Statistical enrichment potential using the SIGH-D in an open-label lead-in trial

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Methodological Issue Being Addressed Assessing whether SIGH-D scores collected in an open-label, site-sponsored trial can be used to identify high-quality candidates for subsequent adjunctive clinical trials.

Introduction Increasing sample homogeneity is a strategy for improving statistical power and enhancing the likelihood of detecting treatment effects in psychiatric trials. However, enrichment approaches must avoid reliance on clinical response or demographic features to preserve trial integrity and generalizability. Traditional sum scores from depression scales, including the SIGH-D, provide limited insight into the multidimensional structure of depressive symptoms and can obscure atypical patterns of symptoms that reduce the ability of a trial to detect true treatment effects. Recent work using the MADRS demonstrates examining how symptoms relate to each other, and not only severity, can identify participants whose symptom structure is similar to a “canonical” depression presentation. Applying these methods to SIGH-D data collected during open-label lead-in designs may allow identification of participants whose symptom organization deviates from canonical depressive profiles before randomization, without reference to treatment response or demographics.

Methods SIGH-D data were obtained from 194 participants enrolled in an open-label antidepressant lead-in at baseline, Day 21 on antidepressant, and Day 42 on antidepressant. To quantify individual structural changes in symptom presentation, we computed variance–covariance difference (VCD) vectors using paired baseline and Day-21 item scores. These profiles quantify and summarize each participant’s unique pattern of symptom relationships. These VCD vectors served as features for an Isolation Forest model, producing anomaly scores reflecting each participant’s deviation from canonical depressive symptom structure. Importantly, this method is agnostic to treatment response and demographics. We evaluated “enrichment rate” by determining the proportion of antidepressant non-responders (defined as Day-42 SIGH-D ≥ 20) whose anomaly scores fell below a previously established MADRS-based cut-off from sponsor-level research.

Results Stability analyses replicated previously published patterns, supporting this implementation was robust. Using the tuned model, we generated anomaly scores for all complete-case participants and calculated enrichment rates. Across the full analyzable sample, 49.5% (n = 96) fell below the canonical-structure threshold. Among antidepressant responders, 41.6% (n = 47) showed canonical structure, whereas a substantially higher proportion of

non-responders, 60.5% (n = 49) met the canonical threshold. The enrichment level of the antidepressant non-responders closely approximates those reported in controlled sponsor-level datasets containing clinically verified canonical depressive presentations.

Conclusion This study demonstrates the feasibility of deriving reliable anomaly scores from site-level SIGH-D data collected during an open-label antidepressant lead-in trial. The finding that non-responders were strongly enriched for canonical symptom structure (at rates comparable to industry-level screening cohorts) suggests that open-label lead-in studies can be leveraged to pre-identify participants who are likely to meet statistical enrichment criteria. These results support the broader use of symptom-structure–based enrichment methods as a response and demographic agnostic strategy to improve trial sensitivity in depression research.

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Guidelines I have read and understand the Poster Guidelines

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