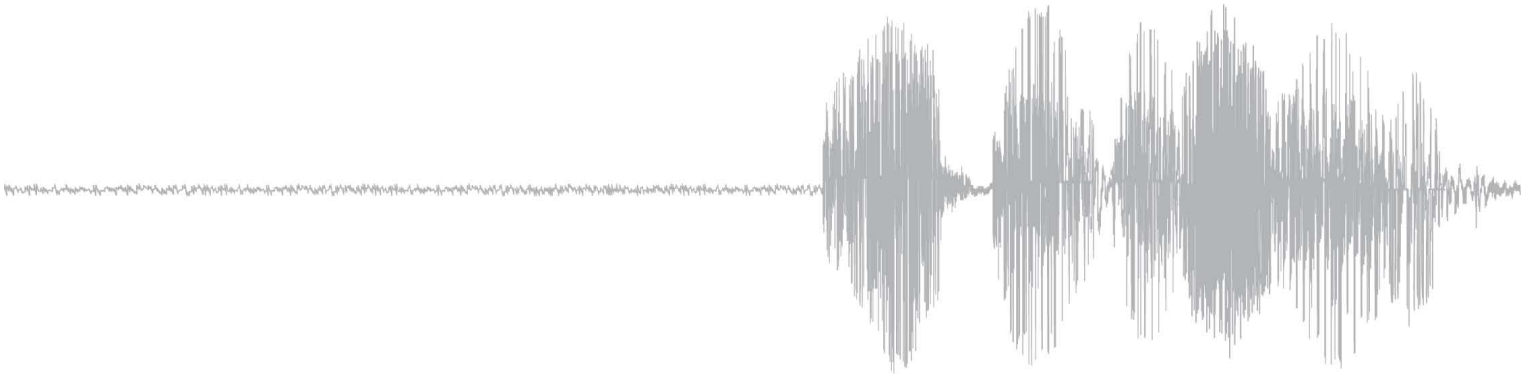

Hearing Loss in Older Adults Study CLTD5693 SAP

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Randomized controlled trial of immediate versus delayed cochlear implantation.

Hearing Loss in Older Adults Study

Investigation Number CLTD5693, Version 9.0

Statistical Analysis Plan

Version 1, May 6, 2019

Version History

Version	Version Date	Author/Title	Summary of Key Changes
1.0	MAY 6, 2019	[redacted] Medical Research Biostatistician	Initial Release

Document Approval

Author	
Authored By	
Signature	
Date	
Role	

Table of Contents

1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected under the Clinical Investigation Plan CLTD5693, Hearing Loss in Older Adults: Randomized controlled trial of immediate versus delayed cochlear implantation, Version 9.0. This SAP should be read in conjunction with the study clinical investigation plan (CIP) and case report forms (CRFs).

Applicable Documents:

Document Number, Version	Document Title
D1168460, Version 9.0	Clinical Investigation Plan CLTD5693, Hearing Loss in Older Adults: Randomized controlled trial of immediate versus delayed cochlear implantation

2 List of Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	Adverse Event
CI	Cochlear Implantation
CIP	Clinical Investigation Plan
CRF	Case Report Form
Enrolled	Subjects will be enrolled in the study once the inclusion/exclusion criteria are met (including attempted and successful implantation of a device).
ITT	Intent-to-Treat
SAP	Statistical Analysis Plan
Screened	Each subject who signs the study Informed Consent Form will be considered a screened subject.

3 Study Objectives

3.1 Primary Objective

To determine the effect of treating hearing loss with cochlear implantation (CI) versus continued use of hearing aids (HA) on hearing satisfaction using the Speech, Spatial and Qualities of Hearing (SSQ12) in older adults.

3.2 Secondary Objective

To assess cognition in older adults with hearing loss with a Cogstate® battery of neuropsychological tests.

4 Study Design

Prospective, 1:1 randomized controlled trial of immediate versus delayed cochlear implantation (CI) on hearing satisfaction, handicap, communicative function, loneliness, mental wellbeing, quality of life and cognitive functioning. The study will contain approximately 60 subjects, with a minimum of 28 subjects in each arm.

4.1 Randomization

Subjects will be randomized after eligibility has been confirmed and confirmed that the subject will participate in the clinical investigation. Randomization will be performed using a random permuted block design stratified by field site with a 1:1 allocation ratio (Arm A: immediate cochlear implant vs. Arm B: hearing aid control). If a subject withdraws from the clinical investigation, they will be not be replaced by another subject. The randomization table will account for 20% subject attrition.

4.2 Blinding

No blinding will be applied in this study.

5 Sample Size Determination.

5.1.1 Primary endpoint

The primary endpoint for the clinical investigation is assessment of the impact of cochlear implantation versus continued hearing aid use on the Speech, Spatial and Qualities of Hearing – short form (SSQ12) test measure at Follow-up Visit 1 (FUV1). Each subject will serve as their own control.

Data from a clinical investigation on the Cognitive Performance of Severely Hearing-impaired Older Adults Before and After Cochlear Implantation (1) was used to estimate the effect of cochlear implantation on the SSQ12.

The sample size estimation for the primary endpoint is based on the mean (SD) change of 3.0 (1.8) for the change in SSQ12 score reported in Claes et al. (pre-operative to postoperatively at six months post-activation) (1). The sample size estimation assumes that the observed mean change and standard deviation of change reported by Claes for SSQ12 is representative of the corresponding values for the clinical population under investigation.

Sample size calculations were conducted using PASS statistical software under the following general assumptions:

1. Two-sample t-test
2. Two-sided 0.025 α levels
3. 80% power
4. No accounting for attrition or lost to follow up

In order to achieve 80% power with an effect size of 1.667 ($d = (\mu_A - \mu_B)/ \sigma$) with 20% attrition, a sample size of 12 per arm would be needed respectively. Therefore, a sample size of 60 supports the effect sizes observed in Claes et al. (2018) as well as possible attrition.

6 Statistical Analyses

6.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) or other widely-accepted statistical or graphical software as required.

6.1.1 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and Clopper-Pearson Exact method for categorical variables.

6.1.2 Visit Windows

Unless otherwise specified, visit assessments will be analyzed for each analysis time point as described in Sections 6.6 and 6.7.

Each test measure by arm/visit abbreviation is described in the table below.

Where:

A = Arm A, B = Arm B, and x = number of months post-baseline measure.

Procedure	Screening POV1	Baseline POV2	FUV1	FUV2	FUV3
HI-MoCA	A0 or B0		A6 or B6	A12 or B12	B18
HHIE-S	A0 or B0		A6 or B6	A12 or B12	B18
Cogstate		A0 or B0	A6 or B6	A12 or B12	B18
SSQ12		A0 or B0	A6 or B6	A12 or B12	B18
UCLA		A0 or B0	A6 or B6	A12 or B12	B18
GDS		A0 or B0	A6 or B6	A12 or B12	B18
LAQ		A0 or B0	A6 or B6	A12 or B12	B18
HUI-III		A0 or B0	A6 or B6	A12 or B12	B18
CNC words		A0 or B0	A6 or B6	A12 or B12	B18
AzBio sentences		A0 or B0	A6 or B6	A12 or B12	B18
Audiometric thresholds	A0 or B0		A6 or B6	A12 or B12	B18

6.1.3 Statistical Significance

Unless otherwise specified, hypothesis testing will be performed at the two-sided 0.05 significance level (or equivalently at a one-sided 0.025 level). P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as “<0.001”. If a p-value is greater than 0.999, it will be reported as “>0.999”.

6.1.4 Reporting Precision

Unless otherwise specified, the following conventions will apply for data display. In general, percentages will be displayed to 1 decimal place. Percentages <0.05% will be reported to 2 decimal places. For continuous parameters, means and medians will be reported to 1 additional decimal place than the measured value while standard deviation will be reported to 2 additional decimal places than the measured value. Minimum and maximum values will be reported to the same precision as the measured value.

6.2 Analysis Populations

The following analysis populations are defined for analysis:

1. **Enrolled Analysis Set:** The enrolled population will consist of all subjects who signed an informed consent form and have been included into the study database.
2. **Intention-to-treat Analysis Set:** The intention-to-treat (ITT) population consists of all enrolled subjects who were subsequently randomized. The ITT set will be analyzed according to randomized treatment assignment regardless of adherence to treatment protocol (e.g. dropout/withdrawal or CIP deviations).
3. **Safety Analysis Set:** The safety population will consist of all ITT subjects who received the device and will be analyzed according to treatment actually received (e.g. this is an as-treated analysis set). If all patients receive study treatment according to randomization, the safety set will be identical to the ITT set.

6.3 Poolability Analyses

All investigational sites will follow the requirements of a common protocol and standardized data collection procedures and forms. The primary endpoints will be presented separately for each site using descriptive statistics. Poolability of the primary endpoints across investigational site will be evaluated using a logistic regression model with fixed effects for treatment, site, and treatment by site interaction.

6.4 Handling of Missing Data

All attempts will be made to limit the amount of missing data. Unless otherwise specified, missing data will be handled by multiple imputation for the primary endpoint (SSQ12) with covariates of gender, age and baseline in the ITT Analyses. For all other analyses, no attempt will be made to impute missing data, and the number of observations available will be reported so the reader can assess the impact of missing data.

6.5 Demographics and Baseline Characteristics

Descriptive statistics will be presented by treatment arm for all clinically-relevant baseline demographic, medical history, and clinical characteristic variables.

6.6 Analysis of Study Endpoints

6.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as assessment of the impact of cochlear implantation versus continued hearing aid use on hearing satisfaction as measured using the SSQ12 at FUV1 (A6 vs B6).

6.6.1.1 Primary Analysis

The primary efficacy endpoint will be assessed with the following hypothesis:

H_0: $\mu_A \geq \mu_B$

H_a: $\mu_A < \mu_B$

Where μ_{A6} is the mean SSQ12 score for the cochlear implantation treatment Arm A and μ_{B6} is the mean SSQ12 score for the hearing aid control Arm B at FUV1. The hypothesis will be evaluated using a regression model with treatment and baseline score as covariates. Significance of the treatment effect will be assessed by the p-value for the treatment arm from the regression model.

For analyses using means in the primary endpoints, where there is evidence the model assumptions are not met (e.g. lack of normality of the residuals), transformations or non-parametric tests will be employed.

6.6.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint is defined as assessment of the impact of cochlear implantation versus continued hearing aid use on cognition with a Cogstate® computerized battery of neuropsychological tests at FUV1 (A6 vs B6).

The Cogstate computerized battery results will be presented using descriptive statistics only and analyzed using a t-test to compare the mean score of the cochlear implant Arm A to that of the hearing aid control Arm B. As the analyses for the secondary efficacy endpoint are exploratory in nature, there will be no adjustment for multiple comparisons and no formal hypotheses testing. The results from the analyses for the secondary efficacy endpoint may be used for calculation of sample size in future clinical investigations.

6.7 Ancillary Analyses/Sensitivity Analyses

Ancillary analyses will be undertaken in the form of secondary and tertiary analyses. No formal hypotheses testing will be conducted for the ancillary analyses.

6.7.1.1 Secondary Analyses

All secondary analyses will be presented using descriptive statistics and analyzed using pairwise correlations to compare the mean score of the cochlear implant Arm A to that of the hearing aid control Arm B. The familywise error rate in the secondary analyses will be controlled by a Bonferroni correction using a significance level of p = 0.01.

Investigating treatment effect on:

- Psychosocial measures:
    - UCLA loneliness Scale:
        - A6 vs B6
    - Geriatric Depression Scale (GDS):
        - A6 vs B6
- Audiologic measures:
    - CNC words:
        - A6 vs B6
    - AzBio Sentences:

- A6 vs B6

- Quality of life:
  - Health Utilities Index Mark III (HUI-III):
    - A6 vs B6

6.7.1.2 Tertiary Analyses

All tertiary analyses will be presented using descriptive statistics and analyzed using a t-test to compare the mean score of the cochlear implant Arm A to that of the hearing aid control Arm B at various time points. As these tertiary analyses are exploratory in nature, there will be no adjustment for multiple comparisons, no formal hypotheses testing and no statement of statistical significance.

Investigating treatment effect on:

- Neuropsychological outcomes:
  - Cogstate[1]:
    - Detection Test – speed of performance
    - Groton Maze Learning Test – number of errors
    - Identification Test – speed of performance
    - One Card Learning Test – accuracy of performance
    - One Back Test – speed of performance
      - A6 vs B6 (treatment effect)
      - A0 vs B0 (population)
      - A6 vs B12 (6 months post-CI)
      - A12 vs B18 (12 months post-CI)
      - A0 vs A6 vs A12 (longitudinal treatment effect)
      - B6 vs B12 vs B18 (longitudinal treatment effect)
  - HI-MoCA:
    - A6 vs B6 (treatment effect)
    - A0 vs B0 (population)
    - A6 vs B12 (6 months post-CI)

[1] A sensitivity analyses will be conducted with test data integrity failures excluded if the integrity failure rate is greater than 10%.

- A12 vs B18 (12 months post-CI)
- A0 vs A6 vs A12 (longitudinal treatment effect)
- B6 vs B12 vs B18 (longitudinal treatment effect)

- Psychosocial measures:
  - UCLA loneliness Scale:
    - A0 vs B0 (population)
    - A6 vs B12 (6 months post-CI)
    - A12 vs B18 (12 months post-CI)
    - A0 vs A6 vs A12 (longitudinal treatment effect)
    - B6 vs B12 vs B18 (longitudinal treatment effect)
  - Geriatric Depression Scale (GDS):
    - A0 vs B0 (population)
    - A6 vs B12 (6 months post-CI)
    - A12 vs B18 (12 months post-CI)
    - A0 vs A6 vs A12 (longitudinal treatment effect)
    - B6 vs B12 vs B18 (longitudinal treatment effect)
- Audiometric measures:
  - HHIE-S:
    - A0 vs B0 (population)
    - A6 vs B12 (6 months post-CI)
    - A12 vs B18 (12 months post-CI)
    - A0 vs A6 vs A12 (longitudinal treatment effect)
    - B6 vs B12 vs B18 (longitudinal treatment effect)
  - SSQ12:
    - A0 vs B0 (population)
    - A6 vs B12 (6 months post-CI)
    - A12 vs B18 (12 months post-CI)
    - A0 vs A6 vs A12 (longitudinal treatment effect)
    - B6 vs B12 vs B18 (longitudinal treatment effect)

- CNC words:
  - A0 vs B0 (population)
  - A6 vs B12 (6 months post-CI)
  - A12 vs B18 (12 months post-CI)
  - A0 vs A6 vs A12 (longitudinal treatment effect)
  - B6 vs B12 vs B18 (longitudinal treatment effect)
- AzBio Sentences:
  - A0 vs B0 (population)
  - A6 vs B12 (6 months post-CI)
  - A12 vs B18 (12 months post-CI)
  - A0 vs A6 vs A12 (longitudinal treatment effect)
  - B6 vs B12 vs B18 (longitudinal treatment effect)
- Audiometric thresholds
  - A0 vs B0 (population)
  - A0 vs A6 vs A12 (hearing preservation)
  - B6 vs B12 vs B18 (hearing preservation)

- Quality of life:
  - Health Utilities Index Mark III (HUI-III):
    - A0 vs B0 (population)
    - A6 vs B12 (6 months post-CI)
    - A12 vs B18 (12 months post-CI)
    - A0 vs A6 vs A12 (longitudinal treatment effect)
    - B6 vs B12 vs B18 (longitudinal treatment effect)

6.8 Safety Analyses

Adverse Events (AE) will reported for the safety population by treatment arm and overall. AEs will be tabulated with the number of events and subjects with event for each event type and overall. Rates will be reported as the number of subjects who experience at least one event during the reporting interval out of the total number of subjects at risk at the beginning of the reporting interval. Serious adverse events will also be tabulated.

Adverse events leading to death or study discontinuation will be provided in listing format.

All device deficiencies will be reported in listing format.

6.9 Subgroup Analyses

No subgroup analyses are planned for the clinical investigation.

6.10 Interim Analyses

No interim analyses will be performed for the clinical investigation.

6.11 Protocol Deviations

Deviations from the procedures outlined in the CIP will be reported by investigational sites on the CRF. Protocol deviations will be summarized for all deviations and by type with event counts and number of subjects with at least one deviation.

7 Changes to Planned Analyses

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis when possible. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

Summary of Changes

Version	Effective Date	Summary of Changes	Change Author
1.0	MAY 6, 2019	Initial Release	[redacted]

8 Reference List

1. Claes AJ, Van de Heyning P, Gilles A, Van Rompaey V, Mertens G. Cognitive Performance of Severely Hearing-impaired Older Adults Before and After Cochlear Implantation: Preliminary Results of a Prospective, Longitudinal Cohort Study Using the RBANS-H. Otol Neurotol. 2018.