

## Enhancing the Development and Use of Patient-Reported Outcomes in Drug Development

July 16, 2014

### Discussion Guide

#### Introduction

Recent health care reform efforts in the United States have increased the focus on improving the quality and outcomes of health care services and interventions. This broader shift in focus can also be seen in the pharmaceutical development space, where attention is increasingly being focused on improving patient engagement and incorporating the patient perspective throughout the drug development process. Developing valid and reliable instruments for measuring patient-reported outcomes (PROs) is the most direct approach to gaining insights from patients about their symptoms, functional status, treatment preferences, and health-related quality of life. While there is growing interest among drug developers, clinicians, payers, regulators, and patients in the development and widespread use of PRO instruments that can be applied across the entire drug development and postmarket spectrum, progress has been slow. In particular, there are ongoing challenges in using PROs to support product label claims. Product labeling is a key source of information for clinicians and patients, as it provides the formal summary of a drug's benefits and risks as approved by the U.S. Food and Drug Administration (FDA). The FDA released final guidance to industry on the use of PRO instruments to support labeling claims in 2009, and in 2014 released guidance on qualifying instruments that may be used over time in multiple drug development programs. However, the interpretation and implementation of those guidances have presented significant challenges, which stem from a variety of structural, methodological, logistical, and communication issues. Addressing those barriers will require the ongoing support and collaboration of all pertinent stakeholders, including drug developers, investigators, patients, PRO instrument developers, and regulatory agencies.

#### Patient-Reported Outcome Instruments in Clinical Research

PROs are typically defined as any report on the status of a patient's health condition that comes directly from the patient, without interpretation by another party.<sup>1</sup> PRO instruments can capture a range of concepts that are important to patients, including symptom changes or burden, level of functioning, health-related quality of life, satisfaction with treatment, and treatment adherence. These instruments can be categorized in a variety of ways, such as by the concepts being measured, the method and mode of administration, data collection and analysis, or whether the measure is specific to a particular disease, population, or concept, or 'generic' (i.e. applies across diseases, populations, or concepts).

#### *PROs in medical product development*

Within the context of medical product development, PRO instruments are used in a variety of ways to assess treatment risks and benefits. They are most commonly used to evaluate products that treat chronic or disabling conditions, where the goal of treatment is focused on alleviating the frequency, severity, or duration of disease symptoms, or improving the level of patient functioning or quality of life.<sup>2</sup> PRO instruments may serve as primary endpoints in clinical trials, particularly for symptomatic conditions like migraines, or functional gastrointestinal disorders like irritable bowel syndrome.<sup>3</sup> PRO instruments may also measure endpoints in evaluating the overall risks and benefits of treatments when: 1) the treatment has a limited

impact on survival but significant impact on outcomes like symptom severity or level of functioning; 2) the treatment demonstrates no improvement over the standard of care in terms of clinical efficacy, but may offer improved PRO-measured benefits; or 3) treatment decisions are based on a combination of objective physiologic measures and patient-reported data.<sup>4</sup>

PRO instruments can also serve as secondary endpoints, which support the primary endpoints in a trial while providing a more comprehensive picture of treatment effect, particularly for diseases where objective physiologic endpoints are well-established.<sup>3</sup> For example, the primary endpoints in evaluating a diabetes treatment might include clinical measures like A1c levels or reduced risk of death, heart attack, or stroke, while secondary endpoints might include treatment satisfaction and improved health-related quality of life. Such data can be particularly important for patients and prescribers weighing the available treatment options.

### *PROs in labeling claims*

The use of PRO instruments in clinical trials has grown in recent years. A 2009 analysis of ClinicalTrials.gov found that 14% of the interventional clinical trials registered between 2004 and 2007 used some sort of PRO measure, compared to 4.2% from the period between 1980 and 1997.<sup>5</sup> However, while their value is widely recognized, their use is often inconsistent, and some have argued that they are underutilized in many disease areas that would benefit from an increased focus on how patients feel or function in relation to their disease, such as in cancer, cardiovascular disease, and diabetes.<sup>6,7,8</sup> Of particular concern is the relative lack of PROs being used to support labeling claims. A recent review observed that the number of PRO claims approved by the FDA for inclusion in drug labeling fell slightly over the last several years. Whereas 30% of drug approvals granted between 1997 and 2002 included a PRO claim, between 2006 and 2010 this rate fell to 24% of drugs approved.<sup>2</sup> Labeling claims constitute the portion of a drug label that manufacturers can legally use to promote their products, and as such are considered to be of primary importance, both to manufacturers seeking to distinguish their products in the market and to clinicians seeking information to support their prescribing choices.

Sponsors routinely use PRO instruments to collect a range of health-related quality of life data in pivotal clinical trials prior to approval. However, this information is typically gathered on an exploratory basis, or is intended to demonstrate the benefit of a new treatment to payers making coverage and reimbursement decisions, rather than to support labeling claims.<sup>9</sup> As a result, these measures may lack analytical or statistical validity, or may not be included in publications on trials results.<sup>6</sup>

### **The Role of Partnerships in PRO Development**

The relative lack of existing off-the-shelf PRO instruments means that sponsors often must develop their own instruments, usually in parallel to the clinical development of a particular drug. However, this can be a time-consuming and sometimes costly process.<sup>1</sup> In addition, some sponsors may be unwilling to share proprietary information about the instruments they are currently developing, or may not believe they have a straightforward path to do so for instruments in development. This can lead to multiple sponsors developing instruments for the same purpose, which creates inefficiencies within both drug development and the regulatory review process. Over the last decade, several collaborative efforts have been established to address these barriers, allowing instrument developers across the public and private sectors to pool resources and develop PRO tools that are rigorously designed and available in the public domain.

---

<sup>1</sup> A 2011 estimate found that the total cost of developing a PRO instrument ranges from \$725,000-\$2,150,000. See: <http://c-path.org/wp-content/uploads/2013/09/consensusciencepatientreportedoutcomesinstrumentsastools.pdf>

The PRO Consortium, formed in 2008 as part of the Critical Path Institute, is one of the most prominent examples of these collaborative efforts. The Critical Path Institute operates as a public-private partnership, and includes representatives from across the pharmaceutical industry, academia, non-profits, and governmental bodies. Within the Institute, the PRO Consortium works to develop PRO instruments that may be used broadly to support labeling claims, with a focus on diseases for which valid instruments are not currently available. It is currently targeting seven disease areas: asthma, Alzheimer's disease, depression, functional dyspepsia, irritable bowel syndrome, lung cancer, and rheumatoid arthritis.<sup>10</sup> In addition, the PRO Consortium has facilitated numerous workshops and conferences, bringing together a diverse set of stakeholders from industry, government and academia to improve the understanding and strategic direction of PRO instrument development and qualification.

The NIH has also invested significant resources in developing rigorous PRO instruments that can be adapted for use within trials. In 2004, the NIH funded a cooperative program for the development of PRO instruments called the Patient-Reported Outcomes Measurement Information System (PROMIS). PROMIS has focused on three areas: developing methodological standards for PRO instruments, applying this methodology towards PRO measurement development, and developing PRO administration software and tools to facilitate utilization. PROMIS is organized around three coordinating centers (the Network, Statistical, and Technical Centers), which work with a broad network of research institutions that receive funding to design and construct PRO instruments that cover a broad range of physical, mental, and social health conditions.<sup>11</sup>

### **FDA Approaches to PROs and Patient-Focused Drug Development**

The FDA has made substantial efforts to encourage and facilitate the use of PRO instruments in clinical drug development. The Study Endpoint and Labeling Development (SEALD) staff was established within the Office of New Drugs to serve as a cross-divisional resource on clinical outcome assessments (COAs), which include PROs, clinician-reported outcomes, observer-reported outcomes, and performance measures. SEALD provides training and consultation for other review divisions on the application of measurement standards, develops agency policy related to the review, approval, and labeling of COAs, and works with a range of external stakeholders to advance the science of measurement in clinical trials.<sup>12</sup> The SEALD staff also played a substantial role in the development of two key guidances related to PRO instrument development and use, which are described in greater detail below.

#### *Using PROs to Support Labeling Claims*

In 2009, the agency published final guidance for industry on developing PROs to support labeling claims.<sup>1</sup> This document outlines the agency's current thinking around the review and evaluation of PRO instruments), and describes the recommended steps in developing an instrument, the evaluation criteria the agency will use to assess it, and the major considerations related to clinical trial design and data analysis. There is clear recognition within the guidance that the instrument development process is iterative in nature, recommending regular communication with the agency as new information about an instrument is collected and analyzed.

As outlined in the guidance, the evaluation of an instrument centers around four main considerations. The first of these is the population that will be enrolled in the clinical trial, and the extent to which the sponsor has demonstrated the relevance of the PRO instrument to that population. The second consideration relates to the objectives and design of the clinical trial, and the role that the instrument will play within it (i.e. whether the measure will be a primary or secondary endpoint). The third key consideration is the instrument's conceptual framework, which explicitly defines the relationship between the concept that is being measured, the individual 'items' or questions that make up the instrument, and the numbers derived from patient responses (also known as scores) that will be used in statistical analysis. The fourth consideration relates to the instrument's measurement properties, including its reliability, validity, and ability to detect change. Of these

properties, the most important is content validity, which is the extent to which the instrument measures the targeted concept and is therefore considered to be ‘fit for purpose’.

The guidance also outlines general clinical trial considerations that sponsors should take into account, as well as the important challenges in data analysis, such as in cases when the trial has multiple endpoints, composite endpoints based on PRO instruments that target complex concepts like patient functioning, or missing data.

#### *Qualifying PRO Tools for Use Across Multiple Drug Development Programs*

As noted above, the financial and opportunity costs associated with developing PRO instruments can be high, and there are significant inefficiencies associated with sponsors developing multiple instruments for similar concepts. As part of the FDA’s efforts to facilitate the use of PRO instruments—along with other promising drug development tools (DDTs) such as biomarkers and new animal models—the agency developed a formal, voluntary process known as DDT Qualification. Qualified DDTs can, under the agency’s definition, be relied upon to have a specific interpretation and application in the drug development and review process, provided that the tool is used within its qualified context. Thus in theory, a tool may be applied across multiple drug development programs without the need to gather additional data to support its use. The FDA released final guidance on this process in January 2014, which provides the framework for engaging with the FDA and outlines the type of data that is needed to support a tool’s Qualification.<sup>13</sup>

The agency has also developed supporting communication tools that provide assistance on how COA developers might approach the Qualification process (see Appendix 1). The Roadmap to Patient-Focused Outcome Measurement outlines how developers can identify the concept of interest, define the specific context of use in which the instrument will be used, and identify the appropriate COA. The Wheel and Spokes Diagram is an updated version of the diagram found in the PRO Guidance, and provides an overview of the COA development process, as well as the key components of the documentation that support Qualification.

The Qualification process is voluntary, and the FDA does not require the use of qualified instruments. Sponsors may still choose to develop tools on a drug-specific basis. However, it is hoped that the Qualification process will encourage multiple parties to collaborate on the development of new tools, thereby spreading out the associated financial and opportunity costs and accelerating the development of publicly available DDTs that can be used widely. At present, the only PRO instrument to be qualified by the FDA is the Exacerbations of Chronic Pulmonary Disease Tool (EXACT-PRO), which was granted Qualification status in the same month that the DDT Qualification guidance was released.<sup>14</sup>

#### *Facilitating Patient-Focused Drug Development*

The agency has taken other steps to incorporate the patient voice more fully within their review process. Under the Prescription Drug User Fee Act reauthorization of 2012, the FDA has committed to standardizing and improving its benefit-risk assessment framework. As a part of this effort, the agency has launched the Patient-Focused Drug Development initiative (PFDD), which began in fall of 2012. Under the PFDD, FDA will convene a series of 20 public meetings, each of which will focus on a different disease area. Through these meetings, the agency will elicit patient perspectives on the aspects of their disease that matter most to them. The ultimate goal will be to build a systematic approach that incorporates this perspective into the agency’s decision-making.<sup>15</sup>

The process of systematically translating patient input into reliable and valid qualitative measures presents several methodological, economical, and logistical challenges, and the agency is still developing its approach to addressing those challenges. However, one of the potential outcomes of this process is the development of rigorous, patient-reported outcomes that accurately and precisely measure concepts that are relevant to the patients living with these conditions.

## Opportunities and Challenges in the Development and Use of PROs

While important progress has been made in recent years to develop and use PRO instruments that can support labeling claims and inform decision-making by patients and prescribers, several key challenges remain. The 2009 PRO Guidance was a significant step for both the FDA and industry, and the guidance was praised both for its intent and the scientific rigor of its approach.<sup>16</sup> However, as noted previously, the rate at which label claims were granted for PRO measures fell slightly following the release of the guidance.<sup>2</sup> Though nearly half of the new drug applications and biologics license applications contained a PRO claim, only 24% of those claims were granted between 2006 and 2010. A review of those rejected PRO label claims determined that most rejections were based on a failure to establish content validity (i.e., the measure was not deemed to be fit for purpose). Issues of study design, data quality, and interpretation of results were also a common reason for rejection.<sup>17</sup>

In addition, most of the label claims granted between 2000 and 2012 were in cases where the PRO was specified as the primary endpoint, rather than as a non-primary endpoint that might provide supportive data on the symptomatic or quality of life effects of the drug. Some have argued that this relative absence of PRO data creates a situation in which patients and prescribers have an incomplete picture of a drug's risks and benefits.<sup>18,19</sup> Efforts to speed the development of qualified PRO instruments that may be used more broadly have also lagged, despite several years of work by initiatives like the PRO Consortium. To date, only one instrument has been qualified by the FDA, and many have argued that its eight-year development process is not a feasible timeline for other instrument developers.<sup>19</sup> These barriers to accelerating the development and use of PRO instruments stem from a range of different sources, and exist at both the industry and agency level.<sup>20</sup>

### *Logistical barriers*

Some of the challenges raised by sponsors and other instrument developers are related to logistical issues. Within industry, sponsors may not prioritize the types of outcomes that are most effectively reported by the patient, and may not allocate resources to PRO instrument development during the early phases of the clinical development program. The likelihood that a drug candidate will fail in early phase testing only reinforces this tendency. In some cases, there may be no existing instruments for a particular condition that are appropriate for the clinical trial context. However, by the later phases of development it may be too late to conduct the important qualitative work to identify or develop the appropriate instrument.<sup>3,20</sup> Smaller companies may be particularly disadvantaged, as they may not have the necessary in-house expertise, and must hire a third party organization to conduct qualitative research, select or develop a measure, provide electronic PRO (ePRO) technology, prepare materials for FDA review (e.g., the "PRO Dossier" specified in the PRO guidance) and to analyze data. Even within large companies, PRO experts tend to work within the post-marketing context, and may not be integrated into the clinical development teams that design and implement pivotal studies.<sup>20</sup>

Many of the major logistical barriers to PRO development and utilization relate to challenges in conducting clinical trials across multinational settings. Such trials recruit diverse populations speaking multiple languages, and obtaining culturally appropriate and accurate translations of a PRO instrument can be a significant burden.<sup>18,19</sup> This burden is magnified each time that the study protocol is amended during the course of the trial. These logistical challenges are complicated by the fact that evidentiary requirements for PRO instruments are not harmonized across regulatory agencies. It can be difficult for sponsors to incorporate PRO instruments into a trial in a way that satisfies the demands of multiple regulatory agencies.

### *Communication barriers*

Some have noted a lack of consistency in the interpretation of the guidance within FDA, both between the various review divisions and between the SEALD team and the review divisions with which it consults.<sup>17,19</sup> While some review divisions appear to be more comfortable with PRO instruments and have granted several PRO labeling claims, others are perceived as being more cautious. Some have argued that recent approval decisions related to PRO labeling claims do not always align with the guidance, which creates uncertainty within industry.<sup>19</sup> Others have pointed out the structure of the review process itself may create barriers. As with industry, the FDA's PRO experts are separate from the clinical review divisions, and may only be included in the review process if the sponsor requests feedback for a particular instrument.<sup>20</sup>

An additional communication challenge relates to the timing of meetings between FDA review divisions and sponsors. Some have argued that the existing formal mechanisms—specifically, the End-of-Phase II and Special Protocol Assessment meetings—are too late in the development process to discuss PRO strategies, and can be more contentious than collaborative.<sup>20</sup> The ideal timing and approach to communication between FDA and sponsors is unclear, though some have suggested that these conversations should begin as early as possible.

### *Methodological barriers*

There are a number of ongoing methodological challenges associated with developing and validating a PRO measure, some of which are cross-cutting, and some of which are of particular concern in a specific disease area or target population. One of the major cross-cutting challenges concerns the stringency of FDA's standards related to fitness for purpose (i.e. content validity). Some have argued that these standards are too high, and that the agency should consider adjusting its criteria.<sup>18,19</sup> A similar challenge relates to the use of generic and health-related quality of life measures, which the FDA generally discourages if the measure has not demonstrated validity within the intended population. The agency encourages sponsors to pursue disease- and population-specific testing and modification of such instruments, but some sponsors may be reluctant to take on the additional costs associated with that process. Other methodological barriers include the particular challenges of developing PRO instruments for pediatric, orphan, and rare disease indications, where patients may be difficult to access in adequate numbers.<sup>19</sup> The application of PROs in open label studies also poses specific challenges, as such trials may be subject to bias from inadvertent unblinding.<sup>18</sup> This is particularly problematic in fields like oncology, where open label studies are common.

## **Meeting Objectives**

The Engelberg Center for Health Care Reform at the Brookings Institution, in cooperation with FDA, is holding an expert workshop that will focus on the major issues related to the development and use of PRO instruments to support labeling claims. This workshop will be the first in a series of meetings, and will include representatives from across industry, academia, patient advocacy groups, and government agencies. Through these meetings, Brookings hopes to create a venue for stakeholders to identify and prioritize for action the most promising strategies to address the major barriers, and identify ways that FDA can facilitate these efforts. This discussion will also help to inform a public workshop that the FDA will hold in spring 2015, which will focus on the development, use, and qualification of drug development tools more broadly and the state of the science around measurement theory.

## Enhancing the Development and Use of Patient-Reported Outcomes in Drug Development

### Session I: Experiences with the FDA Guidance on PROs: Evidentiary Standards

*Objective:* This session will explore perceived challenges and opportunities in meeting FDA's current evidentiary standards for evaluating PROs to support labeling claims.

- What are major strengths of the FDA Guidance on PROs?
- What are the major logistical barriers associated with meeting the current evidentiary standards when developing PROs instruments for:
  - a specific drug development program?
  - Qualification?
- What are the major methodological barriers associated with meeting those standards?
- What are the main challenges associated with understanding and implementing the PRO instrument validation process?
- What approaches exist to modify PRO instrument review and Qualification?

### Session II: Experiences with the FDA Guidance on PROs: Standardizing Communication Processes

*Objective:* Explore strategies to improve communication processes around PRO instrument development and implementation.

- What is the most useful mechanism for engaging FDA in PRO instrument development strategies:
  - a) During drug development (e.g., industry meeting that focus exclusively on PRO development; industry meeting that include other topics in addition to PRO instrument development; general advice letter)?
  - b) During Qualification?
- What are the existing barriers and challenges to engaging FDA?
- How might FDA consider adapting these communication processes to address challenges?
- Are the existing PRO instrument development communication tools (PRO Guidance, Roadmap, and Wheel and Spokes diagrams) useful to broad industry and academic audiences? Please provide examples of how they are useful or not useful.
- What additional types of guidance or educational tools on PRO instrument development and labeling might be useful?

### Session III: Identifying Other Issues Related to the FDA Guidance on PRO Development

*Objective:* Identify additional aspects of the current guidance that create barriers to PRO measure development, and which have not been captured in the previous sessions.

- Aside from those challenges that have been previously identified, what aspects of the PRO Guidance are most difficult or burdensome for sponsors and external stakeholders to implement? Consider providing specific examples from drug development programs if possible.

### Session IV: Challenges to Capturing the Patient Voice Across the Drug Development Continuum

*Objective:* Explore the challenges to capturing the patient voice across the continuum, from initial patient input to developing and implementing PRO instruments in clinical trials to support labeling claims.

- What are the barriers for capturing the patient's voice in medical product development? Within industry? Within FDA?

- Regarding study design considerations, what are the barriers to incorporating PRO instruments in clinical trials?
- What are some possible strategies for addressing these barriers?
- Collaborative PRO instrument development groups such as the PRO Consortium have the potential to eliminate barriers and foster PRO development. What are the strengths and limitations of this approach? What other approaches should also be considered?
- What are the main challenges associated with PRO instrument development and use in the context of multinational trials?
- Why are PRO instruments not being developed for diseases for which there is an unmet need?

#### **Session V: Next Steps in Promoting the Development and Qualification of PROs**

Objective: This session will wrap-up the expert workshop. The participants will identify the day's major themes that warrant future attention and analysis. What is discussed will inform the next expert workshop agenda, as well as the 2015 public meeting agenda.



## References

- <sup>1</sup> U.S. Food and Drug Administration. Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. Retrieved March 20, 2014 from: <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>.
- <sup>2</sup> Gnansakthy A, et al. A Review of Patient-Reported Outcome Labels in the US: 2006 to 2010. *Value in Health*. 2012;15:437-442. Retrieved May 22, 2014 from: <http://www.sciencedirect.com/science/article/pii/S1098301511036011>
- <sup>3</sup> Gnansakthy A, et al. Potential of patient-reported outcomes as nonprimary endpoints in clinical trials. *Health and Quality of Life Outcomes*. 2013;11:83. Retrieved May 22, 2014 from: <http://www.hqlo.com/content/11/1/83>.
- <sup>4</sup> Acquadro C, et al. Incorporating the patients' perspective into drug development and communication: an Ad Hoc task force report of the patient-reported outcomes (PRO) harmonizing group meeting at the Food and Drug Administration, February 16, 2001. *Value in Health*. 2003;6:522-31. Retrieved June 15, 2014 from: [http://www.ispor.org/workpaper/research\\_practices/PROConcepts\\_Definitions.pdf](http://www.ispor.org/workpaper/research_practices/PROConcepts_Definitions.pdf)
- <sup>5</sup> Scoggins, J and D. Patrick. The use of patient-reported outcomes instruments in registered clinical trials: evidence from ClinicalTrials.gov. *Contemporary Clinical Trials*. 2009;30(4): 289-292. Retrieved June 27, 2014 from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2683916/>.
- <sup>6</sup> Basch, E. Toward patient-centered drug development in oncology. *New England Journal of Medicine*. 2013;369(5): 397-400. Retrieved June 27, 2014 from: <http://www.nejm.org/doi/full/10.1056/NEJMp1114649>
- <sup>7</sup> Rahimi K, et al. Outcome selection and role of patient reported outcomes in contemporary cardiovascular trials: systematic review *BMJ* 2010;341:c5707. Retrieved June 27, 2014 from <http://www.bmj.com/content/341/bmj.c5707.pdf%2Bhtml>.
- <sup>8</sup> Barsdorf A, et al. Patient-Reported Outcomes (PROs) in Type 2 Diabetes Clinical Trials. International Society for Pharmacoeconomics and Outcomes Research. PDB70, May 2013, Presentation at the ISPOR 18th Annual International Meeting. Retrieved June 27, 2014 from: [http://www.ispor.org/research\\_pdfs/43/pdffiles/PDB70.pdf](http://www.ispor.org/research_pdfs/43/pdffiles/PDB70.pdf).
- <sup>9</sup> Doward L, et al. Patient-reported outcomes: looking beyond the label claim. *Health and Quality of Life Outcomes*. 2010;8:89. Retrieved May 15, 2014 from: <http://www.hqlo.com/content/8/1/89>.
- <sup>10</sup> For more information, see: <http://c-path.org/programs/pro/>
- <sup>11</sup> National Institute of Health PROMIS Network website. Frequently Asked Questions (FAQs). Retrieved June 11, 2014 from: <http://www.nihpromis.org/faqs>.
- <sup>12</sup> Food and Drug Administration website. Study Endpoints and Labeling Development (SEALD) Staff. Retrieved June 27, 2104 from: <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm349031.htm>
- <sup>13</sup> Food and Drug Administration. Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools. January 2014. Retrieved June 27, 2014 from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>
- <sup>14</sup> Food and Drug Administration. Draft Guidance: Qualification of Exacerbations of Chronic Pulmonary Disease Tool for Measurement of Symptoms of Acute Bacterial Exacerbation of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease. Attachment to Guidance on Qualification Process for Drug Development Tools. January 2014. Retrieved June 27, 2014 from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM380961.pdf>
- <sup>15</sup> Food and Drug Administration. Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making. February 2013. Retrieved June 27, 2014 from: <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf>
- <sup>16</sup> Speight J and S. Barendse. FDA Guidance on Patient-Reported Outcomes. *BMJ*; 2010: 340.
- <sup>17</sup> DeMuro C, et al. Reasons for Rejection of Patient-Reported Outcome Label Claims: A Compilation Based on a Review of Patient-Reported Outcome Use among New Molecular Entities and Biologic License Applications, 2006–2010. *Value in Health*. May 2012;15(3):443-448. Retrieved June 27, 2014 from: <http://www.sciencedirect.com/science/article/pii/S109830151200068X>.
- <sup>18</sup> Basch E. Beyond the FDA PRO Guidance: Steps toward Integrating Meaningful Patient-Reported Outcomes into Regulatory Trials and US Drug Labels. *Value in Health*. May 2012; 15(3):401-403. Retrieved June 27, 2014 from: [http://www.valueinhealthjournal.com/article/S1098-3015\(12\)01451-9/fulltext](http://www.valueinhealthjournal.com/article/S1098-3015(12)01451-9/fulltext)
- <sup>19</sup> Fehnel S, et al. US FDA patient-reported outcome guidance: great expectations and unintended consequences. *Expert Review of Pharmacoeconomics & Outcomes Research*. August 2013;13(4):441-446.
- <sup>20</sup> Basch E, et al. Issue Brief: Symptom Measurement in Clinical Trials. Conference on Clinical Cancer Research. November 2011. Retrieved June 27, 2014 from: <http://www.focr.org/sites/default/files/Panel3FINAL110411.pdf>

# **APPENDIX 1**

# Qualification of **CLINICAL OUTCOME ASSESSMENTS** (COAs)

## V. Modify Instrument

- Identify a new COU
- Change wording of items, response options, recall period, or mode/method of administration/data collection
- Translate and culturally adapt
- Evaluate modifications using spokes I - IV
- Document all changes

**Consider submitting to FDA for qualification of new COA, as appropriate.**

## IV. Longitudinal Evaluation of Measurement Properties/ Interpretation Methods

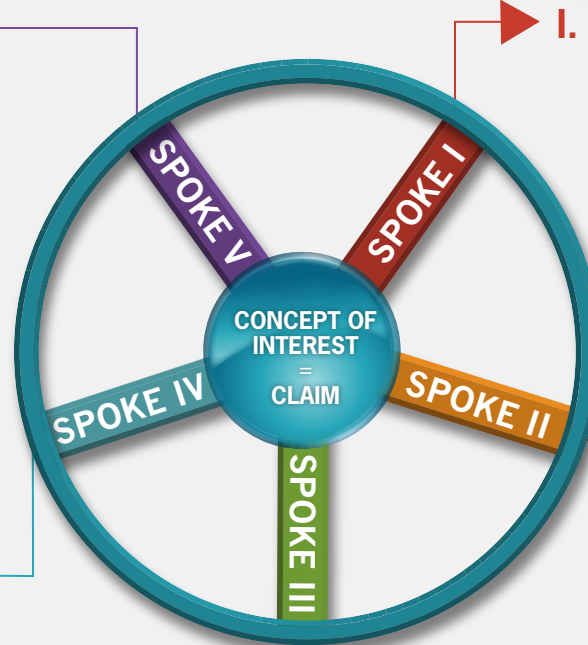
- Assess ability to detect change and construct validity
- Identify responder definition(s)
- Provide guidelines for interpretation of treatment benefit and relationship to claim
- Document all results
- Update user manual

**Submit to FDA for COA qualification as effectiveness endpoint to support claims.**

## III. Cross-sectional Evaluation of Other Measurement Properties

- Assess score reliability (test-retest or inter-rater) and construct validity
- Establish administration procedures & training materials
- Document measure development
- Prepare user manual

**Consider submitting to FDA for COA qualification for use in exploratory studies prior to longitudinal evaluation.**



## I. Identify Context of Use (COU) and Concept of Interest (COI)

- Outline hypothesized concepts and potential claims
- Determine intended population
- Determine intended application/characteristics (type of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework
- Position COA within a preliminary endpoint model
- Document COU and COI

## II. Draft Instrument and Evaluate Content Validity

- Obtain patient or other reporter input
- Generate new items
- Select recall period, response options and format
- Select mode/method of administration/data collection
- Conduct cognitive interviewing
- Pilot test draft instrument
- Finalize instrument content, format and scoring rule
- Document content validity



# Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

## Understanding the Disease or Condition **1**

### A. Natural history of the disease or condition

- Onset/Duration/Resolution
- Diagnosis
- Pathophysiology
- Range of manifestations

### B. Patient subpopulations

- By severity
- By onset
- By comorbidities
- By phenotype

### C. Health care environment

- Treatment alternatives
- Clinical care standards
- Health care system perspective

### D. Patient/caregiver perspectives

- Definition of treatment benefit
- Benefit-risk tradeoffs
- Impact of disease

## Conceptualizing Treatment Benefit **2**

### A. Identify concept(s) of interest (COI) for meaningful treatment benefit, i.e., How a patient:

- Survives
- Feels (e.g., symptoms)
- Functions

### B. Define context of use (COU) for clinical trial:

- Disease/Condition entry criteria
- Clinical trial design
- Endpoint positioning

### C. Select clinical outcome assessment (COA) type:

- Patient-Reported Outcome (PRO)
- Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- Performance Outcome (motor, sensory, cognition)

## Selecting/Developing the Outcome Measure **3**

### A. Search for existing COA measuring COI in COU:

- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

### B. Begin COA development

- Document content validity (qualitative or mixed methods research)
- Evaluate cross-sectional measurement properties (reliability and construct validity)
- Create user manual
- Consider submitting to FDA for COA qualification for use in exploratory studies

### C. Complete COA development:

- Document longitudinal measurement properties (construct validity, ability to detect change)
- Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- Submit to FDA for COA qualification as effectiveness endpoint to support claims

