**Evaluation of Cannabidiol for Reduction of Brain Neuroinflammation**
**NCT05066308**
**Date: 3/3/2022**

**Statistical plan**

A generalized linear mixed-effects model (GLMM) will be used to quantify the association between thalamic [$^{11}$C]PBR28 PET signal, treatment assignment at randomization (CBD, placebo; intent-to-treat) and time (baseline, week 4). The unadjusted model will only regress PET signal onto treatment and time indicators as well as their interaction. An adjusted model will also be constructed that independently accounts for potentially confounding variables (e.g., age, depression severity, sex). Data dependencies will be accounted for using either random intercept or line (intercept and slope) parametrizations. To fully specify our GLMMs, we will initially consider the Gaussian family (identity link). Since PET signal is a strictly positive quantity, we will also consider the binomial family with the cumulative logit link. A residual analysis will be performed to assess modeling assumptions and guide our choice in determining the final model.

Our primary object of inference will be the treatment by time interaction which reflects the absolute difference in the rates of change in PET signal between treatment groups (Gaussian family) or the relative change in odds of having a higher PET signal between treatment groups (binomial family) when holding all other covariates fixed. Linear combinations of parameter estimates will also be computed to summarize secondary objects of interest including cross-sectional treatment comparisons (baseline: CBD vs. control; week 4: CBD vs. control), and treatment-specific temporal comparisons (CBD: week 4 vs. baseline; control: week 4 vs. baseline).

This analysis plan will be repeated using a per-protocol definition of treatment in which we omit subjects who did not reliably take the study medication. Additional secondary and exploratory analyses (Box 1) will follow a similar analysis plan as described above. For these non-primary analyses, we will account for multiple comparisons by computing both unadjusted p -values and false discovery rate adjusted p-values.[105]

**Power justification**

*Primary outcome.* Using a linear mixed-effects model, we estimate the power to detect a temporal (week 4 – baseline) rate of change in thalamic [$^{11}$C]PBR28 PET signal between CBD and control subjects when recruiting 40 subjects per treatment group. We assume: (1) the standard deviations of the [$^{11}$C]PBR28 PET signal measures are 0.05, ADDIN EN.CITE [106] (2) the correlation between repeated measurements ranges between 0.3 to 0.8, and (3) the attrition rate ranges between 5 and 15%, and the type-I error is 0.05. If the within subject correlation is 0.3, and the attrition rate for both treatment groups is 10%, then we will have 80%, and 90%, power to detect mean differences in [$^{11}$C]PBR28 PET signal measures of at least 0.039 and 0.045, respectively (Table 3).

**Table 3.** Detectable mean differences in rates of SUVR change between treatment groups as a function of within subject correlation, attrition, sample size and power

| **Within Subject Correlation** | **Attrition, %** | **Sample Size** | **Detectable Mean Difference** | |
|---|---|---|---|---|
| | | | **Power = 0.80** | **Power = 0.90** |
| **0.3** | 0 | 80 [40/40] | 0.037 | 0.042 |
| **0.3** | 5 | 76 [38/38] | 0.038 | 0.044 |
| **0.3** | 10 | 72 [36/36] | 0.039 | 0.045 |
| **0.3** | 15 | 68 [34/34] | 0.040 | 0.047 |

| | | | | |
|---|---|---|---|---|
| **0.5** | 0 | 80 [40/40] | 0.031 | 0.036 |
| **0.5** | 5 | 76 [38/38] | 0.032 | 0.037 |
| **0.5** | 10 | 72 [36/36] | 0.033 | 0.038 |
| **0.5** | 15 | 68 [34/34] | 0.034 | 0.039 |
| **0.8** | 0 | 80 [40/40] | 0.020 | 0.023 |
| **0.8** | 5 | 76 [38/38] | 0.020 | 0.024 |
| **0.8** | 10 | 72 [36/36] | 0.021 | 0.024 |
| **0.8** | 15 | 68 [34/34] | 0.021 | 0.025 |

**Missing data**

All attempts will be made to minimize missing data, but if present, we plan to multiply impute all missing imaging and behavioral data and make inferences using combined estimates of the fixed effects and their covariance matrices.[107] As a sensitivity analysis, we will repeat each analysis on the subset of subjects with complete imaging or behavioral data.