Welcome!

International Society for
CNS Clinical Trials and Methodology
Orphan Diseases Working Group

08 September 2022
Boston Park Plaza – Boston MA

Today's Objectives

The working group will have a discussion to brainstorm on a stakeholder consensus process to drive development of better methods and endpoints in Orphan Disease. Other potential areas of focus for the coming year for the group will be discussed, including potential topics and speakers for a future full or half day ISCTM session.

Agenda

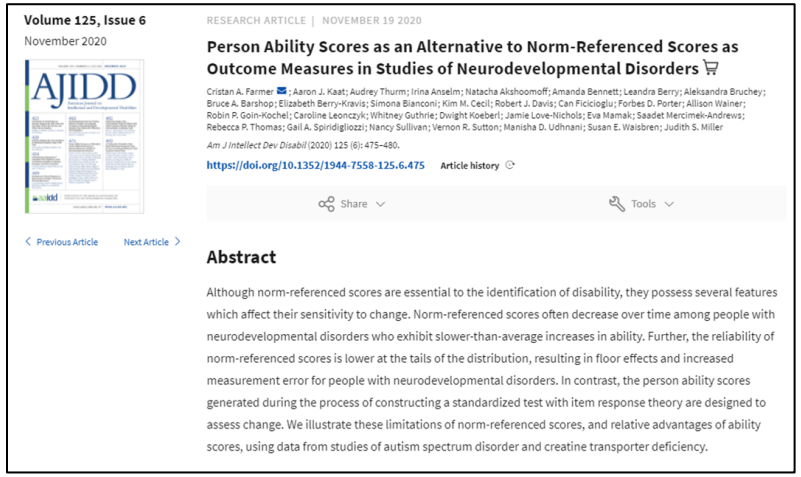
- Review recent WG accomplishments, including accepted papers from pediatric sessions
- Discuss finalization of last paper from session – planned in 2022
- Discuss proposed area of interest on person ability scores as clinical trial endpoints (Farmer, Tillman)
- Discuss future topics for ½ day session

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Person ability scores as clinical trial endpoints

- Person ability scores are transformations of the raw score; product of Rasch/IRT scaling of an instrument
  - Available for any measure developed using Rasch/IRT, including many norm-referenced childhood measures (e.g., Vineland, Bayley, Woodcock-Johnson, Stanford-Binet…)
- Especially when floor or ceiling effects are likely, ability scores have better psychometric and statistical profile than raw, age equivalent, or norm-referenced (standard/scaled/IQ)
  - Equal-interval scale, conditional measurement error, not limited by age
  - Advantage may be more apparent in some contexts (v. low functioning; developmental concepts)
- Current challenge is defining minimal clinically important difference; using several qualitative and quantitatively informed approaches
  - Distribution-based approaches
  - Leveraging known relationship between person ability score, item difficulty parameters, and probability of passing an item to characterize ability score change in terms of probability of passing key milestones

Further background / resources



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RESEARCH ARTICLE | NOVEMBER 19 2020

Person Ability Scores as an Alternative to Norm-Referenced Scores as Outcome Measures in Studies of Neurodevelopmental Disorders

Cristan A. Farmer; Aaron J. Kaat; Audrey Thurm; Irina Anselm; Natacha Akshoomoff; Amanda Bennett; Leandra Berry; Aleksandra Bruchey; Bruce A. Barshop; Elizabeth Berry-Kravis; Simona Bianconi; Kim M. Cecil; Robert J. Davis; Can Ficicioglu; Forbes D. Porter; Allison Wainer; Robin P. Goin-Kochel; Caroline Leonczyk; Whitney Guthrie; Dwight Koeberl; Jamie Love-Nichols; Eva Mamak; Saadet Mercimek-Andrews; Rebecca P. Thomas; Gail A. Spiridigliozzi; Nancy Sullivan; Vernon R. Sutton; Manisha D. Udhnani; Susan E. Waisbren; Judith S. Miller

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Abstract

Although norm-referenced scores are essential to the identification of disability, they possess several features which affect their sensitivity to change. Norm-referenced scores often decrease over time among people with neurodevelopmental disorders who exhibit slower-than-average increases in ability. Further, the reliability of norm-referenced scores is lower at the tails of the distribution, resulting in floor effects and increased measurement error for people with neurodevelopmental disorders. In contrast, the person ability scores generated during the process of constructing a standardized test with item response theory are designed to assess change. We illustrate these limitations of norm-referenced scores, and relative advantages of ability scores, using data from studies of autism spectrum disorder and creatine transporter deficiency.

Farmer et al 2021

ISCTM 2021

Measuring Within-Child Change in Treatment Studies of Low-Functioning Children

Mark Daniel[1,2], Louis-Charles Vannier[1], Stephen M. Maricich[3], Elsa Shapiro[4], Adam Scheller[1]
1: Pearson Clinical Assessments, 2: Mark Daniel Services, LLC. 3: (Formerly of) Allievex Corporation, 4: Shapiro Neuropsychology Consulting, LLC

IRT person ability scores as an alternative to norm-referenced scores in clinical trials of neurodevelopmental disability

Cristan Farmer[1], Audrey Thurm[1], Judith S. Miller[2], and the Vigilan Observational Study Team[1,2,3]
[1]National Institutes of Mental Health, Bethesda, MD, USA; [2]Children's Hospital of Philadelphia, PA, USA; [3]Cincinnati Children's Hospital Medical Center, Duke University, University of Utah, Texas Children's Hospital, University of Toronto Hospital for Sick Children, University of California San Diego, Rush University Medical Center, Boston Children's Hospital

ISCTM proposal:

Measuring change via person ability scores: Advances and challenges in measuring developmental and functional outcomes in neurodevelopmental disorders

Multi-stakeholder group to discuss:

Overview: Challenges in measuring developmental constructs in populations with extreme scores

Technical details: Measurement properties of person ability scores and comparison to other common score types

Clinical trial applications: Approaches to assessing broad clinical benefit with person-ability scores and use of composite endpoints

Interpreting and communicating change in ability scores: Clinical interpretation of change in person ability scores and approaches to define meaningful change in the context of Angelman Syndrome

Regulatory insights: Regulatory considerations regarding the use of person ability scores in clinical trials in NDDs

If interested – arrange a separate video conference to discuss points of convergence with Orphan Disease WG and scope of a potential ISCTM symposium

ISCTM Session Proposal
May 6, 2022

Recommended chairs
Cristan Farmer, Ph.D., National Institute of Mental Health
Julian Tillmann, Ph.D., Hoffman-La Roche

Proposed Length of Session
½ day

Title
Measuring change via person ability scores: Advances and challenges in measuring developmental and functional outcomes in neurodevelopmental disorders

Abstract
Neurodevelopmental disorders (NDD) are a clinically and etiologically heterogeneous group of disorders affecting approximately 3% of the population worldwide. NDDs include conditions such as Autism Spectrum Disorder and Intellectual Disability, and when they are associated with rare genetic conditions the phenotype may be very severe. For all NDDs, development in domains like motor ability, thinking and learning, social abilities, and communication are potential targets for intervention. These developmental concepts are expected to change over time in some predictable way, and so clinical outcome assessments (COAs) are often norm-referenced. Norm-referencing makes it possible to contextualize the performance of a child against that of their age-based peers, which is essential in the diagnostic context, but ill-suited to the response monitoring context. Norm-referenced scores exhibit floor effects within each normative age group, which dramatically reduces responsiveness to change for individuals with extreme impairment. Further, because norm-referenced scores are distribution-based derivations, they exhibit poor reliability at extreme values. Finally, as both result in decreasing norm-referenced scores, it is not possible to distinguish true deterioration from failure to gain skills at the expected rate. This is particularly worrisome for trials of degenerative conditions.

In response to these limitations, those designing clinical trials have considered using one of the other score types available on most developmental COAs, such as raw scores or age equivalents. However, raw scores and age equivalents are measured at the ordinal level and therefore are of limited use as clinical trial endpoints. Unlike norm-referenced, raw, or age equivalent scores, person ability scores, derived through Rasch or item response theory analysis, are designed for the measurement of within-subject change. They measure the amount of the underlying construct on an interval scale, possess conditional standard errors of measurement, and exhibit floor effects only at the floor of the raw scores. While person ability scores have been available on some standardized tests for 45 years, they have been used infrequently as clinical trial endpoints in pediatric NDD populations, and interest in them has steadily gained momentum in recent years. In this session, we will provide an overview of the methodological issues inherent to measuring developmental concepts and outline the advantages and disadvantages of person ability scores as clinical trial endpoints, including the derivation of thresholds for clinically meaningful change.

Specifically, we will discuss:
a) Overview: Challenges in measuring developmental constructs in populations with extreme scores
b) Technical details: Measurement properties of person ability scores and comparison to other common score types
c) Clinical trial applications: Approaches to assessing broad clinical benefit with person-ability scores and use of composite endpoints
d) Interpreting and communicating change in ability scores: Clinical interpretation of change in person ability scores and approaches to define meaningful change in the context of Angelman Syndrome
e) Regulatory insights: Regulatory considerations regarding the use of person ability scores in clinical trials in NDDs

Suggested Speakers
Cristan Farmer, Ph.D., National Institute of Mental Health
Julian Tillmann, Ph.D., Hoffman-La Roche
Mark Daniel, Ph.D., Pearson Assessment
Sonya Powers, Ph.D., Edmentum Inc.
Anne Wheeler, Ph.D., RTI International
Anjali Sadhwani, Ph.D., Boston Children’s Hospital
Audrey Thurm, Ph.D., National Institute of Mental Health