Is it time to rethink proxy-reporting? Feasibility and psychometric considerations for creating ObsROs that adhere to Patient-Focused Drug Development (PFDD) fit-for-purpose guidance

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Introduction & Background

- FDA Patient-Focused Drug Development (PFDD) guidance[1] discourages proxy reporting in favor of observer reporting.

- An established theoretical approach[2] to pediatric outcomes defines measures as:
  - Observational Measures = assess an observable sign, symptom, behavior, or verbalization without requiring interpretation or inference
  - Proxy Measures = asks for the reporter's interpretation or inference of the child's internal state(s)

- Our experience applying PFDD guidance indicates that other types of items could be problematic:
  - Items that ask the reporter to make an attribution of an indicator to an internal state
  - Items that might be answered using information not directly observed by the reporter (subject to 3rd party information)

- Patient-Reported Outcomes Measurement Information System (PROMIS)[3] item banks allow for creating custom short-forms (SFs)
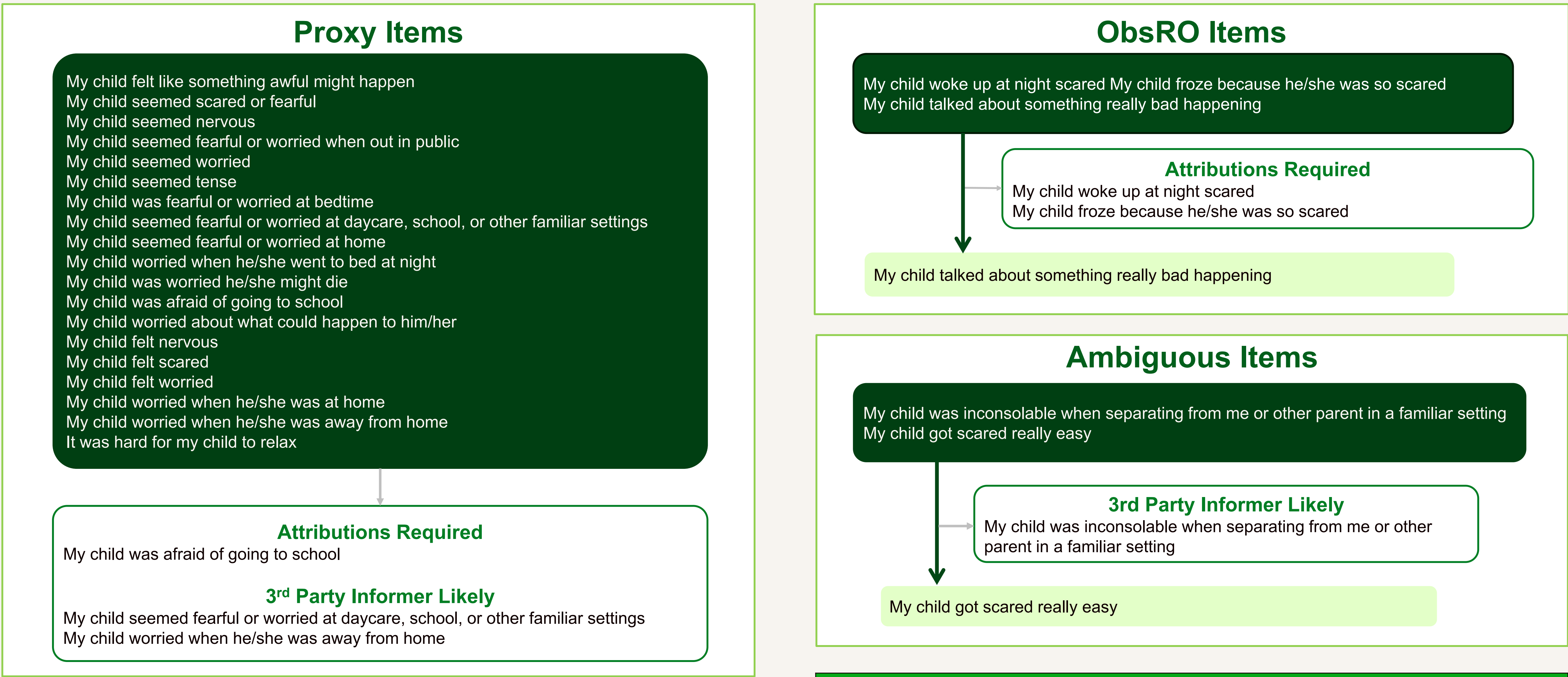
Objective

- Evaluate the feasibility building custom SFs that could qualify as observer reported outcomes (ObsROs) per FDA PFDD guidance.

Methods

- PROMIS Parent Proxy and Early Childhood Parent Report item banks for anxiety and physical activity were evaluated with 24 and 10 unique items, respectively[3].

- Two independent raters coded items as "observable" (assessing observable signs/indicators) or "proxy" (assessing internal states).

- Codebook revision added "ambiguous" to accommodate items with multiple interpretations.

- Items were also reviewed to assess if they were likely to be subject to 3rd party information and if they asked for attribution of indicators to internal states.

- Reconciliation resulted in creation of custom SFs from "observable" items, which were evaluated against PFDD guidance.
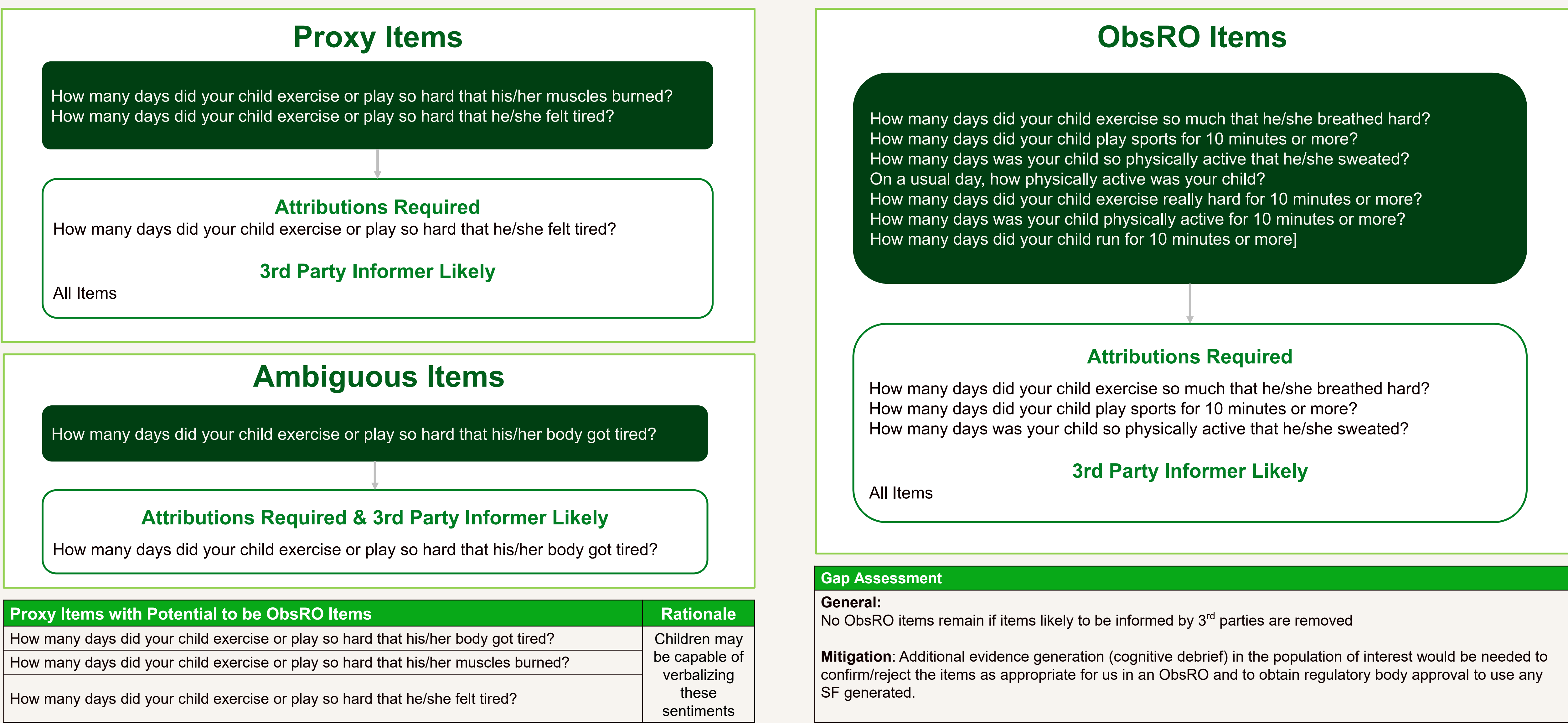
Codebook	
ObsRO Item	An indicator (observable sign or behavior) is mentioned in the item stem.
Ambiguous Item	The concept could be interpreted as an indicator or an internal state.
Proxy Item	No indicators are mentioned in the item stem.
3rd Party Informer Likely	The item stem would likely require a third-party informer (e.g., teacher, other caregiver) or be subject to information obtained from third-party informers
Attribution Required	The item stem explicitly asks the caregiver to attribute an indicator to an internal state.

Anxiety Item Bank

Proxy Items

My child felt like something awful might happen
My child seemed scared or fearful
My child seemed nervous
My child seemed fearful or worried when out in public
My child seemed worried
My child seemed tense
My child was fearful or worried at bedtime
My child seemed fearful or worried at daycare, school, or other familiar settings
My child seemed fearful or worried at home
My child worried when he/she went to bed at night
My child was worried he/she might die
My child was afraid of going to school
My child worried about what could happen to him/her
My child felt nervous
My child felt scared
My child felt worried
My child worried when he/she was at home
My child worried when he/she was away from home
It was hard for my child to relax

Attributions Required
My child was afraid of going to school

3rd Party Informer Likely
My child seemed fearful or worried at daycare, school, or other familiar settings
My child worried when he/she was away from home

ObsRO Items

My child woke up at night scared My child froze because he/she was so scared
My child talked about something really bad happening

Attributions Required
My child woke up at night scared
My child froze because he/she was so scared

My child talked about something really bad happening

Ambiguous Items

My child was inconsolable when separating from me or other parent in a familiar setting
My child got scared really easy

3rd Party Informer Likely
My child was inconsolable when separating from me or other parent in a familiar setting

My child got scared really easy

Proxy Items with Potential to be ObsRO Items	Rationale
My child got scared really easy	"Got scared easily" is likely to be indicated by observable signs
My child felt like something awful might happen]	
My child worried when he/she went to bed at night.	Children may be capable of verbalizing these sentiments
My child was worried he/she might die	
My child was fearful or worried at bedtime	
My child seemed scared or fearful	
My child seemed nervous	"Seemed" language may indicate to make judgements based on observed indicators or verbalizations
My child seemed fearful or worried when out in public	
My child seemed worried	
My child seemed tense	
My child seemed fearful or worried at home	

Gap Assessment

PFDD fit-for-purpose criteria:

SF captures all important aspects
- 3 ObsRO items unlikely to capture all important aspects of anxiety
- 2 of the 3 ObsRO items require caregivers to make an attribution of an indicator to an internal state

Score accurately reflects patient health experiences
- 3 items unlikely to provide an accurate score that reflects patient health experiences

Mitigation: Ambiguous or Proxy items included in a SF may capture additional aspects, but additional evidence generation (cognitive debrief) in the population of interest would be needed to confirm/reject the items as appropriate for us in an ObsRO

Psychometrics:
3 items likely to be insufficient to capture variation and heterogeneity of anxiety

Mitigation: Balance need for ObsRO items with need for broader conceptual coverage. Examination of error variance for Proxy items may inform appropriate use.

Physical Function Item Bank

Proxy Items

How many days did your child exercise or play so hard that his/her muscles burned?
How many days did your child exercise or play so hard that he/she felt tired?

Attributions Required
How many days did your child exercise or play so hard that he/she felt tired?

3rd Party Informer Likely
All Items

Ambiguous Items

How many days did your child exercise or play so hard that his/her body got tired?

Attributions Required & 3rd Party Informer Likely
How many days did your child exercise or play so hard that his/her body got tired?

ObsRO Items

How many days did your child exercise so much that he/she breathed hard?
How many days did your child play sports for 10 minutes or more?
How many days was your child so physically active that he/she sweated?
On a usual day, how physically active was your child?
How many days did your child exercise really hard for 10 minutes or more?
How many days was your child physically active for 10 minutes or more?
How many days did your child run for 10 minutes or more]

Attributions Required
How many days did your child exercise so much that he/she breathed hard?
How many days did your child play sports for 10 minutes or more?
How many days was your child so physically active that he/she sweated?

3rd Party Informer Likely
All Items

Proxy Items with Potential to be ObsRO Items	Rationale
How many days did your child exercise or play so hard that his/her body got tired?	Children may be capable of verbalizing these sentiments
How many days did your child exercise or play so hard that his/her muscles burned?	
How many days did your child exercise or play so hard that he/she felt tired?	

Gap Assessment

General:
No ObsRO items remain if items likely to be informed by 3rd parties are removed

Mitigation: Additional evidence generation (cognitive debrief) in the population of interest would be needed to confirm/reject the items as appropriate for us in an ObsRO and to obtain regulatory body approval to use any SF generated.

Results

- For anxiety, the ObsRO SF retained 3 items
  - None were likely subject to 3rd party information
  - 2 of these asked for attribution of indicators to internal states
  - Of excluded items, 2 were coded "ambiguous", and 19 were coded as "proxy".

- For physical activity, the ObsRO SF retained 7 items
  - All 7 were likely subject to 3rd party information
  - 2 items asked for attribution of indicators to internal states
  - Of excluded items, 1 was coded "ambiguous", and 2 were coded as "proxy".

- Evaluation of the SFs against PFDD guidance suggested risk of insufficient conceptual coverage and error variance related to increased focus on strictly measuring observable indicators.

- In both item banks, some items identified as Proxy items did not name observable indicators but may be answered based on verbalizations or observable indicators – confirmation with study populations would be required

Conclusions

- Dichotomization (Observer versus Proxy reporting) may not be a practical theoretical approach for building SFs.
  - Many items include ambiguous language or language that could be interpreted in multiple ways
  - Parent/caregivers may report on an internal state using observed signs and indicators

- Furthermore, proxy- and observer reporting-type items contribute different potential sources of error variance (e.g., attribution of indicators versus restricted conceptual coverage).

- Balancing the sources of measurement error for each study and its population is required to build fit-for-purpose instrumentation that captures meaningful information reliably.

Abbreviations

PFDD = Patient-Focused Drug Development
PROMIS = Patient-Reported Outcomes Measurement Information Systems
ObsRO = Observer-Reported Outcomes
SF = Short Form

References

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

2. Matza LS, et al. 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. VALUEINHEALTH16(2013)461 - 479

3. PROMIS. https://www.healthmeasures.net/index.php

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