Health Outcomes Research — AN EVOLUTION TOWARDS PERSONALIZED MEDICINE AND THE DIGITAL FUTURE

Health outcomes research has emerged as the science of measuring the benefits to patients of new medical products and empirically substantiating those benefits. The term "health-related quality of life" (HRQL) first began to appear in regulatory submissions for labeling and promotion of new pharmaceutical compounds in the mid-1990s. Since then, increasing interest in individualized therapy and personalized medicine has driven a growing need to closely assess the benefits of new treatments by collecting data about how patients feel and function[1].With this has come an evolution of the vernacular associated with health outcomes. The intent of the evolution has been to create a common language among the sponsors who develop new medical products, the agencies who regulate them and the scientific community.

Outside the health outcomes community and in some small pockets within it, the term "quality of life" continues to circulate. This is despite repeated explanation by regulators and scholars that it connotes a wide array of concepts even beyond health e.g. income, social position. In 2005, the EMA finalized and published a reflection paper on HRQL. This lead to a bit more specificity assigned to the types of outcomes that are meaningful to patients and measurable when evaluating treatment benefit. However, it wasn't until the release of the FDA Draft Patient Reported Outcomes (PRO) Guidance for Industry in 2006 that it became explicit that, for purposes of labeling, the appropriateness of an outcomes measurement tool will be evaluated in the context of the intended claim of benefit for an intended patient population. PRO was defined in this guidance as "a measurement of any aspect of a patient's health status that comes directly from the patient i.e. without any interpretation by a physician or anyone else"[2]. This led to a further distinction between the terms PRO and HRQL. While HRQL is a PRO, not all PROs represent HRQL. For example, symptom frequency and severity are PROs and may be contributing components to HRQL but they alone do not define HRQL fully.

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Clinical Outcomes Assessments (COAs)

In December 2009, the FDA finalized its Guidance for Industry on PRO measures to be used in medical product development to support labeling claims. With this guidance, the FDA emphasizes the importance of the patient perspective. This guidance has introduced awareness of the fact that, for certain aspects of disease, the patient is the primary and possibly sole source of information. The most frequently referenced example of this is the concept of pain. No one can understand the experience of an individual's pain better than the individual him/herself.

More recently, the definition of clinical outcomes assessments (COAs) to include both survival and other not fully objective outcomes assessments has been introduced into the lexicon of terminology. It has also been introduced at industry conferences and at a FDA hosted public workshop in October of 2011 entitled, "Measurement in Clinical Trials: Review and Qualification of Clinical Outcomes Assessments."[3] The outcomes assessments, which are not fully objective, include PROs, clinician-reported, and observer-reported outcomes (ClinRO and ObsRO, respectively). During the workshop, a ClinRO was defined as an assessment determined by an observer with some recognized professional training that is relevant to the measurement being made. In contrast, ObsRO was defined as an assessment determined by an observer that does not have a background of professional training relevant to the measurement being made i.e., a non-clinician observer such as a caregiver.

While the FDA Guidance for Industry on PROs does not explicitly discuss ClinROs, it does discuss special populations such as pediatric and cognitively impaired populations. In these examples, patients themselves may be unable to report and thus the measures that support labeling in these populations are more appropriately directed to an observer of the patient such as a parent, guardian or caregiver. Both ObsRO and ClinRO measures require a direct observation of the concept being addressed by proposed label claim language. These two groups can only report what they see. Despite a title dedicated to PROs, the FDA's guidance methods discuss development and validation issues that are the same regardless of whether it is a patient, clinician or observer reporting the information. Qualitative research and cognitive debriefing are still important for identifying concepts and the context of use of a PRO, ClinRO, or ObsRO. This provides a means for confirming content with the aim of minimizing measurement variability and ensuring a consistent interpretation of the response scale. Implementation of any of these in a clinical development program will

require the same substantial evidence from adequate and well-controlled trials.

Implementing COAs Electronically

Just as the methods and evidence requirements to establish the appropriateness of a measure to support labeling are similar among COAs, the implementation of PRO, ClinRO, or ObsRO measurement strategies in a clinical trial shares common challenges. Harmonizing efforts to linguistically validate and develop training with the appropriate data collection method and site selection process is relevant for all COAs. In the context of state-of-the-art multimode technology options for capturing clinician, patient, and observer (caregiver) COAs, the criteria for selecting a data collection technology will be directed by the intended use of the COA data, e.g. to support approval and labeling. This includes consideration of patient population characteristics and context of use, how frequently the concept being measured changes, how frequently it is to be assessed and whether assessment takes place in a supervised or unsupervised setting.

While there may be subtle nuances specific to the reporting sources of information (patients, clinicians, or observers), training is essential for reducing variability associated with the capability of the reporter to use a scale. Evidence for demonstrating the "usability" of a technology for collecting the outcomes is as essential as the evidence that the concepts and scales within a measurement tool are understood by the assessor. Standardized methods for collecting this evidence will likely emerge in the continued evolution of health outcomes.

Experience with Regulatory Guidance (e.g. FDA PRO Guidance for Industry) addressing the development, use and collection of outcomes data from patients, clinicians and/or caregivers continues to accumulate. In response, efforts to develop novel instruments will likely yield tools which are electronic from conception or in original rendition. Technology solutions offer the capability of capturing health outcomes in real-time and the population of centralized databases quickly. In addition, they can eliminate the issue of data entry errors and provide a means to predefine, monitor and enforce subject and site compliance requirements for data completion.

Going forward, it will be important that technology facilitates the objectives of the methods emphasized in the Regulatory Guidance and not constrain them. It may be difficult in advance to anticipate or to avoid potential constraints that technology might impose. Research and development efforts by technology providers will need to keep pace with and participate in the evolution of health outcomes science. The future of clinical research will eventually shift to a more personalized approach to treating patients. As such, outcomes instruments will likely take a more personalized rendering while still adhering to Regulatory Guidance. It will therefore be important that outcomes data collection technologies be flexible enough to adapt to the personal renderings of a study subject's outcomes e.g. a daily symptoms diary where the symptoms are specific to each subject. The measure of benefit will not reflect the average patient but rather the number of individuals who individually received benefit from treatment or the number of responders.

Conclusion

Health outcomes research has emerged as the science of measuring and interpreting treatment benefits to patients. As the science has evolved so has the associated vernacular, creating a common language among the sponsors who develop new medical products, the agencies who regulate them and the scientific community. The most recent addition to the health outcomes lexicon of terms is the definition of COAs. COAs include both survival and other not fully objective outcomes assessments such as PROs, ClinROs, and ObsROs. The development and validation methods for evaluating the appropriateness of a measure to support labeling are similar among COAs, as are the implementation considerations. Experience with Regulatory Guidance (e.g. FDA PRO Guidance for Industry) addressing the development, use and collection of outcomes data from patients, clinicians and/or caregivers continues to accumulate. In response, efforts to develop novel instruments will likely yield tools which are electronic from conception or in original rendition.

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Editor's Notes: References

1 Laurie Burke, DIA 23rd Annual EuroMeeting, Geneva, 28-30 March 2011

2 FDA Guidance for Industry Patient Reported Outcome Measures, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf

3 http://www.fda.gov/Drugs/NewsEvents/ucm276110.htm