label-information.pdf>.

FOCUS ON:

Patient-Reported Outcomes

Limitations of the EQ5D

continued from page 25

The scoring algorithm for the EQ5D is based on a general public population rating of the value of being in a particular state of health, which is based on those five attributes and three levels. The extent to which health states reflect the full experience of any condition depends on the accuracy of the description. Conditions that affect dimensions not captured in the EQ5D may not be adequately valued in order to reflect accurate health state utilities, particularly in Chronic Obstructive Pulmonary Disease (COPD).

As use of the EQ5D increases, data have emerged suggesting it is unable to detect change associated with effective interventions in certain disease areas, including COPD, urinary incontinence, and visual acuity loss.³⁻⁵ Responsiveness of the EQ5D has an immediate effect on the interpretation of interventions. With little to no change in health state utilities, payers may conclude there is no value in approving or offering the intervention from an economic perspective. This concern arises when condition-specific and clinical measures conclude an intervention results in clinically important change for patients, yet the preference-based instrument does not. The impact on cost-effectiveness models is significant when the benefit of a well known and prescribed pharmaceutical intervention is declared not cost-effective below a threshold of \$50,000, which would leave many patients without a valid and efficacious intervention to treat their condition.⁶

One explanation for the EQ5D's insensitivity to clinically meaningful change could be the broad HRQL focus that captures the health effects of co-morbidities as well as the condition being evaluated. One study found the absolute number of concomitant diagnoses was significantly associated with worse EQ5D utility scores ($p < 0.001$), independent of COPD severity level, while there was no significant interaction between severity level and the presence or absence of co-morbidity.⁷ This causes a concern, particularly in the older population where co-morbidities are quite common. With treatment potentially affecting one dimension of health, for instance cognition or lung function, and the EQ5D measuring HRQL on a global scale, response could be drowned out simply due to co-morbidities remaining unchanged.

Utilities reported from a condition-specific measure have the potential to maintain sensitivity to patient change by focusing on domains that are relevant to the condition at hand. Studies have used condition-specific measures to report utilities after developing a preference-based scoring algorithm, with good results.⁸

In COPD, questions have been raised regarding the EQ5D responsiveness to the effect of treatment on exacerbations. The EXACT-U is a new preference-based algorithm to address this

concern by using data gathered through the Exacerbation of Chronic Pulmonary Disease Tool (EXACT), a daily diary designed to measure the frequency, severity, and duration of an exacerbation (www.exactproinitiative.com).^{10,11} Data from the initial validation study suggest EXACT scores are reliable, valid, and responsive to the day-to-day changes associated with an exacerbation of COPD. The EXACT-U uses select items from the EXACT and a preference-based algorithm from general public ratings to report utilities for an exacerbation. Patients who respond to the EXACT would have data to reflect EXACT-U utilities as well.

The EXACT-U values provided by patients during clinical trials could be used in lieu of EQ5D values, thus addressing the responsiveness concerns around multi-attribute utility measurement in this situation.

For more information, please contact
Jennifer.Petrillo@unitedbiosource.com.

References

- ¹National Institute for Health and Clinical Excellence (NICE). Guide to the Methods of Technology Appraisal. 2008 June. <http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp?domedia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459>
- ²Dolan P. Modeling Valuations for EuroQol Health States. *Med Care*. 1997 Nov; 35(11):1095-1108.
- ³O'Reilly JF, Williams AE, and Rice L. Health Status Impairment and Costs Associated with COPD Exacerbation Managed in Hospital. *Int J Clin Pract*. 2007; 61(7): 1112-1120.
- ⁴Haywood KL, et al. EuroQol EQ-5D and Condition-Specific Measures of Health Outcome in Women with Urinary Incontinence: Reliability, Validity and Responsiveness. *Qual Life Res*. 2008; 17(3): 475-483.
- ⁵Espallargues M, et al. The Impact of Age-Related Macular Degeneration on Health Status Utility Values. *Investigative Ophthalmology and Visual Science*. 2005; 46(11): 4016-4023.
- ⁶Briggs A, Glick H, Lozano-Ortega G, et al. Is Treatment with ICS and LABA Cost-Effective for COPD? Multinational Economic Analysis of the TORCH Study. *Eur Respir J*. 2009 Aug 28 [Epub ahead of print].
- ⁷Rutten-van Molken MP, Oostenbrink JB, Tashkin DP, Burkhart D, Monz BU. Does Quality of Life of COPD Patients as Measured by the Generic EuroQol Five-Dimension Questionnaire Differentiate between COPD Severity Stages? *Chest*. Oct 2006; 130(4):1117-1128.
- ⁸Yang Y, et al. Estimating a Preference-Based Single Index from the Overactive Bladder Questionnaire. *Value Health*. 2009; 12(1): 159-166.
- ⁹Petrillo J, Macker S, Davies E, Cairns J. Development of a Preference-Based Algorithm to Report Utilities for Exacerbations of COPD from the EXACT. Paper presented at ISPOR 12th Annual European Congress.; 25 October 2009; Paris, France.
- ¹⁰Leidy NK, Powers JH, Howard KA, Petrillo JM, Wilcox TW and EXACT-PRO Study Group. The EXACT-PRO Initiative: Development of a Standardized Outcome Measure for Evaluating Exacerbations of Chronic Obstructive Pulmonary Disease, in American Thoracic Society International Conference. 2008; Toronto, Ontario, Canada.

NEWS BRIEFS

United BioSource Corporation Expands Operations in Japan

Recent years have seen sharp increases in clinical trials conducted in the Asia-Pacific region, especially in Japan and China; while the complexity of conducting both local and multi-national clinical trials in this region seems to increase year after year. The ability for life science companies to operate within this global context is vitally important to success in a crowded research field. Due the growing importance of both Japanese clinical trials and Pan-Asian studies on a product's regulatory and commercial success, UBC is reinforcing its commitment to the region with the opening of our first Asian office.

Effective January 2010, UBC is managing operations from a new office located in Tokyo, Japan. The new location permits UBC to provide a streamlined platform of services to both Japanese-based pharmaceutical companies and clinical research organizations. The initial area of focus of the new office lies with UBC's Specialty Clinical Solutions which provides investigator training and certification programs as well as surveillance and monitoring programs for CNS and other indications where subjective assessments are utilized.

The office will be led by Kumpei Kobayashi, PharmD, who brings more than 20 years of experience in the pharmaceutical and life sciences industries. Dr. Kobayashi began his career as a research scientist and most recently served as the Executive Manager for i3 Japan LLC. Dr. Kobayashi will lead all scientific and operational functions for UBC in the Asia-Pacific area.

Joining Dr. Kobayashi will be David Miller, MD, who has served as a key scientific leader on several studies involving Japanese sites, including the first global dementia study in which Japanese investigators took part. Dr. Miller is also participating in an upcoming Pan-Asian study being initiated by a Japanese office of a global pharmaceutical company. In 2009, Dr. Miller represented UBC at the Japanese Society for NeuroPsychopharmacology (JSNP) meeting in Koyoto, Japan, where he presented a poster on Identifying Capable Raters for Global Alzheimer's Disease Clinical Trials in Japan: Challenges and Potential Solutions. In addition, Dr. Miller participated in the World Wide Alzheimer's Disease Neuroimaging Initiative (WW-ADNI) meeting in Sendai, Japan.

Questions about UBC's office in Tokyo can be directed to Dr. Kobayashi at kumpei.kobayashi@unitedbiosource.com.

Karin Coyne, PhD, Promoted to Scientific Director, Center for Health Outcomes Research

■ **Dr. Karin Coyne** has been named Scientific Director of UBC's Center for Health Outcomes Research. Dr. Coyne joined UBC 11 years ago and has taken on progressively more responsibility for the internal scientific direction of outcomes research. This move recognizes her internal leadership as well as her external reputation for consistently producing uncompromisingly high quality work. Dr. Coyne has overseen the development and psychometric evaluation of a number of new health outcomes measures. She brings her substantial therapeutic background in cardiology, urology, and women's health to her work, along with methods innovation. She is known for her diligence and commitment to quality. In addition to her own project work, she continues to actively contribute to UBC's electronic data capture from patients with a focus on ePROs and web-based survey design. As Scientific Director, Dr. Coyne will continue her project-related scientific leadership but will also provide the direction for scientific advancement within the Center.

UBC Adds New Vice President of Safety, Epidemiology and Risk Management



■ **Gretchen S. Dieck, PhD**, has joined UBC as a new Vice President of Safety, Epidemiology and Risk Management. In this role, Dr. Dieck provides strategic consultative services to pharmaceutical and biotech clients to meet client needs in the design, implementation and analysis of epidemiologic and safety studies. Additionally, she consults on risk assessment studies, risk management interventions, and risk evaluation and mitigation strategies (REMS).

Before joining UBC, Dr. Dieck was a Senior Vice President, Safety and Risk Management at Pfizer Inc. where she was for over 23 years having first started as a staff epidemiologist in 1986. While heading the Safety and Risk Management group, she was responsible for providing risk management support and compliance functions across the product portfolio. Included in these responsibilities were the case processing and risk management functions relating to epidemiology and medical safety evaluation as well as safety- and risk management-related analysis and documentation. One of her notable accomplishments while at Pfizer was the conceptualization and implementation of Pfizer's Medicine Safety website. Dr. Dieck was a founding board member of

continued on page 28

NEWS BRIEFS

continued from page 27

the International Society for Pharmacoepidemiology and was a member of the ICH Risk Communication Working Group. In addition, she is past Chair of the Pharmacovigilance and Epidemiology Technical Group of PhRMA and headed the Risk Management Working Group of the Pharmaceuticals Innovation Steering Committee of PhRMA. Dr. Dieck represented PhRMA during PDUFA III and PDUFA IV discussions and co-led the PostMarket Safety Group for PDUFA IV. Dr. Dieck received an AB in biological sciences from Smith College. She received a MPhil and PhD in epidemiology and also completed a postdoctoral fellowship in cardiovascular disease epidemiology at Yale University.

UBC Welcomes New Managing Director, Reimbursement



■ **Sean Coakley, BS**, has joined UBC as a Managing Director, Reimbursement with the Center for Pricing & Reimbursement. Mr. Coakley is responsible for client management and strategic reimbursement consulting for pharmaceutical and biotechnology clients. His particular expertise is in health care policy and coverage and

reimbursement for physician-administered injectable therapies, with an emphasis on Medicare.

Mr. Coakley brings over 16 years of health care reimbursement experience to his Managing Director role. Prior to joining UBC, Mr. Coakley directed regional teams of field reimbursement managers and government account managers for Roche Laboratories, supporting patient and payer access in oncology, osteoporosis, rheumatoid arthritis, and chronic renal failure/anemia. Mr. Coakley also worked in the field as an Oncology Field Reimbursement Manager and Payer Account Manager in 16 Northeast and Mid-Atlantic states. Prior to Roche, Mr. Coakley was employed by GlaxoSmithKline managing the reimbursement support programs for GSK's U.S. pharmaceutical portfolio, and providing strategic reimbursement planning and support for key injectable oncology therapies.

Prior to working with GSK, Mr. Coakley held a number of increasingly responsible management positions within PAREXEL International, including Senior Manager, Payment Strategies. In that capacity, he provided strategic reimbursement consulting around Medicare and Medicaid reimbursement for clients. Additionally, he was responsible for the daily operation and management of 16 reimbursement support programs dedicated to improving appropriate access to coverage and reimbursement for important prescription therapies in oncology, AIDS/HIV, cardiology, nephrology/diabetes, gynecology, radiology, and urology. Mr. Coakley holds a bachelor of science degree in political science from Radford University.

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

HEALTH POLICY CORNER

■ **The American Recovery and Reinvestment Act: Following the AHRQ Money Invested in Comparative Effectiveness Research**

Congress allocated over \$135 billion to the Department of Health and Human Services (HHS) through the American Recovery and Reinvestment Act (ARRA) of 2009,¹ of which \$1.1 billion was earmarked specifically for comparative effectiveness research (CER) and related infrastructure. Of this amount, \$700 million was allocated to the Agency for Healthcare Research and Quality (AHRQ)—\$400 million of which was then statutorily passed through to the National Institutes of Health—and \$400 million allocated to the Office of the Secretary, Health and Human Services (HHS). As the leading Agency for CER in the U.S., the scientific and operational areas into which AHRQ is investing this money provide important indications of areas and issues that will likely play leading roles in development and utilization of CER methods and CER-derived evidence in the near-term future.

As shown in the table on page 32, AHRQ initially laid out broad areas in which it would invest the \$300 million retained from the relevant ARRA funding, focusing primarily on evidence generation (\$172 million) and stakeholder outreach and dissemination efforts (\$44.5 million), including the development of the Clinical and Health Outcomes Initiative in Comparative Effectiveness (CHOICE), described in greater detail below. Within these areas, the Agency has since announced specific funding opportunities in research areas ranging from methods development (e.g., registries, systematic reviews), to infrastructure development and implementation (e.g., fellowships and mentoring).

continued on back page

Recent Presentations

Preventive Medicine 2010

Feb 17 – Feb 20, 2010, Washington, DC, USA

Poster Presentation

Psychosocial Effects of Frequent Heartburn: A Nationally Representative Survey of Frequent Heartburn Sufferers in America

Stull DE, van Hanswijck de Jonge P, Winnette R,
Fennerty MB, Farber M, Ferguson D, Fourcroy J, Sandor DW

Joint DIA / IFAPP Pharmaceutical Policy Forum

Feb 4 – Feb 5, 2010, London, UK

Oral Presentation

Economic and Reimbursement Drivers for Pharma / Healthcare Collaboration

Robert M.A. Thwaites, Senior Executive Director, Europe;
Senior Scientist, Center for Health Economics and Policy,
United BioSource Corporation

Adaptive Designs in Clinical Drug Development

Feb 3 – Feb 4, 2010, London, UK

Presentation

Implementing Adaptive Design: A Technology Perspective

Scott Hamilton, Senior Director, Biometrics and Randomisation
Technologies, United BioSource Corporation

COPD Biomarkers Qualification Workshop

Jan 27 – Jan 28, 2010, Bethesda, MD, USA

Presentation

EXACT PRO

Nancy Kline Leidy, PhD, Senior Vice President, Scientific Affairs
and Senior Research Leader, United BioSource Corporation

XVIII WFN World Congress of Parkinson's Disease and Related Disorders

Dec 13 – Dec 16, 2009, Miami Beach, FL, USA

Poster Presentation

Non-Motor Comorbidities in Patients with Parkinson's Disease: A U.S. Claims Database Analysis

Papapetropoulos S, Tibbetts A, Seitzman R, Kerner J, Barnard J,
Ward A, Michels SL, O'Neil G

Anti-Infective Drugs Advisory Committee Meeting, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA)

Dec 9 – Dec 10, 2009, Gaithersburg, MD, USA

Presentation

Patient-Reported Outcome (PRO) Endpoints in Clinical Trials: Challenges and Opportunities

Invited speaker for an Advisory Committee convened to discuss endpoints and other clinical trial design issues in the development of anti-bacterial products for the treatment of community acquired bacterial pneumonia. The presentation included an overview of patient-reported outcomes with specific reference to methods for evaluating product efficacy in this drug-development area.

Nancy Kline Leidy, PhD, Senior Vice President, Scientific Affairs
and Senior Research Leader, United BioSource Corporation

Health Technology Assessment World Europe 2009

Dec 8 – Dec 11, 2009, London, UK

Workshop

Evaluating Patient Outcomes for Assessing Health Technologies Objectives

Asha Hareendran, PhD, Senior Research Scientist, Health
Outcomes, United BioSource Corporation; **Donald E. Stull,**
PhD, Senior Research Scientist, Center for Health Outcomes
Research, United BioSource Corporation

Presentation

Review of Emerging Trends in the HTA Environment and a Perspective on How Companies are Responding to the Increasing Demands

Robert M.A. Thwaites, Senior Executive Director, Europe;
Senior Scientist, Center for Health Economics and Policy,
United BioSource Corporation

CBI's 3rd Annual Evidence-Based Medicine and Comparative Effectiveness Research Summit

Nov 17 – Nov 18, 2009, Philadelphia, PA, USA

Presentation

Rethinking Randomized Clinical Trials for CER—The Need for Transformational Change

Bryan R. Luce, PhD, Senior Vice President, Science Policy,
United BioSource Corporation; **J. Jaime Caro,** MDCM, FRCPC,
FACP, Senior Vice President, Health Care Analytics, United
BioSource Corporation; **Myoung Kim,** PhD, MA, MBA, Director,
Outcomes Research, Internal Medicine, Ortho-McNeil Janssen
Scientific Affairs

CBI's 5th Forum on Patient Reported Outcomes (PRO)

Nov 17 – Nov 18, 2009, Philadelphia, PA, USA

Presentations

Explore Key Issues in Content Validity

Nancy Kline Leidy, PhD, Senior Vice President, Scientific Affairs
and Senior Research Leader, United BioSource Corporation

Instrument Integrity and Platform Diversity - an ePRO Challenge Whose Time Has Come

Sonya Eremenco, ePRO Program manager, United BioSource
Corporation

Economic Incentives for Safe and Healthy Workplaces

Nov 16, 2009, Bilbao, Spain

Presentation

What is the Incentive in Insurance Premiums?

Radoslaw Wasiak, PhD, Research Scientist, Health Economics,
United BioSource Corporation

The American College of Phlebology 23rd Annual Congress

Nov 5 – Nov 8, 2009, Palm Desert, CA, USA

Presentation

Validating VEINES-Sym to Measure Change Following Endovenous Microfoam Ablation of the Great Saphenous Vein

Gibson KD, **Munavalli GS,** **Morrison N,** **Regan JD,** **Wyrwich KW,**
Suplick G, **Evans E**

2nd Conference Clinical Trials on Alzheimer's Disease (CTaD)

Oct 29 – Oct 30, 2009, Las Vegas, NV, USA

Oral Presentation

Psychometric Properties and Clinical Significance of the Dependence Scale as an Outcome in Alzheimer's Disease

Wyrwich K, **Frank L,** **Leibman C,** **Mucha L,** **McLaughlin T**

SPOTLIGHT ON SCIENCE

Recent Publications

Benedict A, Arellano J, **De Cock E**, Baird J. "Economic Evaluation Of Duloxetine Versus Serotonin Selective Reuptake Inhibitors And Venlafaxine XR In Treating Major Depressive Disorder In Scotland." *J Affect Disord*. 2010 Jan; 120(1-3):94-104.

Benedict A, Cameron DA, Corson H, Jones SE. "An Economic Evaluation Of Docetaxel And Paclitaxel Regimens In Metastatic Breast Cancer In The UK." *Pharmacoeconomics*. 2009; 27(10):857-859.

Calkins H, Reynolds MR, Spector P, Sondhi M, **Xu Y**, **Martin A**, **Williams CJ**, Sledge I. "Treatment Of Atrial Fibrillation With Anti-Arrhythmic Drugs Or Radio Frequency Ablation: Two Systematic Literature Review And Meta-Analyses." *Circ Arrhythmia Electrophysiol*. 2009 Aug; 2(4):359-361. [Epub 2009 Jun 2]

Chan KS, **Chen WH**, Gan TJ, **Hsieh R**, Chen C, Lakshminarayanan M, **Revicki D**. "Development And Validation Of A Composite Score Based On Clinically Meaningful Events For The Opioid-Related Symptom Distress Scale." *Qual Life Res*. 2009 Dec; 18(10):1331-1340. [Epub 2009 Oct 30]

Chen WH, **Revicki DA**, Lai JS, Cook KF, Amtmann D. "Linking Pain Items From Two Studies Onto A Common Scale Using Item Response Theory." *J Pain Symptom Manage*. 2009 Oct; 38(4):615-628. [Epub 2009 Jul 3]

Clark JA, Humphries JE, **Crean S**, **Reynolds MW**. "Topical Bovine Thrombin: A 21-Year Review Of Topical Bovine Thrombin Spontaneous Case Safety Reports Submitted To FDA's Adverse Event Reporting System." *Pharmacoepidemiol Drug Saf*. 2010 Feb; 19(2):107-114.

Coyne KS, **Matza LS**, Brewster-Jordan J. "We Have To Stop Again?": The Impact Of Overactive Bladder On Family Members." *Neurourol Urodyn*. 2009; 28(8):969-975.

Crean SM, **Michels SL**, **Moschella K**, **Reynolds MW**. "Bovine Thrombin Safety Reporting: An Example Of Study Design And Publication Bias." *J Surg Res*. 2010 Jan; 158(1):77-86.

Dagenais S, Roffey DM, Wai EK, Haldeman S, **Caro J**. "Can Cost Utility Evaluations Inform Decision Making About Interventions For Low Back Pain? A Systematic Review." *Spine J*. 2009 Nov; 9(11):944-957. [Epub 2009 Sep 12]

De Lissovoy G, **Fraeman K**, Teerlink JR, Mullahy J, Salon J, Sterz R, Durtschi A, Padley RJ. "Hospital Costs For Treatment Of Acute Heart Failure: Economic Analysis

Of The REVIVE II Study." *Eur J Health Econ*. 2009 Jul 7 [Epub ahead of print]

Feltner D, Hill C, **Lenderking W**, Williams V, Morlock R. "Development Of A Patient-Reported Assessment To Identify Placebo Responders In A Generalized Anxiety Disorder Trial." *J Psychiatr Res*. 2009 Oct; 43(15):1224-1230. [Epub 2009 May 6]

Fleurence RL, **Spackman E**, Hollenbeak C. "Does The Funding Source Influence The Results In Economic Evaluations? A Case Study In Bisphosphonates For The Treatment Of Osteoporosis." *Pharmacoeconomics*.; [In Press]

Fleurence R, **Williamson R**, Jing Y, Kim E, Tran QV, Pikalov AS, Thase ME. "A Systematic Review Of Augmentation Strategies For Patients With Major Depressive Disorder." *Psychopharmacol Bull*. 2009; 42(3):57-90.

Hanmer J, **Vanness D**, Gangnon R, Palta M, Fryback DG. "Three Methods Tested To Model SF-6D Health Utilities For Health States Involving Comorbidity / Co-Occurring Conditions." *J Clin Epidemiol*. 2009 Nov 5 [Epub ahead of print]

Harding G, Schein JR, Nelson WW, Vallow S, Olson WH, Hewitt DJ, Polomano RC. "Development And Validation Of A New Instrument To Evaluate The Ease Of Use Of Patient-Controlled Analgesic Modalities Of Postoperative Patients." *J Med Econ*. 2009 Dec 14 [Epub ahead of print]

International Working Group for HTA Advancement, Neumann PJ, Drummond MF, Jonsson B, **Luce BR**, Schwartz JS, Siebert U, Sullivan SD. "Are Key Principles For Improved Health Technology Assessment Supported And Used By Health Technology Assessment Organizations?" *Int J Technol Assess Health Care*. 2010 Jan; 26(1):71-78.

Ishak KJ, **Proskorovsky I**, **Guo S**, Lin J, **Caro JJ**. "Persistence With Antiarrhythmics And Its Impact On Atrial Fibrillation-Related Outcomes." *The American Journal of Pharmacy Benefits*. 2009 Winter; 1(4):193-200.

Jarbrink K, **Kreif N**, **Benedict A**, Locklear J. "Quality Of Life And Drug Costs Associated With Switching Antipsychotic Medication To Once-Daily Extended Release Quetiapine Fumarate In Patients With Schizophrenia." *Curr Med Res Opin*. 2009 Feb 2 [Epub ahead of print]

Khoury H, **Merikle E**, Roberts C, Wagner M, Johnson S. "Cost-Effectiveness Of Atorvastatin In The Primary Prevention Of Major Cardiovascular Events In Patients With Type 2 Diabetes In Canada." *Canadian Journal of Diabetes*. 2009; 33(4):363-375.

Kongnakorn T, **Mwamburi M**, Merchant S, Akhras K, **Caro JJ**, Nathwani D. "Economic Evaluation Of Doripenem For The Treatment Of Nosocomial Pneumonia In The US: Discrete Event Simulation." *Curr Med Res Opin*. 2010 Jan; 26(1):17-24.

Leidy NK, Gutierrez B, Lampl K, Uryniak T, O'Brien CD. "Can Patients With Asthma Feel Inhaler Therapy Working Right Away? Two Clinical Trials Testing The Effect Of Timing Of Assessment On Patient Perception." *J Asthma*. 2009 Dec; 46(10):1006-1012.

Machnicki G, Allegri RF, Ranalli CG, Serrano CM, Dillon C, **Wyrwich KW**, Taragano FE. "Validity And Reliability Of The SF-36 Administered To Caregivers Of Patients With Alzheimer's Disease: Evidence From A South American Sample." *Dement Geriatr Cogn Disord*. 2009; 28(3):206-212. [Epub 2009 Sep 12]

Malone DC, Boudreau DM, Nichols GA, Raebel MA, Fishman PA, Feldstein AC, Ben-Joseph RH, **Okamoto LJ**, Boscoe AN, Magid DJ. "Association Of Cardiometabolic Risk Factors And Prevalent Cardiovascular Events." *Metab Syndr Relat Disord*. 2009 Dec; 7(6):585-593.

Matza LS, Park J, **Coyne KS**, Skinner EP, Malley KG, Wolever RQ. "Derivation and Validation of the ASK-12 Adherence Barrier Survey (October)." *Ann Pharmacother*. 2009 Oct; 43(10):1621-1630. [Epub 2009 Sep 23]

Meads DM, McKenna SP, Doward LC, **Pokrzywnski R**, **Revicki D**, Hunter C, Glendenning GA. "Development And Validation Of The Asthma Life Impact Scale (ALIS)." *Respir Med*. 2010 Jan 4 [Epub ahead of print]

Mitchell SA, **Leidy NK**, Mooney KH, Dudley WN, Beck SL, Lastayo PC, Cowen EW, Palit P, Comis LE, Krumlauf MC, Avila DN, Atlam N, Fowler DH, Pavletic SZ. "Determinants of Functional Performance In Long-Term Survivors Of Allogeneic Hematopoietic Stem Cell Transplantation With Chronic Graft-Versus-Host Disease (CGVHD)." *Bone Marrow Transplant*. 2009 Sep 28 [Epub ahead of print]

Mossman D, Bowen MD, **Vanness DJ**, Bienenfeld D, Correll T, Kay J, Klyklyo WM, Lehrer DS. "Quantifying The Accuracy Of Forensic Examiners In The Absence Of A "Gold Standard." *Law Hum Behav*. 2009 Sep 22 [Epub ahead of print]

Naci H, **Fleurence RL**, Birt J, Duhig A. "The Economic Burden Of Multiple Sclerosis: A Systematic Review of the Literature." *Pharmacoeconomics*.; [In Press]

Naci H, **Fleurence RL**, Birt J, Duhig A. "The Impact Of Increasing Neurological Disability Of Multiple Sclerosis On Health

- Utilities: A Systematic Review of the Literature." *J Med Econ*. 2010 Jan 4 [Epub ahead of print]
- Pandina GJ, Garibaldi GM, **Revicki DA**, **Kleinman L**, Turkoz I, Kujawa MJ, Mahmoud RA. "Psychometric Evaluation of A Patient-Rated Most Troubling Symptom Scale For Depression: Findings From a Secondary Analysis of a Clinical Trial." *Int Clin Psychopharmacol*. 2010 Jan 7 [Epub ahead of print]
- Pandina GJ, **Revicki DA**, **Kleinman L**, Turkoz I, Wu JH, Kujawa MJ, Mahmoud R, Gharabawi GM. "Patient-Rated Troubling Symptoms Of Depression Instrument Results Correlate With Traditional Clinician-And Patient-Rated Measures: A Secondary Analysis of a Randomized, Double-Blind, Placebo-Controlled Trial." *J Affect Disord*. 2009 Nov; 118(1-3):139-146. [Epub 2009 Mar 25]
- Paramore LC**, **Hunter CA**, **Luce BR**, Nordyke RJ, Halbert RJ. "Value Of Biologic Therapy: A Forecasting Model In Three Disease Areas." *Curr Med Res Opin*. 2010 Jan; 26(1):41-51.
- Pokrzywinski RF**, Meads DM, McKenna SP, Glendenning GA, **Revicki D**. "Development And Psychometric Assessment of the COPD and Asthma Sleep Impact Scale (CASIS)." *Health Qual Life Outcomes*. 2009 Dec 7; 7(1):98.
- Rentz AM**, **Yu R**, Muller-Lissner S, Leyendecker P. "Validation Of The Bowel Function Index To Detect Clinically Meaningful Changes In Opioid-Induced Constipation." *J Med Econ*. 2009; 12(4):371-383.
- Reynolds MW**, **Stephen R**, Seaman C, Rajagopalan K. "Healthcare Resource Utilization Following Switch or Discontinuation in Multiple Sclerosis Patients on Disease Modifying Drugs." *J Med Econ*. 2010 Jan 15 [Epub ahead of print]
- Reynolds MW**, **Stephen R**, Seaman C, Rajagopalan K. "Persistence And Adherence To Disease Modifying Drugs Among Patients With Multiple Sclerosis." *Curr Med Res Opin*. 2010 Jan 13 [Epub ahead of print]
- Revicki DA**, **Chen WH**, **Frank L**, Feltner D, Morlock R. "Development And Analysis Of Item Response Theory Based Short Form Depression Severity Scales Based on the HDRS And MADRS." *Health Outcomes Research in Medicine*.; [In Press]
- Revicki DA**, **Chen WH**, **Harnam N**, Cook K, Amtmann D, Callahan LF, Jensen MP, Keefe FJ. "Development And Psychometric Analysis Of The PROMIS Pain Behavior Item Bank." *Pain*. 2009 Nov; 146(1-2):158-169. [Epub 2009 Aug 15]
- Revicki D**, **Rentz A**, **Harnam N**, Thomas V, Lanzetta P. "Reliability And Validity of the National Eye Institute Visual Function Questionnaire-25 In Patients With Age-Related Macular Degeneration." *Invest Ophthalmol Vis Sci*. 2010 Feb; 51(2):712-717. [Epub 2009 Sept 24]
- Revicki DA**, Schwartz CE. "Intellectual Property Rights And Good Research Practice." *Qual Life Res*. 2009 Dec; 18(10):1279-1280.
- Robinson Jr. D, Aguilar D, Schoenwetter M, Dubois R, Russak S, Ramsey-Goldman R, Navarra S, Hsu B, **Revicki D**, Cella D, Rapaport MH, Renahan K, Ress R, Wallace D, Weisman M. "The Impact Of Systemic Lupus Erythematosus on Health, Family and Work: The Patient Perspective." *Arthritis Care Res*.; [In Press]
- Roehrborn CG, Albertsen P, **Stokes ME**, Black L, **Benedict A**. "First-Year Costs Of Treating Prostate Cancer: Estimates From SEER-Medicare Data." *Prostate Cancer Prostatic Dis*. 2009; 12(4):355-360. [Epub 2009 May 26]
- Rothman M, Burke L, Erickson P, **Leidy NK**, Patrick D, Petrie C. "Use Of Existing Patient-Reported Outcome (PRO) Instruments and Their Modification: The ISPOR Good Research Practices For Evaluating and Documenting Content Validity for the Use of Existing Instruments And Their Modification PRO Task Force Report." *Value Health*. 2009 Sep 25 [Epub ahead of print]
- Stokes ME**, Muehlenbein CE, Marciniak MD, Faries DE, Motabar S, Gillespie TW, Lipscomb J, **Knopf KB**, Buesching DP. "Neutropenia-Related Costs In Patients Treated With First-Line Chemotherapy for Advanced Non-Small Cell Lung Cancer." *J Manag Care Pharm*. 2009; 15(8):669-682.
- Stull DE**, Meltzer EO, Krouse JH, **Roberts L**, Kim S, **Frank L**, Naclerio R, Lund V, Long A. "The Congestion Quantifier Five-Item Test for Nasal Congestion: Refinement of the Congestion Quantifier Seven-Item Test." *Am J Rhinol Allergy*. 2010 Jan-Feb; 24(1):34-38.
- Stull DE**, **Vernon MK**, Legg JC, Viswanathan HN, Fairclough D, **Revicki DA**. "Use Of Latent Growth Curve Models For Assessing The Effects Of Darbepoetin Alfa On Hemoglobin And Fatigue." *Contemp Clin Trials*. 2010 Jan 6 [Epub ahead of print]
- Van der Heijde DM, **Revicki DA**, Gooch KL, Wong RL, Kupper H, **Harnam N**, **Thompson C**, Sieper J, Atlas Study Group T. "Physical Function, Disease Activity and Health-Related Quality-Of-Life Outcomes After 3 Years of Adalimumab Treatment in Patients with Ankylosing Spondylitis." *Arthritis Res Ther*. 2009; 11(4):R124. [Epub 2009 Aug 17]
- Vernon MK**, Dugar A, **Revicki D**, Treglia M, Buysse D. "Measurement Of Non-Restorative Sleep In Insomnia: A Review Of The Literature." *Sleep Med Rev*. 2009 Dec 15 [Epub ahead of print]
- Wagner M, Lindgren P, **Merikle E**, Goetghebeur M, Jonsson B. "Economic Evaluation Of High-Dose (80 Mg/Day) Atorvastatin Treatment Compared With Standard-Dose (20 Mg/Day To 40 Mg/Day) Simvastatin Treatment in Canada Based on the Incremental Decrease in End-Points Through Aggressive Lipid-Lowering (IDEAL) Trial." *Can J Cardiol*. 2009 Nov; 25(11):e362-369.
- Wesnes K**, **Edgar C**, Andreasen N, Annas P, Basun H, Lannfelt L, Zetterberg H, Blennow K, Minthon L. "Computerized Cognition Assessment During Acetylcholinesterase Inhibitor Treatment In Alzheimer's Disease." *Acta Neurol Scand*. 2009 Dec 28 [Epub ahead of print]
- Wong TY, **Mwamburi M**, Klein R, Larsen M, Flynn H, Hernandez-Medina M, **Ranganathan G**, Wirotko B, Pleil A, Mitchell P. "Rates Of Progression In Diabetic Retinopathy During Different Time Periods: A Systematic Review And Meta-Analysis." *Diabetes Care*. 2009 Dec; 32(12):2307-2313.
- Woodward TC**, Tafesse E, **Quon P**, Kim J, Lazarus A. "Cost-Effectiveness Of Quetiapine With Lithium or Divalproex for Maintenance Treatment of Bipolar I Disorder." *J Med Econ*. 2009; 12(4):259-268.
- Wu Y, Aravind S, **Ranganathan G**, **Martin A**, **Nalysnyk L**. "Anemia and Thrombocytopenia in Patients Undergoing Chemotherapy for Solid Tumors: A Descriptive Study Of a Large Outpatient Oncology Practice Database, 2000-2007." *Clin Ther*. 2009; 31P2:2416-2432.
- Wyman JF, **Harding G**, Klutke C, Burgio K, Berriman S, Vats V, Bavendam T, **Coyne KS**. "Contributors To Satisfaction With Combined Drug And Behavioral Therapy For Overactive Bladder In Subjects Dissatisfied With Prior Drug Treatment." *The Journal of Wound Ostomy and Continence Nursing*.; [In Press]
- Wyrwich K**, **Harnam N**, **Revicki DA**, Locklear JC, Svedsäter H, Endicott J. "Assessing Health-Related Quality Of Life In Generalized Anxiety Disorder Using the Quality of Life Enjoyment And Satisfaction Questionnaire." *Int Clin Psychopharmacol*. 2009 Nov; 24(6):289-295.
- Zhang Z, Mahoney EM, Kolm P, Spertus J, **Caro J**, Willke R, Weintraub WS. "Cost Effectiveness of Eplerenone in Patients with Heart Failure after Acute Myocardial Infarction Who Were Taking Both ACE Inhibitors and Beta-Blockers: Subanalysis of the EPHEBUS." *Am J Cardiovasc Drugs*. 2010; 10(1):55-63.

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

HEALTH POLICY CORNER

continued from page 28

While specific awards will continue to be made until September 2010, it is clear that a broad range of methods, interests, and foci will continue to be a part of the national CER discussions that have found new prominence due, in part, to ARRA funding opportunities.

| AHRQ's \$300 million from ARRA ² | Grants Available from AHRQ within the Area of CER ³ |
|--|--|
| <ul style="list-style-type: none"> ■ \$172 million for Evidence Generation, to include <ul style="list-style-type: none"> a. \$100 million for Clinical and Health Outcomes Initiative in Comparative Effectiveness (CHOICE) "...a new, coordinated, national effort to establish a series of prospective pragmatic clinical comparative effectiveness studies that measure the benefits treatments produce in routine clinical practice and will include novel study designs focusing on real-world and under-represented populations (children, elderly, racial and ethnic minorities, and other understudied populations)..." b. \$48 million for patient registries c. \$24 million for additional (unspecified) evidence generation ■ \$29.5 million to support "innovative translation and dissemination" ■ \$20 million to support CER training and development ■ \$9.5 million for CER infrastructure ■ \$10 million to "Citizen's Forum" for stakeholder involvement ■ \$1 million in other grants ■ \$50 million toward existing evidence synthesis contracts ■ \$5 million for translation and dissemination ■ \$3 million for three full-time ARRA-specific positions | <ul style="list-style-type: none"> ■ \$24 million for Enhanced Registries for Quality Improvement and Comparative Effectiveness Research This fund will be allocated to develop the infrastructure and improve methodology for collecting prospective data from electronic clinical databases. The aim will be to generate new evidence on the comparative effectiveness of health care interventions. ■ \$25 million for Scalable Distributed Research Networks for Comparative Effectiveness Research The goal would be to improve capabilities of electronic health networks that are designed for distributed research to conduct prospective CER on outcomes of clinical interventions. ■ \$5 million for AHRQ Institutional National Research Service Award (NRSA) Postdoctoral Comparative Effectiveness Development Training Award ■ \$15 million for AHRQ Mentored Clinical Scientists Comparative Effectiveness Development Award ■ \$4 million for Electronic Data Methods (EDM) Forum for Comparative Effectiveness Research ■ \$44 million for Prospective Outcome Systems using Patient-specific Electronic Data to Compare Tests and Therapies (PROSPECT) Studies: Building New Clinical Infrastructure for Comparative Effectiveness Research This will aim to enhance the nation's ability to systematically collect prospective data, especially in under-represented populations in randomized control trials. ■ \$12 million for the Expansion of Research Capability to Study Comparative Effectiveness in Complex Patients |

References

¹ <http://www.staterecovery.org/Websites/staterecovery/Images/Enclosure%20-%20HHS%20Funding%20for%20States%20Under%20ARRA.pdf>

² <http://grants.nih.gov/grants/guide/notice-files/NOT-HS-09-009.html>

³ AHRQ and the Recovery Act. (<http://www.ahrq.gov/fund/cefarr.htm>)

United BioSource Corporation
7101 Wisconsin Avenue, Ste. 600
Bethesda, MD 20814
Tel: 301-654-9729
Contact: Susan J. Potter
Susan.Potter@unitedbiosource.com

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

www.unitedbiosource.com



United BioSource Corporation

Evidence Matters[®]

©2010 UNITED BIOSOURCE CORPORATION

This publication is printed on recycled paper.