Esketamine for Major Depressive Disorder with Psychotic Features

Documentation for the statistical analysis plan

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Justification

This document should be viewed as a companion to the protocol for a randomized, double-blind, placebo-controlled, parallel clinical trial of sub-anesthetic esketamine for Major Depressive Disorder with psychotic features - ESKETPD, which is published elsewhere (REFERENCE). It is primarily justified by our intent to follow the principles of transparency, openness and reproducibility proposed by the Open Science movement (Crüwell et al., 2019; Kathawalla et al., 2021).

Therefore, this document has two main goals: to further explain the analysis plan and the sample size justification of the clinical trial, and second to make the underlying code openly available. This `.PDF` document was generated by a reproducible `R Markdown` script (Xie et al., 2022), which is built on R (R Core Team, 2020). This script contains the underlying code which can be opened and inspected within R, or at the Open Science Framework repository where it is permanently registered with a digital object identifier (Souza-Marques, 2022).

A brief description of the study design and its relation to our modelling strategy for the statistical analysis plan is discussed. Use of simulation and the assumptions of our analysis plan for this study are presented in detail, followed by a step-by-step process of how we conducted such simulations, and finally a brief discussion of their implications to the study.

Brief study rationale

The study aims to detect possible differences in depressive symptoms between patients treated with intravenous esketamine and those treated with midazolam as an active placebo, in a trial with two parallel arms. Further information on the study methods, including participants and instruments, are available on the protocol (REFERENCE). The main outcome for this analysis is the mean Montgomery-Asberg Depression Rating Scale (MADRS) score at 24h after the last esketamine infusion. The MADRS is a 10-item scale that ranges from 0 to 60, which is reliably used in clinical trials of antidepressants, including rapid-acting antidepressants such as ketamine (Coyle & Laws, 2015; Khan et al., 2002).

Modelling strategy

We focus on the difference in depressive symptoms between periods (baseline vs post-treatment) and groups (esketamine vs placebo), that is, the change in MADRS scores for those treated with esketamine in comparison to those treated with midazolam, which has no known antidepressant effects and acts as an active placebo comparison. This means that the chosen model should contain the factors of Period, Drug, and their interaction, which is the main result of this study.

The “Drug” factor varies between participants, allocated in one of two groups, while “Period” varies within participants, in line with the repeated measuring of depressive symptoms as per study design.

Given these characteristics and the available statistical tools, a Linear Mixed-Effects Model (LMM) is chosen as a modelling strategy for its ability to accommodate both the dependency (data points at baseline and post-treatment are not independent) and hierarchical (multilevel) structure of the study design - for further information on LMMs, see (Bolker et al., 2009; Magezi, 2015). More specifically, we chose a LMM with a random intercept for participants, as limitations on sample size would not allow for a model with random intercepts and slopes. For simplicity and given the , we assume the dependent variable, MADRS scores, will follow a somewhat symmetric distribution, and thus the LMM is run with a Gaussian distribution and identity link.

The main model for this study features MADRS scores as the dependent variable; Period, Drug and their interaction as fixed effects, and Participants as random effects. A simplified LMM model is as follows: $y = X\beta + Z\mu + e$. In our case, $X\beta$ encodes the fixed effects of Period and Drug, $Z\mu$ the random effects, and e the error term. In R code, this model is classically written as `MADRS ~ Period * Drug + (1 | Subj_ID)`.

Using simulations to determine sample size

The sample size for this study was established by means of simulation, which allowed precise determination of the required number of participants given a set of predetermined parameters.

```
summary(cars)
```

```
##      speed           dist
##  Min.   : 4.0   Min.   :  2.00
##  1st Qu.:12.0   1st Qu.: 26.00
##  Median :15.0   Median : 36.00
##  Mean   :15.4   Mean   : 42.98
##  3rd Qu.:19.0   3rd Qu.: 56.00
##  Max.   :25.0   Max.   :120.00
```

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