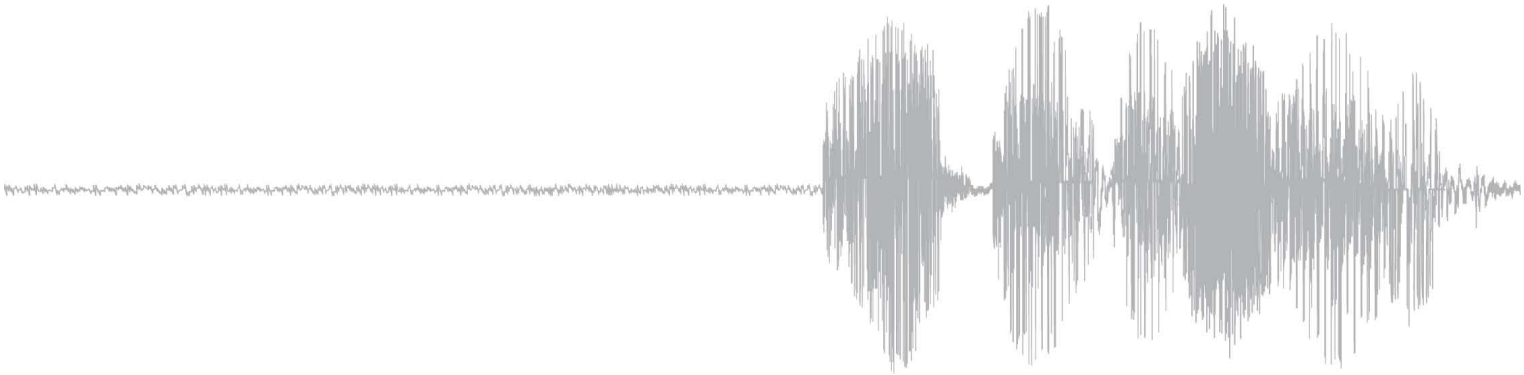

CLTD5626 CI532 audiological outcomes APAC_CIP_review

D748891

Version: 6
State: Approved (T+B)
Approver: Mary-Beth Brinson (Mbbrinson)
Date : 31 Jul 2017

Document Control Note: Hardcopies of this document are non-controlled unless the relevant Transmittal Advice Notification (TAN) information is stamped in the box below.

Hear now. And always

Cochlear®

Number of pages (include Coversheet): 40

CLINICAL INVESTIGATION PLAN (CIP)

Characterisation of audiological outcomes with the Nucleus® CI532 cochlear implant in adult subjects

CHANGE[1] Feasibility Study

CLTD5626

Date: 27 July 2017

Authors: [redacted]

[1] Clinical investigation title registered on ClinicalTrials.gov

Sponsor	Cochlear Limited 1 University Avenue, Macquarie University, NSW 2109
Manufacturer	Cochlear Limited 1 University Avenue, Macquarie University, NSW 2109
Principal Investigator(s)	Assoc. Professor Robert Briggs Department of Otolaryngology Royal Victorian Eye and Ear Hospital 32 Gisborne Street, East Melbourne Victoria 3002 Professor Robert Cowan The HEARing CRC 550 Swanston St Department of Audiology and Speech Pathology The University of Melbourne Carlton Victoria 3053

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

Sponsor, Principal Investigator and Clinical Research Organisation Signed Agreement

Investigation Title	Characterisation of audiological outcomes with the Nucleus® CI532 cochlear implant in adult subjects
Investigation Number	CLTD5626
Short Title	CHANGE feasibility study

Signature on behalf of Sponsor

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

Name	**Title**
Mary Beth Brinson	Director of Quality, Regulatory and Clinical
Signature	**Date** (dd-mmm-yyyy)

Signature of Principal Investigators

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

Name	**Title**
Robert Briggs	Principal Investigator
Signature	**Date** (dd-mmm-yyyy)

Name	**Title**
Robert Cowan	Principal Investigator
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**
Robert Cowan	Chief Executive Officer
Signature	**Date** (dd-mmm-yyyy)

Table of Contents

Table of Figures

Table of Tables

1 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	Characterisation of audiological outcomes with the Nucleus® CI532 cochlear implant in adult subjects.
Investigation number	CLTD5626
Short title	CHANGE[2] feasibility study
Name of investigational device	Approved Nucleus® CI532 cochlear implant
Principal Investigators	Associate Professor Robert Briggs Professor Robert Cowan
Investigation start	October 2015
Total expected duration of the clinical investigation	21 months
Enrolment period	6 months
Expected duration per subject	15 months/subject (upper estimate)
Investigational design	Prospective, single-centre, single arm with sequential enrollment.
Number of subjects	12
Inclusion criteria	1. Meet current cochlear implant indications at the implanting centre 2. In addition to meeting current cochlear implant indications, subjects must also possess preoperative unaided hearing thresholds between 40 to 65 dB HL at 250 & 500Hz in the ear to be implanted. 3. Fluent speaker in the local language used to assess clinical performance 4. Eighteen years of age or older at the time of implantation with no upper age limit
Exclusion criteria	1. Evidence of hearing loss prior to 5 years of age. 2. Sensorineural severe-to-profound hearing loss greater than 20 years at 2 kHz and above. 3. Simultaneous bilateral cochlear implantation or prior cochlear implantation in the ear to be implanted. 4. Additional disabilities that may affect the subject's participation or safety during the clinical investigation. 5. Medical or psychological conditions that contraindicate undergoing general anaesthesia or surgery. 6. Ossification, malformation or any other cochlear anomaly, such as common cavity, that might prevent complete

[2] *CHaracterisation of Audiological outcomes with the Nucleus® CI532 cochlear implant in a Group of adult subjEcts.*

	insertion of the electrode array, as confirmed by medical examination. 7. Hearing impairment due to lesion or neuropathy of the acoustic nerve, VIII nerve or central auditory pathway. 8. Active middle-ear infection, 9. Tympanic membrane perforation 10. Unrealistic expectations on the part of the subject, regarding the possible benefits, risks, and limitations that are inherent to the surgical procedure(s) and prosthetic devices 11. Unwillingness or inability of the candidate to comply with all investigational requirements. 12. Patients with existing CSF shunts or drains, existing perilymph fistula, skull fracture or CSF leak. 13. Patients with recurrent episodes of bacterial meningitis.
Primary objectives	1. Audiometric assessment post CI532 cochlear implantation 2. Safety (monitoring of Adverse Events & Adverse Device Effects)
Secondary objectives	1. Patient reported outcome measures i) SSQ preoperatively and 6 months post-activation ii) GBI at 6 months post-activation
Primary endpoints	1. Report on the degree of hearing as measured by pure tone audiogram 2. Report of clinical performance in quiet and noise 3. Report of medical/surgical and device related adverse events compared to the current approved labelling with regard to type, frequency and seriousness.
Secondary endpoints	1. Report on Patient Reported Outcome Measures for SSQ (pre-operatively to 6 months post-activation) and GBI (at 6 months post-activation)

Table 1: Investigation schedule

Procedure	Pre-op	Surgery	Activation	3 months post-activation	6 months post-activation	12 months post-activation
Medical history	x					
Imaging (X-ray, cone beam CT)		(x)	(x)			
Intraoperative ECAP		x				
Surgical Questionnaire		x				
T/C Levels, Impedances			x	x	x	x
Speech	x			x	x	x
Audiogram	x		x	x	x	x
Aided Audiogram[3]	x		x	x	x	x
Tympanometry	x		x	x	x	x
SSQ	x				x	
GBI					x	
Adverse Events and Device Deficiencies		x	x	x	x	x

[3] Preoperative in both ears; postoperative in implanted ear only.

2 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

Peri-modiolar electrodes such as the Contour Advance™ (CA) are designed to bring electrode contacts closer to the medial wall of the cochlea and so therefore closer to the spiral ganglion. Up until now these "pre-curved" electrodes have required a flexible metallic "stylet" to hold the electrode straight at the point of first introduction into the cochlea to avoid premature curling of the electrode. It is recommended that the electrode is advanced off the stylet™ (AOS) so that it follows the trajectory of the basal turn of the cochlea due to its curved shape. In this way contact with the lateral wall, which may produce trauma, may be avoided. Necessarily the cross-sectional area of the CA is somewhat larger than what may be required for a non-stylet "straight" array and there is always some chance that the stiffer array-stylet combination could still produce trauma if deployment of the electrode is not well handled. Either a classic insertion technique or a poorly-handled AOS technique may result in the electrode array dislocating between scala tympani and scala-media or scala-vestibuli, thus producing trauma to the interstitial membranes. In addition an electrode array in scala vestibuli is at a greater distance from the stimulation target (spiral ganglion cells) compared to one in scala tympani – thus current paths to these cells may be irregular and stimulation will be less selective, potentially reducing performance (1).

The device under investigation is the Nucleus® CI532 cochlear implant (Figure 1, left) which consists of a CI500 Series receiver/stimulator and a pre-curved, perimodiolar electrode array (EA32), which does not incorporate a lumen and stylet. Instead it has a thin electrode carrier which is introduced into the cochlea through a straightening sheath (Figure 1, right). The CI532 cochlear implant is manufactured by Cochlear Ltd, Macquarie University, Australia. Cochlear has been manufacturing cochlear implants for over 30 years.

Figure 1: Left: The CI532 device (not to scale). Right: The EA32 electrode array loaded in the sheath (upper), advanced through the sheath, and with the sheath removed as in final situation (lower).

As for the CA, the EA32 array must be orientated correctly so that its curvature is in the plane of the basal turn, with electrodes towards the modiolus, and the sheath must be immobile during this process. The cross-sectional area of the EA32 is approximately 40% of that of the CA and thus it is overall less stiff than the CA; these two factors may allow the EA32 array to take up a position within scala tympani closer to the modiolus. The sheath is removed and discarded once the electrode is fully inserted.

The CI532 cochlear implant is a single use device intended for long term implantation under the skin in the mastoid region of either side of the head. Cochlear implantation can only be undertaken by an experienced surgical team, or under supervision of such a team.

The CI532 cochlear implant will be used in the current clinical investigation in adults who meet current indications for cochlear implantation in Australia. As the clinical investigation aims to assess the degree of hearing preservation with the CI532 device, candidates who are at the upper range of pre-operative residual hearing (40 to 65 dB HL at 250 and 500 Hz) will be recruited to participate.

The surgical approach will be cochlear implantation via posterior tympanotomy as described in the CI532 Physician's Guide (2). The appearance of the RW and niche will be observed in order determine the choice of surgical approach and if necessary correctly position and drill a cochleostomy hole as mentioned in the Physician's Guide. Insertion of the array will be achieved using the advance-through-the-sheath technique described in the Physician's guide. This ensures that intra-cochlear trauma is minimised and offers the potential for hearing preservation in as many cases as possible.

The EA32 electrode (Figure 1, right) is placed into the cochlea and carries twenty-two electrode contacts. In addition there are two extra-cochlear return electrode contacts; one is connected to the CI500 body via a lead wire and placed under the temporalis muscle and the other is an exposed area of the case of the CI500 (Figure 1, left). With each CI532 an additional cochleostomy sizing tool is provided. The sizing tool allows verification of the size of the cochleostomy hole such that the guide tube (yellow/orange figure 1 right) may easily enter the cochleostomy hole but that the stopper cannot (2).

The CI532cochlear implant has been approved by the TGA in April 2017. Orders for devices will be placed in the Oracle system. Devices are identified by unique serial numbers.

This device when combined with the approved external Nucleus 6 Sound Processor (SP) (CP900 Series) provides electrical stimulation to the auditory nerve which can be interpreted as sound by the hearing impaired recipient. Biphasic current pulses at the electrode contacts are generated by the CI500-series receiver/stimulator which is controlled by the external Sound Processor via a transcutaneous radio link.

Standard activation of the CI532 will be achieved using Custom Sound software running on a PC equipped with a Nucleus Pod programming interface. A software key code will be provided to allow programming the investigational device. Electrically-evoked Compound Action Potentials (ECAPs) may be measured using either Custom Sound or Custom Sound EP software during surgery.

The external envelope materials of the CI532, and sterile accessories, and the Nucleus 6 CP900 Sound Processors are biocompatible according to applicable standards (i.e. ISO 10993: 2009/AC: 2010).

3 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

A multi-centre clinical early feasibility trial was performed with 17 cases being implanted with version 1 of the electrode array/sheath assembly (3). Electrode tip fold-over was identified in 32% of cases and due to this complication, 23% of cases received a commercial back-up device (CI24RE(CA) or CI512). Complications were related to device deficiencies and surgical protocol deviations. Hearing preservation was generally poor and most subjects lost their residual hearing in the implanted ear. The participants recruited for the early feasibility trial met current local indications for a conventional implant. The inclusion criteria specified an unaided hearing threshold in the ear to be implanted of equal to or better than 80 dB HL at 500Hz. Speech perception in quiet and noise significantly improved pre-operatively-to-post-operatively. Follow-up of these cases is now more than 5 years with no device related adverse events reported – all devices remain functional and in place.

Rotation of the electrode in the sheath may have contributed to the adverse device effects seen in the early feasibility trial and lead to further sheath design by Cochlear Limited. Most of the development focussed on the sheath until version 4 where the sheath to guide-tube assembly was reconfigured to further improve handling and visibility. In the intermediate designs tip folding occurrence was reduced by removing rotation and finally by modification of the slit in the sheath. The slit allows the sheath to be removed after the electrode is fully deployed. The final version improved the stability of the sheath especially when some bending of the array and sheath occurs.

Pre-clinical testing with the CI532 was performed with four versions of the electrode-sheath assembly over four rounds of formal temporal bone trials. The temporal data on the EA32 (using the latest sheath design) shows good perimodiolar position in a large majority of cases with a relatively low potential for intra-cochlear trauma shown by a scala dislocation rate of 3.3%. Once use errors were taken into account the tip fold-over rate was 3/110 or <3%.

Currently, a multicentre clinical investigation is being undertaken to determine if a low rate of dislocation can be achieved in clinical cases. Thirty-four adult candidates have been successfully implanted with the CI532 device (Melbourne, Las Palmas, Germany and Toulouse) with no scala dislocation. Anelectrode tip fold-over was reported for one participant in Freiburg which resolved with explantation of the CI532 and reimplantation with a CI512 device. All of the devices show good proximity to the modiolus from flat-panel volume computed tomography. Due to early success in the positioning of the CI532 device, further clinical evaluation is warranted to measure device performance in terms of hearing preservation in a clinical population with greater potential to preserve residual hearing.

The primary objective of the clinical investigation is to assess the degree of hearing with the CI532 cochlear implant. In order to demonstrate the atraumatic nature of the electrode design and insertion technique, as well as the possibility of fitting of the acoustic component

postoperatively, the inclusion criteria has been structured to capture subjects who currently meet the clinical criteria for cochlear implantation but who also possess unaided audiometric thresholds between 40 to 65 dB HL at 250 and 500 Hz. The secondary objectives of this clinical investigation are to evaluate Patient Reported Outcomes (PRO) preoperatively to six months post-activation for the Speech Spatial and Quality of Hearing scale (SSQ) and the Glasgow Benefit Inventory (GBI) at six months post-activation The outcomes from this feasibility study may be used to support the development of a randomised multi-centre clinical investigation evaluating the functional hearing preservation with the CI532 cochlear implant.

4 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

4.1 Anticipated clinical benefits

Analysis of the final positions of EA32 electrode in temporal bones, as reported above, revealed a low incidence of intra-cochlear trauma. The absence of dislocation is correlated with higher speech recognition scores (1, 4). In addition, close proximity of the electrode array to the medial wall is correlated with higher speech recognition scores (1). In both temporal bones and in the previous feasibility study the thinness of the pre-formed EA32 array gave in most cases wrapping factors of ~0.5 as estimated from images of temporal bones – this is at the best-performing end of the distribution presented by Holden et al.(1). Therefore due to low potential for trauma and close proximity of electrode contacts to the modiolus we expect a high clinical benefit for patients from the CI532.

4.2 Anticipated adverse device effects

Subjects are exposed to the anticipated adverse device, and or procedure related effects associated with standard cochlear implant surgery and general anaesthesia.

Adverse effects associated with cochlear implantation are:

- Individuals are exposed to the normal risks associated with surgery and general anaesthesia.

- The surgical procedure may result in infection or bleeding, numbness or stiffness about the ear, injury to or stimulation of the facial nerve, taste disturbance, dizziness, increased tinnitus, neck pain, or perilymph fluid leak. Inner ear fluid leak may result in meningitis.

- The cochlear implant results in a palpable lump under the skin just behind the ear. The presence of a foreign body under the skin may cause irritation, inflammation or breakdown of the skin and, in some cases, extrusion of the device. The electrode array may migrate partially or completely out of the cochlea, resulting in decreased hearing ability. The electrode lead may perforate structures of the external ear, such as the tympanic membrane or canal wall. Misplacement of the electrode array may result in the perception of non-auditory sensations. Such complications may require additional medical treatment, surgery and/or removal of the device.

- Electrical stimulation may result in increased tinnitus, facial nerve stimulation, dizziness or pain.

- Individuals who have residual hearing in the ear selected for the cochlear implant have a slightly greater risk of short-term postoperative dizziness than individuals with no residual hearing in that ear.

- The long term effects of electrode insertion trauma or from chronic electrical stimulation are unknown. Such effects may include new bone growth in the cochlea or deterioration of the nerve cells. These effects may preclude replacement of the electrode array or may lead to eventual deterioration of cochlear response.

- Failure of component parts (both external and internal) could result in the perception of an uncomfortably loud sound sensation or no sound. Failure of various component parts of the implanted device could require removal or replacement of the implant, or a reduction in the number of electrodes used.

- Inserting the electrode into the cochlea may result in complete loss of residual hearing in the implanted ear.

Residual risks for the investigational device compared to a similar device, such as the Nucleus CI512, relate to use errors which may increase the risk of tip fold-over. It should be noted that tip folding is not unknown in similar pre-curved arrays or in straight arrays. The presence of a tip fold-over does not usually produce any clinical symptoms or adverse effect. However it is likely that the distribution of current produced by the electrode array would be perturbed such that performance outcomes could be limited (such as speech recognition scores).

All residual risks for the investigational device will be described in the Patient Informed Consent (PIC)

4.3 Risks associated with participation in the clinical investigation

There are no anticipated adverse reactions specific to the investigational device other than those usually associated with cochlear implantation (as listed above) and concomitant medical treatments (2).

4.4 Risk mitigation

Tip fold-over of the array may necessitate re-implantation: Tip fold-over is typically detected via imaging. In this case the EA32 electrode may be removed from the cochlea, re-loaded and re-inserted or alternatively, the CI532 device may be removed completely and replaced with the Nucleus back-up device.

More detail on device specific risks and how they are mitigated may be found in the Investigators Brochure (IB) and the Physician's Guide (2). All surgeons will receive surgical training in the use and handling of the CI532 cochlear implant as part of study initiation. In addition, a Cochlear surgical support may be present during surgeries performed by the investigational site

4.5 Risk-to-benefit rationale

The improved likelihood of correct scala tympani placement, increased proximity to the modiolus, and reduced potential for trauma for the CI532 may provide a better outcome for patients compared to the existing CI512 or CI24RE(CA) implants equipped with CA electrode arrays.

Peri-operative X-ray and post-operative CT scans are used in a number of cochlear implant centres as a standard procedure in order to assess the quality of final electrode position. The peri-operative X-ray reduces the risk of leaving a very poorly placed array in situ (such as with tip fold-over).

In conclusion, the risk benefit ratio of participating in this study is similar to the risk benefit ratio of receiving treatment with a conventional CI.

5 OBJECTIVES AND HYPOTHESES

5.1 Objectives

5.1.1 Primary objectives

The primary objectives for the clinical investigation are:

1. To characterise audiometric outcomes post CI532 cochlear implantation in individuals who meet current indications for cochlear implantation but also have pre-operative hearing thresholds between 40 to 65 dB HL at 250 and 500 Hz of in the ear to be implanted.
2. An assessment of medical/surgical and device related adverse events compared to the current approved labelling with regard to type, frequency and seriousness at six months post-activation to evaluate safety.

5.1.2 Secondary objectives

The secondary objectives for the clinical investigation are of Patient Reported Outcomes (PRO):

1. The Speech, Spatial and Qualities of Hearing scale (SSQ) (5) measures self-reported auditory disability across a variety of domains: the ability to hear speech in a range of competing contexts; the directional, distance and movement components of spatial hearing; and the quality of the listening experience.

2. The Glasgow Benefit Inventory (GBI) is a measure of patient reported benefit developed especially for otorhinolaryngological interventions (6).

5.1.3 Additional clinical measures

5.1.3.1 Electrode placement

Electrode placement in the cochlea will be assessed by intra-operative lateral and modified Stenver's view X-ray and post-operative cone beam CT imaging.

5.1.3.2 Device characteristics

Device characteristics (impedance, psychophysical T and C-levels and ECAP) will be collected via an anonymous cdx file.

5.1.3.3 Surgical questionnaire

Surgical feedback on the usability and surgical outcomes with CI532 cochlear implant will be collected via a surgical questionnaire.

5.2 Hypotheses

As this is a feasibility study, there is no formal hypothesis to be accepted or rejected on the basis of statistical analysis in the current clinical investigation.

Individual outcomes will be compared, along with group effects, across pre- and postoperative test conditions for the speech perception outcomes. Adverse events will be summarized by event type, severity, seriousness, as well as relatedness to the device and implant procedure will be reported and tabulated.

6 CLAIMS AND INTENDED PERFORMANCE

The claims and intended performance of the investigational device that are to be verified are:

1. The number and percentage of subjects who were able to be fit with the acoustic component postoperatively.
2. Pre-to-post performance benefits with the CI532 cochlear implant for speech recognition.

7 RISKS AND ANTICIPATED DEVICE EFFECTS

For this clinical investigation, safety will be defined as freedom from device or procedure-related adverse events. The risks and anticipated adverse device effects that are to be collected in the clinical investigation are:

1. The number and percentage of subjects with electrode tip fold-overs as determined by X-ray. It is not intended that this data serve as a measure of treatment success since the focus of this study is hearing benefit.
2. The number and percentage of subjects with electrode not fully within the scala tympani as determined by cone beam CT scan
3. The number and percentage of subject with complete loss of hearing as compared to the Contour Advance electrode (CI512).

8 DESIGN OF THE CLINICAL INVESTIGATION

8.1 General

The Implantation of the Cochlear™ Nucleus® CI532 in Adults feasibility study will be conducted as a single-site, prospective, single-arm clinical study, evaluating the safety and functionality of the Cochlear Nucleus CI532 cochlear implant in 12 subjects who meet current cochlear implant indications with low frequency unaided thresholds between 40 to 65 dB HL at 250 and 500 Hz. A single-subject repeated-measures analysis will be employed whereby subjects will act as their own controls. A single-subject research design is appropriate since it accommodates the heterogeneity that characterizes hearing-impaired populations. Blinding procedures are not appropriate for this trial design, as it is not possible to conceal the presence, or absence, of a cochlear implant from device recipients and/or Investigational device and comparator

Subjects will be implanted with the investigational device, the Nucleus CI532 cochlear implant. The device will be activated at approximately 3 – 4 weeks post-operatively according to the investigational sites standard clinical procedures. Activation generally consists of determination of active electrodes via impedance measurements followed by the determination of subjective threshold (T) and comfortable (C) levels of stimulation (current amplitude) for each electrode. The Nucleus CP900 Series Sound Processor, is programmed such that input sound frequencies are allocated across the electrode array with input sound intensities being converted to stimulation levels between Ts and Cs. According to the postoperative audiogram, a subject may also receive the acoustic component. The acoustic component will be determined and fit according to commercial clinical recommendations and training. T and C-levels as well as use of the acoustic component may be re-determined at intervals after activation to take into account acclimatisation of the subject as well as postoperative hearing status

This is a single-arm, single-centre investigation. The comparator device is the sponsor's current commercially available pre-formed or peri-modiolar Contour Advance electrode which may be connected to the CI24RE "Freedom" receiver-stimulator electronics module or the later CI500 module. There is no difference in electronic capability between the CI24RE and CI500; the difference lies in the form factor. There is no proposed concurrent medical device or medication. The investigational site may use systemic application of corticosteroids and/or antibiotics at time of surgery possibly followed by oral application according to clinical standard of care.

8.2 Endpoints

8.2.1 Primary endpoints

The six month post-activation visit serves as the primary endpoint for data collection related to efficacy and safety outcomes post-CI532 implantation:

1. Efficacy endpoints

1.1. Hearing in the implanted ear will be reported as the change in pure-tone air-conduction thresholds (dB HL) pre-operatively to post-activation according to the Cochlear consensus at six months post-activation and 12 months post-activation.

Audiometric data will be summarized at each follow-up time point to assess any changes in hearing sensitivity and to characterize the impact of the procedure on hearing.

To understand if measurable low frequency thresholds can be maintained with implantation using the CI532 cochlear implant and fit with the acoustic component

1.2. Assessment of speech recognition in quiet will be measured using the CNC monosyllabic word test (7). Assessment of speech recognition in noise will be measured using sentences drawn from the Australian Sentence In Noise (AuSTIN) test (8) with speech-weighted noise (SWN) at a fixed +5 dB SNR.

2. Safety endpoints

2.1. Adverse events will be summarized by event type, severity, seriousness, as well as relatedness to the device and implant procedure will be reported and tabulated.

2.2. Report of medical/surgical and device related adverse events compared to the current approved labelling with regard to type, frequency and seriousness.

8.2.2 Secondary endpoints

The six month post-activation visit serves as the secondary endpoint for data collection related to Patient Reported Outcomes (PRO):

1. Speech, Spatial and Qualities of Hearing scale (SSQ)

   The six month post-activation visit serves as the secondary endpoint for data collection related to self-reported auditory disability and quality assessment with the SSQ for the CI532 cochlear implant.

2. Glasgow Benefit Inventory

   The six month post-activation visit serves as the secondary endpoint related to health utility data collection with the GBI for the CI532 cochlear implant.

8.3 Additional clinical measures

8.3.1 Device characteristics

Report of device characteristics related to impedance, psychophysical T and C-levels and ECAP with the CI532 cochlear implant.

8.3.2 Electrode placement

Report of EA32 electrode placement as confirmed by X-ray (preferably a lateral or modified Stenver's view).

8.3.3 Surgical questionnaire

Report on the usability and surgical outcomes with the CI532 cochlear implant as obtained via surgical questionnaire.

8.4 Equipment

Speech perception performance in quiet will be assessed using a loud speaker configuration with the signal from the front (S0). Speech perception performance in noise will be assessed using a loud speaker configuration with signal from the front and noise from the implanted side (S0N90 or S0N270) as shown in Figure 2.

Figure 2: Speaker orientation for speech perception assessment

The loudspeakers are located at head height for a seated subject (reference point). The distance from the loudspeaker from the reference point is approximately one meter. There will be defined locations for the loudspeakers and subject within the test environment. Sound field calibration of the Average Sound Level (Leq) is performed prior to each visit using a sound level meter (SLM) using a dB A-weighting (dBA), slow time weighting. Calibration of the SLM will occur according to the centres' current practise.

8.5 Investigation schedule

The visit dates and measures to be applied are reported in the Investigation schedule in Table 1.

8.6 Subjects

8.6.1 Inclusion Criteria

1. Meet current cochlear implant indications at the implanting centre
2. In addition to meeting current cochlear implant indications, subjects must also possess preoperative unaided hearing thresholds between 40 to 65 dB HL at 250 & 500Hz in the ear to be implanted[4]
3. Fluent[5] speaker in the local language used to assess clinical performance

[4] If it is more than 90 days past the date of the Candidacy Evaluation, candidacy needs to be reconfirmed by repeating hearing threshold test measures at 250 and 500Hz. Any changes observed will need to be reviewed in consultation with the Sponsor prior to surgery occurring.

4. Eighteen years of age or older at the time of implantation with no upper age limit

8.6.2 Exclusion Criteria

1. Evidence of hearing loss prior to 5 years of age.
2. Sensorineural severe-to-profound hearing loss greater than 20 years at 2 kHz and above
3. Simultaneous bilateral cochlear implantation or prior cochlear implantation in the ear to be implanted.
4. Additional disabilities that may affect the subject's participation or safety during the clinical investigation.
5. Medical or psychological conditions that contraindicate undergoing general anaesthesia or surgery.
6. 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.
7. Hearing impairment due to lesion or neuropathy of the acoustic nerve, VIII nerve or central auditory pathway.
8. Active middle-ear infection,
9. Tympanic membrane perforation
10. Unrealistic expectations on the part of the subject, regarding the possible benefits, risks, and limitations that are inherent to the surgical procedure(s) and prosthetic devices
11. Unwillingness or inability of the candidate to comply with all investigational requirements.
12. Patients with existing CSF shunts or drains, existing perilymph fistula, skull fracture or CSF leak.
13. Patients with recurrent episodes of bacterial meningitis

8.6.3 Number of subjects required

The protocol describes a feasibility study within a single site and a limited number of subjects (12 subjects) to characterise the audiological outcomes and the feasibility of fitting of the acoustic component postoperatively associated with the CI532 cochlear implant in adult cochlear implant candidates. As such, there have been no power or sample size estimations performed. It is estimated to take six months to recruit this number of subjects. The enrolment period will be extended if required.

[5] As judged by the investigator i.e. able to complete the speech perception assessment tasks and questionnaires.

8.6.4 Criteria and procedures for subject's withdrawal or discontinuation

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[6]
- Investigator decision[7]
- 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.

During surgery, an alternative device (e.g., CI522 or CI512) may be implanted in subjects where there are substantial difficulties with the CI532. These subjects will continue the clinical investigation and their outcomes will be compared to those subjects who received the CI532 device.

8.6.5 Subject replacement

The total number of subjects enrolled in the clinical investigation is 12. If a subject withdraws pre-operatively, they will be replaced by a newly recruited subject who meets the selection criteria for participation.

8.6.6 Point of enrolment

Subjects are recruited to the study by the investigators usually during the course of medical consultation. Subjects will be sequentially enrolled once Cochlear Asia Pacific receives a properly executed Informed Consent form and has approved the preoperative candidacy evaluation in writing.

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

[7] 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.

8.6.7 Total expected duration of the clinical investigation

The total expected duration of the clinical investigation is 38 months. The total duration will be dependent on the ability to recruit the required number of subjects within the enrolment period.

8.7 Procedures

8.7.1 Medical history (Pre-op)

Information regarding subject hearing-history (e.g., etiology, onset of hearing loss, duration of severe-to-profound hearing loss, amplification use) will be obtained and reported on the respective case-report form. In addition, patients will be carefully and extensively counseled to ensure that their expectations from cochlear implantation are reasonable and appropriate (as determined by the Investigator).

8.7.2 Audiogram (Candidacy, Activation, 3 months, 6 months and 12 months post-activation)

An unaided audiogram will be performed for both ears[8] at candidacy[9], at initial activation, three, six and 12 months post-activation at the following pure-tone frequencies:

Air conduction: 125, 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 & 8000 Hz

Air conduction thresholds >80 dB HL at 125 Hz, >90 dB HL at 250 Hz, >100 dB at 8000 Hz and >120 dB for other test frequencies will be marked NR (no response).

Bone conduction: 125[10], 250, 500, 750, 1000, 1500, 2000, 3000, 4000 Hz

Bone conduction thresholds >20 dB HL at 125 Hz, >30 dB HL at 250 Hz, >60 dB HL at 500 Hz and >70 dB HL for other test frequencies will be marked NR (no response).

Where the recipient reports feeling rather than hearing the acoustic stimuli, the threshold shall be recorded as vibrotactile (VT).

An aided audiogram will be performed for both ears at candidacy, and the implanted ear at initial activation[11], three, six and 12 months post-activation at the following frequencies using warble tones:

Aided thresholds: 125, 250, 500, 750, 1000, 1500, 2000, 3000, 4000 Hz

Tympanometry in each ear at each visit.

[8] The use of tube phones and appropriate masking of the non-test ear is required.
[9] If it is more than 90 days past the date of the Candidacy Evaluation, candidacy needs to be reconfirmed by repeating the air conduction hearing threshold test measure at 250 and 500Hz. Any changes observed will need to be reviewed in consultation with the Sponsor prior to surgery occurring.
[10] Bone conduction measures at 125 Hz are optional based on potential audiometric equipment limitations.
[11] Assessing aided thresholds after the initial activation will only be conducted if there is a shift in unaided hearing of more than 10 dB HL (for the better or worse) at two or more aidable frequencies.

8.7.2.1 Determination of hearing preservation post CI532 implantation

Unaided air conduction (AC) hearing thresholds will be reported for all participants at six months and twelve months post-activation to support the primary efficacy endpoint.

The population implanted with the CI532 device (per protocol population) will be divided into two groups for analysis:

1. Participants with a total hearing loss (no measureable AC threshold at audiometer limits at each frequency)
2. Participants with preserved hearing (measureable AC threshold at 250, 500 and 750 Hz)

Hearing preservation post CI532 implantation will be considered to be functional hearing preservation as defined by the Cochlear consensus[12]:

i. Unaided AC hearing thresholds ≤ 70 dB HL at 250 Hz
ii. Unaided AC hearing thresholds ≤ 90 dB HL at 500 Hz
iii. Unaided AC hearing thresholds ≤ 90 dB HL at 750 Hz

The number of participants with a total hearing loss, preserved hearing and preserved functional hearing post CI532 implantation will be reported for each frequency (250, 500 & 750 Hz[13]).

8.7.3 Speech recognition (Candidacy, 3, 6 and 12 months post-activation)

Speech recognition will be measured pre-operatively, 3, 6, 12 months post activation. Pre-operatively, speech recognition will be evaluated in the unilateral aided condition with the contralateral ear masked or plugged. Post-activation, the best unilateral listening condition will be evaluated; "Implant ear" using the acoustic component and/or the CI SP alone on one ear with the contra-lateral ear plugged or masked. Post-activation speech recognition shall be evaluated with default Nucleus 6 input processing options (SCAN).

Assessment of speech perception in quiet will be measured using two lists of CNC monosyllabic word test (7) at 60 dBA in the S0 speaker orientation (Figure 1).

Assessment of speech understanding in noise will be measured using two lists drawn from the AuSTIN test (8) sentence lists spoken by a female talker at 60 dBA at a fixed +5 dB signal-to-noise ratio (SNR) in the S0N90 or S0N270 speaker orientation (Figure 1). The competing noise will be speech-weighted noise (SWN).

No lists will be repeated for a given subject during the clinical investigation.

Performance benefits are change in scores pre- to post-operatively:

1. Gain in speech recognition in quiet (% correct)

[12] Cochlear clinical consensus for determination of residual hearing preservation (05/11/2015)
[13] The mean or median as statistically appropriate based on distribution of data.

2. Gain in speech recognition in noise (% correct)

8.7.4 Speech, Spatial, Qualities of Hearing scale – SSQ (Candidacy, 6 months post-activation)

Subjective quality assessment will be measured using the SSQ preoperatively and again at 6 months post-activation. The questionnaire will be completed during the visit by interview of the subject with the investigator.

Subjective performance benefits are change in scores pre- to post-operatively:

1. Gain in SSQ score (-10 to +10)

8.7.5 Glasgow Benefit Inventory – GBI (6 months post-activation)

Health Utility assessment will measured using the GBI at six months post-activation. The questionnaire will be completed during the visit by interview of the subject with the investigator.

Subjective performance benefits are change in scores pre- to post-operatively:

1. GBI score (-100 to +100)

8.7.6 Video (Surgery)

Surgery may be recorded via a video camera connected to the surgeon's microscope.

8.7.7 Imaging: X-ray and CT scan (Surgery)

The presence of electrode tip fold-over may be detected intra-operatively via modified Stenver's view X-ray, so that it may be corrected in-situ by removal and re-insertion of the electrode array. If the folding persists the back-up device should be employed. The correct positioning of the electrode within the scala will be assessed by post-operative cone beam CT scan. The resultant scan will be assessed post-operatively by the surgical team.

8.7.8 Electrically evoked compound action potentials – ECAP (Surgery)

ECAP thresholds will be recorded using the AutoNRT algorithm in the CR220 Intra-operative Remote Assistant or Custom Sound EP software.

8.7.9 Surgical questionnaire

Surgeons will complete the CI532 surgical questionnaire CRF to record the usability and surgical outcomes with the CI532 cochlear implant.

8.7.10 Activation (approximately 1 month post-surgery)

The CI532 cochlear implant will be activated with a commercially available Nucleus CP910 or CP920 Sound Processor and Custom Sound programming software as for recipients of existing devices. This will take place approximately 3 – 4 weeks after surgery (plus/minus 2 weeks).

Prior to activation of the sound processor, impedances and T/C levels will be determined. These data will be extracted from anonymized computer record files ("CDX") produced by the Custom Sound software.

Initially the default ACE sound coding strategy will be used with the parameters pulse rate 900 pps per channel, 25 µs / phase, mode MP1+2, and 8 maxima. These parameters may be adjusted afterward according to local procedures to improve subjective sound quality, if deemed necessary by the clinician. The sound processor shall be programmed with the default Nucleus 6 input processing options (SCAN). Additional custom programs can be added to the sound processor in program slots 2, 3 & 4 as required.

8.7.11 Acoustic Component Fitting (approximately 1 month post-surgery)

In the event that a subject retains aidable hearing, they will be fitted with the Nucleus 6 acoustic component (ACO). The ACO will be appropriately fit using the National Acoustics Laboratories' hearing aid fitting strategy and assess the degree to which real-ear targets are met for each subject.

8.7.12 Device characteristics (Activation, 3 months, 6 months and 12 months post-activation)

Device characteristics will be recorded at every postoperative visit and maintained within the subject's anonymous cdx. file (approximately one month post-surgery), at three, six and 12 months post-activation.

8.7.13 Safety

The investigator will complete an Adverse Event (AE) CRF if any AE or Adverse Device Effect (ADE), or a Device Deficiency (DD) CRF if any 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.

8.8 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.

8.9 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, electronic CRF (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.

9 STATISTICAL CONSIDERATIONS

All subjects who are recruited to the clinical investigation will constitute the intention-to-treat (ITT) population for the purposes of safety evaluation. Only subjects implanted with the CI532 will be considered as the completed cases (CC) population and per protocol (PP) analysis of the primary endpoint will be performed.

Where the CC population is insufficient, the sponsor reserves the right to ask the centres to recruit additional cases in order to reach the desired sample size of 12. As this is a feasibility clinical investigation, there have been no formal power or sample size estimations performed for the primary objectives.

To understand if measurable low frequency thresholds can be maintained with implantation using the CI532 cochlear implant and fit with the acoustic component:

1. Audiometric data will be summarized at each follow-up time point to assess any changes in hearing sensitivity and to characterize the impact of the procedure on residual hearing.
2. The degree of hearing will be reported and tabulated as the number of subjects who have measurable residual hearing post CI532 implantation.

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 cochlear implants.

Pre- to post-operative gains in speech and SSQ scores will be tested using paired comparisons (Student's t or non-parametric test if more appropriate). GBI scores will be compared to a hypothesised mean score of 0 (no benefit).

There are no pass/fail criteria to be applied to the results of the clinical investigation.

If required an interim analysis and report on three month speech and hearing threshold data will be provided for the purposes of submission to the TGA.

The characteristics of the study group will be presented descriptively. Quantitative variables such as age will be presented with mean, standard deviation, median, minimum and maximum and 95% CI. Qualitative variables such as age or gender will be presented as percentages and observed frequencies. If differences in outcome are found for subgroups defined by baseline age or gender, analyses will be performed to explore the possible role of other baseline characteristics to explain the results.

Supportive efficacy analyses will include analysis of individual data for all measures to establish the proportions of those subjects showing improvement, no change, and decrement in performance on the primary audiometry endpoint.

9.1 Missing Data

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

In the event a subject is withdrawn prior to the six month post-activation assessment (audiometry), the analysis of the primary endpoint will involve imputing the data point captured (candidacy, activation or three months post activation) for the six month post-activation assessment. The p-value for the primary statistical endpoints will be calculated using this imputation to understand the impact of missing data on the primary results.

10 DATA MANAGEMENT

Data collection is performed through electronic data capturing (EDC) on eCRFs. Site personnel will be trained on the completion of the eCRFs. Data validity has to be confirmed by the investigator through an electronic signature captured by the EDC system. Additional data is to be collected through the clinical fitting and electrophysiology software. The file records should be anonymized and then identified using the study number and the patient's study identifier (e.g. CLTD5626-MEL-01 3 month.cdx4).

Surgical experiences will be collected in written form on questionnaire but in addition the investigator may provide a video recording of the surgery in DVD or other digital format (to be uploaded to the sponsor's file server). Results from intra-operative X-rays can be summarized on the surgical questionnaire but the image or images should remain available for source verification.

An additional eCRF will be provided for summary results obtained from post-operative CT scans. However the anonymized raw image data will also be collected so that the results can be verified by the coordinating investigator and the consultant radiologist. The data should be provided in a standard DICOM format on either machine readable disk (i.e. DVDRom) or uploaded to the sponsor's file server. The file folder should be identified using the patient's study identifier (e.g. CLTD5626-MEL-01 CT scan).

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.

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.

Source data collection is performed on paper Case Report Forms (CRFs). Site personnel will be trained on the completion of the CRFs. Data validity has to be confirmed by the investigator through a signature. In addition, data can be collected through the clinical fitting and electrophysiology software and through x- rays.

Original completed CRFs are collected by Cochlear. 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.

11 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 Committee by the Principal investigator (and the TGA by the sponsor – if applicable).

12 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.

13 DEVICE ACCOUNTABILITY

Investigational devices will be shipped with individual registrations cards indicating the study number. Devices should be registered by the clinic according to usual practice. In addition the clinic is asked to return a copy of the completed registration card to:

[redacted].

14 STATEMENTS OF COMPLIANCE

14.1 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.

14.2 Ethics Committee and Regulatory Authority Approval

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

The Principal Investigator or sponsor shall submit the final approved version of the CIP, the approved PIC and all subsequently approved documents to the EC and the TGA. A copy of the EC and the TGA approval shall be provided to the sponsor if not directly communicated.

The Principal Investigator or sponsor 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 Principal Investigator or sponsor shall continue the communication with the EC and the TGA as required by national regulations, the clinical investigational plan or the responsible TGA.

Any additional requirements imposed by the EC and the TGA shall be followed.

The Principal Investigator or sponsor shall submit the appropriate documentation if any extension or renewal of the EC and the TGA approvals are 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 the TGA.

The Principal Investigator or sponsor will report to the EC and the TGA 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 and the TGA regularly as per local requirements.

Upon completion of the clinical investigation, the Principal Investigator or sponsor shall provide the EC and the TGA with a brief report of the outcome of the clinical investigation as per local requirements.

The clinical investigation is covered by clinical trial insurance meeting Australian requirements.

15 INFORMED CONSENT PROCESS

15.1 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.

In circumstances where the subject is unable to give informed consent (e.g. surgical complications requiring the use of a back-up device), the informed consent of the subject's legally authorized representative, if present, shall be requested.

15.2 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 TGA.

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, CT scan), 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.

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

16.1 Definitions

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

16.1.1 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.

16.1.2 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.

16.1.3 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.

16.1.4 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 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.

16.1.5 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.

16.1.6 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).

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

The investigator shall report all adverse events and adverse device effects and device deficiencies 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 the TGA in the clinical investigation in accordance with local regulations.

The investigator has to report all AEs, SAEs, SADEs and USADEs to the EC and the TGA (if applicable) using the applicable report form as per Australian requirements.

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.

16.3 Data Monitoring Committee

No DMC will be established.

16.4 List of anticipated adverse events and anticipated adverse device effects

For this clinical investigation the listed items in Section 4 of this CIP 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.

17 INCIDENT REPORTING

In cases where the investigational devices are commercially released products (Nucleus 6 System), the Principal Investigator shall report all adverse events to the EC and the 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.

17.1 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.

17.2 Reporting process

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

Name of contact person of the sponsor	[redacted]
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 the EC using the applicable report form as per national requirement.

18 VULNERABLE POPULATION

Not applicable for this clinical investigation.

19 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. Subject follow-up will occur as per the clinic's standard procedures.

An ongoing clinical investigation can be discontinued in case of:

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

20 PUBLICATION POLICY

It is planned to generate a joint publication by the Principal Investigator and the sponsor. The responsibility for writing the publication is with the Principal 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.

21 CHANGE HISTORY

Version	Change	Author	Date
1.0	Introduction of document	M. Knight & C. Morgan	24/8/2015
2.0	Modification of exclusion criteria #2, removal of exclusion criteria #3, addition of speech in noise test condition (+5 dB SNR), test level changed to 60 dBA for quiet and noise.	M. Knight	9/11/2015
3.0	Removal of +10 dB SNR test condition for AuSTIN test (pg.20), correction of inclusion criteria #1 & #2 order (pg.21,)	M. Knight	16/12/2015
4.0	Removal of intraoperative electrophysiology testing from CIP for alignment with US CI532 clinical investigation. Replacement of HEARRING consensus with Cochlear consensus for determination of hearing preservation.	M. Knight	15/03/2016

Version	Change	Author	Date
5.0	Updated CIP after TGA approval of CI532 cochlear implant. Updated investigation duration to align with enrolment period extensions. Note: This version not submitted to HREC	M. Knight	24/04/2017
6.0	Returned investigation duration and recruitment period dates in synopsis to original dates. Improved formatting in Section 8.2.7.1	M. Knight	27/07/2017

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 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
CA	Competent Authority
CER	Clinical Evaluation Report
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.
ITT analysis	The comparison of the treatment groups for all subjects as originally allocated after randomisation to avoid bias.
PASS	Post-authorization safety studies mandated by medical device regulators
PIC	Patient Informed Consent form
PIL	Principal Investigator List
PMS	Post-market surveillance studies
PP analysis	The comparison of treatment groups that includes only those subjects who completed the treatment originally allocated according to the protocol (i.e. a complete dataset). This form of analysis is open to bias is it does not include comparison of treatment groups for all subjects enrolled into the investigation.

23 REFERENCE LIST

1. Holden LK, Finley CC, Firszt JB, Holden TA, Brenner C, Potts LG, et al. Factors affecting open-set word recognition in adults with cochlear implants. Ear Hear. 2013;34(3):342-60.
2. Cochlear. CI532 Physician's Guide.
3. Knight M, Killian M. Clinical evaluation of the Modiolar Research Array Cochlear Implant. 2015 Contract No.: 343015.
4. Aschendorff A, Kromeier J, Klenzner T, Laszig R. Quality control after insertion of the nucleus contour and contour advance electrode in adults. Ear Hear. 2007;28(2 Suppl):75S-9S.
5. Gatehouse S, Noble W. The Speech, Spatial and Qualities of Hearing Scale (SSQ). Int J Audiol. 2004;43(2):85-99.
6. Robinson K, Gatehouse S, Browning GG. Measuring patient benefit from otorhinolaryngological surgery and therapy. Ann Otol Rhinol Laryngol. 1996;105(6):415-22.
7. Peterson GE, Lehiste I. Revised CNC lists for auditory tests. J Speech Hear Disord. 1962;27:62-70.
8. Dawson PW, Hersbach AA, Swanson BA. An adaptive Australian Sentence Test in Noise (AuSTIN). Ear Hear. 2013;34(5):592-600.