Internet-delivered Cognitive Behavior Therapy Compared to Stress Management for Atrial Fibrillation- a Randomized Controlled Trial With Active Control

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Statistical Analysis Plan

The primary outcome of the study is the difference between the treatment groups in AFEQT quality of life measured on a scale ranging from zero (severe symptoms and disability) to 100 (no symptoms and no disability). The patients are observed at baseline and again every week for twelve consecutive weeks. The difference between treatment groups in the mean quality of life score at twelve weeks is estimated with a linear mixed effect model. The quality-of-life score is the dependent variable.

The independent variables are a numeric time variable, a binary treatment indicator, and an interaction term between time and treatment. The model includes subject-specific random intercepts, which are assumed to follow a normal distribution. The random intercept can appropriately handle the potential temporal stochastic dependence in the data. The estimates for the parameter values are obtained by maximizing the corresponding likelihood function.

The linearity of the relationship between mean score and time assumed by the model is evaluated visually and tested formally by introducing restricted cubic splines for time in the model. Link functions are explored if necessary to ensure that the inferences on the mean are within the feasible bounded intervals of each outcome. The significance of each comparison is based on Wald's tests and deemed significant if below 5%.

Between group effect sizes are measured by the Cohen's d statistic, defined as the ratio between the mean score difference at twelve weeks and the baseline standard deviation of the score variable. Standard errors and confidence intervals are estimated with 5,000 cluster-bootstrap samples.

All the secondary and exploratory outcomes are measured by numeric variables. They are analyzed with the same approach as the primary outcome. For the secondary outcomes (AFSS-visits, BSQ, SF-12, GSLTPAQ, ISI-5, PHQ-2, GAD-2, PCS) that have only two measurements over time (baseline and post-treatment) testing for departures from linearity is unfeasible.

The patterns and causes of possible missing values are investigated. The inflated statistical level resulting from the multiple comparisons is taken into account in the interpretation of the results and addressed in reports and manuscripts.

The main manuscript shows the results for the following secondary outcomes: SCL, CAQ, BSQ, SF-12, CSQ and AFFS-visits. The supplement shows the results for the following secondary outcomes: GSLTPAQ, PSS-4, PCS, ISI-5, PHQ-2 and GAD-2.

The measures of non-specific effects that are collected at week 2, Credibility Scale and Working Alliance Inventory are compared between the groups with the t-tests.

Adverse events are collected weekly and at post-treatment, at the latter timepoint with respect to the entire treatment period. The sum and mean severity rating of adverse events for each patient over the treatment period is compared between the groups with the t-test and the Mann-Whitney's U test, respectively. The incidence and severity rating of adverse events at post-treatment will be compared using t-test and Mann-Whitney U test, respectively.

Changes from post-treatment to six-month follow-up will be compared within each group only. No between-groups test will be performed on six-month data because the study was not powered to detect potential differences between the groups six months after treatment completion.