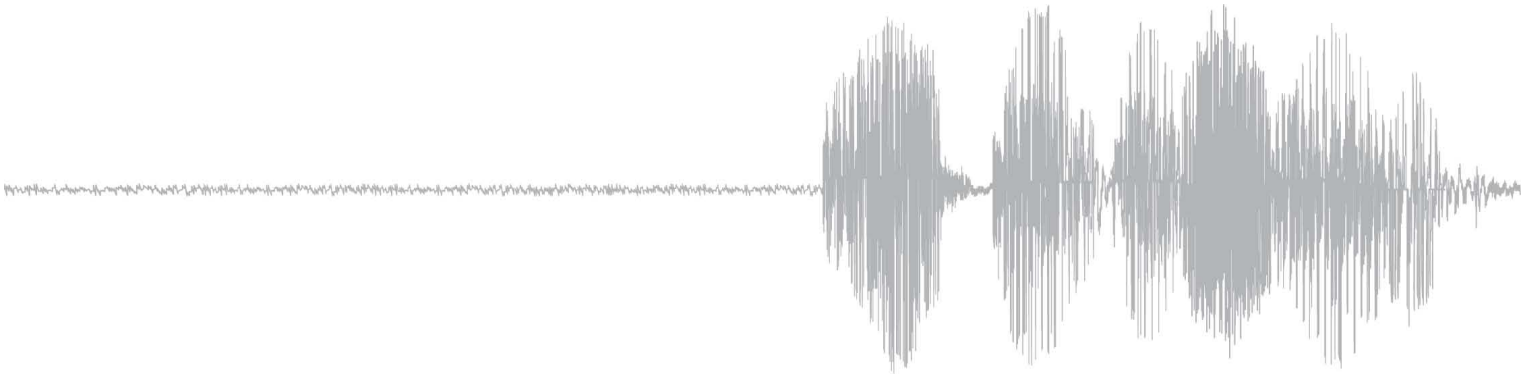

CLTD 5667_Statistical Analysis Plan

D1110134

Version: 3
State: Approved (T+B)
Approver: Kerrie Plant (kplant)
Date : 29 May 2019

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Statistical Analysis Plan

Clinical Investigation Title:	Association Between Intra-Operative Cochlear Response Telemetry and Hearing Preservation (CREST)
Clinical Investigation Short Title:	Influence of CRT on Hearing Preservation
Clinical Investigation Number:	CLTD 5667
Related CIP:	D1041816
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SAP Version:	*3.0*

Contents

1 INTRODUCTION

This document is a companion document to the Clinical Investigation Plan (D1041816). It includes a comprehensive description of the sample size estimation, the intended statistical analyses with reference to the primary and secondary hypotheses, and additional statistical considerations such as the intended treatment of missing data.

Any deviation from the Statistical Analysis Plan will be reported in the Clinical Investigation Report.

2 STUDY POPULATION

The Cochlear Response Telemetry (CRT) system for monitoring the cochlear microphonic (CM) response to acoustic clicks or short tone bursts will be assessed in a clinical population aged 18 years and older, who have received a commercially available Nucleus® CI522, CI532, or Hybrid-L24 cochlear implant.

3 STATISTICS

3.1 Sample Size

Prospective sample size estimation for a two-sample t-test has been conducted, given that the study uses a between-groups design to investigate its primary hypothesis. Specifically, the planned sample size would provide 80% power at the one-tailed 0.05 alpha level to detect at least 15 dB greater deterioration in low frequency acoustic hearing threshold for subjects with compromised CM compared to preserved CM.

The following general assumptions have been made:

- A difference in mean hearing preservation of 15 dB for the compromised CM versus preserved CM groups. This difference is considered clinically meaningful, based on clinical consensus.
- An expected standard deviation of 25 dB HL. It is more conservative, but is based on the SD of 22.26 dB HL observed in low frequency hearing preservation at 3 months post-operative in the US multi-site clinical trial with 52 cochlear implant recipients using the CI422 straight electrode array (IDE G120234). This trial is considered relevant since the majority of subjects in the prospective trial will be similarly implanted with the Slim Straight array (CI522). Furthermore, in the calculation of the SD for this previous trial, low frequency hearing preservation has been calculated in the same manner as it will be in the prospective study (as the average change in threshold (post-activation minus pre-operative) across the frequencies 500 Hz, 750 Hz and 1000 Hz where there is preoperative hearing ≤80 dB HL in the implanted ear).
- One-sided 0.05 alpha level, given that the primary endpoint is based on a directional hypothesis.
- A desired power of 0.8.

Based on the above assumptions, a minimum sample size of 36 subjects with preserved and 36 subjects with compromised CMs is required to reject a false null hypotheses of equivalent or worse hearing preservation for those subjects with preserved CM (using SigmaPlot 13.0).

This minimum sample size will be increased for the following reasons.

a. The sample size will be increased by 15% to 41 subjects per group to allow for the possibility that the hearing threshold data is non-normally distributed and that a nonparametric statistical analysis will be required. This 15% increase is based on what is known as the minimum asymptotic relative efficiency (ARE) of the Mann-Whitney U test relative to the independent t-test. It can be proven that the ARE (or Pitman efficiency) is never less than 86.4%. When the sample size is increased by 15%, the equivalent power should be achieved, since 1.15 is approximately 1/0.864.
b. The sample size will be increased to a total of 43 subjects per group to allow for the prediction that approximately 5% of cochlear implant recipients will not exhibit an intraoperative CM response (Dalbert et al. 2015).

3.2 Analyses

3.2.1 Pass/Fail Criteria

Not Applicable

3.2.2 Primary Hypothesis

The primary hypothesis that there will be significantly greater deterioration in average low frequency post-operative hearing threshold levels at FUV1 in the implanted ear for subjects with intra-operative compromised CM compared to those with preserved CM, will be evaluated with a one-sided independent t-test using an alpha level of 0.05. If there is evidence the normality assumption for the t-test does not hold based on a Shapiro-Wilk test of normality at the 0.05 level, a non-parametric Mann-Whitney U test will be performed instead. If the variance of hearing preservation for compromised CM and preserved CM are significantly different, the Welch test may be computed.

Compromised CM will be defined as a CM with an irreversible reduction in amplitude during surgery; specifically a ≥30% reduction in maximum CM amplitude. This will include those subjects where a transient reduction in CM which recovers is observed (Weder et al submitted). Preserved CM will be defined as a CM with <30% amplitude reduction at any point during the surgery. The mean or median audiometric change for the compromised CM and preserved CM groups will be calculated as the mean or median of individual subjects' low frequency deterioration (3 month post-activation threshold minus pre-operative threshold in the implanted ear). For each subject, the low frequency deterioration will be calculated as the average deterioration across the frequencies 500 Hz, 750 Hz and 1000 Hz, where there is preoperative hearing better than or equal to 80 dB HL in the implanted ear. For example, if a subject's preoperative hearing threshold is better than or equal to 80 dB HL at 500 Hz and 750 Hz but is 90 dB HL at 1 kHz, the hearing deterioration (post-operative threshold minus preoperative threshold) will be computed at 500 Hz and 750 Hz only and then averaged. It is possible that a subject could have hearing deterioration measured at 500 Hz only, if preoperative thresholds at 750 Hz and 1 kHz exceed 80 dB HL. Non-measurable post-

operative thresholds will be assigned a value of 126 dB HL, indicating the level at which the limits of the audiometer were reached. Vibrotactile responses will not be included in the analyses.

If the variance of hearing preservation for compromised CM and preserved CM are significantly different and the normality assumption is not violated (based on the Shapiro-Wilk test), the Welch test may be computed.

The null and alternative hypotheses are as follows:

H_0: $CM^- - CM^+ \leq 0$

H_a: $CM^- - CM^+ > 0$

where:

CM^- = mean or median drop in low frequency postoperative hearing at 4-6 weeks post-activation (FUV1) for the compromised CM group.

CM^+ = mean or median drop in low frequency postoperative hearing at 4-6 weeks post-activation (FUV1) for the preserved CM group.

If additional multiple regression analyses specified in 3.4.4 indicate the presence of covariates explaining a significant amount of variance in acoustic hearing preservation, the primary endpoint will also be tested using a general linear model (ANCOVA) that controls for the influence of covariates. If there is significant departure of the difference in hearing thresholds from normality, the data used in the ANCOVA will be transformed to better approximate normality.

Type 1 error control

Not applicable given that there is only one primary endpoint.

Analysis dataset

The primary hypothesis will be tested using the per protocol dataset (refer to section 3.3 where this analysis dataset is described). Imputation of missing data in an intent to treat analysis is not deemed essential, given that the primary hypothesis is not related to making claims about the efficacy of a device, strategy or processing algorithm compared to a baseline.

There will be no missing data for the pre-operative acoustic hearing thresholds variable, since a subject inclusion criterion is a pre-operative hearing threshold of ≤80 dB HL at 500 Hz. Missing hearing threshold data at FUV in the compromised CM and/or preserved CM groups is possible. However, it is anticipated that there will be less than 5% of missing data and that any missing data will be missing at random.

3.2.3 Secondary Hypotheses

Secondary hypothesis 1

The secondary hypothesis 1 that deterioration in average low frequency post-operative hearing threshold at FUV2 in the implanted ear for subjects with intra-operative compromised CM will be greater than subjects with preserved CM, will be evaluated with a one-sided independent t-test using an alpha level of 0.05. A Mann-Whitney U test will be conducted if

the data is non-normally distributed. The analysis considerations will be identical to those described for the primary hypothesis in 3.2.2.

The null and alternative hypotheses are as follows:

H_0: $CM^- - CM^+ \leq 0$

H_a: $CM^- - CM^+ > 0$

where:

CM^- = mean or median drop in low frequency postoperative hearing at 3 months post-activation (FUV2) for the compromised CM group.

CM^+ = mean or median drop in low frequency postoperative hearing at 3 months post-activation (FUV2) for the preserved CM group.

Secondary hypothesis 2

The secondary hypothesis 2 predicting that earlier onset of CM response during electrode array insertion will be associated with better pre-operative high frequency acoustic hearing thresholds, will be tested using a Pearson Product Moment Correlation coefficient or Spearman rank correlation coefficient with a one-sided alpha level of 0.025.

The onset of the CM response will represented by even numbers from low to high on an interval scale, with low numbers representing earlier onset. The onset of the CM response will be tracked by impedance measures that are interleaved with the ECoG recordings. As each electrode in the array enters the perilymph in the cochlea, there will be a measured sharp drop in impedance. Therefore, CM onset will be defined in terms of the n^{th} electrode (out of the 22 electrodes) to enter the cochlea. For example, CM onset might first occur when impedance sharply drops as the 14^{th} electrode in the 22 electrode array enters the cochlea. Since the impedance measures are not smoothed and instantaneous, the CM onset scale will have precision to every 2^{nd} electrode in order of cochlea entry. Pre-operative high frequency hearing will be defined as the average of pre-operative hearing thresholds in the implanted ear at 2 kHz, 3 kHz, and 4 kHz.

The null and alternative hypotheses are represented as follows, where r refers to the Pearson correlation coefficient.

H_0: $r = 0$

H_a: $r > 0$

If the null hypothesis of no association between CM onset and high frequency acoustic hearing is rejected, a simple linear regression will then be computed to define the predicted influence of the pre-operative acoustic hearing thresholds on the CM response characteristic.

Both the auditory hearing threshold data and the CM response data will initially be assessed for normality and if there is a significant departure from normality, the data will be transformed to better approximate normality. If the data transformation is unsuccessful, a non-parametric Spearman rank correlation will be computed. It is highly probable that the non-parametric correlation coefficient will be used when high frequency acoustic hearing is

expressed as the highest cut-off frequency at which there is measurable high frequency hearing.

3.2.4 Exploratory Hypotheses

The following exploratory hypotheses shall include:

1. *Predictors of the incidence of compromised CM during cochlear implant surgery including influence of electrode type, insertion depth and surgical events*

Descriptive, proportional data will be presented to capture the incidence of the compromised CM for electrode type, electrode array insertion depth and surgical events such as inadvertent moving of the electrode array after insertion completion or during sealing of the round window.

2. *Association of pre-operative high frequency acoustic hearing thresholds with change in latency of CM during electrode array insertion*

It is predicted that greater CM latency (phase shift expressed in ms) during electrode array insertion will be associated with better pre-operative acoustic high frequency hearing thresholds, will be tested using a Pearson Product Moment Correlation coefficient or Spearman rank correlation coefficient with a one-sided alpha level of 0.025. The CM latency change will be measured between two CM onset points that are as widely spaced as possible, where a preserved CM is able to be measured as the electrode array is advanced into the cochlea (e.g. 10th electrode to enter versus the 22nd electrode). This CM onset range for the latency change measurement will be identical for all subjects. It will be selected by analysing the group CM data to 1) be sufficiently wide so that the latency measure is sensitive to the potential influence of surviving hair cell populations along the basilar membrane that respond to a range of frequencies and 2) include enough subjects to have adequate power for the primary endpoint analysis. Greater CM latency change will be represented by higher numbers. Pre-operative high frequency hearing will be defined as the average of pre-operative hearing thresholds in the implanted ear at 2 kHz, 3 kHz and 4 kHz, with lower numbers representing better high frequency hearing. Therefore, a negative correlation is predicted by the alternative hypothesis.

3. *Investigation of the influence of demographic and surgical factors on the morphology and time-course of the CM response during insertion and post-operatively.*

The CM response traces will be examined for any unusual patterns and whether such patterns appear to be associated with any factors (e.g. electrode type). If visual inspection suggests interesting associations in characterizing the CM response, regression analyses will be computed to further understand the predictive influence of the factors on the CM morphology and time-course.

4. *Investigation of the relationship of CM thresholds to postoperative HTLs in the implanted ear.*

This hypothesis will be tested using a repeated measures linear regression to examine the association between CM threshold (independent variable) and behavioural threshold (dependent variable) at FUV2. Thresholds are measured at several frequencies (e.g. 250Hz, 500Hz, 1 kHz, 2 kHz, 4 kHz) and this creates potential correlation within subjects, thus

necessitating repeated measures approach. The thresholds will be expressed in dB nHL. A test of the slope of the CM threshold term against a null hypothesis value of 1 will be performed; a value significantly greater than 1 would indicate behaviour thresholds are higher than the corresponding CM threshold. Frequency will also be examined to understand if there is an effect on the association of CM and behavioural threshold. If the assumption of normality fails based on a Shapiro-Wilk test of normality at the 0.05 level, the data will be arcsine transformed to minimise departure from normality. Descriptive statistics for the CM and behavioural thresholds, the mean (standard deviation) or median (inter-quartile range) as appropriate will be reported by frequency.

5. *Examination of the degree of reduction in CM amplitude that occurs in response to a range of surgical events.*

Quantitative statistics will be used (e.g. mean, standard deviation, median, interquartile range, minimum, and maximum) to describe the CM amplitude degree of reduction for a range of surgical events (e.g. inadvertent moving of the electrode array after insertion completion).

6. *Characterization of changes in intracochlear impedance as a function of CRT observations during and post-surgery.*

Quantitative statistics will be used (e.g. mean, standard deviation, median, interquartile range, minimum, and maximum) to describe the change in intracochlear impedance for a range of CRT observations during and after surgery.

7. *Characterization of changes in different components of the electrocochleography (ECoG) measurement over time.*

Quantitative statistics will be used (e.g. mean, standard deviation, median, interquartile range, minimum, and maximum) to describe the change in different components of the ECoG over time from the baseline measurement taken in surgery immediately after wound closure to FUV (e.g. change in CM and ANN thresholds and amplitude over time).

8. *Examination of hearing preservation for compromised CM and preserved CM groups which have been classified using different criteria of CM amplitude reduction and time course.*

Post-operative hearing preservation (FUV1, FUV2) will be compared for compromised CM and preserved CM groups, which have been classified differently on the basis of degree of CM amplitude reduction and the time course of this amplitude reduction. Between-groups t-tests, Mann-Whitney U tests or Welch tests with one sided alpha levels of 0.05 will be conducted to determine whether there is greater average low frequency hearing deterioration in the implanted ear for the compromised CM group than for the preserved CM group. Pre-operative hearing deterioration will be defined in the same manner as for the primary hypothesis.

3.3 Analysis Datasets

3.3.1 Intent-to-Treat

Not applicable (see rationale provided in 3.2.2)

3.3.2 Per Protocol dataset

This dataset limits data to subjects with bivariate data for each of the primary endpoint correlational analyses (i.e. hearing threshold data and CM response data).

3.4 Additional Statistical Considerations

3.4.1 Missing, Unused or Spurious Data

As mentioned in 3.2.2, there will be no imputation of missing data for the analyses of the primary hypotheses in this study. The rationale for this decision is provided in 3.2.2.

3.4.2 Planned Interim Analysis

Not applicable

3.4.3 Criteria for Termination of the Clinical Investigation

Not applicable

3.4.4 Additional Statistical Analyses

Analysis of baseline characteristics of the study group

This analysis will be a descriptive analysis of quantitative variables such as age, gender aetiology, pre-operative low frequency hearing thresholds and duration of deafness for the group with compromised CM versus the group with preserved CM. The mean, standard deviation and range will be provided where appropriate to the data type. If the data for the variable is non-normally distributed the median and variability expressed in quartiles will be computed.

Regression analyses

The influence of three potential covariates on the dependent variable of hearing preservation will be explored. The variables, age and gender, were previously reported to be significant predictors of hearing loss at 12 months post-activation in a trial of 85 patients who received the hybrid cochlear implant as part of the adult FDA multicentre clinical trial in the USA (Kopelovich et al. 2014). Older age at implantation and the male gender were associated with greater post-implantation hearing loss. A third potential confounding factor - the presence/degree of intraoperative steroids was reported to be a significant predictor in hearing preservation in a meta-analysis study by Causon et al. (2015). Each of these covariates may be incorporated into ANCOVA analysis to examine the effect of each on the comparison of compromised and preserved CM groups, including the potential for confounding and for effect modification (i.e. whether a covariate affects the association of CM group and hearing preservation).

3.5 Conduct of Statistical Analysis

Kerrie Plant will conduct the statistical analyses using SigmaPlot 13.0 and Minitab 17 Statistical Software. Support will be provided from the University of Melbourne Department

of Otolaryngology collaborators Dr Christo Bester and Professor Stephen O'Leary, and Dr John Heasman from Cochlear Limited.

3.6 Quality control on statistical analysis

Dr Pam Dawson will review the statistical analysis for the primary endpoint. The review will include checking that the descriptive, quantitative statistics in the statistical analysis and report tables and figures (e.g. mean or median) for the low frequency hearing deterioration for compromised CM and preserved CM groups matches the quantitative statistics in the monitored electronic data capture reports.

3.7 Presentation of data

A table of subject demographics will be provided in the study report.

Results from the between-groups t-test or Mann Whitney U test to address the primary hypothesis are likely to be presented in a box plot showing variability around the median low frequency hearing deterioration for each of the compromised CM and preserved CM groups at FUV. Scatterplots will be presented to depict the correlational analyses for each of the secondary endpoints, with acoustic hearing presented on the x-axis and the CM characteristic (onset or change in latency) presented on the y-axis.

4 REFERENCES

4.1 Internal References

ID	Document Title	Number
	Influence of Intra-Operative Cochlear Response Telemetry on Hearing Preservation: Clinical Investigation Plan:	D1041816

4.2 External References

ID	Document Title	Number
	Published References Causon, A., Verschuur, C. and Newman, T.A. (2015). A Retrospective Analysis of the Contribution of Reported Factors in Cochlear Implantation on Hearing Preservation Outcomes. *Otology & Neurotology, 36*: 1137-1145. Dalbert, A., J. H. Sim, R. Gerig, F. Pfiffner, C. Roosli, and A. Huber. 2015. 'Correlation of Electrophysiological Properties and Hearing Preservation in Cochlear Implant Patients', *Otol Neurotol*, 36: 1172-80 Kopelovich, J.C., Reiss, L.A.J., Oleson, J.J., Lundt, E.S., Gantz, B.J. & Hansen, M.R (2014). Risk factors for loss of ipsilateral residual hearing after Hybrid cochlear implantation. *Otol Neurotol. 35(8)*: 1403-1408. **Unpublished References** Unpublished data. Electrocochleography in Cochlear Implant Recipients. The Royal Victorian Eye and Ear Hospital Human Research Ethics Committee #14/1171H Weder, S., Bester, C., Collins, A., Shaul, C., Briggs, R.J., O'Leary, S. Towards a Better Understanding of Electrocochleography: Analysis of Real-time Recordings. *Ear and Hearing,* Submitted on: 19th April 2019	

5 CHANGE HISTORY

Version	Change	Author	Date
V1	Introduction of Document	Pam Dawson	14/05/2018
V2	Additional information provided on examination of the cochlear microphonic counts after recruitment of the initial 86 subjects to determine further recruitment to ensure adequate power for examination of endpoints.	Pam Dawson	14/05/2018
V3	Two of the additional exploratory analyses removed Compromised CM definition modified Sample size justification modified to reflect change of global recruitment target from 125 to 86	Ruth English	06/05/2019