Joint ECNP ISCTM Working Group (WG)
Accelerating development of psychopathology outcome measures
In-person meeting Washington DC Feb 24
Chairs: C Arango (ECNP), J Engler (ISCTM) and Nina Schooler (ISCTM)
This was the second in-person meeting for this group. The inaugural meeting took place in Barcelona after the session that sparked creation of the WG to consider modern needs in assessment of psychopathology given that current measures were developed decades ago. The WG, like the Barcelona session focuses on assessment for three indications: schizophrenia, major depressive disorder, and bipolar disorder. The WG met jointly to review prior discussions and to develop timelines and expected work products and then broke into subgroups focused on the three indications. The overall group agreed that an important general work product would be a position paper that addresses achievable goals for new or modified tools that can meet requirements that regulatory agencies, specifically FDA and EMA, require for use in clinical trials that establish efficacy for these indications. There was discussion about insuring harmonization with an already ongoing ECNP Thematic Working Group entitled Clinical Outcomes in Early Phase Clinical Trials led by Silvia Zaragosa Domingo. . The group has produced a document, Clinical Outcomes Assessment Selection - Practical Guidance in Neuroscience Drug Development. Version 2, September 24, 2022 – that is highly relevant to our work. Liaison will be facilitated by Silvia Zaragosa Domingo, as well as other involved in both groups.

The consensus was that the initial focus should be on setting up the three subgroups and allowing them to develop initial timelines and work products. As will be seen from the summaries of the subgroups, they have different initial targets that reflect differences in the status of the existing assessment tools used in clinical trials for each indication. Brief summaries of minutes from the three subgroups are included.

Before reaching consensus, important perspectives were presented about the process in general. It was noted that assessments must capture many facets that may differ during illness course. For example, some outcomes may not be relevant in the short term but may be very important in the long term. It was also noted that evaluations at relapse may need to include measures of context and not just psychopathology. If adaptive testing is envisioned, development of item banks will be a critical task for new scale development. It was pointed out that failed trials, specifically for MDD but potentially for other indications could be examined to assess fit for purpose. Does the FDA have a database that includes these trials and could the WG access it? Analyses examining trials conducted over time to see if the magnitude of difference in drug placebo effect is declining over time with the same scale was discussed. The group agreed that this was a question that the three subgroups focused on indications for schizophrenia, MDD and bipolar disorder could address. Similarly, the question of whether the initial focus should be on modifying existing scales was also considered as a question for the subgroups, since conditions re copyright differ across scales. A comment about the PANSS, the scale being used in Schizophrenia trials was referred to the schizophrenia subgroup.

Following a survey prior to the workgroup, leads were identified for each of the indication subgroup which resulted three separate subgroups to initiate planning. Leads for each subgroup are as follows:

- Major Depressive Disorder: Jenicka Engler (ISCTM) and Koen Demyttenaere (ECNP)
- Bipolar Disorder: Manpreet Singh (ISCTM), Jenicka Engler (ISCTM) and Eduard Vieta (ECNP)
- Schizophrenia: Anzalee Khan ISCTM), Simon Desjardins (ISCTM) and Armida Mucci (ECNP)

Subgroup reports:

<u>Major Depressive Disorder</u>
In Attendance:
Jenicka Engler, Cronos/IQVIA (Chair)
Gary Kay, Cognitive Research Corp
Miriam Evans, Adams Clinical
Heather Belanger, USF
Tony Ortiz, NRC Research Institute
Wenqiong Xue, Boehringer Ingelheim
Barbara Echeverria, WCG

Goals for group: updates to SIGMA first and foremost

- Address double barreling of scoring anchors by separating out 0-6 scores by frequency and severity (like AIRS)
- Add required probes for frequency to SIGMA.
- Address the lookback period issues/standardize recommendations.
- Modification of instructions: include how to assess for euthymic baseline better by focusing on functional impairment, emphasize the difference from euthymic baseline is to be considered on all MADRS items, to assess euthymic baseline on 1st MADRS assessment, document that, and then refer back to that date for all subsequent MADRS, assessing sleep item if medication being used.
- Add line for [Euthymic baseline date] on item 1.
- eCOA carryover recommendations – have the euthymic baseline carry forward from first MADRS assessment, and into the items where referenced.
- More guidance on item 1 vs item 9 pessimism – how to account for it.

Bipolar Disorder

We reviewed the potential working group priorities and products. The group prioritized these initial goals:

1. Systematically review extant literature on the content validity of the YMRS (complete review within 6 months)
2. Develop hypotheses and analytic plans to propose to FDA or conduct with publicly available datasets to determine (initiate collaboration with FDA within the next 3 months; work on analytic plan within 6 months, complete analyses in the next 12 months). There was some discussion about whether a Rasch model would be appropriate for validity testing versus a nominal response model given the variability of anchors.
3. Work with Bob Young on "tweaking" the YMRS to improve reliability and consistency of use - Jenicka shared her initial efforts with the group and there was general agreement this would be worthwhile but not before we've had a chance to evaluate more data to determine focus and scope of what changes could be made (complete in parallel with goals 1 and 2 above).

In attendance were:
Terry Frangiosa (Faegre Drinker; has expertise in targeted reviews for scales and has volunteered to start systematically reviewing the literature on content validity of YMRS; was curious whether there has been a recent evaluation of concept solicitation in applying YMRS in pediatric populations or cognitive debriefing in adults to evaluate its performance).
Josh Langfus (Clinical Psychology doctoral student at UNC-Chapel Hill; has worked with Eric Youngstrom on scale development in pediatric mood disorders and has analysis chops, and willing to engage with FDA to develop an analysis plan to evaluate past registered trial data for item response theory or a nominal response model analysis)
Becky Berman (NIMH - RDoC Scientific Program Manager; still exploring contribution and expressed interest)
Rasmus Licht (Aalborg University, vocal about the need to take a data-driven approach to making updates to the YMRS)
Manpreet Singh - (UC Davis, previously at Stanford, has used YMRS for 20 years in pediatric bipolar and bipolar risk populations; interested in co-chairing and developmental adaptations of the YMRS)
Submitted by:
Manpreet K. Singh, MD MS
Professor of Psychiatry and Behavioral Sciences
University of California Davis

Schizophrenia

In attendance

Larry Alphs, Larry Alphs Consulting
Celso Arango,Hospital Gral Univ Gregorio Marañón - Universidad Complutense Madrid - CIBERSAM
Dragana Bugarski-Kirola, ACADIA Pharmaceuticals GmbH Switzerland
Bill Clark, Dainippon Sumitomo Pharma
Kia Crittenden-Ward, Signant Health
Simon Desjardins, Adams Clinical
Anzalee Khan, The Nathan S. Kline Institute for Psychiatric Research
Steve Marder UCLA
Nina Schooler, SUNY Downstate Health Sciences Center
Adam Simmons, Premier Research
Laura Swett, FDA Office of New Drugs
Monika Vance, Santium
Peter Weiden, Renaissance School of Medicine at Stony Brook University
Glen Wunderlich, Boehringer Ingelheim
Silvia Zaragoza Domingo, Neuropsynchro / Jazz Pharmaceuticals

The subgroup leaders, Khan and Desjardins introduced themselves to the group. Armida Mucci, the third leader was unable to attend. We first discussed the option of modifications to the PANSS. During the group discussions Monica Vance noted the PANSS and SCI-PANSS copyright holder is Pearson Assessments Inc and offered to contact Pearson to determine whether they were open to considering modifications of the PANSS. The consensus was that it was not a useful exercise to modify the PANSS as evaluating the psychometric properties of the PANSS, and constructs measured by the PANSS in a comprehensive fashion may lead to creating a lengthier scale with redundant inquiries. Therefore, the following was determined:

- A better strategy is to identify the limitations and drawbacks with the PANSS which will be articulated in a white paper or a prominent peer reviewed journal. This publication would serve as the rationale for developing an improved scale.
- Although the PANSS item definitions and anchors are copyrighted, other extant scales that can be drawn on are not, e.g. the BPRS and PRS which were the progenitors of the PANSS.
- A new scale would likely need to be multi-modal, incorporating PRO elements as well as COAs, formally recognizing that much of what is included in COA in this indication are derived from patient reports.
- Development of a new scale would first require drafting of items to be measured based on literature reviews, expert opinion and patient focus groups

The next step is to convene a virtual meeting of the subgroup to consider how to proceed including developing a timeline for activities.