Developments and Communication Since the Issuance of FDA’s Guidance to Industry on Patient-Reported Outcomes: Then and Now

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Planning Committee

- **Brooke Witherspoon, BA**, Associate Director, Research & Operations, Endpoint Outcomes
- **Somali Misra Burgess, PhD**, CEO and Research Director, Strategic Outcomes Services,
- **Kristina Fitzgerald, MPH**, Global Head of Patient Centered Outcome for Immunology, Infectious Disease & Ophthalmology, Genentech Inc.
  - Unable to be here today
- **Paivi Miskala, MSPH, PhD**, Founder, PROCON GLOBAL
Overview

1. Introduction to patient-reported outcomes (PROs) and evolution of FDA's PRO guidance
   • Somali Misra Burgess

2. Regulatory considerations for clinical outcome assessments (COAs)
   • Paivi Miskala

3. Additional pathways, including drug development tool (DDT) qualification
   • Kristina Fitzgerald (Brooke Witherspoon presenting on her behalf)

4. Additional information beyond FDA's PRO guidance
   • Brooke Witherspoon

5. Questions
   • Discussion leader: Brooke Witherspoon

Introduction to PROs and Evolution of FDA’s PRO Guidance

Somali Misra Burgess
What is PRO?

“PRO” is patient-reported outcome

“A PRO is any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.”

- Using diaries, questionnaires, or interviews, a PRO measures a “concept(s)” or a treatment effect/benefit perceived by the patient

Effectiveness = Clinical Benefit

- Clinical benefit = how well a patient
  - Survives
  - Feels
  - Functions

- Survival may not always be the only or best endpoint
  - Survival often informed by symptoms and functioning
  - Survival may not be observable in a clinical trial (sensitivity or length of observation issues)
The use of PRO instruments is part of a general movement toward the idea that the patient, properly queried, is the best source of information about how he or she feels.


Why Does the Patient Perspective Matter?

- The patient is often times the best person to give feedback on his/her symptoms and impacts
- Physiological assessments may not reflect how a patient functions or feels (e.g., FEV₁, endoscopy findings, blood pressure)
- Well-developed PRO is more reliable than non-standardized clinician interview
- Only the patient can accurately describe most symptoms
- The patient’s perception is important for some outcomes (e.g., cosmetic effects, body image)
What is the PRO Guidance?

*It is FDA’s Guidance to industry on how PRO endpoints will be evaluated*


- What is the purpose of the PRO Guidance?
  - To emphasize that the FDA recognizes the importance of the patient perspective where appropriate
  - To explain how the FDA evaluates PRO instruments for their usefulness in measuring and characterizing treatment benefit of medical product treatment as perceived by the patient
  - To explain FDA’s evidence requirements when PRO endpoints are used as evidence to support claims

Evolution of the FDA PRO Guidance

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Evolution of the “Wheel and Spokes”

Evolution of Terminology
From “patient-reported outcomes” to “clinical outcomes assessment”

Clinical Outcomes Assessments

- **PRO** Reported directly from the patient
  - Examples: SF36, BPI
- **ClinRO** Reported from a trained HCP
  - Examples: BDI/TDI, CGIS
- **ObsRO** Observation from person other than the patient or HCP
  - Examples: PedsQOL, Zarit Burden Interview
- **PerfO** Task performed by patient per HCP instructions
  - Examples: Cognitive Test, 6-minute Walk

*HCP=Health Care Professional
Clinical Outcome Assessments: Regulatory Considerations

Paivi H. Miskala

Disclosure

- The views and opinions expressed here are those of Paivi H. Miskala and should not be attributed to PROCON GLOBAL, FDA or ISPOR.
Overview

- Regulations
- Roadmap to patient-focused drug development
- Wheel and spokes
- Regulatory review considerations
- Common pitfalls

Code of Federal Regulations (CFR)*

- Official text of U.S. federal agency regulations
- Rules and regulations in the CFR are structured into 50 subject matter titles
- Title 21: Food and Drugs
  - 21 CFR 314.126: “Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is “substantial evidence” to support the claims of effectiveness for new drugs”
  - 21 CFR 314.126(b)(6): “The methods of assessment of subjects’ response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response”

* http://www.ecfr.gov/cgi-bin/ECFR?page=browse
FDA Guidance Documents*

- Documents “that describe the agency’s interpretation of or policy on a regulatory issue”
- “Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA”.
- They “represent FDA's current thinking”

http://www.fda.gov/RegulatoryInformation/Guidances/

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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

2. **B. Patient subpopulations**
   - By severity
   - By onset
   - By comorbidities
   - By phenotype

3. **C. Health care environment**
   - Treatment alternatives
   - Clinical care standards
   - Health care system perspectives

4. **D. Patient/carer or patient perspectives**
   - Definition of treatment benefit
   - Benefit-risk tradeoffs
   - Impact of disease

Conceptualizing Treatment Benefit

1. **A. Identify conceptual(s) of interest (COI) for meaningful treatment benefit, i.e. how a patient:
   - Survive
   - Feel (e.g., symptoms)
   - Function

2. **B. Define context of use (COU) for clinical trial**
   - Disease/Condition entry criteria
   - Clinical trial design
   - Endpoint positioning

3. **C. Select clinical outcome assessment (COA) type**
   - Patient-Reported Outcome (PRO)
   - Observer-Reported Outcome (OObRO)
   - Clinician-Reported Outcome (CObRO)
   - Performance Outcome (motor, sensory, cognition)

Selecting/Developing the Outcome Measure

1. **A. Search for existing COA measuring COI in COU**
   - Measure exists
   - Measure exists but needs to be modified
   - No measure exists
   - Measure under development

2. **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

3. **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 an effectiveness endpoint to support claims

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FDA CDER Review Processes for COAs

- IND & NDA/BLA review
- DDT qualification
When Do Regulators Review Development and Validation of COAs?

- When proposed as a primary or key secondary endpoint in a clinical trial intended to support a medical product labeling claim regarding treatment benefit
  - Drug effectiveness
  - Comparative safety

Regulatory Review Considerations *

- Population enrolled in clinical trials
- Clinical trial objectives and design
- PRO instrument’s conceptual framework
- PRO instrument’s measurement properties, including content validity and other psychometric properties

Regulatory Review Considerations (2)

- Are there any written agreements between FDA and sponsor (regulatory history)?
- Are labeling claims pursued?
- Is it a key study endpoint? How is the endpoint defined in the analysis? Was it in the multiplicity adjustment of the statistical analysis plan?
- What is the magnitude of treatment effect?
- Are there other issues that may impact interpretation? For example:
  - Trial design
  - Masking (blinding)
  - Adverse events of treatment
  - Rescue medication use
  - Comorbidities and their treatment
  - Translation/cultural adaptation issues
  - Missing data

Regulatory Review Considerations (3)

- FDA has specific review considerations, but evaluated in the context of the specific drug development program (i.e., there is flexibility based on my experience)
- The IND stage recommendations typically provide regulatory guidance based on PRO guidance and best practices, however, the NDA/BLA review process generally more pragmatic (i.e., is the instrument good enough)
Common Pitfalls* (1)

- Lack of documented evidence to support use in the clinical trial target population
- COA not specified as a key trial endpoint (i.e., primary or key secondary) and included in the multiplicity adjustment of the statistical analysis plan
- Targeted labeling claim not supported by the COA and considered false/misleading
  - COA used to support a prevention claim places different demands on the performance characteristics of the COA than claims of improvement
  - COA used to support a reduction in progression requires knowledge of symptom development as disease progresses


Common Pitfalls* (2)

- PRO endpoints in open label trials
- Clinical trial population does not have a significant decrement at baseline in the concept of interest and there is no room for improvement

Other Challenges

- Clinical trial target population
  - Issues with disease definition (e.g., functional dyspepsia)
  - Overlapping diseases that may result in same/similar symptoms (e.g., lung cancer and COPD)

Summary

- There are regulatory requirements for “substantial evidence” and “well-defined and reliable” endpoint assessments
- There are specific regulatory review considerations, but evaluated in the context of a specific drug development program (i.e., there is flexibility based on my experience)
- There are pitfalls that can be avoided or minimized by careful planning
Additional Pathways

DDT Qualification

Kristina Fitzgerald
(Brooke Witherspoon presenting on her behalf)

&

Critical Path Innovation Meetings

Brooke Witherspoon

DDT Qualification Program

• Allow CDER to work with COA instrument developers to guide them as they develop or refine a DDT for a specific context of use by rigorously evaluating the submission for use in the regulatory process

• Qualifying a DDT will allow sponsors to use the DDT in the qualified context of use during drug development without requesting that CDER reconsider and reconfirm the suitability of the DDT for the qualified context of use
DDT Qualification Guidance (Finalized January 2014)

Guidance for Industry and FDA Staff
Qualification Process for Drug Development Tools

- Describes a process NOT evidentiary standards

DDT Qualification Program: Mission and Objectives (1)

- To qualify and make DDTs publicly available for a specific context of use to expedite drug development and review of regulatory applications
- To provide a framework for scientific collaboration to facilitate DDT development
- To facilitate integration of qualified DDTs in regulatory review

DDT Qualification Program: Mission and Objectives (2)

- To encourage development of DDTs for contexts of use with unmet needs
- To encourage the formation of collaborative groups to undertake DDT development programs to increase the efficiency and lessen the individual resource burden incumbent with DDT development
- To encourage innovation in drug development

DDT Qualification Considerations

- Qualification is not required
  - Case-by-case evaluation in application review is acceptable
- Qualification is voluntary
- Qualification is intended for COAs that will be used in multiple drug development programs
- Qualified instruments may not always replace old instruments
  - Qualified instruments may provide information that complements existing instruments
- Important to consider timelines
  - No timelines outlined for qualification advice
COAs Undergoing DDT Qualification

Including, but not limited to…

- Acute Bacterial Skin and Skin Structure Infections
- Asthma
- Cancer Fatigue
- Community-Acquired Bacterial Pneumonia
- Crohn’s Disease
- Cystic Fibrosis
- Depression
- Esophagitis
- Functional Dyspepsia
- Irritable Bowel Syndrome
- Mild Cognitive Impairment
- Multiple sclerosis
- Muscle Wasting
- Non-Small Cell Lung Cancer
- Sickle Cell
- Ulcerative Colitis


Status of COA Qualification Projects

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First Qualified DDT (January 2014)

- The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) qualified for the measurement of symptoms of acute bacterial exacerbation of chronic bronchitis (ABECB) in patients with Chronic Obstructive Pulmonary Disease (COPD)
- Qualified for use in Phase 2 studies


Next Steps for EXACT Qualification

- Exploratory analyses encouraged to evaluate the EXACT’s longitudinal measurement properties and the amount of change in an individual patient that can be considered meaningful for use in the interpretation of effectiveness
Critical Path Innovation Meetings (CPIMs)

- Allows for CDER and investigators (industry, academia, patient advocacy groups and government) to discuss technologies or methodologies that may improve efficiency and increase success of drug development

More About CPIMs

- CPIMs can provide...
  - A venue for discussing early phase COA development (not ready for qualification)

- CPIMs are not...
  - Binding for FDA or CPIM requesters
  - Specific to drug development programs
    - Formal meetings guidance still applies
  - Intended to replace meetings held through the DDT process
Additional Information Beyond FDA’s PRO Guidance

Brooke Witherspoon

ISPOR Good Practice for Outcomes Research Reports

- Task Force developed reports that provide additional detail regarding best practices when executing the development, modification, translation, etc., of COAs
- E.g., good research practices for pediatric PRO research:
  1. Consider developmental differences
  2. Establish content validity
  3. Determine if ObsRO is necessary
  4. Design/format appropriate for ages
  5. Consider cross-cultural issues

ISPOR Good Practice for Outcomes Research Reports: Topics

- Assessment of PROs in Children and Adolescents
- Content Validity in Existing PRO Instruments and their Modification
- Content Validity in Newly-Developed PRO Instruments Part 1 – Eliciting Concepts for a New PRO Instrument
- Content Validity in Newly-Developed PRO Instruments Part 2 – Assessing Respondent Understanding
- ePRO Systems Validation
- Measurement Equivalence: Mode of Administration Change from Paper to Electronic
- Mixed Modes to Collect PRO Data in Clinical Trials
- Translation and Linguistic Validation of PRO Instruments
- Clinical Outcome Assessments: A Conceptual Foundation (in development)
- Clinician-Reported Outcomes (ClinROs) Good Measurement Practices (in development)
- Patient- and Observer-Reported Outcomes Measurement in Rare Disease Clinical Trials – Emerging Good Practices (in development)

FDA Clinical/Medical Guidances (1)

- Disease- or indication-specific guidances may provide additional information regarding acceptable endpoints (and therefore help outcome measure planning)

Guidance for Industry
Irritable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment

- Final released May 2012

LINZESS® approved for the treatment of IBS-C and chronic idiopathic constipation in August 2012
FDA Clinical/Medical Guidances (2)

- Recent (2014-present) guidances with PRO supported efficacy endpoints include
  - Non-small cell lung cancer
  - Alcoholism
  - Migraine
  - Upper facial lines
  - Chronic fatique syndrome/Myalgic encephalomyelitis
  - Analgesic indications

- While some are specific about endpoints, they are generally not prescriptive in terms of specific measures to use

- Rather, include recommendations to consider when identifying or developing an instrument


FDA Clinical/Medical Guidances (3)

Upper Facial Lines

- Draft released August 2014

- Recommends co-primary efficacy endpoints that are based on well-defined and reliable ClinRO and PRO assessments that are developed to measure the critical outcomes that contribute to a conclusion of overall success or failure

Guidance for Industry
Upper Facial Lines: Developing Botulinum Toxin Drug Products

**FDA Clinical/Medical Guidances (4)**

*Vulvar and Vaginal Atrophy Symptoms*

- Consider developments outside of the guidances too

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**Guidance for Industry**

*Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation*

- Draft released January 2003
- Recommends mean change from baseline to Week 12 of the most bothersome moderate to severe symptom as identified by the patient

Please visit the following link for more information:


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**FDA Clinical/Medical Guidances (5)**

*Vulvar and Vaginal Atrophy*

- Given the selection of one symptom results in a small number of patients included in analysis, Chen et al 2010 recommend removing most bothersome symptom component from three co-primary endpoints and consider measuring individual symptoms as separate primary endpoints

- FDA statisticians and medical officers (Chen et al 2010) have since published statistical considerations for such endpoints after reviewing multiple NDAs

Summary

- The terminology, “roadmap,” and process for developing (and potentially qualifying) COAs has evolved since the release of the FDA’s PRO Guidance in 2009.

- Regulatory requirements for “substantial evidence” and “well-defined and reliable” COAs have not changed.
  - In light of this, there are additional resources – from regulators and otherwise – that can help developers navigate patient-focused outcome measurement in clinical trials and qualifications of COAs.

Discussion

Questions?