Clinical Investigation Plan

Investigation Title: Intracochlear potentials: Intraoperative measurement clinical investigation.

Volta study

Investigation Number: CLTD5663

Version Number: 3.0

Date: 13-December-2016

Authors: [redacted]

ClinicalTrials.gov ID: NCT02852330

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Clinical Research Organisation (or other institution involved)	The HEARing CRC 550 Swanston Street, Department of Audiology and Speech Pathology The University of Melbourne Carlton Victoria 3053

1 SPONSOR AND PRINCIPAL INVESTIGATOR SIGNED AGREEMENT

Investigation Title	Intracochlear potentials: Intraoperative measurement clinical investigation.
Short Investigation Title	Volta study
Investigation Number	CLTD5663

Signature on behalf of Sponsor

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

Name	**Title**
[redacted]	Clinical Head, Clinical Affairs.
Signature	**Date** (dd-mmm-yyyy)

Signature of Principal Investigators

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

Name	**Title**
[redacted]	[redacted]
Signature	**Date** (dd-mmm-yyyy)

Name	**Title**
[redacted]	[redacted]
Signature	**Date** (dd-mmm-yyyy)

Signature of Responsible Clinical Research Organisation

I agree to the content of this clinical investigation plan, including all appendices, and undertake that the Clinical Research Organisation will conduct the research study in accordance with this plan.

Name	**Title**
[redacted]	[redacted]
Signature	**Date** (dd-mmm-yyyy)

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2 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	Intracochlear potentials: Intraoperative measurement clinical investigation.
Investigation number	CLTD5663
Short investigation title	Volta[1] study.
Name of investigational devices	Unapproved intraoperative Surgical Assistant Research Tool (SA16) software. Approved Nucleus Freedom Sound Processor, Freedom POD, Nucleus 6 CP900 Series Sound Processor, CR220 Intraoperative Remote and accessories.
Investigation start (Mmm yyyy)	March 2017
Total expected duration of the clinical investigation	Twelve months
Enrolment period	12 months
Expected duration per subject	Single visit (surgery)
Investigational design	Prospective, non-randomized, single arm feasibility clinical investigation with sequential enrollment.
Number of subjects	20
Inclusion criteria	1. Meet current cochlear implant indications at the implanting centre for a CI512, CI422, CI522 or CI532 cochlear implant 2. Aged 18 years and older at the time of implantation.
Exclusion criteria	1. Recipient of a Nucleus 24 ABI device 2. Medical or psychological conditions that contraindicate undergoing general anaesthesia or surgery. 3. Ossification, malformation or any other cochlear anomaly, such as common cavity, that might prevent complete insertion of the electrode array, as confirmed by medical examination. 4. Unwillingness or inability of the candidate to comply with all investigational requirements.
Primary objectives	Collection of normative voltage tomography data during and/or immediately after electrode insertion into the cochlea using SA16 research software.

Investigation schedule	**Procedure**	**Pre-op**	**Surgery**			
	Consent	x				
	Medical History	x				
	Voltage tomography		x			
	AE, ADE, DD		x			
	X-Ray		(x)			
	Data file		x			
Primary endpoints	Report on normative voltage tomography data for CI512, CI422, CI522 or CI532 cochlear implant recorded with SA16 research software during and/or immediately after electrode insertion.					

3 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The Surgical Assistant Research Tool (SA16) research software is a software tool developed by Cochlear Limited. The use of the SA16 research software in the current clinical investigation is intended to support Cochlear's research into the development of implant telemetry based surgical tools.

The SA16 research software is designed to perform a series of predefined measurements with minimal intervention both during and immediately following electrode insertion using telemetry from the implant via the Sound Processor to the PC. These measurements include real time continuous measurements, intended for use during the electrode insertion portion of the surgical procedure, and baseline measurements following the completion of electrode insertion, as detailed in Figure 1.

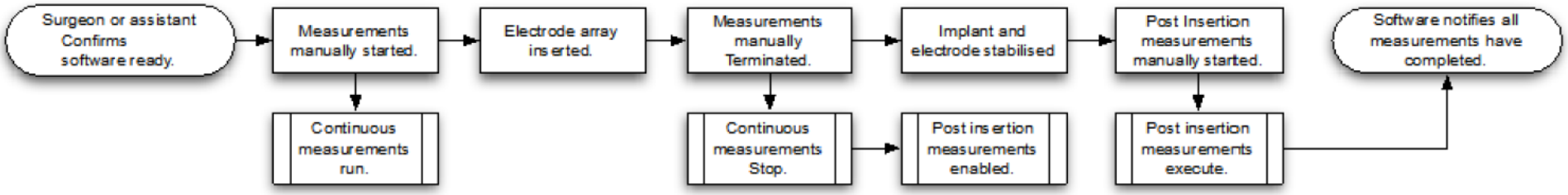

Figure 1: SA16 software usage flow.

The SA16 research software is intended for use in the intra-operative condition, with patients under a general anaesthetic only. The SA16 research software is designed to work with cochlear implants which:

1. Incorporate a fourth generation cochlear neural stimulator integrated circuit
    i. E.g. Freedom, CI400 & CI500 Series implants
2. A minimum electrode pad size of 0.0248 mm^2
    i. Note that all Freedom, CI400 and CI500 series implants (Up to and including CI422, CI522 & CI532) have a guaranteed minimum electrode pad size of at least 0.1mm^2
3. Have 22 electrodes intended for intra-cochlear placement.

The SA16 research software is designed to work with the following hardware:

1. Nucleus Sound Processors and Nucleus 24 coils (excluding the 2m intra-operative coil)
    i. Freedom, CP810 and CP900 Series Sound Processors
2. Personal Computer (PC) or tablet with EN 60950 UL compliance and the MS Windows® 10 operating system.
3. Freedom Programming POD and USB cable
4. Freedom Programming Cable (Z60780) and Programming Shoe (Z60765), CP800/CP900 Programming Shoe and Cable (Z195607)

The SA16 research software will be used in the current clinical investigation in adults who meet current indications for cochlear implantation in Australia. The SA16 research software is not for use with patients who are receiving an implant that directly contacts neural tissue, such as auditory brainstem implants (ABI).

SA16 research software is a device which is not yet commercially available for any purpose. The device will be provided preinstalled on a dedicated PC and POD optimised for use with SA16 by Cochlear Limited. Traceability will be maintained by the Clinical Project Manager.

The external envelope materials of the Nucleus CI512, CI422, CI522 or CI532 cochlear implants, and sterile accessories (coil and cables), and the Nucleus Sound Processors are in biocompatible according to applicable standards (i.e. ISO 10993: 2009/AC: 2010).
All equipment that enters the sterile field, including the programming cable, Sound Processor and coil will be placed in a sterile bag or sleeve by a member of the operating room staff who is dressed and qualified to work inside the sterile field.

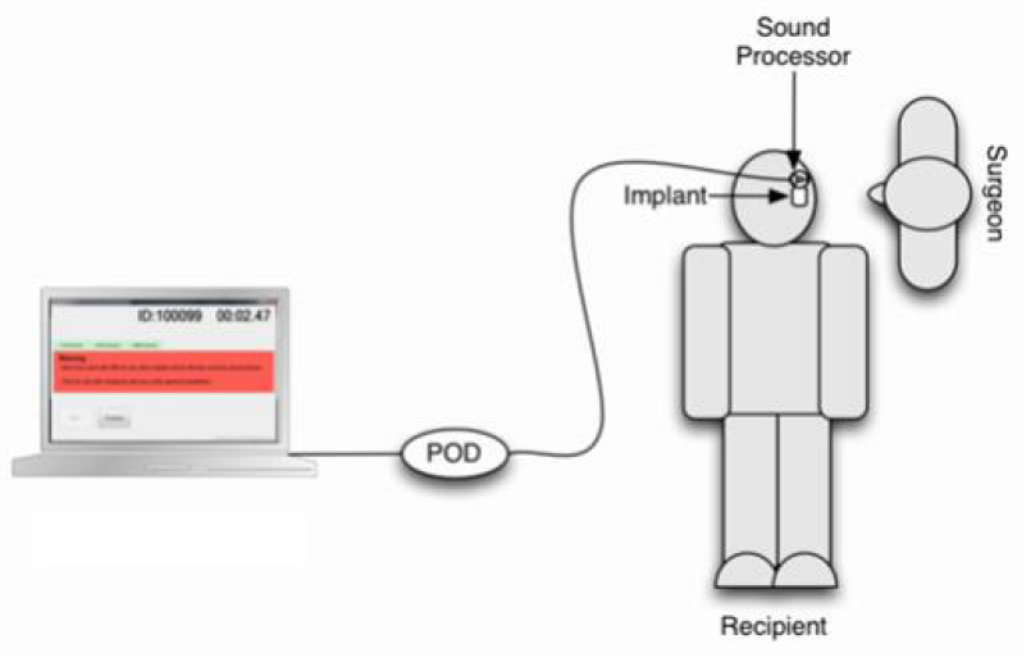

Figure 2: Equipment setup for SA16

In the current clinical investigation only clinicians who have received the necessary training and experience needed to use the SA16 research software will be permitted to collect voltage tomography data.

Other than the recording of normative voltage tomography data during and/or after electrode insertion into the cochlea with the SA16 research software, no other specific medical or surgical procedures are envisaged in the clinical investigation.

This clinical investigation will gather voltage tomography data for retrospective analysis by Cochlear Limited. No real time feedback will be provided to the surgeon during the surgery.

As an alternative to the use of SA16 research software intraoperatively, a future unapproved version of Custom Sound EP software may be used to make voltage measurements..

4 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

The clinical investigation will gather impedance and transimpedance (voltage tomography) data intra-operatively which can be used to characterise the electrical properties of the living cochlea. Outcomes from the clinical investigation will provide normative voltage tomography data during and/or after electrode insertion into the cochlea.

Experiments in computer models, artificial cochleae and temporal bones have shown that electrical measures can be made that may provide information on the position of the electrode array in the cochlea (1, 2). A combination of impedance and transimpedance (voltage tomography) measurements may be used to infer:

- Angular depth of insertion
- Proximity to the modiolus
- Presence of electrode tip fold-over
- Changes in these parameters over time

The current clinical investigation is designed as a prospective, non-randomised, single arm feasibility clinical investigation with sequential enrollment. The clinical investigation will measure impedance and voltage tomography during twenty cochlear implant surgeries to determine the relevant data signatures and to understand normal variability in voltage tomography due to anatomy and other factors.

A summary of the relevant pre-clinical assessment and/or clinical data is provided in the Intracochlear Potentials Investigators Brochure (IB) (3).

5 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

5.1 Clinical Benefits

There are no anticipated clinical benefits for the patient through participation in the clinical investigation. The outcomes from the clinical investigation will be used by Cochlear Limited to support development of implant telemetry based surgical tools.

5.2 Anticipated adverse device effects.

Participants in the clinical investigation are exposed to the anticipated adverse device, and or procedure related effects associated with standard cochlear implant surgery, general anaesthesia and intraoperative Neural Response Telemetry (NRT).

The risks to the participant introduced with the use of SA16 research software are comparable to standard cochlear implant surgery are described within the Investigators Brochure (IB) (3).

Interactions with concomitant medical treatments are not envisaged in the use of SA16 research software during the clinical investigation.

5.3 Residual risks

Residual risks related to the use of the investigational device have been reduced to as low as reasonably possible and are described in the Hazards Analysis (6).

5.4 Risks associated with participation in the clinical investigation

Participants in the clinical investigation are exposed to the anticipated adverse device, and or procedure related effects associated with standard cochlear implant surgery, general anaesthesia and intraoperative Neural Response Telemetry (NRT). The risks to the participant introduced with the use of SA16 research software are comparable to standard cochlear implant surgery are described within the Investigators Brochure (IB) (3).

Interactions with concomitant medical treatments are not envisaged in the use of SA16 research software during the clinical investigation.

5.5 Risk mitigations

Mitigation of identified risks associated in the use of the SA16 research software are described within the Investigators Brochure (IB) (3).

5.6 Risk-to-benefit rationale

The identified risks associated with the use of SA16 research software in this clinical investigation have been mitigated to ensure the incremental risk associated with its use are as low as reasonably possible (6).

Therefore, the risk benefit ratio of participating in this clinical investigation is similar to the risk benefit ratio of undergoing conventional cochlear implant surgery and intraoperative NRT measurements.

6 OBJECTIVES AND HYPOTHESES

6.1 Objectives

6.1.1 Primary objective

The primary objective of the clinical investigation is collection of normative voltage tomography data during and/or immediately after electrode insertion into the cochlea using Surgical Assistant Research Tool (SA16) software.

6.2 Hypotheses

As this feasibility clinical investigation aims to collect normative voltage tomography data for the development of implant telemetry based surgical tools, there are no formal hypotheses to be accepted or rejected by statistical data from the clinical investigation.

6.3 Claims and intended performance

The claims and intended performance of SA16 research software that are to be verified during the clinical investigation are:

1. Measurement of voltage tomography during and/or immediately after electrode insertion to provide a baseline measurement for the CI512, CI522, CI422 and CI532 cochlear implants.

6.4 The risks and anticipated adverse device effects

There are no risks or anticipated adverse device effects that are to be assessed in the clinical investigation.

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 General

The current clinical investigation is designed as a prospective, non-randomized, single arm feasibility clinical investigation with sequential enrollment. The purpose of the clinical investigation is to gather normative voltage tomography data with the SA16 research software. No real time feedback will be provided to the surgeon during surgery.

A single-subject repeated-measures analysis will be employed whereby subjects will act as their own control. A single-subject research design is appropriate since it accommodates the heterogeneity that characterizes hearing-impaired populations. Blinding procedures are not appropriate for this clinical investigation design, as it is not possible to conceal the presence, or absence, of the investigational devices from the investigators.

7.2 Endpoints

7.2.1 Primary endpoint

The cochlear implant surgery visit serves as the primary endpoint for data collection related to normative voltage tomography data during electrode insertion and/or immediately post-insertion for CI512, CI422, CI522 or CI532 cochlear implants as recorded using SA16 research software.

7.3 Equipment

The following equipment will be used for assessment of electrode impedance and transimpedance (voltage tomography):

- A computer (laptop or tablet) with custom designed Cochlear Ltd software installed.
- Programming controller interface (to provide electrical isolation for the participant), Sound Processor (Freedom or CP900) and associated transmitting coil and cabling.

7.4 Visit Schedule

Procedure	Pre-op	Surgery			
Consent	x				
Medical History	x				
Voltage tomography		x			
AE, ADE, DD		x			
X-Ray		(x)			
Anonymized data file		x			

7.5 Investigational device and comparator

The investigational device for assessment of electrode impedance and voltage tomography in the clinical investigation is the Surgical Assistant Research Tool (SA16) research software. SA16 is an unapproved software tool developed by Cochlear Limited, intended to support research into the development of implant telemetry based surgical tools.

The SA16 research software is designed to perform a series of predefined impedance and voltage measurements with minimal intervention during and immediately following electrode insertion. The recordings made by SA16 software will be analysed by Cochlear Limited to provide a baseline measurement for the CI512, CI522, CI422 and CI532 cochlear implants. If an electrode tip fold-over is identified on intraoperative or post-operative X-ray, after surgery, the SA16 recordings will be analysed to further develop the underlying algorithm.

CS19 (1.6.2) software is approved for use in Australia by Cochlear staff members. Electrical impedances and Evoked Compound Action Potentials (ECAP) may be collected intraoperatively with the Nucleus 6 CR220 Remote or Custom Sound EP.

As an alternative to the use of SA16 research software intraoperatively, a future unapproved version of Custom Sound EP software may be used to make intraoperative voltage tomography measurements.

The use of a comparator device is not envisaged in this clinical investigation.

No other medical devices or medications are specified for use during the clinical investigation.

7.6 Subjects

The eligibility criteria for participation in the clinical investigation are described below.

7.6.1 Inclusion criteria

1. Meet current cochlear implant indications at the implanting centre for a CI512, CI422, CI522 or CI532 cochlear implant
2. Aged 18 years and older at the time of implantation.

7.6.2 Exclusion Criteria

1. Recipient of a Nucleus 24 ABI device
2. Medical or psychological conditions that contraindicate undergoing general anaesthesia or surgery.
3. Ossification, malformation or any other cochlear anomaly, such as common cavity, that might prevent complete insertion of the electrode array, as confirmed by medical examination.
4. Unwillingness or inability of the candidate to comply with all investigational requirements.

7.6.3 Subject withdrawal

Any subject may voluntarily discontinue the study at any time without prejudice. The Investigator may discontinue a subject from the study at any time if (s)he considers that remaining in the study compromises the subject's health or the subject is not sufficiently cooperative. In either event, reason(s) for discontinuation should be recorded on a study withdrawal form, provided as part of the CRFs for the study. Possible reasons for study discontinuation include the following:

- AE necessitating discontinuation from the study
- The subject is lost to follow-up
- Voluntary decision to withdraw consent made by the subject[2]
- Investigator decision[3]
- Other reason

In case of a subject lost-to-follow-up, the Investigator must attempt to contact the subject (or relative/family contact) by phone, email or letter at least three times. If attempts are unsuccessful, the 'subject withdrawal' form is to be completed in the study file and reported, as appropriate, in required reports to the Sponsor, EC and TGA.

7.6.4 Point of enrolment

Subjects are enrolled into the clinical investigation when they have signed the Patient Informed Consent form (PIC). The process of obtaining informed consent will be undertaken by the implanting surgeon.

7.6.5 Total expected duration of the clinical investigation

The total expected duration of the clinical investigation is twelve months. The total duration will be dependent on the ability to recruit the required number of subjects within the enrolment period. The expected duration of each subject's participation is a single visit (during surgery).

7.6.6 Number of subjects required to be included in the clinical investigation

The number of subjects required to be included in the clinical investigation is twenty. The estimated time needed to select this number (i.e. enrolment period) is twelve months.

[2] Withdrawal of consent is defined as the subject's voluntary decision to revoke consent to continue participation in the study.

[3] Subject withdrawal from the study is defined as an Investigator decision. The Investigator may elect to withdraw a subject from the study at any time if he/she considers that remaining in the study compromises the patient's health or if the Investigator considers the subject lost to follow-up.

7.7 Procedures

7.7.1 Surgery

The clinical investigation will gather data only. The clinical investigation will not attempt to process the data in real time or provide real time feedback to the surgeon during the surgery. Data gathering will be initiated and controlled by a Cochlear or HEARing CRC staff member not directly involved with the surgery at a time and in a manner as to minimise interference with the surgical procedure.

7.7.1.1 Electrically evoked compound action potentials – ECAP

ECAP thresholds will be recorded using the AutoNRT algorithm in the Nucleus 6 CR220 Intra-operative Remote Assistant or Custom Sound EP software as per standard clinical protocols. AutoNRT will be performed on all electrodes prior to voltage tomography measurements with SA16.

7.7.1.2 Voltage Tomography (SA16)

The following data collection with SA16 research software will occur during electrode insertion and/or immediately following electrode insertion:

- Stimulation and measurement using a variety of stimulation and recording configurations at 230 CL to characterise the electrical properties of the living cochlea during tissue integration of the electrode. Measurement time is approximately ten minutes.

The voltage tomography measurements following electrode insertion may be made after closure within theatre or in recovery.

The recordings made by SA16 software will be retrospectively analysed by Cochlear Limited to provide a normative measurement for the Nucleus CI512, CI422, CI522 or CI532 cochlear implant.

If an electrode tip fold-over is identified on X-ray, the SA16 recordings will be analysed by Cochlear Limited to further develop the underlying algorithm.

7.7.2 Safety

The investigator will complete an Adverse Event (AE) CRF if any AE or Adverse Device Effect (ADE), or a Device Deficiency (DD) Case Report Form (CRF) if any AE, ADE or DD is reported or observed for a subject during the investigation, even if they were acknowledged as risk factors in the Patient Informed Consent (PIC) form.

The number, severity and relationship of adverse events will be reported and tabulated. The rate of device-related adverse events will be compared to known rates of device-related adverse events for the commercially approved Nucleus Custom Sound EP software and cochlear implantation.

7.8 Medical care post-investigation

Routine medical care from the implanting centre will be provided for the subjects after the clinical investigation has been completed. Subjects will be followed-up as per the centres' standard procedures.

7.9 Monitoring Plan

The sponsor will appoint a Study Monitor to perform regular visits at the study site, as defined in the study Monitoring Plan. Prior to the first subject enrolment an initiation visit will be performed by the Clinical Project Manager or delegate and the Study Monitor ensuring that assigned study personnel are familiar with this Clinical Investigation Plan and procedures and device handling, trained in GCP compliance, paper and electronic CRF (CRF and eCRF) completion, AE reporting, and maintenance of study related documentation.

The Study Monitor will ensure compliance with the clinical investigation plan and ISO14155, accurate data recording on the eCRFs, will raise data queries, will monitor recruitment rates and adherence to follow-up schedules. The Study Monitor will also check the upkeep of the investigator file. The investigator shall permit and assist the Study Monitor to carry out verification of completed eCRFs against data in the source documents.

Source documents are defined as any printed, optical or electronic document containing source data (hospital records, audiograms, speech test results, laboratory notes, device accountability records, radiographs, records kept at the investigational site) containing data necessary for the reconstruction and evaluation of the clinical investigation. The extent of source data verification is defined in the Monitoring Plan. The investigator shall provide all requested documentation in a timely and organized manner.

The Study Monitor shall inform the Sponsor about any problems relating to facilities, technical equipment or medical staff at the study site. The Study Monitor shall provide the CPM with written reports, after each visit or contact with the investigational site.

The investigator has to inform the Sponsor about any additional local requirements that may impact the work of a monitor especially if access to source data may be limited by local regulations. This is to ensure any necessary action to be taken before the study start to allow proper monitoring according to the ISO Standard.

8 STATISTICAL CONSIDERATIONS

As this is a feasibility clinical investigation, there have been no formal power or sample size estimations performed for the primary objective.

9 DATA MANAGEMENT

9.1 Source data collection

Source data collection is performed on paper Case Report Forms (CRFs) and/or electronic data capturing (EDC) on electronic CRFs (eCRFs). Site personnel will be trained on the completion of the CRFs and eCRFs. Data validity has to be confirmed by the investigator through a signature and/or an electronic signature captured by the EDC system. In addition, data can be collected through the clinical fitting and electrophysiology software and through x- rays. The file records shall be anonymized and then identified using the study number and the patient's study identifier (e.g. CLTDxxxx-MEL-01 3 month.cdx4).

Original completed paper CRFs are collected by Cochlear Limited. Data from paper CRFs are entered in a suitable database after review by the Investigation Monitor. The Clinical Project Manager may review data from a medical and scientific perspective and create Data Clarification Forms (DCFs) where appropriate. In case of DCFs the investigator should respond within the time windows as agreed upon. Responses to DCFs are entered in the database by Cochlear. Copies of completed CRFs and DCFs will remain at the investigator site.

9.2 Missing data

All efforts will be put forth to ensure near complete follow-up, with particular focus on the assessment of the primary outcome and occurrence of adverse events.

9.3 Data storage

Electronically captured data on e-CRFs are stored in a SQL database located on a server at Cochlear Limited. eCRFs are reviewed by Data Management and electronic data clarification forms (eDCFs) are generated for data inconsistencies, which are sent to the investigational site. EDC has built-in edit checks and generates data clarification forms automatically. In addition, the clinical project manager (CPM) may review the data from a medical and scientific perspective and create DCFs where appropriate. Responses to eDCFs are entered in EDC.

The EDC system is a product that has been verified and validated extensively by the vendor. The installation of the system within Cochlear has been validated by the sponsor. Study specific implementations are validated by Data Management and consist of verification that all required items are included, validity of edit checks and appropriate functionality of conditional fields. The EDC system can only be accessed by those that have been allocated their individual account, which are personal of the investigational sites, CPMs, Study Monitors and Data Management. Upon request investigators will be provided with site specific data (e.g. on a CD-ROM) for national and site specific archiving requirements.

9.4 Data retention

After the final clinical investigation report (CIR) has been approved the data are maintained with the trial master file at the sponsor's site. The data are stored for a period of 15 years.

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.

As the commercially released product (Nucleus 6 System) is required to facilitate the functionality of the investigational devices, the commercial product shall be registered following the standard product registration process.

13 STATEMENTS OF COMPLIANCE

13.1 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.

13.2 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

14.1 Obtaining informed consent

The investigator shall obtain written informed consent using an approved Patient Informed Consent Form (PIC) from the subject prior to any clinical investigation related examination or activity. The rationale for and the details, aims and objectives of the investigation, the risks and benefits and alternative treatments, and the extent of the subject's involvement shall be explained. Ample time shall be provided for the subject to inquire about details of the clinical investigation and to decide whether to participate. All questions about the clinical investigation shall be answered to the satisfaction of the subject or the subject's legally acceptable representative. Subjects shall not be coerced or unduly influenced to participate or to continue to participate in a clinical investigation.

Each subject and the person who conducted the informed consent discussion shall sign and date two original versions of the PIC. Where required, a witness shall sign and personally date the PIC.

One original signed PIC shall be given to the subject. The other original signed PIC shall be archived in the Investigator's File at the investigational site, according to the requirements of the country's health regulations, but for a minimum of 15 years after completion of the clinical investigation.

The subject or the subject's legally acceptable representative shall be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the clinical investigation. The communication of this information shall be documented.

There are no circumstances in the current clinical investigation envisaged where the subject is unable to give informed consent (e.g. paediatric participant).

14.2 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

15.1 Definitions

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

15.1.1 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.

15.1.2 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.

15.1.3 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.

15.1.4 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 a permanent impairment of a body structure or a body function, or
    b) in-patient hospitalization or prolonged hospitalization, or
    c) 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.

15.1.5 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.

15.1.6 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).

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

The medical monitor for the clinical investigation is described below:

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

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

Name of contact person of the sponsor	[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 EC and TGA 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 TGA (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.

15.3 Data Monitoring Committee

Participation in the current clinical investigation is deemed to be low risk (Section 5 of this CIP) and no Data Monitoring Committee has been established.

15.4 List of anticipated adverse events and anticipated adverse device effects

For this clinical investigation the listed items in Section 5 of this CIP and / or the IB are anticipated Adverse Device Effects.

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.

15.5 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]
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 TGA according to governing regulations supplementary to reporting these adverse events to the sponsor.

The sponsor shall report adverse events which classify as reportable events to the TGA using the Medical Device Incident Reporting (MDIR) system.

16.1 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.

16.2 Reporting process

The investigator shall report all incidents without undue delay to the sponsor and the TGA following Medical Device Incident Reporting (MDIR) system.

Name of contact person of the sponsor	[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 TGA 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 forms as per local requirements.

17 VULNERABLE POPULATION

Not applicable for the current clinical investigation.

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. Site's decision

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.

20 REFERENCES

20.1 Internal References

ID	Document Title	Number
1	Electrode Insertion Monitoring using CIM-VT Software in Temporal Bone Report	[redacted]
2	[redacted]	
3	Intracochlear Potentials Investigators Brochure	[redacted]
4	SAFE Research Tool Hazards Analysis Report	[redacted]

20.2 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

21 CHANGE HISTORY

Version	Change	Author	Date
1.0	Introduction of document	[redacted]	11/4/2016
2.0	Modification of Section 5 - Risks and benefits of the investigational device and clinical investigation based on CI surgeon review discussion.	[redacted]	16/5/2016

Version	Change	Author	Date
3.0	Removal of requirement for post-operative assessment visits. Corresponding modification of Clinical Investigation title.	M. Knight	19/12/2016

22 DEFINITIONS

22.1 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.

Term	Description
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.
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).

22.2 Other definitions

Term	Description
SA16	Surgical Assistant Research Software (aka CIM-VT, SAFE)
CIM-VT	Continuous Impedance Measurement – Voltage Tomography (Cochlear Limited development name for SA16).
CSEP	Custom Sound EP
EC	Ethics Committee
IB	Investigator's brochure is a compilation of the current clinical and non-clinical information on the investigational device(s) relevant to the clinical investigation.
NRT	Neural Response Telemetry
PIC	Patient Informed Consent form
RVEEH	Royal Victorian Eye and Ear Hospital
SAFE	Surgical Assistant For Electrodes (Cochlear Limited development name for SA16) used in Oslo clinical investigation.