Study Title:

Demonstration Study of the Effect of Transcranial Direct Current Stimulation (tDCS) for Patients with Depression in Clinical Fields

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Study Protocol with Statistical Analysis Plan (SAP)

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Study Protocol

Purpose

1. Demonstrate the clinical effectiveness of transcranial direct current stimulation (tDCS) for patients with depression in real-world clinical settings.
2. Optimize home-based electroceutical technologies for patient-centered applications.
3. Generate real-world data (RWD) and evidence (RWE) to support the adoption of tDCS in clinical practice.

Design

1. **Overview:**
    - Randomized, double-blinded, multi-site clinical study.
    - Participants: 198 adults aged 19–65 with mild to moderate major depressive disorder (MDD).
    - Duration: 6 weeks of home-based self-applied tDCS.
2. **Device:**
    - MINDD STIM+ (YMS-201B+/201BS+), an FDA-approved tDCS device.
3. **Randomization:**
    - Group A: Active tDCS for 6 weeks.
    - Group B: Active tDCS for 3 weeks followed by 3 weeks of sham stimulation.
4. **Primary Outcome Measures:**
    - Changes in BDI-II (Beck Depression Inventory-II) and MADRS (Montgomery-Åsberg Depression Rating Scale) scores from baseline (V1) to week 6 (V3).
5. **Secondary Outcome Measures:**
    - HAM-A (Hamilton Anxiety Rating Scale) for anxiety.
    - DSST (Digit Symbol Substitution Test) for cognitive function.
    - CESD-R for daily depressive symptom assessment.
    - qEEG (quantitative EEG) and HRV (heart rate variability).

Participant Criteria

- **Inclusion:**
    - Age 19–65, mild to moderate MDD diagnosis.
    - Informed consent capability.
- **Exclusion:**
    - PTSD, psychotic MDD, severe suicidal risk, cranial implants, major cardiovascular or neurological issues.
    - Prior tDCS use or participation in clinical trials within 30 days.

Statistical Analysis Plan (SAP)

General Overview

The statistical analysis will evaluate both primary and secondary outcomes based on intention-to-treat (ITT) and per-protocol (PP) populations.

Primary Statistical Methods

1. **Primary Analysis:**
    - **Dependent Variables:** Changes in BDI-II and MADRS scores from baseline to week 6.
    - **Methodology:**
        - Independent t-tests to compare mean score changes between groups.
        - Mixed-effects models to adjust for repeated measures and site-level variation.
2. **Secondary Analysis:**
    - Evaluate changes in HAM-A, DSST, and CESD-R scores over time using regression analysis.

Adjustments for Multiple Comparisons

To control for Type I error:

- Bonferroni correction for the analysis of multiple secondary outcomes.

Handling Missing Data

- Multiple imputation for missing data assuming data are missing at random (MAR).
- Sensitivity analysis to validate robustness.

Validation of Assumptions

1. **Normality:** Shapiro-Wilk test for residuals.
2. **Homogeneity of Variance:** Levene's test.
3. **Sphericity (if repeated measures):** Mauchly's test.

Safety Analysis

- Descriptive statistics for adverse events (AEs) and serious adverse events (SAEs).
- AE rates compared using Fisher's exact test or chi-square test.