Clinical Investigation Plan

Investigation Title: Cochlear Implant Clinical Care Study

Investigation Number: CLTD-5517

Version Number: 2

Date: 03-Sept-2014

Authors: [redacted]

Sponsor	Cochlear Limited 1 Macquarie Avenue Macquarie University NSW 2109 Australia
Coordinating Investigator	[redacted] Principal Research Audiologist Cochlear Limited, 1 University Avenue, Macquarie University Macquarie NSW Tel: [redacted]
Clinical Research Organisation (or other institution involved)	Not applicable

A complete list of participating Principal Investigators names, titles, and addresses, and the names and addresses of participating institutions (sites) will be maintained by the sponsor and will be distributed as a separate Principal Investigator List (PIL) document (558600).

1 SPONSOR AND COORDINATING INVESTIGATOR SIGNED AGREEMENT

Investigation Title	Cochlear Implant Clinical Care Study
Investigation Number	CLTD-5517

Signature on behalf of Sponsor

I agree with the content in this clinical investigation plan, including all appendices.

Name	**Title**
[redacted]	Head of Global Clinical Affairs & Post-Market Surveillance
Signature	**Date** (dd-mmm-yyyy)
[redacted]	03-SEP-2014

Signature of Coordinating Investigator

I agree to the content of this clinical investigation plan, including all appendices.

Name	**Title**
[redacted]	Principal Research Audiologist
Signature	**Date** (dd-mmm-yyyy)
[redacted]	03-Sep-2014

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2 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	Cochlear Implant Clinical Care Study
Investigation number	CLTD-5517
Name of investigational device	Nucleus Cochlear implants, sound processors and remote assistants programmed via Custom Sound software, Nucleus fitting software, myCochlear software, experimental fitting platform or similar research programming software application.
Investigation start (Mmm yyyy)	June 2013
Total expected duration of the clinical investigation	5 years
Enrolment period	5 years
Expected duration per subject	Up to 12 months
Investigational design	Prospective experimental study where each subject is his / her own control (Repeated-measures single-subject) Usability trial
Number of subjects	Minimum 17 subjects for stages involving speech perception testing Minimum 5 subjects for stages involving usability trial only Minimum 5 subjects for stages involving electrophysiological testing only
Inclusion criteria	Implanted or assessed to be suitable for implantation with a commercially available Nucleus implant, resulting in measurable open set speech understanding.
Exclusion criteria	Unwillingness or inability of the candidate to comply with all investigational requirements Additional handicaps that would prevent or restrict participation in the audiological evaluations
Primary objectives	To evaluate the recipient's speech perception outcomes for programs created using the different programming methodologies. To evaluate the effectiveness of the new measurement methods compared to the currently used methods. To evaluate the ease of use of the research software and / or hardware. To evaluate the subjective preference for different sound processor programs and features.
Secondary objectives	None
Primary endpoints	Report on performance, usability and preference data.
Secondary endpoints	None

Investigation Schedule

Group 1

Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Fitting	X	X	X	X	X	X
Testing		X	X	X	X	X

Group 2

Procedure	Visit 1
Intraoperative testing	X

3 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

Cochlear implants are electronic devices for adults and children who do not receive adequate benefit from conventional hearing aids. The cochlear implant consists of an internal implant and a sound processor. The microphone of the sound processor picks up the sound and turns it into a digital code. The sound processor transmits this digitally coded sound through the coil to the implant. The implant converts this sound into electrical pulses and sends them along the electrode array placed in the cochlea. The electrodes of the implant then stimulate the cochlea's hearing nerve. Programming is done using clinical software connected to the sound processor. Clinicians also perform performance measurements to assist in the programming and management of the CI recipient.

This study evaluates the incremental changes made in the programming and performance assessment software and hardware to improve the efficacy of programming or performance measurements. Custom Sound software, Nucleus fitting software, myCochlear software, experimental fitting platform, performance testing research software or similar research programming software application will be used. The sound processor is used to stimulate the internal implant. The programming pod, remote assistant or other research hardware will be used to deliver inputs to the sound processor and read information from the sound processor. The research software / firmware is used to determine the type of stimulation provided by the sound processor.

These incremental changes are made available based on theoretical considerations, literature data and bench testing experiments. The research software and hardware are assessed for their effect on the safety and efficacy as per the Cochlear's Risk Management Procedure (P41277UE)and in accordance with ISO 14971, "Medical devices – Application of risk management to medical devices". However, there is a need to evaluate the changes in users in real world environments to validate them.

The aim of this study is to systematically and objectively test the changes in software in terms of performance and useability. The outcomes of the study will also help Cochlear to select features that will eventually be used in the future systems.

The study will only include upgrades in sound processor hardware, sound processor firmware and PC software used for fitting of the device or performance evaluation. No changes to the internal parts will be made. In this way, intrinsic subject safety is guaranteed in this project.

4 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

Sound processor fitting and Performance optimisation

Multi-channel cochlear implants have been highly successful in restoring speech understanding to individuals with severe-to-profound hearing loss. Optimal programs need to be created to get a good outcome with the cochlear implant. Current methods of Cochlear implant programming involves measuring the lowest stimulation level at which the recipient is

able to hear through the cochlear implant and also the highest stimulation level that can be tolerated by the recipient. Such measurements are done on electrodes across the electrode array. Thus this process can be very time consuming and can produce varied results depending on the skill of the clinician and the responsiveness of the recipient. Performance measurements like speech perception tests and audiograms are also made to assist the clinician in programming.

It is important to continually improve the speed and efficacy of the procedures to create programs and make performance assessments. When the overall process is simplified, consistent outcomes can be achieved for all recipients when programmed by clinicians with a range of clinical experience, professionals with diverse backgrounds or by recipients themselves.

Cochlear is developing new programming methodologies, with the aim of improving the current programming methodology. One such programming methodology was evaluated by Botros et al 2013 (International Journal of audiology). Cochlear is also developing new methods of assessing performance of the recipients to aid in the fitting process. The aim of the programming and performance evaluation methods is to simplify the process while maintaining the efficacy. Incremental changes will be made to the research software and hardware used for programming and performance evaluations so that the right balance of ease of use and efficacy is maintained. The aim of this study is to evaluate the ease of use and efficacy of each incremental change to the programming software and performance measurement software.

Intraoperative measurements

Electrophysiology measurements, for example Auto-NRT and Impedance telemetry are commonly used test procedures to test the implant function intra-operatively during cochlear implant surgery. These intraoperative measurements utilise the capability of the internal implant to run telemetry tests when commanded by the sound processor. Currently these tests are run either via a computer with the Custom Sound suite software program or with a remote assistant handled by the audiologist or theatre staff, requiring specific hardware like a CR120 Remote Assistant.

Cochlear is developing new methods to improve the speed and efficiency of these intraoperative measurements by exercising the telemetric capabilities of the internal implant even further. This enables more information to be gathered from the test. The evaluation of intraoperative measurements on the remote assistant was evaluated by Maruthurkkara et al 2012 (Proceedings of Objective measures conference, 2012). This study also aims to evaluate the effectiveness and ease of use of the new intra-operative tests in a group of CI implant candidates undergoing CI surgery at their local clinics.

5 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

Benefits

Group 1: Although it is not an aim of this study to improve recipient outcomes, it is possible that a treatment or control program may be preferred by the recipient over the MAP that he or she normally uses. In this case, the recipient is free to retain the preferred MAP after proper consultation with the recipient's hearing professional.

Group 2: There is no direct benefit to the participants of this study.

5.1 Risks

Group 1: During programming, because investigational software may be used there is a small risk that the sound may momentarily be louder than a comfortable level. Should this occur, stimulation will be stopped immediately (by switching off the sound processor or removing the transmitter coil). The software will be tested to ensure that stimulation does not cause any long term damage. There is a small risk that an increase in tinnitus may be experienced (head noises) during testing at certain frequencies. There is a possibility that some programs may not provide the same hearing quality as the participant's own program. They will have access to their own programs and will be able to use that if required.

Group 2: There is a risk that the equipment for the additional intra-operative tests does not work as intended and tests take longer and lengthen the time the participant is under anaesthesia, in this case the surgeon or anaesthetist can abort the testing.

6 OBJECTIVES AND HYPOTHESES

Group 1

1 To evaluate the effectiveness of the different programming methodologies.

2 To evaluate the ease of use of the research software and / or hardware.

Group 2

1 Evaluate the efficacy of new methods and improvements to intraoperative measurements.

7 DESIGN OF THE CLINICAL INVESTIGATION

General

The study is a prospective multi-centre study with sequential enrolment of up to 80 cochlear implant recipients. The subjects will be continuously included in the study. The study is designed as a multi-centre study. The study duration will be up to 5 years. Two separate groups of participants will be enrolled.

- Group 1 will include participants who are already implanted with a Nucleus cochlear implant. For this group the study procedures will be conducted in a clinical setting.

- Group 2 will include participants who are scheduled to be implanted with the Nucleus cochlear implant and the testing will be conducted during the cochlear implant surgery in the operating theatre.

Investigational device and comparator

This study evaluates the incremental changes made in the programming and performance assessment software and hardware to improve the efficacy of programming or performance measurements. Custom Sound software, Nucleus fitting software, myCochlear software, experimental fitting platform, performance testing research software or similar research programming software application. The new software will be compared to the software that is currently used commercially.

Subjects

Inclusion criteria:

Already implanted or scheduled for cochlear implant surgery with a Nucleus cochlear implant.

Exclusion criteria:

1 Unwillingness or inability of the candidate to comply with all investigational requirements.

2 Additional handicaps that would prevent or restrict participation in the audiological evaluations.

Subjects can decide to withdraw from the investigation without indicating any reasons. The investigator may decide to discontinue a patient due to major non-compliance with the CIP requirements (for example, visit schedule not met).

1) the point of enrolment – When written informed consent is obtained

Subjects are enrolled into the clinical investigation when they have signed the Patient Informed Consent form (PIC).

2) the total expected duration of the clinical investigation – 5 years

3) the expected duration of each subject's participation – 12 months

4) the number of subjects required to be included in the clinical investigation

- Minimum 17 subjects for stages involving speech perception testing
- Minimum 5 subjects for stages involving usability trial only
- Minimum 5 subjects for stages involving electrophysiological testing only

5) the estimated time needed to select this number (i.e. enrolment period).

Procedures

Group 1:

The study will be conducted in stages to assess the incremental change of the software functionality during that stage. The participant will be enrolled into one or more stages of the study. Since many features will be tested, some participants may be recruited for multiple stages of the project. At each stage, the new features will be evaluated by using a standard test battery (table 2) where some tests of the battery may be skipped for some stages if they are not relevant.

Evaluation of each feature will be done by within subject repeated measure study design using the test battery, so each participant will be his/her own control. Additionally a usability trial format may also be used to assess the ease of use of the software. Some features will be tested in acute laboratory sessions, but some features will require take-home experience to be able to fully evaluate the benefit and provide their feedback. In case a take-home trial will be performed, a baseline measurement will be done, the feature will be enabled and the test participant will be asked to use the feature in their every day listening environments. Tests may be repeated. When applicable, the cross-over study design will be used during another evaluation session after completion of the second set-up/test condition. Participants will always have access to their baseline programs if they need to revert back to their own settings or programs. Table 1 shows the standard schedule of visits for each stage in group 1.

Table 1: Schedule of visits for each stage in group 1

Visit 1	Take Home use	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Fit	-	Fit / Test	Fit / Test	Fit / Test	Fit / Test	Fit / Test

Upto 6 visits will be planned for each stage. The maximum time for a visit will be limited to maximum 4 hours.

a) Review of MAP/Clinical History

a. The participant's latest available cdx file will be imported into the Custom Sound database as sent from the recipient's local clinic.

b. The investigator will ensure that the participant's own programs are stored in the Custom Sound database so that the participant can be given their own program at the end of the study or if the participant wants to withdraw from the study.

c. The investigator shall review the map and take note of the MAP parameters like strategy, rate of stimulation, maxima, pulse width, smart sound environments and any deactivated electrodes in the map.

b) Programming

a. Up to four programs will be created using different programming methodologies.

b. The software will be used by the clinician or professionals with diverse backgrounds or by recipients themselves.

c. The order of creating the programs will be randomised and balanced across participants where possible according to the participant's study number at each investigational site.

d. A screen recording of the computer screen and / or video recording may be done for programming tasks where possible.

c) Take home use (if applicable)

a. The new programs may be loaded to the participant's sound processor randomised and balanced order.

b. The participants will be asked to use the new programs or software in real world environments and provide feedback.

c. Participants will be encouraged to record their daily experiences in the daily diary or other questionnaires if applicable.

d) Evaluation

a. Speech perception when conducted in free field will be conducted in a sound treated room (calibrated as per NAL specification ATR-2) and where possible all repeat sessions for a participant will be carried out in the same test booth to avoid any differences in the room to affect the results.

b. Speech perception tests may also be conducted by delivering inputs directly to the sound processor through research software and hardware.

c. The software will be used by the clinician or professionals with diverse backgrounds or by recipients themselves.

d. All programs will be tested on the same day for each test. The order of the tests will be randomised and balanced where possible.

e. The following test battery will be performed. Note that (as described above) not all tests may be relevant for every part of the study, naturally, unnecessary tests will be skipped.

Table 2: Test battery for group 1

Nr	Test	Description
1	Tonal Audiometry	Tonal audiogram at the standard audiometric frequencies using the device
2	Phoneme detection and discrimination tests	Evaluation of the peripheral auditory function (cochlea) by the test of phoneme detection and discrimination
3	Speech in quiet	Standard audiological word tests in quiet
4	Speech in noise	Word and sentence tests in noise, with noise either at a fixed level or adaptively adjusted
5	Electrophysiology	Electrical measurement of the compound action potential of the auditory nerve. This is a risk-free, non-invasive test that is also done by default in the clinical follow-up of implant users
6	Questionnaire	Specific anchored questionnaires will be used to ask participants feedback on certain features of the system
7	Video tape	When usability of software or sound processor controls is tested, participants may be video taped
8	Psychophysics	Psychophysical experiments may be performed to test how sensitive implant users are to small differences between stimuli. For example we may play 2 different sounds and ask which one is higher in pitch, or which one is louder

The results of the above mentioned tests will be carefully monitored during the course of the study and compared with the baseline results and with the benchmark results typical for each category of the participants.

Group 2: (Intra operative testing)

In this group the participants will be tested in the operation theatre during cochlear implant surgery. Participants will be continuously enrolled in the study and assigned randomly to test different stages (stage 1, stage 2…) of the study to test the different features of the new system.

a. The standard intraoperative testing will be completed as per current clinical routine.

b. The Sound processor will be placed in a sterile cover.

c. The new intraoperative tests will be conducted.

d. The investigator may request a nurse, the surgeon or a clinician to run the test under the investigators supervision.

e. The Surgeon, clinician or nurse may be asked to provide informal feedback on the ease of use of the implant test and its training materials.

f. Video recording may be done during the testing where possible.

g. If the addition of the new tests takes significantly more time under anaesthesia (as judged by the surgeon) the testing would be aborted.

Monitoring Plan

All sites are subject to monitoring. A monitoring plan will outline the intervals and quantity of monitoring to be done.

Each participant's medical history and data on gender, age and CI use will be required from their local CI clinic. Furthermore each participant's Custom Sound file containing their current CI MAP details, will be used as source data during the study.

Speech perception data will be recorded on paper CRF's and transferred to electronic CRF's. Questionnaire data and session summary forms will be considered source data and relevant information from the source will be transferred to Electronic CRF's via Cochlear's DataLabs management system. Data may also be recorded in spread sheets stored in secure locations.

8 STATISTICAL CONSIDERATIONS

Statistical Analysis

For all of the speech perception measures, parametric (e.g., paired t-tests, repeated measures ANOVA) or nonparametric procedures (e.g., Signed-Ranks test), as appropriate, will be conducted in order to further confirm the results of the single-subject analyses. These tests will be two-tailed, in line with most studies, and applied using an alpha level of 0.05. Individual scores obtained with the existing programs will be compared with those obtained with new programs, on the same measures, based on the binomial model where appropriate (see Thornton and Raffin, 1978; Boothroyd and Nittrouer, 1988). Although the binomial model is the more appropriate statistical model for analysis of single-subject experimental data, conventional group-based statistics will also be applied to the pooled results.

8.1 Sample Size Justification

The assessments used will vary depending on stage of the study. For each stage the minimum number of participants recruited will depend on the largest sample size required for the tests conducted.

Speech testing: Minimum sample size = 17 participants

Given the study uses a repeated measures single subject study, sample size estimation is based on a paired t-test sample size statistic. The value of the minimum clinically meaningful "change to be detected" (i.e. change between conditions) for sentence perception in noise is set at critical difference (1.81) of the SRT in noise test and 5% for CNC words in quiet. These values are set based on clinical consensus. The "expected standard deviation of change" uses the observed standard deviation based on the per-individual results of Botros, Banna and Maruthurkkara (2013) (1.72 dB for SRT and 6.75% for CNC words. Under these

conditions, the minimum sample size needed to reject this study's null hypothesis/es with 80% power is 10 and 17 for SRT and CNC words respectively.

Usability testing: Minimum sample size = 5 participants

As per the ANSI/AAMI ANSI/AAMI HE75:2009 standard a minimum sample size of 5 participants is recommended for formative usability testing.

Electrophysiological testing: Minimum sample size = 5 participants

Given that the study will compare the electrophysiological measurements with new method and the current method, the sample size estimation will be based on the Bland Altman statistics. The sample size for the Bland Altman statistics (Bland JM, Altman DG, 1986) is calculated by the formula:

$$\text{Limits of Agreement} = 1.96\sqrt{(3/n)} * \text{Std Deviation}$$

A standard deviation of 27 was reported by Van Dijk et al (2007) in a study comparing NRT thresholds. A difference of 9 CL was considered as acceptable in that study. Using the std dev of 27 and limits of agreement set to 9 CL the required number of samples is NRT thresholds from 104 electrodes. Measurement of NRT thresholds on all 22 electrodes for 5 participants will provide an n of 110 electrodes.

9 DATA MANAGEMENT

Case Report Forms (CRF)

A Case Report Form (CRF) will be completed for each study participant summarising all clinical and study data. The CRF contains confidential material. Participants will only be referred to in the CRF by their participant number in order to retain participant confidentiality. Specific instructions to complete the CRF shall be provided to the clinical investigation team as appropriate.

The completed original CRFs are to be provided to the Sponsor as soon as practical after completion and review. A copy of each completed CRF is to be retained by the Investigator for a period of time as determined by local regulations.

The following Case Report Forms will be used for each investigation:

a. Screening CRF
b. Session Summary CRF
c. Adverse Event CRF
d. Discontinue Subject CRF

9.1 Data Management

Data from the CRF's will be collected in spreadsheets stored in secured systems or by an Electronic Data Capturing system (Datalabs™ System). Self-evident corrections to data may be carried out by Cochlear data management personnel.

Analysis of the data will take place at Cochlear Ltd. GCP compliant monitoring processes are in place to ensure data is tracked, checked and audited appropriately.

9.2 Data Retention Period

All source documents, CRFs and trial documentation will be kept by the Investigator for the appropriate retention period as stipulated by local regulations and ICH-GCP. In Australia this will be 15 years for adult studies.

10 AMENDMENTS TO THE CIP

No changes in the CIP or investigation procedures shall be effected without mutual agreement of the Principal Investigators and the Sponsor. Changes related to the scientific intent of the study shall be documented in the CIP and requires signatures from the sponsor and the coordinating investigator. Such changes will require notification to the Ethics Committees by the principal investigators (and the Competent Authority by the sponsor – if applicable). Changes relating to the investigation sites shall be documented in a separate Principal Investigator List (PIL) and referenced in the CIP.

11 DEVIATIONS FROM THE CIP

The investigator is not allowed to deviate from the CIP except under emergency circumstances to protect the rights, safety and well-being of the subjects. Such deviation shall be documented and reported to the sponsor and the EC as soon as possible.

12 DEVICE ACCOUNTABILITY

Investigational devices shall be tracked using N34068UE Device Tracking Form.

In cases where the investigational devices are commercially released products, the products shall be registered following the standard product registration process.

In cases where a commercially released product is required to facilitate the functionality of the investigational device, the commercial product shall be registered following the standard product registration process.

13 STATEMENTS OF COMPLIANCE

Declaration of Helsinki and compliance with standards

The clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2013), the ISO 14155:2011 Standard and any regional or national regulations, as appropriate.

Ethics Committee and Competent Authority Approval

The clinical investigation shall not commence prior to the written favourable opinion or approval from the Ethics Committee (EC) and or Competent Authority (CA) (if appropriate) is obtained.

The principal investigator shall submit the final approved version of the CIP, the approved PIC and all subsequently approved documents to the EC. A copy of the EC opinion/approval shall be provided to the sponsor.

The investigator shall forward any amendment made to the approved PIC any other written information to be provided to the subject for review and approval by the sponsor prior to submission to the EC.

The sponsor and principal investigator shall continue the communication with the EC as required by national regulations, the clinical investigational plan or the responsible CA.

Any additional requirements imposed by the EC or CA shall be followed.

The investigator shall submit the appropriate documentation if any extension or renewal of the EC approval is required. In particular substantial amendments to the CIP, the PIC, or other written information provided to subjects shall be approved in writing by the EC.

The investigator will report to the EC any new information that may affect the safety of the subjects or the conduct of the clinical investigation. The investigator shall send written status summaries of the investigation to the EC regularly as per local EC requirements.

Upon completion of the clinical investigation, the investigator shall provide the EC with a brief report of the outcome of the clinical investigation as per local EC requirements.

The clinical investigation is covered by a clinical trial insurance meeting the requirements of the participating countries.

14 INFORMED CONSENT PROCESS

Obtaining informed consent

Written informed consent shall be obtained from the participant, after explaining the rationale for and the details, aims and objectives of the study, the risks and benefits of the trial treatment (and alternative treatments), and the extent of the patient's involvement. The investigator is responsible for ensuring that all patients give written informed consent prior to any study-related examination or activity.

All patients shall sign and date the Informed Consent Form and a copy of the Patient Information and Consent Form shall be given to the patient. All original signed Informed Consent documents shall be archived in the investigator file for a minimum of 15 years after completion of the investigation, or according to specific local ethics committee guidelines.

The sponsor and the investigator(s) shall avoid improper influence on or inducement of the participant, monitor, the investigator(s) or other parties participating in or contributing to the clinical investigation.

Data Privacy

Subjects will be identified on CRFs or similar documents (for example, questionnaires) by a unique subject identification code. Completed CRFs or similar documents are confidential documents and will only be available to the Sponsor and their representatives, the investigator, the investigational statistician, and if requested to the Ethics Committee and national regulatory authorities.

The investigator and site staff will not include the name of any subject in any CRF or other forms, electronic files, imaging items (for example, x-ray), publication, or submission to a regulatory authority; will not otherwise disclose the identity of any subject; and, in any CRF, will refer to each subject by their identification code. The Patient ID log CRF is explicitly excluded from this requirement.

15 REPORTING PROCESS FOR ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

Definitions

All definitions are according to the EN ISO 14155:2011 standard.

Adverse event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons whether or not related to the investigational medical device.

NOTE 1 This definition includes events related to the investigational medical device or the comparator.

NOTE 2 This definition includes events related to the procedures involved.

NOTE 3 For users and other persons, this definition is restricted to events related to investigational medical devices.

Adverse device effect (ADE)

Adverse device effect is an adverse event related to the use of an investigational medical device.

NOTE 1 This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Device deficiency (DD)

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

NOTE Device deficiencies include malfunctions, use errors, and inadequate labelling.

Serious adverse event (SAE)

A serious adverse event is any adverse event that:

1) led to a death,
2) led to a serious deterioration in the health of the subject that either resulted in
    a) a life-threatening illness or injury, or
    b) a permanent impairment of a body structure or a body function, or
    c) in-patient hospitalization or prolonged hospitalization, or
    d) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
3) led to foetal distress, foetal death or a congenital abnormality or birth defect

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious adverse device effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated serious adverse device effect (USADE)

An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report (for the investigational device or its comparator).

Reporting process for adverse events, adverse device effects and device deficiencies

All adverse events will be analysed by an independent team for device relatedness and determine whether it should be reported as a complaint.

Serious adverse events will be assessed by an independent medical professional to confirm the seriousness of the adverse event.

The investigator shall report all serious adverse events without delay to the sponsor.

Name of contact person of the sponsor	[redacted]
Fax	[redacted]
Phone number (business hours)	[redacted]
Phone number (after hours)	+[redacted]
E-mail	[redacted]

If applicable: the sponsor is responsible to report all SAEs, SADEs and USADEs to the relevant NCAs in the clinical investigation in accordance with local regulations.

The investigator has to report all AEs, SAEs, SADEs and USADEs to their EC and / or NCA (if applicable) using the applicable report form as per national requirement.

Subjects shall be carefully monitored during the clinical investigation for potential adverse events and shall be routinely questioned about adverse events at investigation visits. For all adverse events, information obtained by the investigator shall be recorded in the Adverse Event CRF. The investigator shall attempt to assess the relationship between the investigational device and the adverse event.

Data Monitoring Committee

The decision to establish a Data Monitoring Committee (DMC) shall be guided by the risk analysis, taking into account both the risks associated with the use of the investigational device and the risks associated with subject's participation in the clinical investigation.

List of anticipated adverse events and anticipated adverse device effects

For this clinical investigation the listed items in Section 0 of this CIP are anticipated Adverse Device Effects.

Expected adverse events include the following:

- Poor sound quality with a new program
- Non-auditory stimulation
- Onset of tinnitus

Medical occurrences that are related to pre-existing conditions (e.g. diabetes, cardiac problems) are considered as unexpected adverse events in the frame of the clinical investigation.

Device deficiency reporting requirements

The investigator shall report any device deficiency without unjustifiable delay to the sponsor.

Name of contact person of the sponsor	[redacted]	
Fax	[redacted]	
Phone number (business hours)	[redacted]	
Phone number (after hours)	[redacted]	
E-mail	[redacted]	

16 INCIDENT REPORTING

In cases where the investigational devices are commercially released products, the Principal Investigator shall report all adverse events to the EC and NCA according to governing regulations supplementary to reporting these adverse events to the sponsor.

The sponsor shall report adverse events which classify as reportable events (for instance: as Incidents in Europe) to the relevant NCAs.

Definition of Incident

Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject, or USER or of other persons or to a serious deterioration in their state of health.

Reporting process

The investigator shall report all incidents without undue delay to the sponsor and the national competent authority following MEDDEV 2.12-1 rev. 8 (and higher):

Name of contact person of the sponsor	[redacted]	
Fax	[redacted]	
Phone number (business hours)	[redacted]	
Phone number (after hours)	[redacted]	
E-mail	[redacted]	

The Sponsor shall assess all reported incidents with the investigator, co-ordinate appropriate actions, if required, and provide the NCA with a final report.

Appropriate treatment of the subject shall be initiated but the investigation follow up shall continue when ethical.

The investigator shall report all incidents to their Ethics Committee using the applicable report form as per national requirement.

17 VULNERABLE POPULATION

Informed consent will be obtained from the parent or guardian for children participating in the study.

18 SUSPENSION OR PREMATURE TERMINATION

The Sponsor will withdraw from sponsorship of the clinical investigation if:

1) major non-adherence to the CIP is occurring
2) it is anticipated that the subject recruitment will not be adequate to meet the objectives of the clinical investigation

Should the sponsor withdraw from sponsorship of the clinical investigation, the sponsor will continue sponsorship for the subjects already recruited into the investigation.

An ongoing clinical investigation can be discontinued in case of:

1) device failure
2) serious or intolerable adverse device effect, leading to the explant or discontinued use of the device
3) subject's death
4) investigator's decision
5) subject's decision

In any of the above circumstances the participant will be replaced by another participant.

19 PUBLICATION POLICY

It is planned to generate a joint publication by the clinical investigator(s) and the sponsor. The responsibility for writing the publication is with the Principal Investigator or Coordinating Investigator (to be discussed and agreed prior to investigation start). In case of multi-centre investigation, the authorship will be based on contribution of complete datasets and contribution to paper preparation according to the rules of the journal chosen for publication. The joint publication shall be reviewed by the sponsor at least 30 days in advance to any release of publication. If the publication contains information that the sponsor at his discretion finds worth protecting in the form of a patent or trademark etc., the sponsor has the right to delay the publication or presentation for 90 days.

Following acceptance of the joint paper, the investigators will be able to publish as they wish. The publishing investigator will provide the sponsor with a manuscript copy of the abstract and paper at least 30 days in advance of publication or presentation. If the publication contains information that the sponsor at his discretion finds worth protecting in the form of a patent or trademark etc., the sponsor has the right to withhold the publication or presentation for 90 days.

Investigators will be able to publish and/or present the data generated from the investigation after mutual agreement between the Coordinating Investigator, the Co-investigators and the Sponsor. The publishing investigator will provide the sponsor with a manuscript copy of the abstract and paper at least 30 days in advance of publication or presentation. If the publication contains information that the sponsor at his discretion finds worth protecting in the form of a patent or trademark etc., the sponsor has the right to withhold the publication or presentation for 90 days.

20 REFERENCES

Internal References

ID	Document Title	Number
1	PRODUCT RISK MANAGEMENT PROCEDURE	P41277UE
2	Principal Investigator List (PIL) document	558600

External References

ID	Document Title	Number
1	Clinical investigation of medical devices for human subjects – Good clinical practice	ISO 14155:2011
2	World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (2013)	N/A
3	Medical devices – Application of risk management to medical devices	ISO 14971:2007
4	Human factors engineering – Design of medical devices	AAMI HE75
5	Botros, A., Banna, R., & Maruthurkkara, S. (2013). The next generation of Nucleus(®) fitting: A multiplatform approach towards universal cochlear implant management. International Journal of Audiology, 52(7), 485–94.	NA
6	Van Dijk, B., Botros, A. M., Battmer, R.-D., Begall, K., Dillier, N., Hey, M., … Offeciers, E. (2007). Clinical results of AutoNRT, a completely automatic ECAP recording system for cochlear implants. Ear and Hearing, 28(4), 558–70.	NA
7	Maruthurkkara S., and Plasmans A. 2012. Future fitting methods for clinicians with limited cochlear implant experience. Proceedings of 7th international symposium on objective measures in auditory implants, Amsterdam 2012.	NA
8	Bland, J. M., & Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. Lancet, 1(8476), 307–10.	NA
9	Thornton, A.R., Raffin, M.J., 1978. Speech-discrimination scores modeled as a binomial variable. J. Speech Hear. Res. 21, 507-518.	NA
10	Boothroyd A, Nittrouer S. Mathematical treatment of context effects in phoneme and word recognition. J. Acoust. Soc. Am.84:101–114, 1988.	NA

21 CHANGE HISTORY

Version	Change	Author	Date
1	Initial Version	[redacted]	18-09-2013
2	Updated the protocol into a PIC template that is compliant with ISO 14155:2011 Added reference to Principal investigator list	[redacted]	03-09-2014

22 DEFINITIONS

Definitions from ISO 14155:2011

Term	Description
Adverse event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons whether or not related to the investigational medical device. NOTE 1 This definition includes events related to the investigational medical device or the comparator NOTE 2 This definition includes events related to the procedures involved. NOTE 3 For users and other persons, this definition is restricted to events related to investigational medical devices.
Adverse device effect (ADE)	Adverse device effect is an adverse event related to the use of an investigational medical device. Note to the author: NOTE 1 This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Device deficiency (DD)	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE Device deficiencies include malfunctions, use errors, and inadequate labelling.
Incident	Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject, or USER or of other persons or to a serious deterioration in their state of health.
Serious adverse event (SAE)	A serious adverse event is any adverse event that: a) led to a death, b) led to a serious deterioration in the health of the subject that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to foetal distress, foetal death or a congenital abnormality or birth defect NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Term	Description
Serious adverse device effect (SADE)	A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated serious adverse device effect (USADE)	An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report (for the investigational device or its comparator).

Other definitions

Term	Description
CA	Competent Authority
CIP	Clinical Investigation Protocol
CRF	Case Report Form
EC	Ethics Committee
NCA	National Competent Authority
PIC	Patient Informed Consent form
PIL	Principal Investigator List