U.S. FOOD & DRUG ADMINISTRATION

Public Webinar

Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments – Draft Guidance

September 9, 2022

#PFDD

U.S. FOOD & DRUG ADMINISTRATION

Welcome

Shannon Cole, MS
Office of the Center Director
Center for Drug Evaluation and Research

Agenda

12:00 p.m.	Welcome
12:02 p.m.	Opening Remarks
12:05 p.m.	Introduction
12:25 p.m.	Roadmap to Patient-Focused Outcome Measurement in Clinical Trials
1:00 p.m.	Overview of the Evidence-Based Rationale to Justify a COA's Use
1:15 p.m.	Question and Answer
1:25 p.m.	BREAK
1:35 p.m.	Advanced Discussion of Evidence-Based Rationale
2:45 p.m.	Question and Answer
3:00 p.m.	End

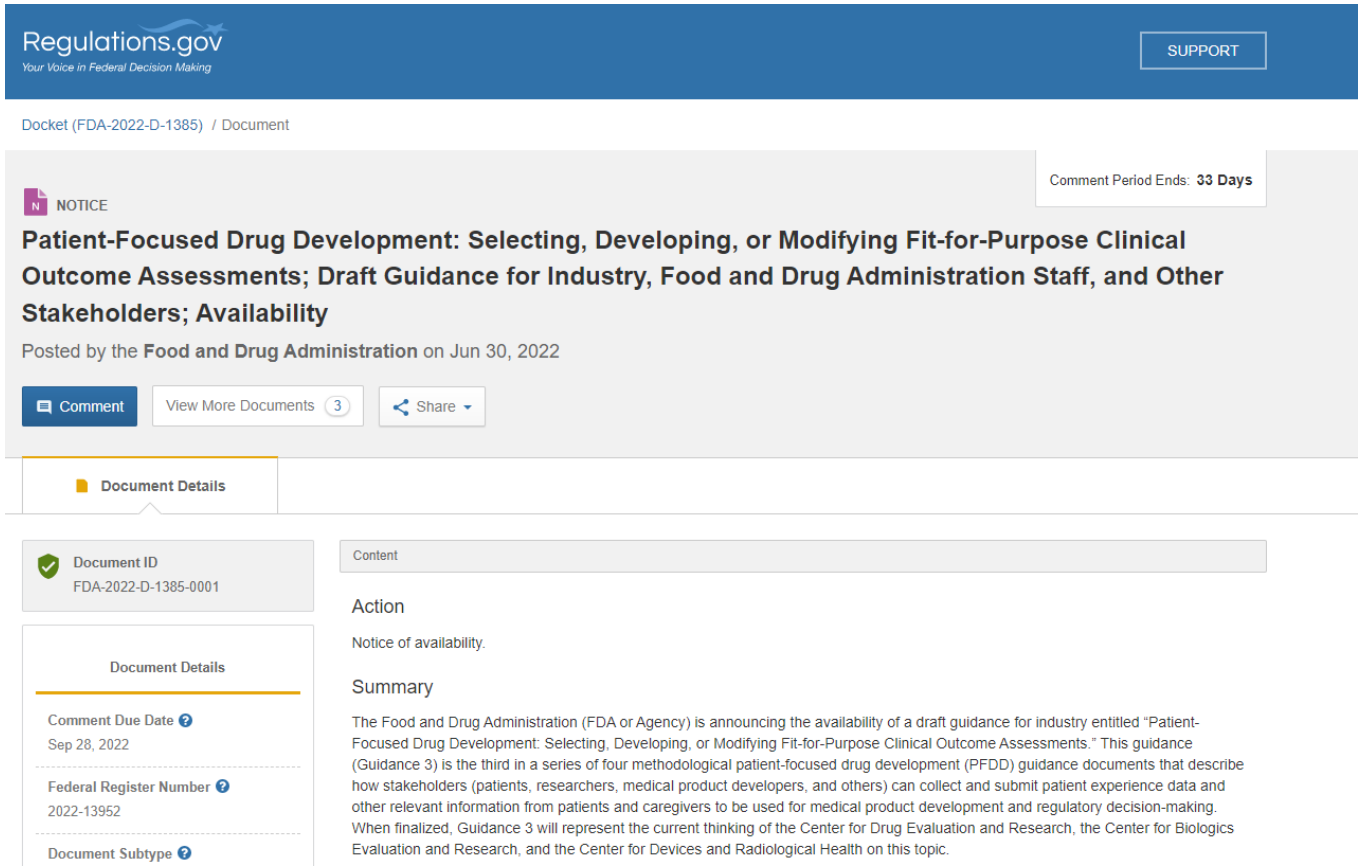
Send us your comments!

Interested stakeholders are invited to submit comments on the draft guidance to the public docket.

The docket will close on September 28, 2022.

How do you submit a comment?

- Please visit: https://www.regulations.gov/docket/FDA-2022-D-1385
- And **Click Comment**



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Opening Remarks

Theresa Mullin, PhD
Associate Director for Strategic Initiatives
Center for Drug Evaluation and Research

Introduction

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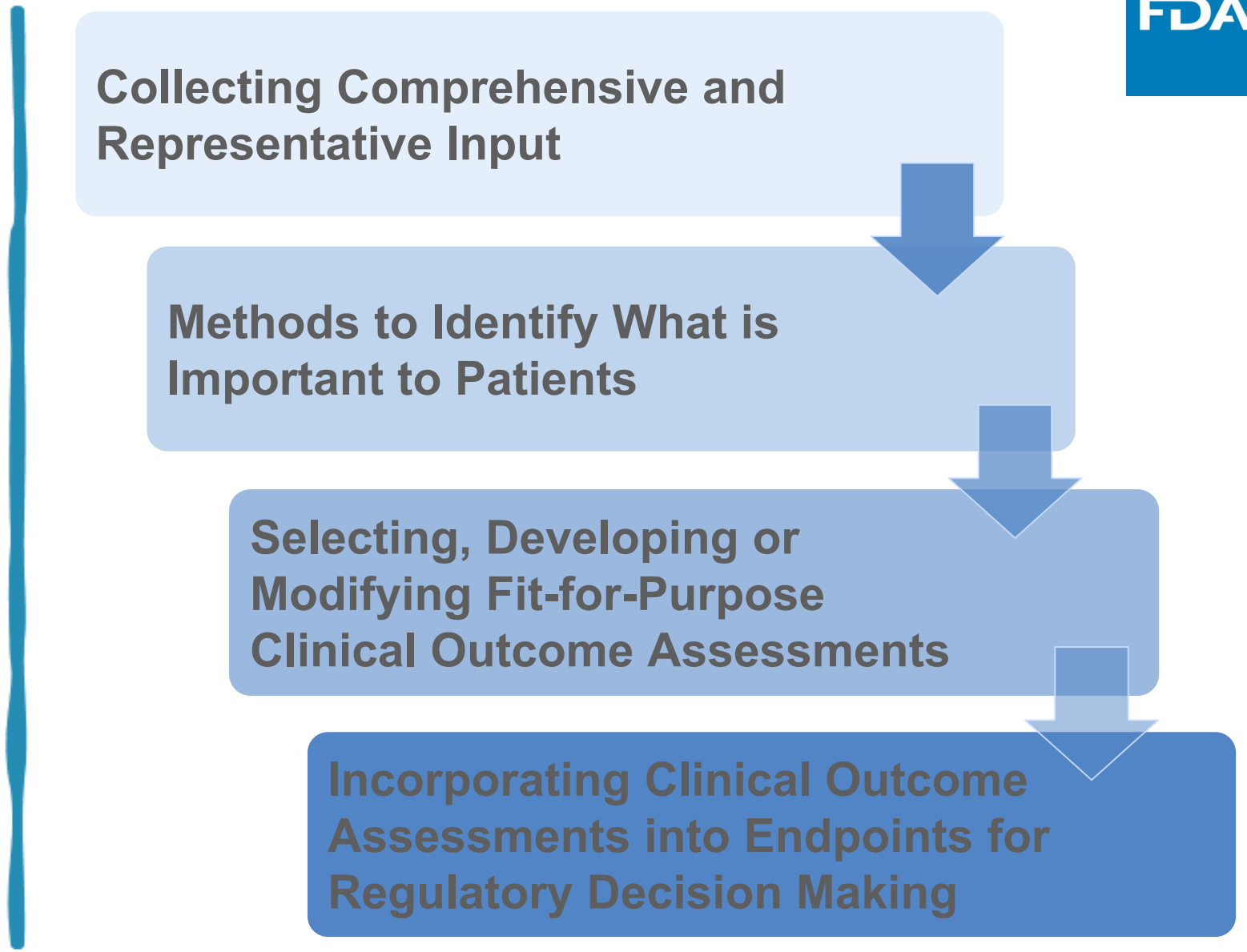
Introduction

David Reasner, CDER, FDA

Methodologic Guidance Documents



https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

PFDD Guidance 3: Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments

- How do you decide what to measure in a clinical trial and select or develop fit-for-purpose clinical outcome assessments (COAs) ?

Status:

- Workshop held on October 15-16, 2018
- Published June 2022

Clinical Outcome Assessment

A measure that describes or reflects how a patient feels, functions, or survives

Nausea Daily Diary
(collected as numeric rating scale)

COA

A measure that describes or reflects how a patient feels, functions, or survives

Nausea Daily Diary
(collected as numeric rating scale)

COA Score

Numeric or rated value generated by a COA through a standardized process

Nausea Severity Rating

COA

A measure that describes or reflects how a patient feels, functions, or survives

Nausea Daily Diary
(collected as numeric rating scale)

COA Score

Numeric or rated value generated by a COA through a standardized process

Nausea Severity Rating

COA-based Endpoint

Precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question

7-day average Nausea Severity Rating at 3 months post-randomization

COA

A measure that describes or reflects how a patient feels, functions, or survives

COA Score

Numeric or rated value generated by a COA through a standardized process

COA-based Endpoint

Precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question

Today's Show

Addressed in PFDD Guidance 3

COA

A measure that describes or reflects how a patient feels, functions, or survives

COA Score

Numeric or rated value generated by a COA through a standardized process

COA-based Endpoint

Precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question

Coming Attraction

Addressed in PFDD Guidance 4

PFDD Guidance 3: Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments

GUIDANCE DOCUMENT

Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments

JUNE 2022

Download the Draft Guidance Document

Draft

Not for implementation. Contains non-binding recommendations.

This guidance is being distributed for comment purposes only.

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Submit Comments Online

Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the FDA considers your comment on a draft guidance before it begins work on the final version of the guidance, submit either online or written comments on the draft guidance before the close date.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-selecting-developing-or-modifying-fit-purpose-clinical-outcome

Overview of Draft Guidance 3

I. Introduction

II. Overview of COAs in Clinical Trials

A. Types of COAs

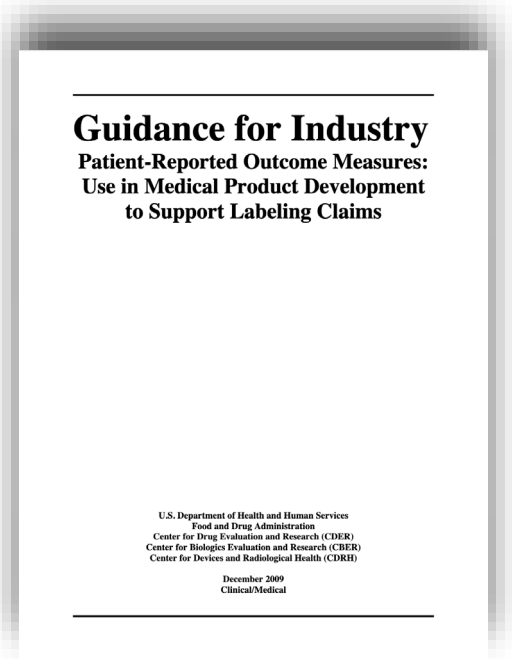
B. The Concept of Interest and Context of Use

C. Deciding Whether a COA is Fit-for-Purpose

III. A Roadmap to Patient-Focused Outcome Measurement in Clinical Trials

IV. Developing the Evidence to Support the Conclusion That a COA is Appropriate in a Particular Context of Use

Relationship with the 2009 PRO Guidance



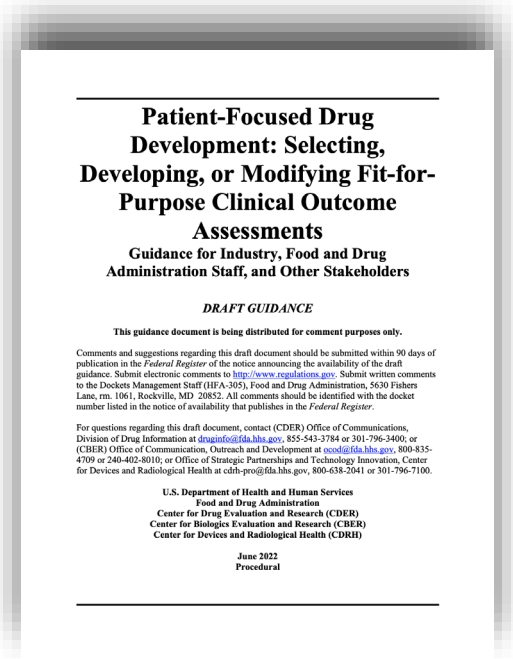
Guidance for Industry

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

Updated and Expanded



Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

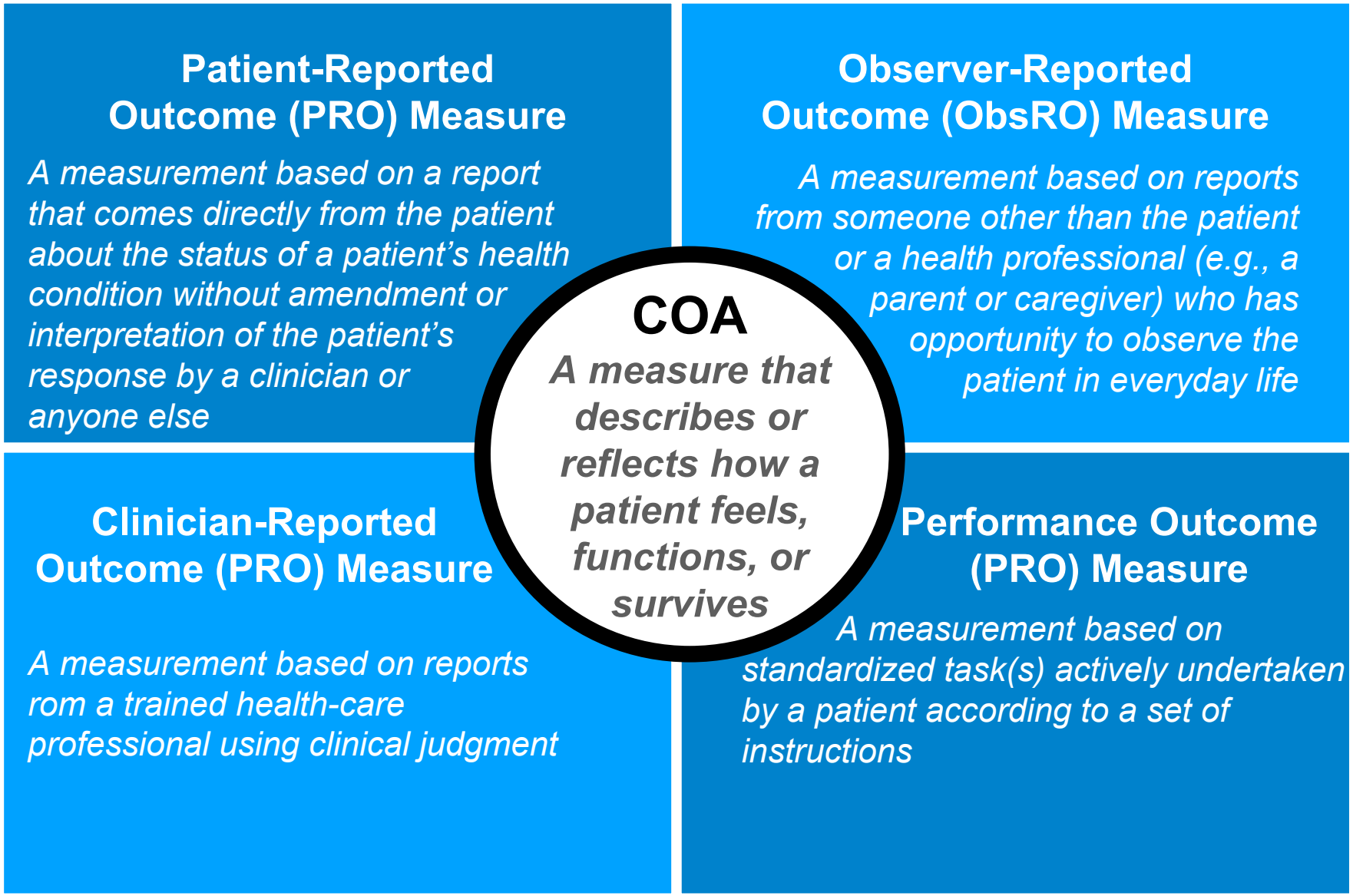
Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (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) Office of Communications, Division of Drug Information at druginfo@fda.hhs.gov, 855-543-3784 or 301-796-3400; or (CBER) Office of Communication, Outreach and Development at ocod@fda.hhs.gov, 800-835-4709 or 240-402-8010; or Office of Strategic Partnerships and Technology Innovation, Center for Devices and Radiological Health at cdrh-pro@fda.hhs.gov, 800-638-2041 or 301-796-7100.

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)

June 2022
Procedural

- Patients and caregivers increasingly and explicitly integrated
- Broadened coverage of all COA types
- Updated validity framework in terms of evidence-based rationales
  - See for example, American Educational Research Association et al. 2014; Kane 2013; Weinfurt 2021, 2022.


Patient-Reported Outcome (PRO) Measure
A measurement based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else
Observer-Reported Outcome (ObsRO) Measure
A measurement based on reports from someone other than the patient or a health professional (e.g., a parent or caregiver) who has opportunity to observe the patient in everyday life
COA
A measure that describes or reflects how a patient feels, functions, or survives
Clinician-Reported Outcome (PRO) Measure
A measurement based on reports rom a trained health-care professional using clinical judgment
Performance Outcome (PRO) Measure
A measurement based on standardized task(s) actively undertaken by a patient according to a set of instructions

Next, Examples from the COA Compendium

- **The COA Compendium is a table that:**
  - Collates information gathered from approved drug labeling
  - Describes how certain clinical outcome assessments have been used in past clinical trials
    - Measured the patient's experience (such as disease-related symptoms)
    - Supported labeling claims
  - Identifies clinical outcome assessments that have been qualified for potential use
    - Drug Development Tool (DDT) Qualification Program

Link to COA Compendium Website

Patient-reported Outcome (PRO) Measure

- Useful for assessment of symptoms (e.g., pain intensity, shortness of breath), functioning, events, or other aspects of health from the patient's perspective

Disease/Condition	Concept	COA Tool & Type	COA Context of Use	Drug Name & Approval Date
Chronic musculoskeletal pain	Pain intensity	Numerical pain rating scale or visual analog scale: **PRO**	Patients with chronic musculo-skeletal pain	Refer to the following draft guid-ance for industry for specific type of chronic musculoskeletal pain
Pain (acute)	Pain intensity	Numerical pain rating scale or visual analog scale: **PRO**	Patients with acute pain	Nucynta (tapentadol hydrochloride) *November 20, 2008*
Pain (chronic)	Pain intensity	Numerical pain rating scale or visual analog scale: **PRO**	Patients with chronic pain	Prialt (ziconotide acetate intrathecal infusion) *December 28, 2004*
Pain (neuropathic)	Pain intensity	Numerical pain rating scale or visual analog scale: **PRO**	Patients with neuropathic pain	1. Qutenza (capsaicin 8% patch) *November 16, 2009* 2. Lyrica (pregabalin) *December 30, 2004*

Observer-Reported Outcome (ObsRO) Measure

- Useful when patients such as young children cannot reliably report for themselves, or to assess observable aspects related to patients' health (e.g., signs, events, or behaviors)

Disease/Condition	Concept	COA Tool & Type	COA Context of Use	Drug Name & Approval Date
Seizure disorder	Seizure frequency	Patient/Observer diary: [**PRO and/or ObsRO**] as appropriate	Adults and pediatrics 6 years and up with partial onset or primary generalized tonic-clonic seizures	Trokendi XR (topiramate) *April 5, 2017*
			Adults and pediatrics 16 years and up with partial onset or primary generalized tonic-clonic seizures	Briviact (brivaracetam) *February 18, 2016*
Seizure disorder: Infantile spasm	Electroencephalogram (EEG)—cessation of hypsarrhythmia	Video/electroencephalogram (EEG): **ClinRO**	Pediatric (1 month–2 years) patients with infantile spasms	Sabril (vigabatrin) *August 21, 2009*
	Complete cessation of seizures	Observer diary: **ObsRO**		
Seizure disorder: Lennox-Gastaut Syndrome (LGS)	Seizure frequency	Patient/Observer diary: [**PRO and/or ObsRO**] as appropriate	Pediatric (2 years and up) and adult patients with LGS	1. Onfi (clobazam) *October 21, 2011* 2. Banzel (rufinamide) *November 14, 2008*
Seizure disorder: Refractory Complex Partial Seizures	Seizure frequency	Patient/Observer diary: **PRO** and/or **ObsRO** as appropriate	Pediatric (2 years and up) and adult patients with refractory complex partial seizures	Sabril (vigabatrin) *August 21, 2009*

Clinician-Reported Outcome (ClinRO) Measure

- Useful when reports of observable signs, behaviors, clinical events, or other manifestations related to a disease or condition benefit from clinical judgment

Disease/Condition	Concept	COA Tool &Type	COA Context of Use	Drug Name & Approval Date
Major depressive disorder (MDD)	Symptoms of MDD	Montgomery-Åsberg Depression Rating Scale (MADRS) version 10: **ClinRO**[1,2,3]	Adults with MDD	1. Rexulti (brexpiprazole) *July 10, 2015* 2. Trintellix (vortioxetine) *September 30, 2013* 3. Viibryd (vilazodone hydrochloride) *January 21, 2011* 4. Pristiq (desvenlafaxine succinate) *February 29, 2008* 5. Cymbalta (duloxetine hydrochloride) *August 3, 2004*
	Symptoms of MDD	Hamilton Depression Rating Scale 24 items or 17 items: **ClinRO**[2,4,5]		
Major depressive disorder (MDD)	Symptoms of MDD	Major Depressive Disorder Scale (SMDDS): **PRO**	Adults with MDD	**COA Qualified Tool** Visit "Clinical Outcome Assessment Qualification Program Submissions" Website for additional information

Performance Outcome (PerfO) Measure

- A measurement based on standardized task(s) actively undertaken by a patient according to a set of instructions

Disease/Condition	Concept	COA Tool & Type	COA Context of Use	Drug Name & Approval Date
Multiple sclerosis (MS)	Physical disability	Expanded Disability Status Scale (EDSS): **ClinRO**	Adults with primary progressive forms of MS	Ocrevus (ocrelizumab) *March 28, 2017*
	Walking speed	Timed 25-foot walk: **PerfO**		
Multiple sclerosis (MS)	Relapse frequency	**ClinRO**	Adults with relapsing forms of MS	1. Ocrevus (ocrelizumab) *March 28, 2017* 2. Zinbryta (daclizumab) *May 27, 2016* 3. Tecfidera (dimethyl fumarate) *March 27, 2013* 4. Aubagio (teriflunomide) *September 12, 2012* 5. Gilenya (fingolimod) *September 21, 2010*
	Physical disability	Expanded Disability Status Scale (EDSS): **ClinRO**		
Multiple sclerosis (MS)	Walking speed	Timed 25-foot walk: **PerfO**	Adults with MS	Ampyra (dalfampridine) *January 22, 2010*
	Ambulatory disability	12-item Multiple Sclerosis Walking Scale: **PRO**		

Concept of Interest

What You Intend to Measure about a Meaningful Aspect of Health

- **The concept of interest is the aspect of an individual's experience or clinical, biological, physical, or functional state that the assessment is intended to capture (reflect).**
- Select concepts of interest that, when measured appropriately:
  - Reflect an aspect of health that is important to patients
  - Have the ability to be modified by the investigational treatment
  - **Could demonstrate clinically meaningful differences between study arms within the time frame of the planned clinical trial**

Context of Use

Where, When, With Whom, and *How* the Measure Will Be Used

- **Use of the COA**: Clinical trial objectives and how the COA will be used to support COA-based endpoints (e.g., computing the mean COA score at 12 weeks)
- **Target Population**: Including a definition of the disease or condition; participant selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities); and expected patient experiences or events during the trial (e.g., that some patients will require assistive devices)
- **Study Context**: The clinical trial design in which the COA is to be used, including the type of comparator group and whether those providing responses or participating in the tasks for the COA (patients, observers, clinicians, trained raters) are masked with respect to treatment assignment and/or study visit)
- **Timing** of when assessment(s) of the COA is conducted
- **COA Implementation**: Including the site for COA collection (e.g., inpatient hospital, outpatient clinic, home); how the COA will be collected (e.g., DHT, paper form); and by whom (e.g., patient, study coordinator, investigator, parent/caregiver.)

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Fit-for-Purpose

- The level of validation associated with a medical product development tool is sufficient to support its context of use" (BEST (Biomarkers, Endpoints and Other Tools) Resource, 2016)
- Based on two considerations
  - Concept of interest and context of use are clearly described
  - Sufficient evidence to support a clear rationale for the proposed interpretation and use of the COA

Link to BEST (Biomarkers, EndpointS, and other Tools) Resource

Guidance Snapshot and Podcast

Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-For-Purpose Clinical Outcome Assessments—Draft Guidance (PFDD G3)

Patient-Focused Drug Development Guidance Snapshot

- Snapshot of *PFDD G3* helps readers understand the highlights of the recommendations in the guidance
- https://www.fda.gov/media/159516/download

First Patient-Focused Drug Development Guidance Podcast

- Subject Matter Experts talk about the importance of the document
- https://www.fda.gov/media/159508/download

About the Guidance Snapshot Pilot

- Leverages various communication tools to increase general public awareness and engagement for FDA guidance documents
- https://www.fda.gov/drugs/guidances-drugs/guidance-snapshot-pilot

Roadmap to Patient-Focused Outcome Measurement in Clinical Trials

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What is the Clinical Outcome Assessment (COA) Roadmap?

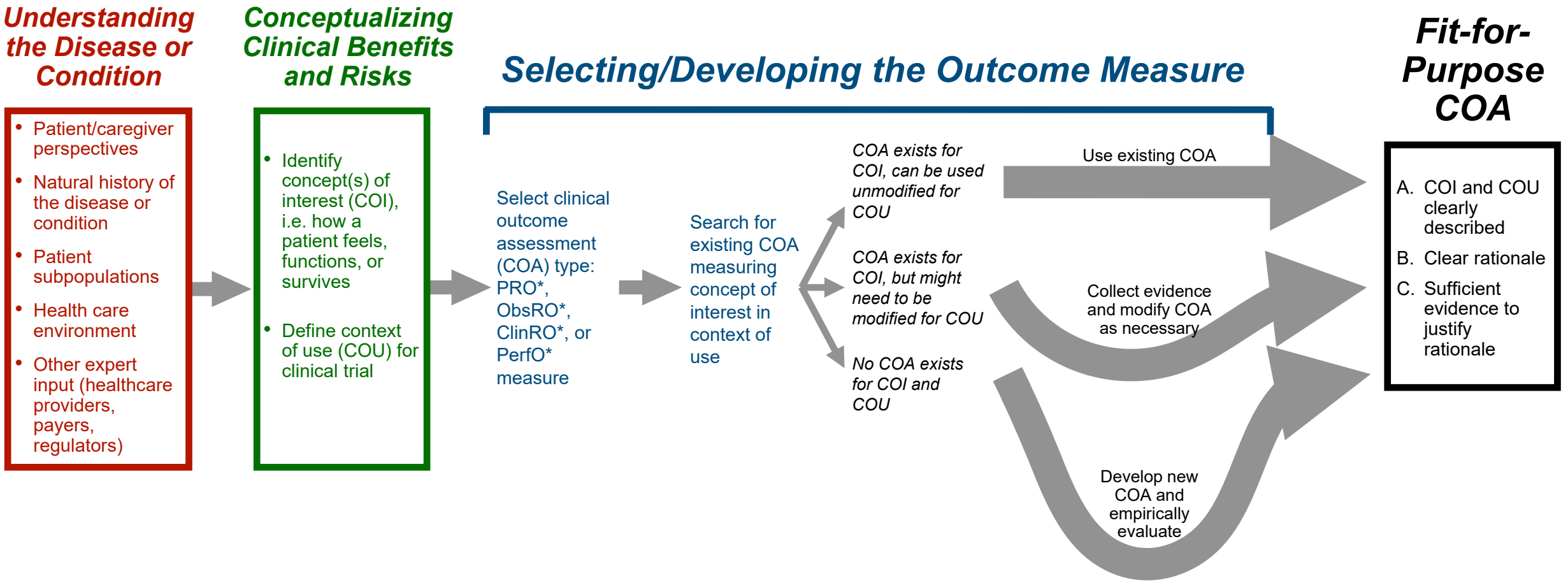
Fraser D. Bocell, Psychometrician, CDRH, FDA

What is the Destination?

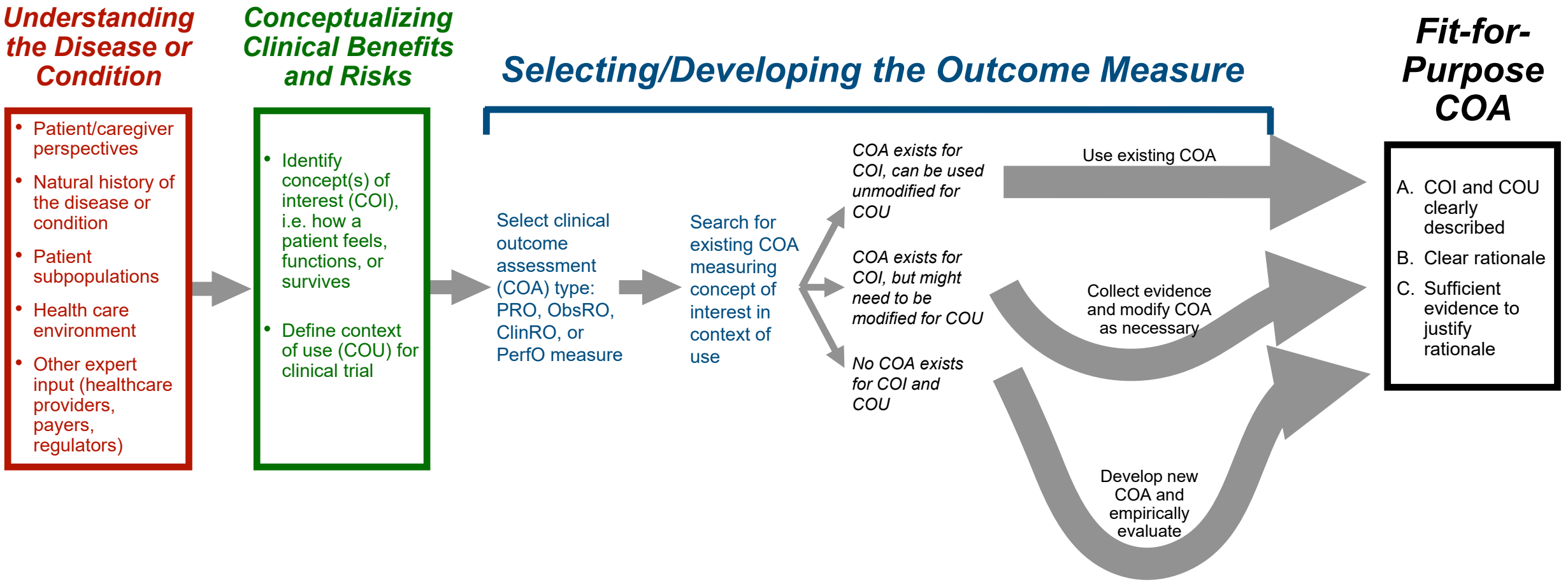
Fit-for-Purpose COA

A. Concept of interest (COI) and Context of Use (COU) clearly described
B. Clear rationale
C. Sufficient evidence to justify rationale

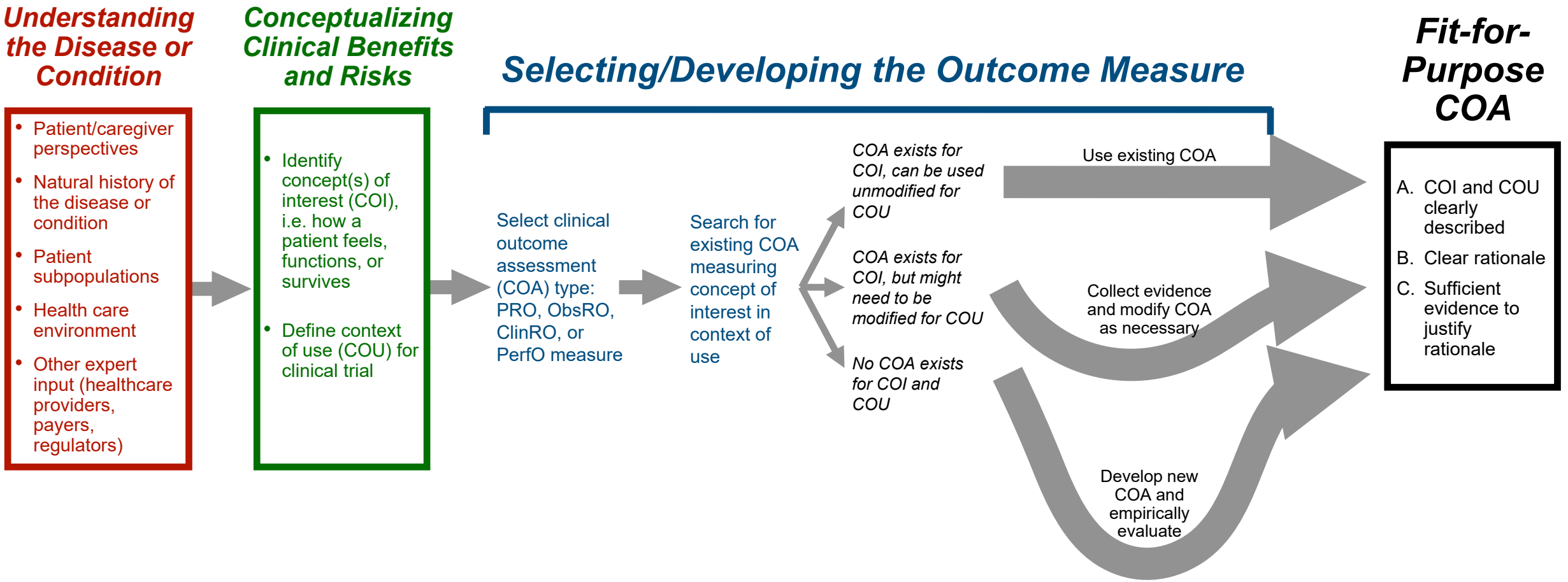
How do you get there?



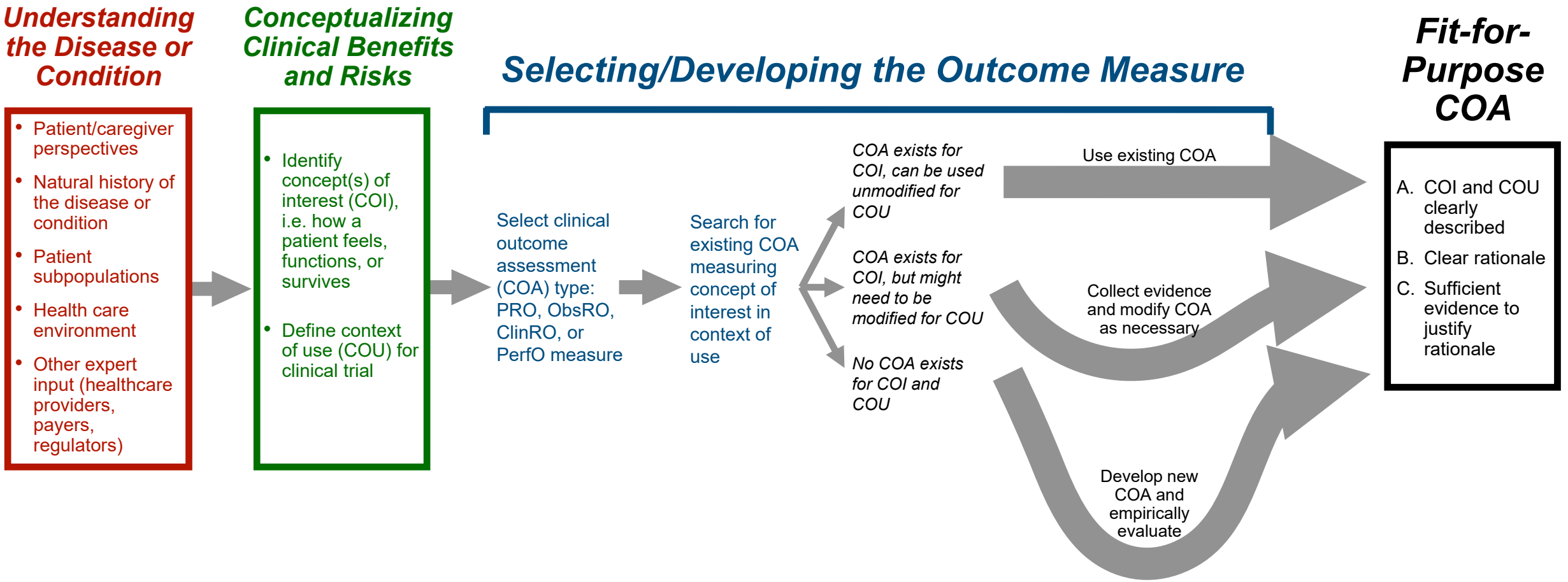
*Patient-Reported Outcome, Observer-Reported Outcome, Clinician-Reported Outcome, Performance Outcome



Think about relevant patient experiences BEFORE searching for a measure.



Consider using or modifying existing measures before deciding to develop a new measure.



An overall conceptual framework can be used to summarize the results of moving through the Roadmap.

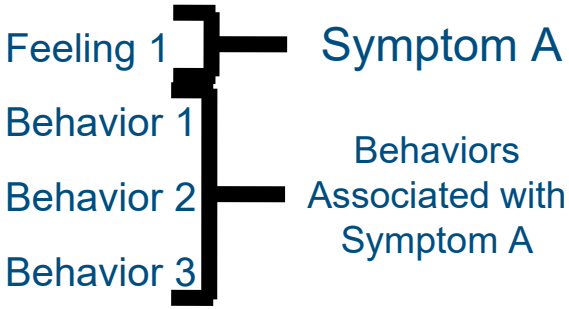
A conceptual framework summarizes . . .

1. Relevant experiences of patients in the target population
2. Specific concepts of interest targeted for assessment
3. Type(s) of COA proposed for each concept of interest
4. A representation of how the particular COA is intended to work in order to generate a score reflecting the concept of interest

Patients in the Target Population	Health Experiences Resulting from Disease/Condition
	Feeling 1 Behavior 1 Behavior 2 Behavior 3

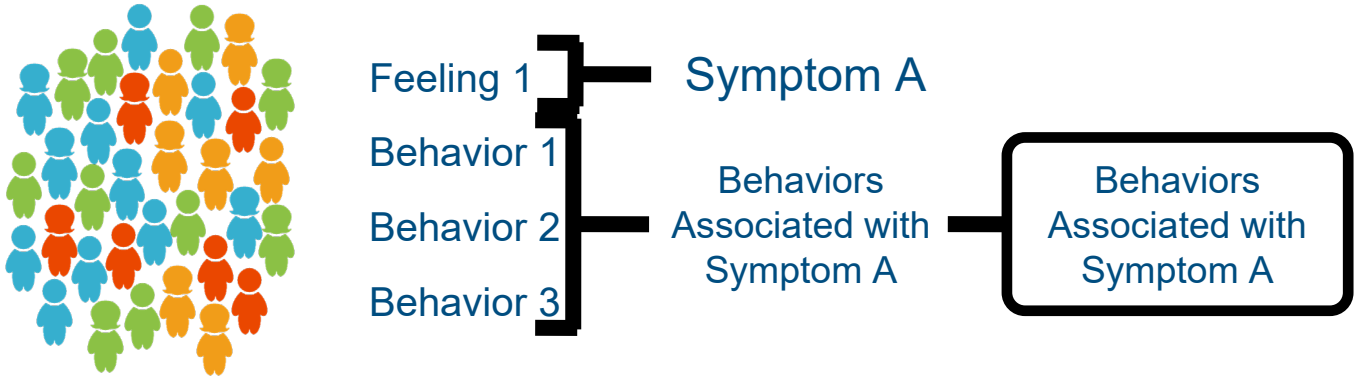
Qualitative studies and clinical expertise identify health experiences related to disease/condition.

Patients in the Target Population	Health Experiences Resulting from Disease/Condition	General Concept(s)



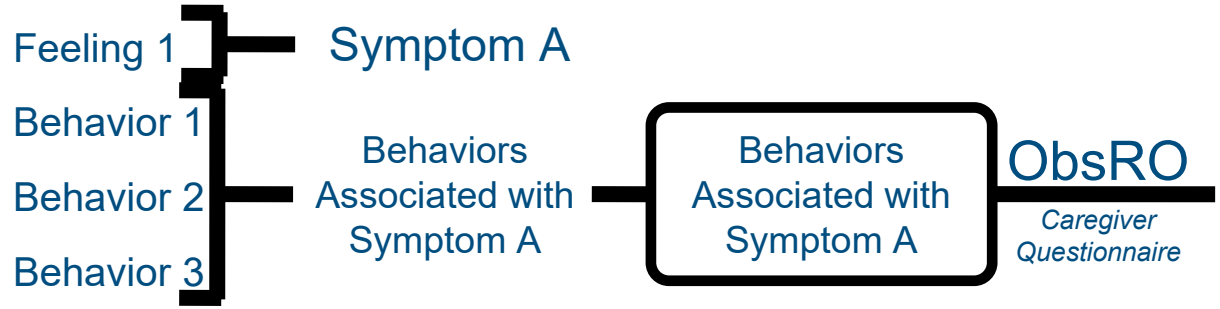
Health experiences are summarized using general concepts.

Patients in the Target Population	Health Experiences Resulting from Disease/Condition	General Concept(s)	Concept of Interest



One or more concepts of interest are selected for assessment.

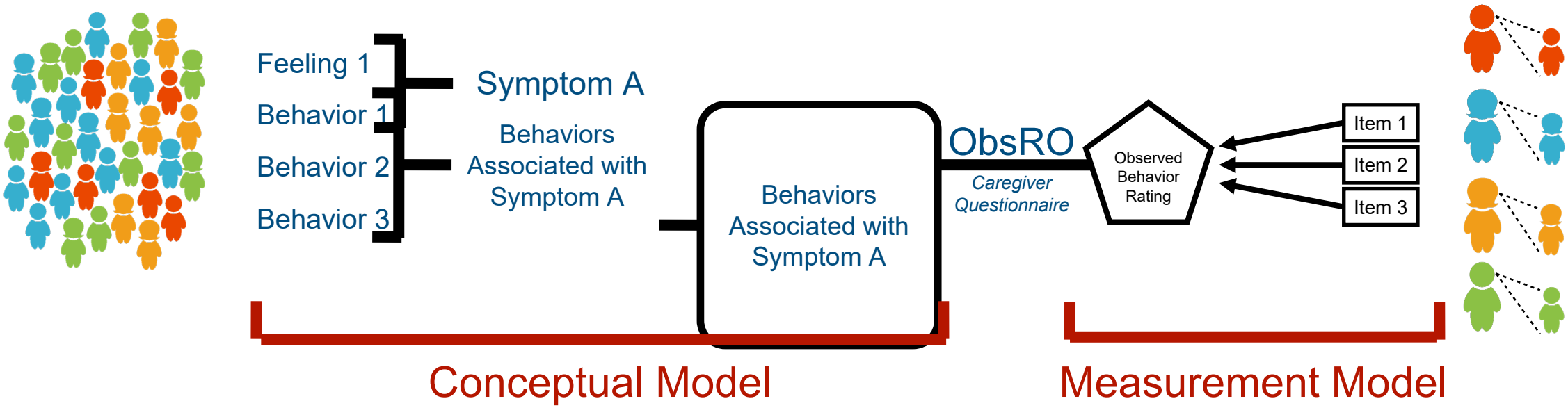
Patients in the Target Population	Health Experiences Resulting from Disease/Condition	General Concept(s)	Concept of Interest	Selected COA



Conceptual Model

The type of COA is selected.

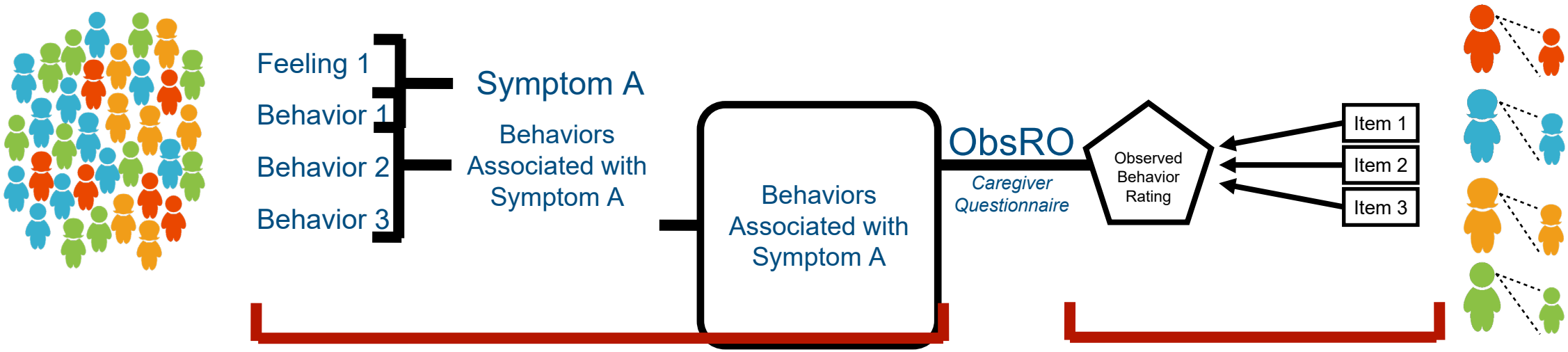
Patients in the Target Population	Health Experiences Resulting from Disease/Condition	General Concept(s)	Concept of Interest	Selected COA and Score(s)	Observers and Patients in Trial Sample



The measure's score and its derivation are represented.

Conceptual Framework

Patients in the Target Population	Health Experiences Resulting from Disease/Condition	General Concept(s)	Concept of Interest	Selected COA and Score(s)	Observers and Patients in Trial Sample



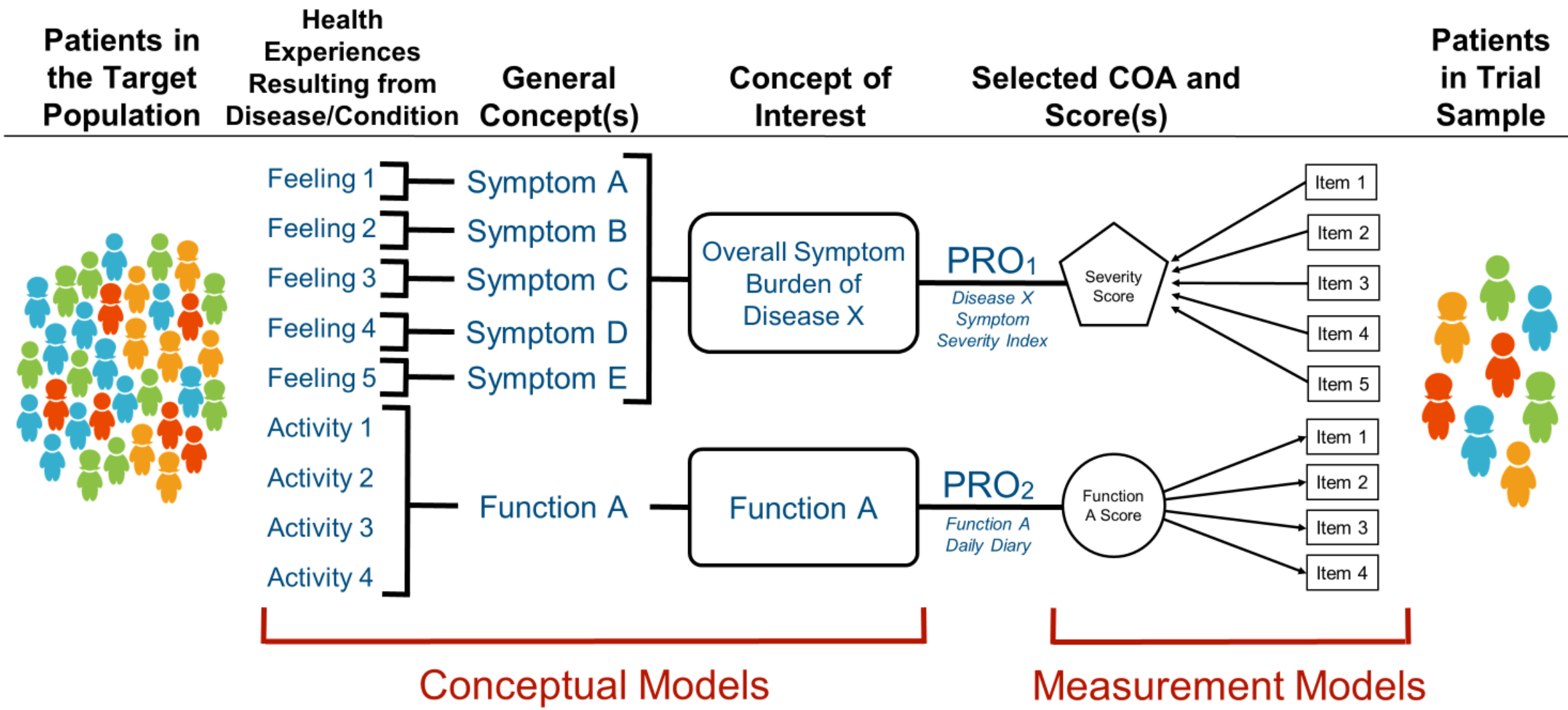
Conceptual Model

The structure of a concept of interest, including the different aspects of the concept and how they relate to patients' experiences

Measurement Model

Representation of how a COA is supposed to work to generate a score(s) that can be interpreted as a measure of the concept of interest in the context of use

Conceptual Framework



Conclusions

- The Roadmap is a general path toward a fit-for-purpose COA
- Think about relevant patient experiences BEFORE searching for a measure
- Consider using or modifying existing measures before deciding to develop a new measure
- An overall *conceptual framework* can be used to summarize the results of moving through the Roadmap
- Seek FDA input as early as possible and throughout medical product development to ensure COAs are appropriate for the intended context of use

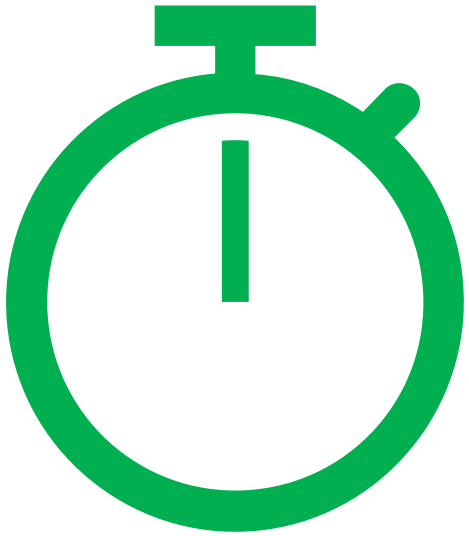
FDA U.S. FOOD & DRUG ADMINISTRATION

Clinical Perspective on the COA Roadmap

Michelle Tarver, M.D., Ph.D.

Deputy Director, Office of Strategic Partnerships and Technology Innovation

Center for Devices and Radiological Health

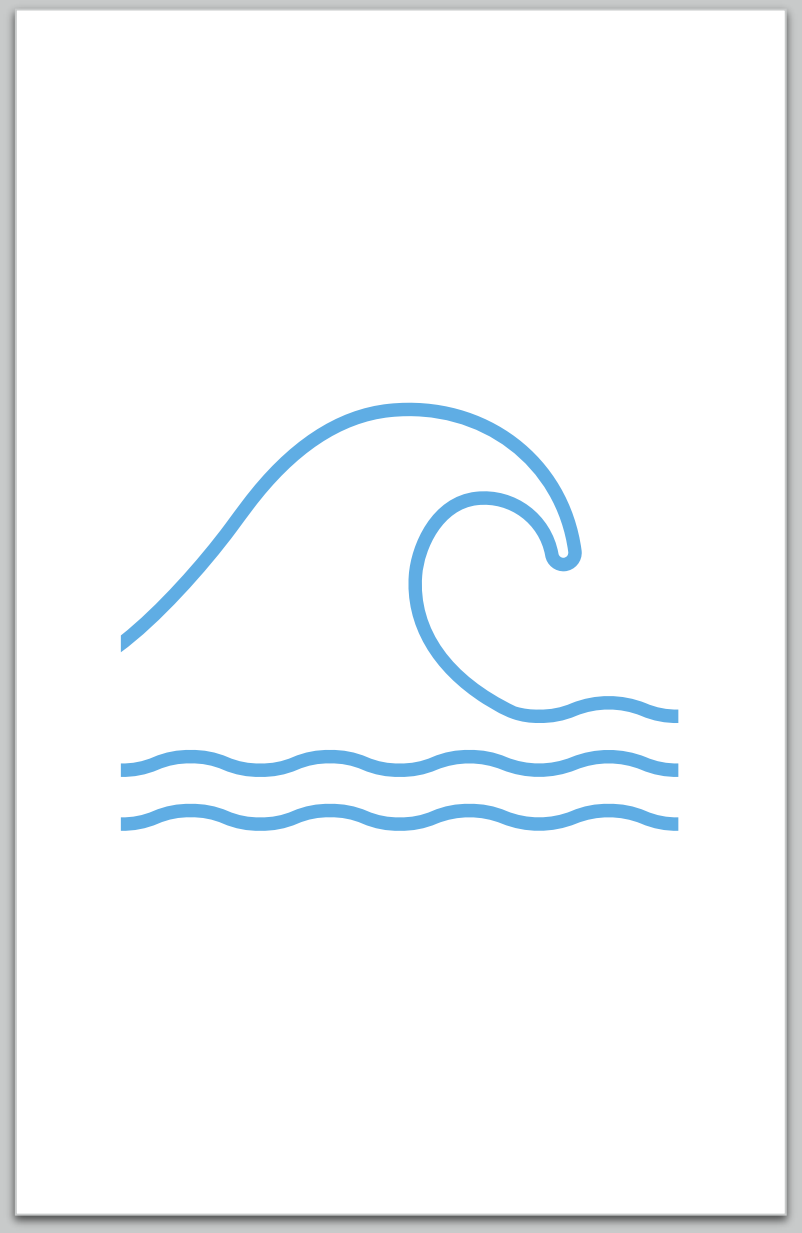


Start with the End in Mind

- Effective planning creates efficiency in study design and conduct
- COAs developed or selected with a clear purpose will be more efficiently designed and applied
  - Will help tailor whether the items need to be more sensitive to one end or the other of the symptom or function spectrum
  - Determine whether an existing measure or novel one is needed or is modification of an existing tool needed for a given condition

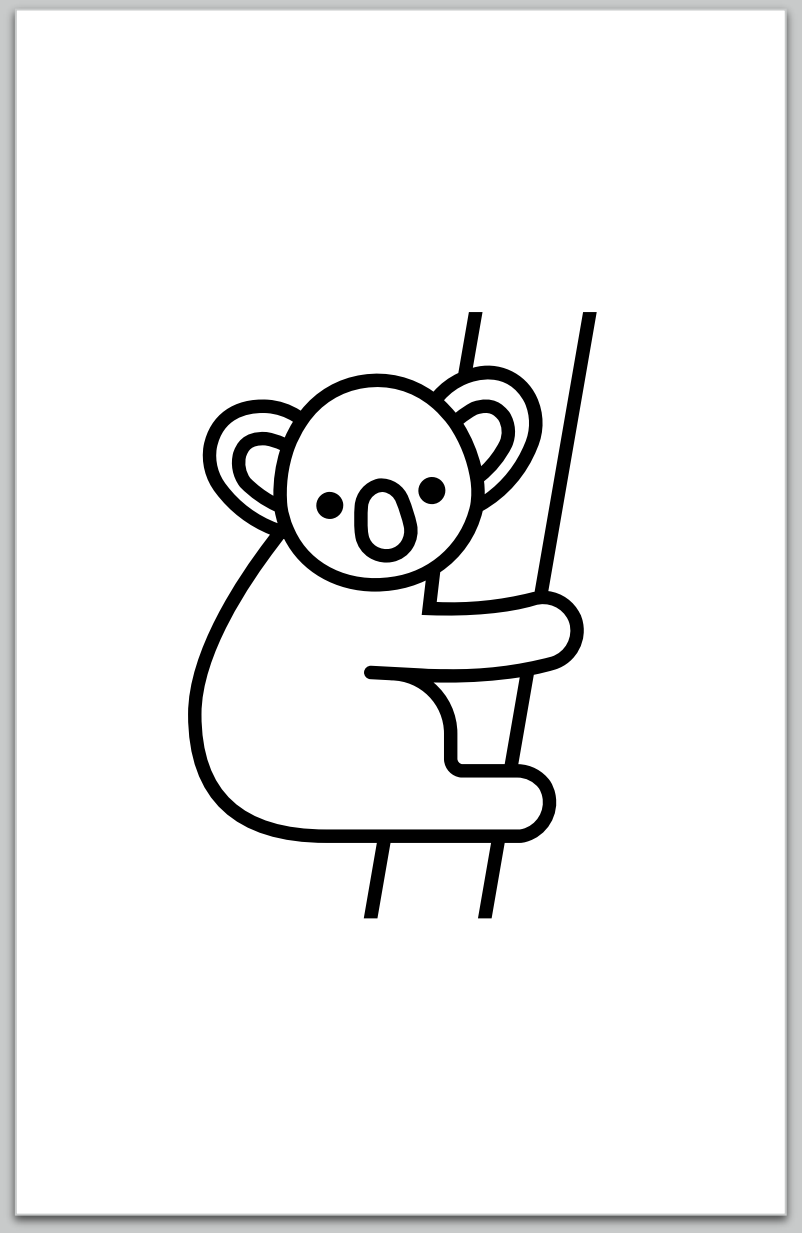
Take Time to Listen

- Patients and providers provide important clues to the outcomes that may be clinically meaningful
  - Clinical acceptance of endpoints are important for use and buy in
  - Does not need to assess all aspects of the condition or need to be a stand-alone measure
- Understand components that are important to patients
  - May reveal unmet needs
  - All goals of treatment are not identical



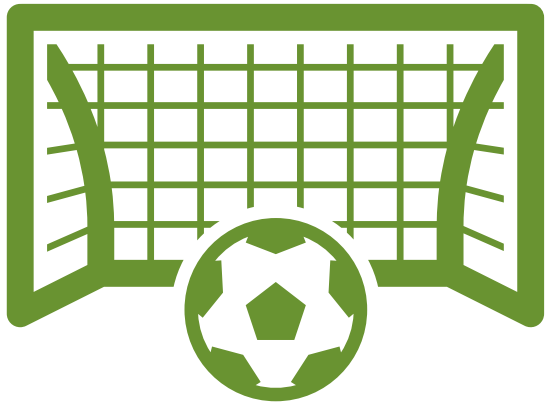
Don’t Muddy the Water or Boil the Ocean

- Clear on concept of interest
  - Critical to have clear understanding of the disease or condition
  - Will assist with prioritizing item selection
  - Ensure value to patients and providers
- Relevant responsiveness of the concept to interventions
- Minimize patient and study staff burden
- Maximize completion of the COA, minimizes missingness



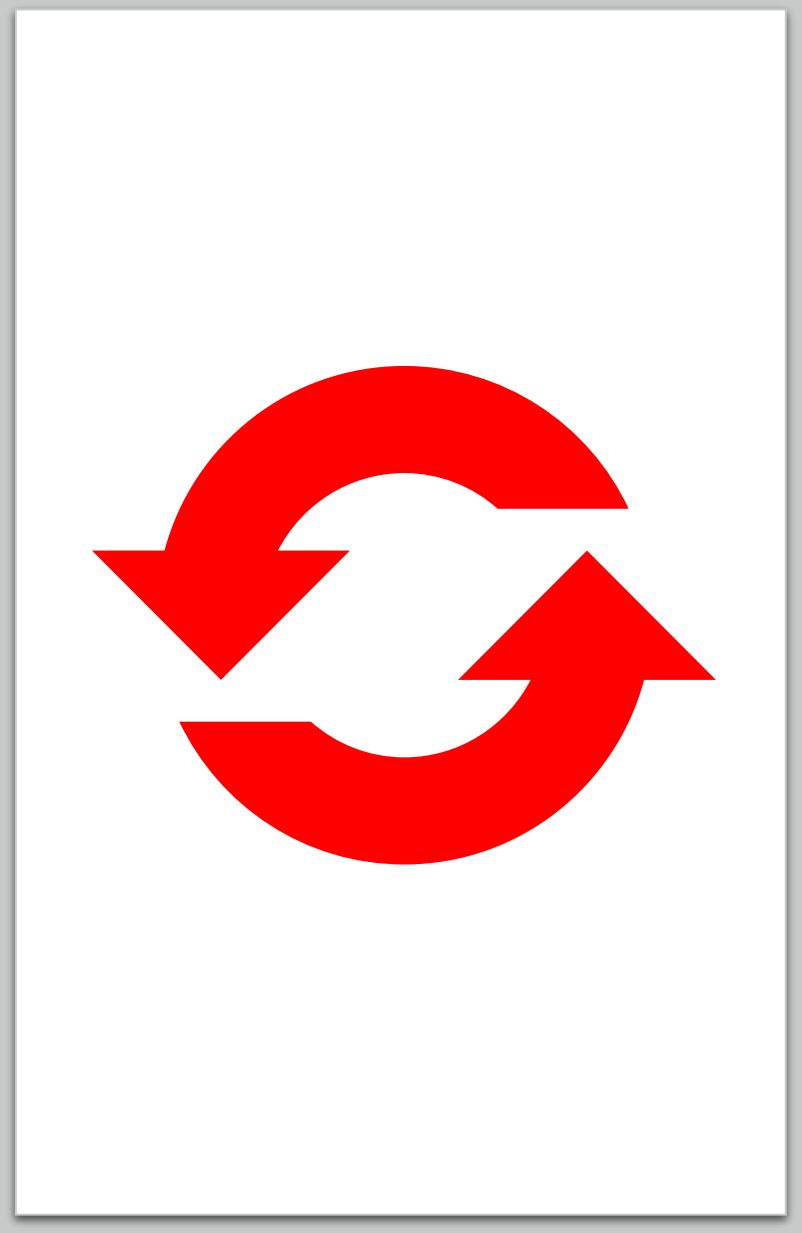
Embrace not Exclude

- Development work to be inclusive of diverse populations to more effectively be used in diverse clinical trials
  - Thoughtful consideration of clinical sites
  - Patient populations bearing greatest burden
  - Administration methods to facilitate data collection is complete and accurate



Simplicity Goal not Always Within Reach

- Some conditions or populations may pose measurement challenges and study complexities
  - Conditions with variable manifestations
  - Relapsing and remitting conditions
  - Progressive conditions
  - Episodic or acute conditions
- Plan for these complexities



Try, Try Again

- COAs are not static but can be iterative
- Evolve as the science and culture evolves

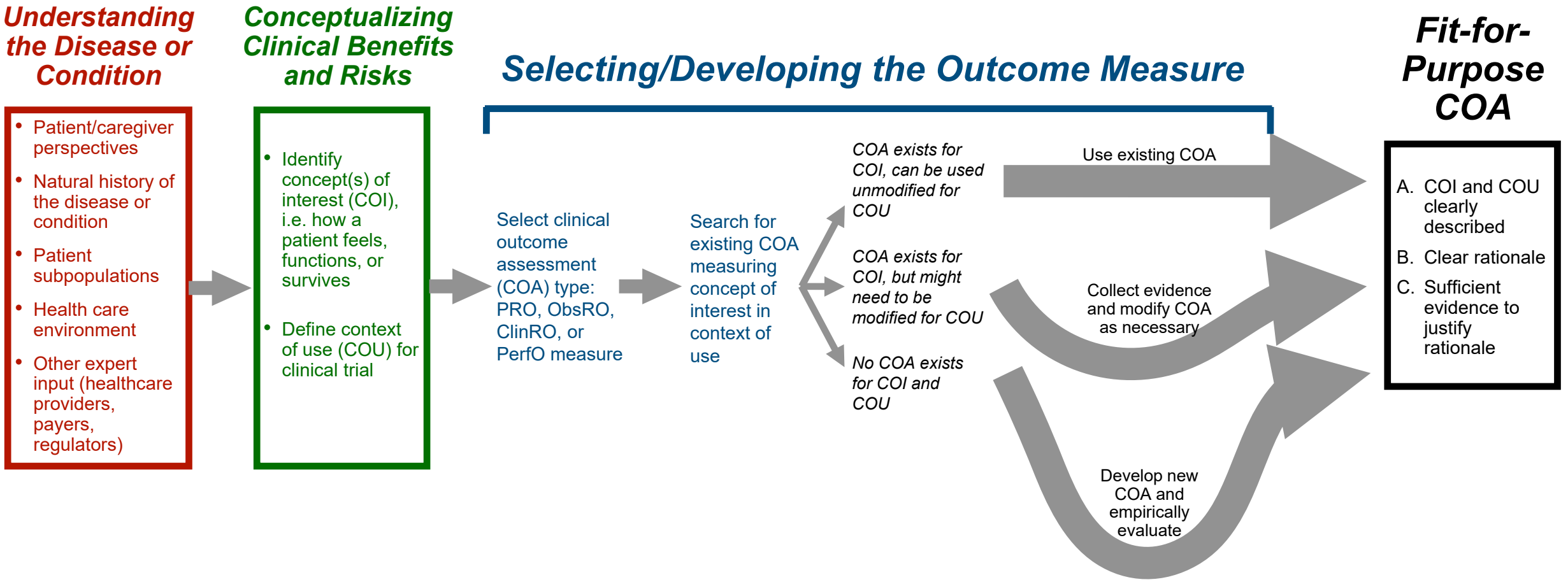
Questions?

Overview of the Evidence-Based Rationale to Justify a COA's Use

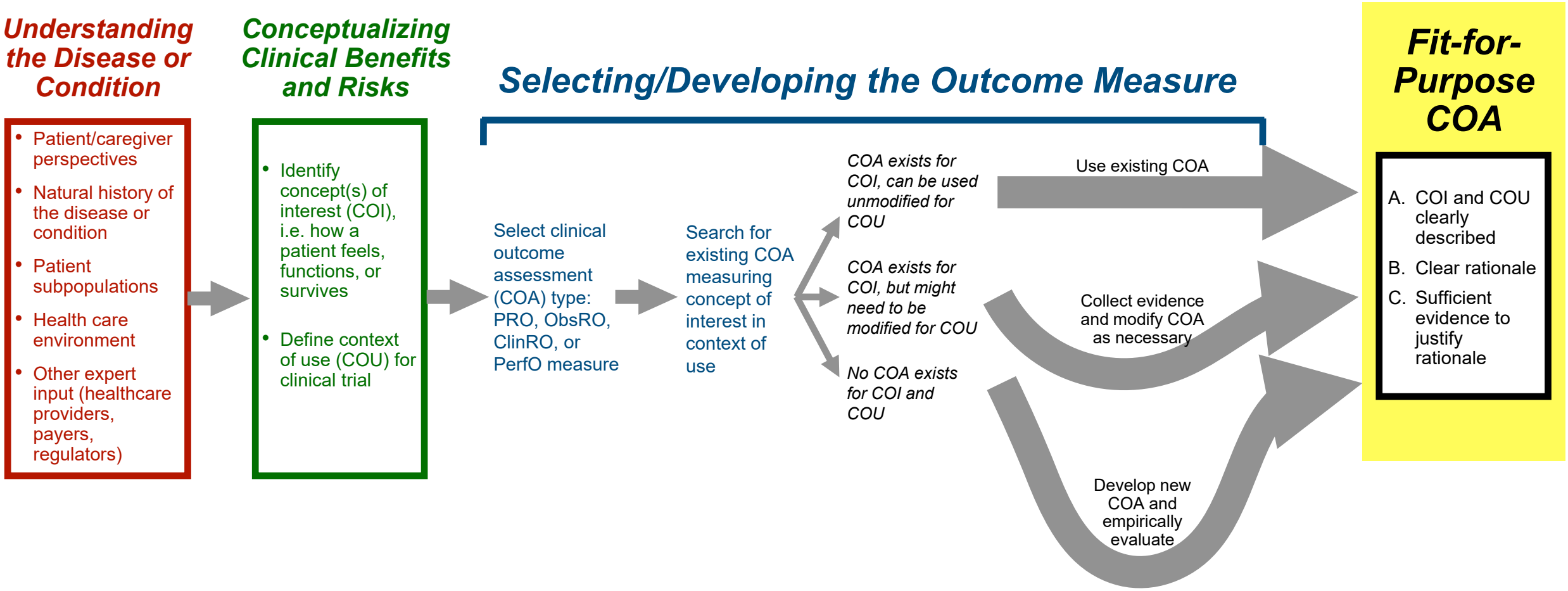
Evidence-Based Rationale to Justify the Interpretation and Use of a COA: An Overview

Lili Garrard, PhD
Division of Biometrics III
CDER/OTS/Office of Biostatistics

The Roadmap


Understanding the Disease or Condition
Patient/caregiver perspectives
Natural history of the disease or condition
Patient subpopulations
Health care environment
Other expert input (healthcare providers, payers, regulators)
Conceptualizing Clinical Benefits and Risks
Identify concept(s) of interest (COI), i.e. how a patient feels, functions, or survives
Define context of use (COU) for clinical trial
Selecting/Developing the Outcome Measure
Select clinical outcome assessment (COA) type: PRO, ObsRO, ClinRO, or PerfO measure
Search for existing COA measuring concept of interest in context of use
COA exists for COI, can be used unmodified for COU
COA exists for COI, but might need to be modified for COU
No COA exists for COI and COU
Use existing COA
Collect evidence and modify COA as necessary
Develop new COA and empirically evaluate
Fit-for-Purpose COA
A. COI and COU clearly described
B. Clear rationale
C. Sufficient evidence to justify rationale

The Roadmap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Evidence-Based Rationale

Fit-for-Purpose COA

A. COI and COU clearly described

B. Clear rationale

C. Sufficient evidence to justify rationale

The Million Dollar Questions

- **How is this COA measure supposed to work? What is the evidence that it does work that way?**
  - ➢ The evidence-based rationale is a way of answering these questions
  - ➢ Makes more explicit what we want to know about the interpretation and use of COA scores and what types of data, analyses, etc. would provide supportive evidence
  - ➢ The **rationale** is a set of reasons or components supported by evidence

Rationale: An Illustrative Example

Rationale for a Proposed Interpretation/Use of Scores

Component A | Component B | Component C | Component D | Component E | Component F | Component G | Component H

Rationale: An Illustrative Example

Rationale for a Proposed Interpretation/Use of Scores

Component A | Component B | Component C | Component D | Component E | Component F | Component G | Component H

Patients understand the instructions and items of the measure as intended by the measure developer.

Rationale: An Illustrative Example

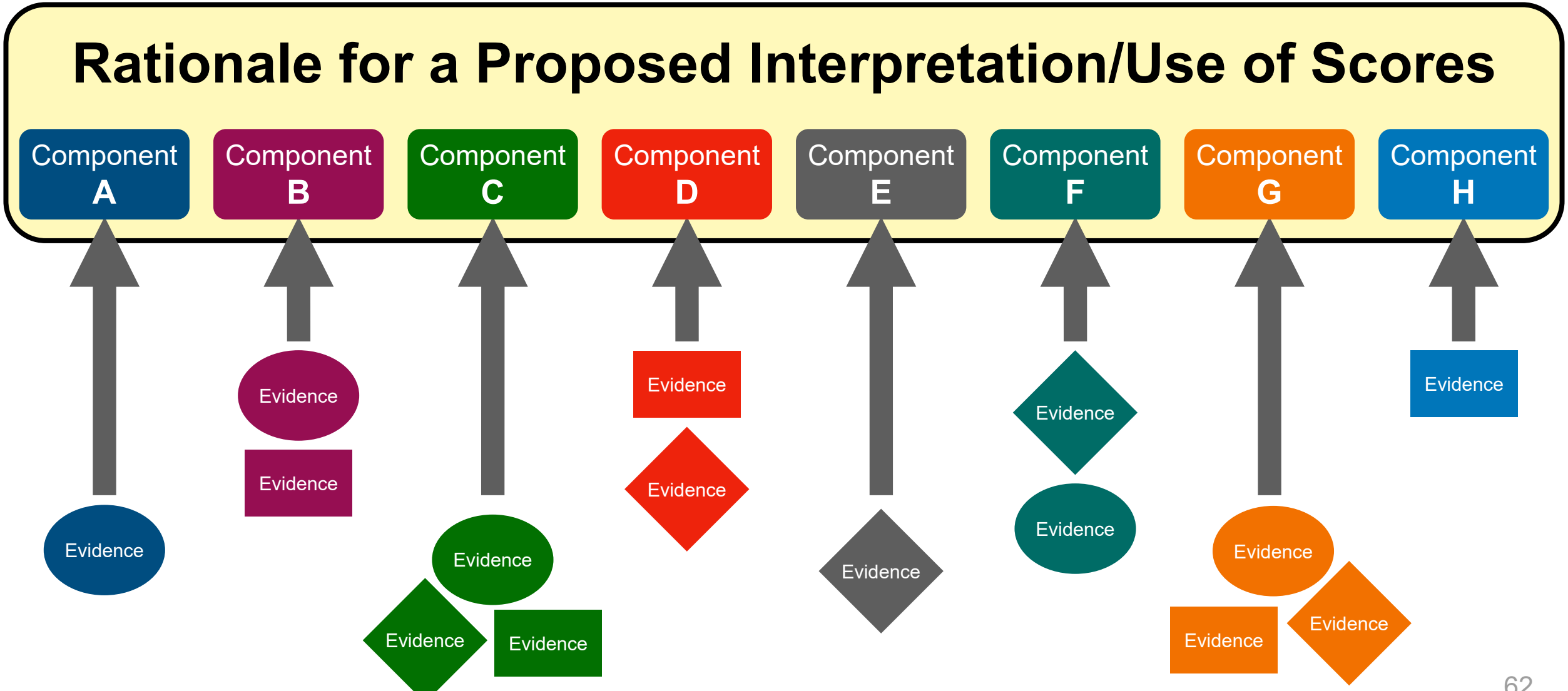
Rationale for a Proposed Interpretation/Use of Scores

Component A | Component B | Component C | Component D | Component E | Component F | Component G | Component H

Patients understand the instructions and items of the measure as intended by the measure developer.

Evidence: Cognitive interviews with respondents from the target population

Rationale: An Illustrative Example



Eight Components of An Evidence-Based Rationale

Table 1. Eight Components Comprising an Evidence-Based Rationale for Proposing a COA as Fit-for-Purpose

A	The concept of interest should be assessed by [*COA type*] because . . .
B	The COA measure selected captures all the important aspects of the concept of interest.
C	Respondents understand the instructions and items/tasks of the measure as intended by the measure developer.
D	Scores of the COA are not overly influenced by processes/concepts that are not part of the concept of interest.
E	The method of scoring responses to the COA is appropriate for assessing the concept of interest.
F	Scores from the COA correspond to the specific health experience(s) the patient has related to the concept of interest.
G	Scores are sufficiently sensitive to reflect clinically meaningful changes within patients over time in the concept of interest within the context of use.
H	Differences in COA scores can be interpreted and communicated clearly in terms of the expected impact on patients' experiences.

Note: Listed components are those that are likely but not necessarily needed in the rationale for a specific COA, concept of interest, and context of use. Each rationale can be tailored to the proposed interpretation and use. Each component should be accompanied by comprehensive supporting evidence and justification.

Eight Components of An Evidence-Based Rationale

A	**The concept of interest can or should be assessed by [COA type], because…**	*Why is a PRO (or ObsRO or ClinRO or PerfO) measure appropriate for measuring this concept of interest?*
B	**The COA measure selected captures all the important aspects of the concept of interest.**	*Corresponds to what was called "**content validity**." Extremely important.*
C	**Respondents understand the instructions and items/tasks of the measure as intended by the measure developer.**	*For the measure to work, respondents need to understand instructions and items/tasks.*
D	**Scores of the COA are not overly influenced by processes/concepts that are not part of the concept of interest.**	*No COA score is a perfect reflection of the concept of interest, but scores should mostly reflect the concept of interest.*

Eight Components of An Evidence-Based Rationale

E	**The method of scoring responses to the COA is appropriate for assessing the concept of interest.**	*The rules for generating a score make sense.*
F	**Scores from the COA correspond to the specific health experience(s) the patient has related to the concept of interest.**	*The score should tell us about how patients feel or function in their daily lives.*
G	**Scores are sufficiently sensitive to reflect changes in the concept of interest within patients over time.**	*Scores should change when the patient's health changes in response to an investigational treatment.*
H	**Differences in COA scores can be interpreted and communicated clearly in terms of the expected impact on people's day-to-day lives.**	*Scores should be interpretable, and one should be able to discuss changes or differences in scores in a way that is clearly tied to how patients feel and/or function. (See upcoming PFDD Draft Guidance 4)*

Preview of Next Section

- In-depth discussion of the eight components
- Example of applying the evidence-based rationale approach for a COA under development will be presented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Question and Answer

Send us your comments!

Interested stakeholders are invited to submit comments on the draft guidance to the public docket.

The docket will close on September 28, 2022.

How do you access the draft guidance document?

Please visit:
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-selecting-developing-or-modifying-fit-purpose-clinical-outcome

How do you submit a comment?

Please visit: https://www.regulations.gov/docket/FDA-2022-D-1385 and click Comment

Advanced Discussion of Evidence-Based Rationale

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Evidence-Based Rationale to Justify the Interpretation and Use of a COA: A Comprehensive Review

Lili Garrard, PhD and Monica Morell, PhD
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CDER/OTS/Office of Biostatistics

From 2009 PRO Guidance to Draft G3

- Same principles as 2009 PRO Guidance apply
- Recasts emphasis on measurement properties (e.g., types of validity, reliability) as emphasis on providing justification and supporting evidence that the COA score can be interpreted as a measure of the concept of interest
- Makes it easier to apply the principles to a broad range of measures
- Makes more explicit what FDA needs to know about the interpretation and use of COA scores and what types of data, analyses, etc. would provide supportive evidence
- Makes it easier to talk about measurement issues with broader group of stakeholders (e.g., non-technical audience)

Eight Components of An Evidence-Based Rationale

Table 1. Eight Components Comprising an Evidence-Based Rationale for Proposing a COA as Fit-for-Purpose

A	The concept of interest should be assessed by [*COA type*] because . . .
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Note: Listed components are those that are likely but not necessarily needed in the rationale for a specific COA, concept of interest, and context of use. Each rationale can be tailored to the proposed interpretation and use. Each component should be accompanied by comprehensive supporting evidence and justification.

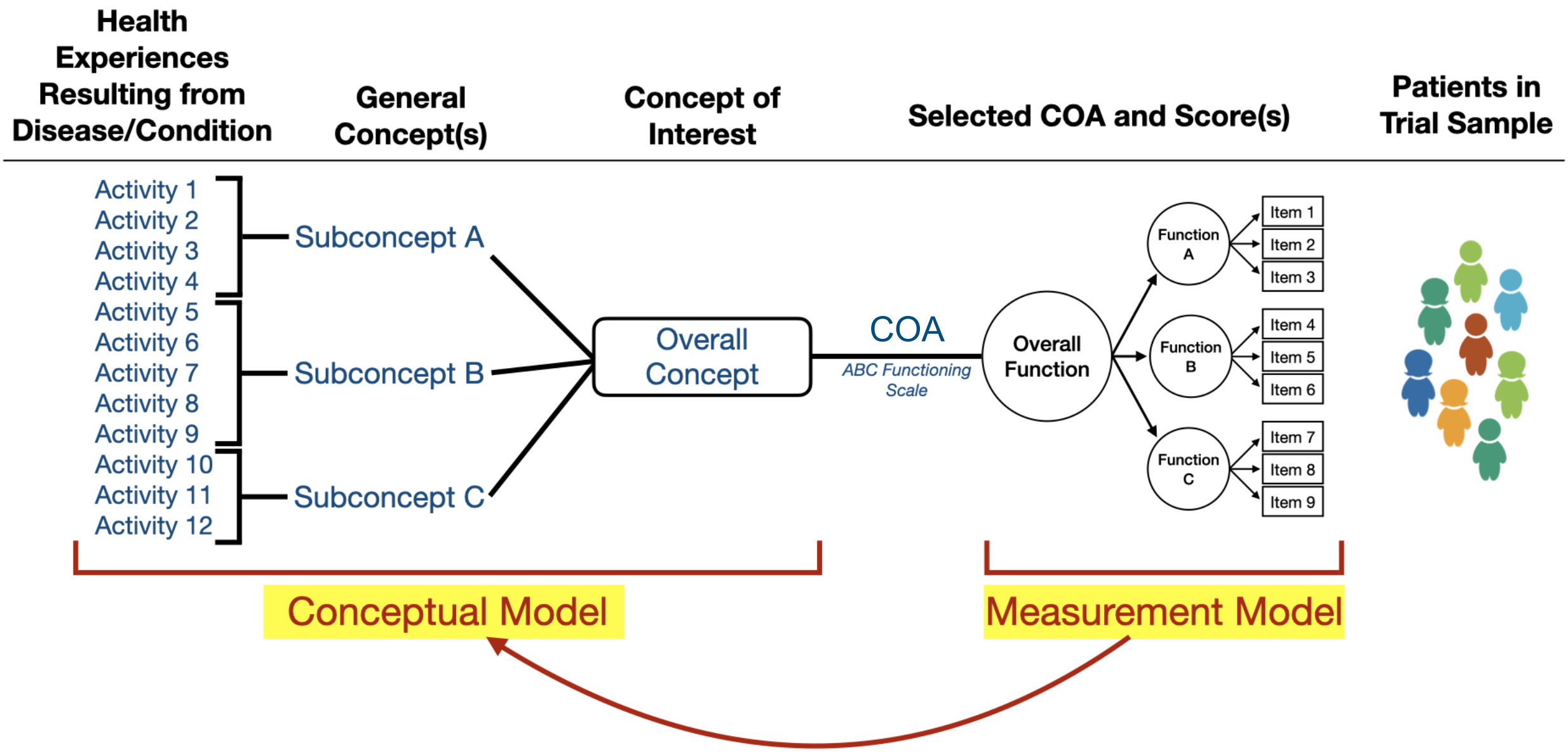
A. The concept of interest can or should be assessed by [COA type], because . . .

- Why is this type of COA (PRO, ObsRO, ClinRO, or PerfO measure) best or appropriate for this concept of interest in this context of use?
- Example concept of interest: pain severity
  - A PRO is the best COA type to assess *pain severity* because patients are able to provide reliable self-report, and the feeling of pain is known only to the patients themselves

B. The COA measure selected captures all the important aspects of the concept of interest

- Corresponds to what used to be called *content validity*
- All important aspects of the concept of interest should be reflected in the content of the COA
  - Narrow/simple concepts vs. more complex concepts
  - Specific attributes, e.g., frequency, intensity, duration
- Conceptual Framework
  - Conceptual model
  - Measurement model

B. The COA measure selected captures all the important aspects of the concept of interest.



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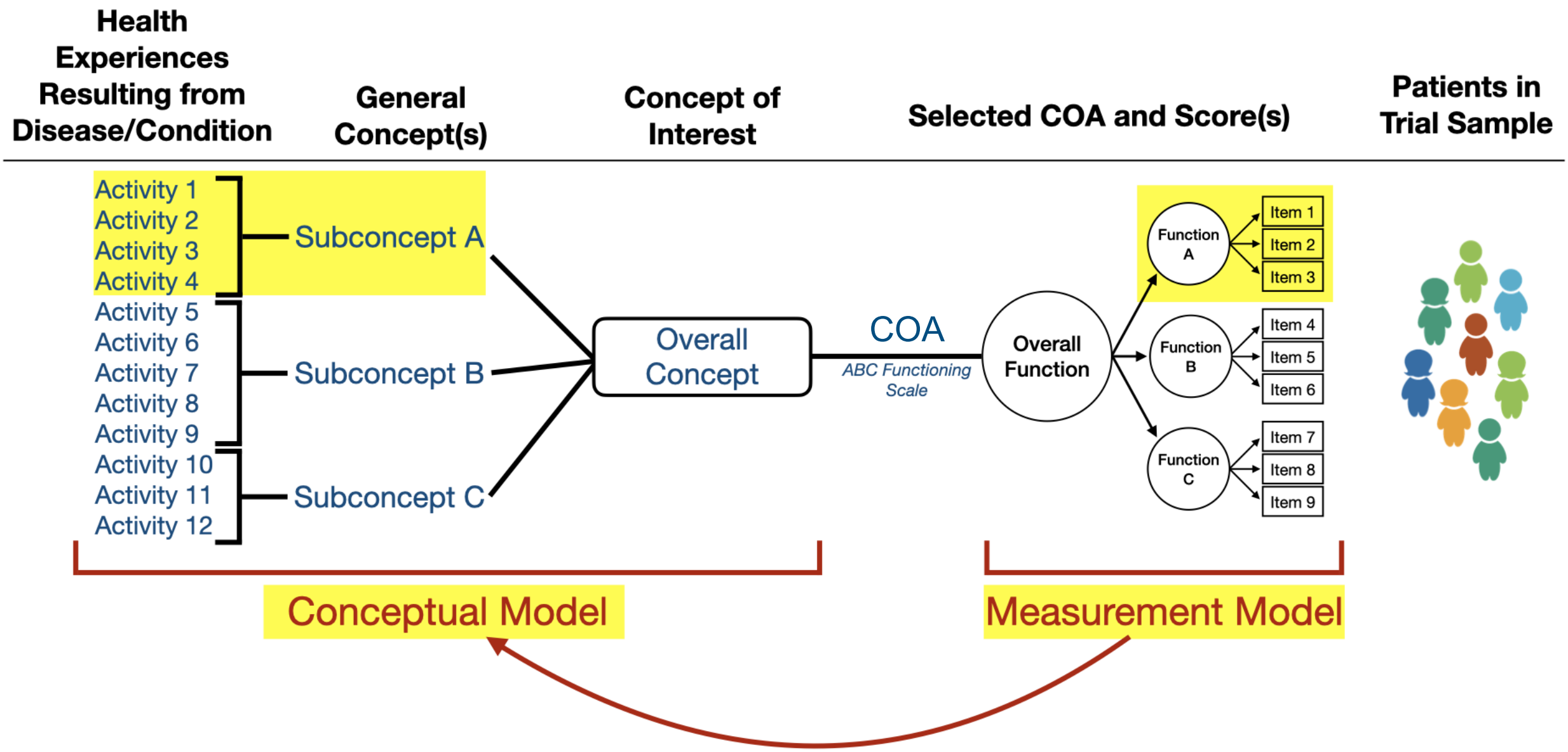

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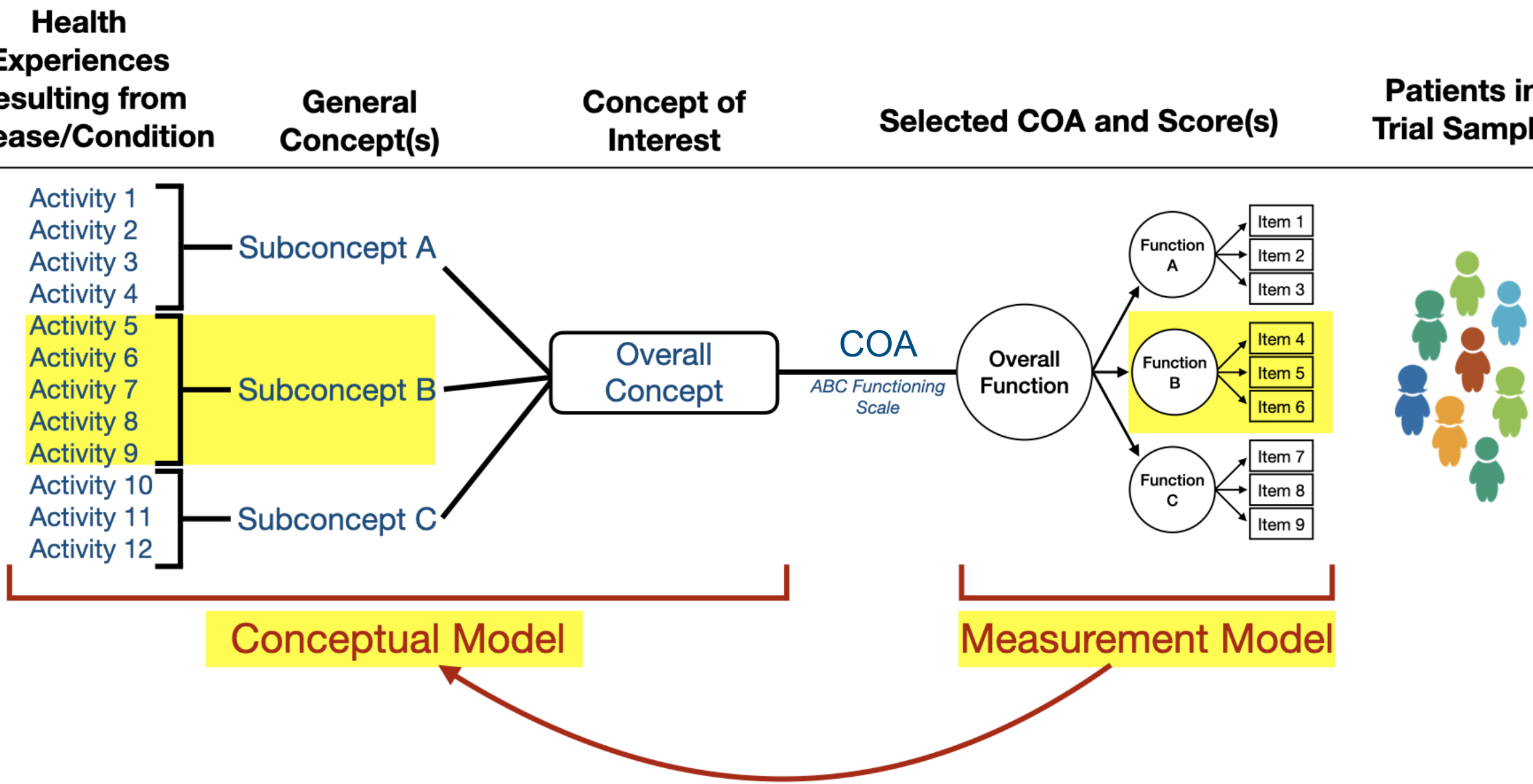

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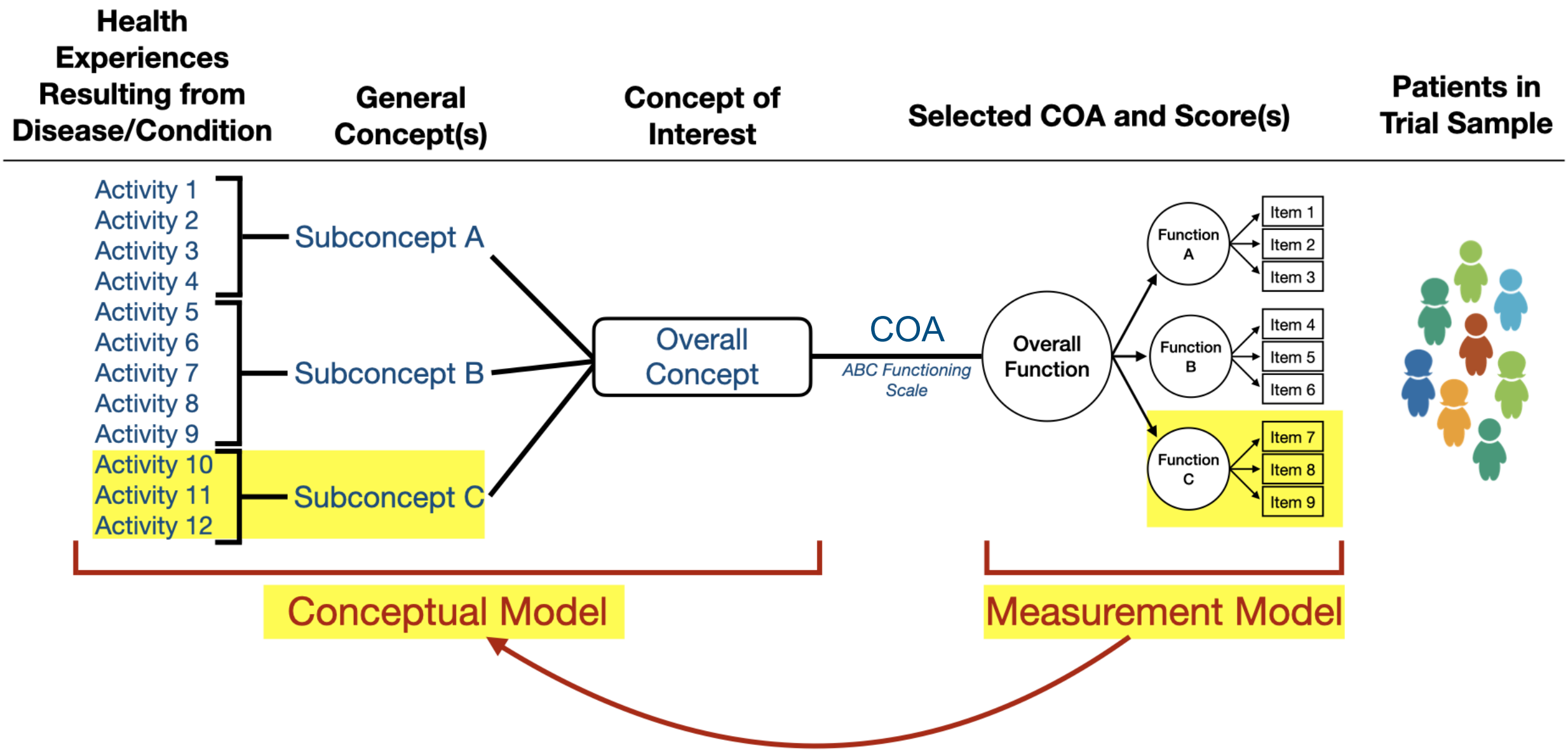


C. Respondents understand the instructions and items/tasks of the measure as intended by the measure developer

- This component of the rationale is self-explanatory
  - ➢ If respondents do not understand the items/tasks → data may not reflect the concept of interest
- Can provide evidence from
  - Cognitive interviews
  - Pilot testing (especially for PerfO measures)
  - Demonstration of adherence to best practices for construction of items/tasks
    - Measure developers should follow good practice in COA design to avoid common pitfalls that could interfere with respondent understanding (recall from PFDD Guidance 2)

D. Scores of the COA are not overly influenced by processes/concepts that are not part of the concept of interest

- In a well-designed measure, it is the concept of interest that predominantly affects a patient's responses to items or tasks
  - There may be other factors that have a small influence on responses
  - The scores should be driven mostly by the concept of interest

- Should consider the most likely interfering influences on responses to items or tasks and assess the presence and strength of those influences

D. Scores of the COA are not overly influenced by processes/concepts that are not part of the concept of interest

- Respondents' demographic characteristics (including sex, age, and education level) or cultural/linguistic backgrounds
- Recollection errors (e.g., recall period of COA)
- Respondent fatigue or burden (e.g., measure length, complexity, frequency)
- The mode of assessment (e.g., different modes across different sites)
- Expectation bias
  - COA scores may be influenced by the respondent's beliefs about how the patient should be feeling or functioning (e.g., based on beliefs about study group assignment)
- Practice effects (especially for PerfO measures)
  - Patients' performance on the tasks may improve over time due to practice rather than to real improvements in the concept of interest

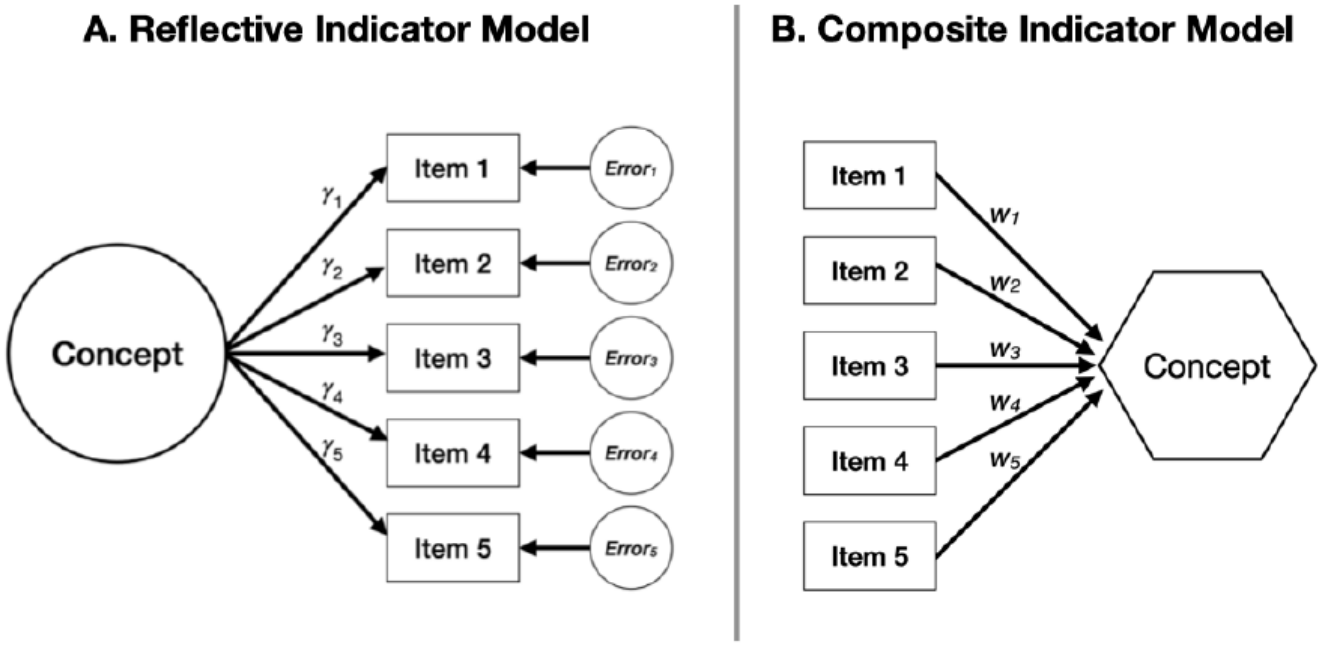
E. The method of scoring responses to the COA is appropriate for assessing the concept of interest

- Response options should be non-overlapping and differences among adjacent response categories should reflect true differences in the concept of interest
- Wording of response options should be clear and concrete
- Instructions for making or recording responses should be clearly understandable
- Support for these considerations can come from cognitive interview data

E. The method of scoring responses to the COA is appropriate for assessing the concept of interest

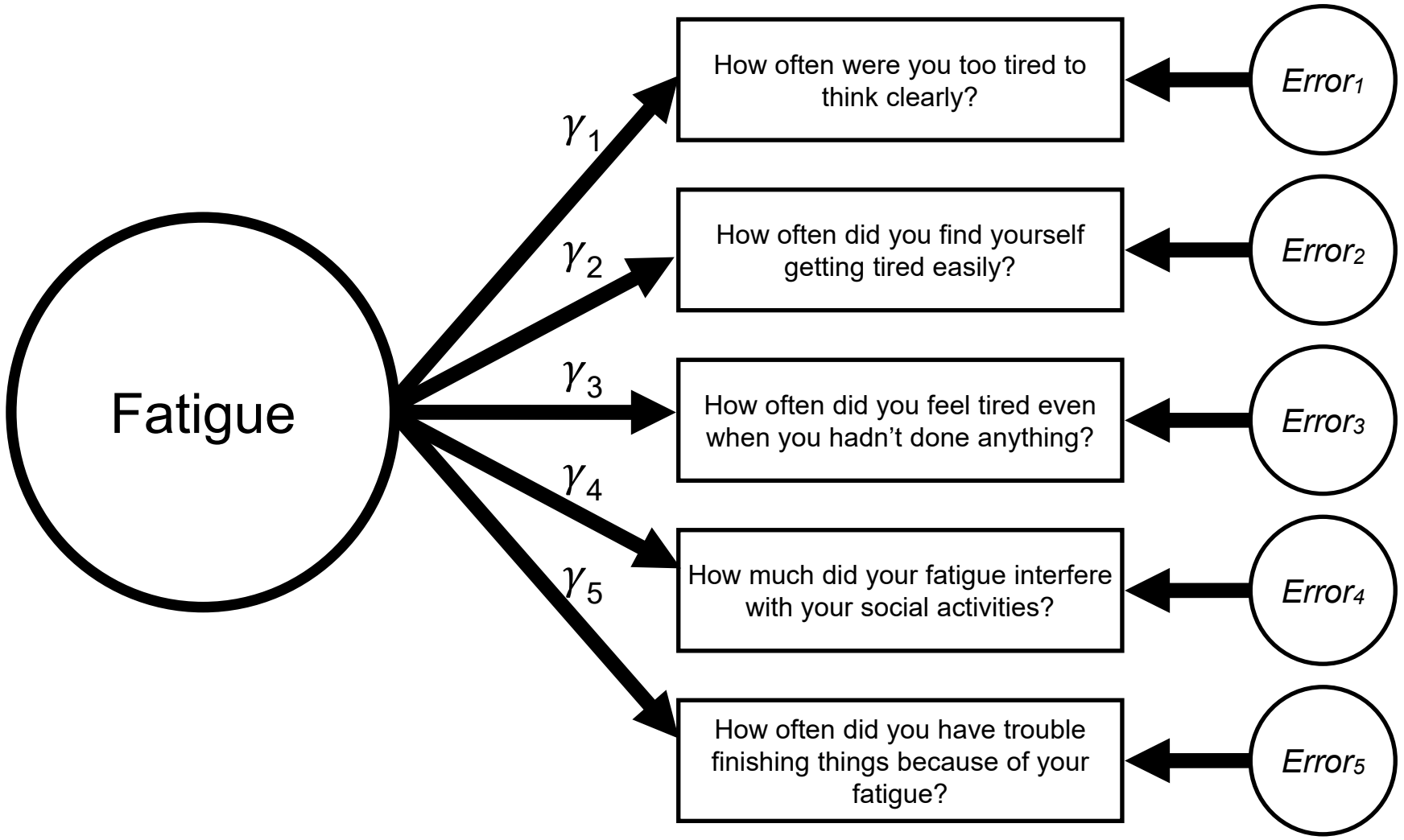
- Rationale for combining responses to multiple items or tasks depends on the type of measurement model

Figure 4. Representations of Reflective (Panel A) and Composite (Panel B) Indicator Models.



Note: In panel A, the concept within a circle is conceptualized as a latent variable; the smaller circles represent measurement error that contributes to the responses of each item; γ denotes the causal effect of the concept on the item response. In panel B, the concept within a hexagon is conceptualized as a composite variable; w indicates the weight (may or may not be equally weighted) used for the item response in computing the calculated composite score that represents the concept.

Reflective Indicator Model



Unidimensionality

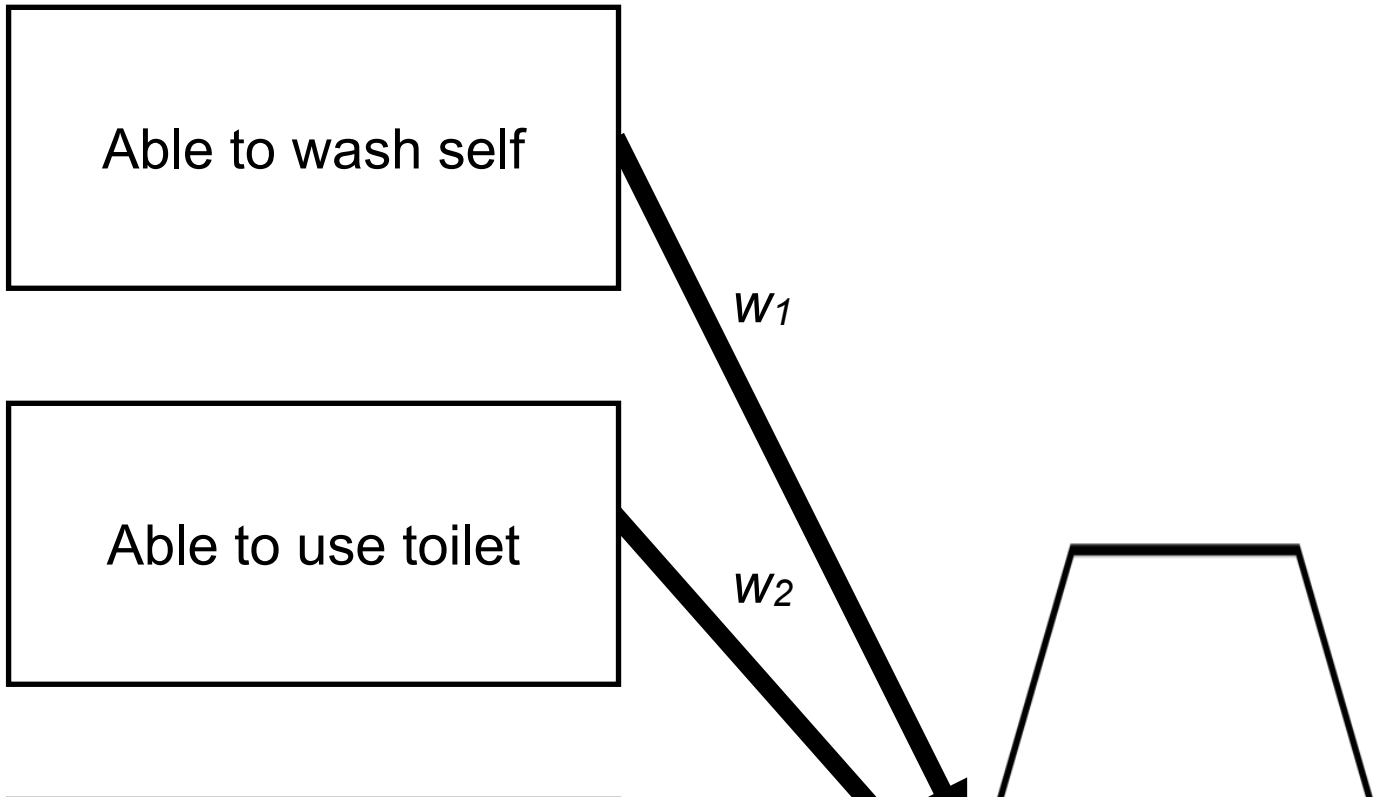
- Item responses should be intercorrelated
- Intercorrelations among the items are best explained by a single, underlying construct (e.g., fatigue)

Example items are from the PROMIS® Fatigue item bank, with a recall period of "in the past 7 days".

Reflective Indicator Model

- Many psychometric modeling approaches may be used (e.g., Classical Test Theory, Item Response Theory [IRT]); should select the approach that best fits your development program
  - Explicitly state the psychometric model that is assumed
  - Provide statistical evidence in support of the model assumptions and fit
  - Provide relevant model parameters

Composite Indicator Model



- Item responses do not need to be intercorrelated
- Each part (item) is necessary to make up the whole (score corresponding to the concept of interest)

Missing Item or Task Response

- Gain understanding on reasons for missingness
- Important to have procedures in place to prevent missing data
- Scoring algorithm should explicitly state the conditions under which a score can still be computed in the presence of missing item/task responses
  - Specifying the minimum number of items/task responses (or other threshold) to compute a score
  - How missing items are to be scored
- Rules for handling missing item or task responses should be justified
  - E.g., Missing data simulation study

Computerized Adaptive Testing (CAT)

- What is CAT?
  - Item bank: the set of potential items to be administered
  - Subsequent item administered to a respondent depends upon a running estimate of the respondent's status based on the respondent's answers to prior items
- Use of CAT has been relatively uncommon in regulatory submissions, and FDA will (and does) consider well-justified approaches
  - Item content aligns with concept of interest
  - All items in the item bank are well understood by patients in the target population
  - Items are well-calibrated in the context of a well-fitting IRT model
  - Items have undergone acceptable process of translation and/or adaptation, when appropriate
  - Stopping rule in terms of the minimum level of measurement precision should also be justified

F. Scores from the COA correspond to the specific health experience(s) the patient has related to the concept of interest

- Depending on the concept of interest and context of use, may seek convergent and/or known-groups evidence

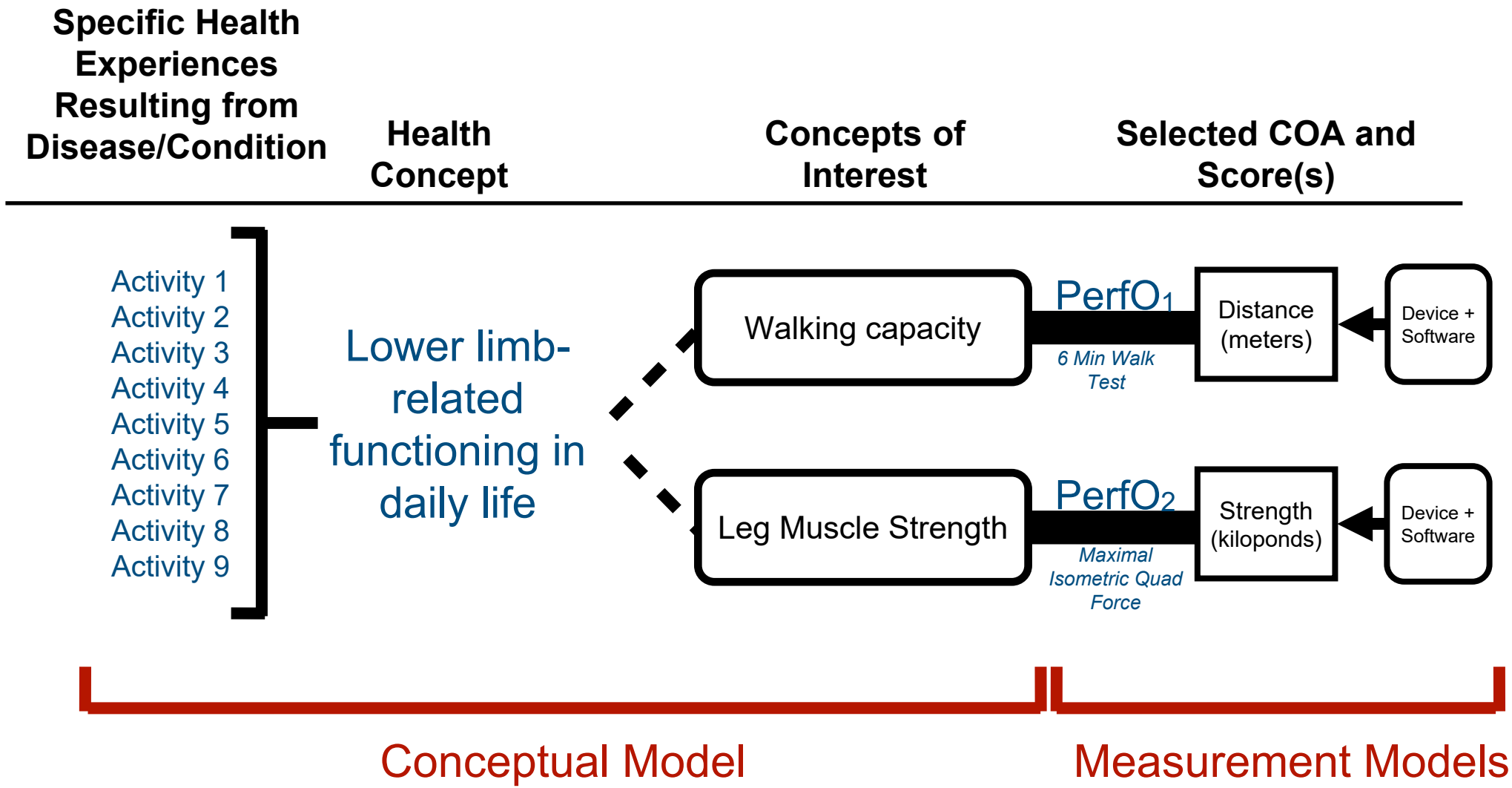
Convergent evidence (previously called *convergent validity*)**:**

- Relationship between scores on the COA and scores on other, related variables
- Should prespecify correlation coefficient cutoffs by considering the *a priori* hypothesized relationships among the concepts measured by the COA and reference measures
- Consider size of the corresponding coefficient of determination and how the distribution of the variables might impact the magnitude of the correlation

Known-groups evidence (previously called *known groups validity*)**:**

- Empirical comparisons of scores for patient groups known to differ with respect to the concept of interest
- Should be based on clinically distinct groups; groups created based on distribution of reference measure scores are ***not*** recommended
- Should propose and justify cutoff values that connote distinct levels of symptom severity and/or impact severity

F. Scores from the COA correspond to the specific health experience(s) the patient has related to the concept of interest



Example based on Walton et al. (2015).

G. Scores are sufficiently sensitive to reflect changes in the concept of interest within patients over time

- Evidence that scores are sensitive enough to detect consequential changes
- **Direct** evidence: *Responsiveness to change*
  - Relationship between changes in the COA's scores and change in another measure of the same or proximal construct
    - Assessed over a comparable time frame
    - Expected to change for the same reason the COA scores should change

G. Scores are sufficiently sensitive to reflect changes in the concept of interest within patients over time

- **Indirect** evidence: Sufficient *reliability/precision* to detect consequential changes

Table 2. Possible Assumptions About Consistency of Scores

		Potential Relevance for COA Type			
Scores are reasonably consistent . . .	**Type of Evidence**	***PRO***	***ObsRO***	***ClinRO***	***PerfO***
. . . over time within clinically stable patients	Test-retest reliability	X	X	X	X
. . . across different raters	Inter-rater reliability			X	X[a]
. . . within the same rater for the same patients (when the patients have not clinically changed)	Intra-rater reliability			X	X[a]
. . . across different but highly related or similar tasks	Evaluation of score differences between related tasks or sets of tasks				X

[a]Applies only if the PerfO measure requires a trained rater as part of the assessment process.

H. Differences in COA scores can be interpreted and communicated clearly in terms of the expected impact on people's day-to-day lives

- We can explain how differences in COA scores translate into differences in people's lives
- Provide plans on how to evaluate meaningful treatment benefit using the most appropriate approaches
  - Upcoming Draft PFDD G4 will discuss different empirical approaches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Presenting a Case for Validity: Two Examples from the MiCOAS Project

FDA Public Meeting
September 9, 2022

R. J. Wirth, PhD

CEO & Managing Partner
Vector Psychometric Group, LLC
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Disclaimer / Disclosure

- My views are mine alone and do not necessarily reflect those of Vector Psychometric Group, LLC

- This presentation was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award UH3FD006795 totaling $2,758,911 with 100 percent funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government

Objective

The goal of this presentation is to illustrate the use of an evidence-based validity rationale for two clinical outcome assessments

MiCOAS™

Migraine Clinical Outcome Assessment System

- Objective: Develop a core set of standardized clinical outcome measures and associated endpoints for acute and preventive migraine clinical trials
  - Project funded by a grant from FDA (2019 – 2023)

MiCOAS™

Migraine Clinical Outcome Assessment System

- **Principal Investigators**
  - R.J. Wirth, PhD
  - Richard Lipton, MD

- **VPG Team**
  - Lexy Bryant, BA
  - Dawn Buse, PhD
  - Calvin Hall, PhD
  - Carrie Houts, PhD
  - Rikki Mangrum, MLS
  - Jim McGinley, PhD
  - Karolina Schantz, PhD

CHAMP
Coalition For Headache And Migraine Patients

- **External Technical Advisory Board**
  - Nicki Bush, MHS
  - Roger Cady, MD
  - David Dodick, MD
  - Peter Goadsby, MD
  - Katie Golden
  - Jason Sico, MD
  - Buzz Stewart, PhD

Thank you to the entire team!

MiCOAS™

Migraine Clinical Outcome Assessment System

- Progress: Currently conducting our 3rd qualitative study with a 4th study about to start
  - How do people experience migraine?
  - How do people living with migraine prioritize treatment outcomes?
  - How does migraine impact people living with it?
  - What language is used to describe/capture these experiences/impacts?
  - What retrospective timeframes are best when asking about experiences/impacts?
  - What response options are best suited for the various domains of interest?

- Products: Will consist of a collection of existing (e.g., headache pain intensity) and new (e.g., cognitive functioning) measures

The Roadmap

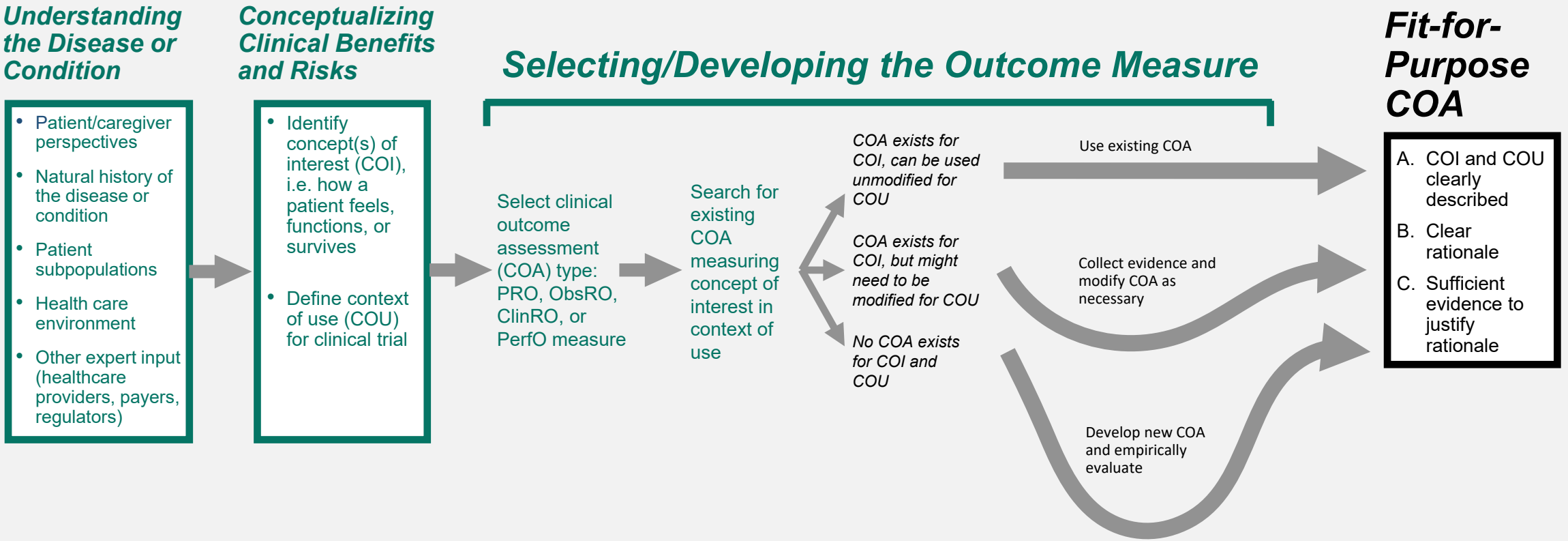


Figure 2: Roadmap to Patient-Focused Outcome Measurement in Clinical trials (p11, Guidance 3)

The Roadmap

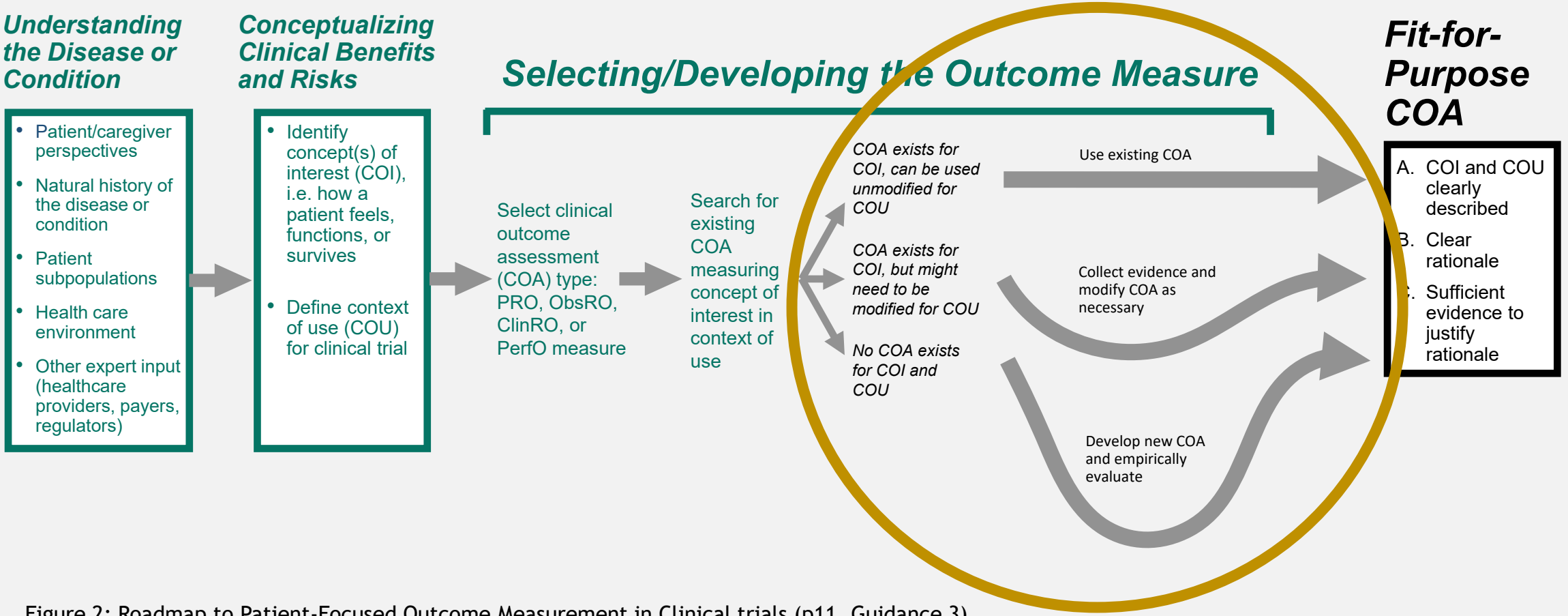


Figure 2: Roadmap to Patient-Focused Outcome Measurement in Clinical trials (p11, Guidance 3)

Example 1: Measure Already in Use

- Pain Intensity Scale (PIS)
  - Single item
  - No standardized wording but something like:
    - **Rate your current head pain**
  - Typically, a 4-point response scale in migraine trials
    - **none, mild, moderate, and severe**
  - Operationalized as a primary endpoint for acute treatment studies
    - **Pain freedom at 2 hours (i.e., head pain = “none”)**

Validity Table Example: Pain Intensity Scale

	Component	Justification
A	Headache pain intensity should be assessed by a PRO measure	A direct report of headache pain intensity is best reported by individual experiencing the headache pain (ObsRO may be possible)
B	The PIS captures all the important aspects of headache pain intensity	Head pain intensity is a narrow concept that is sufficiently covered by the language of the single question asking about pain intensity. In everyday English, the response options (none, mild, moderate, and severe) cover the entire range of pain intensity. On-going qualitative research is being conducted to further support this component
C	Patients understand the instructions and item of the PIS as intended by the measure developer	Wording and response options are very common and have been used in multiple trials successfully. On-going qualitative research is being conducted in support of the instructions, item, and response options

Validity Table Example: Pain Intensity Scale

	Component	Justification
D	Scores of the PIS are not overly influenced by processes /concepts that are not part of headache pain intensity	Qualitative research suggests that people experiencing headache pain can respond to questions about headache pain intensity without being meaningfully influenced by other factors
D.1	Scores of the PIS are not overly influenced by other symptoms of migraine	Qualitative research suggests that people experiencing headache pain can respond to questions about headache pain intensity without being meaningfully influenced by other symptoms of migraine
E	The method of scoring responses to the PIS is appropriate for assessing headache pain intensity	The score is the ordinal numeric code assigned to each answer (i.e., None = 0, Mild = 1, Moderate = 2, Severe = 3)
F	Scores from the PIS correspond to the specific health experience(s) the patient has related to headache pain intensity	Previous research has repeatedly found self-report of pain to accurately reflect an individual's experience

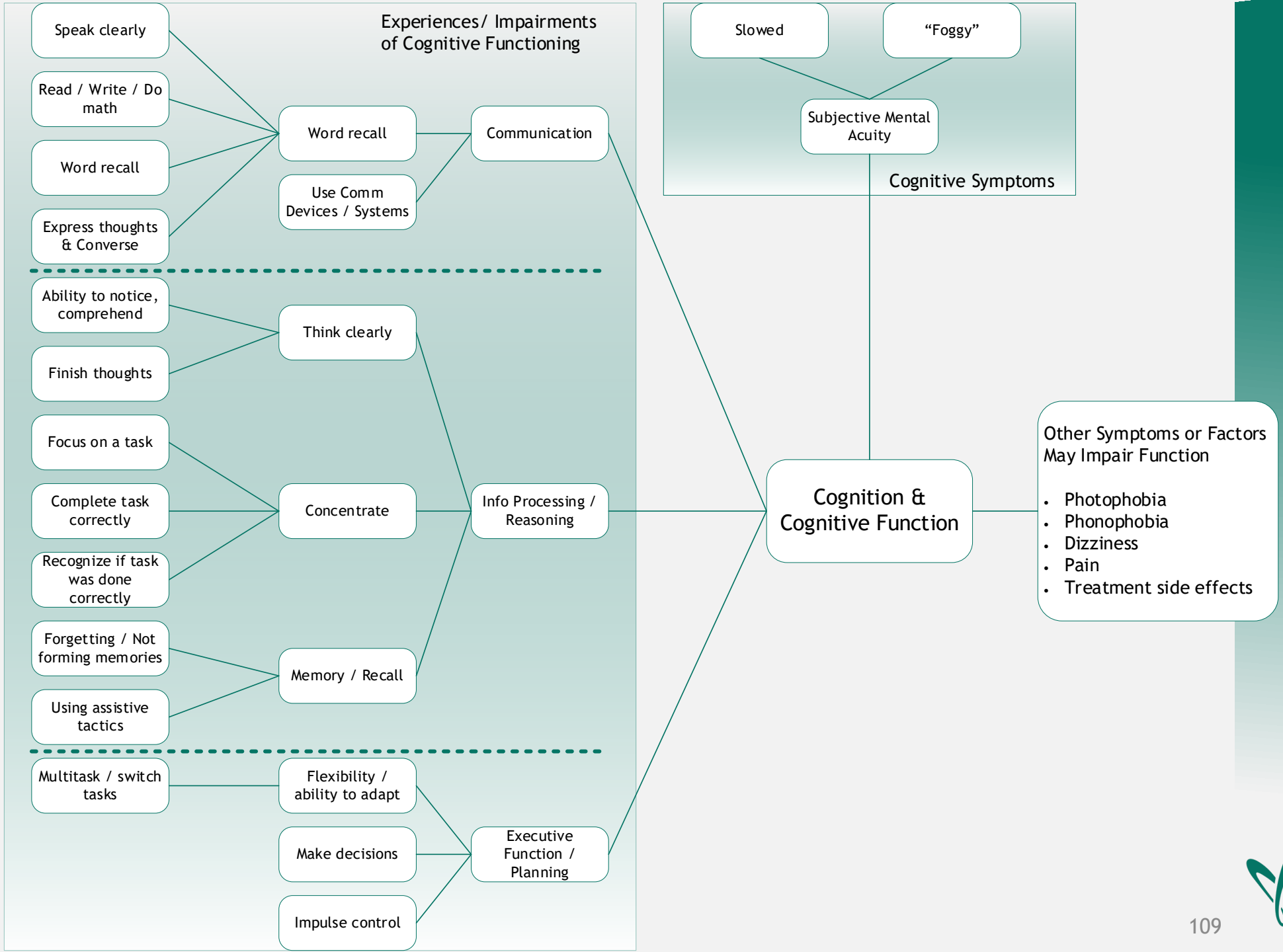
Validity Table Example: Pain Intensity Scale

	Component	Justification
G	Scores are sufficiently sensitive to reflect changes in the PIS within patients over time	It has been demonstrated empirically in numerous clinical trials that the PIS is sensitive to change and treatment effects
H	Differences in COA scores can be interpreted and communicated clearly in terms of the expected impact on people's day-to-day lives	Qualitative research suggests people understand movement between none, mild, moderate, and severe and that this movement is relevant to their treatment goals

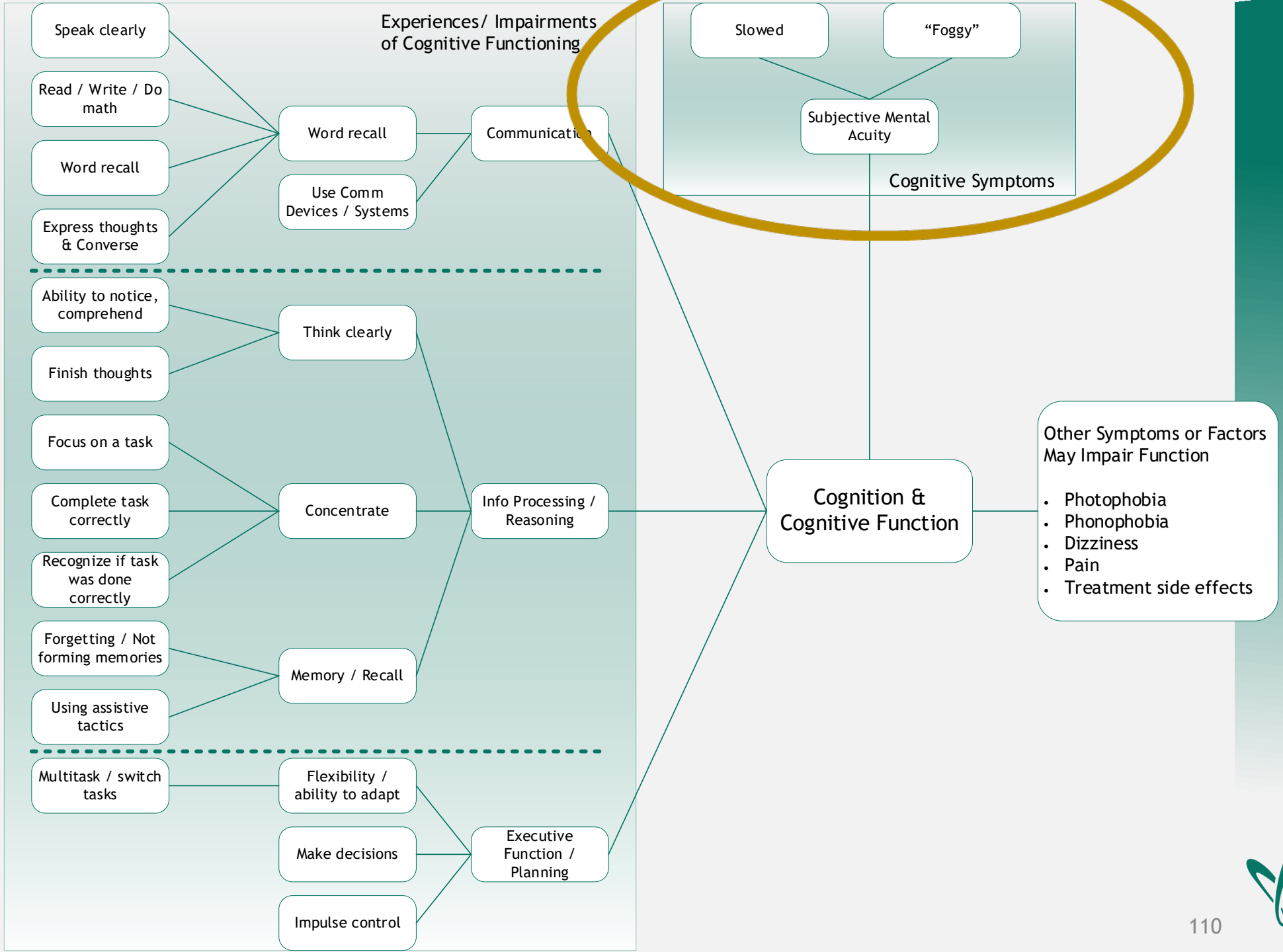
Example 2: Measure Under Development

- MiCOAS-SMA
  - Subjective Mental Acuity
- Multi-item assessment
- Under development
  - Concept elicitation has been completed
  - Cognitive debriefing is on-going
  - No quantitative studies have been completed to-date
- Collection of validity evidence still in process

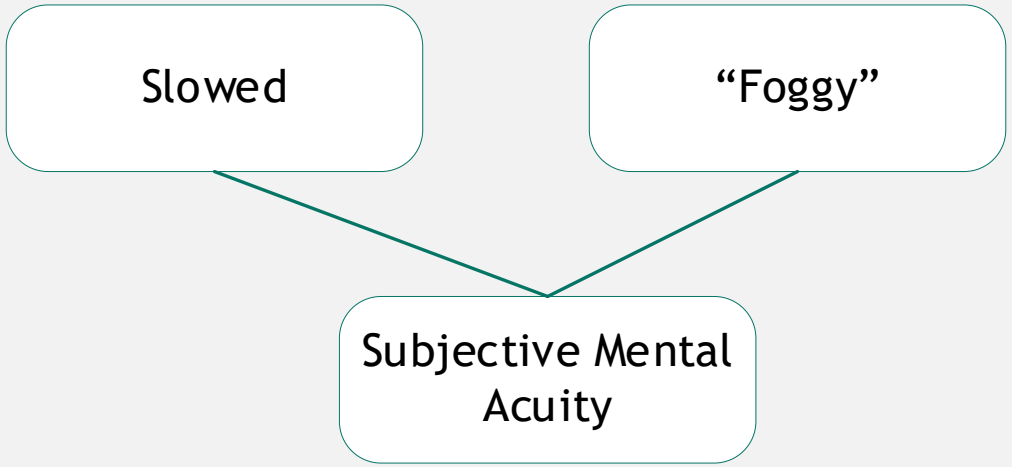
Conceptual Model



Conceptual Model



Conceptual Model: Subjective Mental Acuity (SMA)



- Subjective Mental Acuity
  - Focus on Cognitive Symptoms
  - Two general concepts: Slowed & Foggy

Validity Table Example: Subjective Mental Acuity

	Component	Justification
A	Subjective mental acuity (SMA) should be assessed by a PRO measure	Subjective mental acuity is solely the patient's perspective of their mental acuity
B	The MiCOAS-SMA measure captures all the important aspects of SMA	A conceptual model of SMA is being refined based on qualitative work. Potential items have been written that correspond directly to the health concepts that make up SMA based on previously conducted and on-going qualitative research
C	Patients understand the instructions and items of the MiCOAS-SMA as intended by the measure developer	The instructions, candidate items, and candidate response options are currently being examined in qualitative studies

Validity Table Example: Subjective Mental Acuity

	Component	Justification
D	Scores of the MiCOAS-SMA are not overly influenced by processes/concepts that are not part of SMA	SMA does not include common cognitive functions, as supported by qualitative research and clinician feedback, that could be affected by SMA
D.1	Item interpretations or relevance do not differ substantially according to respondents' demographic characteristics (including sex, age, and education level) or cultural/linguistic backgrounds	Evidence of consistent item interpretation and relevance will be supplied by cognitive interviews. A review of translatability, which is being completed, may highlight cultural/linguistic issues. Sex-specific differences in terminology for this concept were observed in concept elicitation and items reflecting these differences were included in cognitive interviews. Future empirical work will examine, if appropriate, differential item functioning between key groups

Validity Table Example: Subjective Mental Acuity

	Component	Justification
D.2	Recall errors do not overly influence assessment of SMA	A literature review on recall bias for the proposed candidate recall timeframes has been conducted and results presented elsewhere. Future cognitive research will also assess the extent to which people with migraine perceive difficulties with recall across various retrospective timeframes
D.3	Expectation bias does not unduly influence assessment of SMA	People's expectations of their cognition could heavily influence their report of SMA. It is expected that there is no way to assess subjective cognition without a significant influence of their expectations. But the intended context of use is in randomized trials in which study group assignment is concealed from patients, minimizing the influence of expectation bias on an estimate of the treatment effect

Validity Table Example: Subjective Mental Acuity

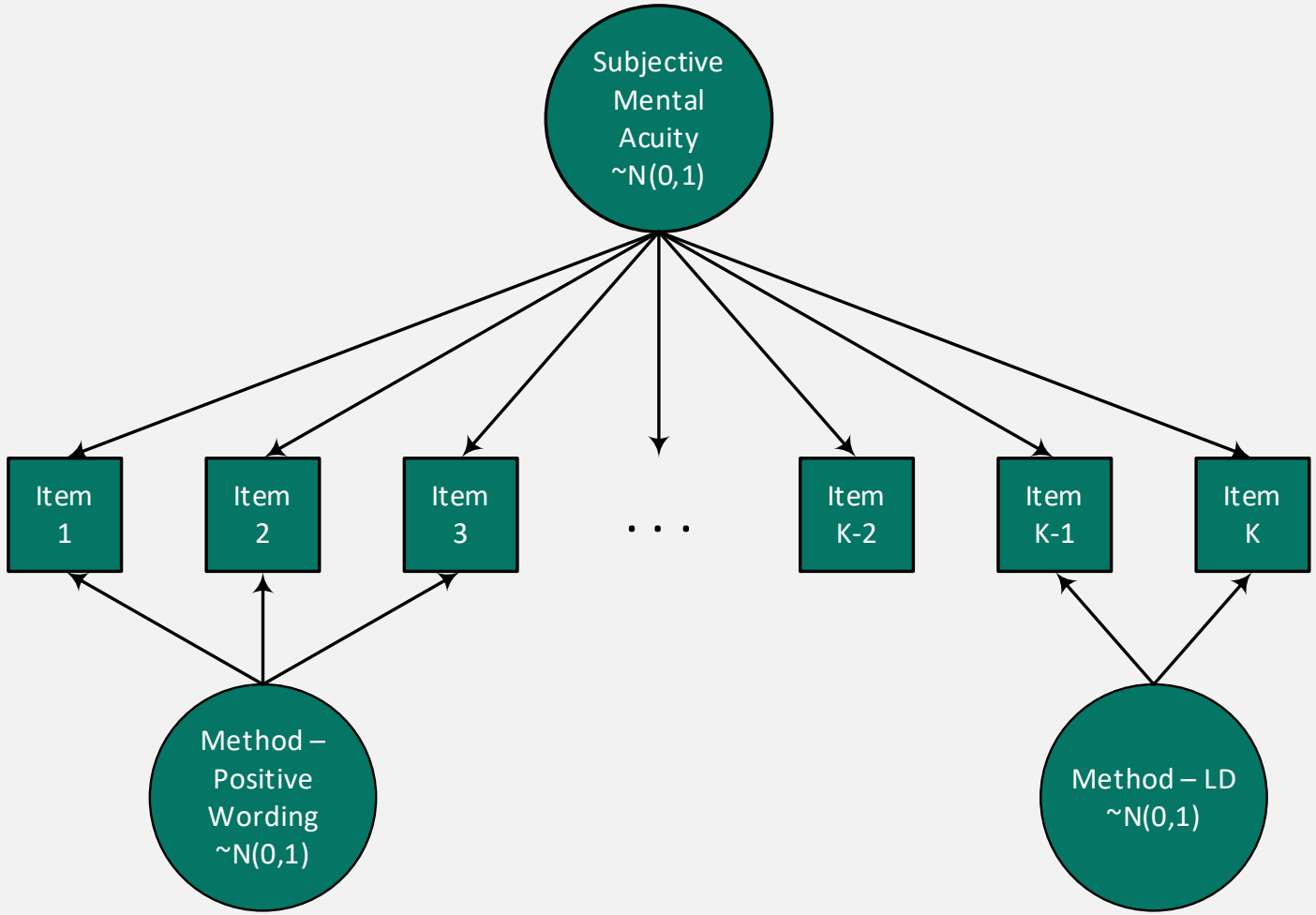
	Component	Justification
E	The method of scoring responses to the MiCOAS-SMA is appropriate for assessing SMA	Item content, recall period, and response options will be supported with qualitative research. It is assumed that all item responses will be ordinal in nature and appropriate empirical methods will be used to 1) evaluate the item specific response characteristics, 2) evaluate the inter-relationship among items, and 3) statistically evaluate *a priori* measurement model(s) that are developed to be consistent with the conceptual model and item characteristics
F	Scores from the MiCOAS-SMA correspond to the specific health experience(s) the patient has related to SMA	Correspondence of SMA scores with scores for cognitive and social/role functions likely to be affected by changes in SMA will be examined. These functions include language (speaking, reading), work/school, and social interactions

Validity Table Example: Subjective Mental Acuity

	Component	Justification
G	Scores are sufficiently sensitive to reflect changes in SMA within patients over time	Empirical evaluation of score reliability and responsiveness will be completed once a candidate scoring rubric has been developed
H	Differences in MiCOAS-SMA scores can be interpreted and communicated clearly in terms of the expected impact on people's day-to-day lives	Quantitative evaluation of MiCOAS-SMA scores and their relationship with important outcomes/experiences will be conducted to aid in the interpretation of scores. Qualitative work may also be conducted to better understand how people living with migraine understand MiCOAS-SMA scores and, importantly, changes in MiCOAS-SMA scores

Example Measurement Model

- Graded Response Model
  - Evaluated using Item Response Theory
- Single Domain
  - Subjective Mental Acuity
- Two Method/Nuisance Factors
  - Positive Wording (items 1, 2, & 3)
  - Local Dependence (items K-1 & K)
- All factors are assumed to be normally distributed with mean zero and variance one (for scaling/identification)
- All factors are uncorrelated
- Items are assumed to be:
  - Ordinal
  - Each with a unique slope(s)
  - Each with unique intercepts



Conclusion

- Valuable framework for thinking about validity
  - Table 1 in section IV of the Guidance should be seen as a starting point
- Focuses conversations and resources
- Learning curve but rich literature available from the broader psychometric community (psychology, education, certification, etc.)
- Encourages us to clearly differentiate and better define conceptual and measurement models
- Allows us to rethink the layout and function of COA Dossiers

Related Publications

Coles et al. Health Qual Life Outcomes (2021) 19:164
https://doi.org/10.1186/s12955-021-01800-1

Health and Quality of Life Outcomes

COMMENTARY Open Access

Enabling patient-reported outcome measures in clinical trials, exemplified by cardiovascular trials

Theresa M. Coles[1*], Adrian F. Hernandez[1], Bryce B. Reeve[1], Karon Cook[2], Michael C. Edwards[3,4], Marc Boutin[5], Elizabeth Bush[6], Arnold Degboe[7], Lothar Roessig[8], Amy Rudolph[9], Pauline McNulty[10], Nikunj Patel[7], Trish Kay-Mugford[9], Margaret Vernon[11], Michael Woloschak[12], Gustavo Buchele[13], John A. Spertus[14,15], Matthew T. Roe[1], Denise Bury[16] and Kevin Weinfurt[1]

Quality of Life Research
https://doi.org/10.1007/s11136-022-03162-7

SPECIAL SECTION: REDUCING RESEARCH WASTE IN (HEALTH-RELATED) QUALITY OF LIFE RESEARCH

Using validity theory and psychometrics to evaluate and support expanded uses of existing scales

Carrie R. Houts[1] · Elizabeth Nicole Bush[2] · Michael C. Edwards[1] · R. J. Wirth[1]

Qual Life Res (2018) 27:1711–1720
https://doi.org/10.1007/s11136-017-1644-z

SPECIAL SECTION: TEST CONSTRUCTION (BY INVITATION ONLY)

Fit for purpose and modern validity theory in clinical outcomes assessment

Michael C. Edwards[1,4] · Ashley Slagle[2] · Jonathan D. Rubright[3] · R. J. Wirth[4]

Article

CLINICAL TRIALS

Clinical Trials
2022, Vol. 19(2) 184–193

DOI: 10.1177/17407745211073609
journals.sagepub.com/home/ctj
SAGE

Constructing and evaluating a validity argument for a performance outcome measure for clinical trials: An example using the Multi-luminance Mobility Test

Kevin P Weinfurt

Thank You

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Question and Answer

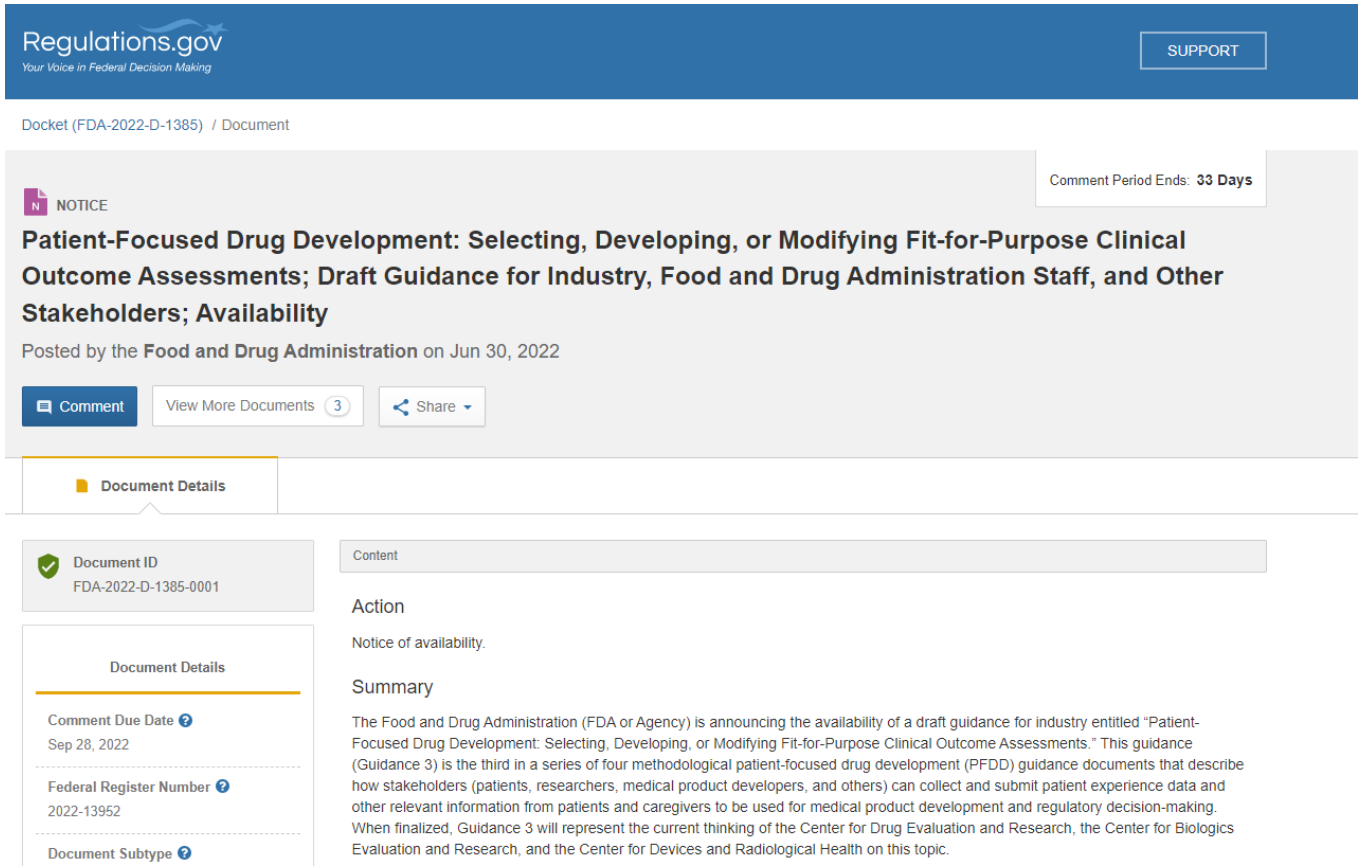
Send us your comments!

Interested stakeholders are invited to submit comments on the draft guidance to the public docket.

The docket will close on September 28, 2022.

How do you submit a comment?

- Please visit: https://www.regulations.gov/docket/FDA-2022-D-1385
- And **Click Comment**



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Thank you!