

2009 Workshops – October 28, 2009

Morning Workshops (1-8)

9:30 am to 12:30 pm

Workshop 1

Qualitative Research in the Development of PRO Questionnaires - Best Practices and Avoiding Pitfalls

Instructors: Kathleen Beusterien, MPH Oxford Outcomes, Bethesda, MD USA and Emuella Flood, BA Oxford Outcomes, Bethesda, MD USA

Workshop content will include a discussion on the use of qualitative data in PRO research, including how focus groups are used to explore concepts, develop conceptual models and generate questionnaire items, and how cognitive debriefings are used to refine questionnaires and support their content validity. We will review best practices for designing PRO questionnaires, including focus group and interview sample size targets, discussion/interview guide development, best practices for conducting focus groups/interviews, and questionnaire formatting. We also will discuss best practices for qualitative data analysis, including data coding and attaining and documenting information saturation. Throughout the workshop, examples based on the speakers' experiences will be presented and discussed as a group. Real-world issues will be presented, and the group will discuss ways to address the issues. In addition, the group will complete group exercises (break out tasks) during the workshop to simulate the development of a PRO measure, including analyzing focus group transcripts and generating questionnaire items. The workshop outline will be as follows: 1) Qualitative methods in PRO research; 2) Initial qualitative steps - focus groups/in-depth interviews; 3) Break out task 1 and reporting back; 4) Model development; 5) Item generation including critiques of existing measures; 6) Break out task 2 and reporting back; 7) Cognitive debriefing research; 8) Pitfalls of qualitative research and how to avoid them. Style of Presentation: 60% Lecture, 25% in class exercise, 15% question and answer

Level: Basic

Workshop 2

Moving beyond Paper: Innovative Methods for Capturing Outcomes and Physiologic Data in the Electronic Age

Instructors: Sonya Eremenco, MA, United BioSource Corporation, Bethesda, MD USA; Ingela Wiklund, PhD United BioSource Corporation, London, United Kingdom; Shae Wilkins, Arrowhead Electronic Healthcare, LLC, Austin, TX USA

The increasing use of electronic patient-reported outcome (ePRO) instruments in a range of clinical and research settings has created opportunities to measure patient experience in innovative ways. This workshop focuses on best practices for leveraging electronic data collection methods to improve data quality and streamline capture of multiple streams of data from patients, clinicians and caregivers. This workshop will draw from a range of examples from the literature, the field, and experience with the EXACT-PRO Initiative to inform a discussion of key issues associated with ePRO development and implementation. Specific topics to be addressed include: new instrument development using electronic platforms in innovative ways; considerations for migrating existing validated instruments from paper to electronic platforms, including regulatory issues outlined in the FDA PRO Draft Guidance when ePRO instruments are to be used to support a labeling or promotional claim. The workshop will also address the use of technology to collect biometric data efficiently through integration with ePRO devices, including how these biometric devices are used in settings ranging from disease management to clinical trials in therapeutic areas such as diabetes and asthma. Other important topics include compliance enhancement, special populations such as older adults and children, and electronic capture of data from clinicians and caregivers.

The workshop will consist of 65% lecture and 35% case studies for discussion of how best to choose the ePRO platform for a specific study, including daily assessments vs. site assessments, and to also discuss cost implications related to different devices and applications. Audience participation will also involve question and answer and hands-on demonstration of ePRO and biometric device integration.

Level: Basic

Workshop 3

PRO Evidence Dossier: Evidence to Support Labeling and Promotional Claims for FDA-Regulated Medical Products

Instructor: Linda Nelsen, Merck Research Laboratories, North Wales, PA USA; Kati Copley-Merriman, M.S., M.B.A RTI Health Solutions, Research Triangle Park, NC USA; Josephine Norquist, MS Merck Research Laboratories, North Wales, PA USA; John Powers, MD George Washington University School of Medicine, Washington, DC USA

Learning Objectives: (1) Understand the steps to complete a PRO Evidence Dossier; (2) How to assemble the document in a clear and easy to follow structure; (3) How to conduct a gap analysis and; (4) When to engage FDA/SEALD to discuss PRO endpoints intended to support US product labeling and promotional claims. A standard and well-organized Patient-Reported Outcome (PRO) information package, i.e. PRO Evidence Dossier, to support labeling and promotional claims for FDA-regulated medical products is critical and will increase efficiency of providing relevant PRO information to the FDA Review Division /SEALD as well as increase efficiency of FDA/SEALD review process of the PRO information. During this workshop participants will be introduced to the 'When', 'What', and 'How' of a PRO Evidence Dossier to support a labeling and promotional claim. Specifically, when to engage FDA/SEALD to discuss the PRO endpoint(s); what are the key elements of a PRO Evidence Dossier; how to assemble the document in a clear and easy to follow structure; and how to conduct a gap analysis. The workshop will include an example claim and corresponding PRO instrument to work through as a class. Handouts will include all slides presented during the workshop and any key publications relevant to this topic. The workshop will be 25% hands-on with the example PRO, and will include time for discussion and Q&A (20% of time). After completing this workshop, participants will have a better understanding on the components to be included in a PRO Evidence Dossier to support a labeling and promotional claim and how to interact with FDA/SEALD during the process.

Level: Basic

Workshop 4

Is It What It Is? A Workshop on the Content Validity of PRO Instruments

Instructors: Nancy Leidy, PhD, United BioSource Corporation, Bethesda, MD USA; Julie McCormack, MA, United BioSource Corporation, Bethesda, MD USA; Donald Patrick, PhD University of Washington, Seattle, WA USA; Laurie Burke, MPH FDA, Silver Spring, MD USA; Elektra J. Papadopoulos, MD FDA, Silver Spring, MD USA; Ann Marie Trentacosti, MD FDA, Silver Spring, MD USA

Maximizing content validity is a critical step in instrument development; evaluating content validity for a given purpose is an important part of the research process. This workshop will address the issue of content validity of patient-reported outcome (PRO) measures used in clinical trials evaluating the effectiveness of health care interventions, with specific reference to evaluating the efficacy of new medical products. Specific topics to be discussed include: 1) Setting the stage: Determining the concept, study hypotheses, endpoint positioning. This topic will include a discussion of the role of the target product profile and claims determination in assuring content validity. 2) Content validity – what it is, and what it is not. This session will use scientific precedent to define content validity and discuss the role concept selection and instrument development methods play in assuring content validity. 3) An overview of qualitative methods used to develop and evaluate PRO instruments - This discussion will include a review of focus group and cognitive interviewing methods that can be used to evaluate an existing instrument for content validity. 4) Analysis - This topic will address the

analysis of qualitative data with specific attention given to procedures for mapping new qualitative data to existing instrument content. 5) Next steps: Tolerance, adaptation, or start again ☒ This discussion will address the alternatives available when assessments indicate less than optimal content validity of a selected instrument, including pros and cons of changing an existing measure and the possibility of alternative study designs. The workshop will consist of 50% lecture, 30% discussion with audience participation, and 20% hands-on exercises involving concept identification, qualitative analyses, and adaptation. *Level: Basic*

Workshop 5

Everything you wanted to know about modern psychometric methods but were afraid to ask

Instructors: Jeremy Hobart, PhD Peninsula College of Medicine and Dentistry, Plymouth, UK; Stefan Cano, PhD Peninsula College of Medicine and Dentistry, Plymouth, UK; Anita Slade, PhD Peninsula College of Medicine and Dentistry, Plymouth, UK; Peter Hagell, PhD Lund University, Lund, Sweden

Confused by classical test theory? Finding item response theory inaccessible? Wrestling with Rasch analysis? Struggling with the statistics? Muddled by the math? Are you like we were: wannabe psychometricians trying to get into modern psychometric methods, but who have attended other workshops and left feeling none-the-wiser? Then this is the modern psychometric methods workshop for you. In reality the basic principles are very simple. So, we have put together a straightforward, non-technical, non-mathematical approach to modern psychometric methods that will help you begin to access the fantastically powerful and illuminating information they have to offer. In this three hour workshop we will describe: the role of quality of life and other types of health rating scales as outcome measures; the basic principles underlying traditional psychometric methods, their limitations and drivers for modern methods; the principles underpinning modern psychometric methods; the similarities and difference between traditional and modern psychometric methods; the similarities and important differences between Rasch analysis and Item Response Theory. This workshop will also provide a ☒hands-on☒ instruction in using the Rasch Measurement Model (RUMM2020) software package in order to analyze data for internal construct validity; reliability; category probability curves; differential item functioning; and scaling characteristics. The three-hour workshop will be divided into three equal sub-sessions: lecture including descriptions of background, principles and comparison of methods; demonstration of Rasch analysis in practice; hands-on class exercise including data analyses using the RUMM 2020 program, and question & answer session (attendees should bring their laptops to the session to fully benefit from the data analysis exercise).

Level: Basic

Workshop 6

Interpreting Utility (Preference-Based) Measures of Health-Related Quality of Life

Instructor: David Feeny, PhD Kaiser Permanente Northwest, Portland, OR USA; Keiko Asakawa, PhD Canadian Agency for Drugs and Technologies in Health, Ottawa, ON Canada; Maria Jose Santana, PhD University of Alberta, Edmonton, AB Canada

The Workshop will be at an advanced level, focusing on the interpretation of utility scores from direct and multi-attribute (indirect) approaches to measurement. The direct approaches will include the visual analogue scale (Feeling Thermometer), time tradeoff, and standard gamble. Major multi-attribute utility measures will include the EQ-5D, Health Utilities Index (HUI), and Short-Form 6D. The Workshop will include hands on experience in the direct assessment of utility scores, completing questionnaires from several systems, and analyzing and interpreting the results. The interpretation of scores will be considered in the context of comparing groups at a point in time as well as comparing within-person change over time. Applications will be drawn from diverse settings including osteoarthritis of the knee, multiple sclerosis, total hip arthroplasty, and acute lymphoblastic leukemia. Evidence on clinically important differences will be discussed. Attendees should, at a minimum, have a basic knowledge of the conceptual foundations and practical approaches of the utility approach to assessing health-related quality of life. *Level: Advanced*

Workshop 7

Advanced Psychometric Methods, Part 1: Use of Exploratory and Confirmatory Factor Analyses in PRO Instrument Development and Evaluation

Instructor: Margaret Vernon, PhD United BioSource Corporation, Bethesda, MD USA and Donald Stull, PhD United BioSource Corporation, Bethesda, MD USA

The development and psychometric evaluation of PRO instruments requires the application of a number of different techniques, including exploratory and confirmatory factor analysis (FA), item response theory analysis, and structural equation modeling (SEM). We will provide a brief overview of psychometric analyses and will then focus on the application of (1) exploratory and confirmatory factor analysis for understanding of new measures and (2) use of SEM for testing construct validity. Exploratory and confirmatory FA can be used to examine the relationships among items with a PRO measure or among different domains or multiple PRO measures. These techniques are useful for understanding the internal structure of PRO instruments and for understanding construct validity. This half-day workshop will describe the main methods of FA and illustrate these methods with examples from the instrument development literature. SEM is a powerful analytic technique that combines FA and path analysis in a simultaneous, confirmatory approach. Using SEM, the researcher can specify and evaluate hypothesized relationships between observed and latent (unobserved) constructs as well as relationships among the latent variables. SEM can also estimate the reliability and validity of measurement models while explicitly modeling measurement error. A researcher specifies a measurement model and a structural model which specifies relationships among the latent variables to examine construct and criterion-related validity. If the observed covariances are consistent with the model-implied covariances, the researcher has evidence supporting the construct validity of the PRO measure. This workshop will demonstrate the main methods, testing assumptions and criteria, and provide examples to illustrate the methods of SEM.

Level: Advanced

Workshop 8

Advanced Psychometric Methods for PRO Development - Item Response Theory

Instructors: Lori McLeod, PhD RTI Health Solutions, Research Triangle Park, NC USA and Cheryl Coon, PhD RTI Health Solutions, Research Triangle Park, NC USA

This workshop is intended to be an introduction to item response theory (IRT) and its value in outcomes research. This is an advanced course and participants should have an understanding of the general principles behind patient-reported outcome (PRO) instrument development and knowledge of basic statistical methods. The learning objectives of the course are to (1) understand the mathematical models that form the foundation of IRT, (2) discover how IRT can be used for scoring, scaling, linking, assessing measurement equivalence, and creating computerized adaptive tests, and (3) recognize the benefits of utilizing IRT when developing and evaluating PROs. The course begins by explaining why PRO developers should be aware of IRT. Models for binary, ordinal, and nominal items are described. The assumptions behind these IRT models and how to assess these assumptions are discussed. The testing of model assumptions leads into the assessment of item fit and model fit, as well as standard errors associated with item parameters and the scale itself. The course then addresses advanced applications of IRT with a discussion of scoring, scaling, linking, differential item functioning, and computerized adaptive testing. The final portion of the workshop consists of a hands-on working example where data, software, and command files are provided and used to demonstrate item analysis and item reduction. In addition to these files, we will provide workshop slides and a reference list of useful books, articles, websites, and software programs. Real-life examples will be used throughout the workshop. The presenters will entertain questions from the workshop participants about the models, methods, and their application. We expect that this workshop will include approximately 70% lecture, 20% in-class exercise, and 10% question and answer with the participants. *Level: Advanced*

Afternoon Workshops (9-16)

1:30 pm to 4:30 pm

Workshop 9

Leave the "Real-World" Data to the PROs: The Inclusion of Patient Reported Outcomes (PROs) in Observational Research

Instructors: Hilary Colwell, MPH ICON Clinical Research, San Francisco, CA USA; Kimberly Miller, Ph.D ICON Clinical Research, San Francisco, CA USA; Eric Elkin, MPH ICON Clinical Research, San Francisco, CA USA

The increased reliance on evidence-based medicine to inform clinical decision making has made it critical to document the benefits & effectiveness of a product in actual clinical practice, in addition to data gathered in randomized clinical trials (RCTs). Observational studies provide an opportunity, in a "real-world" setting, to collect clinical & safety data, as well as patient-reported outcomes (PROs) associated with a particular disease and/or treatment regimen. The objective of this workshop is to present an overview of PRO components in observational studies & to highlight the value of these data to key stakeholders. The workshop will: (1) Emphasize the importance & rationale for the inclusion of PROs in observational studies; (2) Discuss the types of observational studies & strategies to collect data directly from patients; (3) Review the challenges in the implementation of PROs in observational studies & contrast these to the issues encountered in RCTs; (4) Summarize study design issues, including instrument selection & translation, schedule of assessment, & data collection methods; (5) Highlight the methods employed for analysis of PRO data in observational research, with an emphasis on the solutions to the unique challenges of "messy" data that are often present in observational studies & PRO data; (6) Provide examples of dissemination plans through publications, conference proceedings, internal communications, as well as through documents designed to support a product's value and decision-making from payors. Following the workshop, participants will understand PRO instrument inclusion in observational research; the challenges & advantages of studies other than RCTs; and the unique approaches to analysis & dissemination of PRO results from real-world studies. Various case studies will be presented and discussed throughout the workshop. This workshop will include 70% lecture and 30% in-class, interactive exercises. The target audience of this workshop includes researchers who are beginning to use or contemplating using PROs in their non-RCT research.

Level: Basic

Workshop 10

Analysis of longitudinal studies of HRQOL in SAS, SPSS and R

Instructor: Diane Fairclough, DrPH University of Colorado Denver, Denver, CO USA

This course will provide a tutorial of the analysis of longitudinal studies with missing data. We address two scenarios for data with ignorable dropout. For each scenario, we will first discuss the assumptions underlying each model, then will go through the steps of fitting the model in SAS, SPSS and R. The workshop will include time for practice with datasets that will be provided. Participant are encouraged (but not required) to bring laptop computers with SAS, SPSS or R installed. Handouts will include all slides and example code in both SAS, SPSS and R. After completing this workshop, participants will be able to: 1. Choose between a repeated measures and growth curve model for the analysis of longitudinal data 2. Describe the underlying assumptions of these models and alternative models for non-ignorable dropout 3. Build models and construct hypothesis tests in either SAS or R Participants should have experience with linear models and be comfortable programming in SAS, SPSS or R.

Level: Advanced

Workshop 11

Health related quality of life, utility data and patient preferences for supporting reimbursement decisions

Instructors: Andrew Lloyd, DPhil Oxford Outcomes Ltd, Oxford, Oxon UK

This half-day workshop will present methods for estimating utilities for use in economic evaluations for bodies such as NICE. The importance of utilities in driving cost effectiveness will be discussed. The main methods for estimating utilities will be presented including standard gamble and time trade off and also generic instruments such as EQ-5D and HUI. Where such data are not available the use of mapping functions and other algorithms for estimating a utility from a disease specific measure will be described. Other approaches to addressing a lack of utility data will also be described including prospective observational studies, systematic reviews and critical appraisal of published values and lastly the valuation of vignette type descriptions of health. The potential role of patient preference studies using conjoint analysis/ discrete choice experiments will also be explored. Such studies can provide rich data regarding the value that patients place on improvements in health care (e.g. better symptom control, reduced adverse events or better device characteristics). In the final section the different requirements and preferences of reimbursement agencies around the world will be discussed. These differences can impact estimates of cost effectiveness and we will discuss whether greater international standardisation maybe preferable. The workshop will be 65% lecture; 25% break out discussion tasks and 10% Q&A. *Level: Basic*

Workshop 12

Documenting Content Validity of Patient-Reported Outcomes (PRO) to Support Labeling and Promotional Claims for FDA-Regulated Medical Products

Instructors: Josephine Norquist, MS Merck Research Laboratories, North Wales , PA USA; Kelly McQuarrie, BS Wyeth, Collegeville, PA USA; Kathryn Lasch, PhD Mapi Values, Boston, MA USA; Laurie Burke, MPH FDA, Silver Spring, MD USA

Learning Objectives: (1) Understand what content validity is and why it is important for PRO endpoints intended to support US product labeling and promotional claims (2) Describe how and when PRO content validation fits into clinical development of a product. (3) Recognize concepts in product claims. (4) Recognize the steps required to test and document content validity for a PRO endpoint measure, including design, implementation, analysis, and reporting of a content validation study. (5) Practice analyzing and coding segments of patient interviews to support content validity and saturation of concepts. Product promotion and labeling claims for FDA-regulated medical products must be based on endpoints with demonstrated content validity in the product's target population in order to avoid false or misleading claims. Interviews can help support content validity of a PRO endpoint if there is evidence of "saturation" (i.e., all the concepts important to the patient have been identified, and no new information emerges in additional interviews). This ½ day workshop introduces participants to the theory and methods used to assess content validity and to evaluate saturation. A SEALD reviewer will explain the regulatory significance of content validity and how FDA uses content validation studies to evaluate patient-reported outcome (PRO) measures intended to support product claims. Participants will analyze transcripts to identify concepts, test for saturation, and evaluate content validity of PRO instruments intended to support mock product claims.

Handouts will include all slides presented during the workshop and a reference list of key publications relevant to this topic. The workshop will involve 50% lecture, 25% discussion, and 25% interactive exercise. *Level: Basic*

Workshop 13

Successful Implementation of Cognitive Interviews in Special Populations

Instructor: Carla DeMuro, MS RTI Health Solutions, Research Triangle Park, NC USA; Sandy Lewis, BSRN RTI Health Solutions, Research Triangle Park, NC USA; Sheri Fehnel, PhD RTI Health Solutions, Research Triangle Park, NC USA; Dana DiBenedetti, PhD RTI Health Solutions, Research Triangle Park, NC USA

The cognitive interview was initially developed in the early 1980's to identify sources of potential response error within surveys or questionnaires. With the release of the FDA guidance Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (US Department of Health and Human Services, 2006), cognitive interviews have gained importance and relevance in also being utilized to assess content validity of both existing and novel patient reported outcome measures. Standard approaches for the conduct of a cognitive interview such as think aloud, verbal probing, and concurrent and retrospective probing abound and all provide valuable insight. However, such standard approaches may lose utility in a sick or otherwise challenged population. For example, what approach is best for use in pediatric subjects to sustain attention? How does the interview environment impact subjects with dementia, schizophrenia or other cognitive impairment? How do we ask questions about sensitive topics such as sexual functioning, risk behaviors or sexually transmitted infections without introducing bias? This workshop seeks to provide tips and techniques to guide the researcher in methods to foster a successful cognitive interview under suboptimal conditions that will meet the rigor described in the FDA guidance. The workshop will include a didactic slide presentation to orient the group to cognitive interview techniques and create a shared working vocabulary. The didactic component (50% of course) will be followed by break-out sessions (25% of course) to address specific special populations as well as provide for an interactive, hands-on practice session (20% of course) with trained interviewers and mock subjects. A short portion of the course will provide for question and answer (5% of course).

Level: Basic

Workshop 14

Interpreting Change in Health-Related Quality of Life Patient-Reported Outcomes Measures

Instructor: Kathleen Wyrwich, PhD United BioSource Corporation, Bethesda, Maryland USA and Ariane Kawata, PhD United BioSource Corporation, Bethesda, Maryland USA

Several strategies for identifying meaningful shifts in health-related quality of life (HRQOL) measures and other patient-reported outcomes (PROs) have emerged as key methods for interpreting, understanding, and evaluating change over time. This workshop will review, critique and compare the methods that have been applied to establish meaningful change standards, which include anchor- and distribution-based techniques. Also, the importance of linking meaningful changes in HRQOL and PRO measures to established clinical parameters will be discussed. Practical approaches to improving and advancing HRQOL and PRO change evaluations that enhance the interpretation of change, as well as a review of controversies that have developed, will be provided. In addition, this workshop will explore current regulatory guidelines for demonstrating important change in HRQOL measures and other PROs.

Level: Advanced

Workshop 15

Advanced Psychometric Methods, Part 2: Executing and Interpreting Exploratory and Confirmatory Factor Analyses in PRO Instrument Development and Evaluation

Instructors: Margaret Vernon, PhD United BioSource Corporation, Bethesda, MD USA and Donald Stull, PhD United BioSource Corporation, Bethesda, MD USA

This half-day workshop will build on Advanced Psychometric Methods, Part 1, by presenting results from examples of exploratory and confirmatory factor analyses; executing live, interactive analyses; and interpreting results of output, particularly for confirmatory factor analyses and structural equation models. We will work through examples of analyses by presenting hypothesized models, discussing key analytic criteria (e.g., sample size, factor loading size, extraction, rotation, key parameter estimates, cross-loadings and correlated errors, model specification and identification, fit indices, indications of model misfit), and how to interpret output. Annotated examples will be presented from output from selected software (e.g., SAS, Stata, EQS, and Mplus), but the issues are relevant regardless of the users' software.

Level: Advanced

Workshop 16

Developing a global strategy for using ePROs in multi-national clinical trials, highlighting case studies from urology (BPH and Nocturia): Best practices and considerations from conceptual model to commercialization

Instructors: T. Michelle Brown, Ph.D. Abt Bio-Pharma Solutions, Inc., Lexington, MA USA and Tove Holm-Larsen, M.Sc., Ph.D. Ferring Pharmaceuticals A/S, 2300 Copenhagen S, Denmark

Workshop attendees will review the PRO regulatory, methodological, and analytical considerations as they are applied to real-world examples and strategy from urology clinical trials utilizing ePRO instruments. The following content objectives and questions will be addressed in the workshop: Developing a PRO Strategy: Why and when should you start developing your multi-national PRO strategy and what should be included? What are the factors to be considered in a multinational vs. single country clinical trial? Regulatory Issues: How to plan and meet governmental regulatory requirements, from conceptual model design to PRO selection and analysis. Design and Implementation Issues: What issues should be considered (and avoided) in selecting PRO endpoints in light of clinical endpoints? Identifying and selecting ePRO instruments across cultures and languages. What additional validation and equivalence information is necessary and sufficient for ePRO use? What are the pros and cons of using ePROs? What needs to be included in your ePRO measurement model and how to avoid ePRO administration pitfalls. Analytical Issues: What analytical factors need to be considered when pooling multi-national ePRO data? What issues may arise from the use of ePRO data? Missing data? Additional analyses? Regulatory Approvals and Commercialization: What evidence must be presented for registration, label claims, and reimbursement? How can you develop your PRO strategy to maximize the likelihood of successful commercialization?

Workshop level: Basic