NCT 04159480 Study Analysis Plan

Facilitating Assessment of At-Risk Sailors Using Technology (FAAST)

VA Eastern Colorado Health Care System

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Originally, members of the team obtained funding to conduct a randomized controlled trial (RCT) to test the efficacy of Cogito versus active control among Navy personnel; however, significant implementation challenges arose secondary to the COVID-19 pandemic. Thus, with permission from the study sponsor, aims were in part revised as follows: 1) evaluate the feasibility (application download/use and technical challenges) and acceptability (satisfaction) of the Cogito among a cohort of naval personnel; 2) longitudinally characterize time to risk identification by cohort (Cogito/Active Control); 3) identify patterns of symptoms (distress, depressive, post traumatic, suicide-related thoughts and mental and physical health functioning) over time and by study group. However, while the aims of the study changed, the team continued to follow Power Analysis and the original analysis plan. Please see the two sections provided below for greater insight into the changes. Grant funds were used to purchase the use of the Cogito Application for this study. The application is not available for general use, and other than providing technical support, the Cogito Team was not involved with data collection or analyses.

Original statistical analysis plan (SAP) from the protocol:

"Power Analysis. Power is calculated for the two primary hypotheses assessing episodes of distress and distress over the course of the study. We will recruit 1418 participants and expect approximately 33% to decline participation resulting in 950 participants randomized to either the Cogito Companion or Active Control groups, stratified by gender, force and phone type. Assuming 21% attrition, it is expected that 750 participants will complete the entire protocol. While the analysis will include all participants who are randomized, power is based on 750 completed (375 per group). Power to address episodes of distress was estimated using the Poisson regression procedure in Power and Sample Size (PASS) v13. An episode of distress is defined as an OQ-45 total score of ≥ 64 with each participant having a maximum of 6 possible episodes (every 2 weeks for weeks 2-12 of the study, inclusive). We wish to detect a 15% difference in the number of episodes of distress over the 3-month study period, and we assume a two-sided test and a significance level of 0.025 to control for the two primary tests (number of episodes and overall distress). If the Active Control mean response rate is 3.5 (i.e., number of episodes in the 3-month study period) we will have 97% power to detect a 15% difference. For Active Control response rates of 3, 2.5, 2 and 1.5, power is then 94%, 89%, 81% and 68%, respectively. For the second primary hypothesis, we will calculate the Area Under the Curve (AUC) using an estimate statement within a linear mixed model described below. We wish to demonstrate that the Cogito Companion is superior to Active Control by a margin of at least 14 points (minimally clinically significant difference, translates to an AUC difference of 84). Using the Superiority by a Margin procedure in PASS v13, 375 participants per group provides 90% power to demonstrate superiority, assuming a true difference of ≥18.7 points (AUC difference of 112.2) with a significance level of 0.025.

Analysis Plan. All analyses will assume a two-sided test of hypothesis, a significance level of 0.05 (unless otherwise indicated) and will be run in SAS v9.4 or higher, or R v3.3 or higher. To check randomization, demographic and clinical characteristics will be compared between groups using t-tests, chi-square tests or nonparametric tests, as appropriate. If any variable is found to be significantly different between the groups and is also plausibly associated with an outcome, it will be considered as potential confounders in the models described below.

Aim 1. To address the hypothesis regarding episodes of distress first using Poisson regression will be used to model the number (response rate) of episodes of distress as a function of group (0=Active Control, 1=Cogito), any potential confounders, and an offset of log (time) to account for varying lengths of follow-up. If the deviance is estimated to be >1.5, Negative Binomial regression will be used instead, incorporating the same variables. The parameter estimate associated with the group variable will be exponentiated, providing an estimate of the ratio of response rates between the groups and will be reported with a 97.5% confidence interval (CI). To address the hypothesis regarding distress over the course of the study, a linear mixed-effects model will be employed with longitudinal OQ-45 scores as the dependent variable and group, potential confounders, and an interaction between group and time (using either natural cubic B-spline transformations on time or polynomial transformations on time) as independent variables. These transformations will also be applied to the random time effects so that individual trajectories can be calculated. Akaike's Information Criterion will be used to determine which model provides the best fit (both between the B-spline/polynomial models and within them). Once a final

model is determined, the difference in AUC will be calculated and between groups and compared to the clinically meaningful AUC difference of 84 using a one-sided test. Here the null hypothesis is that AUC_{AC} - $AUC_{Cogito} \geq 84$, and the alternative hypothesis is that AUC_{AC} - $AUC_{Cogito} < 84$. The estimated difference will be reported with the one-sided 97.5% CI. For hypothesis 1.2, a Kaplan-Meier estimate will be used to compare the median time to treatment engagement between the groups and each median will be reported with 95% CIs. Treatment engagement is operationalized as a visit with any medical or mental health provider in which a mental health related ICD code is identified. and will be determined by medical record review. Additionally, the total number of mental health visits calculated from the CSRI-EU-R will be modeled using a Poisson or Negative Binomial regression model to estimate the difference in number of visits between the groups over the course of the study. The model will be set up similarly to the OQ-45 model. Hypothesis 1.3 is similar to hypothesis 1.1 such that we wish to look at episodes of depressive symptoms (PHQ-9), post-traumatic symptoms (PCL-5) and suicide-related thoughts (BSS) as well as severity of each over the course of the study. We also wish to look at perceived physical and psychological health functioning (RAND SF-36) over the course of the study. The methods employed to address hypothesis 1.1 will be utilized to estimate the difference in number of episodes of each outcome (excluding the SF-36) as well as the difference in AUC for each outcome. Zero-inflated negative binomial regression will be considered for the BSS if a large proportion of the participants do not exhibit suicidal thoughts and transformations will be considered for the AUC BSS analysis, given that it is likely to be highly skewed. Cutoffs for episodes of depressive/post traumatic symptoms, and suicidal thoughts are ≥10 (PHQ-9),[45] ≥33 (PCL-5),[46] and ≥2 (BSS),[47] respectively.

Aim 2. We will assess the proportion of participants who find the Cogito Companion acceptable, defined as ≥ 70% of participants scoring ≥ 24 on the CSQ. The proportion of Cogito Companion participants with a CSQ score of ≥24 will be calculated with a 95% CI. Additionally, the proportion of participants engaging in activities will be reported with a 95% CI as well as the median (range) amount of time spent on the application. Feasibility will be measured by the proportion of Cogito Companion participants who complete treatment and reasons for termination will be examined.

Exploratory Aim. To explore patterns of distress experienced by participants over the course of the study, individual OQ-45 curves modeled in Aim 1 will be qualitatively clustered into groups based on visual inspection of the trajectory patterns. Once distinct patterns are identified and labeled, baseline demographic and clinical characteristics of participants in each pattern will be summarized and reported. This will be performed for the entire sample, as well as within each group. This is considered a hypothesis generating aim. This analysis will be repeated for the PHQ-9, PCL-5, BSS and SF-36."

Revised and approved aims of the new statistical analysis plan:

"*Aim 1 (Revised - 2022)*. Longitudinally characterize risk by cohort (Active Control – study measures pushed only; Cogito Companion – study measures pushed plus Cogito Companion application [includes feedback from passive monitoring models]). Hypothesis 1.1 First characterization of risk, post-model score availability (7 days after download of app for model scores, 14 days for stability), will occur more quickly for the Cogito Companion group.

Aim 2. Evaluate the acceptability and feasibility of the Cogito Companion among military personnel. Aim 2.1. Acceptability of Cogito Companion will be evaluated based on participant satisfaction, participant engagement in application-related activities, and time spent on the application. Aim 2.2. Feasibility of Cogito Companion will be evaluated based on participant retention and accrual, and number and type of technical challenges noted during implementation.

Exploratory Aim. Identify patterns of distress (OQ-45), depressive symptoms (PHQ-9), post-traumatic symptoms (PCL-5), suicide-related thoughts (BSS; CSSRS Screener), and perceived physical and psychological health functioning (SF-36) over the course of the study among the entire sample, as well as within the Cogito Companion and Active Control groups."