Clinical Investigation Plan

Investigation Title: Association Between Intra-Operative Cochlear Response Telemetry and Hearing Preservation (CREST)

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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.

1 SPONSOR AND COORDINATING INVESTIGATOR SIGNED AGREEMENT

Investigation Title	Association Between Intra-Operative Cochlear Response Telemetry and Hearing Preservation (CREST)
Investigation Number	CLTD 5667

Signature on behalf of Sponsor

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

Name	**Title**
Signature	**Date** (dd-mmm-yyyy)

Signature of Principal Investigator

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

Name	**Title**
Signature	**Date** (dd-mmm-yyyy)

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2 SYNOPSIS

Investigation title	Association between Intra-Operative Cochlear Response Telemetry and Hearing Preservation (CREST)
Investigation number	CLTD 5667
Name of investigational device	Cochlear Response Telemetry (CRT): a system comprising both hardware and software for monitoring the electrophysiological cochlear response to acoustic clicks or short tone bursts. The CRT system is not approved by regulatory agencies.
Investigation start	March 2017
Total expected duration of the clinical investigation	17 months
Enrolment period	12 months
Expected duration per subject	5 months
Investigational design	Prospective, multi-center, observational (non-randomized) investigation consisting of a pre-operative visit and treatment visits at the time of implantation (Day 0), at 4-6 weeks post-surgery follow-up visit (FUV1) and at 3 months post-activation follow-up visit (FUV2). Subjects will be allocated into two groups according to their residual hearing at FUV1. *Visit Schedule:* Pre-Operative Visit POV1 (up to 90 days before D0) Intra-Operative Visit D0 Follow-Up Visit 1 FUV1 (4-6 weeks post-surgery +/- 1 week) Follow-Up Visit 2 FUV2 (3M post-activation +/- 2 weeks)
Number of subjects	Globally: Minimum 86 (Up to 125 depending on monitoring of accruing data affecting proportion of subjects allocated to each group) US: Up to 50; Europe: Up to 40; Australia: Up to 35.

Inclusion criteria	• Candidate for cochlear implantation (with CI522, CI532 or Hybrid-L24 according to local indications • 18 years of age or older at the time of enrolment • Pre-operative audiometric threshold in the implanted ear at 500 Hz of better than or equal to 80 dB HL • Willingness to participate in and to comply with all requirements of the protocol
Exclusion criteria	• Prior cochlear implantation in the ear to be implanted • Ossification or any other cochlear anomaly that might prevent complete insertion of the electrode array • Abnormal cochlear/nerve anatomy on pre-operative CT or MRI imaging (excluding a mild Mondini malformation or Large Vestibular Aqueduct Syndrome) • Deafness due to lesions of the acoustic nerve or central auditory pathway • Diagnosis of auditory neuropathy • Active middle-ear infection • Additional handicaps that would prevent participation in evaluations • Unrealistic expectations on the part of the subject, regarding the possible benefits, risks and limitations that are inherent to the procedure and investigational device
Primary objective	To examine whether compromised cochlear microphonic (CM) response during cochlear implant surgery results in poorer acoustic hearing preservation at FUV1 compared to preserved CM.
Secondary objectives	1. To examine whether compromised cochlear microphonic (CM) response during cochlear implant surgery results in poorer acoustic hearing preservation at FUV2 compared to preserved CM. 2. To investigate whether pre-operative acoustic hearing influences the onset of the CM response during insertion of the electrode array.
Primary endpoint	Deterioration in average low frequency post-operative hearing threshold levels (HTLs) at FUV1 in the implanted ear for subjects with compromised CM compared to subjects with preserved CM during surgery
Secondary endpoints	1. Deterioration in average low frequency post-operative HTLs at FUV2 in the implanted ear for subjects with compromised CM compared to subjects with preserved CM during surgery 2. Association of pre-operative high frequency HTLs with onset of CM response during electrode array insertion

Exploratory analyses	Additional exploratory analyses may be performed. These may include: • Comparison of the primary endpoint for three groups defined by compromised, preserved, and transient CM • Predictors of the incidence of compromised CM during surgery including influence of electrode type, insertion depth and surgical events • Association of pre-operative high frequency HTLs with change in latency of CM during electrode array insertion • Investigation of the influence of demographic and surgical factors on the morphology and time-course of the CM response during insertion and post-operatively • Investigation of the relationship of CM thresholds to postoperative HTLs in the implanted ear • Examination of the degree of reduction in CM amplitude that occurs in response to a range of surgical events • Characterization of changes in electrode impedances as a function of CRT observations during and post-surgery • Characterization of changes in different components of the electrocochleography (ECoG) responses over time • Examination of whether the ratio of the CM amplitude over the ANN amplitude (uVrms) is correlated with lower (better) HTLs (FUV2) at 250Hz, 500Hz and 1kHz • 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

Investigation Schedule

Procedure	POV1 Pre-operative	D0 Surgery	FUV1 4-6 Weeks Post-Surgery (+/- 1 week)	FUV2 3-Month Post-Activation (+/- 2 weeks)
Medical and Hearing History	X			
Otoscopy (Check for Wax Occlusion)	X	X	X	X
Cochlear Response Telemetry (CRT)		X	X (either FUV1 or FUV2)	
Audiometry & Tympanometry	X		X	X
Surgical Questionnaire		X		
Impedance Measures (Standard, 4-point, Voltogram)		X	X (either FUV1 or FUV2)	
Optional (where obtained at sites as part of routine clinical management): Imaging (MRI Pre-Operative; X-Ray or Cone Beam CT Post-Operative)	X	X		

3 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

Cochlear Response Telemetry (CRT) is a system comprising both hardware and software for monitoring the electrophysiological cochlear response (via electric potentials generated within the cochlea and auditory nerve) to acoustic clicks or short tone bursts. There are three components to an acoustic electrocochleogram (ECoG). The cochlear microphonic (CM) is a phase-following response that matches the acoustic stimulus and is generated predominately by outer hair cells. It is a transducer current in the stereocilia and follows the waveform of the acoustic stimulus. The auditory nerve neurophonic (ANN) is a neural response and represents the correlate to neural phase-locking.

Figure 1 illustrates the morphology and time course of the CAP (and SP) and the CM (upper and lower subplots respectively) in response to a 500 Hz acoustic input. The CM, being frequency following (or phase-locked), can be observed to follow the input signal, i.e. in the lower panel below the peaks are 2 ms apart.

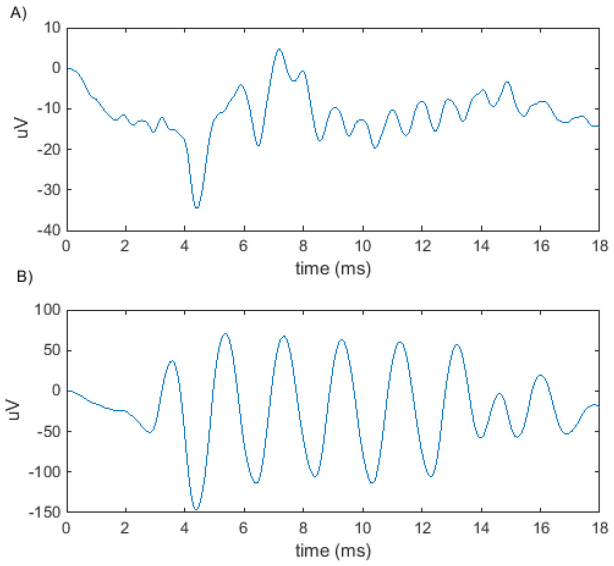

Figure 1. An example trace of an electrocochleogram measured in response to a 500 Hz stimulus. In the upper panel (A) is shown the ANN. In the lower panel (B) is shown the CM.

The CRT system comprises the following components:

- DT9847 or DT9837 USB powered Digital to analog converter
- FiiO E12A Power amplifier
- Dell Laptop
- 2 or 4 port bus powered USB 2.0 Hub
- ER3C Insert earphone
- Cochlear™ Nucleus® Freedom® Programming Pod

- Cochlear™ Nucleus® Freedom® Programming Shoe
- Cochlear™ Nucleus® Freedom® Programming Cable
- Cochlear™ Nucleus® Freedom® Processing Unit
- Cochlear™ Nucleus® Freedom® Coil Magnet
- Cochlear™ Nucleus® Freedom® N24 Coil
- Cables (USB, BNC, Audio)

Acoustic stimulation is achieved via a signal generator coupled to an insert Etymotic earphone (ER3C). Triggering of the external acoustic generator is achieved by delivering a sync pulse from the programming pod such that the recordings from the implant are synchronized with the acoustic input. A block diagram of the CRT system is illustrated in Figure 2.

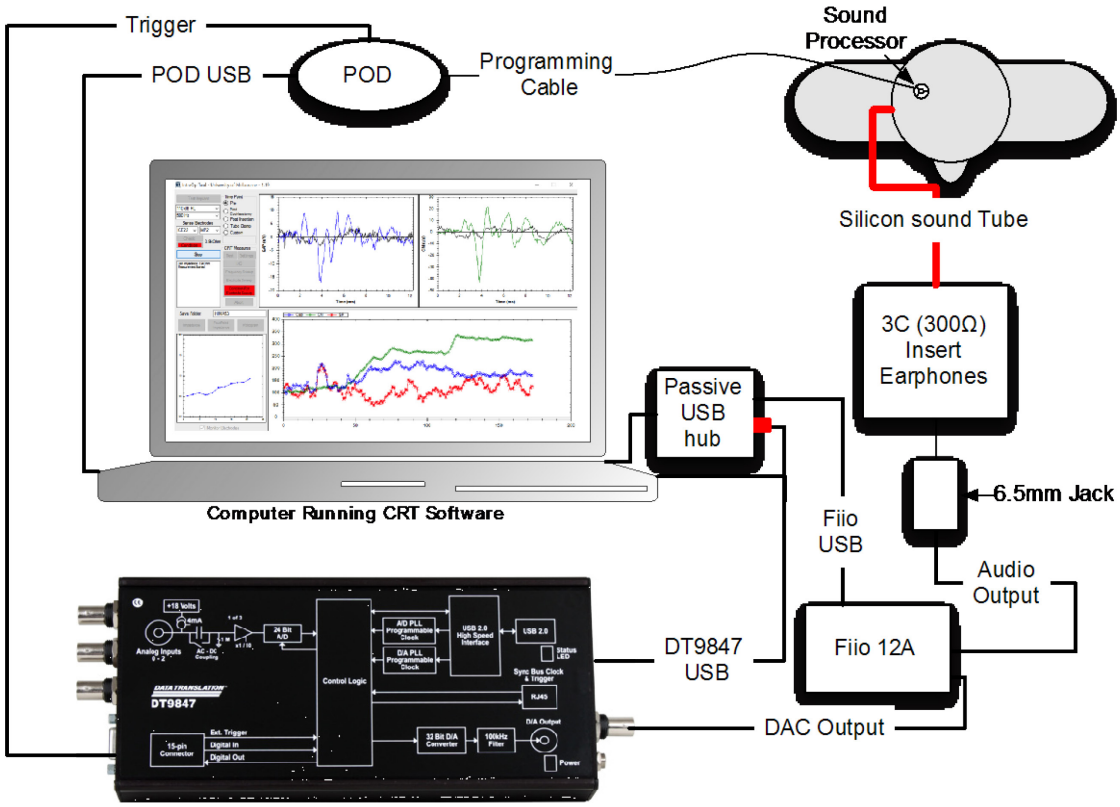

Figure 2. Functional diagram of the CRT measurement method. The bi-directional RF link of the Nucleus® cochlear implant permits both stimulation and recording with the device (receiver-stimulator coil and electronic unit, reference electrodes ECE1/2 and electrode array) and the signal generator and insert earphone permit acoustic stimulation of the cochlea.

The investigational CRT system will be used in the current clinical investigation in adults who meet the inclusion and exclusion criteria for enrolment. The system will be used for acute measurement only during surgery and post-operative assessment.

Subjects will be implanted with commercially available CI522, CI532 or Hybrid-L24 (US only) cochlear implants. Subjects will receive standard follow-up as for any patient implanted with the devices in addition to the study procedures.

4 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

Significant advancements in implantable device technology and refinements to surgical technique have led to progressive improvement in the ability to preserve acoustic hearing after implantation. However, although hearing preservation has been demonstrated with a range of devices (Adunka et al. 2004; Gantz and Turner 2004; Gstoettner et al. 2009; Fraysse et al. 2006; Gantz et al. 2009; Lesinski-Schiedat et al. 2011; Lenarz et al. 2013; Lenarz et al. 2009; Skarzynski et al. 2010; Roland et al. 2016), it is not yet possible to guarantee for an individual candidate that acoustic hearing will be preserved. Although the cause of post-operative hearing loss is likely multifactorial, events that occur during surgery are likely to be of influence. In order to understand the influence of such surgical factors, it is important to develop monitoring and diagnostic tools for use in the clinical setting, and to determine the specific intra-operative events that are associated with acoustic hearing loss. Furthermore, if reliable intra-operative tools were developed it may be possible to provide near real-time feedback to the surgeon as to change in acoustic hearing status during electrode insertion, and for the surgeon to modify or refine the surgical technique to minimize risk to loss of acoustic hearing.

The potential clinical applicability of use of acoustic ECoG measures during cochlear implantation has been investigated by a number of researchers, both with respect to predicting outcomes after implantation (Fitzpatrick et al. 2014; McClellan et al. 2014; Formeister et al. 2015) and in understanding the relationship between observed electrophysiological change in cochlear function with post-operative hearing preservation (Dalbert et al. 2015; Dalbert et al. 2016; Mandala et al. 2012; Adunka et al. 2016; Campbell et al. 2015).

To facilitate ease of measurement of the ECoG responses, the University of Melbourne in collaboration with Cochlear Limited have developed a prototype software and hardware system (termed Cochlear Response Telemetry, CRT). The system utilizes the in-built cochlear implant amplifier of the implant receiver-stimulator to record the evoked responses to acoustic stimuli from intra-cochlear electrodes. Recent research at the University of Melbourne and Royal Victorian Eye and Ear Hospital Cochlear Implant Clinic (Campbell et al. 2016) has demonstrated 15dB better low frequency hearing preservation in patients with preserved CM responses during surgery than in those where the CM was shown to reduce in amplitude during the surgical procedure without recovery. Furthermore, the preliminary findings from that study suggest that the real-time monitoring of the CM might in the future inform optimal electrode placement and identify events in surgery that might be detrimental to ensuring acoustic hearing preservation.

The present investigation primarily aims to confirm the Campbell et al. 2016 finding of better low frequency hearing preservation with preserved intra-operative CM responses in a much larger group of cochlear implant recipients across different centers. Hearing preservation will be investigated at 4-6 weeks and 3 months post-implantation. Of primary interest will be the hearing preservation at 4-6 weeks post-implantation, which is less likely to be impacted by factors other than potentially traumatic surgical events. In contrast to the Campbell et al. (2016) study, this study's categorization of hearing preservation will not include 250 Hz. This acoustic frequency is less likely to be sensitive to the CM measurement, since the hair cell population for 250 Hz lies deeper than the typical electrode array insertion. In the present study, acoustic hearing deterioration will be measured across a range of

frequencies below 1500Hz (500Hz, 750Hz and 1000 Hz), where acoustic hearing preservation for electroacoustic stimulation (EAS) is considered beneficial for spatial hearing and speech understanding (Gifford et al. 2013; Gifford et al. 2014). Specifically, deterioration will be calculated as the average change in threshold 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 at those frequencies. Prior research has suggested that audiometric thresholds greater than 80 dB HL are more likely to be impacted by the presence of detrimental factors such as cochlear dead regions (Baer et al. 2002; Zhang et al. 2014), and spectral distortion and/or broadening of auditory filters with the higher hearing aid output levels needed for audibility (Ching et al. 1988; Hornsby and Ricketts 2001). Unlike the Campbell et al. (2015) study, the present study will exclude in the definition of the preserved CM in those subjects with a transient reduction in CM amplitude. This decision was made to enable more clearly the impact of change in cochlear microphonic on hearing preservation, without uncertainty relating to the impact of transient CM amplitude reduction.

Furthermore, to inform Cochlear's future technology and product development of intra-operative monitoring tools that utilize ECoG measures, it is of interest to examine the influence of pre-operative acoustic hearing status on the characteristics of the CM response during intra-cochlear insertion of the electrode array. Understanding further the factors that influence the characteristics of the CM response (e.g. onset and latency) might enable reference markers to be incorporated within future software monitoring tools as to expected behavior of the CM response for cochlear implant recipients with varying characteristics. Additionally, it may be possible to provide reference data regarding expected responses for different electrode types. The CRT system provides the capability to interleave measures of electrode impedance with the ECoG recordings, which is expected to provide an ability to track the progressive entry of electrodes into the cochlea during insertion (through observed reduction in impedance when electrodes are in contact with perilymph). The combined use of such impedance measures and ECoG recordings will be used to characterize the CM response as a function of the number of electrode contacts inside the cochlea. Earlier CM onset is expected with better high frequency acoustic hearing, since the electrode array initially advances through the basal region of the cochlea passing the outer hair cells that are responsive to the high frequencies. Although maximum hair cell response to the 500 Hz acoustic tone occurs in the apical region the cochlea, hair cell populations in the basal region will also respond to the travelling wave. Latency change will be measured between two CM onset points and is predicted to increase as the advancing electrode passes surviving inner and outer hair cells populations. If there is no measurable high frequency hearing, it is hypothesized that CM amplitude will increase without an increase in latency as the electrode advances towards the apex.

Postoperative CRT sweeps will be conducted immediately following the wound closure (baseline) and at either 4-6 weeks post-surgery or at 3 months post-implantation. This will allow changes over time in different components of the ECoG to be characterized. The relationship between hearing threshold levels (HTLs) in the implanted ear and ECoG responses at FUV1 or FUV2 (e.g. CM and acoustic neurophonic response (ANN) thresholds) will also be examined.

Findings from the study will likely inform future development of commercial technology for both intra and post-operative monitoring of the ECoG responses with cochlear implant recipients.

5 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

5.1 Anticipated Clinical Benefits

There are no anticipated clinical benefits to individuals enrolled in the study, since the study does not involve any modification to surgical procedure or clinical management. Although there are no direct benefits anticipated, the information obtained from the study will potentially be useful in improving understanding of the potential benefits of CRT, and in guiding future research directions and clinical application of the technology.

5.2 Anticipated Adverse Device Effects

There are no anticipated adverse device effects related to use of the investigational device. The investigational device will be used to monitor ECoG responses during the implantation procedure. The surgeon will conduct the procedure as per standard clinical practice and individuals will be exposed only to the normal risks associated with routine cochlear implantation.

5.3 Residual risks related to the use of the investigational device

All residual risks for the investigational device are described in the Patient Informed Consent Form (PICF).

Electrode conditioning, especially at high current levels, may result in very loud or non-auditory percepts that could cause discomfort in awake subjects. During intra-operative testing under anesthetic the sound will not be perceived. However, during the follow-up visits at 3 post-surgery the level at which the sound is comfortable will need to be assessed from the subject providing feedback to the clinician. Similarly, the sound presented to the ear through the acoustic pathway will need to be checked for comfort during the follow-up visit.

5.4 Risks associated with participation in the clinical investigation

All supplied equipment is non-sterile. There is potential for non-sterile equipment of the CRT to enter the sterile surgical field. In order to mitigate this potential risk, all investigational sites must ensure the following non-sterile equipment is placed in a sterile bag(s): Freedom processor, RF coil and programming cable. The following non-sterile equipment must be isolated from the sterile field using the best surgical practices of the hospital performing the surgery: insert earphone foam tip and tubing.

5.5 Possible interactions with concomitant medical treatments

It is possible that prescription of glucocorticoids such as dexamethasone may influence post-implantation hearing preservation within the examined cohort. A surgical questionnaire will be administered to document use of concomitant medications for each subject.

5.6 Risk mitigations

The investigators or qualified delegates will conduct the CRT measurements and will be trained in the use of the software and associated hardware system prior to commencement of the investigation.

All investigators will be informed in advance of the following potential hazards and mitigations associated with use of the investigational device or investigation procedure:

a) All supplied CRT equipment is provided non-sterile. Therefore the Freedom processor, RF coil and programming cable must be placed in a sterilized bag for all intra-operative measures. The insert foam tip and tubing used to deliver the acoustic stimulus, and all other non-sterile equipment must be isolated from the sterile field.

b) It is important to ensure that the correct routine (intra-operative or post-operative) be selected in the software to avoid risk to overly loud and/or non-auditory percept being elicited through inappropriate use of the intra-operative conditioning parameters during the post-operative visits. The software will provide a warning on initiation of the intra-operative routine to minimize the risk of inappropriate use of this routine post-operatively.

c) It is important that the equipment used as part of the CRT research tool must not be connected to mains power or a mains powered accessory during all testing.

d) The surgeon will use his/her discretion as to the acceptable extension to the operating time for each individual, and will terminate use of the CRT tool as needed.

Pre-operative, peri-operative and post-operative use of concomitant medications will be documented for each subject. Use of glucocorticoids will follow each surgeon's and investigational site's standard clinical protocol.

5.7 Risk to benefit rationale

With reference to the risk management summary there are no unacceptable hazards. The software and hardware that will be used has been fully tested for functionality and safety according to verification procedures at Cochlear Limited which demonstrates conformity with the relevant AIMD 90/385 essential requirements. The findings from this clinical investigation will be important to informing future potential application of this technology in the clinical setting.

6 OBJECTIVES AND HYPOTHESES

6.1 Primary Objective

To examine whether compromised CM during cochlear implant surgery results in poorer post-implantation acoustic hearing preservation at FUV1 compared to preserved CM.

6.2 Secondary Objectives

1. To examine whether compromised cochlear microphonic (CM) response during cochlear implant surgery results in poorer acoustic hearing preservation at FUV2 compared to preserved CM.
2. To investigate whether pre-operative acoustic hearing influences the onset of the CM response during insertion of the electrode array.

6.3 Primary Hypotheses

Null Hypothesis:

The deterioration in average low frequency post-operative HTLs at FUV1 in the implanted ear for subjects with intra-operative compromised CM will be equal to or less than subjects with preserved CM.

Alternative Hypothesis:

The deterioration in average low frequency post-operative HTLs at FUV1 in the implanted ear for subjects with intra-operative compromised CM will be greater than subjects with preserved CM.

6.4 Secondary Hypotheses

1) Deterioration in average low frequency post-operative hearing at FUV2 in the implanted ear for subjects with intra-operative compromised CM compared to subjects with intra-operative preserved CM.

   Null Hypothesis:

   The deterioration in average low frequency post-operative HTLs at FUV2 in the implanted ear for subjects with intra-operative compromised CM will be equal to or less than subjects with preserved CM.

   Alternative Hypothesis:

   The deterioration in average low frequency post-operative HTLs at FUV2 in the implanted ear for subjects with intra-operative compromised CM will be greater than subjects with preserved CM.

2) Association of pre-operative high frequency HTLs with onset of CM response during electrode array insertion.

   Null Hypothesis:

   There is no association between pre-operative high frequency HTLs and onset of CM response.

   Alternative Hypothesis:

   There is a positive association between pre-operative HTLs and onset of CM response.

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 General

7.1.1 Design and Randomisation

The design of the clinical investigation is a prospective, observational (non-randomized) multi-center investigation.

7.1.2 Primary Endpoint

Deterioration in average low frequency post-operative hearing threshold levels (HTLs) at FUV1 in the implanted ear for subjects with compromised CM compared to subjects with preserved CM during surgery.

7.1.3 Secondary Endpoints

1. Deterioration in average low frequency post-operative HTLs at FUV2 in the implanted ear for subjects with compromised CM compared to subjects with preserved CM during surgery
2. Association of pre-operative high frequency HTLs with onset of CM response during electrode array insertion

7.1.4 Exploratory Analyses

Additional exploratory analyses may be performed. These may include:

- Comparison of the primary endpoint for three groups defined by compromised, preserved, and transient CM.
- Predictors of the incidence of compromised CM during surgery including influence of electrode type, insertion depth and surgical events.
- Association of pre-operative high frequency acoustic hearing thresholds with change in latency of CM during electrode array insertion.
- Investigation of the influence of demographic and surgical factors on the morphology and time-course of the CM curve during insertion and post-operatively.
- Investigation of the relationship of CM thresholds to postoperative HTLs in the implanted ear
- Examination of the degree of reduction in CM amplitude that occurs in response to a range of surgical events.
- Characterization of changes in electrode impedance as a function of CRT observations during and post-surgery.
- Characterization of changes in different components of the electrocochleography (ECoG) changes over time.
- Examination of whether the ratio of the CM amplitude over the ANN amplitude (uVrms) is correlated with lower (better) HTLs (FUV2) at 250Hz, 500Hz and 1kHz.
- 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.

7.2 Methods

A pre-operative screening visit (or multiple visits if required) will be conducted to ensure eligibility for enrollment and will typically occur as part of routine clinical assessment at each of the participating centers.

A pre-operative interview (as part of the informed consent process) will be conducted by the surgeon and/or audiologist to inform the candidate about all aspects of the study and evaluation schedule. After reviewing the Informed Consent Form, the candidate will be given the opportunity to review and ask questions about the Informed Consent Form and/or the study prior to signing the Informed Consent Form. The candidate will be offered the opportunity to take the form home to discuss with family members should they choose to do so. If he or she signs the Informed Consent Form, the candidate will then be given a copy of the signed Informed Consent Form to take home.

A candidate will not be considered enrolled until a properly executed Informed Consent Form has been obtained and, along with the results of the pre-operative candidacy evaluation, reviewed and approved by the local Cochlear regional representative (evidenced by the return of a signed study approval form to the investigator).

A pre-operative evaluation will be conducted (pre-operative visit 1, POV1) to provide a baseline (pre-operative) measure of acoustic hearing status, and to document hearing and medical history. Where required, the pre-operative evaluation may occur over multiple clinical sessions. Information collected during the pre-operative session will be recorded on the appropriate case report form (CRF). There will be no pre-determined period required between candidacy and baseline measures. However, candidacy must be re-assessed if more than 90 days have elapsed prior to the surgical date. A hearing and medical history will be obtained and documented during the pre-operative evaluation.

Implant surgery will be conducted (at D0). A video recording will be made during the surgical procedure to enable analysis of the CRT in response to specific surgical events. The video will be made via the operative microscope imaging system during the entire insertion, commencing just prior to cochlear opening and ending after closure of the deep (subcutaneous/muscle) layer. The video will be time-stamped to the CRT recordings. Measures of electrode impedance will be obtained during the surgery. At the completion of each subject's surgical procedure a questionnaire will be completed by the surgeon to document aspects of the surgical procedure (including surgical approach, administration of corticosteroids, and ease and depth of electrode insertion).

Post-operative assessment at 4-6 weeks (+/- 1 week) post-activation and 3 months (+/- 2 weeks) post-activation will be conducted, and involve a series of clinical tests including otoscopy, audiometry, tympanometry and electrode impedance assessment. At either 4-6 weeks post-surgery (+/- 1 week), or 3 months (+/- 2 weeks) post-activation, post-operative CRT will also be conducted.

If an intra-or post-operative imaging is performed as part of the routine clinical management at participating site, that data will be analyzed to provide an estimate of electrode array position.

Medical and audiological care throughout the clinical investigation, and at the conclusion of the investigation, will be as per standard clinical protocol for each investigational site, with the exception of the additional measurements taken as outlined.

7.3 Procedures

7.3.1 Audiometric Thresholds and Tympanometry

Unaided audiometric thresholds will be obtained for each ear, with insert earphones, using the standard audiometric technique for pure-tone air-conduction testing. All pre- and post-implantation testing will be completed using a clinical audiometer calibrated to appropriate standards. Pure tone threshold exploration will be completed using the adaptive Hughson & Westlake procedure (1944).

As these subjects have measurable low-frequency hearing, it is important that appropriate consideration be made for masking (procedure outlined in Appendix A).

Testing for both ears will include the following:

- Air conduction thresholds: 125, 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, 8000 Hz;
- Bone conduction thresholds: 250, 500, 750, 1000, 1500, 2000, 3000, 4000 Hz;
- Tympanometry in each ear

Note that responses to pure-tone stimuli presented will need to be confirmed as an auditory ('heard') versus vibrotactile ('felt') response and recorded accordingly.

7.3.2 Surgical Preparation

Preparation for surgery will occur as per standard clinical procedures and following recommendations in the Cochlear Response Telemetry Research Tool User Guide to ensure the sterile field is not compromised. The surgical team must take necessary precautions during preparation to ensure that fluid has not flooded the external ear canal, since that might influence the delivery of the acoustic stimulus to the cochlea. The surgical team must ensure that the drapes are thin and not doubled over at the site where the external coil will be magnetically coupled with the receiver-stimulator.

Video recording of all surgeries is required, to enable analysis of the CRT in response to specific surgical events. The video will be made via the operative microscope imaging system during the entire insertion, with recording to commence just prior to cochlear opening and ending after closure of the deep (subcutaneous/muscle) layer. The video will be time-stamped to the CRT recordings.

7.3.3 Surgery

Surgery will be conducted as per each surgeon's standard clinical practice. No feedback will be provided to the surgeon as to the status of the cochlear microphonic during insertion.

7.3.4 Intra-Operative Cochlear Response Telemetry Recording and Surgical Video

Intra-operative video recording will be obtained prior to cochlear opening and conducted during electrode insertion and until the closure of the subcutaneous/muscle layer.

After the receiver-stimulator package is positioned and secured, the transmitting coil and sound processor will be placed in a sterile sleeve or bag and subsequently the coil magnet placed in position over the implant package. Electrode conditioning will be conducted when the most apical electrode (electrode 22) is first placed into the basal turn of the cochlea, just prior to advancement of the array, or in a saline solution prior to insertion. On the stabilization of the impedance of the apical electrode, the surgeon will be informed that the insertion may commence. Intra-operative recordings obtained during electrode insertion will typically use a 500 Hz acoustic stimulus (of 6 ms duration and an inter-

stimulus interval of 70 ms) presented at 100 dB HL, with recording on the most apical electrode (electrode 22).

The surgical video will be time-stamped to the CRT recordings. This will be achieved with the surgeon clicking surgical tweezers in front of the microscope 3 times at the end of the surgery, whilst the operator records the current index on the CM monitoring trace that will be updating in real-time. The operator of the CRT software will also capture surgical events using the software time-stamped to the CM recording.

Monitoring of the CM will continue throughout the surgical procedure until closure of the deep (subcutaneous/muscle) layer.

Post-insertion measures will be obtained (after closure of the subcutaneous/muscle layer) using a frequency sweep and an electrode sweep routine.

7.3.5 Electrode Impedance Measures

Electrode impedance will be measured using the standard measurement technique used in the Custom Sound programming software, as well as using an investigational measure of 4-point impedance using the CRT tool and the Freedom processor.

Conventional impedance measurements are taken between two electrodes which are also the stimulating electrodes. Stimulating through platinum electrodes induces a platinum-tissue interface impedance, which depends on the size of the electrodes and the type of stimulation used. Therefore, when traditional impedance measurements are taken, the impedance measured includes the tissue impedance as well as the interface impedance at both recording electrodes.

Four-point impedance uses recording electrodes which are different from the stimulating electrodes. This means that no interface impedance is set up at the recording electrode, and that the impedance measured is predominately the tissue impedance. Some impedance is added by the electronics of the implant and the electrodes themselves. Usually, in four-point impedance the recording electrodes are adjacent intracochlear electrodes (ICEs) and the stimulating electrodes are the two ICEs on either side of the recording electrodes. In this method, the stimulation current should flow through the tissue between the two recording electrodes, and hence the impedance measured should be the impedance of the tissue in between the recording electrodes.

Four-point impedance measurements allow the user to investigate the impedance of the tissue, without interference from the platinum-tissue interface impedance, which is typically much higher. This approach aims to provide information about the fibrous tissue growth around the electrode array with less sensitivity to variation in the impedance of individual electrodes.

7.3.6 Imaging

Where post-operative radiological imaging of the cochlea is obtained at participating centers, as part of routine clinical management, the scans will be analyzed to provide an estimate of intracochlear electrode insertion depth (angle relative to round window). Where possible, scala placement will be determined using a co-registration procedure or high resolution ConeBeam. There will not be specific imaging requirements within the CIP, however where obtained during routine clinical procedure the information will be collected and analyzed.

7.3.7 Surgical Questionnaire

The surgeon will complete the surgical questionnaire to document aspects of the surgical procedure, including but not limited to surgical approach, use of corticosteroids, and ease and depth of electrode insertion.

7.3.8 Post-Operative Cochlear Response Telemetry Recording

Post-insertion measures will be obtained using a frequency sweep (with recording from electrode 22 for signals with frequency 250, 500, 1000, and 2000 Hz delivered at a maximum comfortable listening level) and an electrode sweep (with recording using a 500 Hz acoustic signal presented at a maximum comfortable listening level and recording on electrodes 22, 20, 18, 16, 14, 12, 10, 8, 6, 4 and 2). The signal level (typically comprising a 12 ms duration stimulus and 50 ms inter-stimulus interval) will be controlled to ensure comfortable loudness presentation.

7.4 Investigational device and comparator

Comparison of endpoints are made based on subjects with and without a compromised CM response.

7.5 Subjects

7.5.1 Inclusion Criteria

- Candidate for cochlear implantation (with CI522, CI532 or Hybrid-L24 according to local indications
- 18 years of age or older at the time of enrolment
- Pre-operative audiometric threshold in the implanted ear at 500 Hz of better than or equal to 80 dB HL
- Willingness to participate in and to comply with all requirements of the protocol

7.5.2 Exclusion Criteria

- Prior cochlear implantation in the ear to be implanted
- Ossification or any other cochlear anomaly that might prevent complete insertion of the electrode array
- Abnormal cochlear/nerve anatomy on pre-operative CT or MRI imaging (excluding a mild Mondini malformation or Large Vestibular Aqueduct Syndrome)
- Deafness due to lesions of the acoustic nerve or central auditory pathway
- Diagnosis of auditory neuropathy
- Active middle-ear infection
- Additional handicaps that would prevent participation in evaluations
- Unrealistic expectations on the part of the subject, regarding the possible benefits, risks and limitations that are inherent to the procedure and investigational device

7.6 Monitoring Plan

The study will be monitored for data quality, and adherence to ISO14155 or equivalent FDA guidelines and regulatory requirements as outlined in the study monitoring plan. Site initiation and training will be provided to ensure that study site personnel understand the protocol and schedule of activities, mechanics of the study device, study staff responsibilities, data capture and regulatory requirements. Due to the short nature of the study, Interim Monitoring activity (remote or on-site) will be completed once a site completes a multiple of 5 study subjects (i.e., after 5, 10, 15 etc. subjects are completed) or in the event of protocol compliance or GCP concerns. Completed CRT data will be collated and reviewed by the Sponsor throughout the duration of the study, to ensure that data collection is complete and consistent with the requirements of the investigation. The study close-out effort will be conducted at the conclusion of the site's participation in the study.

8 STATISTICAL CONSIDERATIONS

The primary hypothesis will be tested with a between-groups t-test or non-parametric Mann-Whitney U test using a one-sided alpha level of 0.05. This analysis will compare group mean low frequency postoperative hearing deterioration at FUV1 in the implanted ear for subjects with compromised CM compared to subjects with preserved CM. Compromised CM will be defined as a CM with an irreversible reduction in amplitude during surgery; specifically a ≥30% reduction in maximum CM amplitude that does not recover to within 10% of the maximum amplitude. Preserved CM will be defined as a CM with <30% amplitude reduction at any point during the surgery. Subjects not falling into the compromised or preserved CM groups will not be included in the analysis. The mean or median threshold drop for the CM compromised and CM preserved groups will be separately calculated as the mean or median of individual subjects' low frequency deterioration (4-6 week post-surgery threshold minus pre-operative threshold in the implanted ear) for the corresponding CM group. 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 1 dB above the level at which the limits of the audiometer were reached. Vibrotactile responses will not be included in the analyses.

Sample Size Estimation

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 four 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 paired or matched-pairs 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).

Considering the following assumptions, a total sample size of 125 subjects may be required.

c. The sample size may need to be further increased to 52 subjects, to allow for the prediction that approximately 20% of subjects will show a transient intraoperative CM drop that recovers by the end of the surgery (unpublished data, 14/1171H, Royal Victorian Eye and Ear Hospital Human Research Ethics Committee). This transient CM drop will not be categorised as a preserved CM or as a compromised CM due to uncertainty as to the likely impact of such a change on hearing preservation.
d. The total sample size of 104 subjects (52 subjects in each group) may need to be further increased by 20%, given that the allocation of subjects to groups occurs post-implantation, and so there is no ability to control the allocation of subjects. This increase to the total sample size in anticipation of unequal groups allows for a marked difference in group size up to a ratio of 2.0, with no loss in statistical power.

Both the proportion of subjects with a transient intraoperative CM drop and the allocation of subjects in the preserved CM versus compromised CM groups are nuisance parameters not

directly related to a potential difference in outcome between the groups. Since "breaking the blind", i.e. having access to the outcomes by CM groups, is not required to assess these parameters, modifications to the sample size may be made to the planned enrolment to ensure adequate power in the case that the assumptions outlined here (i.e. 20% of subjects show a transient CM drop, the allocation ratio between groups is different than 2.0). Such modifications do not affect the type I error rate of the study.

9 DATA MANAGEMENT

Source data collection is performed through DataLabs or alternative web-based system for electronic data capturing. Site personnel will be trained to use this system. Data validity has to be confirmed by the investigator through an electronic signature. An audit trail is kept by this system and data clarifications may be generated by the system and Sponsor personnel after review of data.

DataLabs or the alternative web-based system has been verified and validated by the vendor. Installation of the system within Cochlear has been validated as well. Investigation-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 investigation-specific data in DataLabs can only be accessed by those that have been allocated their individual account, which are personnel of the investigational sites, Clinical Project Managers, Investigation Monitors and Data Management. Electronic data saved within the CRT system and the surgical videos will be stored in a centralized and secure location.

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 required.

The procedure for recording and reporting CIP deviations shall be via a CIP Deviation CRF in the EDC system. Analysis of CIP deviations shall be undertaken by the Sponsor and Data Management.

In the event of a CIP deviation, the investigator shall notify the Sponsor within the required notification window. The Sponsor shall notify the EC and competent authority where necessary, of all CIP deviations annually.

12 DEVICE ACCOUNTABILITY

Investigational devices shall be tracked and returned to the Sponsor upon completion of the study.

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 Regulatory Agency Approval

The clinical investigation shall not commence in a particular region prior to the written favorable opinion or approval from the local Ethics Committee (EC), and regional regulatory agency (i.e., Competent Authority, Food and Drug Administration, or other relevant agency) 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 and regulatory agency (RA) where applicable. A copy of the EC and RA opinion/approval shall be provided to the Sponsor if not directly communicated.

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 RA and EC as required by national regulations, the clinical investigational plan or the responsible RA and EC.

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

The investigator shall submit the appropriate documentation if any extension or renewal of the EC or RA 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 and RA.

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

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

A copy of the signed PIC shall be given to the subject. The 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

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.

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 21 CFR Part 812, 50, 54, 56 & 11 as well as 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
   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 fetal distress, fetal 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 investigator shall report all serious adverse events without delay to the Sponsor. Investigators are to inform their respective EC/IRBs and the Sponsor immediately if an unanticipated adverse device effect is suspected (no more than 10 working days after the investigator learns of the effect). If the case is determined to be an unanticipated adverse device effect, the investigator will fill out an "Unanticipated Adverse Device Effect Form". The Sponsor will report the results of an evaluation of the unanticipated adverse device effect to all reviewing ECs and investigators within 10 working days after first receiving notice of the event.

The details of the Medical Monitor for the clinical investigation are:

Name of Medical Monitor	Mike Brownen
Phone number (business hours)	+1 (866) 9228673
Phone number (after hours)	+16828886884
E-mail	mbrownen@cochlear.com

If applicable: The Sponsor is responsible to report all SAEs, SADEs and USADEs to the relevant RAs 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 RA (if applicable) using the applicable report form and reporting timelines 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

Since routine surgical procedures will be applied, a DMC will not be established.

15.4 Device Deficiency Reporting Requirements

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

Name of Medical Monitor	Mike Brownen
Phone number (business hours)	+1 (866) 9228673
Phone number (after hours)	+16828886884
E-mail	mbrownen@cochlear.com

16 INCIDENT REPORTING

Not applicable for this clinical investigation.

17 VULNERABLE POPULATION

Not applicable for this 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) subject's decision

19 PUBLICATION POLICY

A description of this clinical investigation will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

It is planned to generate a joint publication by the Principal Investigator(s) and the Sponsor. The responsibility for writing the publication is with the Coordinating Investigator or the Sponsor. 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

20.2 External References

List in alphabetical order the standards of practice and external references referenced in this template.

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	Code of Federal Regulations Title 21 CFR Part 812, 50, 54, 56 & 11	

20.3 Referenced Literature

Adunka, O. F., C. K. Giardina, E. J. Formeister, B. Choudhury, C. A. Buchman, and D. C. Fitzpatrick. 2016. 'Round window electrocochleography before and after cochlear implant electrode insertion', *Laryngoscope*, 126: 1193-200.

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Unpublished data. Electrocochleography in Cochlear Implant Recipients. The Royal Victorian Eye and Ear Hospital Human Research Ethics Committee #14/1171H

21 CHANGE HISTORY

List the details of the changes made since the previous approval.

Version	Change	Author	Date
1.0	IDE Submission	Kerrie Plant & Pam Dawson	19 December, 2016
2.0	Amendments requested from FDA	Kerrie Plant & Pam Dawson	9 March, 2017
3.0	Clarification re FUV1 and FUV2 windows added	Aaron Parkinson	23 August, 2017

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 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 fetal distress, fetal 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).

22.2 Other definitions

Term	Description
CA	Competent Authority
CER	Clinical Evaluation Report
EC	Ethics Committee, alternatively referred to as Institutional Review Board in the U.S.
RA	Regulatory Agency
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.
NCA	National Competent Authority
PASS	Post-authorization safety studies mandated by medical device regulators
PIC	Patient Informed Consent
PICF	Patient Informed Consent Form
PIL	Principal Investigator List
SAP	Statistical Analysis Plan
CRT	Cochlear Response Telemetry
CM	Cochlear Microphonic
SRT	Speech Reception Threshold
DMC	Data Monitoring Committee
AuSTIN	Australian Speech Test in Noise
CRF	Case Report Form
EC	Ethics Committee
ECoG	Electrocochleography
POV	Pre-operative Visit
FUV	Follow-Up Visit

23 APPENDIX A: INSTRUCTIONS FOR MASKING

a) Pure tone threshold is established in the test ear

b) Masking noise is introduced to the non-test ear at the initial masking level (10 dB above the established threshold in the non-test ear). Pure tone threshold is then re-established.

c) Level of the masking tone or noise is increased subsequently by 5 dB. If there is a response to the tone in the presence of the noise, the level of the noise is increased by 5 dB. If there is no response to the tone in the presence of the noise, the level of the tone is increased by 5 dB steps until a response is obtained.

d) A plateau has been reached when the level of the noise can be increased over a range of 15 to 20 dB without shifting the threshold of the tone. This corresponds to a response to the tone at the same HL when the masker is increased in three to four consecutive levels.

e) Masked pure tone threshold corresponds to the HL of the tone at which a masking plateau has been established.