

## Study Document Cover Page

**Official Title:** Brain Dynamic Audio Stimulation for Improving Sleep Quality and Circadian Rhythm in Healthcare Workers

**Short Title:** Brain Dynamic Audio Stimulation

**Document Type:** Statistical Analysis Plan

**IRB Number:** CMMC IRB No. 11404-012

**Organization Name:** Chi Mei Medical Center (CMMC)

**Principal Investigator:** Hong-Min, Lin

**Document Date:** 2026-01-01

**Version:** 2.0

**Confidentiality Statement:** This document contains confidential information intended for regulatory and research purposes only.

## Statistical Analysis Plan (SAP)

**Study Title:** *Effectiveness of Brain Dynamic Audio Stimulation for Improving Insomnia and Sleep Cycles in Healthcare Professionals (BDAS-HP)*

**Protocol No.:** 11404-012

**Version:** 2.0

**Date:** January 1, 2026

**Sponsor/Institution:** Chi-Mei Medical Center

**Principal Investigator:** Dr. Hong-Min Lin

# 1. Analysis Objectives and Endpoints

## 1.1 Primary Objective

To evaluate the effect of Brain Dynamic Audio Stimulation (BDAS) on insomnia severity as measured by the **Insomnia Severity Index (ISI)** before and after a two-week intervention.

## 1.2 Secondary Objectives

To assess the effect of BDAS on objective sleep-related parameters, including:

- Sleep onset success rate
- Sleep onset latency
- Sleep efficiency
- Short-term sleep stage distribution derived from EEG-based hypnograms

## 1.3 Endpoints

### Primary Endpoint

- Mean change in total ISI score from baseline (pre-intervention) to post-intervention (after 2 weeks)

### Secondary Endpoints

- Sleep onset success rate following BDAS exposure
- Mean sleep onset latency (seconds) before and after 2 weeks of BDAS use
- Mean sleep efficiency (%) before and after BDAS intervention
- Proportion of time spent in each sleep stage (Wake, N1, N2, N3, REM) during EEG recording sessions

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## 2. Analysis Populations

Population	Definition
Full Analysis Set (FAS)	All participants who received at least one BDAS session and provided baseline ISI data
Per-Protocol Set (PPS)	Participants completing $\geq 80\%$ of BDAS sessions without major protocol deviations
Safety Set	All participants who initiated BDAS intervention

- Primary analyses will be conducted on the **FAS**
- Sensitivity analyses will be performed using the **PPS**

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## 3. General Statistical Principles

- All statistical analyses will be conducted using **SPSS (v28 or later)** or **R (v4.3 or later)**
- All tests will be **two-tailed**
- Statistical significance will be defined as **p < 0.05**
- Continuous variables will be summarized as:
  - Mean  $\pm$  standard deviation (SD), or
  - Median and interquartile range (IQR) if non-normally distributed
- Categorical variables will be summarized as counts and percentages
- Normality will be assessed using **Shapiro–Wilk tests** and visual inspection (Q–Q plots)

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## 4. Handling of Missing Data

- For ISI analysis, participants with both baseline and post-intervention data will be included
- No imputation will be performed for missing objective sleep measures
- Sensitivity analyses excluding incomplete cases will be conducted to assess robustness

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## 5. Statistical Methods

### 5.1 Primary Analysis: ISI Score

- **Paired-sample t-test** will be used to compare pre- and post-intervention ISI scores
- If normality assumptions are violated, the **Wilcoxon signed-rank test** will be applied
- Effect sizes will be reported using:
  - **Cohen's d**
  - **Hedges' g**
- Mean difference with **95% confidence intervals (CI)** will be presented

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### 5.2 Secondary Analysis: Sleep Onset Success Rate

- Sleep onset success will be defined as transition from wakefulness to any sleep stage during the recording period
- Success rates will be summarized descriptively as proportions (%)
- No inferential testing is planned due to the exploratory nature of this endpoint

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### 5.3 Secondary Analysis: Sleep Onset Latency

- Sleep onset latency is defined as time (seconds) from recording start to first epoch of sleep
- **Independent-sample t-tests** will be used to compare latency between:
  - Initial use
  - After 2 weeks of BDAS use
- Each sleep session will be treated as an **independent observation** to maximize statistical power
- Effect sizes will be reported using Cohen's d and Hedges' g

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### 5.4 Secondary Analysis: Sleep Efficiency

- Sleep efficiency is defined as: **(Total sleep time / total recording time) × 100%**
- Independent-sample t-tests will be used to compare sleep efficiency before and after BDAS intervention
- Effect sizes (Cohen's d, Hedges' g) and 95% CIs will be reported

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## 5.5 Exploratory Analysis: Sleep Stage Distribution

- Sleep stages will be classified according to **AASM criteria**
- Proportion of time spent in each stage (Wake, N1, N2, N3, REM) will be summarized descriptively
- Where appropriate, paired-sample t-tests or Wilcoxon tests will be applied for exploratory comparisons
- Results will be interpreted descriptively due to short recording duration

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## 6. Outlier and Data Quality Management

- Outliers ( $>3$  SD from the mean) will be reviewed against raw EEG and recording logs
- Artifactual recordings (movement, muscle noise) will be excluded prior to analysis
- A minimum of **80% usable recording time** is required for inclusion in EEG-based analyses

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## 7. Sample Size Considerations

- This study is exploratory in nature
- Based on prior observations of ISI improvement (mean reduction  $\approx 5$  points, SD  $\approx 4$ ), a sample size of **15 participants** provides sufficient power to detect large within-subject effects
- No formal hypothesis-driven power calculation is applied for secondary outcomes

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## 8. Interim and Sensitivity Analyses

- No interim analyses are planned
- Sensitivity analyses will include:
  - Reanalysis excluding identified outliers
  - Non-parametric alternatives where appropriate
  - PPS-based comparisons

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## 9. Reporting of Results

- Results will be reported as:
  - Mean  $\pm$  SD
  - Mean difference (95% CI)
  - p-values and effect sizes
- Graphical presentations may include:
  - ISI pre-post boxplots
  - Sleep onset latency distributions
  - Sleep efficiency comparison plots
  - Sleep hypnogram examples

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## 10. Deviations from the Statistical Analysis Plan

Any deviations from this SAP will be:

- Documented with justification
- Approved prior to final database lock
- Clearly described in final reports and publications