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General Information

Key Personnel (in addition to PI):
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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/coi_6.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00391222 - RISBMN3001 - A Randomized, Double Blind, Placebo and Active Controlled Parallel Group Study to Evaluate the Efficacy and Safety of Risperidone Long-acting Injectable (LAI) for the Prevention of Mood Episodes in the Treatment of Subjects With Bipolar I Disorder
2. NCT00132678 - RISBIM3003 - A Randomized, Double-blind, Placebo-controlled Study to Explore the Efficacy and Safety of Risperidone Long-acting Intramuscular Injectable in the Prevention of Mood Episodes in Bipolar 1 Disorder, With Open-label Extension
3. NCT00094926 - RIS-BIP-302 - A Prospective, Randomized, Double-blind, Placebo-controlled Study of the Effectiveness and Safety of RISPERDAL CONSTA Augmentation in Adult Patients With Frequently-relapsing Bipolar Disorder
4. NCT00237289 - CR002653 (CAPSS-168) - Topiramate Versus Placebo as add-on Treatment in Patients With Bipolar Disorder in the Outpatient Setting

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Consistency checks to improve measurement with the Young Mania Rating Scale (YMRS)

Narrative Summary:

Symptom manifestations in studies of psychiatric disorders can be subtle. Small imprecisions in measurement can lead to over- or under-estimation of change. One strategy to improve measurement is to conduct logical consistency checks within and across measures. The International Society for CNS Clinical Trials and Methodology convened an expert working-group that assembled consistency/inconsistency flags for the Young Mantia Rating Scale for the purpose of improving the quality of measurement when using this scale. Flags will be applied to assessments derived from clinical trials to help understand how often various potential scoring inconsistencies

occur.

Scientific Abstract:

Background: Symptom manifestations can be subtle. Small imprecisions in measurement can lead to over- or under-estimation of change. One strategy to improve measurement is to conduct logical consistency checks between item responses (i.e., cross-sectionally) and across test administrations (i.e., longitudinally) of rating scales, bearing in mind that some degree of inconsistency is to be expected due to subject-based variability. Objective: Test consistency flags for the YMRS on clinical trial data. Study Design: International Society for CNS Clinical Trials and Methodology convened an expert Working Group that assembled consistency/inconsistency flags for the Young Mania Rating Scale (YMRS). Participants: Data sets are being requested from sponsors who conducted clinical trials that used the YMRS. Primary and secondary outcome measures: Primary outcome measure is the frequency with which each of the potential scoring inconsistencies occurs. Secondary outcome is the frequency with which ratings have multiple inconsistencies. Statistical analysis: Descriptive analysis of frequency of occurrence of each of the potential scoring inconsistencies. Trials or investigators will not be identified in the reporting of the results.

Brief Project Background and Statement of Project Significance:

Symptom manifestations can be subtle. Small imprecisions in measurement can lead to over- or under-estimation of change. One strategy to improve measurement is to conduct logical consistency checks between item responses (i.e., cross-sectionally) and across test administrations (i.e., longitudinally) of rating scales, bearing in mind that some degree of inconsistency is to be expected due to subject-based variability. The International Society for CNS Clinical Trials and Methodology (ISCTM) expert Working Group focusing on improving consistency in measurement has been developing algorithms for flags to identify possible errors in use of rating scales widely used in our field. The model includes developing an algorithm based on the "expert opinion" of the working group and then testing it in data sets. Recommendations have been published for the Positive and Negative Syndrome Scale (PANSS) (Rabinowitz and Rabinowitz, 2021; Rabinowitz et al., 2017), the Personal and Social Performance (PSP) scale (Rabinowitz et al., 2021), the Montgomery-Asberg Depression Rating Scale (MADRS)(Rabinowitz et al., 2019) and the Hamilton Rating Scale for Depression (HAM-D) (Rabinowitz et al., 2022). The value of our approach of flagging inconsistencies on improving signal detection has recently been demonstrated (Opler et al., 2021).

Specific Aims of the Project:

Apply algorithm developed based on expert opinion to detect scoring inconsistencies in the use of the YMRS scale. Algorithm to be applied to data sets from various clinical trials. Recommendations based on this work to be published.

What is your Study Design?:

Methodological research

What is the purpose of the analysis being proposed? Please select all that apply.

Research on clinical trial methods

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Data on all subjects with available data on YMRS (Young Mania Rating Scale). We are requesting YMRS item level data and where available CGI-s data. All data by visit with sequential subject identifiers. Please note that we do not

need patient demographic, psychiatric history, or safety data.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

The primary outcome measure is the frequency with which each of the potential scoring inconsistencies("flags") occurs. Secondary outcome is the frequency with which YMRS administrations have multiple inconsistencies. Flags are included as an attachment to this request.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Potential scoring inconsistencies are defined based on the inconsistency flags developed by the expert working group of the International Society for CNS Clinical Trials and Methodology.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

YMRS item level data to be used to compute and apply flags.

Statistical Analysis Plan:

The frequency with which each of the expert-derived logical consistency flags occurred in the clinical trial data will be assessed. Then, using the norms that we derived from the trials, we will apply all of the following empirically-based checks of outlier rating administrations: (1) Underuse of a value (e.g., rarely choosing a score of 4), (2) Overuse of a value; (3) Disproportionate use of even or odd response choices; (4) "Long-string," using the same response on several consecutive items--the assumption is that careless raters may choose the same response option to many questions in a row and that attentive raters will not use the same response option for large numbers of consecutive items; (5) Inter-item standard deviation which checks for random patterns of response within a YMRS administration as measured by how much an individual administration strays from its own midpoint across the YMRS items, and (6) Outlier response choices on multiple items as measured by the Mahalanobis distance that shows when an individual is on the outskirts of the multivariate distribution formed by responses to all items. Outliers were predefined as administrations that were in the top or bottom 2.5 percent of one or more of the measures, or 5% on only one side for skewed items where lower 2.5% does not exist (to approximate a p-value of .05). To identify the outlier cutting points for overuse or underuse of values, disproportionate use of odd/even values, longest consecutive use of same response choice in each YMRS administration, and intra-item standard deviation and multivariate outliers (Mahalanobis distance), we examined the frequency distributions for each of these measures.
In a final round of analyses, we will evaluate the overlap in flagging by outlier-pattern and expert-derived flags in our clinical trial samples. In addition, we sought to determine how these flags would perform in a sample of administrations completed in a random fashion to simulate what one might find in the case of careless/inattentive subjects or raters. To accomplish this, we will generate a "simulated random" dataset using Monte Carlo methods such that responses were uniformly distributed for each item, without regard to the values of other items. Multivariate outliers were detected using the Mahalanobis distance. Longest consecutive use of values with the same response was examined using the code for detecting long-string responding. Intra-item standard deviation which shows how much each YMRS a administration strays from its midpoint across the YMRS items was computed as per Marjanovic et al (2015) as the standard deviation of responses across the items for an individual YMRS administration. All analyses will be conducted in R version 4.1.3 and using the package 'careless' (Yentes, 2021).
Software Used:
RStudio
Project Timeline:

The working group of experts has already prepared consistency flags. Once we have obtained data sets we will apply these to the data sets. Data management and analysis are anticipated to take 4 months. We anticipate producing a manuscript for publication within 12 months.

Dissemination Plan:

As we have previously done for the Positive and Negative Syndrome Scale (PANSS) (Rabinowitz and Rabinowitz, 2021; Rabinowitz et al., 2017), the Personal and Social Performance (PSP) scale (Rabinowitz et al., 2021), the

Montgomery-Asberg Depression Rating Scale (MADRS)(Rabinowitz et al., 2019) and the Hamilton Rating Scale for Depression (HAM-D) (Rabinowitz et al., 2022) we anticipate producing a journal manuscript presenting the inconsistency flags for the YMRS, the
frequency of their occurrence in available data and our recommendations. Target journal: Journal of Affective Disorders

Bibliography:

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/flags_for_young_mania_rating_scale_version_4_yoda.docx