How do threshold MADRS eligibility criteria influence MADRS scoring?

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SUBMISSION DETAILS

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Methodological Issue Being Addressed How do threshold MADRS eligibility criteria influence MADRS scoring?

Introduction The aim of this study is to compare the impact of MADRS protocol inclusion criteria on MADRS total score in 3 similarly designed MDD studies that varied in their MADRS protocol inclusion criteria. We hypothesized that requirement criteria have potential to cause score inflation defined as a greater difference between Screening (SCR) and Baseline (BL).

Methods We selected 3 studies (initiated after 2012) that were double-blind, placebo-controlled, randomized Phase 2 and 3 adjunctive treatment trials investigating safety and efficacy of an investigational medicine in MDD patients with inadequate response to antidepressants in which MADRS was the primary efficacy outcome measure. The MADRS raters in all three studies were experienced clinical trial raters with at least 2 years of experience administering MADRS assessments. They were trained by the same vendor who also provided MADRS quality monitoring.

We defined three study types:

1. Type A: MADRS total score inclusionary criterion at Screening and Baseline.
2. Type B: MADRS total score inclusionary criterion only at Screening.
3. Type C: No MADRS total score as inclusionary criterion at Screening nor at Baseline.

We compared mean SCR to BL MADRS total score change and the percentage of subjects with MADRS ratings indicative of subsyndromal depression (having fewer than 4 items on the MADRS assessed with at least moderate severity).

Results Type B data (N=273) showed a 1.24 point decrease in MADRS total score from SCR (mean=34.11, SD=5.32) to BL (mean=32.85, SD=6.02). Type A data (N=5052) showed a 0.05 point increase in MADRS total score from SCR (mean=31.62, SD=3.59) to BL (mean=31.68, SD=3.74). Type C data (N=1500) showed 0.2 increase in MADRS total score from SCR (mean=32.2, SD=4.87) to BL (mean=32.42, SD=4.95).
Type B was found to be statistically significantly different from Type A and C using a t-test ($p<0.05$). We also analyzed the percentage of subsyndromal subjects in Type B and found that it increased from SCR (10.21%) to BL (16.78%). For Type A, percentage of subsyndromal subjects was 22.5% at SCR and 21.2% at BL, for Type C it was 22.6% (SCR) and 20.6% (BL).

Conclusion We found the largest MADRS score change from SCR to BL when threshold eligibility

criteria are specified only for the screening visit. Consistent with this finding is that in this type of study, the percentage of subsyndromal patients decreased from SCR to BL, suggesting that the subjects were scored with a higher symptom severity at SCR when it was required for inclusion, and then lower severity at BL when it was not. Our findings seem to show that some raters or patients may report desired severity when required for inclusion, whether intentionally or not. Some limitations of our research include selecting only one study of each type, disparities in sample size between study types, and other protocol specifics which may have influenced our results. Future research can investigate whether another pre-specified criterion, like a CGI-S measure that is not used for inclusion would also show similar findings.

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Guidelines I have read and understand the Poster Guidelines

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