Cochlear Americas

An Evidence Based Delivery Model of Care for Newly Implanted Adult Cochlear Implant Recipients

Investigation Number: 5753

Statistical Analysis Plan

Version 1.0, 25 April 2019

Version History

Version	Version Date	Author/Title	Summary of Key Changes
1.0	25 April 2019	[redacted]	Initial Release.

Sponsor	Study	Version
Cochlear Americas	An Evidence Based Delivery Model of Care for Newly Implanted Adult Cochlear Implant Recipients	1.0

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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 Protocol "An Evidence Based Delivery Model of Care for Newly Implanted Adult Cochlear Implant Recipients".

This SAP should be read in conjunction with the study clinical investigation plan (CIP) and case report forms (CRFs). This version of the SAP has been developed with respect to the Clinical Investigation Protocol "An Evidence Based Delivery Model of Care for Newly Implanted Adult Cochlear Implant Recipients" Version 6.2 April 2019. Any revisions to the protocol or case report forms that impact the planned analyses may require updates to this document. This Statistical Analysis Plan supersedes analyses described in the protocol.

Applicable Documents:

Document Number, Version	*Document Title*
Version 6.2 April 2019	Clinical Study: An Evidence Based Delivery Model of Care for Newly Implanted Adult Cochlear Implant Recipients Investigation number: 5753

2 Abbreviations

Abbreviation/Term	*Definition*
SSQ-12	Speech hearing rating scale, Spatial rating scale and sound Qualities rating scale (Gatehouse & Noble, 2013).

3 Study Objectives

3.1 Primary Objective

To evaluate the total amount of clinical time, as defined by number and duration of visits, required in patients receiving a new model of care after cochlear implant compared to a traditional clinical care schedule. Thus, comparisons are to be made between two groups of implant recipients within a cohort:

Group A (intervention): Aftercare guided by clinical outcomes and artificial intelligence processing of data.

Group B (standard): Traditional aftercare.

3.2 Secondary Objective

To compare between implant recipients from group A and group B:

- Speech perception in a quiet environment: CNC words in the ear with implant.
- Subject hearing outcome satisfaction: SSQ-12 self-assessment and Client Oriented Scale of Improvement (National Acoustic Laboratories).
- Device and accessory use of subjects: device use questionnaire and data logs.
- Clinician satisfaction: questionnaire developed in-house by Cochlear Americas.
- Speech perception in noisy environment: AzBio +10 SN in everyday listening situation using each subject's preferred noise program and accessory, if appropriate.

4 Study Design

This study is a prospective randomized investigation comparing clinical care guided by clinical outcomes and artificial intelligence processing with the traditional model of care after cochlear implant in up to 50 newly implanted adults with post-lingual onset hearing impairment.

Patients meeting study criteria will be enrolled across five cochlear implant centers in North America. Each study site will be expected to take six months to recruit eligible cochlear implant recipients and each study participant will be followed up to a maximum of six months after cochlear implant surgery.

4.1 Randomization

Study participants will be randomized after giving informed consent. Randomization will be performed with stratification by study site with a 1 to 1 allocation ratio to either aftercare guided by clinical outcomes and artificial intelligence processing of data (intervention: group A) or the traditional model of care (control: group B).

4.2 Blinding

Blinding will not be applied in this study. The assessors (audiologists) will be aware of use of the artificial intelligence software and related functions in the testing and programming of cochlear implants. Implant recipients in group A will receive a self-learning package before their switch-on visit and experience a different testing regime as part of their intervention.

4.3 Study Assessments

Data on primary and secondary outcomes will be collected from implant recipients under the following timetable. We anticipate these visits will take place within three weeks of each scheduled time point. Delayed or missed visits will be documented in the clinical investigation report. Visits occurring outside this timetable will be documented along with its date, reasons and action taken in unscheduled visit forms.

Visit	Pre-op		Switch-on		1-2 weeks		1 month post-op		3 months post-op		6 months post-op	
Group	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
Informed consent	X	X										
Clinician satisfaction											X	X
Time measurement			X	X		X	X	X	X	X	X	X
Communication documentation			X	X		X	X	X	X	X	X	X
CNC words	X	X							X	X	X	X

AzBio + 10 SN	X	X								X	X
Usage data						X	X	X	X	X	X	X
Service satisfaction			X	X						X	X
SSQ-12	X	X								X	X
COSI	X	X							X	X	X	X
Materials / Tools questionnaire			X	X			X	X	X	X	X	X
Adverse events and Device Deficiencies			X	X			X	X	X	X	X	X

5 Sample Size Determination

Our hypothesis is the mean total length of time of clinical care (in minutes) in group A recipients to be different from group B recipients in the first six months after activation of cochlear implant, excluding the 1-2 week visit for group B recipients. Each group will have three scheduled visits (1 month, 3 months, and 6 months) after cochlear implant surgery/switch-on/initial assessments, and the length of each scheduled visit is not pre-determined. Unplanned visits for programming, counselling, troubleshooting or any other clinical reason are documented in unscheduled visit forms.

We made the following assumptions in estimating the number of patients required for this study:

- Two sample Student's t-test
- Two-sided statistical significance at 0.05 level

- Study power of 0.8
- No attrition or lost to follow-up

Based on previous experience, each clinic visit lasts, on average, 90 minutes (range: 60 – 180 minutes) for cochlear implant recipients under the traditional aftercare model. Aftercare of cochlear implant recipients under the new model is expected to require 60 minutes per clinic visit (range: 30 – 90 minutes). Three follow-up visits are expected for each subject.

A planned sample size of 50 total subjects should provide greater than 90% power as long as the above ranges cover the majority of aftercare clinic visits and the expected mean times for visits for the two groups hold. This result was verified via simulations examining how power varies as a function of the hypothesized coverage of visit ranges.

The final sample size will be based on logistical considerations (i.e. rate of enrollment) but not on any interim results.

6 Statistical Analyses

6.1 General Considerations

The following generally accepted principles apply to planned statistical analyses, which will be programmed in SAS version 9.4 or later (SAS Institute Inc, Cary, NC) or other widely-accepted statistical or graphical software as appropriate.

6.1.1 Descriptive Statistics

Continuous variables will be summarized as sample mean, median, standard deviation, minimum and maximum. Categorical variables will be presented as frequency counts and percentages.

6.1.2 Statistical Significance and Confidence Intervals

We will carry out two-sided hypothesis testing at a significance level of 0.05, and report significance probability to two decimal places or to two significant figures if more appropriate. If a significance probability is estimated to have a value below 0.01, it will be reported as "$P < 0.01$".

We present confidence intervals where appropriate and they will be reported at 95% level.

6.1.3 Precision

Estimates such as percentages will be presented to one decimal place. Means, quartiles and other estimates of continuous parameters will be presented to one decimal place more than measured values and standard deviations to two decimal places more than measured values. 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. **Intention-to-treat Analysis Set**: The intention-to-treat population consists of all enrolled study participants who were subsequently randomized. The intention-to-treat set will be analyzed according to the treatment assigned by randomization, regardless of the treatment actually received.

2. **Per-Protocol Analysis Set**: The per-protocol population consists of all intention-to-treat study participants who were treated according to their assigned treatment and had no major protocol deviations related to informed consent, inclusion or exclusion criteria violations or incomplete primary and secondary endpoint data. Protocol deviations will be reviewed and exclusions from the per-protocol population will be finalized prior to analysis.

3. **Safety Analysis Set**: The safety population will consist of all intention-to-treat study participants 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 intention-to-treat set.

The primary analysis set for all study outcomes and results will be the intention-to-treat set.

6.3 Handling of Missing Data

All attempts will be made to limit the amount of missing data. To avoid bias in the analysis of the primary endpoint for the total length of clinical time due to missing visits, multiple imputation will be use to address missed visits among those visits contributing to the endpoint (i.e. the 1 month, 3 month, and 6 month post-op visits). Imputation employ MCMC methods, with imputations performed separately by randomized group to avoid treatment effect contamination. Missed visits (or missed times) from these visits will be imputed individually, and the total time summed. Imputation will be based on 100 imputed data sets and the hypothesis test will account for variation due to imputation

following the methodology (Little, R. J. A., and Rubin, D. B. (2002). Statistical Analysis with Missing Data. 2nd ed. Hoboken, NJ: John Wiley & Sons).

6.4 Demographics and Baseline Characteristics

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

6.5 Analysis of Study Endpoints

6.5.1 Primary Analysis

The primary endpoint is the total length of clinical time, as defined by number and duration of visits, required in patients receiving a new model of care after cochlear implant compared to a traditional clinical care schedule.

The primary endpoint will be assessed with the following hypothesis:

Null Hypothesis H_0: $\mu_A = \mu_B$

Alternative hypothesis H_a: $\mu_A \neq \mu_B$

where μ_A is the mean length of time in group A and μ_B is the mean length of time in group B. Time will be based on the total amount of time for aftercare visits for the 1 month, 3 month, and 6 month post-op visits. The 1-2 week visit is explicitly not included in this time because it is only relevant for group B; including this time in the comparison would introduce bias. Multiple imputation will be employed as described in Section 6.3.

The hypothesis will be evaluated using a regression model with length of time as the response and study group as one of the explanatory variables. If there is any evidence of violation of regression model assumptions, transformation or non-parametric methods may be used instead.

As an additional sensitivity analysis, the analysis will be repeated incorporating the "switch on" visit, any unscheduled visits that occur more than 2 weeks after switch-on. This analysis will also employ imputation for the 1 month, 3 month, and 6 month visits as described in Section 6.3.

As an additional set of sensitivity analyses, the analysis will be repeated based on only the programming time (total time minus time for "other activities" and for other activities (total time minus programming time). For these analyses, time will be based on the 1 month, 3 month, and 6 month visits. This analysis will also employ imputation for the 1 month, 3 month, and 6 month visits as described in Section 6.3.

6.5.2 Secondary Endpoints / Additional Analyses

The following secondary endpoints will be assessed. Comparisons will be based on nominal significance levels of 0.05 without adjustment for multiple comparisons.

- Comparison of the randomized groups for the mean CNC word score. Analysis will be based on a repeated measures linear regression model, incorporating the CNC word score at 3 and 6 months and accounting for within-subject correlation via a compound symmetric covariance structure.
- Comparison of randomized groups for the Speech, Spatial, Qualities of Hearing Scale (SSQ-12) at 6 months. Analysis will be based on a linear regression model,
- Comparison of randomized groups for device and accessory use at 6 months
- Comparison of randomized groups for clinician satisfaction at 6 months
- Comparison of randomized groups for change in AzBio + 10 S/N at 6 months in the everyday listening condition from the baseline

Additional exploratory analyses as described in the protocol will be performed:

- Evaluation of the number and reasons for unscheduled visits outside new and traditional models and comparison between the randomized groups
- Evaluation of Client Oriented Scale of Improvement (COSI) and Speech, Spatial, Qualities of Hearing Scale (SSQ-12) and relationship (correlation) between the two measures, overall and separately by randomized group
- Evaluation of test administration between clinics, separately by randomized group
- Comparison of randomized groups for the percentage of subjects with a ≥ 20% improvement in CNC word score from baseline to 3 months
- Evaluation of the communication documentation form, separately by randomized group
- Comparison of randomized groups for the percentage of subjects with a ≥ 30% improvement in CNC word score from baseline to 6 months
- Evaluation of clinic site differences in subject reported service satisfaction between sites, by randomized group

- Evaluation of the effectiveness of self-guided subject materials, separately by randomized group

6.6 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 sites will be evaluated in a regression model with fixed effects for treatment, site, and treatment by site interaction. Sites enrolling less than five subjects will be combined to form one-quasi site.

6.7 Safety Analyses

Adverse events will be tabulated with the number of events and subjects with event for each event type and overall, by randomized group. Rates will be reported as the number of subjects who experience at least one event during the analysis interval out of the total number of subjects with follow-up to the beginning of the analysis interval. Serious adverse events will also be tabulated. The rate of all adverse events and serious adverse events reported in the study will be reported.

6.8 Subgroup Analyses

We have not planned any subgroup analysis for this study.

6.9 Interim Analyses

No interim analyses are planned.

6.10 Protocol Deviations

Deviations from the procedures outlined in the protocol will be reported by investigational sites on the case report form. 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 from 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.