SAFETY AND EFFICACY OF REMOTE PROGRAMMING OF NUCLEUS COCHLEAR IMPLANTS

STATISTICAL ANALYSIS PLAN

CIP Version (Date)	Version 1.0 (03Aug2015)
SAP Version (Date)	Version 1.1

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Table of Contents

1 PURPOSE

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of data collected under the Cochlear IDE Study titled, "Safety and Efficacy of Remote Programming of Nucleus Cochlear Implants."

2 SCOPE

This SAP should be read in conjunction with the study protocol. This version of the plan has been developed with respect to the Cochlear IDE Study protocol version 1.0, dated 03-Aug-2015. Any further changes to the protocol may necessitate updates to the SAP.

3 APPLICABLE DOCUMENTS

Document Number	Document Title
	Cochlear IDE Protocol Version 1.0 (03Aug2015)
STATSOP-002	Statistics Standard Operating Procedure – Statistical Analysis Plan

4 SOFTWARE

All statistical analyses will be completed using SAS software (SAS Institute, Inc., SAS Campus Drive, Cary, NC 27513, USA.) In the event an analysis is required that is better suited for a statistical package other than SAS, another package (e.g. R) will be used.

5 ABBREVIATIONS AND DEFINITIONS

Abbreviation / Term	Definition
ADE	Adverse Device Effect - any untoward and unintended response to an investigational medical device
AE	Adverse Event - any untoward medical occurrence in a subject
CI	Cochlear Implant
CRF	Case Report Form
eCRF	Electronic Case Report Form
Enrolled	A subject is enrolled when he/she meets all inclusion/exclusion criteria and signs the informed consent form
Facilitator	A trained staff member at the programming site
IDE	Investigation Device Exemption
Live Programming	Traditional face to face programming interaction between a recipient and an audiologist at the same physical location
MAP	A program that defines the individualized parameters of recipients for a specific speech coding strategy
Remote Programming	A programming interaction between a recipient and an audiologist that occurs via telecommunication technology when the two parties are at different physical locations
SAE	Serious Adverse Event – an adverse event that: • Led to death • Led to a serious deterioration in the health of the subject, that

	either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient hospitalization or prolongation of existing hospitalization, or resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death or a congenital abnormality or birth defect
SAP	Statistical Analysis Plan

6 STUDY OBJECTIVES

The purpose of this study is to characterize the safety and demonstrate the efficacy of CI programming via telecommunication.

7 STUDY POPULATION

The study population will include up to 40 subjects (12 years of age or older) who have unilateral or bilateral cochlear implants and are capable of completing the study evaluation.

8 SAMPLE SIZE

Based on the variability observed in earlier studies, it was determined using PASS (NCSS Statistical Software) that a minimum of 26 subjects would provide at least 90% power for hypothesis testing of the two co-primary endpoints at the 0.025 alpha level.

The planned sample size of 40 subjects will provide adequate power for hypothesis testing of the two co-primary endpoints at the 0.025 alpha level. The following general assumptions have been made:

- Paired T-tests of difference scores to test for non-inferiority with a non-inferiority margin of 10% for CNC word recognition
- One-sided 0.025 alpha level
- Assumed distribution for population (standard deviation)
- Desire for 90% power

The power analyses for the primary test metrics are provided below.

Sample size calculation for CNC word recognition:

Scenario (Non-inferiority)	Minimum Evaluable Sample Size Required
One-sided 0.025 alpha, 90% power, SD = 15%, NIM = 10% , true difference = 0	26

More subjects will provide additional power or a similar degree of power for more conservative assumptions. Because the non-inferiority sample size calculation assumes a true difference of 0 between remote and live MAP programming, we propose a sample size of 40 subjects to allow for:

1. the possibility that variability will be greater than expected,
2. the possibility that the true difference may be greater than 0, and
3. the possibility of subject attrition.

9 STATISTICAL ANALYSES

9.1 General Considerations

Continuous measures will be summarized with sample size, mean, median, standard deviation, minimum and maximum; categorical measures will be presented with the counts and percentages of subjects in each category.

10 STUDY ENDPOINTS

10.1 Safety Endpoint

An adverse event (AE) is any undesirable clinical or medical occurrence associated with the use of the device, procedure, or participation in the study, which does not result in serious injury or illness related to the surgical procedure or the device.

Adverse events will be counted regardless of severity, seriousness, onset, duration, or relation to study treatment.

A serious adverse event (SAE) is any untoward medical occurrence that

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- requires medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- leads to fetal distress, death, or congenital abnormality or birth defect
- is a medically important event or reaction

For any SAE, if the Primary Investigator judges that there is a logical connection (caused or contributed to) between the use of the device and the occurrence, the SAE will be noted as device-related.

10.1.1 Safety Endpoint

The objective of the safety analysis is to characterize the safety profile of device and/or procedure related adverse events associated with facilitated remote MAP programming, unassisted MAP programming and audiologist live MAP programming.

All Adverse Events will be tabulated according to the study interval, the number of procedure-related events, and the number of device-related events. Procedure- and device-related adverse events will be summarized as rates, where the numerator for each rate will be the number of subjects with at least one procedure- or device-related event, and the denominator will be the total number of subjects.

10.2 Primary Efficacy Endpoints

There are two primary efficacy endpoints in this clinical investigation. The two primary efficacy endpoints will be based on analyses of CNC word recognition. The objective of the two primary efficacy endpoints is to test for non-inferiority of remote MAP programming via telecommunication compared to live MAP programming.

For each of the two primary endpoints, a one sample t-test will be used to test for treatment effects.

10.2.1 Primary Efficacy Endpoint 1

The objective of the first primary efficacy analysis is to demonstrate non-inferiority of facilitated remote MAP programming via telecommunication compared to traditional audiologist live MAP programming for word recognition in quiet as evaluated with the CNC test. Success for the first primary endpoint will be based on rejection of the null hypothesis of inferiority, with a non-inferiority margin of 10% based on clinical judgment and variability observed in previous studies. The treatment effect will be estimated using a one sample t-test. If the upper limit of the two-sided 95% confidence bound is less than 10, statistical significance will be met at the 0.025 alpha level. The first primary endpoint is represented by the following hypotheses:

H_0: $CNC_{diff} \geq 10\%$

H_a: $CNC_{diff} < 10\%$

where:

CNC_{diff} = Live Audiologist MAP - Facilitated Remote MAP programming treatment difference for CNC word recognition.

10.2.2 Primary Efficacy Endpoint 2

The objective of the second primary efficacy analysis is to demonstrate non-inferiority of unassisted remote MAP programming via telecommunication compared to traditional audiologist live MAP programming for word recognition in quiet as evaluated with the CNC test. Success for the second primary endpoint will be based on rejection of the null hypothesis of inferiority, with a non-inferiority margin of 10% based on clinical judgment and variability observed in previous studies. The treatment effect will be estimated using a one sample t-test. If the upper limit of the two-sided 95% confidence bound is less than 10, statistical significance will be met at the 0.025 alpha level. The second primary endpoint is represented by the following hypotheses:

H_0: $CNC_{diff} \geq 10\%$

H_a: $CNC_{diff} < 10\%$

where:

CNC_{diff} = Live Audiologist MAP - Unassisted Remote MAP programming treatment difference for CNC word recognition.

10.3 Secondary Efficacy Endpoint

The objective of the secondary efficacy analysis is to demonstrate non-inferiority of unassisted remote MAP programming via telecommunication compared to facilitated remote MAP programming via telecommunication for word recognition in quiet as evaluated with the CNC test. Success for the second co-primary endpoint will be based on rejection of the null hypothesis of inferiority, with a non-inferiority margin of 10% based on clinical judgment and variability observed in previous studies. The treatment effect will be estimated using a one sample t-test. If the upper limit of the two-sided 95% confidence bound is less than 10, statistical significance will be met at the 0.025 alpha level. The secondary efficacy endpoint is represented by the following hypotheses:

H_0: $CNC_{diff} \geq 10\%$

H_a: $CNC_{diff} < 10\%$

where:

CNC_{diff} = Facilitated Remote MAP - Unassisted Remote MAP programming treatment difference for CNC word recognition.

11 TYPE 1 ERROR CONTROL

Study success will be defined by rejection of the null hypotheses in the comparison of facilitated remote MAP programming via telecommunication to live MAP programming and/or the rejection of the null hypothesis in the comparison of unassisted remote MAP programming via telecommunication to live MAP programming for CNC word recognition. Because study success is based on two separate endpoints, type I error will be maintained at an overall one-sided alpha level of 0.025. The secondary efficacy objective will be tested only in the event both co-primary efficacy objectives are met. Thereby preserving the overall 0.025 alpha level

12 ADDITIONAL ANALYSES

No formal statistical hypothesis testing will be conducted for the additional endpoints. Statistical comparisons may be presented for descriptive purposes only without adjustment for multiplicity. A nominal $p<0.05$ will be used to determine statistical significance.

12.1 Subject Disposition

Subject disposition will be presented by:

- Summary of subjects per visit
- Summary of early withdrawal and reason for early withdrawal

12.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics of enrolled subjects will be summarized.

12.3 Within-Subject Differences in CNC test scores

The critical differences (.05 level of confidence) adapted from Thornton and Raffin (1978) will be used for comparison of CNC word recognition scores between each 2 condition comparison. The number of subjects with significantly lower, significantly higher, and similar scores based on the binomial model presented Thorton and Raffin (1978) will be reported for the following comparisons: facilitated remote MAP programming via telecommunication compared to traditional audiologist live MAP programming, unassisted remote MAP programming via telecommunication compared to traditional audiologist live MAP programming, and unassisted remote MAP programming via telecommunication compared to facilitated remote MAP programming via telecommunication.

12.4 Remote Programming Satisfaction Survey

At Visits 2 and 4, the remote programming satisfaction survey will be completed. This survey uses a satisfaction rating scale to gather subjects' opinions regarding the ease, quality, and comfort of the remote programming sessions.

12.5 Speech, Spatial, and Qualities of Hearing Scale (SSQ-C)

At Visits 3 and 5, the SSQ-C will be completed. The SSQ-C will be used as a subject self-assessment in three categories (speech hearing rating scale, spatial rating scale, and sound qualities rating scale). The SSQ-C is the "comparative" version of the SSQ. It can be used for comparing two different hearing

technologies. In this study, the SSQ-C will compare the subject's familiar map (Program #1) and remote MAP (Program #2).

12.6 Telemedicine Experience Questionnaire

At Visit 5, the telemedicine experience questionnaire will be completed. This 5-question survey was specifically designed to examine subjects' evaluations of the telemedicine experience. It includes a response rating scale, as well as the opportunity for open ended feedback.

12.7 Electrical Charge

At Visits 1, 2, and 4, electrical charge information will be collected. Comparisons of T and C levels between MAPs will be conducted using descriptive statistics.

12.8 Exploratory Analyses

Additional, ad hoc exploratory analyses may also be conducted.

12.9 Other Data

Protocol deviations will be listed and tabulated.

13 POOLING ACROSS SITES

Pooling data from study sites will be justified based on the following: all sites will have the same protocol, the sponsor will monitor the sites to assure protocol compliance, and the data gathering mechanism (case report forms and data acquisition) will be the same across all study sites.

Consistency of the primary efficacy endpoints will be assessed by testing for a difference between sites in the difference between facilitated remote MAP programming via telecommunication and live MAP programming for CNC word recognition and by testing for difference between sites in the difference between unassisted remote MAP programming via telecommunication and live MAP programming for CNC word recognition. Testing will be conducted via an analysis of variance model, with difference between testing conditions as the outcome and site as the factor. A p-value for the site factor of less than 0.15 will be considered evidence of differences between sites for one of the primary efficacy endpoints. If there is evidence of a difference, additional analyses will be performed to explore the possible role of baseline characteristics to explain the results. Results for the primary efficacy endpoint will also be presented separately by site, irrespective of the test of differences between sites, to help understand both qualitative and non-significant differences between sites

14 MISSING DATA

All efforts will be put forth to ensure near complete follow-up, with particular focus on the assessment of the primary outcomes and occurrence of adverse events. A reminder of subject follow-up due dates will be provided to participating centers to facilitate scheduling of the follow-up visits.

Sensitivity analysis will be conducted to address the potential impact of missing endpoint data using a multiple imputation analysis with 10 imputed datasets. Missing data for CNC score under each condition will be imputed. The imputed datasets will then be combined for inference using standard methods such as those available in SAS PROC MIANALYZE or other valid statistical software. In addition, comparisons of baseline characteristics between those with missing data and those without will be conducted. This will provide an assessment as to whether there are systemic differences in subjects who miss visits.

15 REFERENCES

Thornton AR and Raffin MJM. (1978). Speech-Discrimination Scores Modeled as a Binomial Variable. *Journal of Speech and Hearing Research*, 21(3), 507-513. 1978

16 VERSION HISTORY

Version	Date	Changes
1.0	27Oct2015	
1.1	04Dec2015	Added section 12.7 Electrical charge. Added additional detail to section 14: Missing data (second paragraph regarding multiple imputation).