Technology Enabled Clinical Endpoint Innovation

Foundational Concepts and Pathway for Development

Advances in Clinical Trial Technology: Impact on Methodology and Signal Detection

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The views expressed are those of the author, and do not necessarily represent a Janssen position

Outline

- Key Elements / Terminology
  - Treatment benefit, Outcome assessment, Endpoint
- Key Concepts and Principles of Assessments
  - Assessment-related Concepts
  - Interpretability
- Outcome Assessment Evaluation and Performance
  - Reliability, Responsiveness, Interpretation
  - Context of Use
- Good Outcome Assessment Development Principles
- CTTI Guide to Endpoint Development
  - Steps to Formulate Objective
  - Elements of Development Process

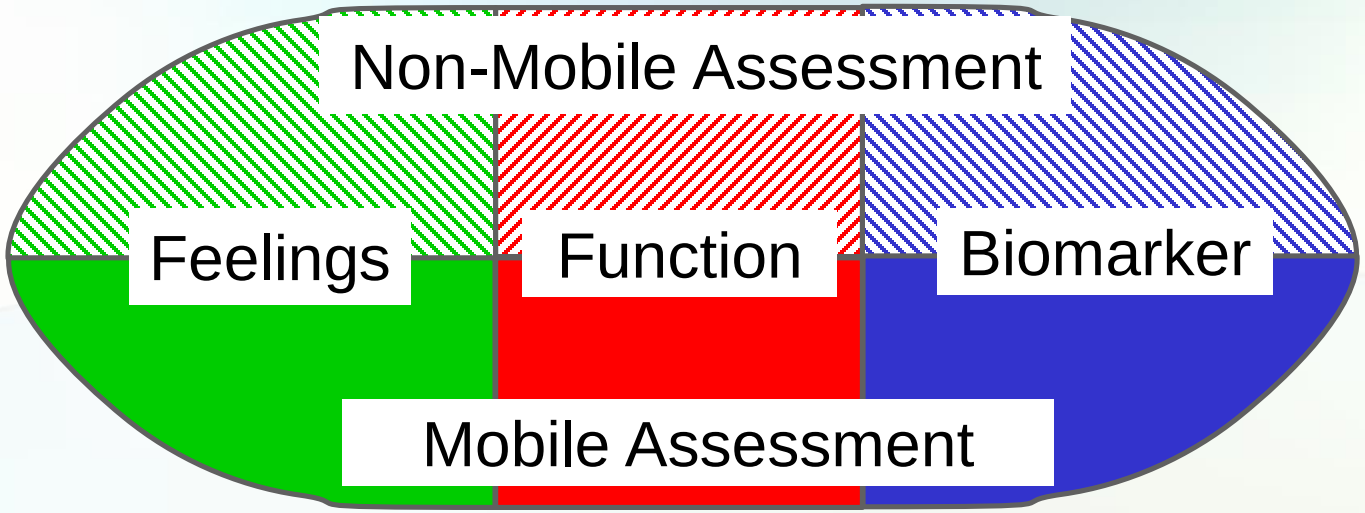
Efficacy: Treatment Benefit

- A favorable and meaningful effect on an aspect of a patient's life
- How a patient feels, functions, or survives
- Feels
  - A patient's physical sensation or perceived mental state related to health within typical 'daily' life, e.g., Pain, Severely low mood
  - Only PROs can assess
- Functions
  - A patient's ability to perform an activity that is a meaningful part of typical 'daily' life
  - Not ability to perform actions not part of usual life, nor low-level motor activity

Outcome Assessments and Endpoints

- Outcome Assessment
  - Evaluation (measurement) of the person's health or health-related state
  - The assessment in isolation is not a study endpoint
- Study Endpoint
  - Defined by
    - A specified outcome assessment,
    - Measured in a specified manner at specified(s) times during a study
    - Analyzed in a specified way
  - Regulatory decisions require "reliable and well defined"endpoints (including interpretability)
  - The interpretability and statistical properties of the endpoint are affected by the specified elements

The Universe of Outcome Assessments



Feelings Assessments:
PRO only

Function Assessments:
Performance Observations – PerfO
Clinician Reported – ClinRO
Observer Reported – ObsRO
PRO

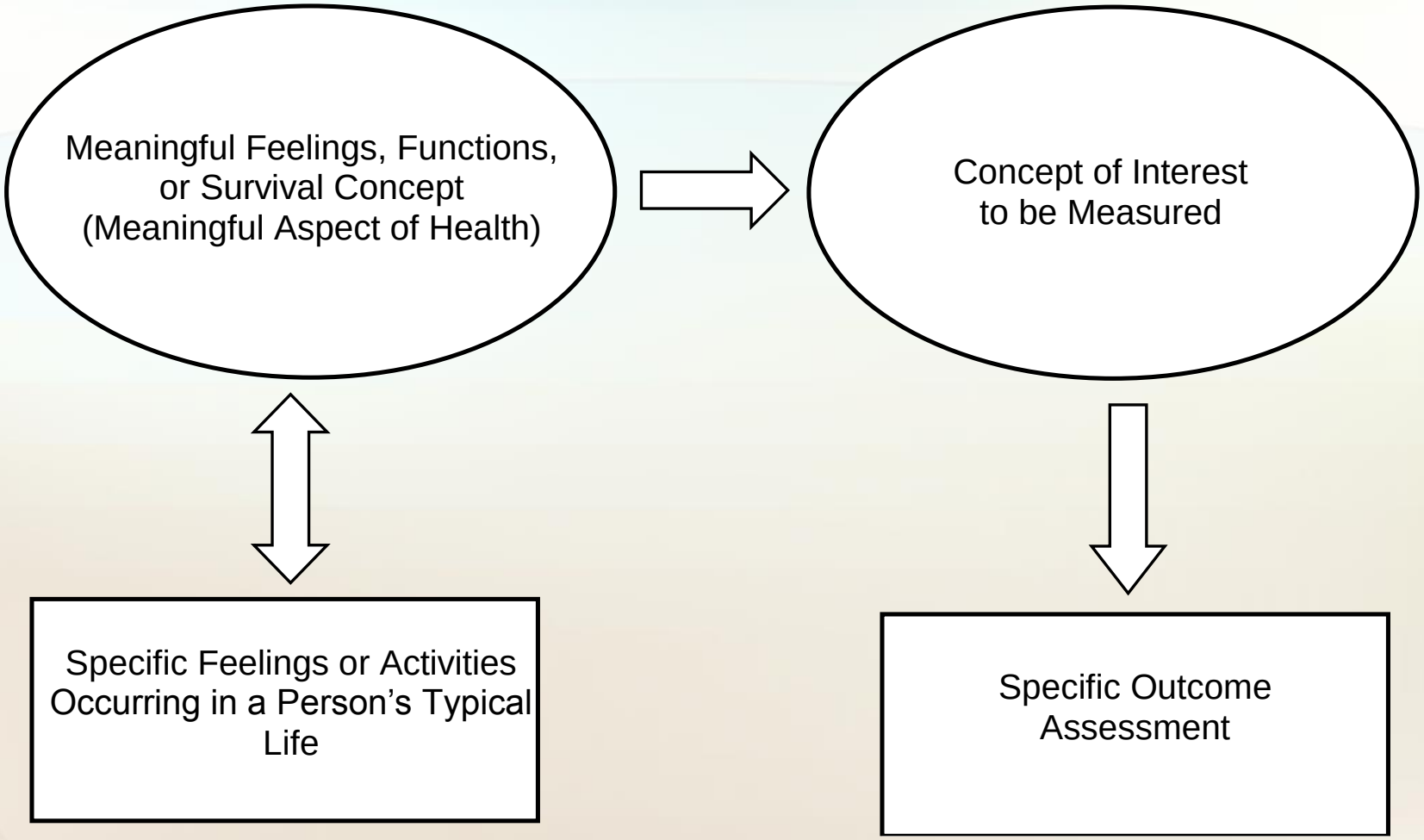
Many endpoints already exist & accepted (e.g., FDA compendium)

Why create a new assessment / endpoint?

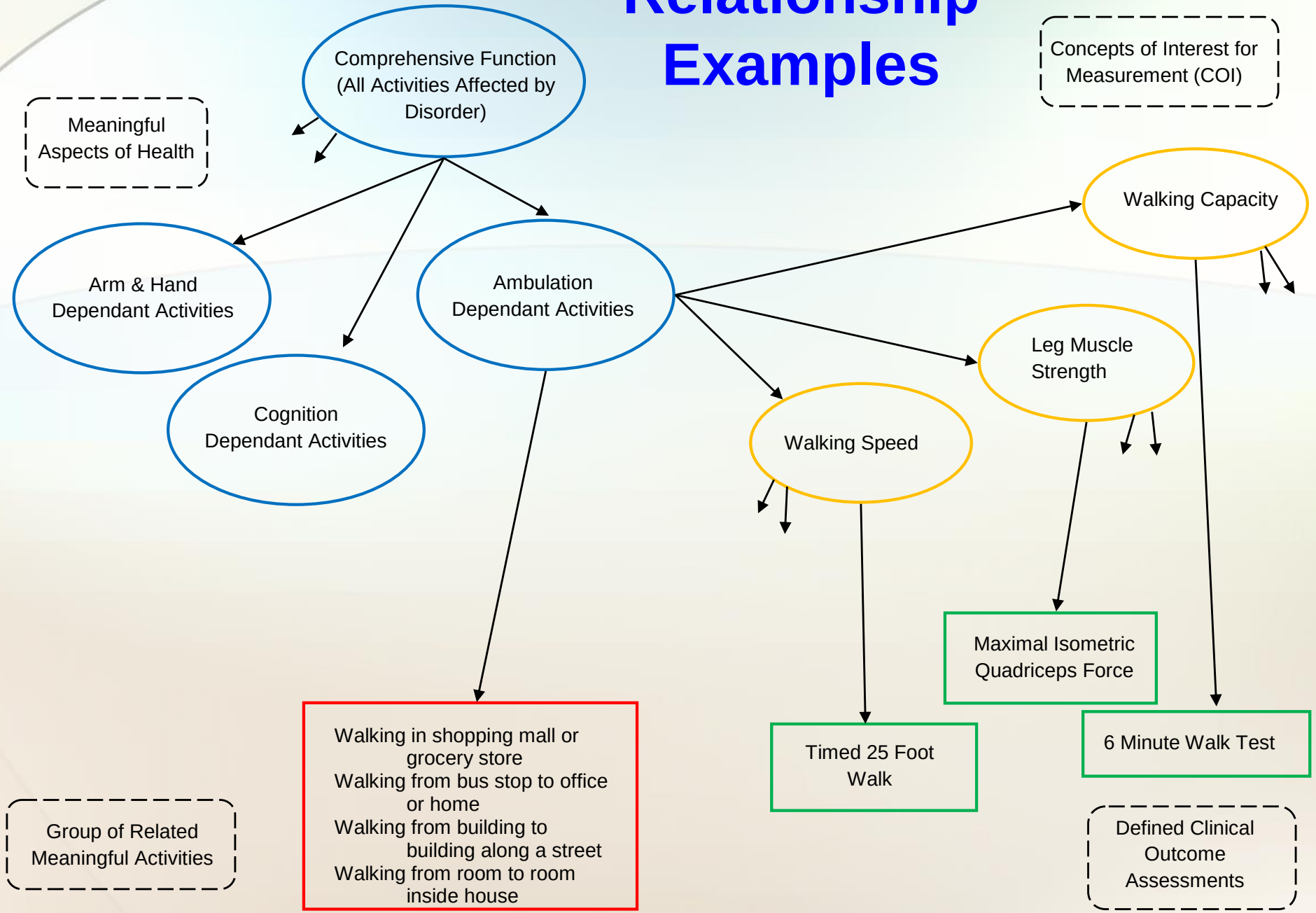
Overarching Concepts and Relationships for Assessments

- Meaningful Health Aspect (MHA)
  - An aspect of feels or functions as occurs in 'typical' daily life; or survival
  - Identifies the intended Treatment Benefit
- Concept of Interest for Measurement (COI)
  - Concept thought related to the MHA and is measurable OR is the MHA itself (direct measurement)
  - Clinical COI - often a more basic (simpler) element of the MHA
  - Biomarker COI – often thought causative of the MHA
- Assessment = Practical expression of the COI enabling measurement (an operationalized approach to the COI)

Overarching Concepts and Relationships



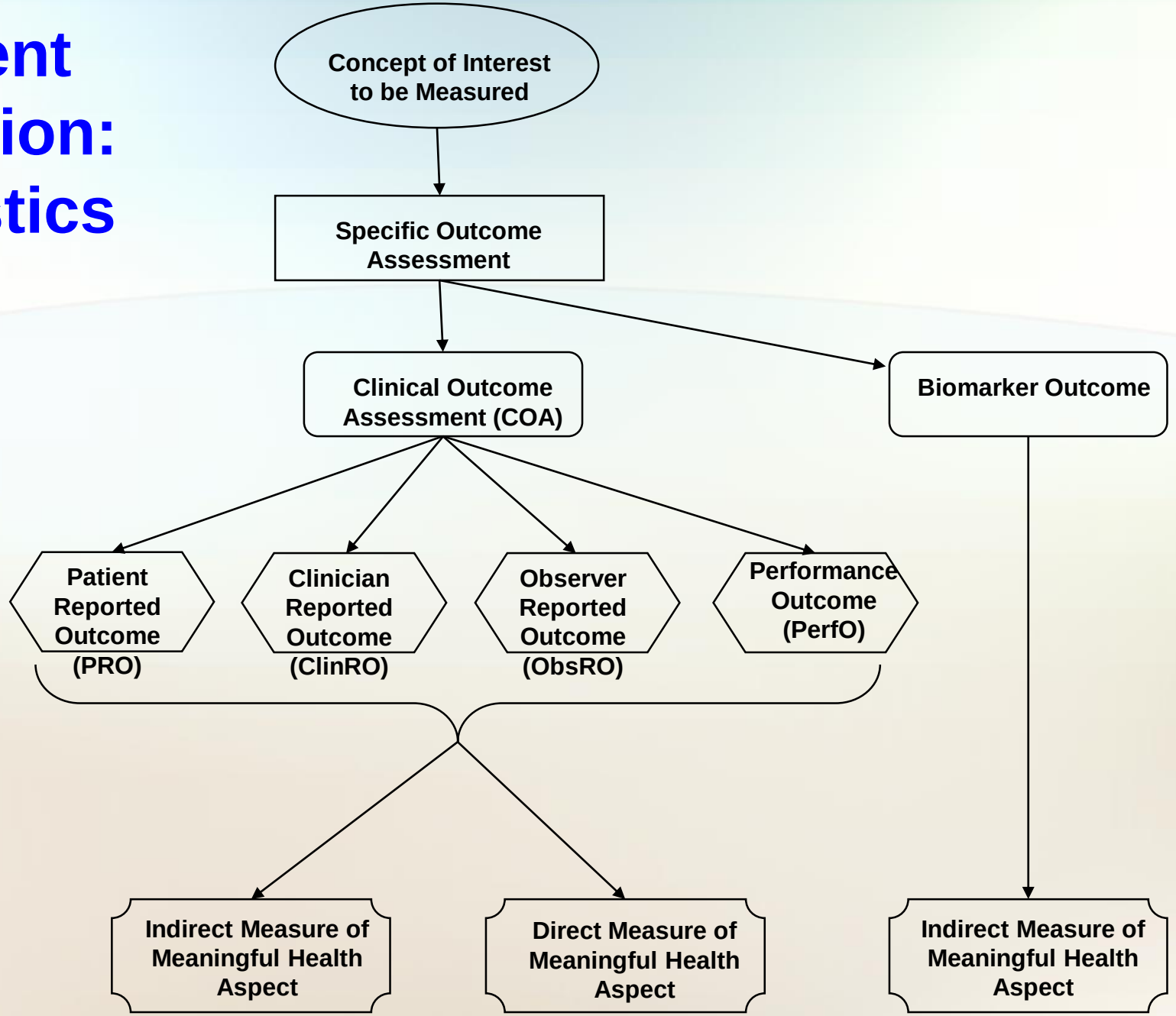
Relationship Examples



Two Major Categories of OAs

- Clinical Assessments (COA)
  - Affected by evaluator judgment or patient volition
  - "Clinical" as *term of art* – not general language manner of use
  - Outcome assessment – an assessment used to measure Tx effect in a clinical trial
  - Several types of COA distinguished by 'rater'
    - PRO; ClinRO, ObsRO, PerfO
- Biomarker Assessment
  - Does not rely on judgment or volition
  - An 'analyte' that exists outside of patient choices
- Mobile technology can be used for COA or biomarker

Assessment Categorization: Characteristics



Interpretability of Efficacy Outcomes

- Do differences or changes in the measurement mean something?
  - *To the patient*
  - Efficacy OAs are intended to inform regarding some specific conceptualized meaningful aspect of patient's life
- Why Interpretable?
  - Interpretability of meaning allows **benefit-risk assessment** to be formed
- How to evaluate?
  - Comparison to existing measures of similar intent
  - Comparison to "unvalidated" PRO
  - Consider if intended interpretation is to be broad or narrow (e.g. target very specific function or disease broadly)
- Clinically significant is not identical to statistically significant
  - Meaningfulness of change vs Sensitivity to change

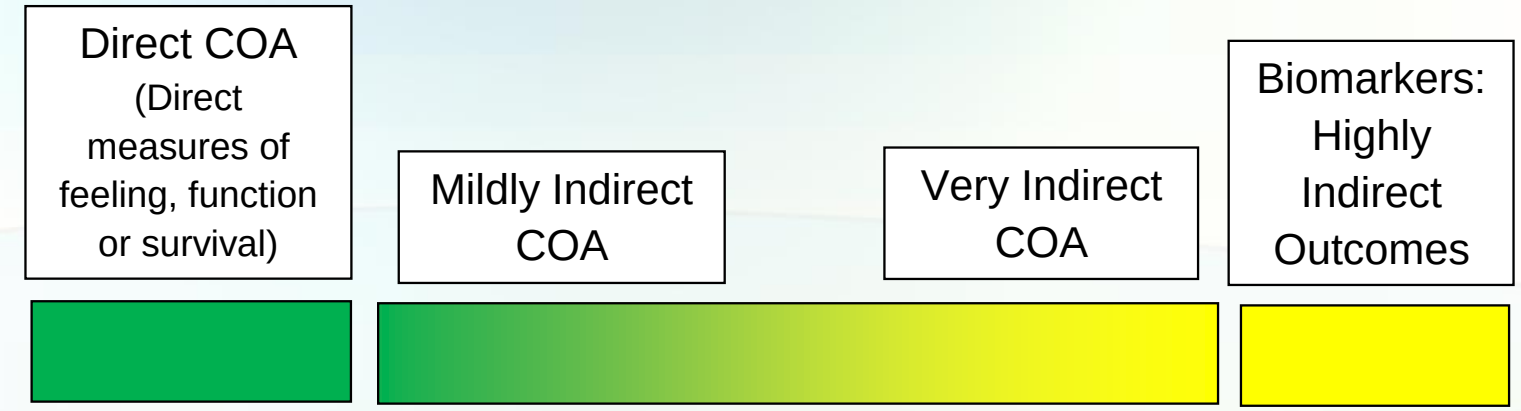
Interpretability: Direct and Indirect OAs

- COA may directly measure the MHA or measure a COI thought to informative of the MHA status
- Direct COAs
  - Generally clear what a difference means to a patient in a 'typical' daily life
- Indirect COAs
  - Meaning to patient of a difference not intrinsically clear
  - Establishing meaning may be difficult, but is important
  - "Indirectness" is a graded characteristic
- Indirect OAs have been often selected over direct OAs
  - Feasibility to measure reliably and interpret

Direct and Indirect OA

- OA can Directly describe meaningful feeling or function or Indirectly reflect it

- Indirectness is a graded characteristic



Brief Pain Inventory
McGill Pain Questionaire
St. George Respiratory Questionaire
Beck Depression Inventory
Epworth Sleepiness Scale

6-Minute Walk Test
PANSS
ALS Functional Rating Scale
Sleep onset (time to)
Visual acuity – ETDRS Scale
BPRS (brief psych rating)
Psoriasis Area and Severity Index
Montgomery-Asberg Depression Scale
Rankin Stroke scale
Pulmonary Function Test (FVC, FEV1)
Ashworth Spasticity Scale
ADAS-COG
SDMT

Serum Cholesterol
HIV Viral Load
Phenylalanine
XRay Feature
HgbA1c
Hgb
MRI Brain Lesion Volume

- Type of evidence and amount of effort to obtain evidence establishing relationships can vary

Overarching Aspects of OA Evaluation

- Content Validity
  - Does the OA actually represent the intended COI?
- Interpretability
  - Does the COI actually reflect the meaningful health aspect?
    - When does the MHA benefit occur relative to when the COI is measured?
    - Important difference between OA reflecting current state of the patient and OA predicting some future state
  - If COI is the exact MHA interpretability is often self-evident

Key Performance Characteristics of the OA

- Reliability
  - Consistency of measurement
    - Within and between patients
    - Between observers (reporters) or study staff
    - Over time
    - Over full range of circumstances intended for use
- Responsiveness (sensitivity)
  - Does the measurement change when the COI changes
- Quantitative interpretation
  - What is a meaningful change
    - Direction: increase may not = decrease
  - Not always self-evident even if the COI = MHA
- Development & evaluation: Relevant to the clinical trials in future Tx development (Context of Use)

Context of Use

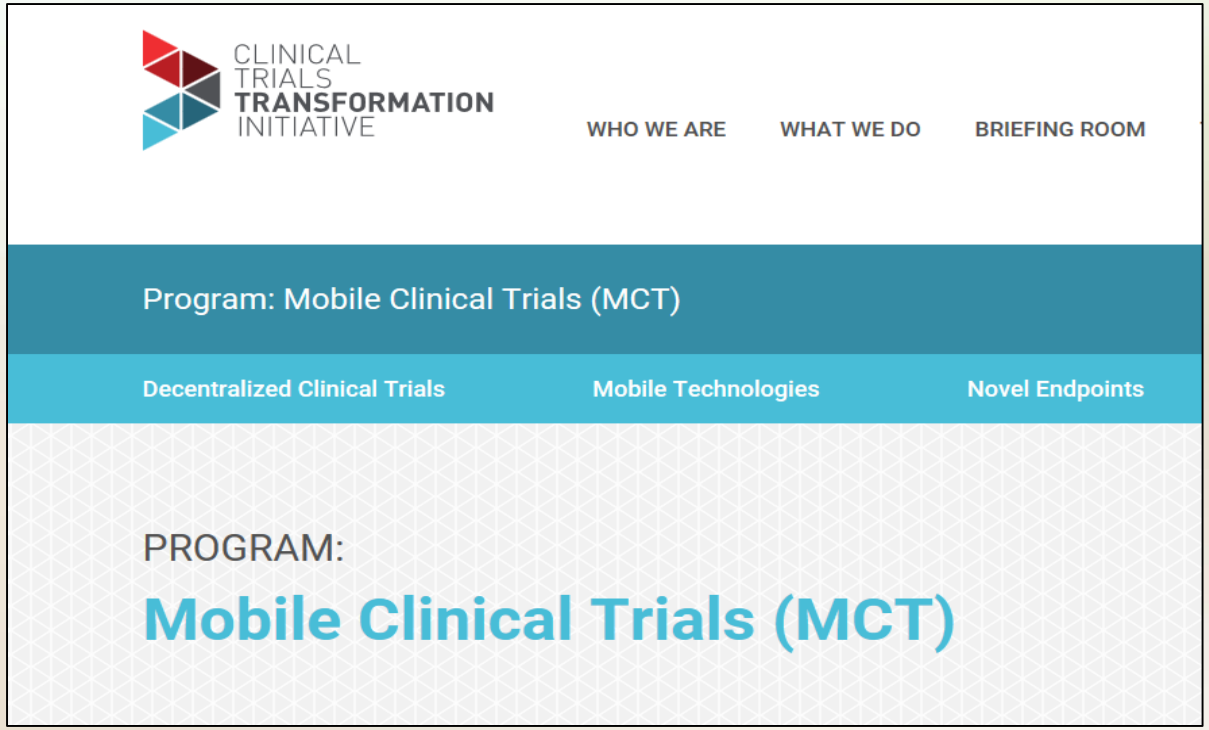
- OA utility varies in different contexts of use
- A comprehensive statement of
  - Circumstances and manner of use
  - Purpose of use in clinical trial
  - How results applied to decision making
- Evidence to justify use should be relevant to the intended COU
- COU includes:
  - Patient population or subpopulation fully specified
  - What is sampled
  - How sample is measured (including study features)
  - When measured
  - How measurements analyzed in an endpoint
  - How interpreted and results applied
    - Endpoint positioning

Good Outcome Assessment Principles

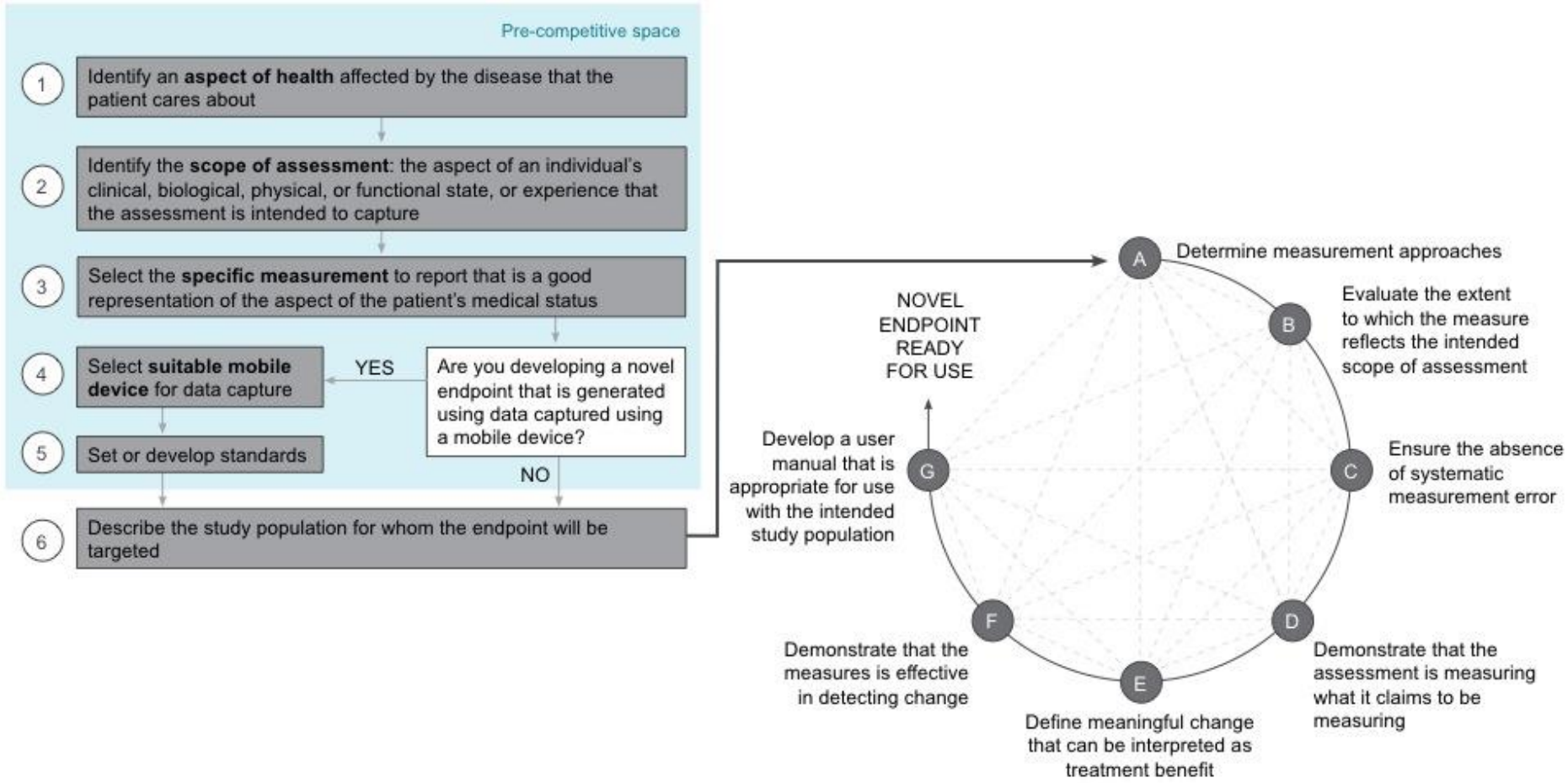
- Define context of use (COU)
- Identify the meaningful health aspect (MHA) that will be affected (treatment benefit)
- Identify (define) the concept of interest for measurement (COI)
- Evaluate the relationship of the MHA to the COI
- Define the OA
- Evaluate content validity of OA
- Evaluate performance characteristics of OA
  - May change with different ways of use in and endpoint
  - Interpretability, sensitivity, reliability
- Re-evaluate intended conclusions/actions based on OA and other parts of COU

Clinical Trials Transformation Initiative: Novel Endpoints Project

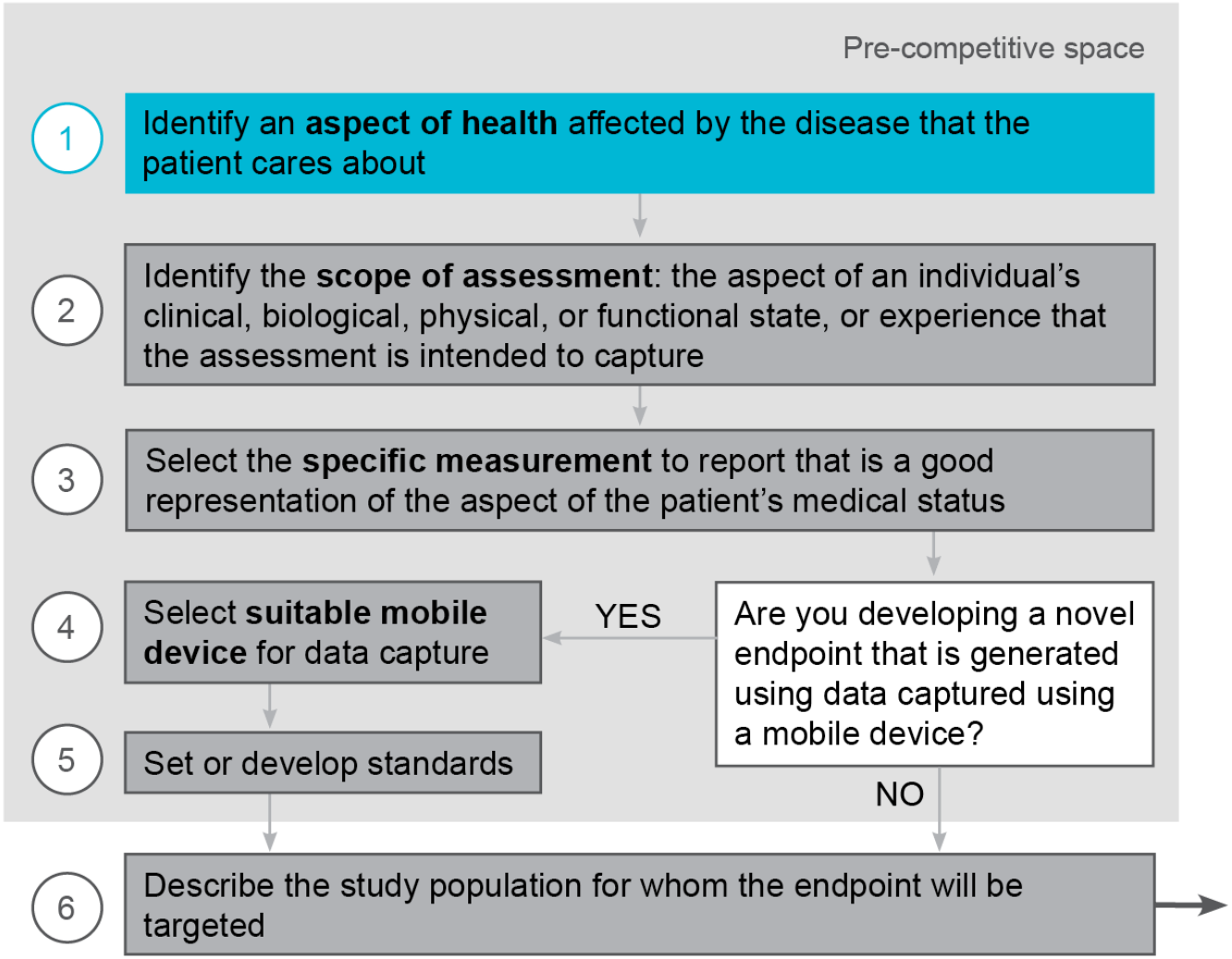
- To promote development of new endpoints for clinical trials based on mobile recording devices
- "Mobile technology can … provide new kinds of information that were previously difficult or impossible to access"
- "Novel endpoints … can make clinical trials more efficient, less burdensome …[providing] real-world understanding about patient … outcomes that goes beyond the brief data "snapshots" typically gathered…"
- "…rarely used in clinical trials… due to … uncertainty about how to identify and choose novel endpoints"
- "CTTI's Novel Endpoints Project … has developed recommendations and tools to … clarify the best pathways for identifying, selecting, and developing novel endpoints derived from mobile technologies."



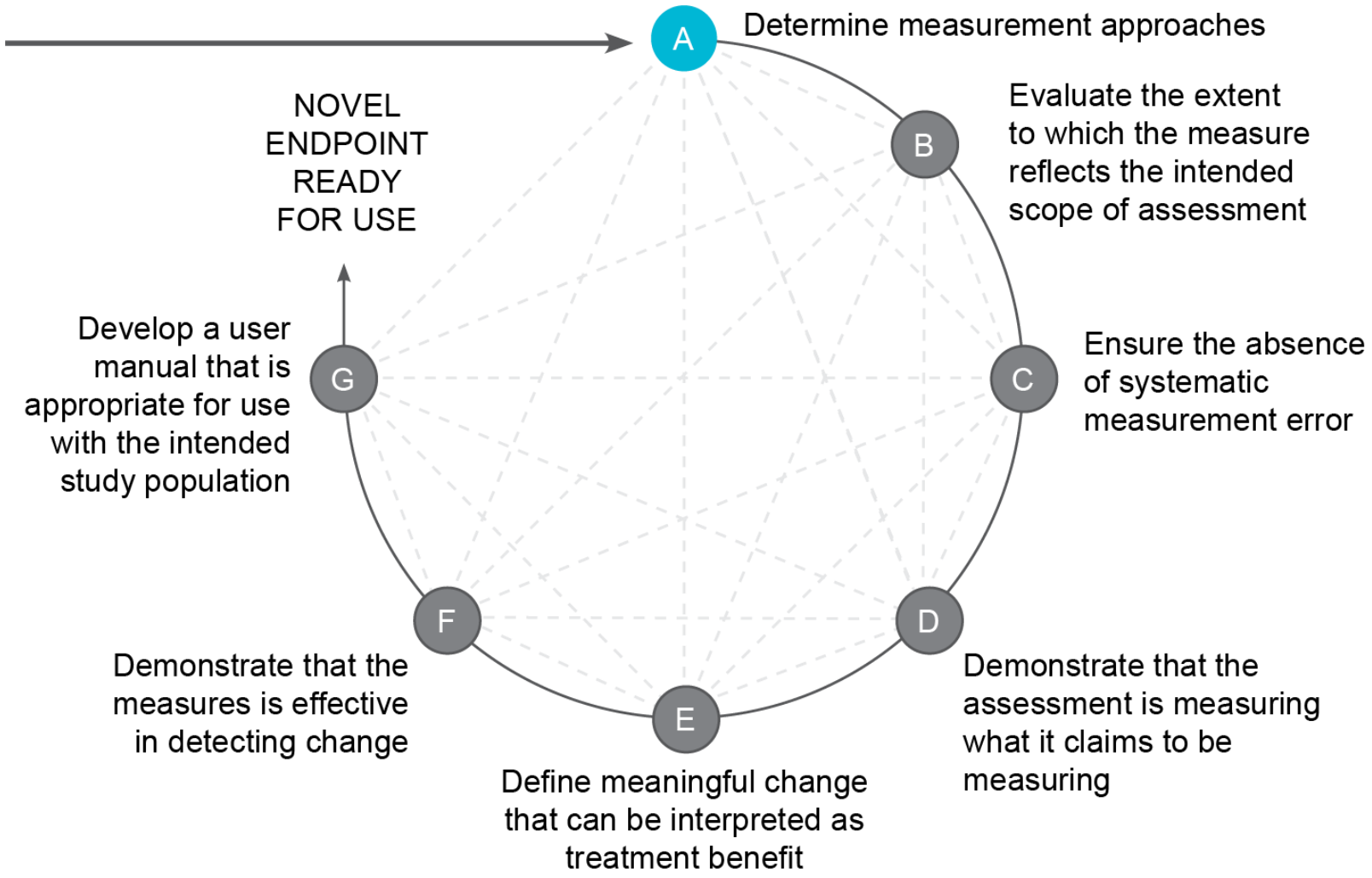
Steps for Novel Endpoint Development



Steps for Novel Endpoint Development – Objective



Process of Novel Endpoint Development



Additional Information

- Powers et.al., Clinician-Reported Outcome Assessments of Treatment Benefit: ISPOR Clinical Outcome Assessment Emerging Good Practices Task Force. 2017; Value in Health 20:2-14

- Walton et.al., Clinical Outcome Assessments: Conceptual Foundation – ISPOR Clinical Outcome Assessment Emerging Good Practices Task Force. 2015; Value in Health 18:741-752.

- Clinical Trials Transformation Initiative, Mobile Clinical Trials Program, Novel Endpoints Project;

  https://www.ctti-clinicaltrials.org/projects/novel-endpoints

- FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009.