FORKS IN THE ROAD

CRITICAL DECISION POINTS AND FDA INSIGHTS FROM SIX YEARS OF PHYSICAL FUNCTION COA DEVELOPMENT

THE STARTING POINT

- COA development is typically disease-specific: each program builds its own measures from scratch, even when patients share similar functional limitations.
- Rare diseases are underserved- small populations and limited commercial incentive leave many without validated endpoints for drug development
- **Could we create a single set of physical function COAs relevant to multiple conditions and still meet FDA qualification standards?**
- Six years, one FDA cooperative agreement, and many critical decisions later: today you will hear about the choices that shaped this project

THE ROAD AHEAD

Format

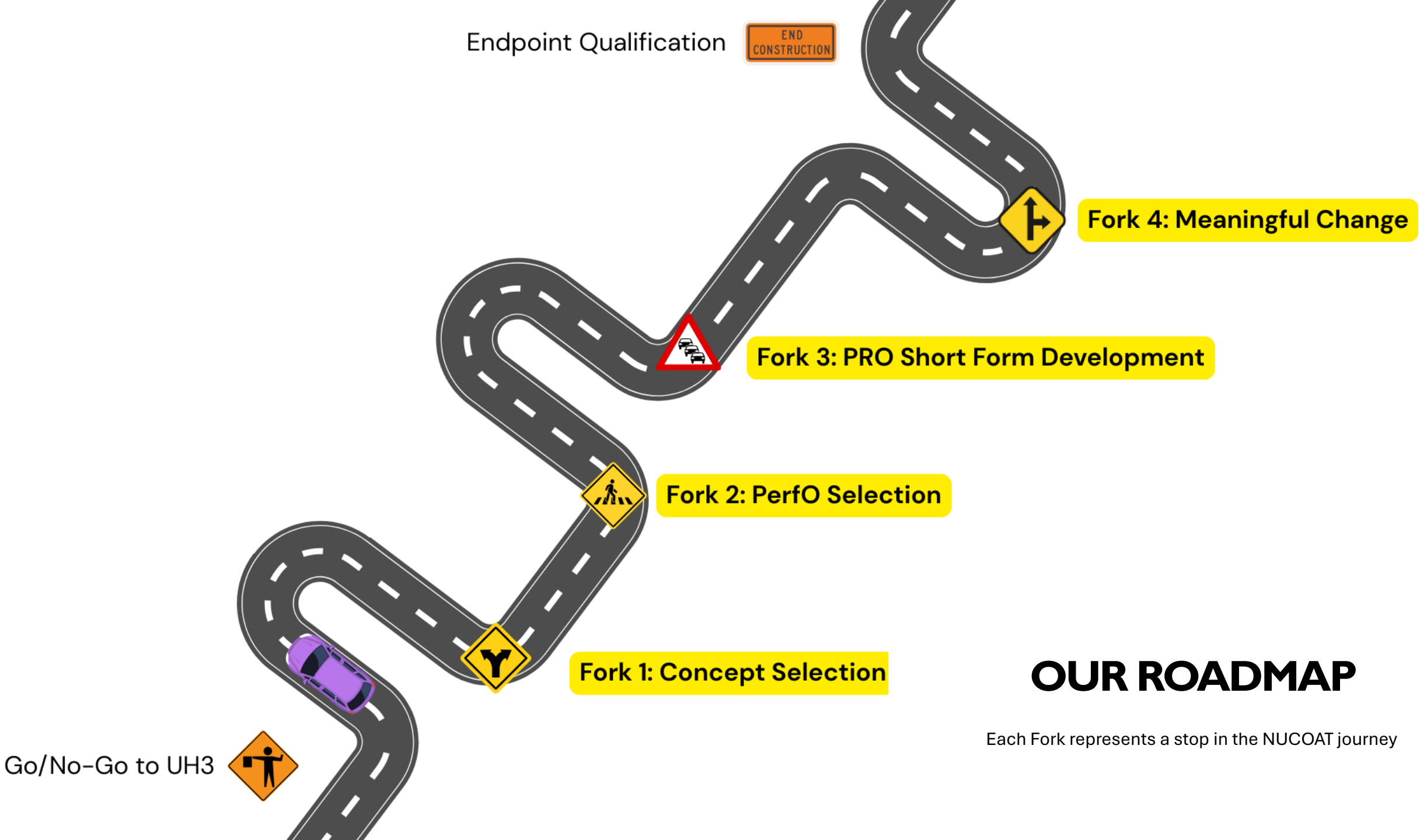
- Polling at each Fork
- Discuss with neighbors
- Hear what NUCOAT did and why
- Moderated by Maja Kuharic, PhD, Assistant Professor, Northwestern University Feinberg School of Medicine, Department of Medical Social Sciences

Speakers

- Robyn Bent, MS, RN, Director, Patient-Focused Drug Development (PFDD), FDA Center for Drug Evaluation and Research (CDER)
- David Cella, PhD, NUCOAT PI; Professor Emeritus, Northwestern University Feinberg School of Medicine, Department of Medical Social Sciences
- Courtney Hurt, MSW, NUCOAT PM; Senior Project Manager, Northwestern University Feinberg School of Medicine, Department of Medical Social Sciences

OUR ROADMAP

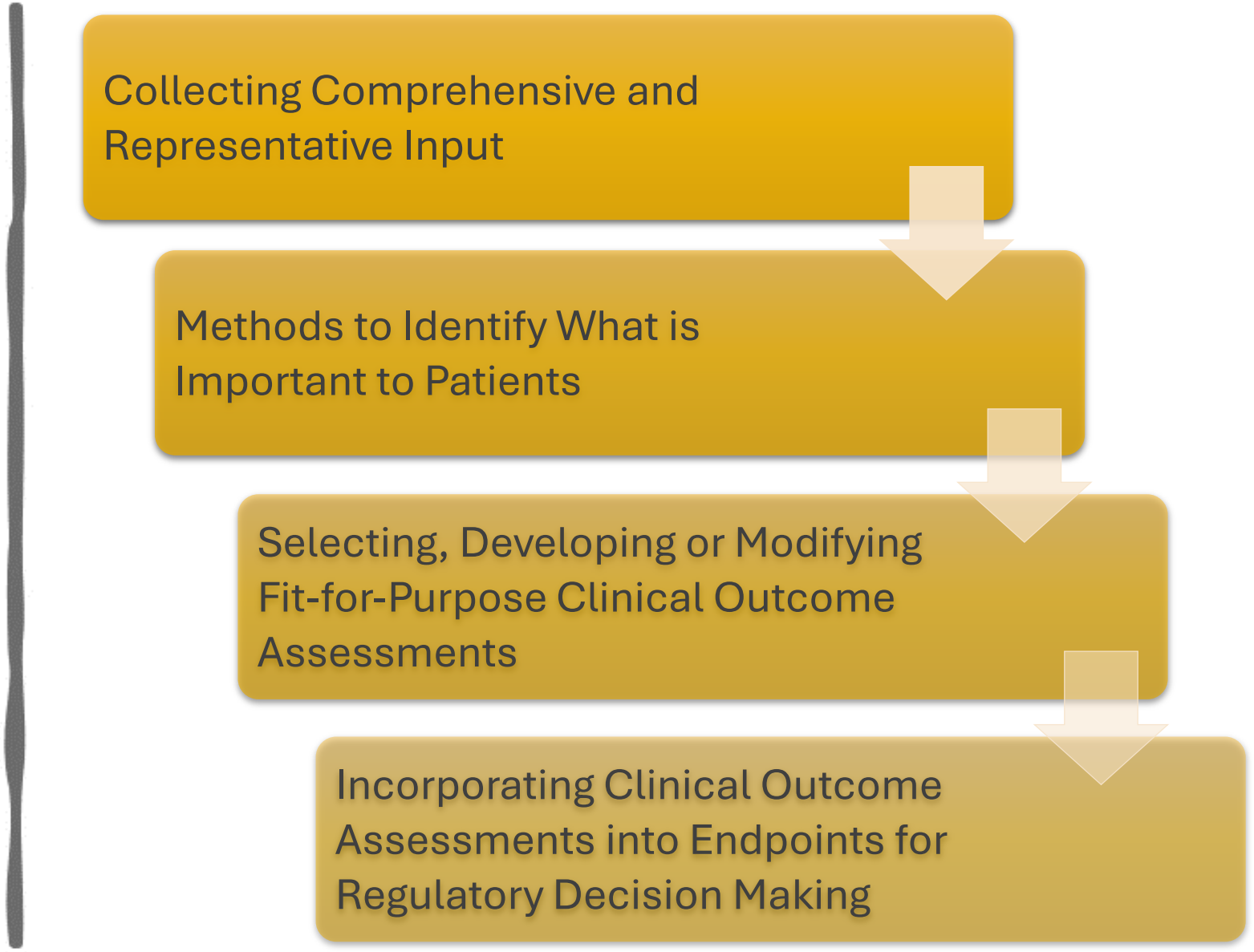
Each Fork represents a stop in the NUCOAT journey



PFDD GUIDANCE & PILOT GRANT PROGRAM

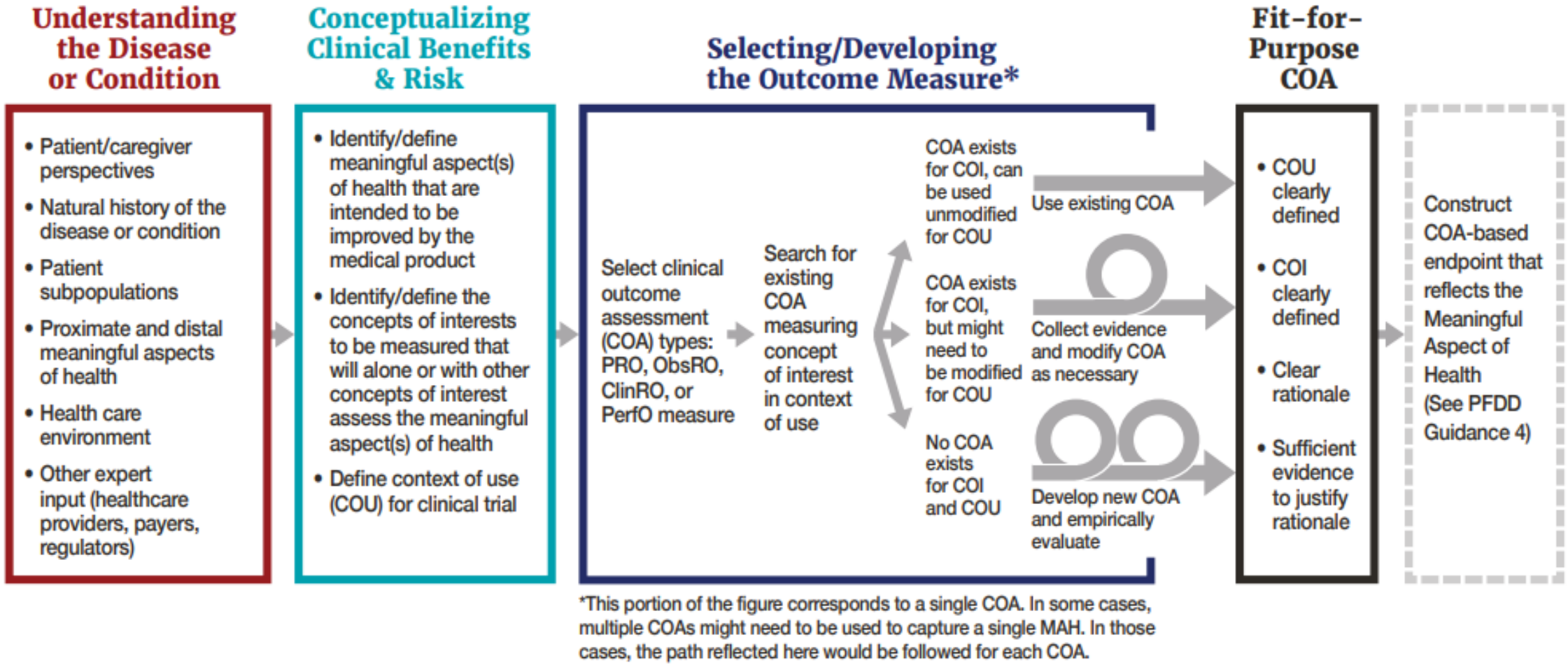
Robyn Bent, RN, MS
Director, PFDD, FDA CDER

PFDD METHODOLOGIC GUIDANCE SERIES



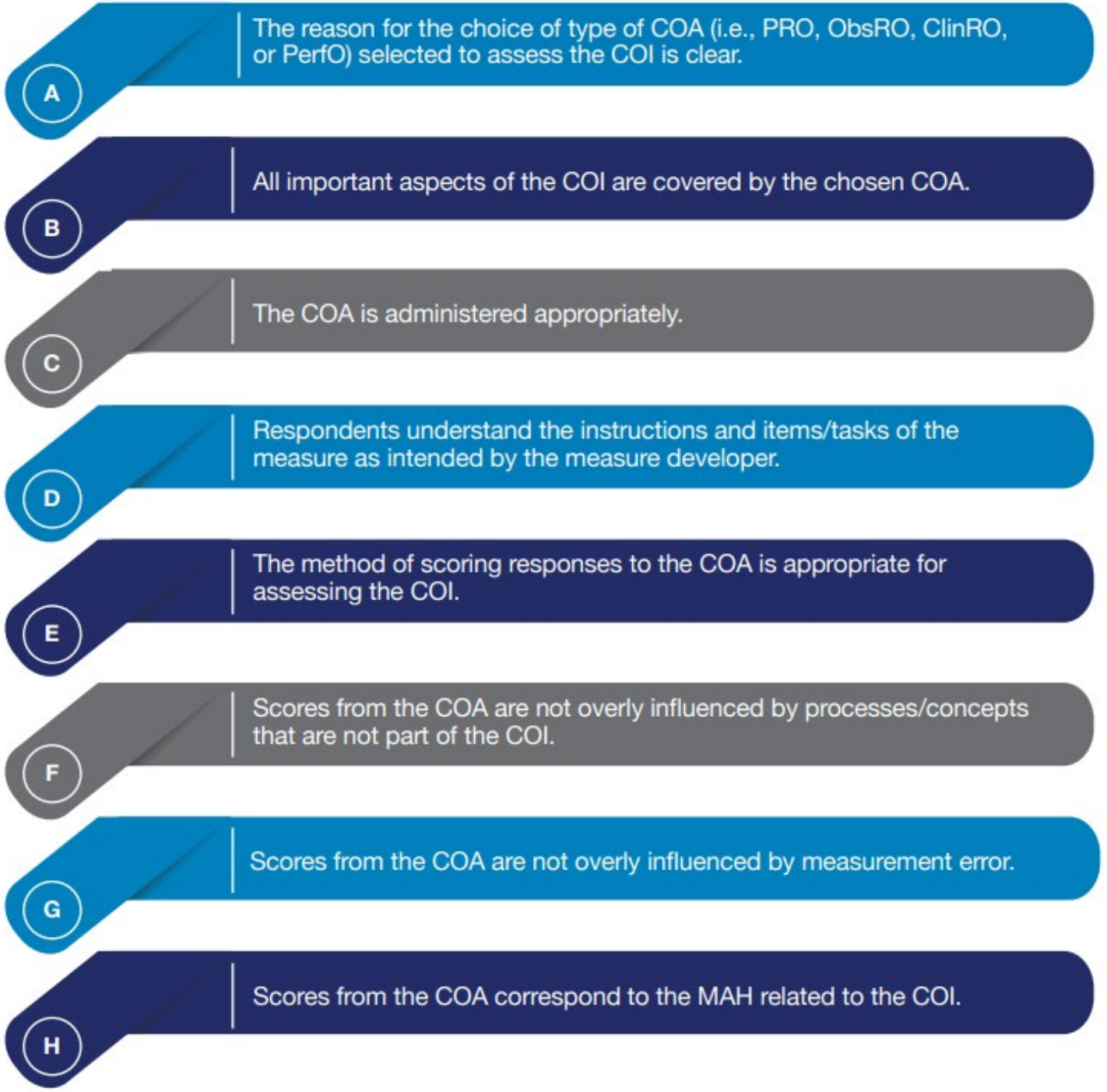
https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

ROADMAP FOR DEVELOPING A FIT-FOR-PURPOSE, PATIENT-FOCUSED COA



*This portion of the figure corresponds to a single COA. In some cases, multiple COAs might need to be used to capture a single MAH. In those cases, the path reflected here would be followed for each COA.

8 EVIDENCE-BASED CONSIDERATIONS FOR SUPPORTING A COA AS FIT-FOR-PURPOSE



NUCOAT PROJECT

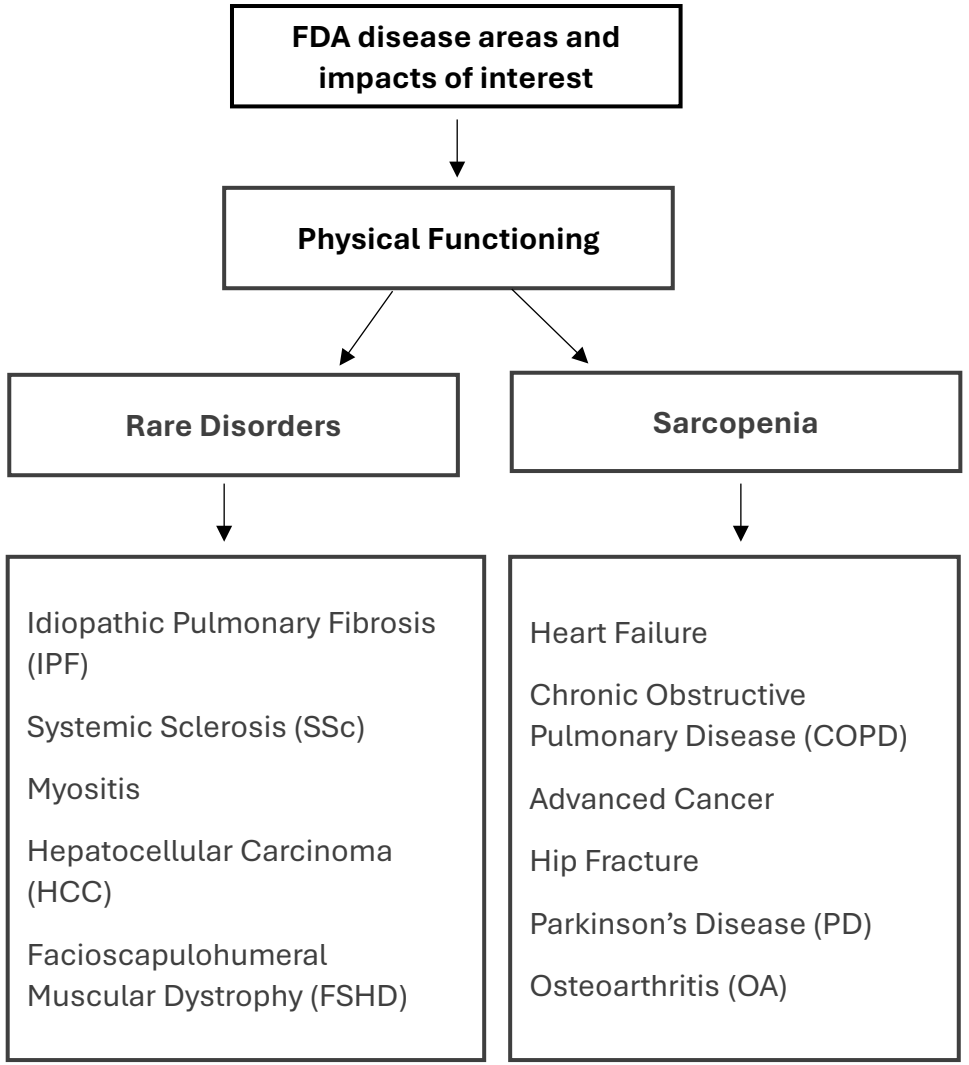
- Pilot FDA cooperative agreement program to *support the development of a publicly available standard core set(s) and their related endpoints for specific disease indications*
- Northwestern University proposed developing PROs and PerfOs measuring disease impacts on physical function
  - UG3: collaborative condition selection + gap analysis
  - UH3: COA development and validation

FORKS IN THE ROAD

CHARTING A COURSE

FORKS IN THE ROAD

- UG3: Collaborated to identify 12 candidate rare diseases and sarcopenia comorbid conditions
  - Literature review
  - Gap analyses
  - Patient interviews
  - Stakeholder feedback
  - Feasibility assessments



CHARTING A COURSE

- **3 rare conditions:** Idiopathic pulmonary fibrosis (IPF); Systemic sclerosis, (scleroderma, or SSc), myositis
- **1 common condition:** primary sarcopenia

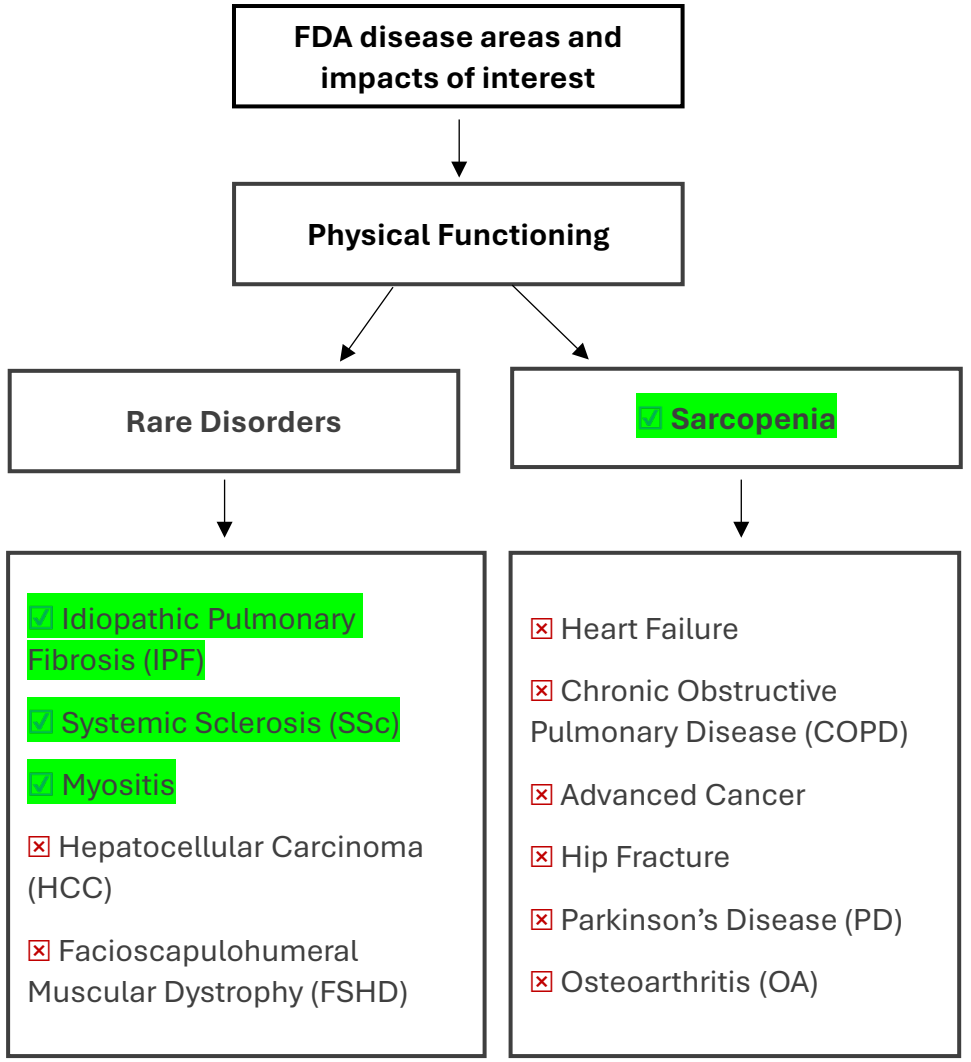
FORKS IN THE ROAD

These conditions met the criteria outlined in the RFA:

☑ Chronic, symptomatic, or affect functioning and activities of daily living

☑ Represent a broad range: size of the affected population, including common conditions experienced by large numbers of patients and rare diseases that affect much smaller patient populations

☑ Impacts that are relevant to patients' experience across a range of disease areas



PROJECT OVERVIEW, FORKS 1 & 2

Courtney Hurt, MSW

Senior Project Manager, Northwestern University

FORKS IN THE ROAD

PROJECT OVERVIEW

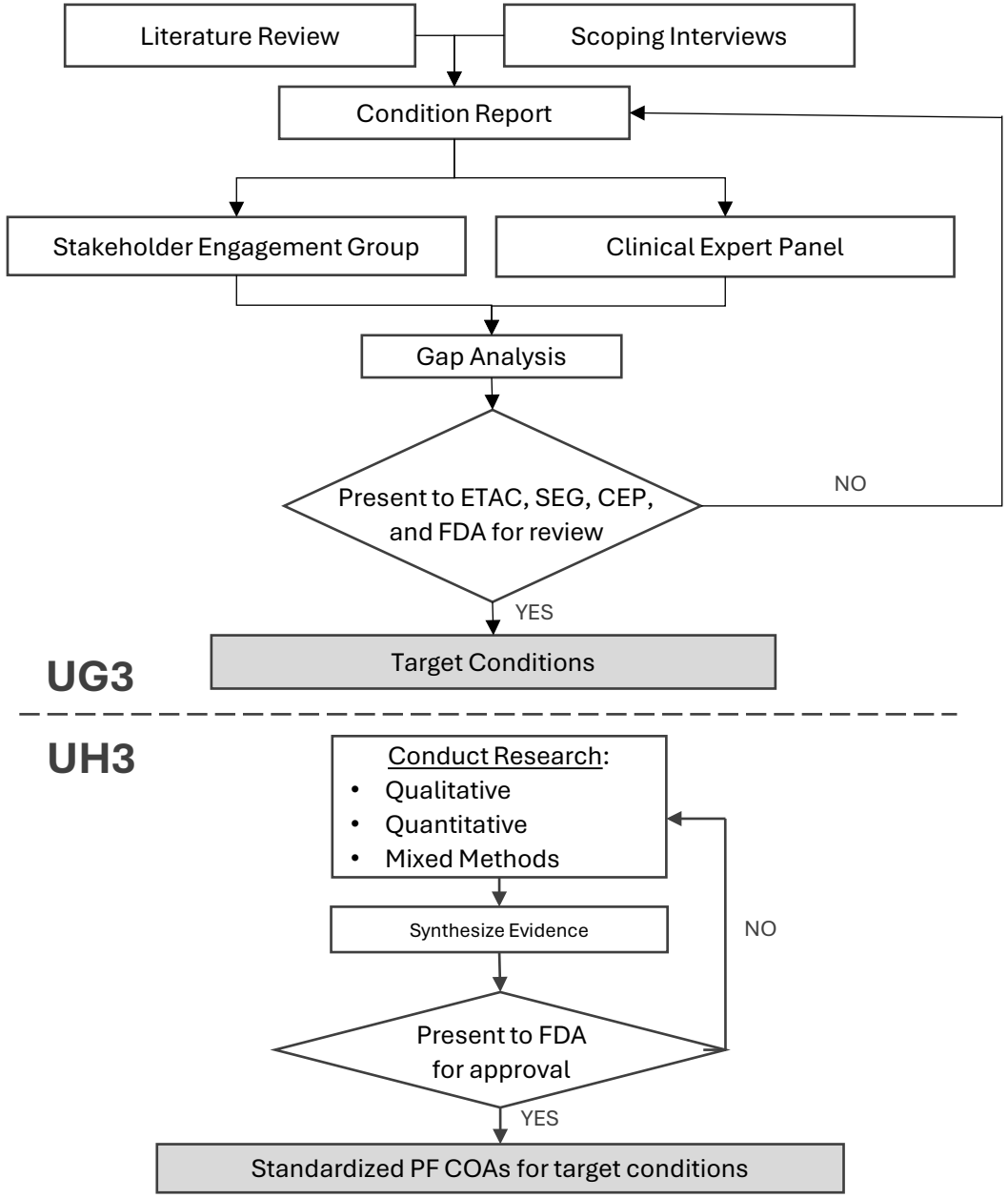
- UG3 phase (2 years) + UH3 phase (3 years) + NCE (1 year)

AT A GLANCE

UG3 – Define & Select: Landscape review, stakeholder review, gap analysis → target conditions

UH3 – Execute & Validate: Qualitative + quantitative studies, evidence synthesis → standardized PF COAs

Consultation throughout: ETAC, SEG, CEP, & FDA

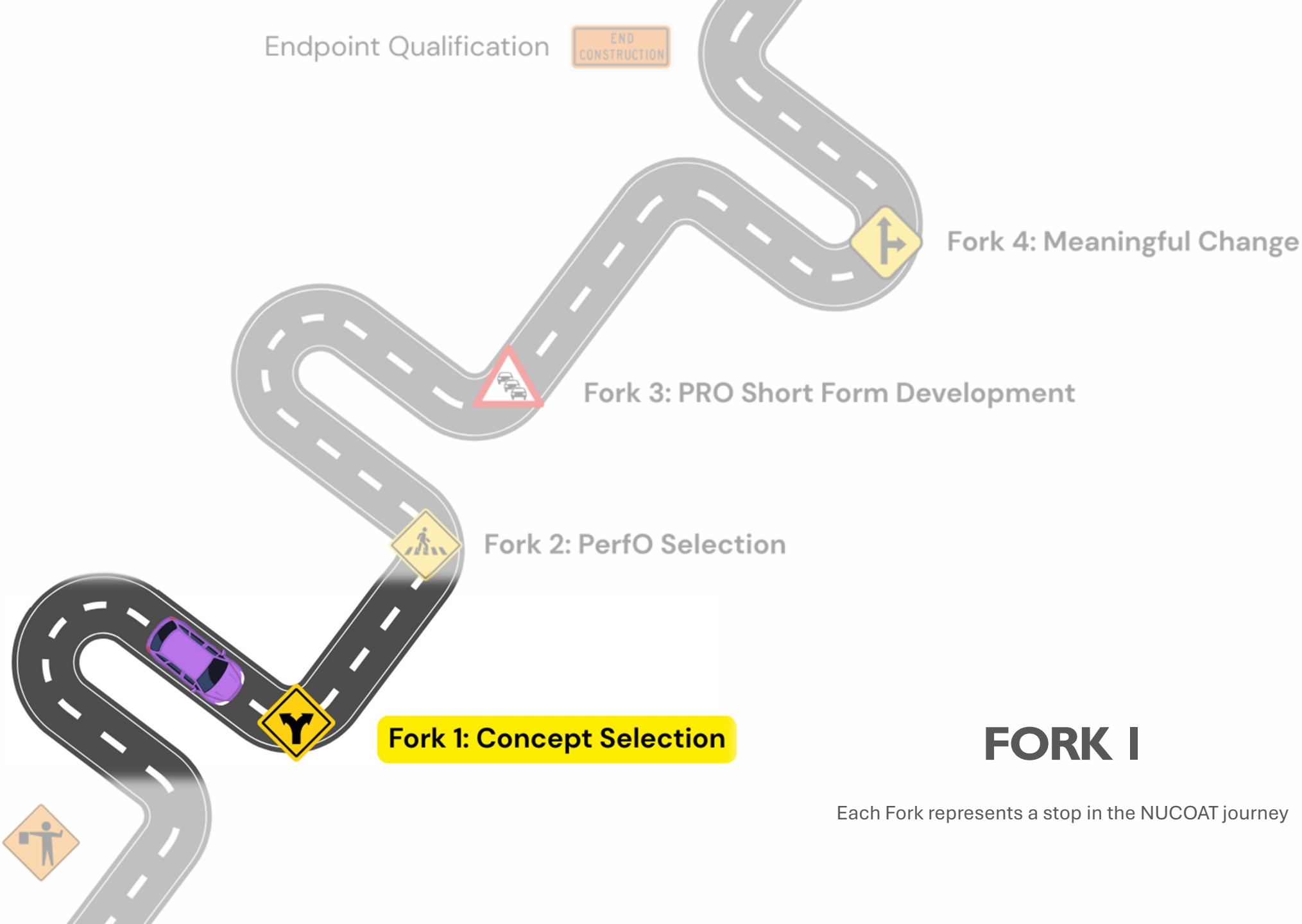


CONCEPT SELECTION

- 54 concept elicitation interviews → 62 unique concepts
- Concepts were prioritized:
  - Frequency of report
  - 0-10 importance to HRQoL
  - Presence across conditions
- All prioritized concepts were mapped to PerfOs and items in the PROMIS PF v2.0 Item Bank

Domain	Concept	IPF	SSc	Myo	Sarc
Mobility and Physical Activity	Walking	X	X	X	X
	Climbing stairs	X	X	X	X
	Descending stairs			X	X
	Lifestyle physical activities	X	X	X	X
	Standing	X	X	X	X
	Balance	X	X		X
	Running / jogging	X	X	X	
	Getting into or out of a car		X	X	
	Getting up from the floor	X	X	X	
I / ADLs	Heavy household chores / Yardwork	X	X	X	X
	Shopping	X	X	X	X
	Getting dressed		X	X	X
	Carrying groceries or heavy objects	X	X	X	X
	Washing, bathing, showering	X	X	X	X
	Washing / styling hair		X	X	X
Upper Extremity and Dexterity	Reaching overhead	X	X	X	X
	Opening jars, cans, bottles		X		X
	Grasping and holding objects		X		X
	Manipulating small objects		X		X
	Reaching down low		X		X
Central / Axial	Picking up objects from the floor	X	X	X	X
	Bending, kneeling, or stooping	X	X		X
	Standing from a seated position			X	X

FORKS IN THE ROAD



FORK 1

Each Fork represents a stop in the NUCOAT journey

FORKS IN THE ROAD

FORK 1: CONCEPT SELECTION

You've completed concept elicitation interviews to identify PF concepts across multiple rare disease populations and sarcopenia.

Upper extremity concepts seem to mostly be specific to dexterity and strength, particularly in 2 of the 4 conditions of interest.

FDA flags that more upper extremity content could be important — particularly for patients who progressively lose mobility.

What do you do?

A) Add more upper extremity-specific items to address FDA's suggestion

B) Maintain content driven by your data; document and defend your rationale

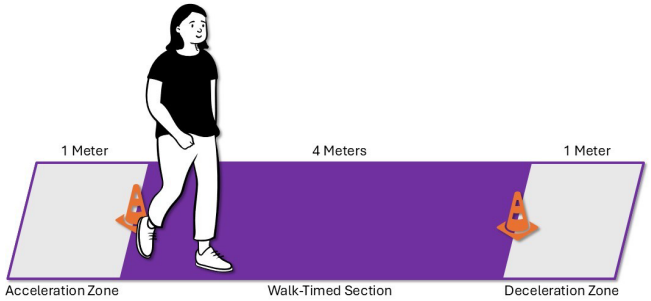
Let your data lead, then document the rationale clearly so the FDA can follow it and react.

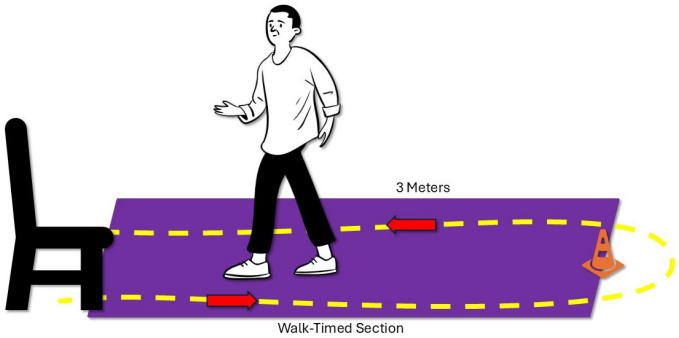
ITEM TRACKING MATRIX

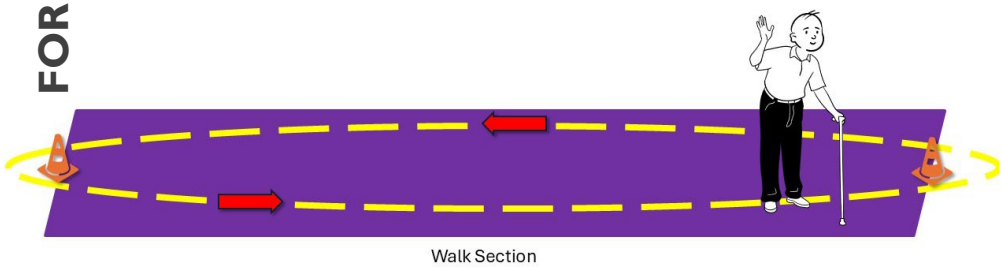
Concept	Item	Round 1 (Qual review)	Round 2 (Quant review)	Round 3 (Stakeholder and FDA review)	Round 4 (Cognitive debriefing)
Walking	Item ID…	**DROP** (Conceptually redundant to preferred item)	--	--	--
I/ADLs	Item ID…	**RETAIN**	**DROP** (Known issues with DIF)	--	--
I/ADLs	PFA17	**RETAIN**	**RETAIN**	**RETAIN**	**RETAIN**
Balance	PFA31r1	--	--	**NEW** (Stakeholder feedback)	**RETAIN**
Exercise	PFA2	--	--	--	**NEW** (Debriefing results)
		112 → 49	**49 → 28**	**28 → 30**	**30 → 31**

PERFO SELECTION

FORKS IN THE ROAD

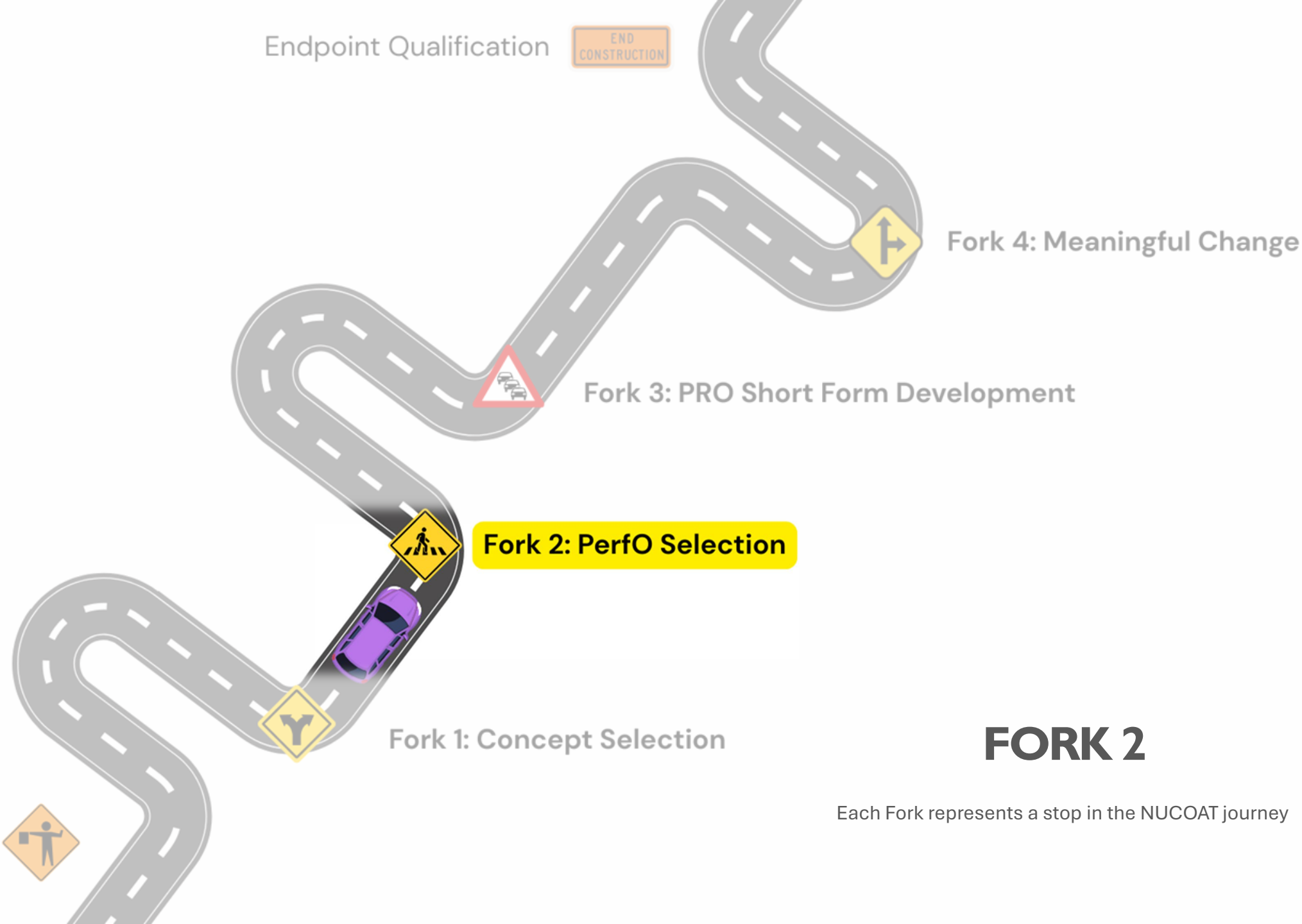






	Mobility / Physical Activity	I / ADLs	Upper Extremity / Dexterity	Central / Axial
SPPB Gait Speed	●			
SPPB Balance	●	●		
SPPB Chair Stand	●			●
Timed Up and Go	●			●
Grip strength		●	●	
9-Hole Pegboard		●	●	
6-Minute Walk	●	●		

FORKS IN THE ROAD



FORK 2

Each Fork represents a stop in the NUCOAT journey

FORK 2: PERFO SELECTION

6-Minute Walk Test emerges as an important measure of endurance for patients with these conditions, however the FDA raises concerns about using it in the NUCOAT study, flagging potential for inconsistent administration.

Additionally, you have concerns about feasibility of the test, given the recommended 30-meter walking course.

What do you do?

A) Modify the test with a shorter course and develop a standardized administration protocol

B) Try to identify alternative PerfOs to replace the 6MWT

Ensure your PerfO validity and reliability evidence is collected in a detailed, highly standardized way.

AVOIDING POTHOLES

- Cooperative agreement allowed for iterative feasibility discussions and a better understanding of FDA criteria
- FDA expects standardization and strong justification for all data collection, study design, and COA selection decisions:
  - Incorporating existing test instructions into our standardized testing protocol
  - Measure assistive device use at every time point
  - Clear, well-vetted patient-facing materials for remote assessments
  - Demonstrated infeasibility of remote grip strength and 6MWT administration

FORKS 3 & 4

David Cella, PhD

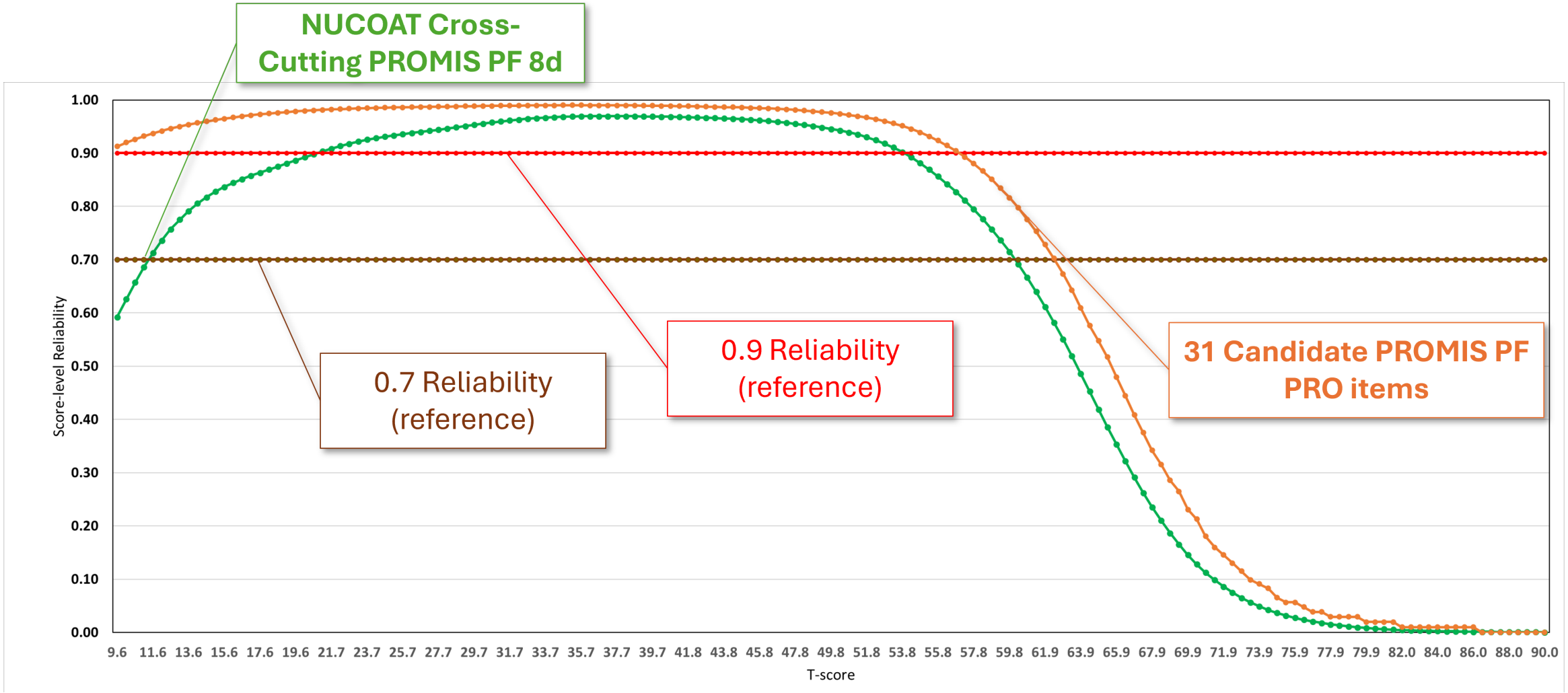
Professor Emeritus, Northwestern University

VALIDATION STUDY

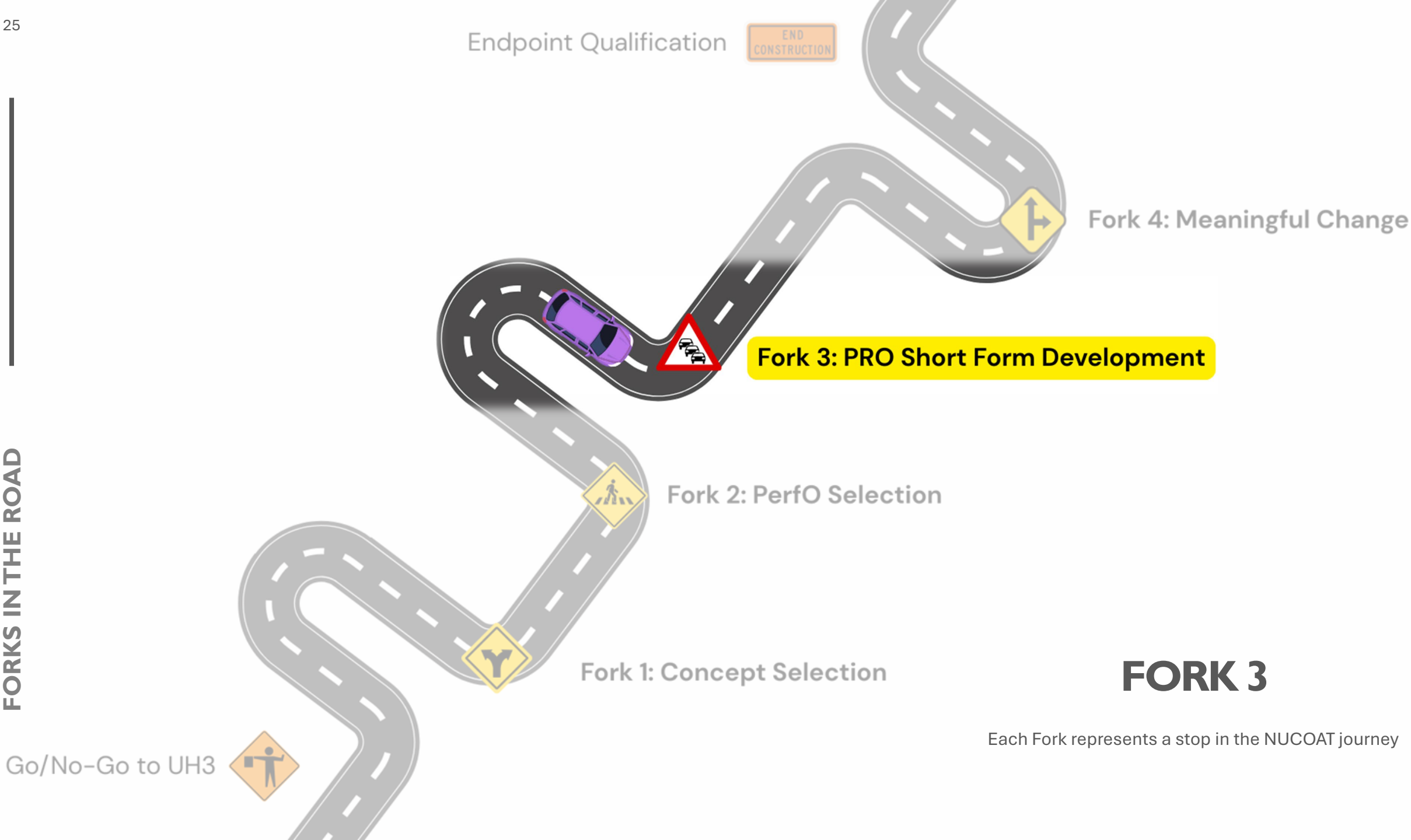
- Target N = 240
  - 237 completed the study (95% retention rate)
    - 18 were remote
- Timepoints: Baseline and 16-Week
  - 45 completed retest within 2 weeks of BL
- 7 PerfOs
  - Relevance to daily life
  - Instruction clarity and comprehension
  - Difficulty compared to important daily activities
- 31 candidate PROMIS PF items
  - Too long (patient burden)

PRO SHORT FORM DEVELOPMENT

FORKS IN THE ROAD



FORKS IN THE ROAD



FORK 3

Each Fork represents a stop in the NUCOAT journey

FORK 3: PRO SHORT FORM DEVELOPMENT

After concept elicitation and psychometric validation, you still have a large pool of candidate items.

You need to create a PRO short form so it is feasible for use in trials.

What are your next steps?

A) The item tracking matrix is complete based on qualitative data analysis. Now it's time to apply standard psychometric criteria and let the statistics drive further reduction.

B) Continue the item tracking matrix by documenting conceptual, clinical, and statistical rationale for every retention and elimination decision, revisiting the qualitative data as needed.

Item tracking doesn't end after cognitive debriefing. Use the matrix for quantitative data to tell the full story of your measure's development from beginning to end.

ITEM TRACKING MATRIX

FORKS IN THE ROAD

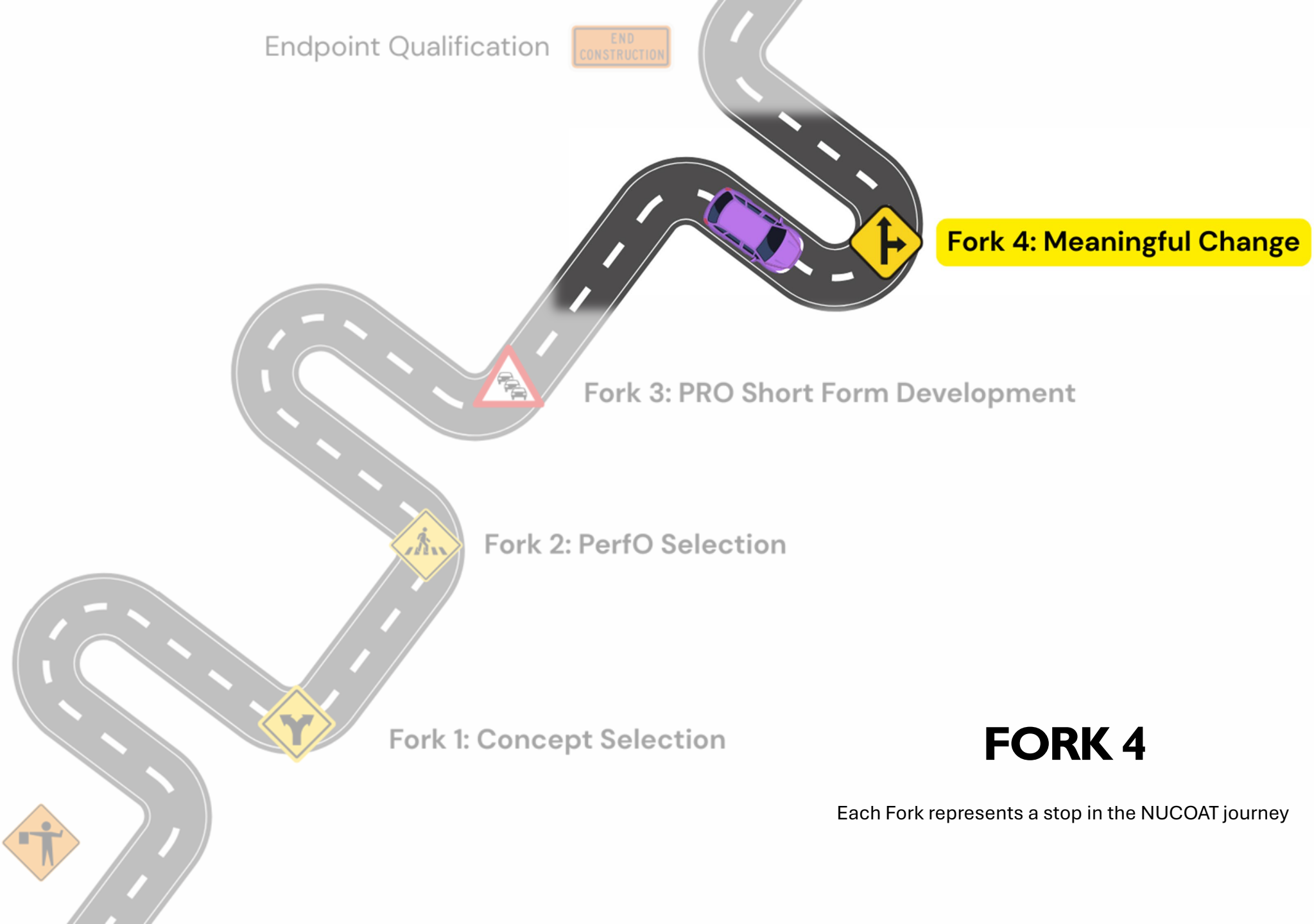
Concept	Item	Round 1 (Qual review)	Round 2 (Quant review)	Round 3 (Stakeholder and FDA review)	Round 4 (Cognitive debriefing)	Round 5 (Qual review)	Round 6 (Quant review)	Round 7 (Qual + Quant)	Round 8 (NUCOAT + FDA)
Balance	**PFC39**	--	--	**NEW**	**RETAIN**	**DROP** (disease specific)	**--**	**--**	**--**
ADLs	**PFA17**	**RETAIN**	**RETAIN**	**RETAIN**	**RETAIN**	**RETAIN**	**DROP** (lower information + precision)	**--**	**--**
Exercise	**PFA2**	--	--	--	**NEW**	**RETAIN**	**RETAIN**	**RETAIN**	**DROP** (less universal applicability; better higher function items)
		112 → 49	**49 → 28**	**28 → 30**	**30 → 31**	**31 → 21**	**21 → 18**	**18 → 10-12**	**8 core cross-cutting items**

PERFO FINALIZATION

- Clear instructions:
  - Participants: 99-100%
  - Administrator: 97-100%
- Relevant to daily life: 97-100%
- Aligned difficulty level: ≥50%

	Sarc	Myo	IPF	SSc	Coverage across conditions
SPPB Balance Tests	●	●	●	●	100%
SPPB 4-Meter Gait Speed Test	●	●	●	●	100%
SPPB Chair Stand Test	●	●	●	●	100%
Timed Up and Go	●	●	●	●	100%
NIH TB 9-Hole Pegboard Test				●	25%
NIH TB Grip Strength Test			●	●	50%
6-Minute Walk Test	●	●	●	●	100%

FORKS IN THE ROAD



FORK 4

Each Fork represents a stop in the NUCOAT journey

FORK 4: MEANINGFUL CHANGE

Estimates of meaningful change are a regulatory priority and are increasingly expected.

But in your observational validation study, your population did not show much change.

You have a limited quantitative signal on what could constitute meaningful change from earlier research.

What do you do?

A) Triangulate — bring together the qualitative support and available quantitative change information to make a preliminary case, even if incomplete

B) Do more research before estimating meaningful change. Meaningful change cannot be adequately characterized at this stage and needs further study.

Don’t let the perfect be the enemy of the good. Build and develop your qualitative foundation while gathering accumulated evidence. Like validity, meaningful change is not a binary product of an instrument.

FDA PFDD guidance paves the road to develop a fit-for-purpose COA. You decide the best route to get there.

But share your trip log once you arrive. FDA will want to know why you chose your path.

Endpoint Qualification

Fork 4: Meaningful Change

Don't wait for perfect change data. Start building your qualitative foundation early.

Fork 3: PRO Short Form Development

Item tracking doesn't end after cognitive debriefing. Use the item tracking matrix to tell the full story of your measure's development.

Fork 2: PerfO Selection

Ensure your PerfO validity and reliability evidence is collected in a detailed, highly standardized way.

Fork 1: Concept Selection

Let your data lead, then document the path clearly so the FDA can follow it.

Go/No-Go to UH3

THANK YOU AND Q&A

Maja Kuharic, PhD

Assistant Professor, Northwestern University