Eligibility Review Using the Mini International Neuropsychiatric Interview for Acute Schizophrenia Trials: Usability & Common Issues

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SUBMISSION DETAILS

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Methodological Issue Being Addressed 1) Is MINI eligibility review outcome associated with differences in MINI or PANSS duration, PANSS Total Score, study completion, screen failure, or other variables? 2) For acutely psychotic schizophrenia trial participants, is the MINI adequate to confirm diagnostic eligibility criteria? 3) What are common MINI administration issues in this population?

Introduction The Mini International Neuropsychiatric Interview (MINI) for Psychotic Disorders Studies is a widely used diagnostic screening assessment for schizophrenia trials. It is a structured clinical interview incorporating clinical judgment scoring mostly binary (yes/no) questions over approximately 20 minutes with the participant. The MINI has been studied in various populations. However, less is published on use in acutely psychotic inpatient trial populations hallmarked by high levels of disorganization and reality distortion. Notably, the MINI scale author has recently required rater training via Harm Research Institute to standardize the training materials.

Methods 100% of screening MINI and Positive and Negative Syndrome Scale (PANSS) assessments at screening and baseline were audio/video recorded by site raters and reviewed by blinded independent raters . MINI rater training was provided via Harm Research Institute as required. MINI scale adherence and scoring accuracy were assessed as Fail or Pass based upon Modules A (Major Depressive Episode), C (Manic and Hypomanic Episodes), I (Alcohol Use Disorder), J (Substance Use Disorder), and K (Psychotic Disorders) to align with study inclusion and exclusion criteria, while the PANSS were assessed using the Rater Applied Performance Scale (RAPS) and proprietary pass/failure algorithms. MINI Fail reasons were qualitatively coded (e.g., adherence, follow-up, unclear clinical judgement, participant presentation) and a senior unblinded reviewer followed up with the site/sponsor. Resolution actions (e.g., clarification using additional information, re-recording missed items) were also coded. Independent samples t-test and chi-square investigated the relation between MINI review status and MINI and PANSS duration, total PANSS score, and study completion. Pearson correlation coefficient was used to evaluate the relation between MINI and PANSS duration.

Results 101 MINI and PANSS screening assessments were reviewed (MINI Mean = 28 min, SD = 17 min; PANSS Participant Interview Mean = 38 min, SD =13 min) with approximately 25% of MINI administrations (n=25) deemed Fails. Fifty-two percent (n=13) were single issue Fails (adherence, unclear clinical judgment, or participant presentation). Alone or in combination, 64% (n=16) of Fails were due to MINI adherence (mostly Psychotic Disorders Module K), 48% (n=12) participant presentation, and 20% (n=5) unclear clinical judgment. The 36% of Fails due solely to poor MINI adherence (n=9) required re-recording missing questions. Participant presentation Fails were

mostly due to disorganization (e.g., concurrent symptom endorsement and denial, incoherent responses) (n=8), often combined with reduced insight endorsing primary Mood or Schizoaffective Disorders (n=6). Three Fails were due to over-endorsing current substance use. One Fail was due to defensiveness, denying hallucinations and positive symptoms. Notably, all Fails due to participant presentation and adherence were resolved with additional information (e.g., medical records, labs, sober living historical drug testing results), rater remediation and re-recording. The Clinical Eligibility Review Service failed 1 participant on the MINI where the site acknowledged they met criteria for schizoaffective and cannabis use disorders, while 2 participants were failed due to total PANSS score baseline below eligibility threshold. MINI duration was significantly longer for Fails (Mean = 43 min, SD = 24 min) than Passes (Mean = 24 min, SD = 9 min) [$t(26.33) = 4.03$, $p<0.001$]. Additionally, screening participant interview PANSS duration was also significantly longer for MINI Fails (Mean = 45 min, SD = 14 min) than Passes (Mean = 36 min, SD = 12 min) [$t(99) = 3.02$, $p=0.003$]. MINI and PANSS duration was significantly correlated [$r(94) = .47$, $p<0.0001$]. MINI duration at screening was significantly associated with baseline (but not screening) PANSS RAPS failures (MeanFAIL = 19 min, SDFAIL=0.96; MeanPASS = 30 min, SDPASS=18). MINI duration at screening was significantly higher for baseline (but not screening) PANSS RAPS Pass compared to Failures (MeanPASS = 30 min, SDPASS=18; MeanFAIL = 19 min, SDFAIL=0.96; $t(71.93) = 4.88$, $p<0.001$). MINI duration and review status weren't associated with PANSS total score, study completion, or screen failure. PANSS screening duration was not associated with PANSS screening or baseline RAPS Pass/Failure, screen failure status, or study completion.

Conclusion Findings support the use of independent eligibility review in conjunction with objective information to verify diagnostic and trial eligibility in an acutely psychotic population. This is an important consideration for conduct of trials given the unreliability of acutely psychotic individuals to provide accurate histories of illness, and that nearly 16% of this sample had industry-standard diagnostic assessments performed incorrectly that impacted trial eligibility, despite receiving the new standardized MINI training. In this analysis, eligibility review combined with objective additional information prevented the inclusion of trial participants who did not receive a properly conducted standardized diagnostic interview to confirm they met trial eligibility criteria, the inclusion of inappropriate trial subjects with regard to symptom severity and/or diagnostic eligibility, and reduced screen-fail rates. In the opinion of the sponsor, this activity was feasible given the rapid turnaround (24-72 hours) of the eligibility review and ability to gather additional clinical information quickly via email or phone correspondence between the eligibility review service provider, sponsor, and raters. Additional costs associated with recording rater assessments are undeniable; however, previously published data has already supported its use in trial conduct to improve and maintain rater quality and trial data integrity. This analysis further underscores the value of this additional cost through prevention of inappropriate subject enrollment, and high screen failure rates, both of which contribute to increased costs of conducting a trial. Future work is needed with a larger sample size to determine if participant presentation characteristics responsible for MINI Fails is related to other factors like screen failures, trial completion, PANSS total scores, and screening and baseline PANSS RAPS pass/fail status. The analysis of the MINI Fails will be re-run for the poster to determine if the larger sample size will detect differences regarding these factors. Importantly, rater adherence issues may be improved with training tailored for the MINI for Psychotic Disorders Studies (which the scale author has indicated to us he would like to improve, based upon these

findings). Additionally, the feasibility of using a more standardized method for MINI reviews (e.g., RAPS) based upon this pilot for future programs should be explored. MINI duration findings may improve risk-based data monitoring (RBDM).

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