Study title: Do Discounted Vouchers for Medical Cannabis Reduce Opioid Use in Adults with Pain (ReLeaf-V)
NCT number: NCT04495725
SAP version: 1.0
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Blinding statement: This Statistical Analysis Plan (Version 1.0) was finalized prior to database lock and unblinding of treatment allocation.

I. INTRODUCTION

This document describes the planned statistical analyses for ReLeaf, a 14-week, pragmatic randomized, double-blind, four-arm parallel-group trial evaluating the effect of discounted vouchers for: 1) a placebo soft-gel capsule product, 2) high THC: low CBD soft-gel capsule product (4.3 mg THC/0.7 mg CBD), 3) equal THC:CBD soft-gel capsule product (2.5 mg THC/ 2.5 mg CBD), or 4) low THC: low CBD soft-gel capsule product (0.2 mg THC/4.8 mg CBD) on cumulative opioid analgesic use. The ReLeaf Study randomized participants 1:1:1:1 across four arms.

This Statistical Analysis Plane (SAP) was developed prior to unblinding and database lock.

II. OBJECTIVES AND HYPOTHESES

a. **Primary Objective:** To determine whether assignment to the four arms (placebo, high THC:low CBD, equal THC:CBD, low THC:high CBD) results in a difference in cumulative opioid analgesic dose compared to placebo coupon at 14 weeks.
   i. **Null Hypothesis (H_0):** Participants randomized to vouchers for deeply discounted soft-gel capsules containing high THC:low CBD, equal THC:CBD, or low THC:high CBD will experience a greater reduction in opioid dose compared to vouchers for deeply discounted placebo capsules.
   ii. **Alternative hypothesis:** Opioid dose and adverse events will defer by randomized voucher arm.

b. **Secondary Objectives:** We will also measure outcomes with strong associations with cannabis or opioid analgesic use, including pain, substance use, symptoms of mental illness, and potential adverse events). Secondary analyses will be considered exploratory.

III. STUDY DESIGN AND RANDOMIZATION

This study is a pragmatic, double-blind, randomized, parallel-group controlled trial.

a. Allocation ratio: Participants are allocated 1:1:1:1 to each arm.
b. Randomization method: Block randomization to ensure equal randomization over time. We stratified by history of cannabis use (cannabis naïve, non-daily cannabis use, daily cannabis use), baseline opioid use (chronic opioid use versus sporadic opioid use), and primary pain condition (neuropathic versus non-neuropathic pain). Chronic opioid treatment is defined as prescribed opioids for greater than or equal to 90 overlapping days in the past 182 days.
c. Blinding: Participants, investigators and outcome assessors are blinded to allocation of vouchers.

Unblinding will occur after database lock and finalization of this SAP.

IV. ANALYSIS POPULATIONS

a. Intention-to-Treat (ITT) Population: All randomized participants will be included and analyzed according to their assigned treatment group, regardless of voucher or product use. The ITT population will serve as the primary analysis population.

b. Per-Protocol (PP) Population: The PP Population will be determined by using a continuous measure of adherence to study protocol through reporting on the New York State Prescription Monitoring Program and through self-report questionnaires. PP analyses will be considered supportive.

c. Safety population: All participants who redeemed at least one voucher or used study product**.**

V. ENDPOINTS

a. **Primary endpoint: Opioid analgesic use:** weekly cumulative dose of opioid analgesics over 14 weeks.
   i. **Measurement instrument:** Reported opioid dispensed to New York State Prescription Monitoring Program
   ii. **Timepoint:** at baseline and completion of randomized trial (14 weeks)

VI. SAMPLE SIZE AND POWER

a. We based our power analysis on a difference of 10% change in opioid analgesic dose between randomization arms over 14 weeks, which is clinically meaningful.
b. **Alpha level:** 0.05, two-tailed, and 0/167 to correct for multiple comparisons between four arms.
c. **Power:** Our sample size estimates incorporate a statistical power of 80% and 90%
d. **Assumptions:** 15% attrition
e. **Target sample size:** 276 (69 per arm)

VII. STATISTICAL METHODS

a. **Primary Outcome Analysis:** We will use linear mixed-effects regression analyses (SAS, PROC MIXED) to examine whether assignment to the randomized voucher intervention at enrollment (independent variable) is associated with changes over time in weekly cumulative dose of opioid analgesics in morphine milliequivalents (dependent variable). We will examine intervention and time effects, as well as intervention-by-time interactions. To account for within-participant correlation across repeated weekly observations, we will include a random intercept for participant. We will follow the intention-to-treat principle, including all randomized participants in their originally assigned treatment groups. We will include covariates that differ at baseline or potential moderators, including gender and age. We will use a two-sided alpha of 0.05 and 95% confidence intervals.

b. **Secondary Outcomes:** Using a similar approach to Aim 1, we will examine whether the initial soft gel capsule dispensed product with different THC/CBD content leads to adverse events. Each adverse event will be included in a separate model. For dichotomous (e.g., cannabis use disorder) or continuous outcomes (e.g., ASI drug subscale score), we will use mixed-effects linear or logistic regression analyses, respectively (SAS, PROC MIXED or PROC NLMIXED) to examine intervention and time effects, as well as intervention-by-time interactions. We will repeat this model using the initial soft gel capsule dispensed product as an instrumental variable to analyze the average effect of each medical cannabis product among those who continued taking the original product. We will also repeat this model using alternative measures of medical cannabis (cumulative dose of THC and CBD).

c. **Sensitivity Analyses:** To fully understand the intervention effect, we will also conduct per-protocol analyses. If key variables are unequally distributed among randomized arms, we will conduct adjusted analyses.

VIII. MISSING DATA

a. Missing outcome data in the primary outcome analysis will be handled using multiple imputation under the missing-at-random assumption. Intervention effects will be pooled across imputed datasets using Rubin's rules.[1]

IX. INTERIM ANALYSES

a. No interim analyses for efficacy are planned.

X. MULTIPLICITY CONTROL

a. No adjustment required.

XI. STATISTICAL SOFTWARE

a. SAS 9.4

XII. DATA MONITORING AND BLINDING

a. Database lock occurs- after all data cleaning and planned analyses are completed.
b. Analysis will be performed by study statistician: Dr. Chenshu Zhang
c. Unblinding occurs after database lock
d. Statisticians are blinded

REFERENCES

1. Dempster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data via the EM algorithm. *Journal of the Royal Statistical Society: Series B (Methodological)*. 1977;39(1):1-22.