U.S. FOOD & DRUG ADMINISTRATION

Clinical Outcome Assessments for Pediatric Clinical Trials

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How Do We Measure How Patients Feel & Function?

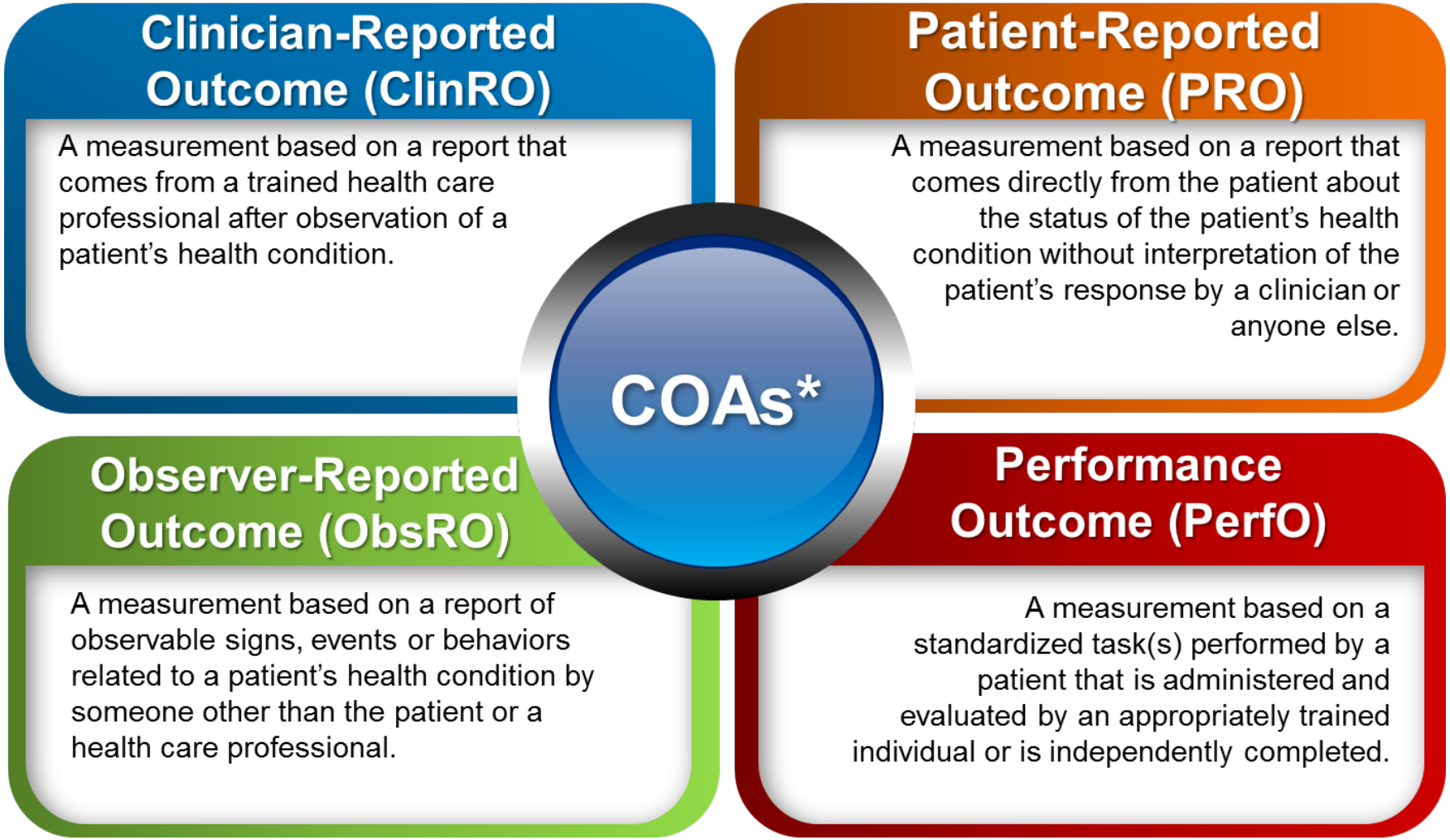
SIGNS!

Symptoms

function

Clinical Outcome Assessments (COAs)

COA: Assessment of a clinical outcome made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment

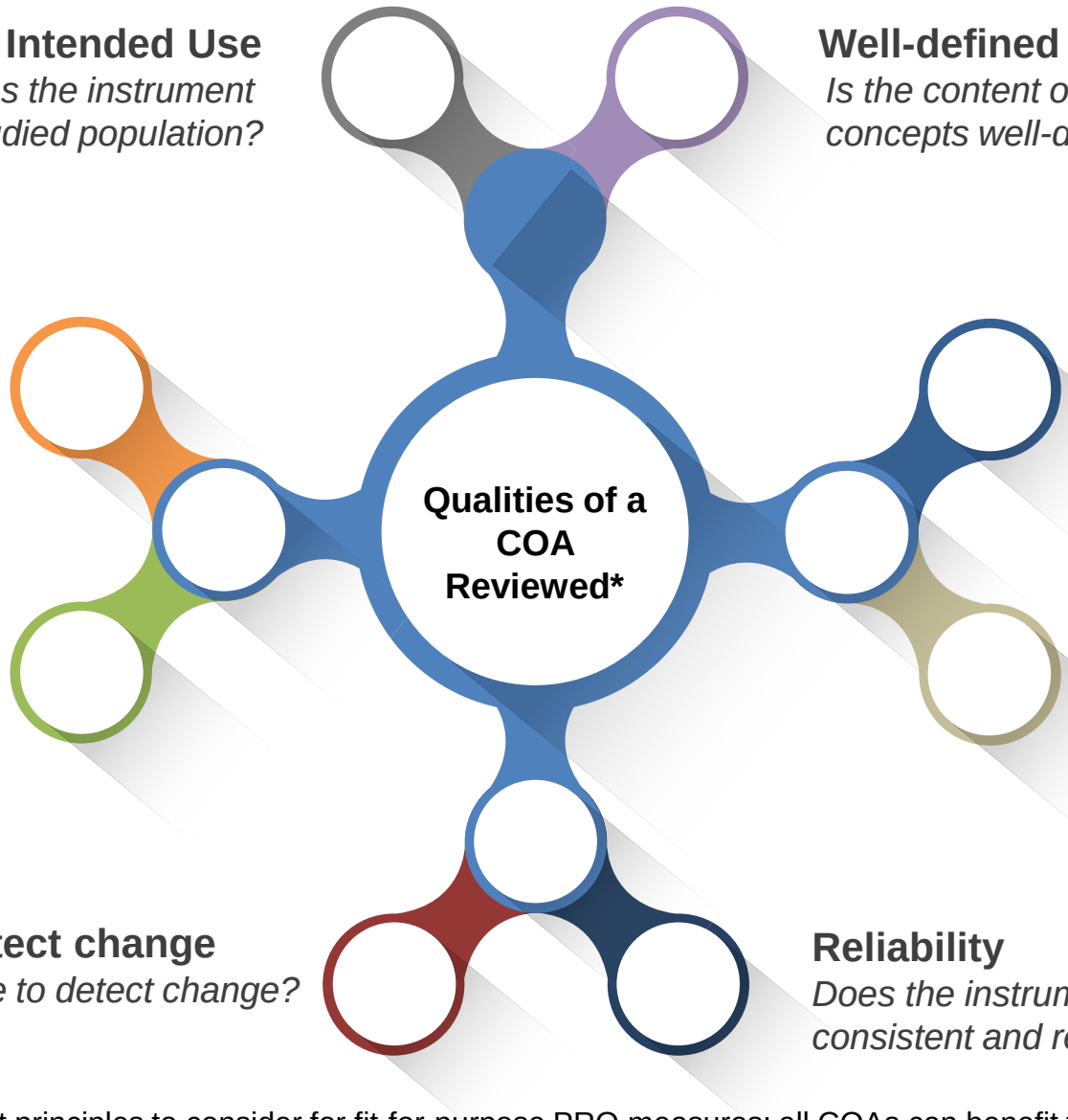


*Digital health technology (e.g., activity monitors, sleep monitors) can also be used to collect clinical outcomes.

Fit-For-Purpose Instruments

- Appropriate for its intended use
  - Study design
  - Patient population
- Validly and reliably measures concepts that are
  - Clinically relevant
  - Important to patients
- Can be communicated in labeling in a way that is accurate, interpretable, and not misleading

How to Determine Whether a COA is Fit-For-Purpose?



Intended Use
Was the instrument evaluated in the studied population?

Well-defined
Is the content or concepts well-defined?

Score Interpretability

Is the score change reflective of meaningful change?

How much change in scores is meaningful?

Content Validity
Does the instrument measure the concept of interest?

Is there qualitative evidence in support of validity?

Construct Validity
Is there quantitative evidence in support of validity?

Ability to detect change
Is the instrument sensitive to detect change?

Reliability
Does the instrument generate consistent and reproducible?

*FDA PRO Guidance defines good measurement principles to consider for fit-for-purpose PRO measures; all COAs can benefit from this guidance

PRO Assessments in Childhood Cancer

Challenges

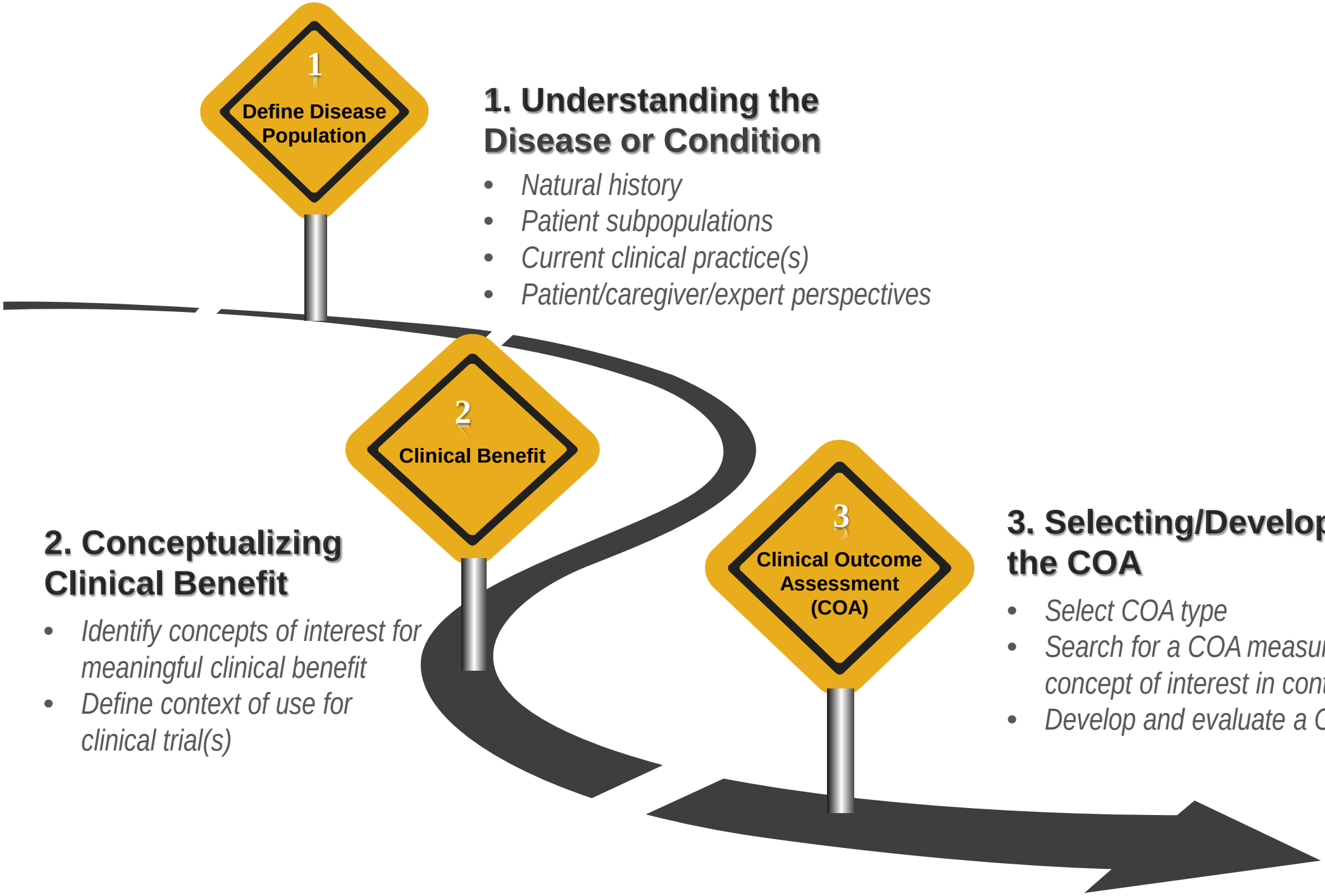
Fit-for-purpose pediatric-specific COAs do not exist for many diseases/conditions

Rapid and variable development in children

Age-related vocabulary and comprehension of health concepts

Age of when children can reliably and validly self-report

Assessment of unobservable concepts in children who cannot reliably and validly self-report



1. Understanding the Disease or Condition

- *Natural history*
- *Patient subpopulations*
- *Current clinical practice(s)*
- *Patient/caregiver/expert perspectives*

2. Conceptualizing Clinical Benefit

- *Identify concepts of interest for meaningful clinical benefit*
- *Define context of use for clinical trial(s)*

3. Selecting/Developing the COA

- *Select COA type*
- *Search for a COA measuring the concept of interest in context of use*
- *Develop and evaluate a COA*

Determining the Appropriate Reporter

Observable concepts

Report by a trained HCP is needed

Clinician-Reported Outcome (ClinRO)

A measurement based on a report that comes from a trained health care professional after observation of a patient's health condition.

Unobservable concepts

Self-report is feasible + appropriate

Patient-Reported Outcome (PRO)

A measurement based on a report that comes directly from the patient about the status of the patient's health condition without interpretation of the patient's response by a clinician or anyone else.

Observable concepts

Self-report is not feasible + appropriate

Observer-Reported Outcome (ObsRO)

A measurement based on a report of observable signs, events or behaviors related to a patient's health condition by someone other than the patient or a health care professional.

Performance Outcome (PerfO)

A measurement based on a standardized task(s) performed by a patient that is administered and evaluated by an appropriately trained individual or is independently completed.

*Digital health technology (e.g., activity monitors, sleep monitors) can also be used to collect clinical outcomes.

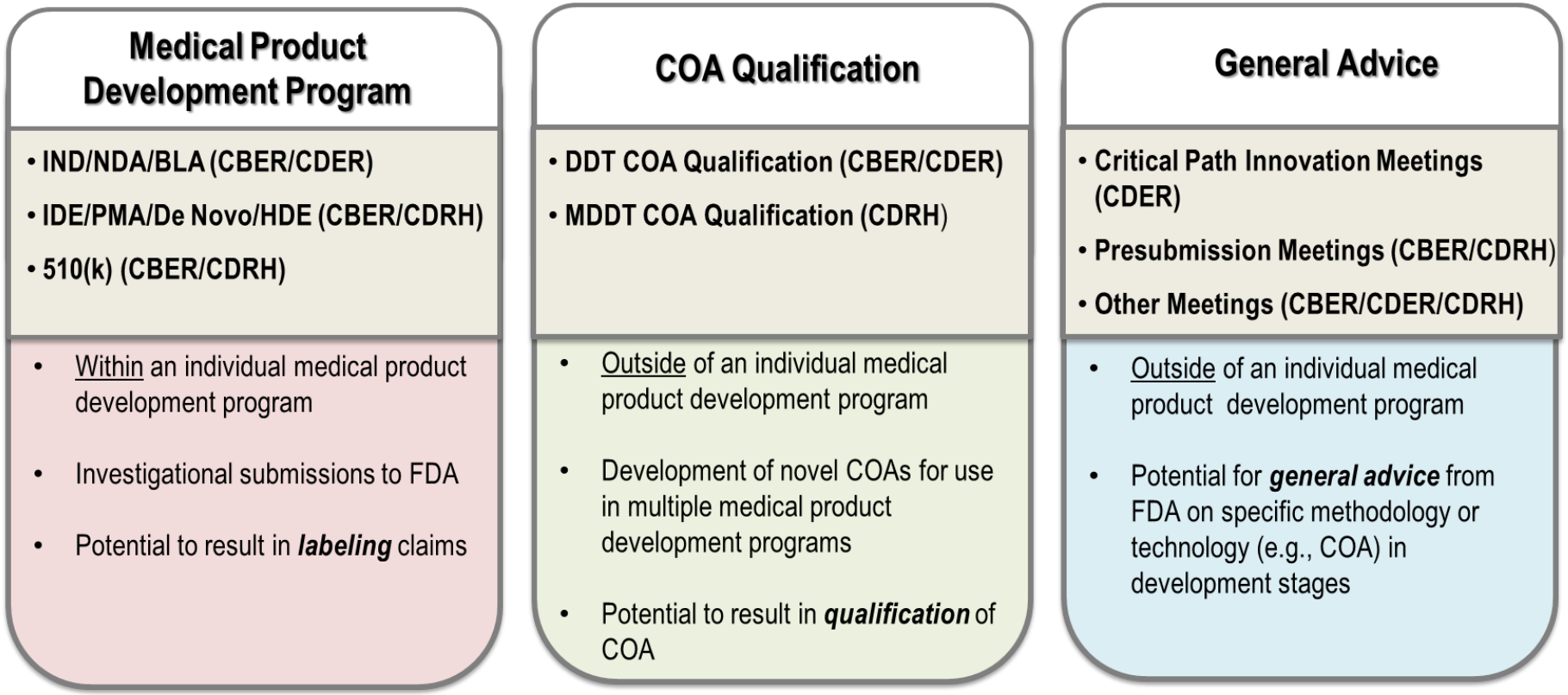
Considerations for Using Pediatric-specific COAs[1, 2]

- **Consider developmental differences and determine age-based criteria for PRO administration**
- **Establish content relevance of pediatric-specific COAs**
- **Determine whether an observer-reported outcome instrument is necessary**
  - Observable vs. Unobservable concepts
  - A proxy-reported outcome instrument is not an observer-reported outcome instrument
  - Develop a strategy to determine the appropriateness of self-report among children in the target population
- **Ensure that the instrument is designed and formatted appropriately for the target age group**
- **Consider cross-cultural issues**

[1]Matza LS, Patrick DL, Riley AW, Alexander JJ, Rajmil L, Pleil AM, Bullinger M. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. Value Health. 2013 Jun;16(4):461-79.

[2]Papadopoulos, E. J., Patrick, D. L., Tassinari, M. S., Mulberg, A. E., Epps, C., Pariser, A. R. and Burke, L. B. (2013) Clinical Outcome Assessments for Clinical Trials in Children, in Pediatric Drug Development: Concepts and Applications (eds A. E. Mulberg, D. Murphy, J. Dunne and L. L. Mathis), John Wiley & Sons Ltd., Chichester, UK. doi: 10.1002/9781118312087.ch42

Pathways for FDA Review & Advice: COAs



BLA = Biologics Licensing Application; **COA =** Clinical Outcome Assessment; **DDT =** Drug Development Tool; **HDE =** Humanitarian Device Exemptions; **IDE =** Investigational Device Exemption; **IND =** Investigational New Drug; **MDDT =** Medical Device Development Tool; **NDA =** New Drug Application; **PMA =** Pre-Market Approval

Summary

- Early planning to meet challenges associated with measurement of clinical benefit in pediatric populations is critical
- Pediatric-specific COAs are evaluated using the same good measurement principles as adult measures (e.g., fit-for-purpose)
- Age appropriateness of self-report for any instrument intended for pediatric use is important
- Develop a strategy for determining the appropriateness of self-report among children in the target population
- For children who are unable to provide a reliable and valid self-report, an observer-reported outcome or clinician-reported outcome that includes observable concepts will need to be developed