STATISTICAL ANALYSIS PLAN for CLINICALTRIALS.GOV

Perioperative mental health intervention for depression and anxiety in older adults undergoing surgery

Statistical Analysis Plan
(Abridged)

Version: 1

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Table of Contents

Abbreviations

CPMH	Center for Perioperative Mental Health
NIMH	National Institute of Mental Health
BA	Behavioral Activation
MO	Medication Optimization
RCT	Randomized Controlled Trial
PHQ-ADS	Patient Health Questionnaire Anxiety and Depression Scale
mITT	Modified Intent-to-Treat
BPI	Brief Pain Inventory
PPSP	Persistent Postsurgical Pain

1 INTRODUCTION

Inadequate management of preoperative mental health disorders often contributes to poor postoperative outcomes [1], including increased rates of readmission, delirium, falls, and mortality [2-5]. However, very little work has been done to improve perioperative mental health. In particular, there have not been any systematic efforts to identify evidence-based behavioral interventions that were originally developed for depression and anxiety in otherwise medically well psychiatric patients, adapt them for use in surgical populations, test their effectiveness in these patient populations, and study implementation strategies.

The proposed study will focus on comparing a perioperative mental health intervention of behavioral therapy focused on Behavioral Activation (BA), plus Medication Optimization (MO), compared to enhanced usual care, among older adults undergoing cardiac, orthopedic or oncologic procedures with anesthesia (N=300; n=100 each surgical type). We chose to use enhanced usual care to provide some harmonization between the participants in the usual care arm. Providing resources to participants in both arms increases the possibility of benefit for all participants, which may potentially improve recruitment and retention.

We hypothesize that the mental health intervention can mitigate anxiety and depression symptoms during the perioperative period [6]. Towards this end, we propose to test the effectiveness as well as the implementation potential of the intervention in a Hybrid Type 1 Effectiveness-Implementation RCT Design.

This study includes adults aged 60 and older with current depression/anxiety symptoms (PHQ-ADS ≥10) and that are undergoing major orthopedic, cardiac or oncologic procedures. Each patient is randomized to the perioperative mental health intervention vs enhanced usual care.

2 ANALYSIS OBJECTIVES

Aim 1. Examine the effects of a perioperative mental health intervention, composed of a wellness program and medication optimization, on depression/anxiety symptoms compared to enhanced usual care in patients undergoing a scheduled cardiac, orthopedic or oncologic surgical procedure.

H1: A greater decrease in depression/anxiety symptoms will occur in patients randomized to the perioperative mental health intervention compared to patients randomized to enhanced usual care.

3 ANALYSIS SETS/ POPULATIONS/SUBGROUPS

We will randomize older adults aged ≥60 to either the perioperative mental health intervention or enhanced usual care. The modified intent-to-treat analyses will include all patients that underwent a orthopedic, cardiac or oncologic surgical procedure. The goal target in the mITT group is 300 patients, with approximately 100 patients in each surgical cohort. Patients can choose to refuse any component of this study.

4 DATA SOURCE

Below is a schedule of the primary outcome measures

Effectiveness Outcomes		**Data Source**	**Description**	**Data Collection Mechanism**	**Time points**
Primary (Clinical)	3-month change in anxiety and/or depression symptoms	PHQ-ADS [7]	A validated composite of symptoms of depression and anxiety	Patient self-report	Baseline; 1mo and 3 mo

Note. PHQ-ADS = Patient Health Questionnaire Anxiety and Depression Scale;

5 RANDOMIZATION

All eligible and consented participants will be randomized in a 1:1 ratio to receive either the perioperative mental health intervention or enhanced usual care. The study biostatistician generates the randomization table using a variable block sequence. The assignment of the treatment condition for each individual participant will be done by the REDCap® randomization module [15,16] after confirming trial eligibility. For participants assigned to the intervention, a randomization table will be generated using a similar block sequence design, and the data manager will manually select the individual intervention team member according to the randomization table and record that information in REDCap®. This process will trigger an automatic notification via REDCap® to the assigned interventionists.

6 BLINDING

Research coordinators responsible for collecting outcome data throughout the study will be blinded until data collection is complete. At the end of the 3-month follow-up, the research coordinators will complete a blinding question to guess the arm to which each participant was allocated. This will allow the team to determine the effectiveness of the blinding procedures [17]. Upon completing this form, it will be locked by the data manager, and the participant's assignment will be revealed to the research coordinators to conduct the end-of-study interviews with the participants in the intervention arm.

7 MINIMIZATION OF BIAS

Enrollment will not be based on sex or ethnic background. Standard Care will not be affected for any of the patients due to study participation. Completion of the outcomes will be entirely patient-reported, to minimize the assessor's bias in interpreting patient responses.

8 ENDPOINTS AND COVARIATES

Primary outcome

The primary outcome of the study is the change in PHQ-ADS from baseline to 3-month visit. All models will be adjusted for covariates which strongly associate with the outcome and which may differ across patient sub-populations.

9 HANDLING OF MISSING VALUES AND OTHER DATA CONVENTIONS

The data is regularly reviewed to identify missing data. All models will be fit with SAS or R using a maximum likelihood criteria which utilizes all available information yielding optimal solutions in the face of missing data as long as it is missing at random. Multiple imputation will be used where the statistical model does not already provide appropriate protection for data missing at random.

- For the clinical assessments, if the scale consisted of 6-10 items and a participant is missing one item, then the average of the other items will be used to fill in the missing item. If more than 1 item is missing, then that participant's data will not be used for that scale. For a 1-5 item scale, any missing data will exclude that participant's data for that scale. For scales with greater than 10 items, a 10% cutoff rule will be employed for missing data.

10 STATISTICAL PROCEDURES

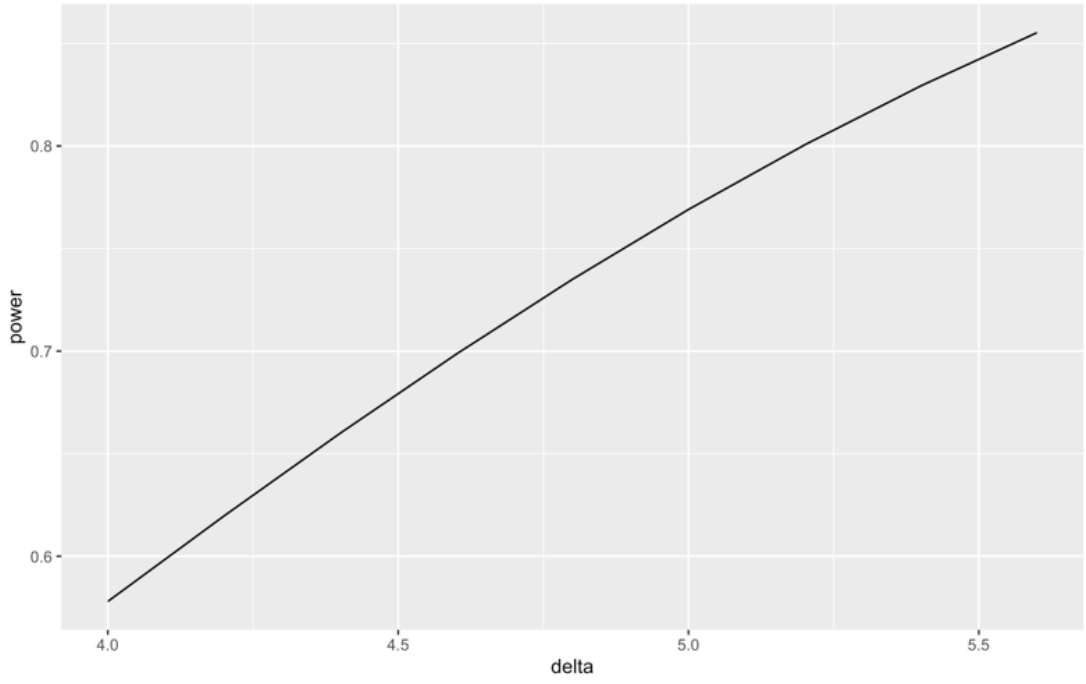
10.1 Primary Outcome Analyses

The primary outcome of the study is the change in PHQ-ADS from baseline to 3-month visit. In each surgical cohort, a mixed model repeated measures ANOVA with a treatment group by time point design will be run to determine the overall impact of the intervention on the change in the PHQ-ADS. The results will be synthesized using a prespecified fixed-effects meta-analysis of the three trials, and the plan is for this to be the primary analytic strategy to demonstrate effectiveness of the intervention across all surgical subgroups. The mixed model within each cohort is ideal because it uses all available data and is robust despite missing data. The population used for the primary analysis is a modified Intent to Treat (mITT) group consisting of those randomized participants who actually undergo the surgery (ie, for randomized participants in whom the surgery is cancelled or indefinitely delayed, they are not part of the analysis sample). Participants will still be included in the analysis if they died post-operatively or were lost to followup, prior to the end of the trial. Statistical significance will be set at 0.05 and relevant changes in PHQ-ADS will be estimated along with 95% confidence intervals. Any data available at baseline, 1 month or 3 months are included in the repeated measures model. The three-month response is the primary outcome and is tested with an appropriate contrast to compare the change between the two groups from baseline to 3 months.

10.2 Power

We based sample size on the need to have adequate power to examine intervention effects within each of the individual surgical subgroups (n=100 each), as well as the planned meta-analysis (N=300). To estimate the power, we examined the manuscript that provided the original validity and reliability studies for the PHQ-ADS [49] and one of the trials that provided data for that study (Stepped Care to Optimize Pain care Effectiveness (SCOPE)) [84,85]. The PHQ-ADS authors estimate the minimal clinically important difference (MCID) from the standard error of measure as 3-4 points [49]. Since the SCOPE trial was a pain relief study without a requirement for anxiety or depression, we conducted a blinded sample size reassessment after 125 participants had completed the 3-month assessment in the 3 cohorts. The average change in the PHQ-ADS was 6.7 with a standard deviation of 8.8 (d= 0.76). These 125 subjects were from 135 in the mITT group, or 7% dropout. With the chosen sample size of 50 mITT subjects in each group, we estimated the power for a simple t-test between the two groups of size 46, a 2-tailed significance level of 0.05, and a difference between the two groups of >4 points as shown in figure 1 below. These power calculations are somewhat conservative as they are based on a simple t-test and we will be using a repeated measures ANOVA for the actual analysis.

Figure 1: Power calculation curve suggesting a power of at least 55% for groups of size 46, calculated from a mITT sample size of 50 in each group with a 7% dropout, and a difference between groups >4 points.



11 QUALITY CONTROL PLANS

Data quality will be assessed using REDCap validation methods and ongoing review of data (e.g., identification of missing data, outliers, etc.). Range and consistency checks will also be employed.

12 PROGRAMMING PLANS

Statistical software (SAS and R) will be used to produce results and raw data will be available for accompanying papers to be submitted for publication (following approval by Principal Investigators).

13 FUNDING AND ACKNOWLEDGMENTS

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