

SAGE Part 1 Statistical Analysis Plan

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Overview

SAGE Part 1 is a pilot randomized trial designed to estimate the effect of positive versus neutral post-sedation educational framing on depressive symptoms after propofol infusion. This plan prespecifies the primary outcome, primary contrast, analysis populations, and decision rules.

- **Design:** Parallel-group, 1:1 randomization (N = 20; 10 per arm) to response-focused educational framing vs. diagnosis-focused educational framing. Allocation uses permuted blocks of 4, with no stratification.
- **Primary outcome:** Change in MADRS total score from baseline (~1 week [7 ±2 days] prior to intervention day) averaged across post-intervention days 1, 2, and 3.
- **Estimand:** The difference between arms in mean MADRS change over days 1-3 in all randomized participants who receive the propofol infusion.
- **Baseline:** The day -7 MADRS is the baseline for all change scores. The screening MADRS is used for eligibility only.

Analysis population

- All randomized participants who receive the propofol infusion and educational intervention, analyzed by assigned arm.

Primary analysis

The primary analysis estimates the between-arm difference in mean MADRS change across days 1-3, using a linear model for repeated measures (MMRM) adjusted for baseline MADRS. The adjusted difference is reported with a 95% confidence interval, along with a standardized effect size.

Prespecified covariate-imbalance contingency

Additional baseline covariates may be added to the primary model if the arms are meaningfully imbalanced on them.

- **Candidate covariates:**
 - Pre-randomization expectancy score
 - Antidepressant use at enrollment
 - Sex
- **Trigger:** $|SMD| > 0.5$.
- **Rule:** If one or more covariates exceed the trigger, the single covariate with the largest $|SMD|$ is added to the primary analysis model as a main effect. No more than one contingent covariate is added, to protect model stability with only 10 participants per arm.
- **Reporting:** Baseline SMDs for all candidates are reported. If a covariate is added, the model adjusted for baseline MADRS only is also reported.

Secondary outcomes: response and remission

Response and remission are defined from each participant's mean MADRS across days 1-3, matching the primary outcome window.

- Response: $\geq 50\%$ reduction from baseline MADRS.
- Remission: Mean MADRS ≤ 10 .
- Analysis: Proportions and risk difference by arm with 95% confidence intervals, using exact methods appropriate to the sample size.
- Missing data: Participants with no post-baseline MADRS are counted as non-responders and non-remitters. Participants with at least one post-baseline MADRS are classified from their available days. Secondary analyses are exploratory. No adjustment for multiplicity is made.

Missing data

The primary model (MMRM) uses all available post-baseline MADRS observations under a missing-at-random assumption, with no imputation. The number and pattern of missing assessments are reported by arm and day.

Sensitivity analyses

Each sensitivity analysis reports the same between-arm contrast as the primary analysis.

- **Contingent covariates:** If a covariate is added under the imbalance rule, the model adjusted for baseline MADRS only is also reported.
- **Model specification:** An alternative model, such as ANCOVA on each participant's mean change across days 1-3, to check that results do not depend on modeling choices.

General conventions

- All tests are two-sided at an alpha of 0.05.
- Given the pilot design, results are primarily interpreted by effect size and confidence interval, with statistical significance as a supporting measure.
- MADRS raters are blinded to condition/randomization.
- Any deviation from this plan will be documented and justified in the final report.