CTD & GAMT Outcome Measurement Tools in Pediatric Clinical Trials

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Introduction

- There has been a recent increase in clinical trials for genetic conditions associated with neurodevelopmental disorders, including intellectual disability (ID).
  - While there are efforts to both personalize and systematize such trials, there has been little attention to expanding evidence of validity of outcome measures through their use across such trials.
  - To study the validity of outcome measures, the field requires consensus on the "concepts of interest" each outcome measure is capturing.
- We focus here on five domains identified by a Delphi group as being the most important for CTD/GAMT deficiency.
  - These domains serve as priorities for treatment studies.

Here we explore how studies report on these measures to understand what kinds of measures can capture each of these domains of functioning in CTD/GAMT deficiency.

[1]Nasseri Moghaddam, Z., Reinhardt, E. K., Thurm, A., Potter, B. K., Smith, M., Graham, C., Tiller, B. H., Baker, S. A., Bilder, D. A., Bogar, R., Britz, J., Cafferty, R., Coller, D. P., DeGrauw, T. J., Hall, V., Lipshutz, G. S., Longo, N., Mercimek-Andrews, S., Miller, J. S., Pasquali, M., … Wallis, H. (2024). Establishing a Core Outcome Set for Creatine Transporter Deficiency and Guanidinoacetate Methyltransferase Deficiency. *medRxiv : the preprint server for health sciences*, 2024.09.06.24313213. https://doi.org/10.1101/2024.09.06.24313213

Methods

- A scoping review of clinical trials in the ID population was conducted using a systematic search of bibliographic databases on December 19th, 2024, from 2019-2024.
- Completed clinical trials involving medications, supplements or devices including children with ID, focused on the five outcome domains were included.

- The scoping review was conducted by multiple reviewers in multiple phases.
  - Note: data were extracted by one reviewer and verified by a second reviewer.

STUDY DETAILS
Title, authors, country, study design details (blinding, arms, trial phase, etc.), intervention type, conditions included

OUTCOME DETAILS
Outcome measure, measure subset (if relevant), domain assessed – of 5, outcome type (primary/secondary)

Workflow of Scoping Review

Studies screened in duplicate in two phases
n=8,161

Studies with outcome measures assessing one of the five domains
n=79

Subset of studies with a **primary** outcome measure assessing one of the five domains
n=25

n=8,082 excluded

- We identified 79 studies that had at least one outcome measure relating to one of the 5 domains,
  - We identified 25 studies that had primary outcomes relating to one of the 5 domains

Predefined Terminologies Used for Each Domain

Adaptive Functioning: adaptive behavior, adaptive functioning, daily living skills, life skills
Cognitive Functioning: cognitive abilities, cognitive processes, cognition, mental functioning, intellectual functioning
Emotional Dysregulation: emotional instability, emotion regulation, depression, volatility, anxiety, maladaptive emotions
Expressive Communication: Expressive language, speech, language use
Fine Motor Functions: manual dexterity, finger coordination, precise movement, small muscle control

Results

Measures Identified

Measure	All Studies (n=79)	Study with Measure as Primary Outcome (n=25)
Vineland Adaptive Behavior Scales	19 (24%)	4 (16%)
Bayley Scales	14 (18%)	4 (16%)
WISC	8 (10%)	4 (16%)
Aberrant Behavior Checklist (ABC)	8 (10%)	2 (8%)
WPPSI	7 (9%)	3 (12%)
Mullen	6 (8%)	3 (12%)
BRIEF	6 (8%)	0 (0%)
Child Behavior Checklist (CBCL) / Caregiver-Teacher Report Form	5 (6%)	1 (4%)
Kaufman Assessment Battery for Children, Second Edition	3 (4%)	0 (0%)
Anxiety, Depression, and Mood Scales (ADAMS)	2 (3%)	1 (4%)
Behavior Assessment System for Children, 3rd Edition (BASC-3)	2 (3%)	1 (4%)
CANTAB Tasks	2 (3%)	1 (4%)
Clinical Global Impression (CGI)	2 (3%)	1 (4%)

Scan QR Code for full table with all measures included →

Most Frequent Measure Used in Each Domain

Domain of Interest	Measure	All outcomes	Primary outcomes
Adaptive Functioning	Vineland Adaptive Behavior Scales	17/26 (65%)	4/7 (57%)
Cognitive Functioning	Bayley Scales	13/43 (30%)	4/14 (29%)
Emotion Dysregulation	Aberrant Behavior Checklist (ABC)	8/23 (35%)	2/5 (40%)
Expressive Communication	Vineland Adaptive Behavior Scales (Communication Subscale)	5/26 (19%)	2/5 (40%)
Fine Motor Function	Bayley Scales (Fine Motor Subscale)	3/19 (16%)	1/1 (100%)

Note: each denominator refers to the number of studies included that had "x" domain as an outcome, either overall or primary

Scan QR Code for all domain-specific measure categorizations →

Discussion

What we learned:

- There is **significant variability** in the types of measures used to assess these domains in intellectual disability.
  - Authors use different words to talk about each measure and map them onto domains. One measure can map onto more than one domain given what subset is used.
- There is a **complexity** of classifying measures onto domains:
  - E.g., "Emotion Dysregulation" can encompass a broad spectrum of behaviors and psychopathologies.
  - Researchers also do not use standardized terms for these domains.
    - Scan QR code →

What's next:

- Publication of a streamlined, accessible manuscript, with data on measures used, terminology used and groupings for the five domains in order to:
  - Allow stakeholders, including researchers, caregivers and healthcare providers to make informed decisions about how to classify and consider tests of specific domains of functioning important in CTD/GAMT deficiency

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