

FDA Perspective on Clinical Outcome Assessments

IMMPACT XX Meeting

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Speaker Disclaimer

- The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.
- I have no actual or potential conflict of interest in relation to this activity.

Outline

- **Patient-focused drug development (PFDD)**
 - Capturing the patient voice (21st Century Cures Act of 2016)
 - FDA flexibility
- **Roadmap to clinical outcome assessment (COA) selection/development**
 - Defining the target patient population and conceptualizing clinical benefit
- **Content validity of a COA**
 - Evidence from qualitative research that one is assessing the concept of interest
- **Use of COAs for Pain and Urgency Assessment**

Patient-Focused Drug Development (PFDD)

- PFDD is part of FDA commitments under **Prescription Drug User Fee Act (PDUFA) V**
<https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/>
 - Conduct 20 public meetings each focused on a specific disease area
 - Each meeting results in a Voice of the Patient report that faithfully captures patient input from the various information streams
- **21st Century Cures Act of 2016** includes new statutory provisions for PFDD (under Title III Subtitle A)
<https://www.congress.gov/bill/114th-congress/house-bill/34/text>

21st Century Cures Act of 2016



Section 3002: PFDD Guidance

Publish Guidance for Industry addressing:

- Collection of accurate and representative patient experience data
- Collection of data on patients' burden of disease, burden of treatment, and benefits/risks in disease management
- Identification and development of methods to measure impacts (e.g., burden of disease/treatment) to patients
- **Collection and analysis of COAs for purposes of regulatory decision-making**

Conduct public workshop on:

- **COAs and better ways to incorporate COAs into endpoints**

Evidence of Clinical Benefit to Patients

- Direct evidence of clinical benefit is derived from studies with endpoints that measure survival, or how patients feel and function in daily life
- Indirect evidence of clinical benefit is derived from studies with endpoints that measure other things that are related to how patients survive, feel or function (e.g., surrogates, biomarkers)

What Is a Clinical Outcome Assessment (COA)?

Definition: Clinical outcome assessment (COA)

Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician observer, or through a performance-based assessment. There are four types of COAs:

- Clinician-reported outcome (ClinRO)
- Observer-reported outcome (ObsRO)
- **Patient-reported outcome (PRO)**
- Performance outcome (PerfO)

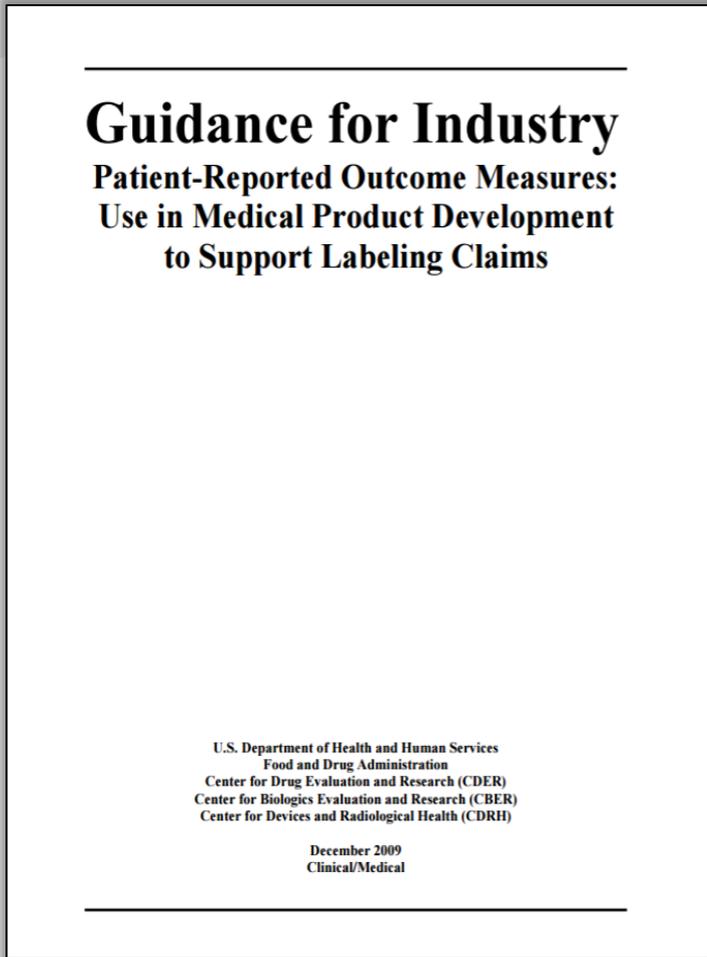
COA Tools and Guidance



FDA has developed a number of tools to help guide the development of **fit-for-purpose COAs**:

- FDA PRO Guidance for Industry (2009)
- Roadmap to Patient-Focused Outcome Measurement in Clinical Trials
- Wheel and Spokes Diagram
- Drug Development Tool (DDT) Qualification Guidance for Industry (2014)
- Pilot CDER COA Compendium (2016)

FDA PRO Guidance for Industry (2009)



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)

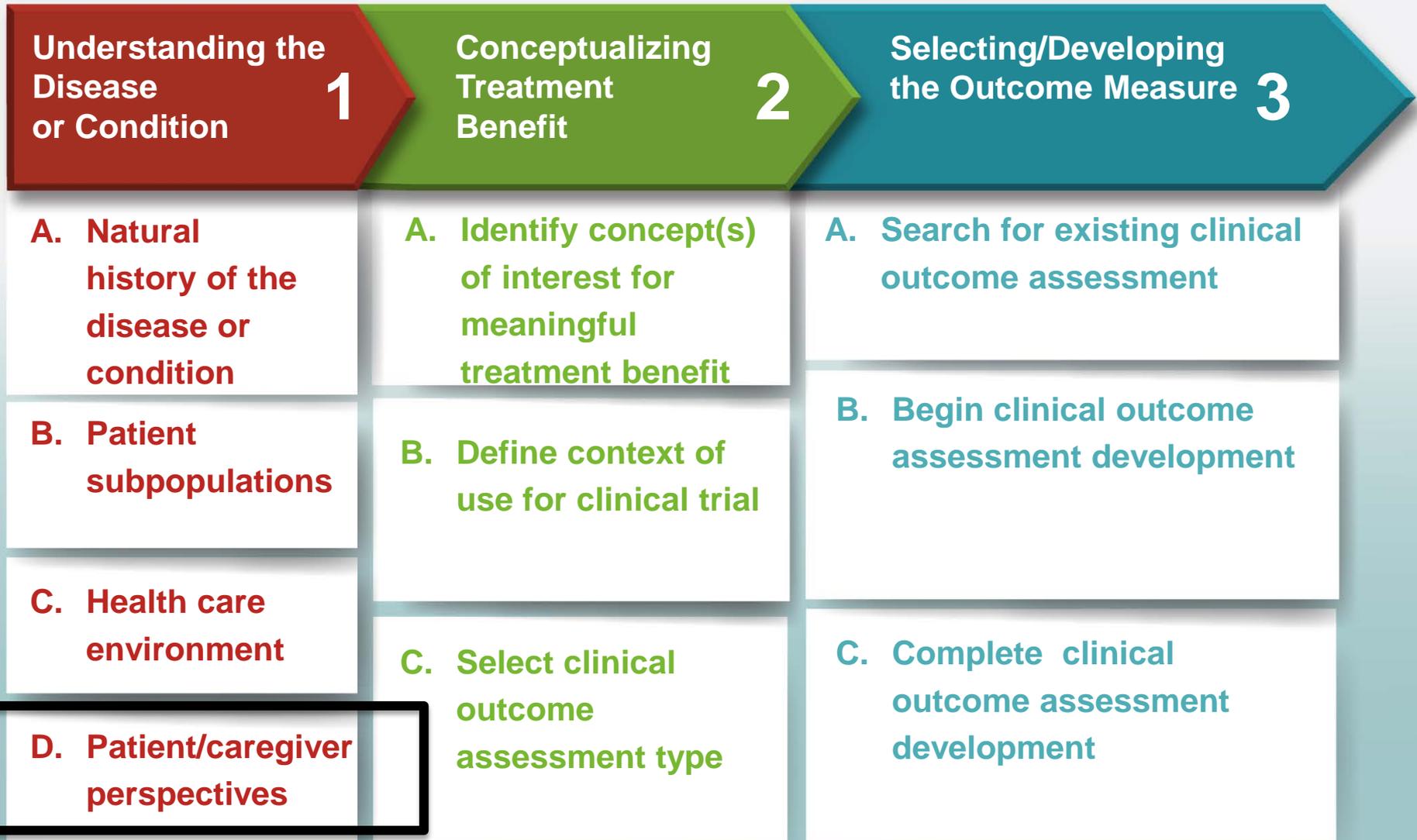
December 2009
Clinical/Medical

- Defines *good measurement principles* to consider for “*well-defined and reliable*” (21 CFR 314.126) PRO measures intended to provide evidence of clinical benefit
 - Goal: Avoid labeling statements that may be false or misleading
- All clinical outcome assessments can benefit from the good measurement principles described within the guidance
- Provides *optimal approach* to PRO development; *flexibility and judgment* needed to meet practical demands
- *Flexibility is necessary*

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



Link to detailed version of Roadmap diagram:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/UCM370174.pdf>

Updated 4/28/15



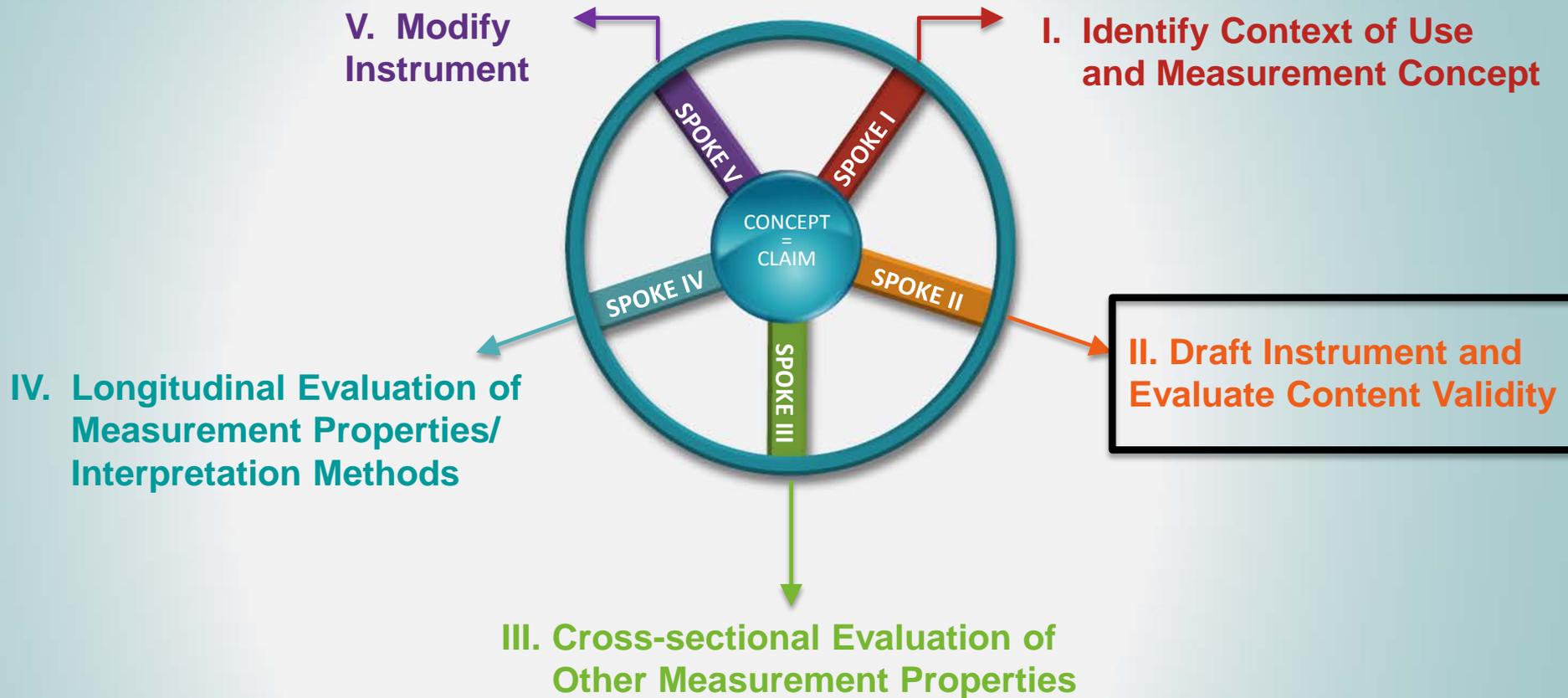
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
<http://www.fda.gov/Drugs>

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Spoke II: Content Validity

Development of **CLINICAL OUTCOME ASSESSMENTS**



Qualitative Research to Support Content Validity



- Qualitative research (i.e., focus groups; one-on-one interviews) for PRO tool development should be conducted in a sample of patients **matching the eligibility criteria of the target clinical trial patient population.**
- With PRO tool development, patients should be asked in cognitive interviews:
 - How they **define** the items' instructions and concepts
 - Whether they can **distinguish** between the item concepts (e.g., abdominal symptoms) and response options to determine whether a one-category improvement is clinically meaningful to patients.

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Assessing Pain

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

We recommend evaluating abdominal pain intensity by using an 11-point (i.e., 0 to 10) numeric rating scale that asks patients daily to rate their *worst abdominal pain over the past 24-hours*.¹⁰

Guidance for Industry Analgesic Indications: Developing Drug and Biological Products

a. Pain intensity

Pain intensity is the fundamental measure that defines the efficacy of an analgesic drug. There are no objective measures for pain intensity. As PROs, pain intensity can be measured by numerical rating scales, visual analog scales, or categorical scales. Each of these measurement techniques has advantages and disadvantages that should be considered in the design. It is important also to choose the endpoint measure appropriate to the patient population and clinical situation being studied. When disease-specific pain measures are available, they may be preferable to nonspecific measures if adequately developed because they may be more sensitive to change and more interpretable.

Pain Scales

➤ 11-point numeric rating scale (NRS)

- Example: The Brief Pain Inventory – Short Form (BPI-SF) Item 3
- Well-documented measurement of pain intensity

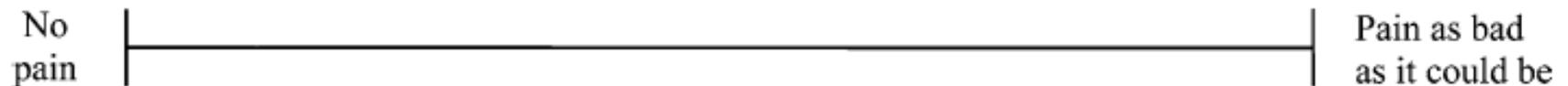
3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

http://www.npcrc.org/files/news/briefpain_short.pdf

➤ Visual analogue scale (VAS)

- Concerns with consistent line length; some difficulty of use



Haefeli M and Elfering A. Pain assessment. Euro Spine J 2006; 15: S17–S24.

Challenges & Considerations when Using COAs for Assessment of Pain



- Include **localization** of pain (e.g., abdominal/bladder/pelvic) in the item instructions and stem/question
 - Pictures with location of pain circled
 - Need for qualitative research with patients
- **Recall period** – past 24 hours versus past week
- **Average versus worst** pain
- Capture patients' concomitant **analgesic use**
- Optimize the **frequency and timing of assessments** of pain assessments in order to capture meaningful data
 - **Chronic versus episodic** pain

Challenges in Using COAs for Assessment of Urgency



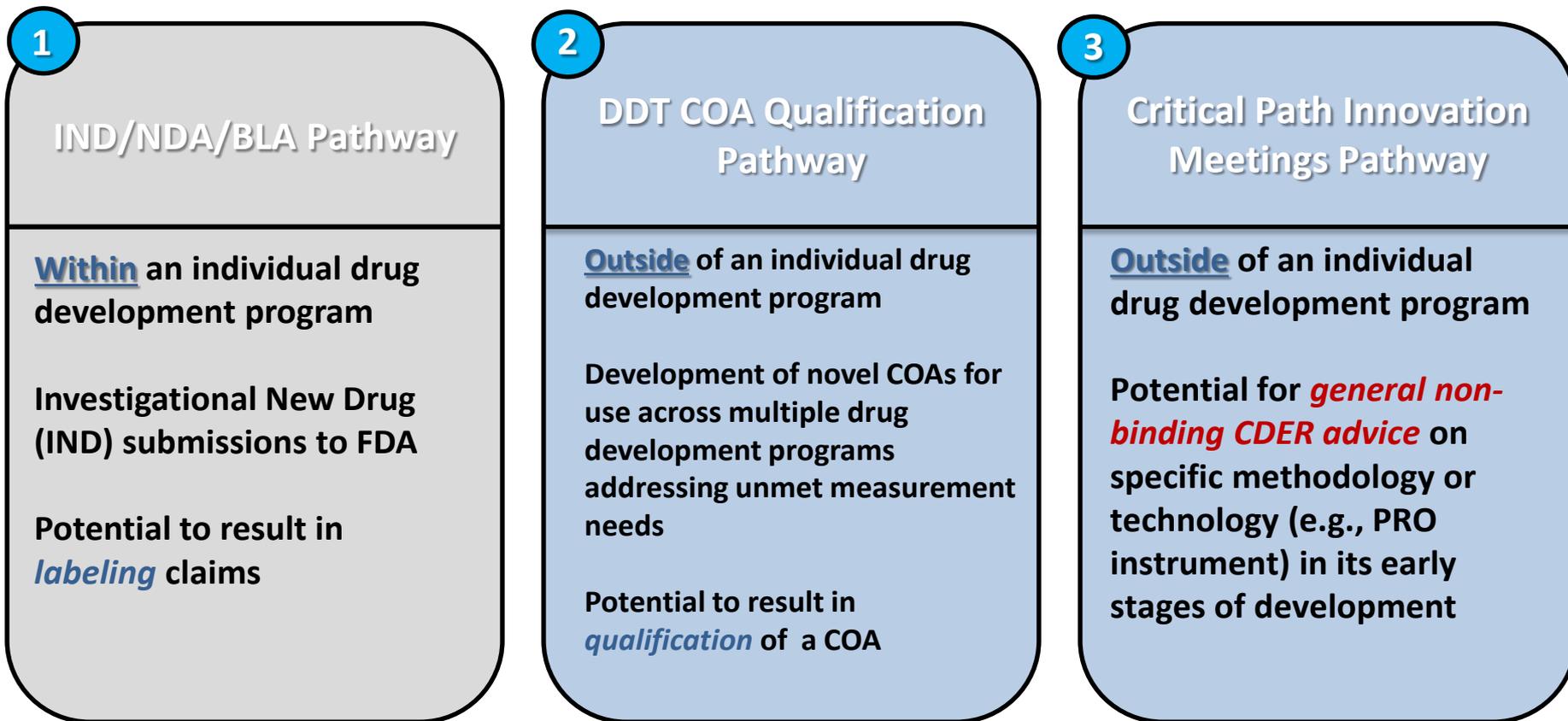
- Urgency sometimes included in the **definition of a patient population**
 - Urinary urgency characterizes overactive bladder syndrome
 - Pain associated with urinary urgency characterizes interstitial cystitis
- **Patient input is needed** to better define “urgency.”
- **Difficult to measure** urgency without knowing what severity and frequency of urgency is considered normal functioning and what is considered normal to the patient.
- Need for qualitative research with patients to better establish **what is considered meaningful improvement** in feelings of urinary urgency and bowel urgency

Practical Considerations when Including COAs in Clinical Trials



- Phase 2 trials represent an **opportune time** to evaluate psychometric properties and performance of the PRO tool
 - Document evidence to support a responder definition prior to inclusion of the PRO tool in phase 3
- Patient global impression of severity and change (PGI-S and PGI-C) scales should be included in both **phase 2 and 3 clinical trials**
- Same PRO items and response options should be used across all phase 2 and 3 clinical trials for **comparability of PRO data**
- Submit psychometric evaluation study **protocols to FDA**

Pathways for FDA Clinical Outcome Assessment (COA) Review & Advice



BLA = Biologics Licensing Application; CDER = Center for Drug Evaluation and Research (FDA); DDT = Drug Development Tool; NDA = New Drug Application; PRO = Patient-Reported Outcome

Summary

- **Patient's voice is important** to consider when developing PRO tools intended to assess how patients feel or function
- Regulatory standards (21 CFR Part 314) to determine whether a COA is “**well-defined and reliable.**”
- **FDA maintains flexibility** in our evaluation of evidence, taking into account evidentiary standards , feasibility, and practicality.
- There are challenges and considerations when assessing patients’ pain and urgency symptoms
- Early planning and discussion with FDA important to ensure clinical trial assessments are **fit-for-purpose** and measure what is most important to patients.
- FDA has developed numerous tools and pathways for COA development, review, and advice and is open to **engagement early and throughout** clinical trial endpoint development

Helpful links

- **FDA COA Staff Website:**
<https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductandsandtobacco/cder/ucm349031.htm>
- **PRO Guidance for Industry (2009):**
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>
- **DDT Qualification Guidance for Industry (2014):**
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>
- **COA DDT Qualification Website:**
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm>
- **Critical Path Innovation Meeting Website & Guidance:**
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm>
- **Pilot CDER COA Compendium:**
<https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm459231.htm>

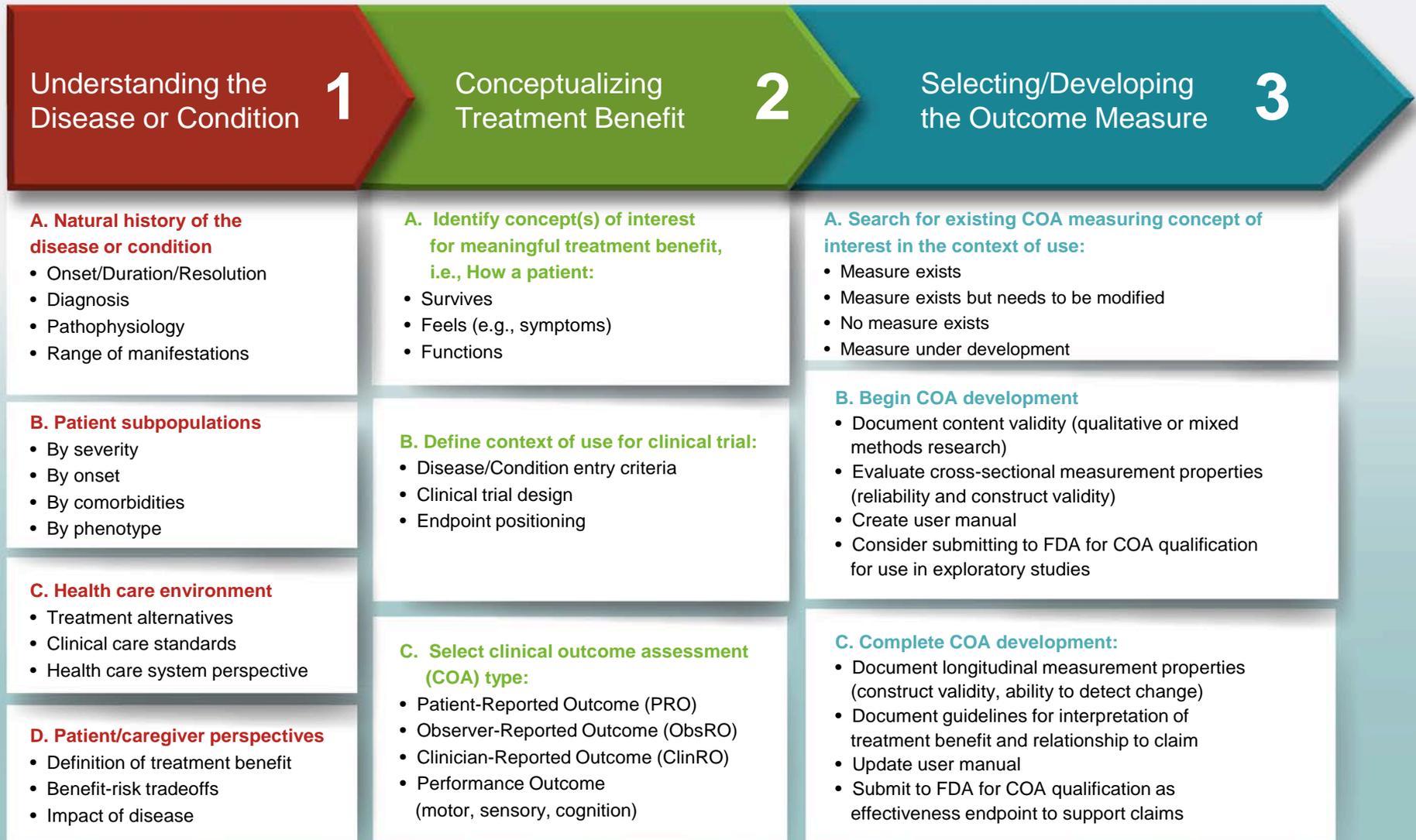






BACKUP SLIDES

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



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

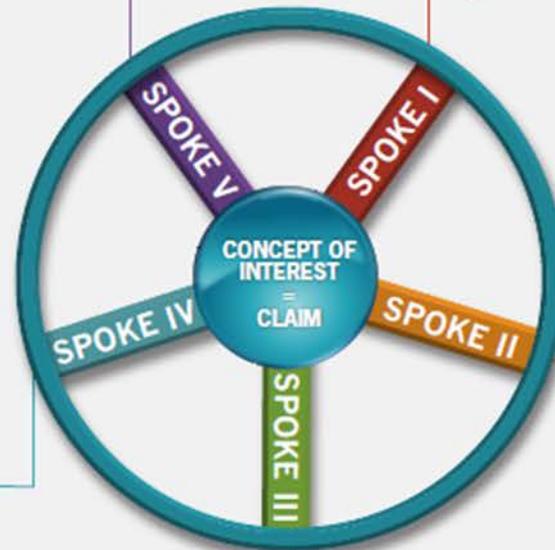
- Assess ability to detect change and construct validity
- Identify responder definition(s)
- Provide guidelines for interpretation of treatment benefit and relationship to claim
- Document all results
- Update user manual

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

Link to detailed version of Wheel and Spokes diagram:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/UCM370175.pdf>

