Channeling the Power of Feedback

The principle of a feedback loop is effortless: Provide individuals with information about their actions in real time, and then give them a chance to change those actions, pushing them toward better behaviors. Our team has found that sponsors, clinical trial sites, and research organizations are constantly seeking feedback on performance in the clinical trial. For example, a component of the performance appraisal is training raters to increase the accuracy of providing accurate results to sponsors and research organizations. A major focus of 2013 has been to utilize research from our statistical findings to train raters to decrease biases, increase accuracy of evaluations, increase behavioral accuracy to improve observational skills, and also, increase rater confidence. Over the years a number of strategies have been developed to ensure all components of the clinical trials have decreased errors/biases.

In moving forward to a new year, clinical trials development can borrow from the technology field and harness the power of the feedback loop and its four distinct stages. First, is the data: A behavior must be quantified, captured, and saved. This data can be used to guide training efforts, selection of endpoints and trial development. Second, the knowledge must be communicated to the individual, in a framework that makes it expressively meaningful. Speaking in technical terms and bellowing statistical concepts does not reach everyone. Yet valuable information is ineffectual if we don’t comprehend it, which leads to a third stage, consequence. The knowledge must inform future direction. Lastly, the fourth stage is action. There must be a distinct instant when the individual can attune a behavior, make decisions, and act. Once that action is assessed, the feedback loop can operate all over again, leading to our goals of effective study development and outcomes.

In 2013, it was important to focus on using psychometrics to drive optimal training, research, scale development and surveillance. Our team has seen that traditional forms of rater training, have not been successful at increasing rater accuracy even though it minimizes scaling rater errors; traditional forms of statistical analysis have shown disparate results from modern statistical techniques, and traditional forms of surveillance be enhanced. Updating some of these traditional forms as disease areas are being scientifically updated is a foremost goal. Enhancing positive clinical trial outcomes should include, performance dimensions training, modern psychometric theory, efficacy endpoint evaluation, development of new measures when one is lacking, and most importantly, channeling the power of the feedback loop.
Advancing Science, Advancing Psychometrics

One can never be sure that measurement is perfect. Is the weight reported on your bathroom scale perfect? Even precisely calibrated instruments can be littered with measurement errors, including human errors. All measurements (including assessment tools utilized in clinical trials as outcome measures) are plagued by numerous challenges that can lower measurement accuracy. Additionally, as science advances and new information is gathered about disease areas, assessments used to measure efficacy of a treatment, and techniques used to analyze assessments also need to advance.

In response to fundamental shifts in scientific views of assessments and outcome measures, it is important to shift the focus of statistical analysis on developing and applying psychometric models to support the development, analysis and scoring of a new generation of assessments.

As clinical trials and academic research enters a new world of assessment with advanced computer/human interaction, adaptive feedback and data mining, there is much to be discovered about how to aptly influence advances in technology and statistics toward the creation of a new generation of valid assessments. In order to prepare researchers and developers to create assessments that is valid in this new world, suitable psychometrics need to be utilized. For example, determining whether to use reliability change indices combined with clinical change, or item analysis is a step in that direction. Mukherjee et al. “Dysexecutive and amnesic AD subtypes defined by single indicator and modern psychometric approaches: relationships with single nucleotide polymorphisms (SNPs)” differentiated amnesic and dysexecutive people with AD using a conventional approach and a modern psychometric approach and found higher proportions of SNPs associated with dysexecutive vs. amnesic groups in predicted directions using the modern psychometric approach (Item Response Theory) than using the conventional approaches.

A PubMed.gov review conducted by ProPhase LLC Research & Training Development found an increase in modern psychometrics such as rasch analysis and Item Response Theory over the years, as compared to standard reliability and validity procedures. Similarly, a PubMed.gov search conducted for disease areas revealed development of refinement of new assessments has increased over the past 20 years, primarily in the area of Depression.
Randomized clinical trials are a significant means of advancing medical knowledge. The British Medical Journal (the BMJ) reported that almost one in three large clinical trials remain unpublished five years after completion. Of these, 78% have do not have results publicly available. Several researchers worry that studies that do not substantiate a treatment is effective are more likely to remain unpublished, distorting the clinical trial outcomes and causing a detriment to patients by giving an artificial vestige of treatments’ efficacy. Since the BMJ findings, many clinical trials media outlets have addressed the topic in relation to ethical practices; however, few have focused on legitimate reasons for results to remain unpublished. For example, manuscripts could have been submitted to scientific journals and were rejected. Also, the assessments used for primary and secondary efficacy may not have shown significant findings or may have been biased.

Despite the findings on unpublished studies by the BMJ, a review of primary and secondary efficacy measures should be assessed. Selecting the appropriate endpoints and providing training, surveillance and monitoring of results are essential to study outcomes. It should not be assumed that all unpublished studies did not show significant findings, or that the pharmaceutical industry may be diffident to publish negative results, as published studies were as likely to have been industry-funded as were the unpublished ones.

Trends in psychometric testing analysis of rating scales (development, reliability and validity)

Training, Measurement & Unpublished Studies

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The root of the investigation for why studies remain unpublished should focus on the study design and selection of endpoints. The appropriate selection of outcome measures for disease-specific clinical trials is a focus of ongoing debate. While recognizing that appropriate outcome assessment is influenced by the exclusive design physiognomies and resources of the study, endpoints should be selected in a mode that augments the effectiveness and importance of the clinical trial in terms of focusing on the burden of the disease. While choosing less decisive endpoints may make allowance for shorter studies and unproblematic assessment, they may not produce beneficial information about how effective the treatment was for real world outcomes. When erroneous endpoints are selected, key questions remain. This in turn, can lead to additional trials necessitating more time, money and subject burden.

The importance of registries (such as ClinicalTrials.gov, World Health Organization’s International Clinical Trials Registry Platform etc…) in maintaining additional records of list of assessments, whether training was provided on endpoints, who provided training on endpoints, sample size appropriateness, and psychometric properties of endpoints should help to close some of the gaps as to why studies remain unpublished. Resources can be utilized by sample size reviews, and selecting, at the start of testing, a well-trained study team on endpoints that provide the strongest indications of the efficacy of the treatment being examined.
Alzheimer’s Association Walk to End Alzheimer’s

The Wellness Committee at ProPhase, LLC recognizes the impact Alzheimer’s has on families and the healthcare system. Our team participated in the Alzheimer’s Walk in Riverside Park, New York, NY in October 2013. We hope to provide an opportunity to enhance awareness of Alzheimer’s disease and to assist in raising much needed funds to further efforts to minimize the incidence of Alzheimer’s disease through the advancement of research, to enhance care and support, and to promote brain health.

Supporters began the Alzheimer’s Walk in Riverside Park on a bright fall day. Photo courtesy of Beretzi Garcia

Team ProPhase ready to begin the walk. Photo courtesy of Beretzi Garcia

Presentations & Awards

Research & Training Development (R&TD) presented posters at scientific conferences and meetings.

The process of defining clinical significance remains a challenge. R&TD Statistician, Ms. Linda Gao and CEO, Mark Opler, presented on the use of reliable change indices at the Fall meeting of the International Society for CNS Clinical Trials and Methodology (ISCTM) in September 2013. As an attempt to develop a standard method of estimating clinically significant change, ProPhase presented on strategies to identify reliable change following participation in a clinical trial: (1) Reliable Change Index (RCI), (2) clinical significance (CS). Studying RCI and CS has shifted the outcomes model from studying treatment groups to studying individual change within those groups. Endpoint measures must move beyond symptom focus and assess individuals a propos the multifaceted domains of their functional, real-world, lives in which clinically significant change is operationalized.

The R&TD team also presented on the significance of social cognition in schizophrenia, in collaboration with Investigators at Manhattan Psychiatric Center and Nathan S. Kline Institute for Psychiatric Research. Given the significant role of functional outcomes in schizophrenia, there has been increasing importance in factors that may underlie these outcomes. If the characteristics of these factors can be defined, interventions may be developed to improve them, which, in turn, will have a parallel impact on long term functioning and outcome. The presentation supports a causal model that indicates that social cognition underlies and is causally primary to functional outcomes.

The R&TD team also attended the Clinical Trials for Alzheimer’s Disease, November 2013, San Diego, CA. Dr. Brian Rothman and Dr. Luka Lucic presented preliminary results demonstrating item variability in the Alzheimer’s Disease Assessment Scale – Cognitive (ADAS-Cog). Primarily, different items on the ADAS-Cog are representative of different stages of cognitive decline (e.g. Mild Cognitive Impairment, and AD). There were significant differences in response to a number of items on the ADAS-Cog, possibly caused by a lack of consistency in testing administration, or scoring...
Presentations & Awards (continued)
parameters of the ADAS-Cog. The choices made during analysis will substantially affect the results, and our analysis have described and illustrated that the subgroups may have different impact on different items affecting outcome.

As more clinical trials now include video, audio or external rater surveillance measures, little research is done examining participant's perspective. Recorded interviews and scoring may influence the study outcomes and how patients and raters perform during the interview. At the CNS Summit in November 2013, Boca Raton, FL, Dr. Mark Opler and Dr. Sofija Jovic presented on ProPhase's current endeavors in assessing subject perceptions of recording interviews during clinical trials. Our research has identified, recordings may present many important sources of variability. Although, audio recordings encourage inter-rater reliability, it is important to examine the patient's perceptions of the audio recording process and whether or not their perceptions influence their responses and rapport with the interviewer.

Publications
The following have been published since our last issue (October, 2013):


Where are we next?

WASHINGTON, DC
February 18-20
Meet Dr. Opler, Dr. Khan, Dr. Jovic, and Ms. Linda Gao at the upcoming ISCTM Spring Conference

MUNICH, GERMANY
March 1-4
Our team: Dr. Khan, Dr. Rothman, and Dr. Ivanova will be presenting at the European Psychiatric Assoication

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