Patient-Reported Outcomes (PROs) and the Food and Drug Administration Draft Guidance

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6 March 2008 10:45 – 11:05

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Dr. Patrick is a Special Government Employee working with the Food and Drug Administration on the use of patient-reported outcomes in the evaluation of medical products. This presentation represents the personal views of the author and should not be attributed in any way as representing an official opinion of the FDA

Outline

- What are PROs?
- Why are PROs important?
- What is the FDA draft guidance?
- What are key regulatory issues in the US?

What is a PRO?

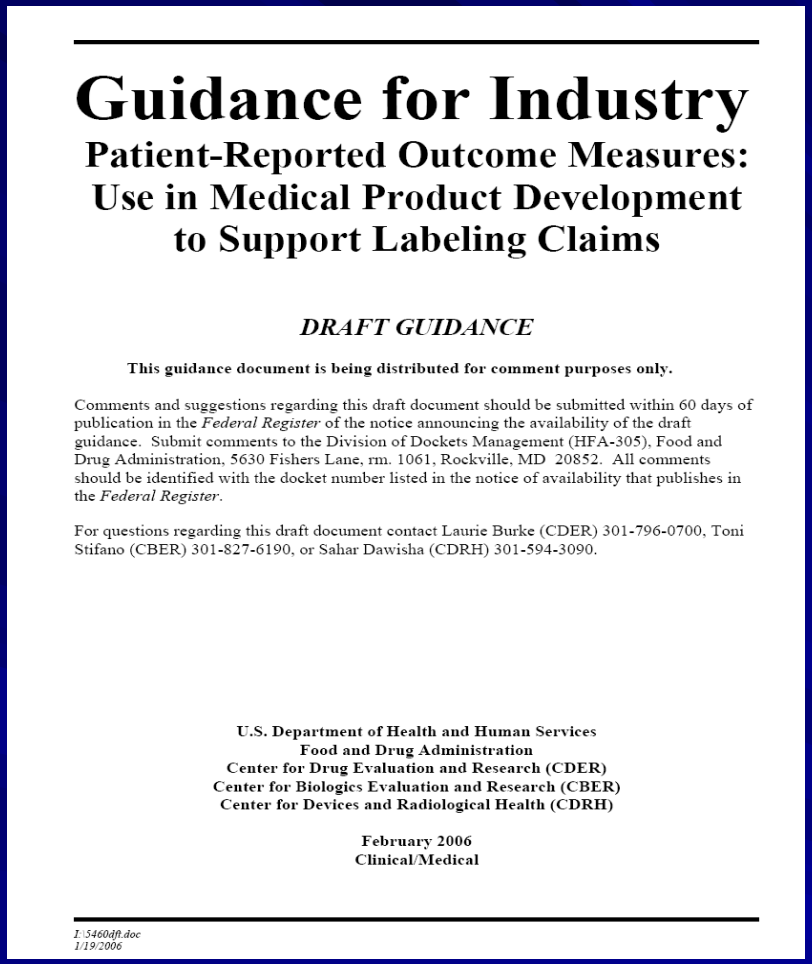
- PRO: Any report coming directly from patients, without interpretation of the patient's response by clinicians or anyone else. In clinical trials evaluating medical interventions, these are reports about how patients function or feel in relation to a health condition and its therapy (from diaries, questionnaires, interviews, etc.)
- PRO Concept: The specific goal of measurement (i.e., the *thing or event* that is to be measured by a PRO instrument)
- PRO Instrument: A means to capture data plus all the information and documentation that supports its use (e.g., instructions, mode, scoring and interpretation)
- PRO Endpoint: PRO statistical outcome used to compare treatment groups in a particular trial

Treatment Benefit and Patients

- PROs are direct measures of treatment benefit, i.e., improvement in how a patient ***survives, feels or functions*** as a result of treatment.
- Measures that do not directly capture the impact of treatment on how a patient survives, feels or functions are **surrogate** measures of treatment benefit (eg, tumor size).

Why PROs?

- Some treatment effects known **only** to the patient, i.e. pain, symptoms, feelings
- Survival may not be only outcome of interest
- Small changes in survival further informed by symptoms, function, and feelings
- Physiologic measures may not reflect how patient functions or feels
- Well-developed assessment by patients is as reliable if not more reliable than global ratings by clinicians



Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Laurie Burke (CDER) 301-796-0700, Toni Stifano (CBER) 301-827-6190, or Sahar Dawisha (CDRH) 301-594-3090.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

February 2006
Clinical/Medical

1\5460dft.doc
1/19/2006

Published Feb 2, 2006

www.**fda**.gov/cder/**guidance**/5460dft.pdf

Represents FDA's current thinking on the use of PRO measures to support labeling claims for medical products regulated by all three centers of FDA

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

Why a PRO Guidance?

- Sponsors can increase the efficiency of their discussions with the FDA during the product development process
- Helps streamline the FDA's review of PRO instrument adequacy, and provide optimal information about the patient's perspective for use in making conclusions about treatment benefit at the time of product approval.
- Different strategies and methods can be used to address FDA review issues.
- There is no single correct way to develop a PRO instrument. FDA will review any strategy or method to support PRO instrument adequacy.

i. Hypothesize Conceptual Framework

- Outline hypothesized concepts & potential claims
- Determine intended population
- Determine intended application\characteristics (types of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework
- Place PROs within preliminary endpoint model
- Document preliminary instrument development

ii. Adjust Conceptual Framework & Draft Instrument

- Generate new items
- Create instrument
- Select recall period, response options, & format
- Select mode of administration / data collection
- Conduct cognitive debriefing
- Pilot test draft instrument
- Document content validity

iii. Confirm Conceptual Framework & Assess Other Measurement Properties

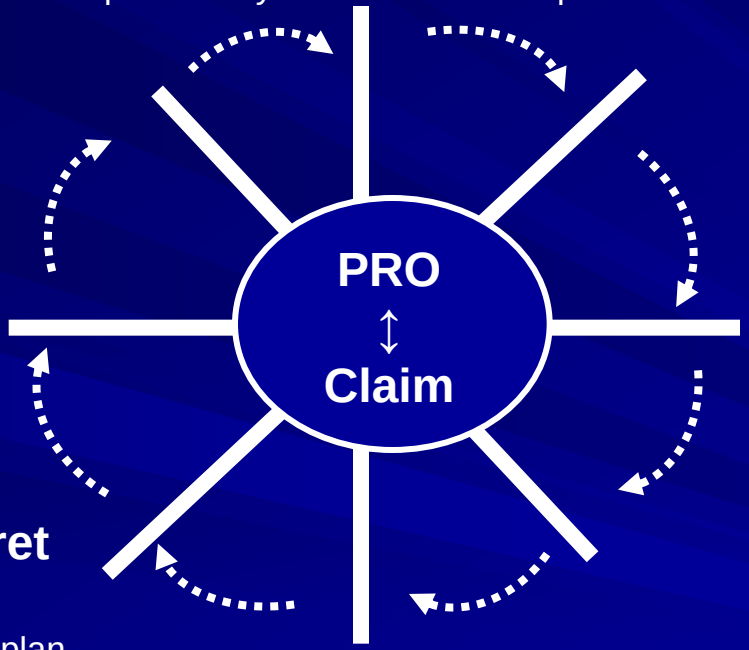
- Confirm conceptual framework with scoring rule
- Assess score reliability, construct validity, & ability to detect change
- Finalize instrument content, format, scoring, procedures & training materials
- Document measurement development

iv. Collect, Analyze, & Interpret Data

- Prepare protocol & statistical analysis plan (final endpoint & responder definition)
- Collect & analyze data
- Evaluate treatment response using cumulative distribution of response & responder definition
- Document interpretation of treatment benefit in relation to claim

v. Modify Instrument

- Change wording of items, populations, response options, recall period, or mode of administration/ data collection
- Translate & culturally adapt to other languages
- Evaluate as appropriate
- Document all changes



What is a Claim to the FDA?

- Statement or implication of ***treatment benefit***
- Requires substantial evidence by regulation in two well-controlled clinical trials
- PROs may relate to safety or efficacy claims depending on context
- Secondary endpoint does not mean secondary importance
- Claims both in labeling (indications, clinical studies) and in promotion (pamphlets, media, literature)

PRO ≠ QOL ≠ HRQL
not interchangeable terms

- **PRO is not just another name for**
  Quality of Life or *Health-Related Quality of Life*
- **QOL** = multidimensional measure of an individual's life situation including concepts unrelated to health.
  - *QOL is not appropriate as clinical trial endpoint.*
- HRQL = multidimensional measure of the health and treatment experience reported by a patient
  - *HRQL may be a relevant endpoint for clinical trials*
    - ***BUT*** HRQL ***difficult*** to measure adequately in all populations for a specific condition
    - Different concepts\domains of HRQL may apply to different populations, conditions and treatment
    - Emphasis on concepts and domains in claims

Match PRO Evidence to Claims

- *Target Product Profile* (TPP) useful to identify potential claims or statements of treatment benefit from all endpoints
- Link claims to concepts measured, **not** a specific instrument
- Use instruments consistent with concept implied by claim
- Address methodological challenges flowing from this requirement

Example: Head and Neck Cancer

Claim	*Concept*
Reduces tumor	Tumor size
Improves swallowing	Swallowing
Increases daily activities	Daily activities
Improves ability to speak	Speaking

Linking PRO Concepts to Claims: Head and Neck Example

Figure 3. Three Concepts of Head and Neck Cancer: Simple Conceptual Framework

Items		*Concept*
Difficulty in **•Swallowing saliva** **•Swallowing liquids** **•Swallowing solid foods**	→	**Swallowing**
Difficulty in **•Eating** **•Dressing** **•Bathing** **•Toileting (using the bathroom)** **•Transferring (moving back and forth from bed to chair)** **•Remaining continent**	→	**Basic Activities of Daily Living**
Difficulty in **•Speaking loud enough** **•Being understood by others**	→	**Speaking**

Content Validity: A Key Challenge

Content validation involves a qualitative judgment of the extent to which the PRO instrument captures the most relevant and important items concerning this concept

1. Use multiple sources for item generation
2. Involve patients in item generation
3. Determine importance of content to patients
4. Use cognitive debriefing to confirm that important concepts were included and adequately reflected in the items?

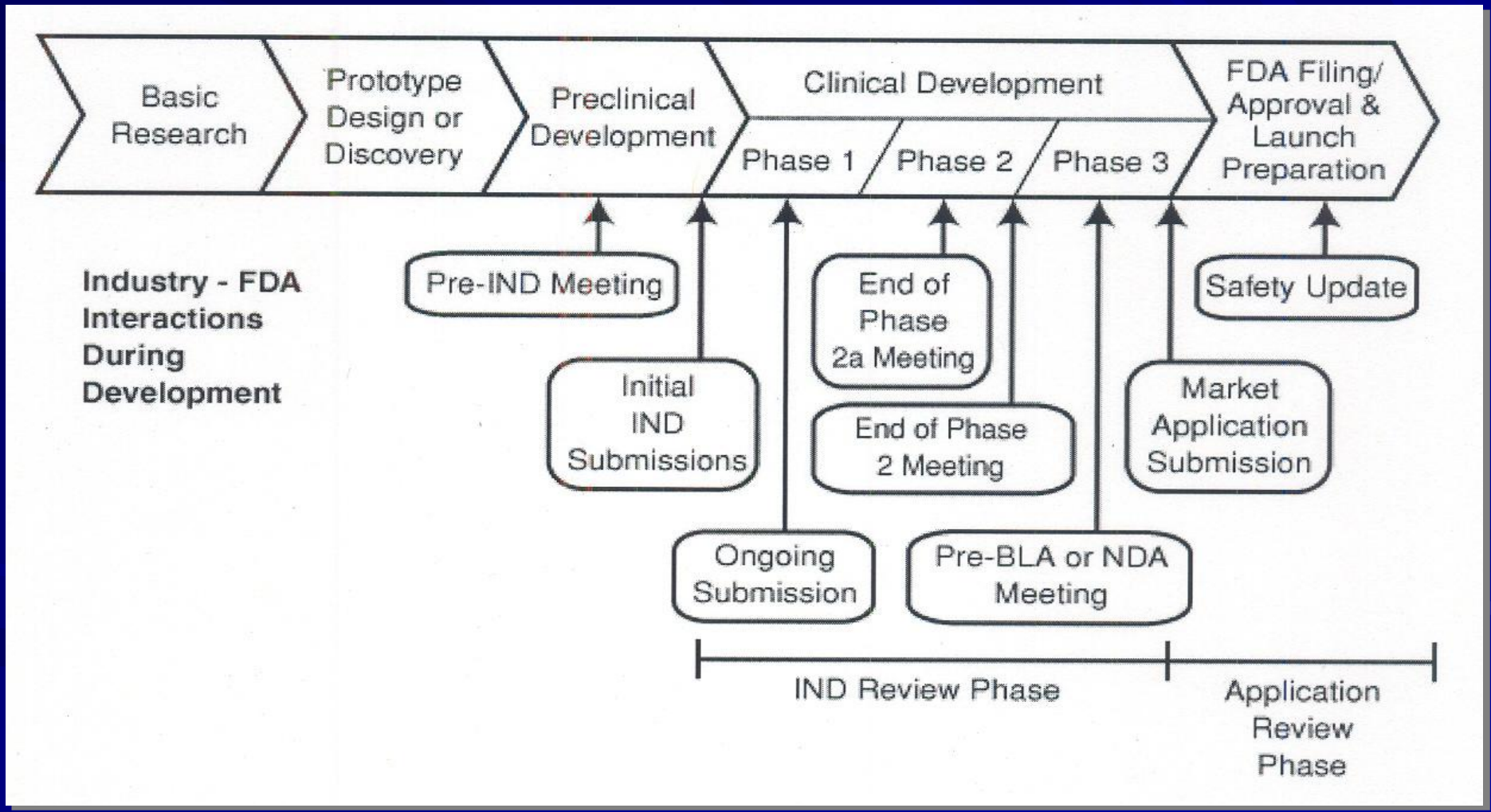
FDA Evaluation of Content Validity

- Review of research designs, conduct and results that were used to produce PRO instrument proposed for trial
- Review of strategies, participants and results of interviews:
  - Protocol for instrument development study
  - Interview guide/schedules
  - Transcripts of interviews (s/b available upon request)
  - Concept and item tracking grids
  - Documentation of “saturation”
- Review of origin, modification, deletion & addition of each item and instruction statement

FDA Reviews All Aspects of PROs

- Patient involvement in instrument development
- Stability of scores over time when no change is expected (test-retest reliability)
- Relationship of the measure to related measures by *a priori* hypotheses (construct-related validity)
- How PRO endpoints are interpreted

Critical Path opportunities to discuss PRO measurement issues



Communicating about PROs with the FDA: *Is there one best way?*

- No one best way and varies by Division
- End of Phase I never too early to begin development as ideas about treatment benefit already in mind
- Questions may be posed to the Division who remains point of contact
- Questions may be posed to Study Endpoints and Labeling
- Special Protocol Assessments helpful

Waiting Until End of Phase II or Phase III

- High risk strategy
- Concept identification and content validity cannot be easily assessed at this stage
- Measurement properties difficult to assess in clinical trialsnts, test-retest reliability
- Usually looks like an afterthought by sponsors
- Does not integrate PROs into medical product evaluation

Desirable Documentation for Item Generation and Selection

- Summary of strategies, participants and results of interviews and focus groups
- Criteria used for item selection
- History of item origin, modification, deletion or addition
- Record of the path to final PRO instrument as used in studies to make claims
- Provide what documentation exists

Documentation Needed

- Study report with sufficient detail to permit replication by others
- Measurement properties specific to conceptual framework, questionnaire, scoring algorithm, administration procedures in light of study population, study, design, and statistical analysis plan
- Measurement properties of a PRO need to be confirmed in every trial

Simple Item Tracking Matrix with Swallowing Measure as Example

Long List of Items	Item Source	Final Decision
How much difficulty do you have swallowing?	Qualitative interviews\ Focus groups	Dropped –high frequency, low severity, too vague in meaning, didn't discriminate between severity levels
How much difficulty do you have swallowing liquids?	Qualitative interviews\ Focus groups	Retained – high frequency of report, high importance to patients, worked well in cognitive debriefing and discriminated between severity levels
How much difficulty do you have swallowing soft foods?	Qualitative interviews\ Focus groups	Dropped – highly correlated with swallowing solid foods and will be covered by this item
How much difficulty do you have swallowing solid foods?	Existing swallowing diary (SWALLOW)	Retained – worked well in cognitive debriefing and discriminated between severity levels
How often do you need to spit?	Qualitative interviews\ Focus groups	Dropped – highly correlated with swallowing saliva—related to other conditions.
How much difficulty do you have swallowing your saliva?	Qualitative interviews\ Focus groups	Retained – worked well in cognitive debriefing – high importance to patients

Final Guidance is Coming!

- Expect clarification of FDA's current thinking
- When?
- Use consultations and special protocol assessment wisely

Conclusions

- All evaluation of PRO endpoint data made in the context of claim, i.e., proposed statement of treatment benefit
- Guidance and not ***guidelines***
- Attention to PROs increases attention to all study endpoints