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# Exploring Clinical Outcome Assessments in Rare Disease Trials

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# Focus on Measurement in Rare Diseases

- Need for better information about medical treatments
- Many rare diseases have no existing outcome measure
- Growing appreciation for direct measures of treatment benefit
  - Survival
  - Symptoms
  - Functioning
- Growing interest in increased trial efficiency
  - Measures that are less dependent on investigator skills
  - Measures that have less variability

# Growing interest in “Patient-Reported Outcomes”

- Mid-1990s: “Health-related quality of life” began to appear in regulatory submissions for labeling and promotion
- Evidence to support a HRQL claim was discussed and harmonized internationally

# “Health-Related Quality of Life”

- A multidomain concept that represents the patient’s general perception of the effect of illness and treatment on physical, psychological, and social aspects of life

# HRQL

- Claiming a statistical and meaningful improvement in HRQL implies:
  - that all HRQL domains that are important to interpreting change in how the clinical trial's population feels or functions as a result of the targeted disease and its treatment were measured;
  - that a general improvement was demonstrated; and
  - that no decrement was demonstrated in any domain.

# “Patient-Reported Outcome”

- A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of the patient’s health condition without amendment or interpretation of the patient’s response by a clinician or anyone else.
- The concept of measurement varies, but the measurement attributes necessary to meet the “well-defined and reliable” regulatory standard for outcome assessments are uniform



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**Guidance for Industry**  
**Patient-Reported Outcome Measures:**  
**Use in Medical Product Development**  
**to Support Labeling Claims**

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)

December 2009  
Clinical/Medical

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# PRO Measures: Standard of Evidence

Feb 2006: Draft

Dec 2009: Final

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>

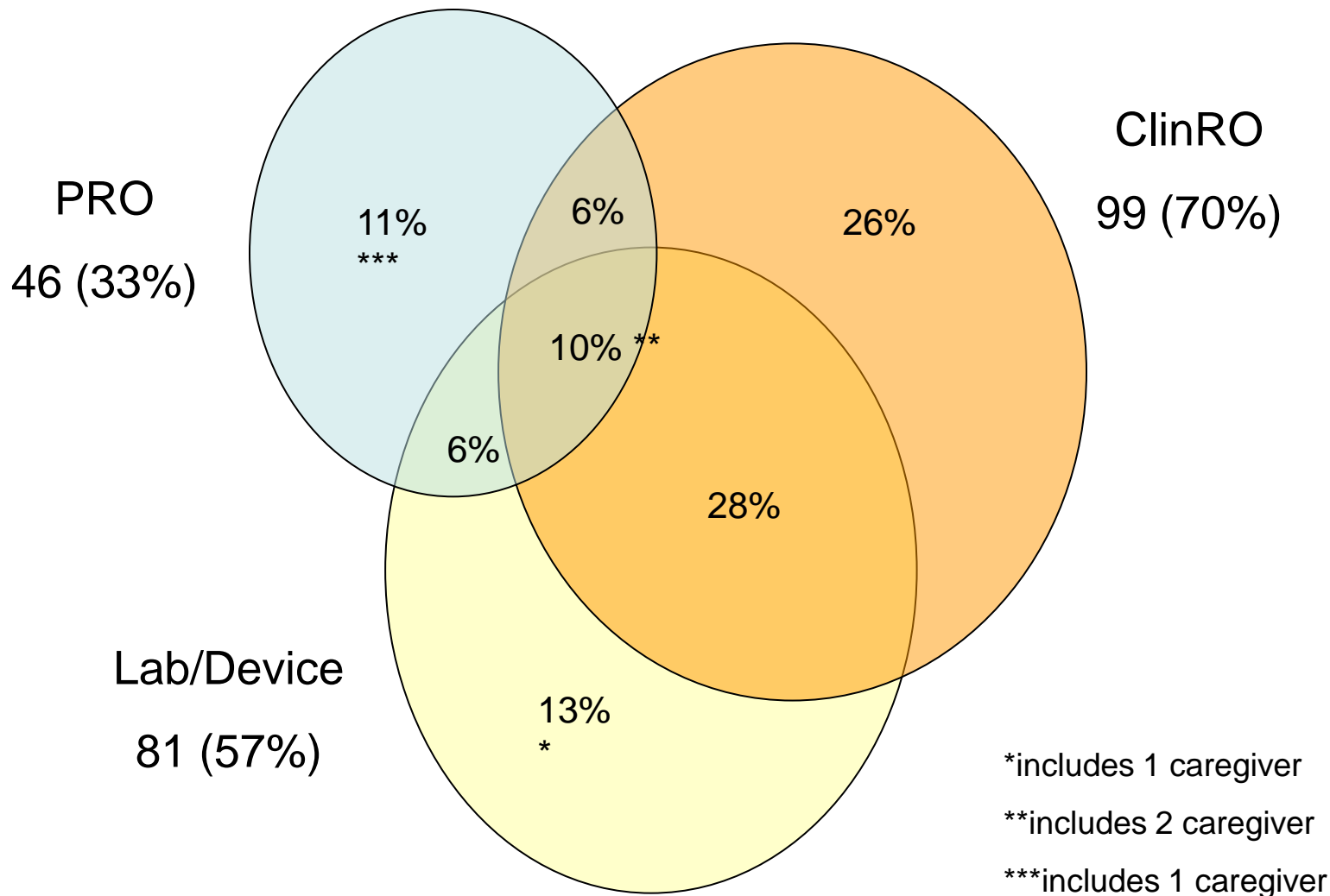
# FDA PRO Guidance

- Explains how FDA evaluates PRO instruments for their usefulness in measuring and characterizing treatment benefit as perceived by the patient.
- Explains how FDA reviews and interprets evidence that a PRO instrument measures the concept represented by a treatment benefit claim.

# Types of Outcome Assessments in Clinical Trials

- Biomarkers (non-clinical)
- Clinical Outcome Assessments
  - Patient Reported (PRO)
  - Observer Reported (ObserverRO)
  - Clinician Reported (ClinRO)

# Endpoints in Labeling for 141 NMEs 2003-2008



# NMEs Approved 2003-2008 Based Only on a PRO

- Relistor (constipation)
- Vimpat (seizures)
- Toviaz (OAB)
- Amitiza (constipation)
- Omnaris (rhinitis)
- Sanctura (OAB)
- Vesicare (OAB)
- Enablex (OAB)
- Prialt (pain)
- Emend (N & V)
- Aloxi (N & V)
- Levitra (ED)
- Elestat (ocular itching)
- Cialis (ED)

# Observer Report

## (ObserverRO)

- Provides observations but **not interpretations** of the patient's health condition from the observer (e.g., caregiver)
- Not a PRO measure
- Useful when the patient is unable to convey their subjective state
- The observer is typically the person who takes care of the patient most of the time

### Examples:

- Parent assessment of how many times a baby vomited in the past 24 hours
- Teacher assessment of a child's ability to attend to tasks (inattentiveness)



# Clinician Report (ClinRO)

Any assessment of the status of a patient's health condition based on clinicians **observations and interpretations**



# FDA Review of ClinROs/ObsROs vs. PROs:

## **SAME:**

- I. Instrument
- II. Targeted Claims or Target Product Profile (TPP)
- III. Endpoint Model
- IV. Conceptual Framework
- V. Content Validity Documentation
- VI. Assessment of Other Measurement Properties
- VII. Interpretation of Scores
- VIII. Language Translation and Cultural Adaptation
- IX. Data Collection Method
- X. Modifications
- XI. Clinical Trial Design and Data Analysis Issues
- XII. Key References

## **DIFFERENT:**

**Nothing**

# A “Concept”

- **Concept** = the “thing” that is measured
  - Latent (pain intensity) or Observed
  - Core symptoms/signs/functional impairments of a disease or condition or the impact of the disease/condition on other concepts



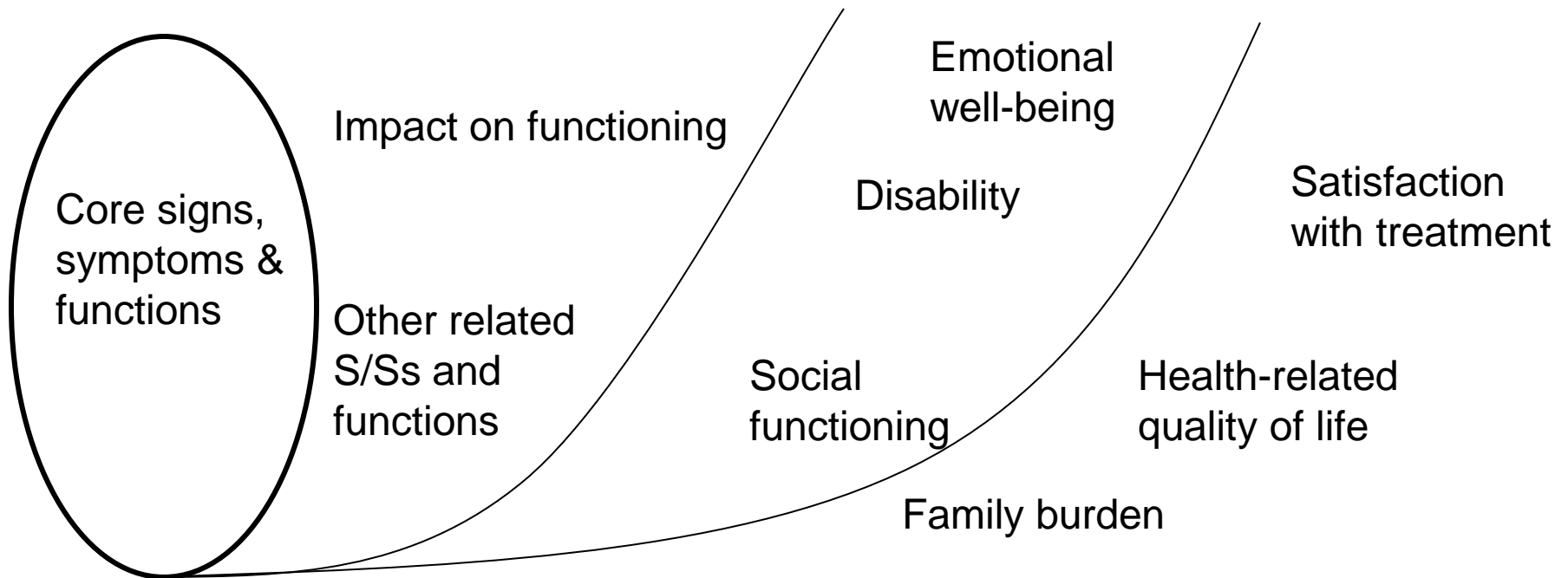
# Assessing Treatment Benefit

Disease-defining  
concepts

Proximal disease  
Impact concepts

Distal disease  
Impact concepts

Disease impact on  
g<sup>al</sup> life concepts



# Content Validity

- Evidence that:
  - The score represents the intended concept in the context of use studied
  - The items in the assessment adequately cover the concept

## Content Validity

- Content validity is established for the intended purpose
  - Measurement concept matches targeted claim
  - Item content development includes target population input (qualitative research)
  - Item content captures the intended concept in the intended treatment population
  - Measurement concept conforms with the proposed clinical trial objectives

# Importance of Content Validity in Rare Diseases

- Subject variability identified
- Contributors to measurement error identified
- Measurement mistakes avoided
- Contributors to experiment error avoided

↳ **Variability of a COA minimized** ⇒ **Increased assay sensitivity** ⇒ **Better clinical study efficiency**



# Content Validity: Establishing and Reporting the Evidence in Newly-Developed Patient-Reported Outcome (PRO) Instruments for Medical Product Evaluation - Good Research Practices

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- Part I: Eliciting Concepts for a New PRO Instrument
- Part II: Assessing Respondent Understanding



# Part 1: Eliciting Concepts

## *Five Steps*

1. Determine the context of use.
2. Develop the research protocol for qualitative concept elicitation and analysis.
3. Conduct the concept elicitation interviews and focus groups.
4. Analyze the qualitative data.
5. Document concept development and elicitation methodology and results.

## Step 1: Determine the Context of Use

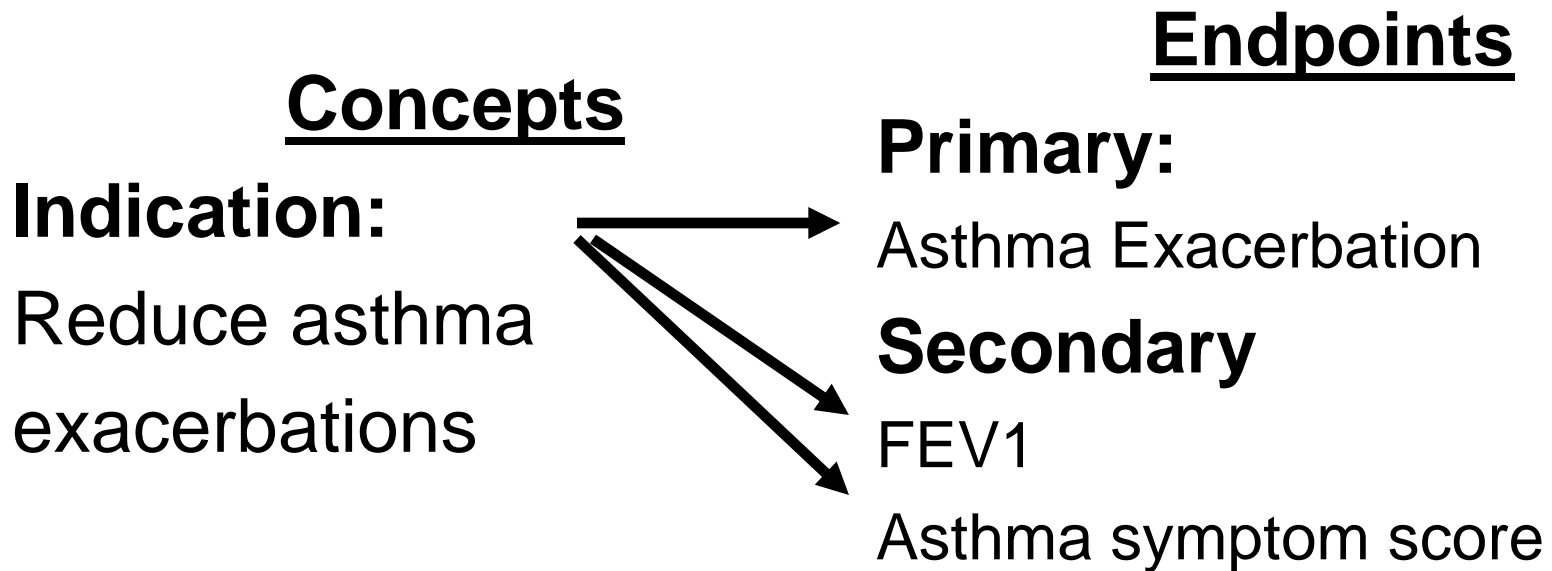
A comprehensive and clear statement that describes the manner and purpose of use and plans for interpretation of a clinical outcome assessment (COA)

- Concept measured
- Target claim
- Target population
- Intrinsic and extrinsic sources of heterogeneity considered
- Type of treatment
- Type of trial (endpoint model)

# Clinical Trial Endpoint Model

A diagram or description of the hierarchy of hypothesized relationships among all endpoints in a clinical trial

Example:

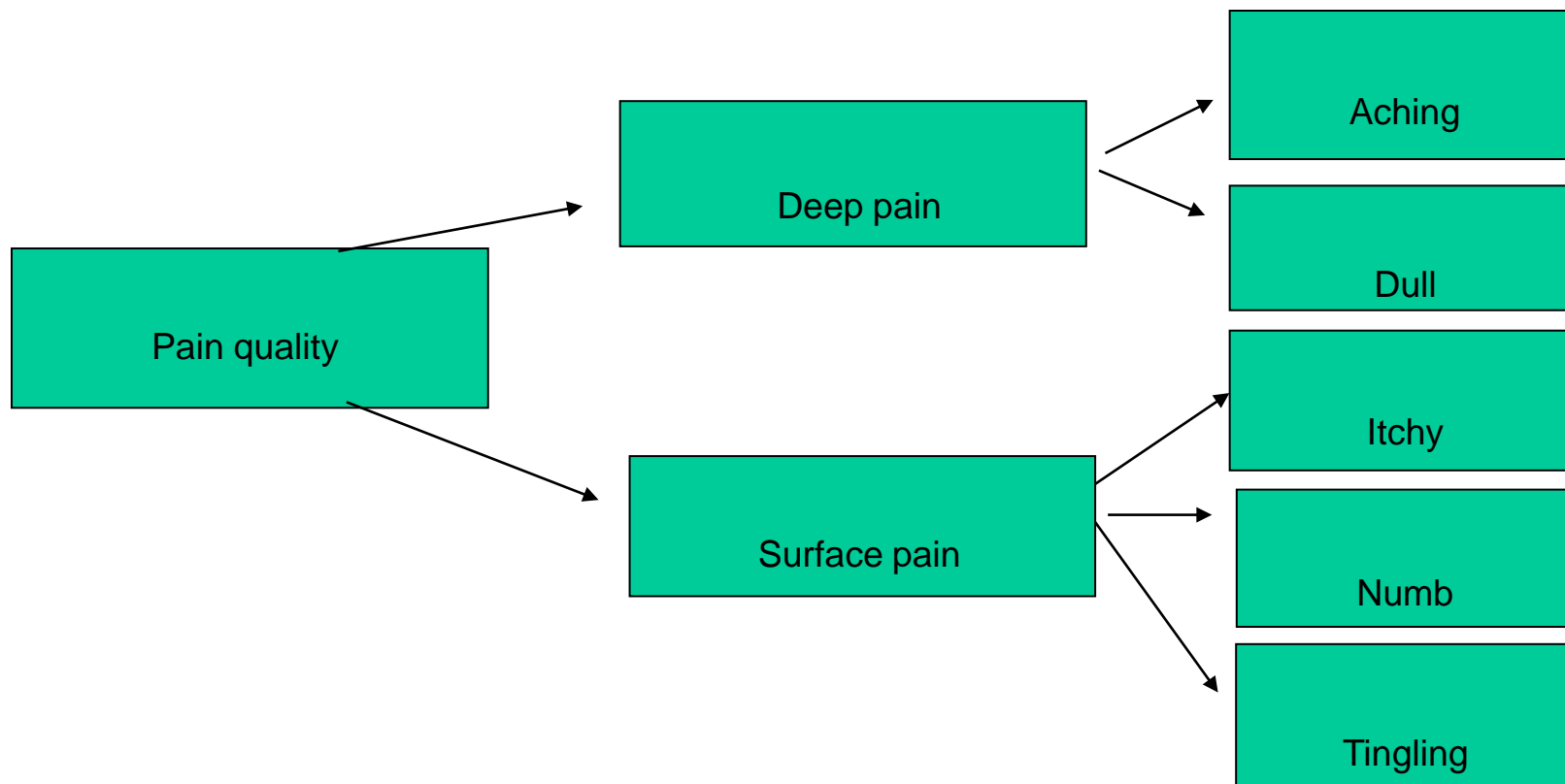


## **Step 1: Determine the context of use**

### *continued*

- Select and define the target population including cultural/language groups
- Make preliminary decisions on the range of instrument content and structure.
- Select a theoretical approach to guide qualitative methods for content validity.
- Develop an hypothesized conceptual framework for the proposed instrument.

**Figure 2: *Example* conceptual framework for a PRO evaluating the concept of pain quality**



## Step 2: Develop research protocol for concept elicitation & analysis

- Define the target sample characteristics.
  - Clinical and demographic characteristics
  - Sample size/saturation
- Select the data collection method - focus groups, individual interviews, both.
- Determine the setting and location for data collection.
- Develop the interview guide – Draft, pilot, revise.
  - Not a script – stimulate discussion

## **Step 3: Conduct the concept elicitation interviews & focus groups**

- Obtain IRB approval.
- Recruit and train sites.
- Recruit participants; monitor sample characteristics to assure representation.
- Select and train interviewers.
- Conduct interviews – implement quality control measures.
- Record or videotape interviews.
- Transcribe and clean transcripts.

## **Step 4: Analyze the qualitative data**

- Analyze qualitative data according to theoretical approach used.
- Establish preliminary coding framework; update as data are coded.
- Establish coding procedures and train coders.
- Organize data using a qualitative research software. program
- Assess saturation.
- Interpret results.

## **Part II: Assessing Patient Understanding**

### *Five Steps*

1. Develop items based on findings from concept elicitation.
2. Design cognitive interview process for the planned context of use.
3. Conduct cognitive interviews.
4. Make decisions to revise the PRO instrument.
5. Document cognitive interview results for evaluation of content validity.

# **Step 1: Develop items based on findings from concept elicitation**

- Develop criteria for item development and evaluation.
- Choose concepts to measure.
- Select recall period and modes of administration.
- Draft Instructions
- Develop items and match to response scales
- Assess readability
- Determine order and sequence

# Sample item criteria

- The item captures the concept that is intended.
- The item is worded in a manner consistent with the expressions used by patients.
- The item represents a single concept, rather than a multidimensional concept.
- The content of the item is appropriate for the mode of administration

## **Step 4: Make decisions to revise the PRO instrument**

- Employ an iterative process.
- Reduce ambiguity in item language.
- Assess saturation.
- Balance respondent input with principles of item construction and decisions on conceptual framework.

## **Step 5: Document cognitive interview results for evaluation of content validity**

- Complete Item Tracking Matrix including final item, final response scale, any preliminary domain assignment, description of intent of item, and patient quotes supporting item intent.



## Figure 2: Example Item Tracking Matrix

Concept Name	Pain	Sleep Impact	Emotional Impact
Item Number	Item #	Item #	Item #
Concept Definition	Pain related to (condition)	Disturbance to sleep quality caused by condition-related pain	Emotional difficulties caused by condition related pain
Original Item	Since you woke up this morning, how severe was your pain?	How many times did you wake up in the night because of your pain?	How worried have you been because of your pain?
Original Item Response Options	0-10 scale (0= not severe at all, 10=as severe as I can imagine)	Enter number: _____	0-10 scale (0= not worried at all, 10=as worried as I can imagine)
Attribute to measure	Severity	Frequency	Magnitude (of worry)
Change from 1st group of cognitive interviews	Since you woke up this morning, how severe was your pain at its worst?	How many times did you wake up last night because of your pain?	No changes in first group of cognitive interviews.
Rationale for Change	Patients were not sure if they should think about their overall or most intense experience.	Patients reported seeing "in the night" as general and could mean "any night" as opposed to specifically "last night."	
Examples of Patient Quotations	<i>"I had pain several times today, some I would rate low because it didn't bother me so much, but one pain was really bad.."</i>  <i>"I'm not sure if I should think about all pain in the day and average it, or just pick one I remember best to answer about..."</i>	<i>"I was thinking in an average night, how many times do I usually wake up"....</i>  <i>"most nights I only wake up once or twice"</i>	



## Next Steps and Manuscript Submission

- Submission to *Value in Health* in June.
- Questions or comments, please email Donald Patrick:  
[donald@u.washington.edu](mailto:donald@u.washington.edu)  
or [pro@ispor.org](mailto:pro@ispor.org)

# Psychometric Testing

- Begins AFTER content validity is established and the instrument is in its final form
- Includes testing for construct validity, reliability and ability to detect change
- This can be performed concurrently with the phase 3 trial provide adequate planning occurs



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## Guidance for Industry

### Qualification Process for Drug Development Tools

***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 90 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 (CDER) Shaniece Gathers, 301-796-2600.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

October 2010  
Clinical/Medical

# DDT Qualification Process

Oct 2010: Draft

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>

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## DDT Qualification

- Regulatory conclusion that within the stated context of use, the results of measurement can be relied upon to have a stated interpretation and utility—“fit for purpose”
- Data produced by the PRO measure (i.e., instrument) can be interpreted as clinically meaningful and can be used as a primary or key secondary endpoint to support a claim in labeling
- Meets the standards set forth in the PRO guidance

# Drug Development Tool (DDT) Qualification Process

- DDT developer provides background information so FDA can decide whether or not to participate in the qualification process for the DDT
  - Applicant may submit a **Feasibility document** (letter of intent) for
    - Targeted endpoint model
    - Targeted claim
    - Hypothesized conceptual framework
    - Rationale for DDT qualification
    - Methodology to collect evidence to support DDT qualification
  - FDA reviews Scoping document before agreeing to start the qualification process

- *Qualification Stage 1: Consultation and advice*

- **Qualitative research summary** { e.g., qualitative research protocols (concept elicitation, cognitive debriefing), transcripts, reports, draft of the instruments, revised CF, translation methodology, item map
- **Instrument finalization summary** { e.g., protocols for item reduction, analyses plan, scoring algorithm, draft of the instruments, item map
- **Quantitative research summary** { e.g., protocols, analyses plan, report, final instrument, item map, interpretation,

- Once DDT is ready for qualification, the Agency will conduct the final review of the **Qualification Package**
- Public notice of DDT qualification
- Public availability of DDT tool

# Benefits of Collaboration

- Allows FDA to work with multiple partners to leverage expertise and resources toward PRO instrument development
  - Improved/transparent FDA internal (review) processes
  - Pooling of industry know-how and resources
  - Provide a basis for eventual comparison of labeling claims by physicians
  - Issuance of best practices and guidances toward future instruments and product development

# Summary

- Terminology is becoming standardized
  - Concept
  - Treatment benefit
  - Context of use
  - Content validity and other measurement properties
  - Clinical Outcome Assessments (COAs)
- Good measurement begins with content validity and principles apply to all COAs--PROs, ObserverROs and ClinROs
- The regulatory qualification process offers the potential for increased efficiency in the development of “well-defined and reliable” outcome assessments for use in clinical trials