Methodology for Development of Indication-Specific Outcome Measures in Rare Disease Trials: An Innovative Research Approach

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Background

- Fragile X syndrome (FXS) is a rare neurodevelopmental disorder caused by a genetic mutation and is associated with intellectual disability, anxiety disorders, behavioral and learning challenges, and various physical disabilities (Chevreul, 2015). As in many rare diseases, FXS is quite heterogeneous (Chaste et al., 2012).
- Heterogeneity in symptomology poses a significant challenge when developing a clinical outcome assessment strategy to measure treatment benefit and to support drug development.
- In rare disease trials, including FXS, input from multiple sources (caregivers, clinicians, direct assessments) is critical to capture the range of symptoms.
- In some indications, direct assessments with patients is not possible, so caregiver report is even more paramount.
- A Visual Analogue Scale (VAS) is a common approach for assessing symptoms/behaviors in CNS-based clinical trials.
- However, current outcome assessments for CNS-based trials have clear limitations which are further magnified in rare disease trials.
- There is a pressing need to create novel outcomes that:
  - Have improved specificity
  - Assess constructs proximal to the targeted mechanism
  - Include input from key stakeholders

Objective

Develop an indication-specific Visual Analog Scale (VAS) for Fragile X Syndrome clinical trials. Methodology can be applied to additional rare disease indications.

Method

Results

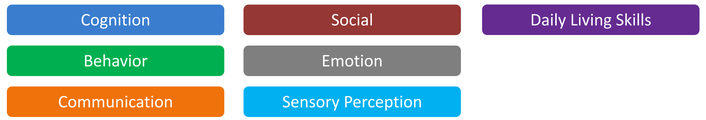
Visual Analog Scale for FXS

Part 1- VAS: Top 3 Concerns in Behavior

For Part 1 of the VAS, caregivers generate three primary concerns related to the subject. This open-ended approach is:

- Family/patient-centered
- Flexible in consideration of the heterogeneity of the condition
- Allows caregivers' concerns to be clearly captured

Building from prior work on conceptual models of outcome assessments (Lee et al., 2018), a trained clinician then maps each caregiver-generated concern onto one impact concept relevant to FXS.



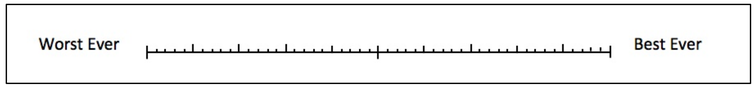
Part 2- VAS: FXS-Specific Domains

For Part 2 of the VAS, three FXS- specific domains were selected based on literature review, clinical experience, qualitative interviews with caregivers.

Three Domains:

- Domains cover constructs not well-measured with published scales
- For each domain, VAS includes clear anchors and clinically-relevant examples of behaviors

For both Part 1 and Part 2 of VAS, caregivers rate how much of a problem each symptom/behavior has been for the individual.



Conclusions

- Sample sizes in rare disease trials are often, by necessity, small. Therefore, refined outcome measures that are targeted specifically to the indication and mechanism of action are needed to detect a signal (i.e., detect a potential change in functioning).
- Given the significant cognitive, behavioral, and physical impact of rare diseases on the individual and his/her family, involvement of key stakeholders is imperative, in both development of outcome measures and in reporting change in clinical trials.
- The current VAS was developed by integrating information from multiple perspectives, including from key stakeholders.
- The VAS includes key elements for applicability in clinical trials:
  - Specific and granular assessment of target symptoms/behaviors
  - Symptoms/behaviors proximal to target mechanism
  - Captures range of heterogeneity in indication
  - Clear anchors to support reliable and objective ratings
  - Adaptable for multiple responders (e.g., caregiver-, subject-, clinician- report)
- Current work is a FXS-specific VAS, but the methodological approach employed can be used as a model for future work in rare disease trials to continue to improve and refine existing outcome assessments and rating scales.

References

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