ISCTM
International Society for CNS Clinical Trials and Methodology

Orphan Disease Working Group

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Washington, DC

Joan Busner, Ph.D

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Co-Chairs

Agenda

- 1) Welcome and Introductions
- 2) Person Ability Scores – Cristan Farmer, Ph.D, NIH/NIMH and Julian Tillmann, Ph.D., Roche
- 3) Idea for new white paper: CGI in Rare Disease Drug Development – Jim Youakim, M.D.
- 4) Update on Stakeholder manuscript – Gahan Pandina, Ph.D.
- 5) Patient Centric Drug Development – Phelan-McDermid Foundation – Gahan Pandina, Ph.D.
- 6) DocMatter Responses – Rare Diseases Being Studied by Current ISCTM Members – Joan Busner, Ph.D.
- 7) Update on pediatric manuscripts (3 in press) – Joan Busner, Ph.D.

Person Ability Scores as Clinical Endpoints

Cristan Farmer, Ph.D.

Julian Tillmann, Ph.D.

What are ability scores?

- Raw scores are converted to an equal-interval scale using the Rasch measurement model
  - available on many standardized norm-referenced tests (under trade names like W-score, GSV, CSS)
  - used primarily in education
- Like a raw score:
  - represents absolute performance on a test
  - do not have normative meaning; cannot meaningfully be compared between tests
- Used to compare absolute performances on a test by different people or by the same person at different times

Daniel M, Vannier LC. Growth scale value (GSV): Theory, development, and applications (Growth Scale Value Technical Report Number 1). Pearson; 2023.

Why use ability scores?

- Intended for response monitoring context
  - Differences have consistent meaning across levels (interval)
  - Conditional SEM per value reflecting that test is not uniformly precise
- More valid interpretation
  - Monotonic relationship with raw score
  - Reflects absolute ability, not ability relative to some population that may or may not be relevant to study population
  - Can be used out-of-age-range (i.e., one test for wide age range)
  - Can be expressed as probability of success on items not administered
- Better statistical properties[1]
  - No floor effects beyond test range
  - Interval (raw and age equivalent = ordinal)
  - Significantly improved power to detect effects in RCT

[1] *Farmer C, Thurm A, Troy JD, Kaat AJ. Comparing ability and norm-referenced scores as clinical trial outcomes for neurodevelopmental disabilities: a simulation study. Journal of Neurodevelopmental Disorders. 2023;15(1):4. doi:10.1186/s11689-022-09474-6*

Why might this matter to the OWG?

- Trajectory-altering therapies on horizon (e.g., gene therapy) but measurement limitations may preclude adequate evaluation
- Regulatory agencies need psychometric data and guidance on use and interpretation of developmental measures and endpoints
- Enhance usability of existing measures
- Opportunities for new insights from existing clinical data
- Applications in other populations (e.g., dementia)

CGI Whitepaper

Jim Youakim, M.D.

Joan Busner, Ph.D.

CGI White Paper

- Issues
- Prescribed vs nonprescribed anchors
- Global vs specific symptoms
- Conflicting guidance?
- Member experiences
- Other topics?

Volunteers for subgroup

Update on Stakeholder Manuscript

Gahan Pandina, Ph.D.

Patient Centric Drug Development – Phelan-McDermid Foundation

Gahan Pandina, Ph.D.

DocMatter Responses

Joan Busner, Ph.D.

1,958 Discussion Views
7 Responses

QUESTION: Could those working in CNS rare/orphan diseases let us know which disorders you're working on? As the Orphan Disease Working Group develops and expands, it would be helpful to get a fuller understanding of the disorders and types of signs/symptoms with which ISCTM members are engaged.

James M. Youakim

HI Joan, We have been working on Rett syndrome. Thanks! Jim

Christian Yavorsky

Hi Joan. Christian here from Valis Bioscience; we are working on a range of rare and orphan disorders that impact cognition and motor functioning including Canavan disease and classic galactosemia. I think one of the important issues for the group may be around scale selection due to the lack of research in these areas. Sometimes the norm referenced scales like the Bayley, Vineland etc are not exactly what we might need because of the unique characteristics of these populations. Let me know what you and your group think.

Michael Kiefer

Hi Joan, I'm primarily working on Canavan, GM2 and Duchenne. I would agree with Christian regarding the limitations of currently available / commonly used outcome measures for these populations, especially performance based motor assessments (I'm a PT). - Mike

Margaret Moline

Hi Joan - At Eisai, we are working on Narcolepsy, Dravet, and Dominantly Inherited AD.

William Jacobson

Myotonic Dystrophy, type 1, Prader-Willi Syndrome, Narcolepsy, Idiopathic Hypersomnia

Tom Macek

I work primarily in Spinal Muscular Atrophy

Gary K. Zammit

Current projects at Clinilabs Drug Development Corporation include Friedrich's ataxia and narcolepsy. There is significant activity in the latter industry-wide, now that narcolepsy is know to be caused by orexin deficiency and orexin agonists have been identified.

Update on Pediatric Manuscripts In Press

Joan Busner, Ph.D.

Update on manuscripts

- We received word that all 3 manuscripts will appear in one issue
- Still slated for the January- March issue of Innovations in Clinical Neuroscience