Orphan Diseases Working Group

February 21, 2025

21st Annual ISCTM Meeting, Mayflower Hotel, Washington, DC

Chairs: Joan Busner, Ph.D. and Gahan Pandina, Ph.D.

Welcome and Introductions to New Members

Updates

- Highly productive group!
- Yesterday's session "Using Novel Biomarkers and Advanced Analytics to Optimize Measurement, Endpoint Selection, and Signal Detection: Lessons for the Broader Neuroscience Community from Orphan Disease Trials"
  - Results of a year's worth of meetings and planning – many thanks to all!!
- As you know our group has already published 5 excellent papers
- Now focusing once again on manuscript development
- **Three manuscripts underway**
  - **CGI in Rare Disease Trials**
  - **Measuring Cognition in Rare Disease**
  - **Ethical Issues in Rare Disease Trials**

Manuscript Development

- Committed to streamlining development
- On our December 17 teleconference we agreed to:
  - 1) appoint leads and interested parties for each of the 3 manuscripts
  - 2) develop outline to share at February in-person meeting…
- DONE☺

MANUSCRIPT 1: CGI in Rare Disease Trials – DRAFT OUTLINE

Leads: Joan Busner and Gahan Pandina

Interested: Busner, Pandina, Acosta, Farmer, Horrigan, Macek, Roy, Sasinowski, Walton, (Knoble)

Background: CGI development in psychiatry clinical trials as a clinical anchor (Guy 1976 ECDEU). Consult Nina Schooler on background

- How it is reflected in psychiatry product labels, prescribers, journal editors
- What does it mean
- Requires expert clinician with experience in disease state

  - Original purpose was meant to reflect the thinking of the expert clinician in the field, not a research expert per se.
  - CGI should refer to the disease under study only. Do not consider / include adverse events unless they affect the disease under study ie, do not change CGI score due to a AE that is not specific to the condition under study.

- CGI is usually NOT implemented as the primary endpoint, but contextualizes clinical meaningfulness vs. disease specific measure
  - May be allowed / required as co-primary
- CGI -- general condition vs. specific symptom / domain
- Number of anchor points has varied over time
  - Generalizability and comparability to other literature
- What are some differences in orphan disease in how CGI is implemented?
  - There are some differences here – long term genetic conditions may be less likely to remit fully (ie, 1 = no longer have the disorder)
  - No one gold standard across orphan conditions – sometimes includes conflicting feedback from regulators within programs
    - Specificity of anchors varies based on regulator position / compound - threshold for severity highly explicated vs. left high level and to clinical judgement

CGI Outline continued

- Some sponsors are requiring blinding of CGI rater, even blinding to baseline data (ie, do not allow to refer to notes from baseline)
- Value (if any) of disease-specific versus traditional CGI approaches
- Validation of CGI against the primary efficacy scale typically not done ahead of / outside clinical program of interest
  - CGI is meant to reflect the expert clinician's view of the patient's disease severity
    - Informed, but not dictated by, other rating scales
    - Clinical judgment is "independent" of other scales (essence - "what does my doctor think")
- May be very idiosyncratic ways to approach in genetic diseases
  - particularly for genetic conditions, some functional outcomes may change while disease severity might not change

- Outside of psychiatry, very limited experience with CGI concept
  - Requires greater standardization, more examples, and training, and consensus-building
- Provide examples from membership
  - Emphasize points below
  - Survey group
- Relationship to Patient Global Impression (PGI)
  - Often required to be used alongside the CGI and symptom rating scales to get patient "perspective" of disease severity
  - Even more variable than CGI
    - More specific examples, multi-component, etc.
    - Relates to the individual's non-expert viewpoint
    - May or may not provide examples or context or training
- What is position of group on key CGI concepts

MANUSCRIPT 2: Ethical Considerations in the Conduct of Rare Disease Neuroscience Clinical Trials
DRAFT OUTLINE

Leads: Kemi Olugemo and Joe Horrigan

- **Introduction**

- Rationale for ethics paper
- Myriad issues related to the conduct of orphan disease trials, including ethical dilemmas. Need for recommendations from organizations such as ISCTM.

- **Equity and Equipoise**

- Equipoise is an important consideration in randomized control trials (RCTs), which is the standard method for evaluating treatment effectiveness
- Access related to jurisdictions, likelihood of marketing authorization, under-represented groups, etc.
- Eligibility criteria considerations balanced with the need for enrichment, particularly given the heterogeneity in rare diseases

- **Placebo-control**

- Discuss pros and cons of various control groups, and when placebo use is justified
- Elaborate on use of adaptive designs to minimize placebo use
- Discuss sham control – pros and cons

Ethics Outline, continued

- **Gene therapy**

- Who agrees to be in the alpha group
- Access to biologics and potentially life-saving treatment
- Medical implications of participating in an “alpha” gene therapy trial when more advanced approaches may be imminent (the participant may be disqualified)
- Consent vs assent
- Other vulnerable populations

- **Data-sharing**

- Best practices for engaging with PAGs
- Communicating changes to clinical programs, particularly discontinuation for lack of funding or corporate prioritization

- **Compassionate use programs**

- Best practices

- **Practical ethical issues**

- **Blood draw volumes in children**

Ethics Outline, continued

- **ISCTM Author list**
- *TBD*
- **Target Journals**
- Home page | Orphanet Journal of Rare Diseases
- Neuroscience Applied | Journal | ScienceDirect.com by Elsevier
- Frontiers in Neuroscience

MANUSCRIPT 3: Assessment of Cognition Across Development and Functional Levels for Orphan Disease Populations and Relevance to Treatment and Clinical Trial Outcomes

LEADS: Cristan Farmer and Gahan Pandina

- Interested: Judy Kando, Sarah Barnum, David McLaughlin, Monika Vance, Estibaliz Arce, Manpreet Singh, Silvia Zaragoza Domingo

- Consider examples of specific orphan or genetic diseases to augment key points

- Background / focus of paper
    - Cognition is an indicator of "normal" development
        - Cognition is measured the context of age-appropriate development
        - "Normal" course of cognitive trajectories in children with disabilities, neuropsychiatric conditions is less well known
    - Cognition is often what parents/caregivers are concerned about in orphan / genetic diseases, but it is unclear whether their definition of cognition is the traditional definition
        - May not be school-based / normative performance as measured by cognitive tests
        - What might parents mean when they say they want to see improved cognition?
            - Increase in functional ability
                - Paying attention and following directions better
                - Self-monitoring / care behavior is better/ more developmentally appropriate
                - Want their child to "know better:" age appropriate knowledge regarding safety and/or self-monitoring behaviors (more aware of consequences of behavior, less impulsive).
            - Improved communication (needs, wants, thoughts, and feelings)
            - Increased goal-directed behavior in "normal social context" (autism)

Cognition Outline, continued

- In a clinical trial, improving *capacity* of cognition may not manifest in skills without training / learning / more experience.
- May also not "look normal" or follow a typical developmental course, so normative data may not be as relevant as a comparison

- Measurement of cognitive functioning encompasses many things
  - Cognitive function / tests
    - IQ – broad cognitive ability
    - Domain-based cognitive abilities
      - Sensory-motor, attention, verbal and visual learning and memory, executive function / achievement / school based performance
    - Measured typically by "normed" cognitive tests (computer and paper/pencil)
      - Comparison vs. "normal" development by age, sex, grade etc.
    - Used to assess strengths / weaknesses, monitoring status / clinical outcomes over time, including in clinical trials
- Normal cognitive development / performance is often negatively impacted in neuropsychiatric and neurodegenerative disorders
  - More variable course of development, may have delays / fail to make age appropriate gains
  - Course of development less predictable per normative data from known cognitive assessment tools/ procedures
- Cognition and cognitive trajectory is even MORE different in orphan diseases
  - Many orphan diseases are associated with dramatically atypical development (altered developmental trajectory), including vastly delayed cognitive development
    - Comparing with natural course of cognitive development may not be helpful/appropriate
  - In treatment trials for orphan disease (vs. ADHD or MDD), time course could be months or years before seeing clinically meaningful improvement
    - How should we measure in this situation?
  - We may be treating the symptoms of a disorder, but also target developmental outcomes that involve new learning
    - Developmental vs. medical model perspective

Cognition Outline, continued

- Are we measuring the right thing when we measure cognition / shift to normal cognitive development in orphan disease?
  - Often use typical performance on cognitive measures / typical development as the goal for outcome
    - Are normative data always required, or even measuring the right thing?
  - Improving cognitive or functional ability may not look “more typical” so measuring against normative data may not be appropriate (particularly not expecting return to a normal trajectory or “next step”)
  - There is a bias against caregiver reported assessment of cognitive ability vs. functional assessment
    - May be particularly problematic for subtle changes that are not picked up by typical cognitive tools
- Goal for measuring cognition in clinical trials
  - Often measure cognition as a safety outcome versus as an efficacy outcome
  - Improvements in cognition are not accepted as “real” or as potential label claims unless they are a primary or key secondary outcome
    - ADHD is a unique case here, as attention / impulsivity are cognitive outcomes that are associated with the core condition
    - Most other psychiatric and neurologic conditions do not have cognitive function as a core symptom for treatment, but cognition is negatively affected by the disorder itself
      - Epilepsy, MDD
      - Don’t get an “indication” for a drug to improve cognitive functioning in these conditions

Cognition Outline, continued

- Especially for a neurodevelopmental disorder or neurodegenerative disorder (as in many orphan diseases / genetic condition), a change in cognitive ability as a result of a treatment (ie, genetic treatment) may not manifest in change in performance without learning
- For gene therapy trials in orphan disease…
  - If the therapy works, what is expected to change in cognition "so late" in development
  - Is comparing to the normal trajectory even appropriate
    - Standard deviations vs. normal are understood as clinically relevant in normal developmental context
    - Smaller changes may be much more meaningful, MCID may be smaller
    - May be important HOW impaired at baseline (ie, 1st vs. 50th percentile)

- Other important topics
  - Volition / motivation / communication deficit may make assessing true cognitive abilities difficult
  - For degenerative conditions – loss of functioning over time impacts engagement
  - What is the association with functional / behavioral outcomes (ie, Vineland ABS) or expected outcomes (ages and stages)
  - Interference of behavioral problems or other comorbidities may mask/affect cognitive measurement

Timelines – Deadlines

- Paper 1: CGI (leads: Joan, Gahan)
- Let's set up meetings:
  - ~~1) Meeting to discuss outline and identify section leaders~~
  - 2) First draft of manuscript
    - Date____
  - 3) Final draft for submission – target July 1st
- Other thoughts? More meetings needed?

Timelines – Deadlines

- Paper 2: Cognition (leads: Cristan, Gahan)
- Let's set up meetings:

  - ~~1) Meeting to discuss outline and identify section leaders~~
    - ~~Date_____~~
  - 2) First draft of manuscript
    - Date____
  - 3) Final draft for submission – target July 1st

- Other thoughts? More meetings needed?

Timelines – Deadlines

- Paper 3: Ethics (leads: Cristan, Joe, Kemi)
- Let's set up meetings:

  - ~~1) Meeting to discuss outline and identify section leaders~~
    - ~~Date_____~~
  - 2) First draft of manuscript
    - Date____
  - 3) Final draft for submission – target July 1st

- Other thoughts? More meetings needed?

Other Manuscripts Will Keep For Round 2

- Maybe begin this summer?
- Ideas submitted
  - Development of Endpoints for Disease Modifying Therapies (example: Rett Syndrome)
  - Biomarkers as Early Indicators of Drug/Biologic Action
  - Confirmatory Evidence – Key to Single Study Approvals
  - Streamlining Pediatric Trials
  - OTHERS…

Next Steps

- Dates of next meetings will be circulated
- See you in Amsterdam?