CRITICAL PATH INSTITUTE

RARE AND ORPHAN DISEASE PROGRAMS

Clinical Outcome Assessments – Initial Public Discussion

WELCOME

Building a rare disease community that works. Together.

April 23, 2024

Agenda

12:00 Welcome and Opening Remarks

12:10 Presentation

Overview of Patient-Focused Drug Development and endpoints that inform regulatory decision making

Summary of work to date on concepts and tools

Next steps for engaging with people with lived experience

12:50 Q&A

12:58 Wrap Up

Building a rare disease community that works. Together.

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Welcome

Collin Hovinga, PharmD, MS, FCCP

Critical Path Institute (C-Path)

Vice President, Rare and Orphan Disease Programs

Presenters

Michelle Campbell, PhD
U.S Food and Drug Administration
Associate Director, Office of Neuroscience, CDER

Cheryl D. Coon, PhD
Critical Path Institute
Vice President, Clinical Outcome Assessment Program

Teresa Buracchio, MD
U.S Food and Drug Administration
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Presentation

Building a rare disease community that works. Together.

Patient-Focused Drug Development

Michelle Campbell, PhD
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research
April 23, 2024

What We Learned from FDA PFDD Meetings

- **Patients are uniquely positioned** to inform regulatory understanding of the burden of disease and current available treatments
- **Patients** are experts on what it is like to live with their condition
- **Patients** "chief complaint" may not be factored explicitly in to drug development plans

What is patient-focused drug development (PFDD)?

- A systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into the development and evaluation of medical products throughout the medical product life cycle.

Patient experience data: An umbrella term

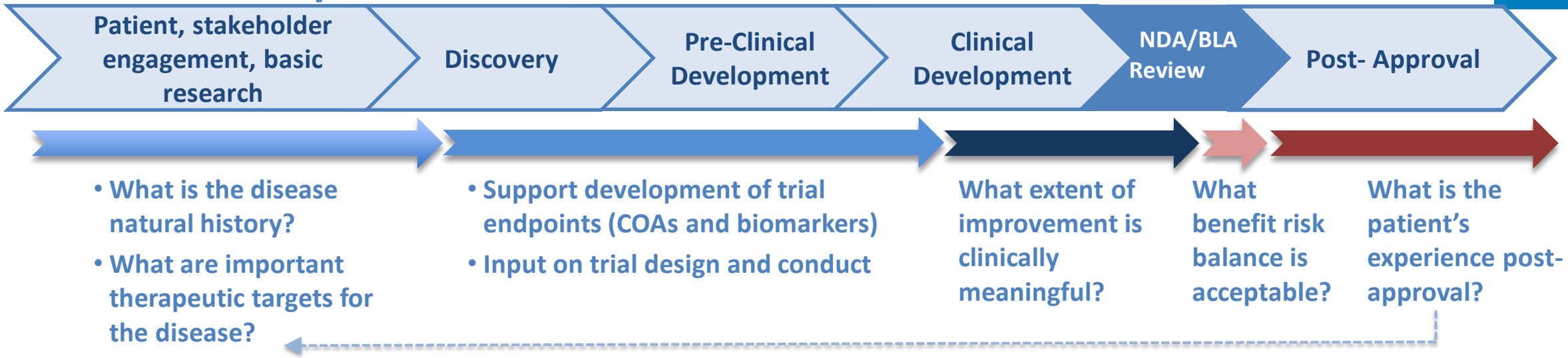
- **Patient experience data***: …data that are collected by any persons and are intended to provide information about patients' experiences with a disease or condition.
- Information that captures patients' experiences, perspectives, needs, and priorities related to (but not limited to):
  1) the symptoms of their condition and its natural history
  2) the impact of the conditions on their functioning and quality of life
  3) their experience with treatments
  4) input on which outcomes are important to them
  5) patient preferences for outcomes and treatments
  6) the relative importance of any issue as defined by patients

*Defined in Title III, section 3001 of the 21st Century Cures Act, as amended by section 605 of the FDA Reauthorization Act of 2017 (FDARA)[1]

Patient experience data: An umbrella term

- Ranges from :
  - Patient Listening Session
  - Patient-Focused Drug Development Meeting
  - Use of Clinical Outcome Assessments
  - Patient Preference Studies
  - Thoughts on Benefit/Risk
  - Thoughts on Clinical Meaningfulness

How can patient experience data be used across the lifecycle?



Key areas of input from patients can include:

- Impact of disease on patient: important goals and targets for therapy
- Developing appropriate "tools"
- Progression of disease over time: understanding "natural history"
- Impact and burden of treatments and unmet needs
- How clinical trials can be improved, facilitating participation
- What benefits do patients seek and what risks are they willing to accept?

Source: Dr. Peter Stein (Critical Path Institute PRO Consortium Annual Meeting April 24, 2019)

Understanding and Accounting for the Patient Experience

- What disease impacts matter most to patients?
  - *How does that vary by subgroup group of patients (e.g., a pediatric subpopulation, geriatric subpopulation, subpopulation with major co-morbidities)? Severity of disease? Other life circumstances?*
- How well do the most commonly studied endpoints in clinical trials for a given disease area align with outcomes or aspects of disease that matter most to patients?
  - *How does that vary by subgroup?*
- Are currently conducted clinical trials in a given disease area excluding patients who want to enroll?
  - *If so, why and how might it be addressed?*
- Are currently or commonly used clinical trial protocols intolerable or otherwise unworkable for some patients who are otherwise eligible to participate?
  - *Why? What might be done to address that?*

Clinical Outcome Assessments to Support Clinical Trial Endpoints

- COAs are used to support clinical trial endpoints
- Efficacy trial endpoints needs to demonstrate clinical benefit
  - Improvement in how a patient feels, functions or survives

Clinical Outcome Assessments

Assessment of a clinical outcome can be made through by report from a clinician, a patient, a non-clinician observer, or through a performance based assessment

- Patient-reported outcomes (PROs)
- Observer-reported outcomes (ObsROs)
- Clinician-reported outcomes (ClinROs)
- Performance outcomes (PerfOs)

BEST Glossary: https://www.ncbi.nlm.nih.gov/books/NBK338448/

Example

- May not provide a clinically meaningful information
  - Clinician reporting exam changes of decreased vibratory sense, decreased movement against resistance, or decreased reflexes in arms/hands.
  - Changes may suggest a change in the disease status but do not reflect any impact on patient symptoms or daily functioning.
- Does provide clinically meaningful information
  - Numbness in hands that interferes with the ability to button clothes
  - Weakness in hands that interferes with ability to hold spoon and eat
  - Weakness in arms causing difficulty carrying groceries

Clinical Outcome Assessments to Support Clinical Trial Endpoints

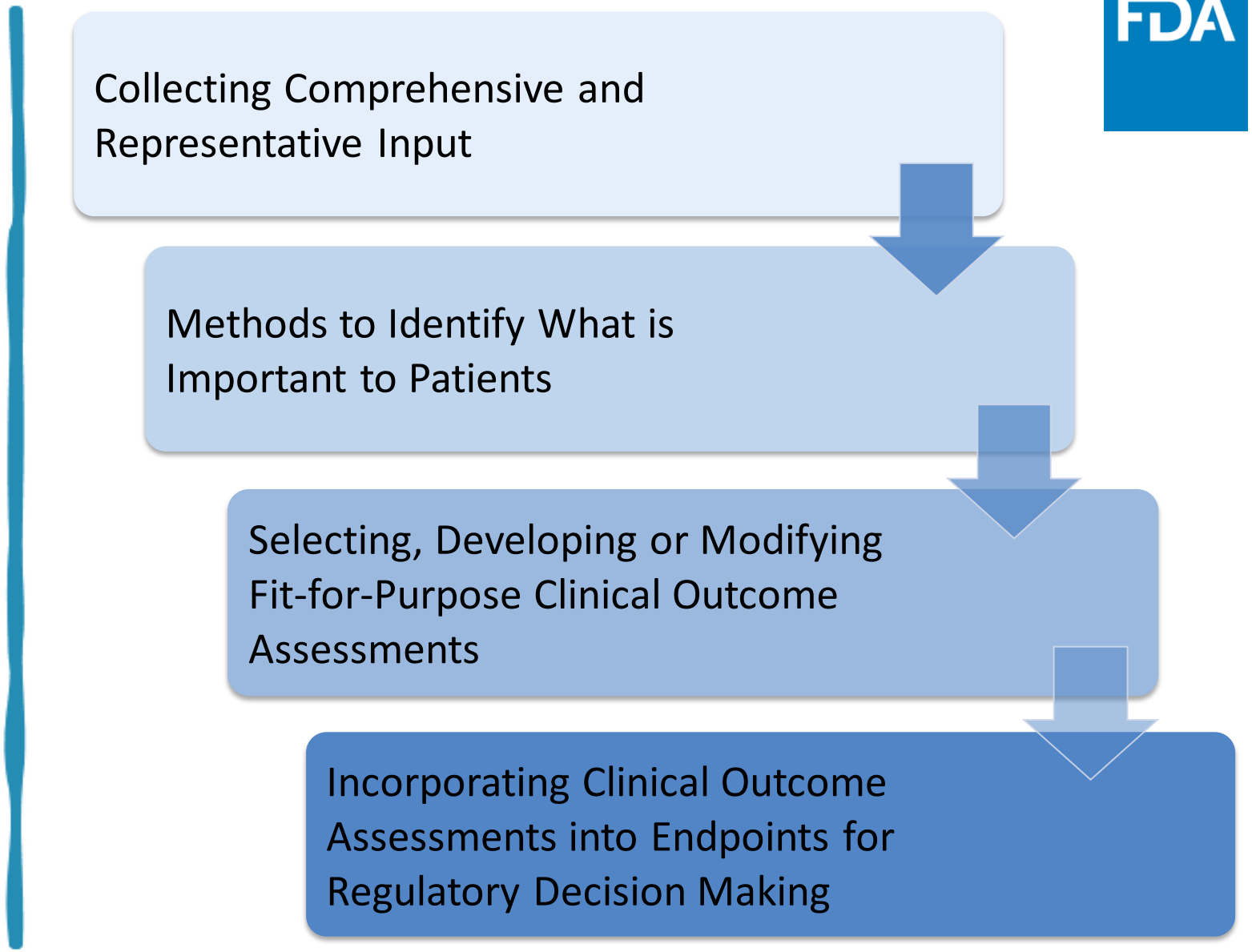
- We need COAs to be Fit-for-Purpose
  - A conclusion that the level of validation associated with a COA is support to support its proposed use
- Appropriate for its intended use/context of use e.g.,
  - Patient population
  - Study design
- Validly and reliably measures a concept that is
  - Important to patients
  - Clinically relevant
- Can be communicated in labeling in a way that is accurate, interpretable, and not misleading (i.e., well-defined)*

* If the COA is appropriately applied in medical product development (21CFR 314.126)

Patient Focused Drug Development

METHODOLOGIC GUIDANCE SERIES

Methodologic Guidance Documents



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

Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment

Guidance for Industry

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)

September 2019
Clinical/Medical

https://www.fda.gov/media/130964/download

2. *Effectiveness Endpoints*

Although existing outcome measures that have been developed for ALS may be appropriate, FDA supports the development and use of new outcome measures capable of measuring clinically meaningful effects in patients. FDA encourages the use of patient input and experience in the development of these new measures. Sponsors can also consider novel technologies (e.g., wearable biosensors), as appropriate.

In general, effectiveness should be established by the demonstration of a treatment effect (e.g., less decline, stabilization, improvement) on function in daily activities as measured, for example, by the ALS Functional Rating Scale-Revised or similar scales. In general, in addition to the primary endpoint, sponsors should include assessments of various effectiveness outcomes in trials, including patient-reported outcomes (PROs). For effective drugs, the results of these additional outcomes would be expected to be supportive.

PRO assessments, including those measuring activities of daily living, can be designed to assess the abilities and experiences of patients across a spectrum of disease stages and severities. PRO assessments can be useful to assess the clinical meaningfulness of an objective finding (e.g., muscle strength) even if of relatively small magnitude, and they therefore contribute to assessments of benefits and risk. In general, PRO instruments for ALS trials should include a limited number of items that assess the most important aspects of the outcome of interest (e.g., specific aspects that contribute to health-related quality of life, such as physical functioning). PRO instruments that are overly lengthy may increase responder burden and fatigue, increasing the potential for missing data. PRO instruments that are overly broad can be difficult to interpret and may be insensitive to meaningful change in the outcomes of major interest.

Goals of COAs in ALS Effort

- Follow the Roadmap to PFDD as described Guidance 3
- Focus on COAs that are fit-for-purpose and can support clinical trial endpoints


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Literature Review on Concepts and Tools

- Cheryl D. Coon, PhD
- Vice President, Clinical Outcome Assessment Program

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Project Overview

Research Question: How do we get to fit-for-purpose clinical outcome assessment tools that are meaningful to people with lived experience (PWLE)?

Project Goals:

1. To identify concepts that are meaningful to PWLE
2. To identify the tools that measure those concepts
3. To assess the need for further development of the tools for their use in clinical trials for ALS

Project Activities

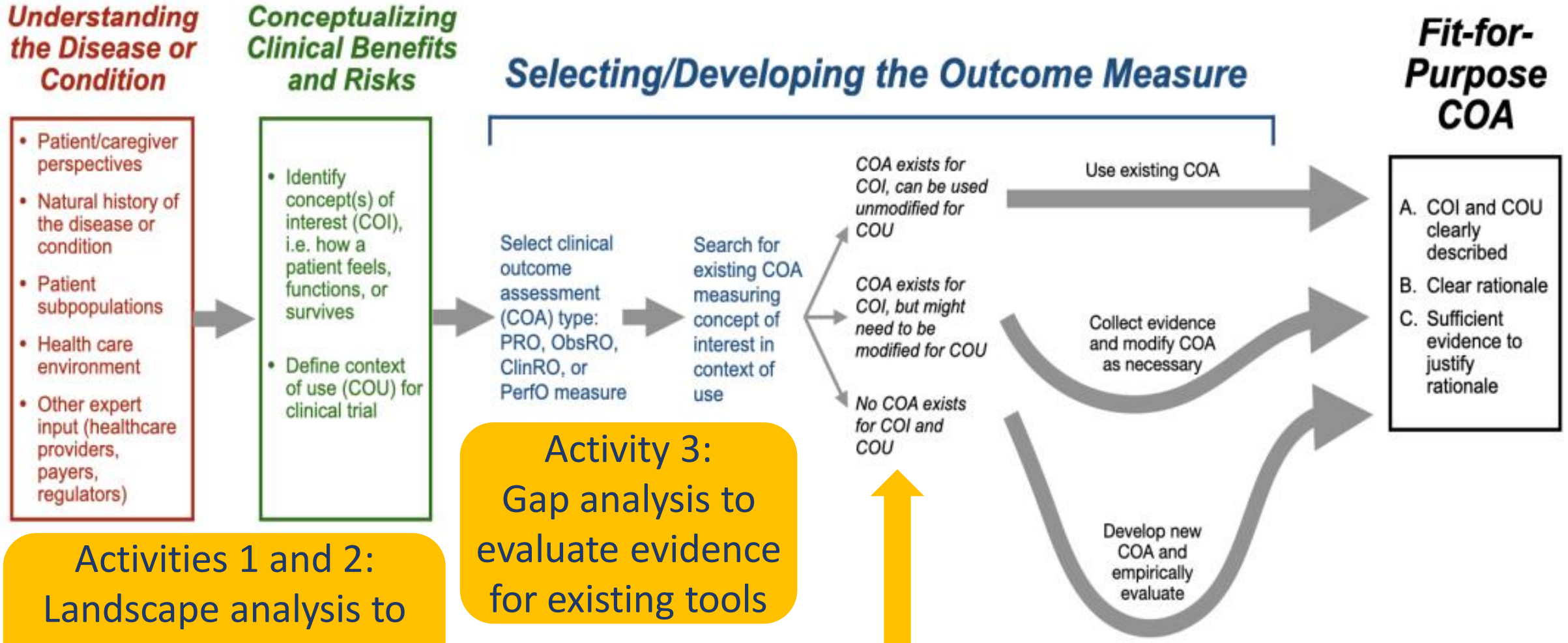
1.Conduct a **landscape analysis** to understand concepts important in ALS

2. Identify the most relevant **concepts** to be measured in clinical trials

3. Conduct a **gap analysis** of tools that have been developed for or used in measuring these concepts ALS

4. Provide **recommendations** for using existing tools, modifying existing tools, or developing new tools

PFDD Roadmap: What's Being Addressed by This Project?



Activities 1 and 2: Landscape analysis to identify concepts to measure in clinical trials

Activity 3: Gap analysis to evaluate evidence for existing tools

Activity 4: Recommendations for next steps to fill gaps

Methods

1. Search for publications
2. Review and selection of articles
3. Full text review of selected articles
4. Data extraction and analysis
5. Identification of concepts and tools
6. Gap analysis of tools
7. Make recommendations on how to fill identified gaps

Concepts of interest identified through literature search

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Activities of daily living	Behavioral	Bulbar	Cognitive	Digestive
Economic	Emotional	Fatigue	Global quality of life	Mental health
Mobility	Motor	Nutrition	Pain	Physical symptoms
Psychosocial	Respiratory symptoms	Sex life	Sleep	Social/ Relationships

Concepts of interest identified…that may be used to support clinical trial study endpoints

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Activities of daily living	**Behavioral**	**Bulbar**	**Cognitive**	**Digestive**
		Fatigue		**Mental health**
Mobility	**Motor**	**Nutrition**	**Pain**	**Physical symptoms**
	Respiratory symptoms		**Sleep**	

Concepts of interest identified…that are unlikely to support clinical trial study endpoints

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Economic

Emotional

Global quality of life

Psychosocial

Sex life

Social/ Relationships

Clinical outcome assessments identified

ALS Assessment Questionnaire	ALS Specific Quality of Life Short Form
ALS Assessment Questionnaire 5-item	ALS Supportive Care Needs
ALS Cognitive Behavioural Screen	Center for Neurological Study Bulbar Function Scale
ALS Depression Inventory	Coping Index ALS
ALS Frontotemporal Dementia Cognitive Screen	Dysphagia in ALS Questionnaire
ALS Health Index	Dyspnea ALS Scale
ALS Health Index Short Form	Edinburgh Cognitive and Behavioural ALS Screen
ALS Impairment Multidomain Scale	Motor Neuron Disease Behavioural Scale
ALS Respiratory Symptom Scale	Preference-based ALS Health Related Quality of Life Scale
ALS Severity Scale	Rasch-built Overall ALS Disability Scale
ALS Specific Quality of Life	Sickness Impact Profile ALS, 19 Item
ALS Specific Quality of Life, revised	

Note: Focus was on tools beyond ALSFRS-R COA because it is already well known.

Clinical outcome assessments identified…that were chosen for further consideration

ALS Assessment Questionnaire	~~ALS Specific Quality of Life Short Form~~
ALS Assessment Questionnaire 5-item	~~ALS Supportive Care Needs~~
ALS Cognitive Behavioural Screen	Center for Neurological Study Bulbar Function Scale
~~ALS Depression Inventory~~	~~Coping Index ALS~~
~~ALS Frontotemporal Dementia Cognitive Screen~~	~~Dysphagia in ALS Questionnaire~~
~~ALS Health Index~~	~~Dyspnea ALS Scale~~
~~ALS Health Index Short Form~~	Edinburgh Cognitive and Behavioural ALS Screen
ALS Impairment Multidomain Scale	Motor Neuron Disease Behavioural Scale
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ALS Severity Scale	Rasch-built Overall ALS Disability Scale
~~ALS Specific Quality of Life~~	~~Sickness Impact Profile ALS, 19 Item~~
~~ALS Specific Quality of Life, revised~~	

Clinical outcome assessments added to the list for further consideration

COAs Selected from Literature Search	Additional COAs to Consider
ALS Assessment Questionnaire	Center for Neurological Study Lability Scale
ALS Assessment Questionnaire 5-item	
ALS Cognitive Behavioural Screen	
ALS Impairment Multidomain Scale	
ALS Severity Scale	
Center for Neurological Study Bulbar Function Scale	
Edinburgh Cognitive and Behavioural ALS Screen	
Motor Neuron Disease Behavioural Scale	
Rasch-built Overall ALS Disability Scale	

Note: Please see hyperlinks in table to see the items and concepts measured by each tool.

Next steps

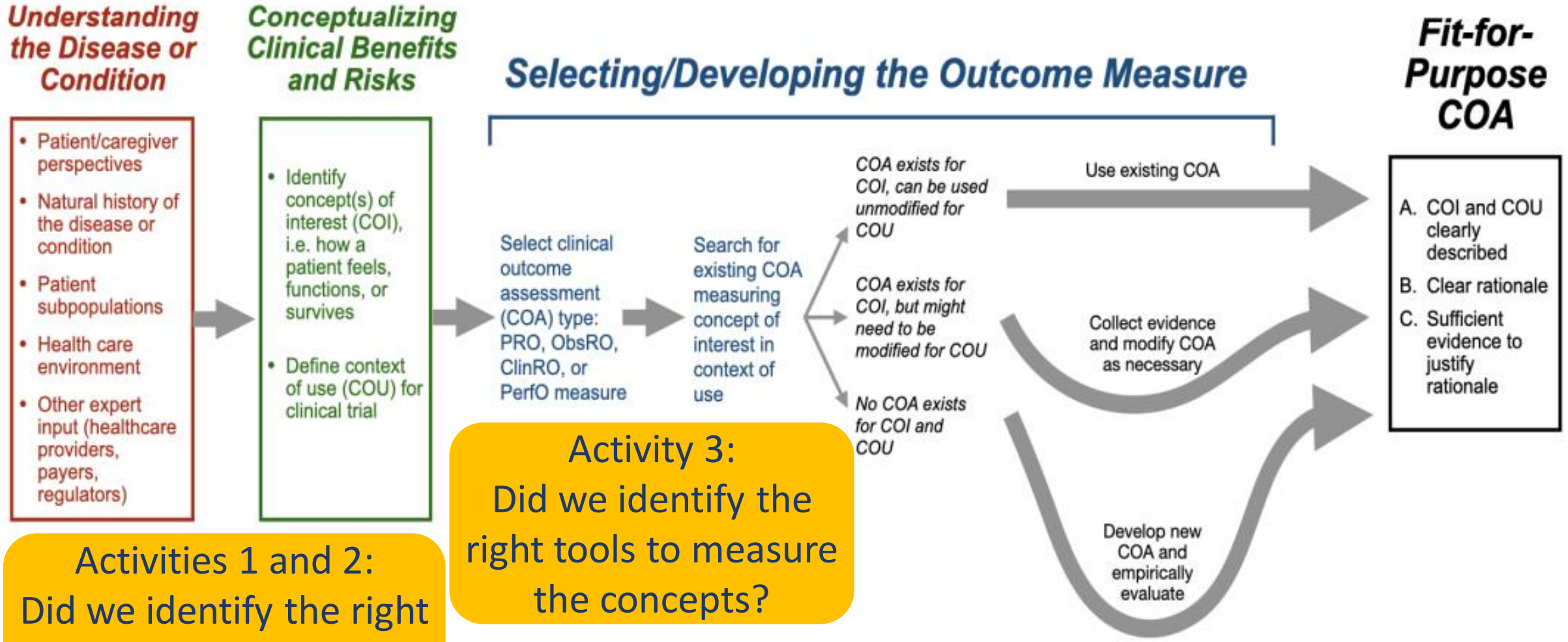
The gap analysis is currently under development for the 10 selected tools.

Once gaps are identified and confirmed, activities needed to fill those gaps will be defined.

- Examples:
  - Individual interviews with PWLE to confirm concepts measured by the tools are relevant, important, and understood.
  - Psychometric analysis to confirm that scores produced by the tools are reliable, valid, sensitive to change, and interpretable.

Throughout this process, we want to know that we're on the right track, which means engaging with you, the experts.

PFDD Roadmap: Where We Need Your Help



Activities 1 and 2:
Did we identify the right concepts for clinical trial endpoints?

Activity 3:
Did we identify the right tools to measure the concepts?

Question and Answer

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To Share Feedback:

- Email CP-RND@c-path.org
- Use Subject line "**COA Feedback**"

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- Materials Available

Materials from today's presentation will be available online (just scan this QR code)

Or visit us at:

www.c-path.org/cp-rnd

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