Statistical analysis plan

1. Introduction

The study evaluates the efficacy of Synaptic Adaptation Therapy in the treatment of tinnitus in patients following sudden hearing loss. Data are drawn from a pilot randomized trial with an active treatment group (n=27) and a placebo group (n=10) , and from the study procedures description .

2. Objectives and Hypotheses

- **Primary Objective:** To compare the percentage reduction in tinnitus distress (scale 0–10) after 4 months of therapy between the active and placebo groups.
- **Null Hypothesis (H_0):** There is no difference in mean percentage reduction in tinnitus distress between groups.
- **Alternative Hypothesis (H_1):** The mean reduction in the active group is greater than that in the placebo group.

3. Definitions and Endpoints

1. **Analysis Populations**
    - **ITT (intention-to-treat):** All randomized patients (n=37), regardless of protocol adherence.
    - **PP (per-protocol):** Patients who completed the 4-month therapy and provided outcome data.
2. **Endpoints**
    - **Primary Endpoint:** Percentage reduction in tinnitus distress, defined as

% reduction=pre-treatment score−post-treatment scorepre-treatment score×100% \%\text{ reduction} = \frac{\text{pre-treatment score} - \text{post-treatment score}}{\text{pre-treatment score}} \times 100\%% reduction=pre-treatment scorepre-treatment score−post-treatment score×100%

    - **Secondary Endpoints:**
        - Change in raw tinnitus distress scores (0–10).
        - Daily device wear time (hours/day).
        - Safety: incidence and type of adverse events.

4. Analysis Strategy

1. **Baseline Descriptives**
    - Demographic and clinical characteristics (age, sex, tinnitus duration, degree of hearing loss) – frequencies and means ± SD .
2. **Primary Analysis**
    - Comparison of mean percentage reductions between groups using an independent-samples Student's t-test (if approximately normally distributed), otherwise Mann–Whitney U test.
    - Additional ANCOVA including baseline distress score as a covariate.
3. **Secondary Analyses**
    - Absolute change in distress score: same tests as for primary analysis.
    - Correlation between device wear time and percentage reduction (Pearson or Spearman correlation coefficient).
    - Categorical distribution of percentage reduction (0%, 10–30%, 40-60%. 70-80%, 90–100%).
4. **Safety Analysis**
    - Number and percentage of patients with ≥1 adverse event, compared by chi-square or Fisher's exact test.
    - Detailed listing of events (type, severity, relationship to therapy).

5. Handling of Missing Data

- Primary endpoints: Last Observation Carried Forward (LOCF) for missing post-treatment measurements.
- Sensitivity analyses: complete-case (CC) analysis and multiple imputation (MI).

6. Significance Level and Software

- Two-sided tests, $\alpha = 0.05$.
- Software: R (version ≥4.0) or SAS.

7. Presentation of Results

- **Tables**
    1. Baseline characteristics (ITT, n, mean ± SD or n [%]).
    2. Primary and secondary outcomes (mean differences, 95% CI, p-values).

3. Safety analysis.

- **Figures**
    - Boxplots of percentage reduction in both groups.
    - Histogram or bar chart of percentage-reduction categories.