Treating Insomnia to Reduce Inflammation in HIV: A Pilot Trial
NCT04721067
Updated July 29, 2022

STATISTICAL DESIGN AND POWER

Sample Size Justification and Power Analysis

The goal of this application is to provide proof-of-concept data and effect sizes of SHUTi on inflammation/monocyte activation endpoints in support of a future, definitive R01-funded trial. **As such, the proposed sample size is based on the enrollment time period and the funding allowance of the R21 mechanism, not for definitive superiority testing.** We will enroll 50 participants with the expectation that 40 (20 in each arm) will complete the 24 week study. Using the standard deviations and correlations between baseline and week 24 for hsCRP (this trial's primary endpoint) from our depression trial, we have 80% power (α=0.05) to detect mean differences between study groups of 3.41mg/L. This detectable difference is clinically meaningful as it is similar to that found to be predictive of CVD events and overall mortality in the SMART trial (66, 124).

For the primary and secondary endpoints, the following table demonstrates the effect sizes that can be observed between study groups (N=20 in each arm) assuming similar variances and correlations as observed in our pilot trial of internet CBT for depression in PWH. Of note, the detectable difference in IL-6 is also clinically meaningful given that differences of 1.3-2.2 pg/mL were associated with greater risks of CVD and mortality in the SMART trial (66, 124).

Outcome	SD	Correlation	Detectable mean difference (N=20 per group)
hsCRP (mg/L)	4.87	0.64	3.41
IL-6 (pg/mL)	2.34	0.32	2.02
sCD14 (ng/mL)	751	0.70	488
sCD163 (ng/mL)	19.12	0.89	7.97
%CD14+CD16+ monocytes	5.54	0.31	4.77

Data Management and Validation

Data Management Systems: IU REDCap – an easy-to-use tool for creating secure, web-based data entry systems – will be used to capture demographics, vital signs, medications, medical/psychologic history, diagnoses, interview, survey, and EHR data. The following IU REDCap databases will be created: Recruitment and Screening, SHUTi Intervention Delivery, Active Control Delivery, Screening Visit, Entry Visit, Week 12 Visit, and Week 24 Visit. Data will be exported from IU REDCap in SAS format. Assay data from the Translation Core Analyte Laboratory (hsCRP, IL-6, sCD14, sCD163) and the Angio BioCore (CD14+CD16+ intermediate monocytes) will be converted from Excel to SAS format and merged with the IU REDCap data by Dr. Liu, the study biostatistician.

Methods of Data Cleaning: Data cleaning procedures will assess for out-of-range values, outliers, normality, and very low frequency classes for each variable using SAS statistical software. Frequencies will be examined to identify out-of-range (i.e., impossible) values. Identified out-of-range values will be checked against the source data and corrected if due to data entry errors. If these values cannot be corrected, they will be deleted and set to missing. Z scores (≤ -3.3 or ≥ 3.3) for all continuous variables will be computed to identify outliers. Identified outliers will be checked against the source data and corrected if due to data entry errors. If not due to data entry errors, these values will be noted, retained in primary analyses, and may be altered or removed in sensitivity analyses. Skew (≤ -3 or ≥ 3) and kurtosis (≤ -10 or ≥ 10) values will be examined to assess normality of continuous variables. If the normality assumption is not met, variable transformations to normalize distributions and/or distribution-free nonparametric tests for the primary analyses will be considered.

Tracking of Emergency Department Visits and Hospitalizations: For the DSMB reports prepared by Dr. Gupta every 6 months, Ms. Danielle Huber will query the relevant EMR to extract data (type of medical visit and diagnostic codes) to be stored in an Excel file. Dr. Gupta will report the total number of emergency department visits and hospitalizations among randomized participants in the DSMB reports. If evidence of treatment group imbalance emerges, further investigation by Dr. Gupta will be initiated (e.g., examining reasons for the visits), and the results will be reported to the DSMB for their consideration.

Methods for Monitoring the Quality and Consistency of Data Collection: We will use our IU REDCap assessment databases to ensure the collection of high-quality data in a consistent fashion over time. These

databases will serve as both the operations manual and the data collection instrument for study contacts. Specifically, each database will include step-by-step instructions (e.g., from the scheduling call to the closing of a visit) with a box to be checked by the team member when each step is completed. All interview questions and questionnaire items will be embedded in the databases, along with radio buttons, checklists, drop-down menus, or open fields to capture participant responses. There will be open fields to capture height, weight, and vital signs. Instructions for the electronic health record chart reviews and the corresponding data fields will also be embedded to capture relevant data (e.g., concomitant medications and insomnia care received outside the trial). Data quality (e.g., % missingness) will be assessed every 6 months before DSMB meetings, and data quality metrics will be reported to the DSMB every 6 months in Dr. Gupta's DSMB report.

Policies and Methods for Ensuring Blinding of Study Results: To ensure unbiased results, all outcomes assessors will be blinded to treatment group assignment, and all patients will be blinded to study hypotheses until the proposed trial is complete. Drs. Gupta and Stewart and the study personnel involved in treatment delivery (SHUTi vs. sleep education/hygiene) will not be blinded by necessity. Dr. Liu and Ms. Huber will have the master randomization list but will not share it with the blinded PIs and laboratory personnel performing the endpoint inflammation assays (Drs. Considine and Pollok). At the Entry Visit, randomization will occur at the end of the session after all data collection for that visit is complete.

Data Confidentiality and Subject Privacy: All research material will be kept strictly confidential. All investigators and study personnel have completed or will complete the Collaborative Institutional Training Initiative (CITI) courses in Human Subjects Research and Good Clinical Practice and will make every effort to ensure confidentiality. All electronic and hard copy data will be identified using only the unique participant identification number assigned when each patient is enrolled (participant identifying information will not be included). All electronic data will be saved on password-protected and encrypted computers and secure servers, and all hard copy data will be stored in secure and locked file cabinets. The key linking participant names with the participant identification numbers will be kept in a separate secure and locked file cabinet. Data will be analyzed and reported as an aggregate, with no individual identifying information.

To protect participant privacy, all in-person data collection will be conducted in private rooms at the Infectious Diseases Research Clinic. In addition, all study phone calls will be conducted from private rooms in Dr. Stewart's Cardiovascular Behavioral Medicine Laboratory. No identifying information will be entered into the internet CBT-I program (SHUTi). Instead, participants will log on using their participant identification number and a password they create. Finally, participants will be instructed to complete study calls and SHUTi sessions in private rooms or areas in their homes or other locations they choose.

Statistical Analyses

To test our hypotheses, we will use intention-to-treat analysis of covariance models to test for treatment group differences in Week 24 levels of inflammation biomarkers adjusted for baseline levels. P-values will be two-sided and considered significant at $\alpha=0.05$. Adjustments for multiple comparisons will not be performed due to the relatively small sample size and exploratory nature of this phase II trial.

In secondary/exploratory analysis, multivariable linear regression models will be constructed to include treatment group and other potentially confounding baseline and time-updated variables that differ significantly between groups and which may account for differences in outcomes. Baseline characteristics that may be included in the models are demographics, ISI scores, tobacco/adherence questionnaire results, ART drugs/regimens (including efavirenz, rilpivirine, and integrase inhibitors), anti-insomnia medication use, co-morbidities, CD4 cell counts, and HIV-1 RNA levels. Time-varying characteristics that may be included are changes in ISI scores, questionnaire results, CD4 cell counts, ART drugs/regimens, and HIV-1 RNA levels.

We will also perform 'per protocol' secondary analyses comparing the $ISI_{4\text{-}6}$ subgroup vs. the active comparator control group to determine if greater SHUTi engagement leads to greater differences in the endpoints of interest.

We will also examine relationships between changes in questionnaire scoring, especially ISI scores, and the inflammatory endpoints using Pearson correlations.

All of these models will be repeated for comparing 12 week changes in the endpoints in addition to the primary models for 24 week changes.

Missing Data Approach: Missing data mechanisms will be examined by comparing completers with incompleters on the baseline factors. Multiple imputation (SAS proc mi and mianalyze) will be used if a substantial amount (>10%) of missing data exist. Of note, our trial biostatistician (Dr. Liu) is an expert on longitudinal and missing data analysis, which are critical for contemporary trial analysis.

Sex as a Biological Variable: In exploratory analyses, we will examine sex as a potential moderator of treatment effects on all outcomes by testing treatment group x sex interactions. Given that the proposed trial is not powered to detect such interactions, models will also be run separately for males and females to assess whether there are clinically important differences in the treatment group-outcome relationships between sexes.