ISCTM Orphan Disease Working Group Meeting
21-Feb-2024, Mayflower Hotel

Meeting Overview

All participants introduced themselves and signed the attendance sheet, which was returned to the administrative staff. The agenda was reviewed and discussion of key topics ensued.

Recommendations for follow up actions

The following concepts for half-day sessions at ISCTM were discussed:

- Composite approaches to analysis of endpoints / clinical trial data
    - Multidomain Response index, composite EPs, global ratings (including CGI)
- Biomarkers in rare diseases
    - Utility for stratification or enrichment of study populations or identification of responsive subpopulations
        - Examples include
            - DMD 95% stride velocity (approved by EMA only)
            - SMA - actigraphy
        - Approaches to engagement with FDA
            - Filing a LOI into the biomarker qualification program
            - Could this mechanism facilitate EP development and qualification for rare diseases

The following potential publications were discussed:

- CGI
    - Includes pros and cons of prescribed anchors
    - Includes pros and cons of 1 global vs multiple domain-specific versions
    - Includes PGI - Use of caregiver (for the most part) or potential for self-report (in select cases)
    - Rare disease has specific challenges, particularly with genetic disorders where symptom presentations are multifactorial (eg, motor, language, cognitive impairment, physiological symptoms, psychiatric comorbidities, etc.)
    - Includes conflicting mandates from regulators on number of anchor points, level of disease specific: position paper from ISCTM may be very helpful
- Measuring cognition as an outcome in rare disease
    - Atypicality of development and lack of long-term outcomes in rare diseases due to lower survival rates, etc.
    - Normative scores vs. expected naturalistic trajectory / history
    - Developmental perspective
    - Cultural issues and language influence ability to validate measures globally
    - Bayley scales may be more useful given language is limited vs. WISC where newer versions may not be available in all languages due to need for renorming.
    - Examples of other functional outcomes or applied cognitive outcomes such as the VMCAT and UPSA
    - Domain specific scores
    - Ability/functioning (VABS) vs. cognition
- Ethics of clinical trials in rare diseases
    - Development programs or trials may be stopped in rare diseases due to challenges with funding, etc., including recent high-profile example in gene disorders.
    - Often leads to dissatisfaction with the research process, reluctance for future participation, and real issues related to access to potentially helpful (though unapproved) medications
    - Protracted development timelines and inconsistent funding mechanism for rare disease drug development can make communication about progress, or study stoppage, more difficult
    - Establishing better guidelines for communication with stakeholders around development programs, especially with trial participants / families, and advocacy.
- Development of endpoints for disease modifying therapies. Example: Retts Syndrome.

Other actions:

- Gahan and Joan will follow up with participants to gauge interest and identify champions for the papers and ½ day sessions, including potential speakers.
- The group expressed interest in continuing periodic meetings (perhaps bi-monthly) between 6-monthly face-to-face WG sessions at ISCTM.