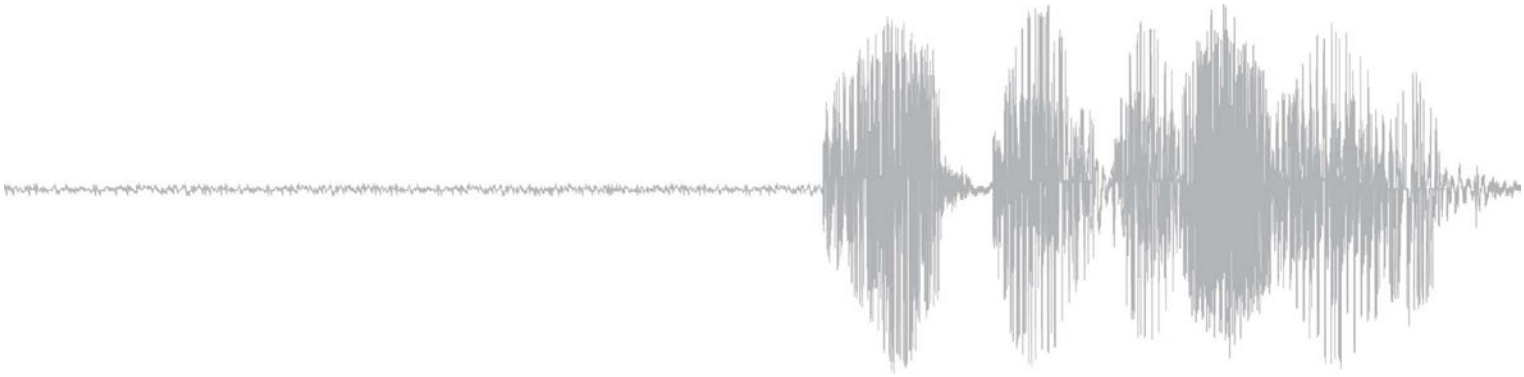

TICI Feasibility CIP
D1106820

Version: 10
State: Approved (T+B)
Approver: [redacted])
Date : 27 Jun 2019

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Clinical Investigation Plan

Feasibility of the Cochlear™ Nucleus® TI1012 Cochlear Implant in a Newly Implanted Adult Population

TICI Study

Investigation Number: CLTD5679

Version Number: 10.0

Date: 24-Jun-2019

Author: [redacted]

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Manufacturer	Cochlear Limited 1 University Avenue, Macquarie University, NSW Australia 2109
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1 SPONSOR AND COORDINATING INVESTIGATOR SIGNED AGREEMENT

Investigation Title	Feasibility of the Cochlear™ Nucleus® TI1012 Cochlear Implant in a Newly Implanted Adult Population.
Investigation Number	CLTD5679
Short Title[1]	TICI study

Signature on behalf of Sponsor

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

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

Signature of Principal Investigators

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

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

[1] Clinical Investigation name as registered on clinical trials registry

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

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2 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	Feasibility of the Cochlear™ Nucleus® TI1012 Cochlear Implant in Adults.
Investigation number	CLTD5679
Short title	TICI Study
Name of investigational device	Investigational TICI System (Nucleus® TI1012 cochlear implant (V 3.1.0), TC1001 charger and CDI Tool)
Principal Investigators	[redacted]
Investigation start	August 2018
Number of sites	The Royal Victorian Eye and Ear Hospital - surgical The HEARing CRC – non-surgical
Total expected duration of the clinical investigation	Thirty-eight months
Expected duration per subject	Twenty-six months
Investigational design	Prospective, single treatment arm with repeated measures.
Number of subjects	Eleven adults
Inclusion criteria	1. A bilateral moderately severe to profound post-linguistic sensorineural hearing loss with ≤ 15 dB difference between masked air conduction and bone conduction hearing thresholds (i.e. air-bone gap) at a given frequency, and who have compromised functional hearing with hearing aids or receive no benefit with hearing aids. 2. Fluent speaker in the local language used to assess clinical performance as judged by the investigator. 3. Eighteen years of age or older at the time of enrolment with no upper age limit. 4. A 30 day trial and/or experience with appropriately fit hearing aids.
Exclusion criteria	1. Deafness due to lesions of the acoustic nerve or central auditory pathway. 2. Active middle-ear infections. 3. Tympanic membrane perforation. 4. 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.

Exclusion criteria (cont'd)	5. Evidence of severe-to-profound hearing loss prior to 5 years of age. 6. Pre-existing cochlear or bone conduction implant. 7. Medical or psychological conditions that contraindicate general anaesthesia or surgery. 8. Additional disabilities that may affect the subject's participation or safety during the clinical investigation. 9. 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 as determined by the Investigator. 10. Unwillingness or inability of the candidate to comply with all investigational requirements as determined by the Investigator. 11. Existing CSF shunts or drains, existing perilymph fistula, skull fracture or CSF leaks 12. Recurrent episodes of bacterial meningitis. 13. Pre-existing skin condition that could jeopardize wound healing as judged by the investigator e.g. psoriasis, dermatitis, use of corticosteroids, uncontrolled diabetes. 14. Pre-existing medical condition that requires serial MRI. 15. Pre-existing medical condition of peripheral neuropathy.
Primary objective	The TI1012 cochlear implant is a feasible treatment for restoring hearing (speech recognition) in adult patients with sensorineural hearing loss.
Safety objective	The treatment of adult patients with the TI1012 cochlear implant is feasibly safe in an adult population.
Secondary objectives	The treatment of adults with the TI1012 cochlear implant is an effective treatment for restoring hearing (patient reported outcomes) in adult patients with sensorineural hearing loss.
Co-primary endpoints	1. Mean speech perception performance for an open-set CNC monosyllabic word recognition measure with the external Sound Processor (EH mode) in the unilateral listening condition at six months post-activation of TI1012 implant. 2. Mean speech perception performance for AuSTIN sentence in noise recognition measure with the external Sound Processor (EH mode) in the unilateral listening condition at six months post-activation of TI1012 implant. 3. Mean speech perception performance for an open-set CNC monosyllabic word recognition measure without the external Sound Processor (IH mode) in the unilateral listening condition at six months post-activation of TI1012 implant. 4. Mean speech perception performance for AuSTIN sentence in noise recognition measure without the external Sound Processor

	(IH mode) in the unilateral listening condition at six months post-activation of TI1012 implant.
Safety endpoint	Medical/surgical and device related adverse events at six months post-activation of TI1012 implant.
Secondary endpoints	1. Patient Satisfaction Survey (PSS) at six months post-activation of the TI1012 implant. 2. Tinnitus Handicap Inventory (THI) score at six months post-activation of the TI1012 implant. 3. Mean global Health Utility Index mark 3 (HUI2/3) score at six months post-activation of the TI1012 implant.

3 INVESTIGATION SCHEDULE

Table 1 below describes the investigation schedule.

Table 1. Investigation Schedule

	Pre-operative						Post-activation										
Procedure	**Candidacy**	**Baseline**	**Surgery**	**1 wk. post-surgical review**	**Activation (2 wks post-surgery)**	**2 wks**	**1 mth**	**1.5 mths**	**2 mths**	**2.5 mths**	**3 mths**	**6 mths**	**7 mths**	**9 mths[2]**	**12 mths**	**18 mths**	**24 mths**
Visit name	Candidacy	Baseline	Surgery	Review	Activation	Week 2	Week 4	Week 6	Week 8	Week 10	Week12	Week26	Week 30	Week 39	Week52	Month 18	Month 24
Visit window				*(+/- 3 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+30 days)*	*(+/-15 days)*	*(+/- 30 days)*	*(+/-30 days)*	*(+/- 30 days)*	*(+/-30 days)*
Medical history	x																
Consent	x																
Imaging (X-ray, CT, video)			x (X-ray & video)	x (CT)													
Surgical questionnaire			x														
POSAS					x						x	x					
Impedances			x		x	x	x				x	x			x		x
T/C Levels					x	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]			x[3]	x[3]	x[3]

[2] Visit can be split over multiple days within visit window.

[3] If required.

	Pre-operative						Post-activation										
Procedure	**Candidacy**	**Baseline**	**Surgery**	**1 wk. post - surgical review**	**Activation (2 wks post-surgery)**	**2 wks**	**1 mth**	**1.5 mths**	**2 mths**	**2.5 mths**	**3 mths**	**6 mths**	**7 mths**	**9 mths[4]**	**12 mths**	**18 mths**	**24 mths**
Visit name					Activation	Week 2	Week 4	Week 6	Week 8	Week 10	Week12	Week26	Week 30	Week 39	Week52	Month 18	Month 24
Visit window				*(+/- 3 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+30 days)*	*(+/-15 days)*	*(+/- 30 days)*	*(+/-30 days)*	*(+/- 30 days)*	*(+/-30 days)*
Microphone calibration					x	x	x	x	x	x	x	x			x	x	x
Power optimisation					x	x	x	x	x	x	x						
Audio recordings			x		x	x	x	x	x	x	x	x	x		x	x	x
Speech Perception		x										x		x	x		
Listening mode changes												x	x				
Diagnostics			x		x	x	x	x	x	x	x	x	x	x	x	x	x
Audiogram	Unaided	Aided			Unaided & Aided	Aided[5]	Aided[5]	Aided[5]	Aided[5]	Aided[5]	Unaided & Aided[5]	Unaided & Aided[5]			Unaided & Aided[5]		
SSQ12		x										x					
THI		x										x	x				
HUI2/3		x										x					

[4] Visit can be split over multiple days within visit window.

[5] Perform if T/C levels are modified during this visit.

	Pre-operative		Surgery	1 wk. post - surgical review	Activation (2 wks post-surgery)		Post-activation										
Procedure	**Candidacy**	**Baseline**				**2 wks**	**1 mth**	**1.5 mths**	**2 mths**	**2.5 mths**	**3 mths**	**6 mths**	**7 mths**	**9 mths[6]**	**12 mths**	**18 mths**	**24 mths**
Visit name					Activation	Week 2	Week 4	Week 6	Week 8	Week 10	Week12	Week26	Week 30	Week 39	Week52	Month 18	Month 24
Visit window				*(+/- 3 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*(+30 days)*	*(+/-15 days)*	*(+/- 30 days)*	*(+/-30 days)*	*(+/- 30 days)*	*(+/-30 days)*
Loudness scaling														x			
Patient Satisfaction Survey		x										x					
PSQI		x										x	x				
Usability						x	x		x		x						
Data logging						x	x	x	x	x	x	x	x	x	x	x	x
AE, ADE, concomitant medication and Device Deficiencies			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

[6] Visit can be split over multiple days within visit window.

4 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The Investigational Totally Implantable Cochlear Implant (TICI) System comprises the:

- TI1012 cochlear implant with Contour Advance electrode with an integrated rechargeable Lithium Ion battery (Figure 1, left).
- Carina™ pendant microphone integrally attached to the TI1012 receiver-stimulator module and implanted subcutaneously (Figure 1, left).
- Nucleus 6 Sound Processor (CP910) with customised firmware needed to communicate with the TI1012 implant designed for use in External Hearing (EH) mode.
- Nucleus 6 Remote (CR210)
- Custom body-worn charger (TC1001) that allows simultaneous charging of the TI1012 internal Li Ion battery and hearing in Invisible Hearing (IH) mode (Figure 1, right).
- CDI Tool software to program the Investigational TICI System.
- TI1000 Series Surgical Instruments

Figure 1. TI1012 cochlear implant and TC1001 charger

The TI1012 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.

The TI1012 cochlear implant will be used in the current clinical investigation in adults aged 18 years and older who meet the eligibility criteria of the clinical investigation. The surgical approach will be cochlear implantation via posterior tympanotomy as described in the TI1012 Physician's Guide (1). Surgery is anticipated to take only slightly longer than conventional CI surgery due to the larger implant bed and anchoring of the pendant microphone appropriately.

The TI1012 device, when combined with the Nucleus 6 CP910 Sound Processor (SP) with modified firmware (EH mode), provides electrical stimulation to the cochlea in the same manner that provided by commercially available Nucleus Cochlear Implant Systems. In addition, electrical stimulation is provided to the cochlea without the use of externally worn Sound Processor, with audio input from the implanted microphone (IH mode). Invisible Hearing (IH) mode uses the subcutaneous microphone attached to the TI1012 cochlear implant for audio input rather than the microphone on the externally-worn Sound Processor in External Hearing (EH) mode. It is anticipated that hearing performance in IH mode may be poorer than EH mode and that subjects will use IH mode during times when it is either impractical or inconvenient to use an externally-worn device (sleeping, water activities, cosmesis, and dirty/dusty/humid environments). The TC1001 charger enables charging of the TI1012 internal Lithium Ion (Li Ion) battery.

Activation of the TI1012 will be achieved using CDI Tool software running on a personal computer (PC) equipped with a Nucleus® Pod programming interface. The Investigational TICI System (TI1012 cochlear implant, TC1001 charger and CDI Tool software) is fully described within the Investigational TICI System Investigator Brochure (2).

Device traceability shall be achieved through unique TI1012 implant serial numbers and is discussed further in Section 13 of this document.

The external envelope materials of the TI1012, TC1001, sterile accessories, and the Nucleus 6 CP910 Sound Processor are biocompatible according to applicable standards (i.e. ISO 10993: 2009/AC: 2010).

5 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

The current clinical investigation is designed as a prospective design, with a single treatment arm to evaluate the feasibility of the Cochlear Nucleus® TI1012 cochlear implant in eleven adult subjects. A prospective, single treatment arm design is employed when the objective of the clinical investigation is to obtain preliminary evidence of the efficacy of the treatment and to collect additional safety data (3), and compares clinical outcomes before and after an intervention (4). The current research design is appropriate for first-in-human implantation with the TI1012 cochlear implant. Outcomes from the current clinical investigation will inform the design of future clinical investigations with the commercial TI1100 Series cochlear implant.

5.1 Pre-clinical Assessment

The Totally Implantable Cochlear Implant (TI1012) device is intended to build on the existing highly successful CI500 Series devices primarily by offering an optional Invisible Hearing (IH) mode in which the functions of the external Sound Processor are provided by components of the internal implant. Use of IH mode is anticipated to be beneficial in specific listening situations, such as:

- When it is uncomfortable or impractical to wear the external Sound Processor, such as while sleeping or wearing a sports helmet.
- When there is risk of damage to the external Sound Processor, such as in dirty/dusty/humid environments, during contact sports or while swimming/bathing.
- When the user wishes to avoid use of the external processor for cosmetic reasons.

As IH mode requires the use of a subcutaneous microphone, with reduced sensitivity relative to an external microphone, it was anticipated that listening performance may not match that obtained in conventional (External Hearing) mode. Thus, the two principal general goals in developing the TI1012 were:

1. Listening performance in External Hearing (EH) Mode should be at least equivalent to that obtained with the current CI500 Series and other equivalent CI devices.
2. Invisible Hearing (IH) mode should provide functional performance in specific situations (e.g. sleeping, water activities, physical activities) and its availability is dependent on the functional lifetime of the implanted battery (estimated at ten (10) years post-implantation).

The design of the TI1012 cochlear implant has been developed through surgical usability trials with cadavers and reported within the TI1012 Surgical Usability Validation Report (5). Outcomes are discussed in Section 5.2.2of this document. The report concluded that the usability of the TI1012 Implant, the TI1012 Physician's Guide (1) and the TI1000 Series of surgical instruments is ACCEPTABLE. No safety related use errors were observed during validation testing.

The Investigational TICI System has been assessed to demonstrate System compliance against the TICI System Requirements Specification (6) and compliance to relevant International Standards[7].

5.2 Existing clinical evidence

5.2.1 Tirkandi Feasibility Study

An early totally implantable research device, known as the Tirkandi, was implanted in three adult recipients in Melbourne, Australia, as part of a Cochlear-Sponsored study, between October 2005 and January 2006. The Tirkandi was constructed using the same biocompatible materials as the Nucleus CI24RE cochlear implant and using Cochlear's

[7] EN 45502-2-3:2010, ISO 14708-7:2013, AIMDD ER14.1, AIMDD 90/385/EEC.

manufacturing and sterilization methodologies. *In vitro* and animal studies were undertaken to assess the function and optimize the design of the totally implanted microphone, which was mounted on the upper surface of the titanium receiver-stimulator package. The aim of this early feasibility study was to:

1. Explore the potential of a totally implanted device,
2. Identify limitations of the research technology used, and
3. The impact of internal body noises.

Surgical experiences, subjective perceptions and objective speech understanding for the initial 12 months of device use were reported by Briggs et al. (7). Surgery was uneventful, with no perioperative or post-operative complications. Speech understanding was substantially superior in External Mode (using the ESPrit 3G™ Sound Processor) than in Invisible Mode, but all three subjects regularly used Invisible Mode to varying degrees. Briggs et al. reported that the subcutaneous microphone provided situational communication benefits to all three recipients and provided a sound basis for continued development of totally implanted technology (7).

The Tirkandi feasibility study informed development of the final TI1000 design. The first TI1000 Series device planned for commercial production is the TI1012, which uses the Contour Advance (CA) electrode, in common with the currently approved CI512 cochlear implant.

Comparison of the TI1012 and Tirkandi implants is provided in Table 2 below.

Table 2. Comparison of TI1012 and Tirkandi implants

	TI1012 implant	**Tirkandi implant**
Size	7.7mm (T) x 32mm (W) x 56mm (L)	7.6mm (T) x 28mm (W) x 60mm (L)
Microphone	Dual element pendant with adaptive microphone directionality	Single element integrated with no directionality
Body noise cancellation	Active Body Noise Cancellation (BNC) algorithm	Not available
Electrode	Contour Advance	Contour Advance
Extra cochlea electrode	2 x platinum plate on stimulator body	1 x platinum plate on stimulator body 1 x platinum ball electrode on lead
Implanted battery	Lithium Ion	Lithium Ion
Anticipated implanted battery life (capacity)	12hrs (50 mAh)	18hrs (36 mAh)

Implant off functionality	CP910 Sound Processor or TC1001 charger coil magnet and CP910 Sound Processor or TC1001 charger off button	Charger button
Emergency off switch	By any of the methods listed above	ESPrit 3G Program 2 Emergency ESPrit 3G
Sound Processor	CP910 (Nucleus 6)	ESPrit 3G
Remote	CR210	Not available
Implanted battery charger	TC1001 (modified Freedom BW controller)	Modified Freedom BW controller
Chipset	NEOS	Guri
Sound Processor input processing	SCAN (ADRO, ASC, SNR-NR, WNR)	ADRO, ASC
Stimulation mode	Dual Electrode stimulation mode, 489/978 pps, 8-12 maxima	Dual Electrode stimulation mode, 500 pps, 8 maxima
Materials	Titanium case, platinum and silicon as used in commercial Nucleus implants	Titanium case, platinum and silicon as used in commercial Nucleus implants
Programming software	CDI Tool running on Windows 7 OS	Tirkandi programming software running on Windows 98 OS

The intended use and indications for use of the Investigational TICI System (TI1012 implant, CR210 remote, TC1001 charger and CDI Tool) is unchanged from the Tirkandi Prototype device assessed and reported by Briggs et al. (7).

5.2.2 Surgical Feasibility

Formal surgical usability validation testing of the TI1012 cochlear implant, TI1012 Physician's Guide and TI1000 Series Surgical Instruments was performed by four experienced CI surgeons with cadaver heads in order to identify any issues relating to surgical placement of the receiver-stimulator and microphone and to validate design features in terms of orientation of the coil relative to the electronics housing and microphone and electrode lead lengths. Key outcomes from these evaluations included:

(i) A relatively standard cochlear implantation approach is likely to be acceptable, but may require a slightly longer incision to allow suitable access for placement of both the implant and the microphone,
(ii) Microphone and electrode leads are appropriate and microphone screw fixation near the tip of the mastoid is adequate with fixation of both straps,
(iii) For ease of fixation, alignment of the coil and receiver-stimulator on the skin side is preferred over alignment at the skin side, as this would result in a flatter profile under the skin, and
(iv) Clear diagrams of correct microphone handling procedure are needed to avoid damage to the microphone during fixation.

Usability issues identified during surgical validation led to updates to the Physician's Guide (1) in order to improve the overall ease of use of the product. The validation testing

concluded that the usability of the TI1012 Implant, the TI1012 Physician's Guide (1) and the TI1000 Series of surgical instruments has been met.

No safety related use errors were observed during validation testing (5).

5.2.3 Carina Percutaneous Plug study

The TI1012 is substantially equivalent to the CI24RE and CI500 implants in core function. The key differences, relative to the CI512, are the incorporation of a rechargeable battery, implantable microphone and new electronics. Major sub-components are derived from the Carina™ acoustic implant. The Carina is a fully implantable system intended to compensate auditory deficits in individuals aged 14 or older with moderate to severe sensorineural, conductive or mixed hearing loss, providing mechanical stimulation applied to the ossicular chain or round/oval windows. The Carina was developed by Otologics LLC and acquired by Cochlear Ltd in 2012.

The TI1012 uses a modified version of the implanted pendant microphone used in the current Carina device, with additional shielding and partial over coating. The microphone response is shaped using a new "spectral matching" fitting method and a front-end "Body Noise Canceller" algorithm. Performance of the implanted microphone has been evaluated through extensive bench testing and clinically in a Cochlear-Sponsored clinical trial (CTC5405), in which established users of the Nucleus Freedom cochlear implant and the Nucleus 5 CP810 or Nucleus 6 CP910 Sound Processors were implanted with the Carina microphone connected to a percutaneous pedestal on the contralateral side. The output from the microphone/pedestal was processed by a "Carina-in-a-box" device, and delivered to the direct input of the CI Sound Processor. In this way it was possible to switch between the equivalent of external and Invisible Hearing modes, and the study subjects evaluated the experimental system over a four month period. This was an extension of a pilot study on four Nucleus Freedom device users reported by Jenkins & Uhler (8). For speech understanding in a quiet environment at conversational level only a minor performance reduction was observed when switching to Invisible Mode. Decrement of speech recognition by the use of the internal microphone was equivalent to that observed with the Tirkandi device, which used a microphone integrated into the titanium electronics package. The Body Noise Canceller (BNC) produced an average attenuation of 21 dB and the subjects rated body noises as audible but acceptable in terms of annoyance when the BNC algorithm was activated (9).

The Carina percutaneous plug study (CTC5405) successfully demonstrated the effectiveness of the Carina microphone and informed development of the TI1012 implant design for use in the current clinical investigation.

5.2.4 Incidence of tinnitus

The incidence of tinnitus in individuals with profound bilateral sensorineural hearing loss has been reported to vary between 66-88% (10-16). Electric stimulation via a cochlear implant has been shown to suppress tinnitus, as a secondary effect of treating deafness (10, 11, 13, 15, 17-22). The handicapping nature of tinnitus has been broadly divided into four categories:

(a) thoughts and emotions, (b) hearing, (c) sleep and (d) concentration (10, 23). A study by Pan et al. (10) reported that of 153 of 244 adult CI recipients who had tinnitus preoperatively, 94 (61%) patients reported total suppression and 59 (39%) reported a partial reduction in their tinnitus with cochlear implant use. The largest reductions in the Tinnitus Handicap Questionnaire (THQ) score pre- to post-implantation involved social handicap and hearing. Souliere et al. (19) reported on an investigation with 33 post-lingually deafened CI recipients; the majority (74%) thought that their cochlear implant was helpful in tinnitus suppression, especially in the ear with the implant. Residual inhibition of tinnitus from cochlear implant use ranged from 60 seconds to several hours was reported by 50% of patients, predominantly in the ear with the implant in the Souliere et al. study. Tinnitus suppression through the use of a cochlear implant has also been demonstrated in unilaterally implanted adult populations (21, 22, 24). Tinnitus suppression, relief from sound intolerance and improved hearing, resulted in the active use of the cochlear implant in a unilaterally implanted population (21).

It has been hypothesized that continual access to electrical stimulation via Invisible Hearing compared with External Hearing (i.e. the benefit of 24 hour hearing) may minimise the impact of tinnitus for recipients of a TI1012 cochlear implant.

6 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

6.1 Anticipated clinical benefits

The anticipated clinical benefits for subjects participating in the investigation when using the externally-worn CP910 Sound Processor are comparable to those obtained with conventional cochlear implants. In addition, it is anticipated that the subject will benefit from access to Invisible Hearing in a variety of daily listening situations such as during water activities, sleeping, dusty/dirty/humid environments, and when it is otherwise not convenient to wear an external device.

6.2 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 any cochlear implant as described in the Cochlear Nucleus CI500 series implants Physician's Package Insert (25) 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.

Anticipated adverse device effects, and or procedure related effects associated with the TI1012 cochlear implant are:

- Poorer hearing performance outcomes with Invisible Hearing (IH) mode when compared with External Hearing (EH) mode.
- 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.
- Once the implanted battery is no longer functional, Invisible Hearing (IH) mode will no longer be available. The device will continue to function like a standard cochlear implant with the external Sound Processor in External Hearing (EH) mode.

The characteristics of the Investigational TICI System which could impact safety of the device have been assessed and reported in the Investigational TICI System Hazards Analysis Report (26) and fully described within the Investigator Brochure (2).

6.3 Risks associated with participation in the clinical investigation

Anticipated device, and or procedure related effects associated with TI1012 investigational device compared with a similar device, such as the CI512, are summarised in the TICI Clinical Evaluation Report (27) and the Investigator Brochure (2) and relate to potential:

1. Increased risk of harm resulting from a longer duration of anaesthesia required to achieve fixation of the receiver/stimulator and implanted microphone,
2. Increased risk of harm resulting from a larger incision required to achieve fixation of the receiver/stimulator and implanted microphone,
3. Increased risk of harm resulting from increased volume of drilling required to achieve fixation of the receiver/stimulator and implanted microphone.
4. Increased risk of harm resulting from increased tenting of the periosteum and scalp as a consequence of the larger receiver/stimulator and implanted microphone.
5. Risk of harm resulting from an implanted rechargeable Lithium Ion battery.

Possible interactions with concomitant medications are not anticipated in this clinical investigation. All residual risks for the TI1012 investigational device are summarised in the TICI Investigational System Risk Management Summary Report (28) and are described within the Participant Informed Consent (PIC).

6.4 Risk mitigation

The following will be performed during the clinical investigation as mitigations to the risks identified above:

1. All surgeons will receive surgical training in the use and handling of the TI1012 cochlear implant as part of study initiation. In addition, Cochlear surgical support may be present during surgeries performed by the investigational site(s).
2. All adverse events and advice device effects will be reported out to two years post-activation for all subjects.
3. Surgical and post-operative complications will be assessed with the Patient and Observer Scar Assessment Scale (POSAS) to six months post-implantation for all subjects.
4. Active post-investigation clinical follow up will occur on an annual basis from two to 10 years post-activation.

6.5 Risk-to-benefit rationale

The risk benefit assessment for the Investigational TICI System (TI1012 cochlear implant, TC1001 charger and CDI Tool) is presented in the TICI System Clinical Evaluation Report (27).

The TICI System Clinical Evaluation Report concludes that the clinical safety (risks) and performance benefit of devices relevant to anticipated performance of the TI1012 have been evaluated, and the data demonstrate that these devices are safe and effective. The Cochlear-Sponsored clinical studies, and systematic literature review, coupled with the

design verification/validation and post-market surveillance data, establish that the risk benefit ratio for the TI1012 is favourable.

7 OBJECTIVES AND HYPOTHESES

7.1 Objectives

7.1.1 Primary Objective

The TI1012 cochlear implant is a feasible treatment for restoring hearing (speech recognition) in adult patients with sensorineural hearing loss.

7.1.2 Safety Objective

The treatment of adult patients with the TI1012 cochlear implant is feasibly safe in an adult population.

7.1.3 Secondary Objectives

The TI1012 cochlear implant is a feasible treatment for restoring hearing (patient reported outcomes) in adult patients with sensorineural hearing loss.

7.2 Hypotheses

The primary hypotheses, to be accepted or rejected by statistical data from the clinical investigation include:

7.2.1 Quiet

7.2.1.1 External Hearing

H_0: The clinical benefit obtained (postoperatively at six months post-activation) in the ear implanted with the TI1012 cochlear implant with an external Sound Processor (EH mode) does not show superiority to the monosyllabic word in quiet benefit preoperatively in the unilateral aided listening condition.

H_a: The clinical benefit obtained (postoperatively at six months post-activation) in the ear implanted with the TI1012 cochlear implant with an external Sound Processor (EH mode) is superior to the monosyllabic word in quiet benefit preoperatively in the unilateral aided listening condition.

The change (average of two monosyllabic word lists at six months post-activation minus the average of two monosyllabic word lists at preoperative baseline) will be analysed.

$$P = \left(\frac{\text{6 month post-activation score}}{\text{total number of words}} \times 100\right) - \left(\frac{\text{preoperative score}}{\text{total number of words}} \times 100\right)$$

Where P = the average change in % correct monosyllabic word score, the null and alternative hypotheses for the test of superiority are as follows:

H_0: P ≤ 0
H_a: P > 0

If parametric assumptions are not violated, a paired t-test will be performed. If parametric assumptions are violated, a non-parametric Wilcoxon Rank sum analysis will be performed.

7.2.1.2 Invisible Hearing

H_0: The clinical benefit obtained (postoperatively at six months post-activation) in the ear implanted with the TI1012 cochlear implant without an external Sound Processor (IH mode) does not show non-inferiority to the monosyllabic word in quiet benefit preoperatively in the unilateral aided listening condition.

H_a: The clinical benefit obtained (postoperatively at six months post-activation) in the ear implanted with the TI1012 cochlear implant without an external Sound Processor (IH mode) is non-inferior to the monosyllabic word in quiet benefit preoperatively in the unilateral aided listening condition.

The value of 10% is selected as the non-inferiority margin as one that can be tested with reasonable power and is clinically meaningful in that differences in % words correct less than this value are not considered relevant and are considered within in the bounds of test/re-test variability. The change (average of two monosyllabic word lists at six months post-activation minus the average of two monosyllabic word lists at preoperative baseline) will be analysed.

$$P = \left(\frac{\text{6 month post-activation score}}{\text{total number of words}} \times 100\right) - \left(\frac{\text{preoperative score}}{\text{total number of words}} \times 100\right)$$

Where P = the average change in % correct monosyllabic word score, the null and alternative hypotheses for the test of non-inferiority are as follows:

H_0: P ≤ 10%
H_a: P > 10%

If parametric assumptions are not violated, a paired t-test will be performed. If parametric assumptions are violated, a non-parametric Wilcoxon Rank sum analysis will be performed.

If for a given endpoint, the test for non-inferiority leads to rejection of the null hypothesis, a test for a superiority null hypothesis will be employed (29, 30). There is no issue with regards to multiplicity as this process corresponds to a closed hierarchical test procedure and the pre-specification of the margin prevents bias.

H_0: The clinical benefit obtained (postoperatively at six months post-activation) in the ear implanted with the TI1012 cochlear implant without an external Sound Processor (IH mode)

does not show superiority to the monosyllabic word in quiet benefit preoperatively in the unilateral aided listening condition.

H_a: The clinical benefit obtained (postoperatively at six months post-activation) in the ear implanted with the TI1012 cochlear implant without an external Sound Processor (IH mode) is superior to the monosyllabic word in quiet benefit preoperatively in the unilateral aided listening condition.

The change (average of two monosyllabic word lists at six months post-activation minus the average of two monosyllabic word lists at preoperative baseline) will be analysed.

$$P = \left(\frac{\text{6 month post-activation score}}{\text{total number of words}}\right) \times 100 - \left(\frac{\text{preoperative score}}{\text{total number of words}}\right) \times 100$$

Where P = the average change in % correct monosyllabic word score, the null and alternative hypotheses for the test of superiority are as follows:

H_0: $P \leq 0$
H_a: $P > 0$

If parametric assumptions are not violated, a paired t-test will be performed. If parametric assumptions are violated, a non-parametric Wilcoxon Rank sum analysis will be performed.

7.2.2 Noise

7.2.2.1 External Hearing

H_0: The clinical benefit obtained (postoperatively at six months post-activation) in the ear implanted with the TI1012 cochlear implant with an external Sound Processor (EH mode) does not show superiority to the open-set sentence in noise (S0N0 speaker orientation) benefit preoperatively in the unilateral aided listening condition.

H_a: The clinical benefit obtained (postoperatively at six months post-activation) in the ear implanted with the TI1012 cochlear implant with an external Sound Processor (EH mode) is superior to the open-set sentence in noise (S0N0 speaker orientation) benefit preoperatively in the unilateral aided listening condition.

A single open-set sentence list at preoperative baseline versus a single open-set sentence list at six months post-activation will be analysed.

The change (single open-set sentence score list at six months post-activation minus the single open-set sentence list score at preoperative baseline) will be analysed.

$$P = \left(\frac{\text{6 month post-activation score}}{\text{total number of words in sentence}}\right) \times 100 - \left(\frac{\text{preoperative score}}{\text{total number of words in sentence}}\right) \times 100$$

Where P = the average change in % words correct in a sentence score, the null and alternative hypotheses for the test of superiority are as follows:

H_0: P ≤ 0
H_a: P > 0

If parametric assumptions are not violated, a paired t-test will be performed. If parametric assumptions are violated, a non-parametric Wilcoxon Rank sum analysis will be performed.

7.2.2.2 Invisible Hearing

H_0: The clinical benefit obtained (postoperatively at six months post-activation) in the ear implanted with the TI1012 cochlear implant without an external Sound Processor (IH mode) does not show non-inferiority to the open-set sentence in noise (S0N0 speaker orientation) benefit preoperatively in the unilateral aided listening condition.

H_a: The clinical benefit obtained (postoperatively at six months post-activation) in the ear implanted with the TI1012 cochlear implant without an external Sound Processor (IH mode) is non-inferior to the open-set sentence in noise (S0N0 speaker orientation) benefit preoperatively in the unilateral aided listening condition.

The value of 10% is selected as the non-inferiority margin as one that can be tested with reasonable power and is clinically meaningful in that differences in % words in a sentence correct less than this value are not considered relevant and are considered within in the bounds of test/re-test variability.

The change (single open-set sentence score list at six months post-activation minus the single open-set sentence list score at preoperative baseline) will be analysed.

$$P = \left(\frac{\text{6 month post-activation score}}{\text{total number of words in sentence}}\right) \times 100 - \left(\frac{\text{preoperative score}}{\text{total number of words in sentence}}\right) \times 100$$

Where P = the average change in % words correct in a sentence score, the null and alternative hypotheses for the test of non-inferiority are as follows:

H_0: P ≤ 10%
H_a: P > 10%

If parametric assumptions are not violated, a paired t-test will be performed. If parametric assumptions are violated, a non-parametric Wilcoxon Rank sum analysis will be performed.

If for a given endpoint, the test for non-inferiority leads to rejection of the null hypothesis, a test for a superiority null hypothesis will be employed (29, 30). There is no issue with regards to multiplicity as this process corresponds to a closed hierarchical test procedure and the pre-specification of the margin prevents bias.

H_0: The clinical benefit obtained (postoperatively at six months post-activation) in the ear implanted with the TI1012 cochlear implant without an external Sound Processor (IH mode) does not show superiority to the open-set sentence in noise (S0N0 speaker orientation) benefit preoperatively in the unilateral aided listening condition.

H_a: The clinical benefit obtained (postoperatively at six months post-activation) in the ear implanted with the TI1012 cochlear implant without an external Sound Processor (IH mode) is superior to the open-set sentence in noise (S0N0 speaker orientation) benefit preoperatively in the unilateral aided listening condition.

The change (single open-set sentence score list at six months post-activation minus the single open-set sentence list score at preoperative baseline) will be analysed.

$$P = \left(\frac{\text{6 month post-activation score}}{\text{total number of words in sentence}}\right) \times 100 - \left(\frac{\text{preoperative score}}{\text{total number of words in sentence}}\right) \times 100$$

Where P = the average change in % words correct in a sentence score, the null and alternative hypotheses for the test of superiority are as follows:

H_0: $P \geq 0$
H_a: $P < 0$

If parametric assumptions are not violated, a paired t-test will be performed. If parametric assumptions are violated, a non-parametric Wilcoxon Rank sum analysis will be performed.

Study success is predicated on the successful rejection of all primary null hypotheses using a closed set hierarchal test procedure as described in the Feasibility of the Cochlear Nucleus TI1012 cochlear implant in a Newly Implanted Adult Population Statistical Analysis Plan (31).

7.3 Claims and Intended Performance

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

1. The medical/surgical and device–related adverse event profile of the TICI implant will be compared to the medical/surgical and device-related adverse event profile in current labelling (type, frequency & seriousness) at six months post-activation.
2. Hearing performance with the TICI implant (External Hearing mode) in this study population at six months post-activation is no worse than performance with the participant's own hearing aid preoperatively.
3. Hearing performance with the TICI implant (Invisible Hearing mode) in this study population at six months post-activation is no worse than the hearing performance with the participant's own hearing aid preoperatively.

4. Patient reported levels of tinnitus (THI) at six months post-activation with the TICI implant is no worse than the levels of tinnitus with the participant's own hearing aid preoperatively.

7.4 Risks and anticipated adverse device effects to be assessed

The risks and anticipated adverse device effects as identified in Sections 6.2 and 6.3will be assessed in the clinical investigation through reporting of all adverse events out to two years post-activation and the Patient and Observer Scar Assessment Scale (POSAS) (32) at six months post-activation.

Safety data adjudication will be conducted by the Sponsor's Chief Medical Officer as well as an independent Data Safety Monitoring Committee (DSMC), in accordance with the Cochlear Limited Standard Operating Procedures.

8 DESIGN OF THE CLINICAL INVESTIGATION

8.1 General

The current clinical investigation will be conducted as a prospective design with a single treatment arm to evaluate the feasibility of the Cochlear Nucleus® TI1012 cochlear implant in eleven adult subjects who meet the eligibility criteria of the clinical investigation. The procedures for the clinical investigation of the TI1012 cochlear implant are described within the Procedures document (33).

The clinical investigation will use repeated measures within subject comparison, with comparison before and after cochlear implantation for a period of two years post-activation. After the completion of the clinical investigation at two years post-activation, the TI1012 cochlear implant recipients will be clinically managed by the Cochlear Care Centre and RVEEH as per the centres standard procedures for routine clinical follow up. During these routine visits, safety data will continue to be collected and reported on an annual basis only by Cochlear Limited out to ten years post-activation.

A single-subject repeated-measures analysis will be employed whereby subjects will act as their own control. A single-subject research design is appropriate since it accommodates the heterogeneity that characterizes hearing-impaired populations. Comparison between the subjects before and after cochlear implantation will be performed.

The clinical investigation will also quantify the change in patient reported tinnitus as measured by the Tinnitus Handicap Inventory (THI) and the Pittsburgh Sleep Quality Index (PSQI) at six months post-activation from the preoperative baseline, and between six months to seven months post-activation, where access to IH mode will be disabled for a period of one month (Figure 2).

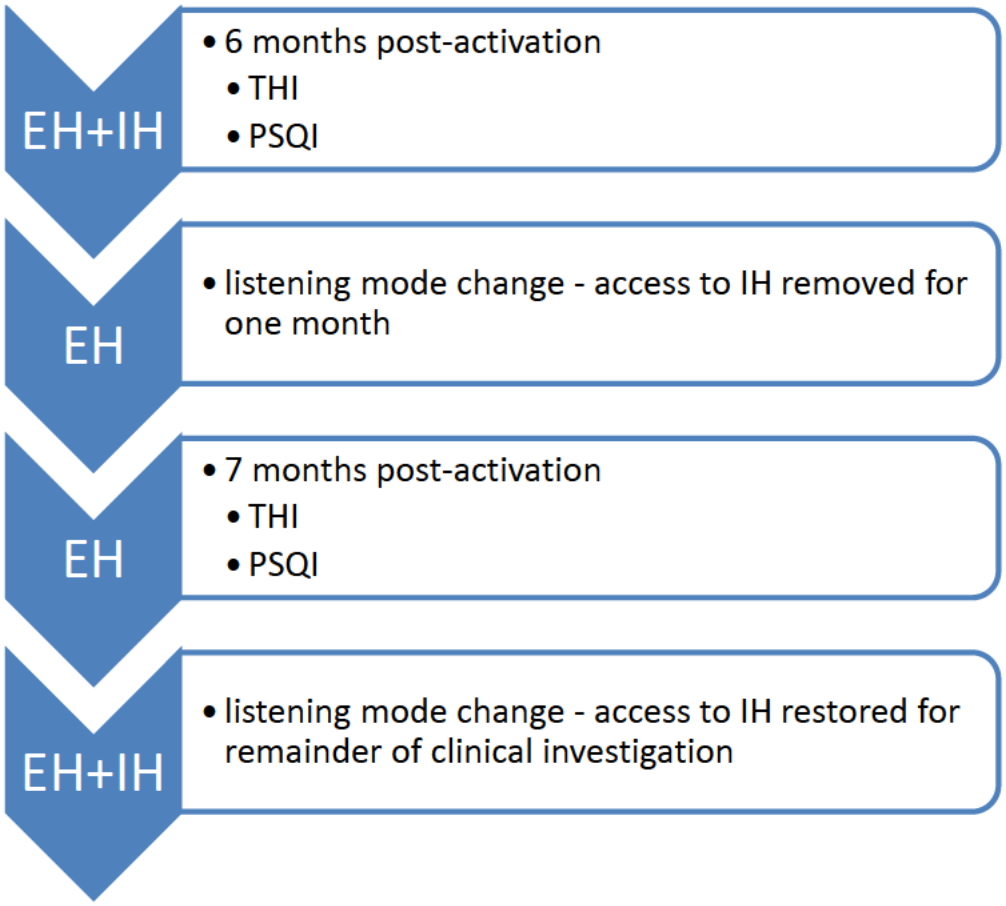

Figure 2. Listening mode changes at 6-7 months post-activation

Where: EH – External Hearing, IH – Invisible Hearing, THI – Tinnitus Handicap Inventory and PSQI - Pittsburgh Sleep Quality Index

Blinding procedures are not appropriate for this trial design, as it is not possible to conceal the presence, or absence, of Invisible Hearing from participants and/or clinical investigators. However, a single blinded analysis of the Patient Reported Outcome Measures (SSQ12, PSQI and THI) will be performed.

A superiority investigational design is employed in the proposed clinical investigation to demonstrate:

1. Hearing performance for monosyllabic words in quiet with the TI1012 cochlear implant using the externally worn Sound Processor (EH mode) at six months post-activation is superior to performance preoperatively in the unilateral aided listening condition.
2. Hearing performance for open-set sentences in noise (S0N0 speaker orientation) with the TI1012 cochlear implant using the externally worn Sound Processor (EH mode) at

six months post-activation is superior to performance preoperatively in the unilateral aided listening condition.

A non-inferiority investigational design is employed in the proposed clinical investigation to demonstrate:

1. Hearing performance for monosyllabic words in quiet with the TI1012 cochlear implant without using the externally worn Sound Processor (IH mode) at six months post-activation is non-inferior to performance preoperatively in the unilateral aided listening condition.
2. Hearing performance for open-set sentences in noise (S0N0 speaker orientation) with the TI1012 cochlear implant without using the externally worn Sound Processor (IH mode) at six months post- activation is non-inferior to performance preoperatively in the unilateral aided listening condition.

Eleven (11) adult candidates for cochlear implantation who are capable of completing the evaluations described within this clinical investigation plan will be invited to participate. The minimum number of subjects required to provide adequate power for the primary efficacy endpoints is six subjects. The total of number of subjects to be enrolled into the clinical investigation (n=11) will enable generalisation of outcomes, both performance and safety with the TI1012 cochlear implant to a wider adult clinical population.

8.2 Endpoints

8.2.1 Co-primary endpoints

The Co-primary endpoints for the clinical investigation are:

1. Mean speech perception performance for an open-set CNC monosyllabic word recognition measure with the external Sound Processor (EH mode) in the unilateral listening condition at six months post-activation.

2. Mean speech perception performance for AuSTIN sentence in noise (S0N0 speaker orientation) recognition measure with the external Sound Processor (EH mode) in the unilateral listening condition at six months post-activation.

3. Mean speech perception performance for an open-set CNC monosyllabic word recognition measure without the external Sound Processor (IH mode) in the unilateral listening condition at six months post-activation of TI1012 implant.

4. Mean speech perception performance for AuSTIN sentence in noise (S0N0 speaker orientation) recognition measure without the external Sound Processor (IH mode) in the unilateral listening condition at six months post-activation of TI1012 implant.

8.2.2 Surgical endpoint

Medical/surgical and device related adverse events at six months post-activation of the TI1012 cochlear implant.

8.2.3 Secondary endpoints

The secondary endpoints for the clinical investigation are:

1. Mean Patient Satisfaction Survey (PSS) at six months post-activation of the TI1012 implant.
2. Tinnitus Handicap Inventory (THI) score at six months post-activation of the TI1012 implant.
3. Mean global Health Utility Index mark 2/3 (HUI2/3) score at six months post-activation of the TI1012 implant.

Both preoperative and postoperative patient reported outcomes will be assessed in the best aided listening condition. Post-operative patient reported outcomes will be assessed prior to any programming changes for hearing mode (Figure 2).

8.3 Additional analyses

8.3.1 Surgery

8.3.1.1 Surgical questionnaire

The course of each surgery will be recorded on a TI1012 surgical questionnaire.

8.3.1.2 Imaging

Intraoperative procedures will be recorded via a video camera connected to the surgeon's microscope and a video camera mounted on a tripod. An X-ray will be obtained (preferably a lateral or modified Stenver's view) to confirm proper electrode placement. A post-operative Cone Beam CT scan will be obtained to confirm scala location of the electrode within the cochlea.

8.3.1.3 Device Characteristics

Intraoperative impedance measurements and audio recordings from the implanted microphone are made at the time of surgery as described in the Clinician's Guide – CDI Tool (34) and the Procedures document (33).

8.3.1.4 Diagnostic testing

Diagnostic tests of device integrity using the Microphone Fluid Ingress Test will be made at the time of surgery and post-operatively as described in the Clinician's Guide – CDI Tool (34) and the Procedures document (33). This data will be retrieved from the TI1012 device and exported in anonymized data logs (.xml files).

8.3.2 Audiometric assessment

Unaided audiometric thresholds obtained for each ear, using the standard audiometric technique for pure-tone air and bone conduction testing preoperatively to establish candidacy for cochlear implantation and participation in the clinical investigation. Unaided pure-tone audiograms for each candidate will be reviewed by the Sponsor prior to enrollment. Written confirmation of eligibility will be provided by the Sponsor to the Investigational Site.

Unaided audiometric thresholds will be obtained for the implanted ear only -post-operatively for pure-tone air conduction testing in the implanted ear to assess the impact of cochlear implantation on levels of residual hearing. Aided thresholds will be obtained in the ear to be implanted preoperatively and the implanted ear at each post-operative visit if cochlear implant psychophysics levels (T- and C-levels) change as described in the Investigation Schedule Section 3. The contra-lateral ear will be plugged or masked during threshold measurement.

8.3.3 Post-operative Healing

The Patient and Observer Scar Assessment Scale (POSAS) (32) will be used as a subjective tool to evaluate vascularity, pigmentation, thickness, relief, pliability and surface area of linear scars by medical observers. Subjects will use the POSAS to subjectively evaluate pain, itching, colour, stiffness, thickness and relief post-operatively.

8.3.4 Speech perception in noise (S_0N_{CI} speaker orientation)

Speech perception in noise in the signal in front and noise at ear to be implanted/implanted ear side (S_0N_{CI}) speaker orientation will be assessed as the 'worst case' test condition for speech in noise. No formal hypotheses are associated with this speech perception in noise test condition. All data will be presented as descriptive statistics. If the participant does not have a hearing aid for the ear to be implanted preoperatively (e.g. dead ear or limited/no access to the aided speech spectrum), a loaner hearing aid will be fitted to complete aided assessment per protocol.

8.3.5 Speech perception performance intensity function

The performance intensity function for monosyllabic words in quiet will be assessed at multiple input levels in the unilateral listening condition for both External and Invisible Hearing modes at nine months post-activation. Testing will be undertaken over two sessions within the visit window.

8.3.6 Categorical loudness scaling task

A categorical loudness scaling task will be undertaken at multiple input levels and stimuli. Subjective assessment of loudness will be made using a standardized 11-point loudness rating scale for External and Invisible Hearing modes at nine months post-activation. Testing will be undertaken over two sessions within the visit window.

8.3.7 Patient Reported Outcome measures

8.3.7.1 Speech, Spatial and Qualities of Hearing scale (SSQ12)

The short form of the Speech, Spatial and Qualities of Hearing scale (SSQ12) (35) comprises 12 questions which cover aspects of speech perception, spatial hearing, and more general qualities of hearing, such as listening effort to directly measure the benefits offered by a hearing intervention - in this case cochlear implantation – compared to performance before the intervention was applied (aided pre-operative condition).

8.3.7.2 Tinnitus Handicap Inventory (THI)

The Tinnitus Handicap Inventory (THI) is a 25 question measure which identifies difficulties the patient may be experiencing because of their tinnitus (36). The THI allows patients to be classified into four levels of severity of handicap caused by tinnitus based on their total THI score. This enables treatment-related changes to be quantified by tracking movement of patients from one tinnitus category to another as a result of the intervention.

8.3.7.3 Health Utilities Index (HUI®)

The Health Utilities Index (HUI®) is a generic health profile and preference-based system for the purposes of measuring health status, reporting health-related quality of life, and producing utility scores. Health Utilities Index mark 2/3 is a 15-item questionnaire for self-administered, self-assessed, one-week health status assessment. HUI2/3 provides comprehensive, reliable, responsive and valid measures of health status and HRQL for subjects in clinical studies (37-39). HUI is currently defined as including both HUI2 and HUI3 systems. Therefore, current HUI questionnaires cover both systems. The HUI has been used to access health status, reporting health-related quality of life, and producing utility scores in previous clinical investigations for cochlear implantation (40-44) and hearing impairment (45, 46).

8.3.7.4 Patient satisfaction survey

An internally-developed patient satisfaction survey comprised of 24 questions has been designed to measure self-reported satisfaction with the TI1012 cochlear implant in areas related to the emotional benefits of independence, simplicity and always being able to hear. The patient satisfaction survey will be administered preoperatively and postoperatively to assess the change in self-reported satisfaction with the TI1012 cochlear implant.

8.3.7.5 Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) is 19 item self-rated question generic measure to assess the quality and patterns of sleep in adults (47). It differentiates “poor” from “good” sleep quality across seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. The PSQI provides a global score with lower scores correlating to better sleep quality.

8.3.8 Usability

8.3.8.1 Patient Usability Checklist

A patient usability checklist will be used as part of the clinicians counselling/training process for each participant to gain objective data on the participants’ interaction with the user interface of the system. The participant will be asked to perform a set of known (and expected) tasks with the system whilst the clinician observes and takes note of their ability to complete each task and whether or not it was performed with or without difficulty or support.

8.3.8.2 Patient Usability Questionnaire

A patient usability questionnaire shall be provided to the participants to gain subjective feedback on their interaction with the user interface of the system. The questionnaire will

comprise a combination of open ended questions and rating questions related to more specific features of the user interface. The questionnaire seeks to understand the strengths and potential weaknesses of the user interface of the implant and to gain an insight into the participants' ability, perceptions and opinions.

8.3.8.3 Patient Interview

A face to face interview will be conducted to explore and gain further insights into the participants' experience and established daily routines with the system (identify and understand behaviour patterns, challenges and preferences). An interview guide is provided for this purpose.

8.3.9 Device characteristics

8.3.9.1 Device use in different hearing modes

The use of Invisible Hearing (IH) compared to External Hearing (EH) modes and duration of time with the TI1012 implant off will be examined through the collection of anonymized data logs (.xml files) retrieved from the TI1012 device.

8.3.9.2 Programming parameters

Device characteristics such as impedance measurements, programming map parameters, and psychophysical threshold and comfort levels will be exported from the personal computer (PC) into an anonymous .csv data file.

8.3.9.3 Audio recordings

Audio recordings from the implanted microphone will be obtained intraoperatively, at activation and at post-activation appointments as required to assess the function of the TI1012 implanted microphone. The microphone recording data will be anonymously exported from the TI1012 cochlear implant as a .wav audio file.

8.4 Equipment

Speech perception performance in quiet will be assessed using a loudspeaker configuration with the signal from the front (S_0) with the contra-lateral ear plugged. Speech perception performance in competing background noise for sentences will be assessed using a loud speaker configuration with signal and noise from the front (S_0N_0) and with signal from the front and noise from the implanted side (S_0N_{CI}) with the contra-lateral ear plugged. The procedures for the clinical investigation are fully described within the Feasibility of the Cochlear Nucleus TI1012 cochlear implant in a Newly Implanted Adult Population Procedures document (33).

8.5 Investigational device and comparator

Participants will be implanted with the investigational device, the Nucleus TI1012 cochlear implant. Both External Hearing (EH) and Invisible Hearing IH) will be activated at approximately two weeks post-operatively. Activation of the 22 intracochlear electrodes will

occur in a manner comparable to conventional cochlear implants with CDI Tool clinical programming software. The Nucleus CP910 Sound Processor (modified with firmware to enable communication with the TI1012 implant) will be programmed in a manner comparable to conventional cochlear implants with CDI Tool clinical programming software. Maps are typically re-evaluated at intervals after activation for fine tuning and to take into account acclimatization of the recipient to electrical stimulation. Software on the Sound Processor and TI1012 implant may be upgraded as it becomes available. In this eventuality, the Investigator Brochure will be updated and training of investigators documented.

The comparator device to support the primary and secondary performance endpoints is the participant's own hearing aid in the unilateral preoperative listening condition. There is no proposed concurrent medical device or medication in the clinical investigation.

8.6 Subjects

8.6.1 Inclusion Criteria

1. A bilateral moderately severe to profound post-linguistic sensorineural hearing impairment with ≤ 15 dB difference between masked air conduction and bone conduction hearing thresholds (i.e. air-bone gap) at a given frequency, and obtain limited benefit from appropriately fit binaural hearing aids.
2. Fluent speaker in the local language used to assess clinical performance as judged by the investigator
3. Eighteen years of age or older at the time of enrolment with no upper age limit.
4. A 30 day trial and/or experience with appropriately fit hearing aids.

8.6.2 Exclusion Criteria

1. Deafness due to lesions of the acoustic nerve or central auditory pathway.
2. Active middle-ear infections.
3. Tympanic membrane perforation.
4. 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.
5. Evidence of severe-to-profound hearing loss prior to 5 years of age.
6. Pre-existing cochlear or bone conduction implant.
7. Medical or psychological conditions that contraindicate general anaesthesia or surgery.
8. Additional disabilities that may affect the subject's participation or safety during the clinical investigation.

9. 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 as determined by the Investigator.
10. Unwillingness or inability of the candidate to comply with all investigational requirements as determined by the Investigator.
11. Existing CSF shunts or drains, existing perilymph fistula, skull fracture or CSF leaks
12. Recurrent episodes of bacterial meningitis.
13. Pre-existing skin condition that could jeopardize wound healing as judged by the investigator e.g. psoriasis, dermatitis, use of corticosteroids, uncontrolled diabetes.
14. Pre-existing medical condition that requires serial MRI scan.
15. Pre-existing medical condition of peripheral neuropathy.

8.6.3 Hearing Aid Trial

A 30-day trial of appropriately fitted hearing aids, or prior history of hearing aid use in the ear to be implanted is an eligibility requirement for the clinical investigation. In the event that the ear to be implanted does not have measureable unaided thresholds at the limits of the audiometer (e.g. dead ear), there is no requirement to undertake a 30-day hearing aid trial.

If aided hearing in the ear to be implanted is not functional as determined by the clinician (e.g. limited or no access to the aided speech spectrum), there is no requirement to undertake a 30-day hearing aid trial.

If the participant does not have a hearing aid for the ear to be implanted (e.g. dead ear or limited/no access to the aided speech spectrum) a loaner hearing aid will be fitted to complete aided assessment per protocol.

8.6.4 Number of subjects required

The proposed study is designed to collect feasibility data associated with the performance and safety of the TI1012 cochlear implantation in an adult population who meet current selection criteria for cochlear implantation at the investigational site. The protocol describes a feasibility study at a single site and eleven adult subjects. The expected duration per subject is 26 months. Subject enrolment is estimated to take twelve months post site enrolment. The enrolment period may be extended if required. The total duration for the clinical investigation is expected to be 38 months.

Other than meeting the inclusion criteria above, subjects will be recruited into the study sequentially with no pre-selection based on age (other than being an adult, 18 years of age or older), ethnicity or gender.

Prior to recruitment of any subjects into the study, written approval of the investigational plan including informed consent form will be obtained from the TGA and the reviewing Royal Victorian Eye and Ear Hospital Human Research Ethics Committee (RVEEH HREC).

8.6.5 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:

- Adverse Event (AE) necessitating discontinuation from the study
- The subject is lost to follow-up
- Voluntary decision to withdraw consent made by the subject[8]
- Investigator decision[9]
- Device failure (non-stimulable in External Hearing (EH) mode (using the Sound Processor))[10]
- 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 initial implantation surgery, an alternative device (e.g., CI512, CI532 or CI522) may be implanted in subjects where there are substantial difficulties with implantation of the TI1012 device. These subjects will continue to receive standard clinical care at the implanting centre and will not be required to complete post-operative assessments and will be withdrawn from the clinical investigation and not entitled to ongoing support from the Sponsor.

In the event that the TI1012 cochlear implant is non-stimulable in External Hearing (EH) mode (using the Sound Processor) within ten (10) years of implantation, the device may be explanted at the discretion of the subject in consultation with their surgeon, and an alternative device (e.g., CI512, CI532 and CI522) may be implanted. If explantation occurs during the clinical investigation period (up to two year post-activation), these subjects will continue to receive standard clinical care at the implanting centre and will not be required to complete further post-operative assessments and will be withdrawn from the clinical investigation and not entitled to ongoing support from the Sponsor.

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

[9] Participant withdrawal from the study is defined as an Investigator decision. The Investigator may elect to withdraw a participant 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 participant lost to follow-up.

[10] Loss of Invisible Hearing is not considered to be a device failure for the purposes of this clinical investigation.

8.6.6 Subject replacement

The total number of subjects proposed for this feasibility clinical investigation is eleven adults. If a subject withdraws or is discontinued pre-operatively, they will be replaced by a newly recruited subject who meets the selection criteria for participation. If a subject withdraws post-operatively, there will be no replacement. Post-operative subjects who do not meet the eligibility criteria will continue as an Intention-To-Treat population (ITT).

8.6.7 Point of enrolment

Subjects are recruited to the study by the investigators usually during the course of medical consultation. The Sponsor will review the pre-operative audiogram of all candidates prior to enrollment into the clinical investigation. Written confirmation of eligibility will be provided by the Sponsor to the Investigational Site.

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

8.6.8 Total expected duration of the clinical investigation

It is expected that subject participation will involve a 26 month commitment, allowing for candidacy assessments, preoperative baseline evaluations, and implantation of the device, post-surgical medical review, activation and post-operative testing. There is a +/-3 day visit window for the post-surgical medical review, a +/-7 day visit window for activation and post-activation visits till three months post-activation, a +30 day window for the six month post-activation visit, a +/- 15 day window for the seven month post-activation visit, and +/- 30 day visit window for the 9[11], 12, 18 and 24 months post-activation visits. Unplanned visits may be scheduled as deemed clinically necessary where the participant may undergo additional assessment to quantify the issue and assess mitigation efficacy. Data collected during the clinical investigation will lead to changes to clinical programming recommendations which will be documented in the updated Procedures document (33). Unplanned visits may be scheduled to optimise programing of the TI1012 cochlear implant for participants in 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.

[11] Visit can be split over multiple days within visit window.

8.6.9 Completed subject assessment

Each subject in the study will be considered completed when all assessments through two years post-activation have been performed in accordance with the study protocol. To be considered a primary endpoint success, subjects must retain their originally implanted device until six months post-activation in accordance with the study protocol. Participants will be followed up on an annual basis during routine clinical follow up appointments with the Cochlear Care Centre and RVEEH for continued collection and reporting of safety data out to ten years post-activation of their TI1012 cochlear implant.

8.7 Procedures

Procedures for the clinical investigation, including subject randomisation, are fully described within the Feasibility of the Cochlear Nucleus TI1012 cochlear implant in a Newly Implanted Adult Population Procedures document (33).

8.7.1 Medical and audiological care post-investigation

Routine medical and audiological care from the Royal Victorian Eye and Ear Hospital Cochlear Implant Clinic and Cochlear Limited will be provided for the subjects during, as well as after, the clinical investigation has been completed. Subjects will be followed-up as per the centre's standard clinical procedures. Ongoing support of study subjects implanted with the TI1012 implant will be provided by the Sponsor at no charge as follows:

1. If the whole and/or any parts of the Nucleus 6 CP910 Sound Processor, CR210 Remote or the TC1001 charger cease to function effectively within ten (10) years of implantation, the Sponsor will promptly repair or replace them as necessary.
2. Support with clinical trial programming software until clinical programming software for ten (10) years post-implantation.
3. If the TI1012 cochlear implant is non-stimulable in External Hearing (EH) mode (using the Sound Processor) within ten (10) years of implantation, the study subject can elect to be re-implanted with a commercially available Nucleus® cochlear implant (excluding a Totally Implantable cochlear implant).

As the clinical trial programming software is provided by Cochlear Limited, the TI1012 cochlear implant cannot be programmed by other cochlear implant clinics. This includes the Melbourne Cochlear Implant Clinic at The Royal Victorian Eye and Ear Hospital or Cochlear Care Centre. At the end of the ten year commitment period Cochlear may no longer provide programming support and recipients may need to consider removal of the TI1012 implant and replacement with a commercially available (non-research) device. Any decision to proceed with TI1012 implant replacement must be made in consultation with the Principal Investigator (surgical) Associate Professor Robert Briggs.

The anticipated lifetime of the implanted battery is estimated to be ten (10) years. When the battery expires, Invisible Hearing will no longer be available and the subjects can continue to use their TI1012 cochlear implant in External Hearing mode with the CP910 Sound

Processor. The anticipated lifetime of the implanted battery will be fully disclosed in the Patient Informed Consent (PIC) form.

8.8 Monitoring Plan

The monitoring plan for the clinical investigation are fully described within the Feasibility of the Cochlear Nucleus TI1012 cochlear implant in a Newly Implanted Adult Population Monitoring Plan (48).

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 TI1012 cochlear implant and completed per the protocol will be considered as the Per Protocol (PP) population for the primary endpoint efficacy evaluation.

A sample size of eleven (11) subjects provides > 95% power at the 0.025 α level if the observed mean and standard deviation for CNC monosyllabic words, AzBio sentences and CUNY sentences reported for the Nucleus 5 System and Tirkandi device is representative of the corresponding values for the clinical population under investigation. Study success is predicated on the successful rejection of the co-primary superiority null hypotheses with an external Sound Processor and the non-inferiority null hypotheses without an external Sound Processor using a closed hierarchal test procedure. Both an Intention-To-Treat (ITT) and a Per Protocol (PP) analysis will be performed and reported for the efficacy endpoints in order to support a conclusion of noninferiority as described in the Statistical Analysis Plan (31).

Additional analyses for which there is no formal hypothesis are for the secondary efficacy endpoints related to Patient Reported Outcomes (THI, PSQI and HUI2/3). The change in Patient Reported Outcomes six months post-activation of the TI1012 cochlear implant to preoperatively in the best aided condition will be analysed.

An interim statistical analysis will be performed at six months post-activation for the primary efficacy endpoints. Statistical considerations for the clinical investigation are fully described within the Feasibility of the Cochlear Nucleus TI1012 cochlear implant in a Newly Implanted Adult Population Statistical Analysis Plan (31).

10 DATA MANAGEMENT

Data collection is performed through electronic data capturing (EDC) on electronic Case Report Forms (eCRFs). All study data will be entered into an Electronic Database Capture (EDC) system. Site personnel will be trained on the completion of the eCRFs prior to obtaining their own Login/Password. Access to clinical study information will be based on an individual's role and responsibilities.

The application provides hierarchical user permission for data entry, viewing, and reporting options. For optimum security, all communications between the users and the EDC operate

on a secured socket layer (SSL) using 256-bit encryption. Sponsor's web servers are protected by a managed firewall from potential web and network attacks and the network is guarded by an intrusion detection and protection surveillance system against malicious threats. This application is designed to be in full compliance with International Conference on Harmonization and Good Clinical Practices (ICH-GCP).

The data quality assurance tool has been designed as an automatic feature of the EDC system. When a form is submitted the system conducts instantaneous validation and cross-form validation checks. A query is generated and sent to the site coordinator so that data may be verified and corrected. All changes made to a form are stored in an audit trail. 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 progress report has been approved by the agency, the data are maintained with the trial master file at the Sponsor's site. The data are stored for at least 2 years after shipment and delivery of the last device for investigational use and TGA have been notified of study closure.

In addition to the data collected on the eCRF, electronic data will also to be collected through the TI1012 Investigational System and exported via the clinical fitting software. The electronic file records shall be anonymized and unique alphanumeric code will identify the subject throughout the course of the study. For example, AUxx-1012-5679, where:

- AU = a two letter acronym to identify the country e.g. Australia,
- 01 = a sequential numeral corresponding the order in which a subject is enrolled into the study, in this case this would correspond to the first subject recruited into the study,
- 1012 = a unique, numeric device identification
- 5679 = a unique, numeric study identification.

10.1 Record Keeping and Retention

Data generated for the study shall be stored in a limited-access file area and be accessible only to representatives of the study site, the Sponsor and its representatives, and relevant health authorities/regulatory agencies. All reports and communications relating to study subjects will identify subjects only by subject unique identification code. Complete subject identification will be kept by the Investigator. This information will be treated with strict adherence to professional standards of confidentiality.

An Investigator must in reasonable time, upon request from any properly authorized officer or employee of relevant health authority or regulatory agency, permit such officer or employee to have access to requested records and reports, and copy and verify any records or reports made by the Investigator. Upon notification of a visit by the TGA, the Investigator will contact the Sponsor or its designee immediately. The Investigator will also grant Sponsor representatives the same privileges offered to relevant health authority or regulatory agents/officers/employees.

The Investigator must provide the Sponsor or its designee with the following documents at the time of site qualification and prior to study initiation and retain a copy in the site study file:

- Signed and dated curriculum vitae for the Principal Investigator.
- A copy of the original approval for conducting the study by the RVEEH HREC. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by EC policy and a copy of the approved and dated renewal provided to the Sponsor.
- A copy of the RVEEH HREC approved informed consent form along with any modifications initiated by the Sponsor over the course of the study.
- An Investigator Agreement for this protocol signed and dated by each Investigator.

In addition to the documents listed above, the study site will also retain the following items and make them available for Sponsor review upon request.

- Certifications, applicable study equipment (audiometers, etc.) calibration records and laboratory reference ranges for all local laboratories used for this study. The Sponsor will verify all equipment requirements at the study qualification and/or initiation. Sites with outdated and/or non-compliant equipment will either not be approved for study participation or will be advised to discontinue study-related activities should non-compliance be noted during regular study monitoring visits.
- All original informed consent forms with required signatures.
- All RVEEH HREC correspondence (i.e., informed consent [including any approved revisions], protocol, AEs, advertisements, newsletters).
- Copy of the Study Monitoring Log Sheet.
- Clinical and non-clinical supply shipment forms and device accountability logs.
- Copies of all correspondence pertaining to the study between Sponsor and the site.
- Copies of all AE reports submitted to the Sponsor.
- Copies of all TGA progress reports submitted to the site by the Sponsor.
- Site Delegation Signature Log.
- Financial Disclosure Statements.

All study-related records must be maintained for at least two years after a marketing application (PMA) is approved for the study device; or if the application is not approved, until at least two years after shipment and delivery of the last device for investigational use is discontinued and health authorities or regulatory agencies have been notified of study closure. The Sponsor will notify the principal Investigator when records are no longer needed. The Investigator will not discard any records without notifying the Sponsor. If the Principal Investigator moves from the current investigational site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the

records at the investigational site or the new address at which the records will be stored. The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

11 AMENDMENTS TO THE CIP

The Sponsor will document modifications to the protocol in the form of a written amendment. Protocol modifications that impact subject safety or the validity of the study must be approved by RVEEH HREC before implementation.

12 DEVIATIONS FROM THE CIP

A protocol deviation refers to a study-related activity that is not in compliance with the investigational protocol. Protocol deviations require prior written approval from the Sponsor prior to implementation. Deviations that are required to protect the life or well-being of a subject do not require prior approval from the Sponsor and should be implemented immediately. Such deviations shall be reported as soon as possible to the RVEEH HREC and Sponsor, but in no event later than 5 (five) calendar days from the emergency.

If a subject is unable to return for follow-up before the closure of a study visit window (+/- 3 day for post-operative review, +/- 7 day for the two week, one, 1.5, 2 and 2.5 and 3 month post-activation, + 30 day for the six month post-activation visit, +/-15 day for the seven month post-activation visit, and +/- 30 day for the nine, twelve, 18 and 24 month post-activation study visits), or if protocol defined assessments or parts thereof are omitted or completed incorrectly, the event is to be communicated to the Sponsor and noted on the Protocol Deviation Log provided to the Investigator in the Study Master File. Depending on the type or severity of the deviation the Investigator may be required to notify the RVEEH HREC and/or Sponsor if the deviation impacts safety or performance of the subject or data integrity.

13 DEVICE ACCOUNTABILITY

Investigational devices will be shipped to the investigational site with individual registrations cards indicating the study number. Investigational devices will be quarantined at the investigational site and clearly labelled as a 'Clinical Investigation Device'. Devices should be registered by the clinic according to usual practice. At the end of the clinical investigation, all unused investigational devices shall be returned to the Clinical Project Manager.

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

14 STATEMENTS OF COMPLIANCE

14.1 Declaration of Helsinki and compliance with standards

The clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2013), the ISO 14155:2011 Standard, and International Conference on Harmonization and Good Clinical Practices (ICH-GCP).

15 QUALITY CONTROL AND ASSURANCE

All clinical investigations Sponsored by Cochlear Limited are conducted according to internationally recognised ethical principles for the purpose of gaining clinical safety and effectiveness knowledge about medical devices according to the Cochlear Limited Standard Operating Procedures. Sponsor employees and/or their contracted representatives utilize Standard Operating Procedures (SOP) designed to ensure that clinical study procedures and documentation are consistently conducted and compliant to ISO 14155: 2011 Good Clinical Practise (GCP), and 2003/94/EC GMP Medicinal Products for Human and Veterinary Use Annex 11: Computerised Systems.

16 ETHICS COMMITTEE (EC)

Prior to the initiation of the study, the Protocol, the Participant Informed Consent (PIC) form, and other supporting documentation must be submitted to the Royal Victorian Eye and Ear Hospital Human Research Ethics Committee (RVEEH HREC) for approval. A copy of the RVEEH HREC approval letter for the Protocol, the PIC, and the Protocol Signature page must be submitted to the Sponsor prior to the consent of the first subject. The study site must maintain an accurate and complete record of all reports, documents, and other submissions made to the RVEEH HREC concerning this protocol.

A list of the RVEEH HREC members, their titles or occupations, and their institutional affiliation, and their contact information must be provided to the Sponsor or its designee prior to release of study supplies.

TGA relevant health authority regulations require that all advertisements for subject recruitment be approved by an RVEEH HREC prior to implementation. The complete text and format must be submitted to the Sponsor or its designee for approval prior to RVEEH HREC submission.

17 PARTICIPANT INFORMED CONSENT (PIC)

The investigator shall obtain written informed consent using an approved Participant 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 an original version of the PIC. Where required, a witness shall sign and personally date an original version of the PIC.

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, 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.

18 CONFIDENTIALITY

Subjects will be identified on CRFs or similar documents (for example, questionnaires) by a unique subject identification code AUxx-1012-5679.

Where: AUxx = subject number

1012 = cochlear implant device number

5679 = Study identification number

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 RVEEH HREC and or 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 the TGA; 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.

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

19.1 Definitions

All definitions are according to the EN ISO 14155:2011 standard and described in Section 25.1 of this document.

19.2 Reporting process for adverse events

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 provided in the study. The investigator shall attempt to assess the relationship between the investigational device and the adverse event.

19.2.1 Unanticipated Adverse Device Effects

Unanticipated Adverse Device Effects (UADEs) must be reported directly to the RVEEH HREC and the Sponsor, Cochlear Limited, within 10 working days of knowledge of the event, or as dictated by the specific EC policy, whichever is sooner. Information regarding the UADE will be recorded on the *Adverse Event CRF* provided in the study.

19.2.2 Adverse Event Follow-up

All AEs must be followed until resolution, or the condition stabilizes. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other health care professionals. Cochlear or its designee may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. AE follow up information will be recorded using the Adverse Event CR*F* provided in the study.

19.2.3 Sponsor's Responsibilities

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

19.2.3.1.1 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.

19.2.3.1.2 Reporting process

The investigator shall report all incidents without undue delay to the Sponsor and TGA 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 RVEEH HREC using the applicable report form as per national requirements.

19.3 Data Safety Monitoring Committee

An independent Data Safety Monitoring Committee (DSMC) will be established by the Sponsor prior to commencement of the clinical investigation. The composition and purpose of the DSMC will be described in detail in the DSMC Charter.

19.4 List of anticipated adverse events and anticipated adverse device effects

For this clinical investigation the listed items in Section 6 of this CIP and / or the Investigator Brochure (2) 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.

19.5 Device deficiency reporting requirements

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

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

Device deficiencies will be captured in the EDC System as described in Section 10. Export of all device deficiencies from the EDC System into JIRA will occur daily at a minimum.

20 VULNERABLE POPULATION

Not applicable for the current investigation.

21 SUSPENSION OR PREMATURE TERMINATION

The Sponsor discontinue 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 discontinue the clinical investigation, the Sponsor will continue Sponsorship for the subjects already implanted with the device being studied will continue to be supported, independent of any decision made about study continuation.

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

22 PUBLICATION POLICY

A description of this clinical trial will be available on an international clinical trials registry platform maintained by the World Health Organization (WHO) which meets the requirements of an International Clinical Trials Registry Platform (ICTRP).

The aggregate data resulting from this study will be the proprietary information of the Sponsor and may be made public after all data have been analyzed and the study results are available. None of the data resulting from this study will be allowed to be presented or published in any form, by the Investigator or any other person, without the prior written approval of the Sponsor. The responsibility for writing the publication lies with the Principal Investigator. The 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.

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24 CHANGE HISTORY

Version	Change	Author	Date
1.0	Introduction of document	[redacted]	30/8/2016

Version	Change	Author	Date
2.0	Updated correct reference for pre-clinical studies section of document. Added Tirkandi and TICI comparison table. Added 60 dB SPL test level and corrected text to reflect current labelling for inclusion criteria 1.b. Added GRIS number. Changed sponsor representative from M. Knight to MB. Brinson. Removed HUI3 measure.	[redacted]	21/9/2016
3.0	Corrected clinical investigation site location for Tirkandi from Sydney to Melbourne	[redacted]	2/12/2016
4.0	Addition of exclusion criteria in line with FDA feedback and device verification. Modification to exclusion criteria relating to existing CI. Specification of two sites in Synopsis. Update to start date in Synopsis. Addition of three extra visits for datalog collection and modification of visit windows. Change of clinical trial registration details. Change of sponsor contact details. Addition of Pittsburgh Sleep Quality Index. Addition of 30 day hearing aid trial inclusion criteria. Addition of peripheral neuropathy exclusion criteria. Specification of Independence for Data Monitoring Committee Specification of comparable performance to conventional CI when using externally-worn sound processor in section 5.1. Version 4.0 not submitted for HREC review	[redacted]	08/11/2017
5.0	Extension of clinical investigation to two years post-activation, update of anticipated adverse device effects and risks for participants, modification to subject ID, inclusion of usability tasks. Document baselined for PIP milestone 6. Version 5.0 not submitted for HREC review	[redacted]	02/05/2018

Version	Change	Author	Date
6.0	Updated to expand to n=11 adult participants. Updated to include restricted access to IH to access impact on post-operative tinnitus and sleep with the addition of a visit at 7 months post-activation. Included hypotheses and sample size estimation. Updated to include HUI3 and CT test measures. Updated to explicitly describe participant considerations after 10 year Cochlear Commitment period ends.	[redacted]	14/06/2018
7.0	Updated to remove unilateral candidates from inclusion criteria, CT exclusion criteria and addition of S0N0 test condition at baseline, 6 mths and 12 mths post-activation. Updated to include Health Utilities Index mark 2/3 - a 15 item questionnaire for self-administered, self-assessed, one-week health status assessment. Updated to include Subject ID. Clearer definitions of study duration (to 2 years post-activation) and post-investigation safety reporting as part of routine clinical follow up at CCC and RVEEH (up to 10 years post-activation) and corrected schedule to include intraoperative testing	[redacted]	24/09/2018
8.0	Changed Short Title from Bilby Study to TICI Study. Updated to include microphone fluid ingress testing intraoperatively and inclusion of speech perception performance index and categorical loudness scaling at nine months post-activation. Reduction of visit window for post-surgery medical review from +/- 7 day to +/- 3 day, seven month post-activation visit from +/- 30 day to +/- 15 day and addition of visit window to Investigation Schedule. Note: not submitted to RVEEH HREC	[redacted]	03/05/2019

Version	Change	Author	Date
9.0	Updated to correct footnote in the investigation schedule, specification of SNHL, exclusion of prior ear surgery in ear to be implanted. Sponsor review of unaided audiometric assessment preoperatively. Correction to expected duration of clinical investigation to reflect longer recruitment period. Specification of hearing aid trial and use of hearing aid in preoperative assessment. Alignment of minimum sample size (n=6) to Statistical Analysis Plan. Definition of ITT and PP analysis populations as described in the Statistical Analysis Plan.	[redacted]	18/06/2019
10.0	Removal of exclusion of prior ear surgery in ear to be implanted	[redacted]	24/06/2019

25 DEFINITIONS

25.1 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.

Term	Description
Incident	Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject, or USER or of other persons or to a serious deterioration in their state of health.
Serious adverse event (SAE)	A serious adverse event is any adverse event that: a) led to a death, b) led to a serious deterioration in the health of the subject that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to foetal distress, foetal death or a congenital abnormality or birth defect NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
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).

25.2 Acronyms

Term	Description
BNC	Body Noise Cancellation algorithm
CDI Tool	Cochlear Device Interface Tool
CI500	Nucleus Profile cochlear implant
CP910	Nucleus 6 Sound Processor with firmware to enable compatibility with the TI1012 cochlear implant
CR210	Nucleus 6 Remote
EH	External Hearing mode uses the externally worn CP910 Sound Processor microphone for audio input.
HUI2/3	Health Utilities Index mark 2/3 is a 15 item questionnaire for self-administered, self-assessed, one-week health status assessment provided under licence without a manual.

Term	Description
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.
IH	Invisible Hearing mode uses the subcutaneous microphone attached to the TI1012 cochlear implant for audio input.
ITT	All subjects who are recruited to the clinical investigation will constitute the Intention-To-Treat (ITT) population for the purposes of safety evaluation
PIC	Participant Informed Consent form
PIL	Principal Investigator List
PP	Subjects implanted with the TI1012 cochlear implant and completed per the protocol will be considered as the Per Protocol (PP) population for the efficacy evaluation
pps	Pulses per second
PSQI	Pittsburgh Sleep Quality Index
RVEEH	Royal Victorian Eye and Ear Hospital
S_0	Speaker orientation where signal is presented from directly in front of the subject.
S_0N_0	Speaker orientation where signal and noise presented from directly in front of the subject.
S_0N_{CI}	Speaker orientation where signal is presented from directly in front of the subject and noise presented to the ear to be/implanted ear.
SSQ12	Speech, Spatial and Qualities of Hearing Scale short form
TGA	Therapeutic Goods Administration
TI1012	Nucleus Totally Implantable Cochlear Implant with Contour Advance electrode.
TICI	Nucleus Totally Implantable Cochlear Implant