Accelerating development of psychopathology outcome measures- Joint ISCTM/ECNP Working Group
In-person meeting
San Diego, CA
Sept 2024

The Accelerate working group is currently functioning as three separate subgroups, linked by common goals. These goals are to advance the assessment of psychopathology signs and symptoms (Clinical Outcome Assessments - COAs) in three conditions that are currently treatment indications for both FDA and EMA, namely schizophrenia, bipolar disorder and depression. Interest in improving COAs come both from recognition that the scales currently used are quite old, do not reflect either modern scale development parameters, or the current advances in understanding of psychopathology and MOAs of many drugs currently in development.

In addition to in-person attendees, the group was joined via Zoom by ECNP Accelerate co-chair Celso Arango (CA) and schizophrenia sub-group ECNP co-chair Armida Mucci (AM). Koen Demyttenaere (KD), ECNP co-chair of the depression subgroup, and Eduard Vieta (EV), ECNP co-chair of the bipolar subgroup, were unable to attend the meeting. After a brief review of activities to date, the three subgroups met separately and reconvened at the end to provide summaries to the full group. Reports from each subgroup follow.

Schizophrenia. Led by subgroup chairs Anzalee Khan (AK) and Armida Mucci (AM), as well as WG chair Nina Schooler (NS), the group has a draft manuscript developed since the last meeting that addresses the limitations of the widely used PANSS. The manuscript was drafted in sections and the version reviewed consolidated the sections but did not address the considerable overlap among them. The group discussed the draft and agreed that AK would edit, those edits would be reviewed by NS and then distributed to all authors and other interested parties for review. The goal is to submit for publication before the end of '24. The group discussed target journals and agreed that Schizophrenia Bulletin would be the target journal. In addition, a shorter review would be considered to the ISCTM journal innovations in Clinical Neuroscience. NS will contact Jim Gold, the Editor of Schizophrenia Bulletin to determine if they would be interested in such an article prior to submission. The group also agreed that a symposium focusing on both the limitations of the PANSS and the strategies for developing improved assessment measures should be submitted for the Schizophrenia International Research Society meeting (April'25) with AK and AM as chairs.

Bipolar. Led by subgroup co-chair Manpreet Singh (MS) the group discussed limitations and modifications to the currently used YMRS and the structured interviews associated with it. The discussion yielded the basis for an article focused on YMRS limitations. MS agreed to create a first draft. They also reviewed efforts to obtain data from studies that have used the YMRS to evaluate its performance in more detail than has been possible based on data presented in published reports which tend to focus on total scores rather than evaluating individual items; EV has requested access to sponsor datasets to facilitate analysis. Further, given that the YMRS focuses on symptoms of Mania so that it is often used concurrently with a depression rating scale, the group agreed that a future requirement for studies of bipolar disorder would be a scale that addresses the course of illness incorporating periods of mania, depression and euthymia. In

addition to prior work products identified and underway (e.g., updating and revising the YMRS with scale author Bob Young), the subgroup would like to target a novel assessment thereafter.

Depression. Led by subgroup co-chair Jenicka Engler (JE). The depression group had originally planned to focus on improvements to the structured interviews used to assess the MADRS and Hamilton Depression Rating Scale but concerns about the legal implications of that effort redirected the discussion to consideration of development of a new scale while JE and ISCTM leadership are pending legal consultation related to updating the SIGMA and SIGH-D. Considerations for new MDD scale development centered around the following concepts: tailoring the scale to account for more variability within a primarily outpatient MDD trial population (e.g., highest scoring anchors are typically not used on most items for current measures as they are accounting for more inpatient-level severity which reduces the spread of the scale); both psychopathology and wellness constructs. We will be targeting a work product for one novel MDD assessment with consideration of DSM-5 criteria for additional items for screening version (e.g., hypersomnolence; appetite/weight gain) vs. standard version for baseline and visits beyond. This assessment will include a specific Rapid Acting/Psychedelics Subscale and instructions for assessment over past 24HR lookback and this RAAD subscale will exclude items that aren't as reliably assessed over 24HR lookback (e.g., sleep, appetite, weight items). Of consideration in this novel MDD assessment: functional impairment question; keep the euthymic baseline comparison and enhance the instructions for assessment); include open ended intro question: How has your mood been this [LOOKBACK PERIOD]?; specific instructions to rate up if between ratings; addressing double barreling of frequency/severity by separate scoring for both on each item, as well as separating double barreling of overlapping symptom constructs (e.g., irritability from anxiety, affective numbness from loss of interest, self-referential vs. future-oriented negative cognitions). Of consideration is also adding some measure of cognitive alterations due to MDD (e.g., memory, attention, executive functions) - for which JE would recommend a word generation task as that covers most EF constructs noted above plus cognitive flexibility which is likely to capture neuroplasticity of interest for RAADs and can additionally be coded for emotional valence. For future validation consideration of IRR within countries/region/cultural considerations was discussed as well.