Clinical Investigation Plan

Investigation Title:

A pivotal, prospective, multi-centre, randomised control, blinded study evaluating the efficacy of a dexamethasone eluting Slim Modiolar electrode (CI632D) in the reduction of fibrosis as compared to a standard Slim Modiolar electrode (CI632) in a newly implanted adult population with bilateral, post-linguistic, moderate to profound sensorineural hearing loss.

Short Title:	**The CI-DEX Study**
CIP Number:	**CLTD5759**
Version and Date:	**Refer to system version control**
Sponsor:	**Cochlear Limited** **1 University Avenue** **Macquarie University** **NSW 2109** **Australia** **+61 2 9428 6555**

ClinicalTrials.gov ID: NCT04750642
Approval date: 07 Nov 2022

This clinical investigation shall be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, International Standard ISO 14155:2020 Clinical investigation of medical devices for human subjects - Good Clinical Practice, and any regional or national regulations, as applicable.

Manufacturer	Cochlear Limited 1 University Avenue Macquarie University NSW 2109 Australia
Sponsor Organisation(s)	Cochlear Limited 1 University Avenue Macquarie University NSW 2109 Australia
Funding Source	Cochlear sponsored study
Lead Investigator	[redacted]
Clinical Research Organisation	Monitoring Avania LLC [redacted] Avania Pty Limited 13/76 Reserve Road, Artarmon NSW 2064 Australia
Contract Services	Statistical analysis and IDMC NAMSA, [redacted]
Safety Contact	[redacted]

A complete list of participating Principal Investigators' names, titles and addresses, and the names and addresses of participating institutions (sites) will be maintained by the Sponsor and will be provided as a separate Principal Investigator List. The definitive Principal Investigator list will be provided in the Clinical Investigation Report.

INVESTIGATOR AGREEMENT

Investigator Declaration

By my signature below, I confirm that I have read, understood and will strictly adhere to the requirements therein. I undertake to ensure that all staff with delegated responsibilities in the conduct of this CIP have also read, understood and will strictly adhere to the requirements therein. This CIP will not be implemented without prior written approval from the Ethics Committee, any applicable National Competent Authorities, and the Sponsor. If amendments to this plan become necessary, written approval by the Ethics Committee and any applicable National Competent Authorities will be obtained before the changes are clinically implemented per the amendment, except under emergency circumstances to protect the rights, safety, and well-being of subjects.

I also agree that my personal information may be provided to regulatory agencies and public clinical trial registry platforms, and stored in their systems in order to comply with regulatory requirements. Examples of the type of personal information include my name, signature and summary of qualifications.

Name	**Title**
Site Name	**Site Address**
Signature	**Date**

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1 DEFINITIONS AND ABBREVIATIONS

Term	Description
ADE	Adverse Device Effect
AE	Adverse Event
AT	As Treated population
CER	Clinical Evaluation Report
CI	Cochlear Implant
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CI532	Cochlear™ Nucleus® CI532 cochlear implant with Slim Modiolar electrode
CI632	Cochlear™ Nucleus® CI632 cochlear implant with Slim Modiolar electrode
CI632D	Cochlear™ Nucleus® CI632D cochlear implant with Slim Modiolar dexamethasone eluting electrode
CRF	Case Report Form
CRO	Contract Research Organisation
DCF	Data Clarification Form
DD	Device Deficiency
DEX	Dexamethasone
DHI	Dizziness Handicap Inventory
DTQ	Dizziness & Tinnitus Questionnaire
EC	Ethics Committee Synonymous abbreviations/terms include: IRB (Institutional Review Board) IEC (Institutional Ethics Committee or Independent Ethics Committee) HREC (Human Research Ethics Committee)
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practices
HUI3	Health Utilities Index III
HS	Health Survey
IB	Investigator's Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IFU	Instructions for Use (Physician's Guide)
ITT	Intent-To-Treat population

Term	Description
IMD	Investigational Medical Device
MP1+2	Monopolar 1+2
NCA	National Competent Authority
PP	Per Protocol population
PI	Principal Investigator
PIL	Principal Investigator List
PMS	Post-Market Surveillance
PTA	Pure-Tone Average
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
THI	Tinnitus Handicap Inventory
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

2 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	A pivotal, prospective, multi-centre, randomised control, blinded study evaluating the efficacy of a dexamethasone eluting Slim Modiolar electrode (CI632D) in the reduction of fibrosis as compared to a standard Slim Modiolar electrode (CI632) in a newly implanted adult population with bilateral, post-linguistic, moderate to profound sensorineural hearing loss.
Short title	The CI-DEX study
Investigation number	CLTD5759
Name of investigational medical device(s)	Cochlear™ Nucleus® CI632D cochlear implant with Slim Modiolar dexamethosone eluting electrode (CI632D).
Intended use of investigational medical device(s)	The investigational device, Cochlear™ Nucleus® CI632D is intended for individuals 18 years of age or older who have bilateral postlinguistic sensorineural hearing impairment and who obtain limited benefit from appropriately fitted hearing aids. The investigational medical device is not approved by a regulatory body; it is premarket.
Name and description of comparator device/product(s)	Cochlear™ Nucleus® CI632 cochlear implant with Slim Modiolar electrode (CI632)
Estimated recruitment period	28 Months
Expected duration per subject	14 Months
Number of subjects planned	Up to 120 randomised subjects
Number of investigational sites planned	5-25 sites in Australia, New Zealand and United States
Inclusion criteria	Subjects must meet all the inclusion criteria described below to be eligible for this clinical investigation. 1. Post-lingual, bilateral, moderate to profound sensorineural hearing loss, defined by a pure-tone average (PTA): a. ≥ 40 dB HL at 250 through 1000 Hz and, b. ≥ 65 dB HL at 2000 through 8000 Hz. 2. Preoperative aided word score is 40% correct or less in the ear to be implanted (60% or less in the contralateral ear). 3. 18 years or older at time of consent. 4. Willing to be randomised into either a treatment (CI632D) or control (CI632) arm. 5. Evidence of pneumococcal vaccination (e.g., Pneumovax) according to local guidelines prior to randomisation. 6. Fluent speaker in the local language used to assess clinical performance as judged by the investigator. 7. Willing and able to provide written informed consent
Exclusion criteria	Subjects who meet any of the exclusion criteria described below will not be eligible for this clinical investigation.

	1. Deafness due to lesions of the acoustic nerve or central auditory pathway. 2. Diagnosed active middle-ear infections or history of middle ear infection within the past six months prior to randomisation. Must not have had surgery, drainage, pain, or need for oral or topical antibiotics within the past six months in the ear to be implanted. 3. Previously reported diagnosis of auditory neuropathy. 4. Previously reported diagnosis of Large Vestibular Aqueduct Syndrome (LVAS), Meniere's disease, or cochlear hydrops. 5. Prior history of surgery in the ear to be implanted (excluding grommets). 6. Current use of grommets or evidence of unhealed tympanic membrane perforation. 7. Ossification, otosclerosis, malformation or any other cochlear anomaly, such as common cavity, that might prevent complete insertion of the electrode array, as confirmed by imaging. 8. Existing cerebrospinal fluid (CSF) shunts or drains, existing perilymph fistula, skull fracture or CSF leaks. 9. History of bacterial meningitis. 10. Known allergic reaction or contraindication to dexamethasone or corticosteroids. 11. Use of ototoxins and/or steroids (does not include topical or inhaled steroids) up to 30 days prior to randomisation. Note: Systemic ototoxin and/or steroids therapy must be completed at least 7 days prior to Screening/Baseline audiometric and speech testing. 12. Evidence of severe or greater sensorineural hearing loss prior to five years of age, as reported by the subject. 13. Severe to profound sensorineural hearing loss for more than 20 years, as reported by the subject. 14. Existing contralateral cochlear implant. 15. Medical plan to implant a contralateral cochlear implant during the clinical investigation. 16. History of recurrent otitis media or chronic otitis media in the ear to be implanted. 17. Medical or psychological conditions that contraindicate general anaesthesia, surgery or participation in the clinical investigation. 18. Pregnant or breastfeeding women. Women who plan to become pregnant during the course of the investigation. 19. 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. 20. Additional disabilities that may affect the subject's participation or safety during the clinical investigation. 21. Unable or unwilling to comply with all the requirements of the clinical investigation as determined by the Investigator. 22. Investigator site personnel directly affiliated with this study and/or their immediate families; immediate family is defined as spouse, parent, child, or sibling. 23. Cochlear employees or employees of Contract Research Organisations or contractors engaged by Cochlear for the purposes of this investigation.

	24. Currently participating, or participated within the last 30 days, in another interventional clinical investigation/trial involving an investigational drug or device.

Primary objectives	To show the efficacy of a dexamethasone eluting electrode in an adult population with post-lingual, bilateral, moderate to profound sensorineural hearing loss: • In the reduction of fibrosis (as measured by impedance) when compared to a conventional, non-dexamethasone eluting electrode. • In the improvement of speech recognition from preoperative baseline.
Secondary objective	Demonstrate that the safety of a dexamethasone eluting electrode is similar to a standard electrode by comparison of adverse events and speech outcomes in an adult population with post-lingual, bilateral, moderate to profound sensorineural hearing loss.
Primary endpoint(s)	Difference between CI632D and CI632 mean MP1+2 impedance measurements of the available electrodes at 6 months post-cochlear implantation. Difference between CI632D mean speech perception performance for open-set monosyllabic word recognition in quiet in the unilateral listening condition at six months post-implant compared to preoperative baseline.
Secondary endpoint(s)	1. Comparison of CI632D and CI632 procedural and device related adverse events at 6 Months and 12 Months post-cochlear implant. 2. Difference between CI632D and CI632 mean speech perception performance for open-set monosyllabic word recognition in quiet in the unilateral listening condition at six months post-cochlear implant. 3. Difference between CI632D and CI632 mean speech perception performance for sentence recognition in quiet in the unilateral listening condition at six months post-cochlear implant. 4. Comparison of CI632D and CI632 Custom Sound® estimated remaining battery life of the sound processor at all data collection time points.
Exploratory endpoint(s)	1. Comparison of CI632D and CI632 mean change of four point impedance levels at all data collection time points. 2. Characteristics of MP1+2 impedance changes at all data collection time points and electrodes/electrode regions of CI632D and CI632. 3. Difference between CI632D mean speech perception performance for open-set monosyllabic word recognition in quiet in the bimodal listening condition at six months post-implant compared to preoperative baseline. 4. Difference between CI632D and CI632 mean speech perception performance for open-set monosyllabic word recognition in quiet in the bimodal listening condition at six months post-cochlear implant. 5. Difference between CI632D and CI632 mean speech perception performance for sentence recognition in quiet in the bimodal listening condition at six months post-cochlear implant. 6. Difference between CI632D and CI632 modelled mean battery life calculation at 6 Months post-cochlear implant. 7. Rate and change of post-operative dizziness as compared to Baseline and compare at all data collection time points.

	8. Mean change in global Health Utilities Index III (HUI3) score from Baseline at all data collection time points. 9. Rate and change of post-operative tinnitus as compared to Baseline and compare at all data collection time points. 10. Characterise change in acoustic hearing thresholds at all collected time points of CI632D and CI632. 11. Compare electrical hearing thresholds at collected time points of CI632 and CI632D. 12. Correlation between MP1+2 impedance levels from CI632 (Control) arm and automated CI532 impedance data (collected from a Custom Sound® database) with age at implant and sex at all data collection time points. 13. Characterise the surgeon's assessment following cochlear implant procedure of CI632D and CI632.

3 SCHEDULE OF EVENTS

Visit Type	Screening /Baseline	Randomisation	Surgery	Visit 1	Visit 2[a]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	EOS
Timing of Investigation		**≤90 Days before Surgery**	**Day 0**	**10 Days after Surgery**	**15 Days after Surgery (Activation)**	**30 Days after Activation**	**3 Months after Surgery**	**6 Months after Surgery**	**9 Months after Surgery**	**12 Months after Surgery**	
Visit window (±)				**1-10 days**	**± 7 days**	**± 5 days**	**90 days, ± 14 days**	**180 days, ± 14 days**	**270 days, ± 30 days**	**365 days, +30 days**	
Procedures											
Written informed consent[b]	X										
Demographics	X										
Eligibility	X										
Hearing history	X										
Device history	X										
Medical history	X										
Audiogram	X[c]					X	X	X	X	X	
Speech Perception testing	X[c]						X	X		X	

[a] *Visits 1 and 2 may be conducted in combination (i.e., Visit 1+2), occurring within a single session on the same day, as long as the visit occurs within the compliance window indicated above. Specifically, Visit 1+2 can occur 8-10 days post surgery. Assessments that are required for Visits 1+2 only need to be completed once and should be recorded on Visit 2. If sites cannot schedule Visit 1+2 within 8-10 days post surgery, the two visits should remain separated (i.e., Visit 1 & Visit 2) and occur within their respective time window as indicated above.*

[b] *Written informed consent must be obtained prior to completing study specific assessments, assigning a subject identification code and entering data into EDC.*

[c] *Baseline audiogram and speech perception testing must be completed within 90 days prior to Randomisation.*

Visit Type	Screening /Baseline	Randomisation	Surgery	Visit 1	Visit 2[a]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	EOS
Timing of Investigation		**≤90 Days before Surgery**	**Day 0**	**10 Days after Surgery**	**15 Days after Surgery (Activation)**	**30 Days after Activation**	**3 Months after Surgery**	**6 Months after Surgery**	**9 Months after Surgery**	**12 Months after Surgery**	
Visit window (±)				**1-10 days**	**± 7 days**	**± 5 days**	**90 days, ± 14 days**	**180 days, ± 14 days**	**270 days, ± 30 days**	**365 days, +30 days**	
Imaging	High Resolution CT[d]		HRCT, Intra-op X-ray or fluorosopy[e]	High Resolution CT[f]							
Hearing-Impaired Montreal Cognitive Assessment Impaired (HI-MoCA)	X[g]										
Health Utilities Index III (HUI3)	X[g]					X	X	X		X	
Dizziness/Tinnitus Questionnaire (DTQ)	X[g]					X	X	X	X	X	
Dizziness Handicap Inventory (DHI)	X[g]					X	X	X	X	X	

[d] *Baseline High Resolution CT must be completed within 2 years prior to Randomisation.*
[e] *Intra-operative imaging (HRCT, X-ray, or fluoroscopy) after final CI placement. May need to be repeated if there is adjustment to electrode placement.*
[f] *High Resolution CT imaging required within 3 months after cochlear implant capturing placement of electrode in the cochlea. Not applicable if completed post insertion during surgery.*
[g] *HI-MoCA, HUI3, DTQ, DHI, THI and HS must be completed within 90 days prior to Randomisation.*

Visit Type	Screening /Baseline	Randomisation	Surgery	Visit 1	Visit 2[a]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	EOS
Timing of Investigation		**≤90 Days before Surgery**	**Day 0**	**10 Days after Surgery**	**15 Days after Surgery (Activation)**	**30 Days after Activation**	**3 Months after Surgery**	**6 Months after Surgery**	**9 Months after Surgery**	**12 Months after Surgery**	
Visit window (±)				**1-10 days**	**± 7 days**	**± 5 days**	**90 days, ± 14 days**	**180 days, ± 14 days**	**270 days, ± 30 days**	**365 days, +30 days**	
Tinnitus Handicap Inventory (THI)	X[g]					X	X	X	X	X	
Health Survey (HS)	X[g]			X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	
Randomisation[i]		X									
Blinding Questionnaire					X			X			
Surgical Questionnaire			X								
Discharge Summary			X								
Impedances (MP1+2, Four point)			X[j]	X	X[k]	X[lm]	X[lm]	X[lm]	X[lm]	X[lm]	

[h] *The Health Survey should be completed prior to impedance measurements.*
[i] *Independent Sponsor representative must have provided an approval for Randomisation. Subject is not required to visit clinic for Randomisation assignment.*
[j] *Testing should be completed after final placement of electrode and device in the following order: 1) impedances, 2) NRT.*
[k] *Measure impedances two times with Custom Sound® software: 1) before activation 2) after activation and CI optimisation / mapping is complete.*
[l] *Post-activation, Remote Programming may be used as an alternative should a subject not be able to return to the clinic due to impact of COVID-19 pandemic. This applies to Visits 3, 4 5, 6, and 7.*
[m] *Testing should be completed after CI optimisation / mapping is complete.*

Visit Type	Screening /Baseline	Randomisation	Surgery	Visit 1	Visit 2[a]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	EOS
Timing of Investigation		**≤90 Days before Surgery**	**Day 0**	**10 Days after Surgery**	**15 Days after Surgery (Activation)**	**30 Days after Activation**	**3 Months after Surgery**	**6 Months after Surgery**	**9 Months after Surgery**	**12 Months after Surgery**	
Visit window (±)				**1-10 days**	**± 7 days**	**± 5 days**	**90 days, ± 14 days**	**180 days, ± 14 days**	**270 days, ± 30 days**	**365 days, +30 days**	
AutoNRT® (9 electrodes)			X[j]								
Device Activation					X						
CI optimisation / Mapping					X	X[l]	X[l]	X[l]	X[l]	X[l]	
Battery life estimation Test[lmn]						X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X
Device Deficiencies			X	X	X	X	X	X	X	X	X
Device Exposure			X	X	X	X	X	X	X	X	X
Concomitant medications[o]	X	X	X	X	X	X	X	X	X	X	X
Protocol Deviations	X	X	X	X	X	X	X	X	X	X	X
Reason for Exit											X

[n] *Required parameters for testing battery life includes Stim Rate of 900 Hz/channel and Maxima of 8. No testing required if subject's own MAP has the same parameters.*

[o] *Include all medication: includes all prescription medications, pharmaceuticals used during surgery, routine over-the counter medications, and any use of steroids (up to 90 days prior to randomisation).*

4 BACKGROUND INFORMATION AND RATIONALE

4.1 Introduction

The Cochlear™ Nucleus® CI632 cochlear implant with Slim Modiolar electrode (CI632) is one of the latest product developments from Cochlear™ Limited in an adult population with post-lingual, bilateral, moderate to profound sensorineural hearing loss and who have compromised functional hearing with hearing aids or would receive no benefit with hearing aids. The Slim Modiolar electrode is the thinnest perimodiolar electrode for insertion into the cochlea in the Cochlear™ electrode portfolio.

During implantation of CI632 and other cochlear implants, corticosteroids (such as dexamethasone) are routinely given locally or systemically in association with cochlear implant surgery to inhibit the inflammatory response caused by insertion trauma of the electrode array (Kuthubutheen et al., 2016).

To allow for long-term delivery of dexamethasone, CI632 has been modified to include dexamethasone in the electrode within wells (CI632D), which will passively elute directly into the cochlea over at least [redacted]

The clinical investigation aims to assess if passive elution of dexamethasone reduces the level of fibrosis following cochlear implantation, as measured by change in electrode impedance. Reduced impedances would indicate less fibrotic obstruction caused by trauma associated with the electrode insertion. The intended purpose of the CI632D investigational medical device (IMD) in the proposed clinical investigation is to improve the outcomes affected by fibrosis, while maintaining the same indications and benefit of improved hearing as a conventional CI632. The investigation will test the traditional benefit of cochlear implant by comparing speech perception outcomes pre- and post-operatively. The CI632D IMD may provide additional improvements in hearing performance by reducing the fibrosis caused by the cochlear implantation procedure.

4.2 Findings of Previous Nonclinical and Clinical Studies

4.2.1 Nonclinical Data

4.2.1.1 Data from published studies

Elution of dexamethasone from an implanted electrode array has the potential to be a clinically viable route of administration because it enables prolonged delivery of the drug directly into the cochlea with a consistent therapeutic dose, which would standardise a varied clinical practice. The use of dexamethasone-eluting cochlear implant (CI) electrode arrays has been found to be associated with no additional insertion trauma or risk of infection in animal models (Astolfi et al., 2016, Bas et al., 2016, Douchement et al., 2015, Eshraghi et al., 2011, Farhadi et al., 2013, Liu et al., 2015, Nguyen et al., 2015, Niedermeier et al., 2012, Stathopoulos et al., 2015, Stathopoulos et al., 2014, Wilk et al., 2016).

The level of hearing protection observed with dexamethasone in animal studies ranges from no evidence for protection against auditory brainstem response (ABR) threshold shifts (Stathopoulos et al., 2014, Wilk et al., 2016, Wrzeszcz et al., 2015, Chambers et al., 2019) to significant levels of hearing protection (Bas et al., 2016,

Eshraghi et al., 2011, Liu et al., 2015) that increases with higher concentrations of dexamethasone (Bas et al., 2016).

The benefits of local delivery of corticosteroids via drug-eluting arrays can include reduced infiltration of inflammatory cells into the cochlea (Farhadi et al., 2013), reduced bone formation (Chambers et al., 2019), reduced formation of fibrotic tissue (Bas et al., 2016, Wilk et al., 2016, Wrzeszcz et al., 2015), better preservation of spiral ganglion neurons (Bas et al., 2016, Chambers et al., 2019) and lower electrode impedances (Bas et al., 2016, Wilk et al., 2016), compared to the use of electrode arrays that do not elute dexamethasone.

In the absence of surgical trauma, dexamethasone has little influence on hearing thresholds (Stathopoulos et al., 2014). Conversely, it is unable to fully protect against threshold increases in the presence of high levels of electrode insertion trauma (Wilk et al., 2016, Chambers et al., 2019). These findings suggest that dexamethasone may be most effective where surgical trauma is within the mild-to-moderate range.

A likely consequence of reduced electrode impedances is that lower stimulation levels are required and power consumption is reduced. Ramos Miguel et al. (2015) investigated the relationship between the thickness of bone between the intracochlear and extracochlear electrodes, which affects resistivity and impedance, current and relative power in mathematical and temporal bone models. The investigators found that as bone thickness (and impedance) increased, the current generated decreased, increasing power consumption for stimulation. Increased impedance would be expected in patients with cochlear ossification, which increases resistivity of the tissue.

4.2.1.2 Impedance and fibrosis in the presence of a dexamethasone-eluting array

Twenty-five adult female guinea pigs were bilaterally implanted with a dexamethasone-eluting array (left ear) and a non-eluting control array (right ear). The two arrays were connected in a bifurcated design. One week after implantation, all arrays were electrically stimulated daily for 4 weeks, and electrode impedance measured both before and after stimulation. The study was completed for 16 animals.

Analysis of histological images and resin-imbedded specimens revealed that the electrode arrays were consistently implanted in the scala vestibuli rather than the scala tympani. The mean percentage of fibrotic tissue and new bone growth was lower on the side with the dexamethasone-eluting array than the side with the standard array, but the difference was not statistically significant. There were no differences between groups in the density of spiral ganglion cells after implantation.

Monopolar (MP1+2) impedance was higher in dexamethasone-eluting arrays on the day of surgery and prior to daily electrical stimulation. After daily electrical stimulation, no differences were evident between the arrays. There was a positive correlation between the percentage of fibrotic tissue and the change in monopolar impedance before and after stimulation with the dexamethasone-eluting array, but not the control array.

In contrast, four point impedance did not differ between electrode arrays for the first week of stimulation, but thereafter was significantly lower in the dexamethasone-eluting array than the standard array before and after daily stimulation. Four point impedance is a measure of impedance between two intracochlear electrodes when charge is passed across them, and reflects the local environment overlying the electrode. Four point impedance could therefore be more sensitive to changes at the electrode surface, such as adhesion for fibrosis, than monopolar impedance.

The results suggest that daily electrical stimulation with dexamethasone-eluting and standard arrays are likely to have differing effects on the local electrode-tissue interface. This study is published in Needham et al. (2019).

4.2.1.3 Long-term electrical stimulation of a dexamethasone-eluting intracochlear array and effects of fibrous tissue growth on impedance

Adult guinea pigs were bilaterally implanted with a dexamethasone-eluting array and a standard non-eluting array. The array had a bifurcated design consisting of eight electrodes embedded in a silicone rubber carrier. Dexamethasone was loaded into the longer array of each device by back-filling a V-shaped groove in the rear surface of the array with a mixture of liquefied silicone rubber (60%) and micronised dexamethasone base (40% w/w). Two weeks after implantation, all arrays were electrically stimulated daily for up to 13 weeks and electrode impedance was measured before and after stimulation. Histological assessment of fibrous tissue, new bone growth and spiral ganglion neuron density was assessed at the end of the 15-week period, along with a comparison of hearing thresholds. In total, 17 animals completed 90 days of the study and some electrode impedance recordings continued for up to 105 days.

Impedance was measured on the day of implantation (day 1), at three points prior to the onset of electrical stimulation (typically at days 4, 7 and 10), and then immediately preceding and following electrical stimulation, which commenced on day 14-15.

A reduction in MP1+2 impedance relative to switch-on was observed in both the standard and dexamethasone-eluting arrays over the course of 15 weeks but there were no significant differences in MP1+2 impedance between the arrays.

Four point impedance in the dexamethasone-eluting array was maintained at a stable level for the duration of the study, but a steady increase in four point impedance was observed for the standard array from seven weeks. There were significant differences between array types for both pre- and post-implantation data.

The trans-impedance matrix revealed consistently lower impedance in the dexamethasone-eluting array beginning from the day of implantation until day 70 and this trend was maintained up to 100 days after implantation for the most apical pairs.

The percentage of fibrosis observed in the scala tympani was significantly larger in the standard array, as was the percentage of loose fibrous tissue. There were no statistical differences in dense fibrous tissue, new bone growth, spiral ganglion neuron density or hearing threshold between the different arrays. There was a positive and statistically significant correlation between mean four point impedance and both total fibrous tissue and loose fibrous tissue.

In conclusion, this study showed that electrode impedances (four point and trans-impedance matrix) are reduced in the presence of dexamethasone and daily electrical stimulation up to 15-week after implantation. This outcome suggests a change in the local tissue-electrode interface in the presence of sustained, local release of dexamethasone.

4.2.2. Clinical Data

4.2.2.1 Data from published studies

Dexamethasone, hearing thresholds and electrode impedance

A review of the literature with the objective of identifying publications related to CI surgery, dexamethasone and electrode impedance found evidence that atraumatic surgical techniques that include the use of dexamethasone can result in lower electrode impedances (Gu et al., 2016) and better hearing preservation (Bento et al., 2016) than surgical procedures that involve cochleostomy. Preservation of hearing and vestibular function was achieved for five patients who were given intraoperative dexamethasone infusions (8mg) plus postoperative dexamethasone for 6 days (daily doses of 8 mg, 8 mg, 4 mg, 4 mg, 2 mg and 2mg) (Usami et al., 2011). When patients who were given dexamethasone preoperatively and during surgery were compared with patients who were not given dexamethasone preoperatively (5 mg dexamethasone given 1 day and then 1 hour before surgery); and during surgery (0.5mL of 5 mg/mL dexamethasone injected into round window and then 0.5 mL injected into middle ear cavity after receiver fixation) were compared with patients who were not given dexamethasone, there were significantly smaller increases in hearing thresholds and significantly more subjects with complete or partial hearing preservation at twelve months in the treatment group than in the control group (Cho et al., 2016). However, the use of different electrode array types in the two groups is a potential confounding factor.

Kuthubutheen and colleagues observed significantly lower hearing thresholds at 3 and 12 months after surgery in patients who received dexamethasone via transtympanic injection (TT) than those who were given oral prednisolone prior to surgery (Kuthubutheen et al., 2017). However, this confounded by lower preoperative hearing thresholds in the TT group. There was a tendency for the absolute change in low frequency hearing threshold to be smaller in the TT group than the other groups, but this was not statistically significant. A greater rate of hearing preservation in the TT group than the oral group was seen at three months but not 12 months, but there were no significant differences in speech perception between groups. The statistical power of this study was limited by small sample sizes.

In the studies summarized above, dexamethasone was given as a single dose or multiple doses, but not for an extended period comparable to continuous passive drug elution. In a study that compared hearing preservation in patients who were given intravenous dexamethasone for three days (nine patients), patients who were given additional prolonged oral dexamethasone therapy (five patients) and a no-steroid control group (22 patients), the prolonged therapy group was the only group whose hearing thresholds remained stable over the six-month study period. Only the extended therapy group had significantly better hearing preservation than the control group, but there was no significant difference between the two steroid treatment groups (Skarzynska et al., 2018).

Extended effects on electrode impedances were observed after local application of methylprednisolone prior to surgery (Enticott et al., 2011). In this study, a polymeric sponge composed of carboxymethylcellulose and hyaluronic acid was presoaked in 125 mg/mL methylprednisolone and applied to the round window 30 minutes before cochleostomy was performed. Impedances for the middle electrodes were significantly lower in the group given the drug compared to the control group up to 9 months after surgery.

Although they do not involve administering dexamethasone at the time of cochlear implant surgery, two case studies suggest that sustained-release dexamethasone could increase the duration of benefit (Plontke et al., 2017). Both cases involved long-term CI users who experienced symptoms related to vestibulopathy with raised CI electrode impedances. In both cases, the patients were initially treated with IV steroids, which reduced symptoms and electrode impedances for short periods. Subsequent treatment with a biodegradable extended-release dexamethasone implant corresponded to reduced electrode impedances for periods of

approximately three to six months. Pharmacokinetic data from animal models indicate that intracochlear extended-release dexamethasone implants can provide stable drug concentrations in the scala tympani for several weeks (Plontke et al., 2017).

Factors influencing sound processor battery life.

The length of time that a fully charged sound processor battery can provide power for stimulation is influenced by multiple factors that affect power consumption. These factors include the efficiency of the RF link between the sound processor coil and the implant receiver coil, which can be affected by the thickness of the skin flap over the implant. Other factors that are determined by the recipient's individual MAP parameters, including the current level, pulse width, rate of stimulation and number of maxima will also influence sound processor power consumption.

There is evidence from published clinical investigations that changes to electrode design can reduce power consumption for stimulation and, consequently, improve sound processor battery life. Saunders et al. (2002) compared the threshold (T) and comfort (C) loudness levels and impedances in patients implanted with CIs with lateral wall or perimodiolar electrode arrays. The radial distance from the modiolus was positively correlated with T and C levels for most patients and impedance levels, corrected for electrode surface area, were significantly lower for the perimodiolar electrode array. Contrasting results were reported for two studies that investigated stimulation levels and battery life in paediatric patients who had been implanted with a CI with a straight electrode array in one ear and a perimodiolar device in the other ear. Whereas Park et al. (2017) found no differences in T and C levels and battery life between lateral wall and perimodiolar devices, Jeong et al. (2015) reported that T and C levels were consistently lower with the perimodiolar device than the lateral wall device. This translated to longer battery life in three out of six individuals.

4.2.2.2. Evidence from Cochlear-sponsored studies

Pilot Evaluation of Combined Investigational Device CI4CID with Controlled Dosage of dexamethasone (CLTD5495).

[redacted]

The primary objectives of this prospective pilot study were to obtain surgical feedback, to assess the safety of the CI4CID over 24 months post-implantation follow-up and to compare clinical outcomes to a population implanted with the CI24RE(CA). Longitudinal changes in electrode impedance were also characterized for both the CI4CID and CI24RE(CA) electrode.

Twenty-four subjects were included in the study (10 implanted with the CI4CID and 14 with CI24RE(CA). Surgeons rated the ease of insertion of the electrode as uncomplicated or acceptable in all cases for the CI4CID and 11/13 cases for CI24RE(CA). Direct comparison between the CI4CID and the CI23RE(CA) indicated that the insertion was of 'similar difficulty' to the CI24RE(CA). There were no serious device-related adverse events. There were two non-serious adverse events related to the CI4CID (electrode translocation with vertigo and tinnitus after surgery). Nine possible or definite device-related adverse events were recorded for the CI24RE(CA), related to pain, tissue breakdown at implant site, dizziness and balance issues.

Group mean MP1+2 electrode impedances were significantly lower for the CI4CID than for the CI24RE(CA) and this was consistent across all regions of the electrode array. There were no significant differences between intraoperative impedances for the two devices, but the CI4CID had significantly lower group mean impedances at subsequent time points.

For four point impedance, the main effect of device was non-significant. However, post hoc comparisons revealed that impedance was significantly greater in the basal region of the CI24RE(CA) than the CI4CID from six months and in the medial region at 12 and 24 months. There was a significant increase in impedance in the basal region of the CI24RE(CA) between three and six months after surgery. There were no other significant changes or trends in any electrode region for either device.

4.3 Study Rationale

The aim of this clinical investigation is to assess the efficacy of long-term delivery over at least [redacted] of dexamethasone from a novel drug-eluting cochlear implant (CI632D) by comparing it to a standard electrode that does not elute dexamethasone (CI632). The primary endpoints will be the comparison between CI632D and CI632 mean MP1+2 impedance measurements of the available electrodes and speech perception testing at 6 months post-cochlear implantation. The intended purpose of the CI632D IMD is the restoration of hearing function in an adult population with post-lingual, bilateral, moderate to profound sensorineural hearing loss and who have compromised functional hearing with limited or no benefit from appropriately fitted hearing aids. Dexamethasone is commonly delivered acutely during cochlear implant procedures. [redacted].

Inflammation is a response to the trauma of cochlear implant electrode insertion and the presence of a foreign body (Seyyedi and Nadol, 2014, O'Malley et al., 2017). Chronic unresolved inflammation can result in fibrosis or scarring caused by the formation of excess connective tissue. Glucocorticoids, including dexamethasone, are commonly used to inhibit the inflammation that occurs as a response to tissue damage. Dexamethasone was chosen for use in this study because of its strong anti-inflammatory properties and because it has previously been used to treat inflammation in the cochlea, especially in cochlear implant surgery (see section 4.2.2).

Electrode impedance, a measure of the opposition to the flow of alternating current between the electrode and surrounding tissue, is influenced by inflammation and fibrotic tissue and is a likely indicator of tissue damage that results from device implantation (Choi et al., 2017). There is a long-established connection between the presence of inflammatory cells, fibrosis, new bone growth and increased electrode impedances, which was demonstrated in an animal model by Clark et al. (1995).

Over time, fibrotic tissue may ossify leading to the development of new bone in the cochlea and there is evidence that bone formation in the cochlea is related to the loss of spiral ganglion cells due to surgical trauma (Fayad et al., 2009). Furthermore, last recorded hearing performance was found to be positively correlated with spiral ganglion cell counts, and negatively correlated with the relative volume of new bone growth in a study with temporal bones from patients who were cochlear implant recipients (Kamakura and Nadol, 2016).

Therefore, reducing inflammation and its consequences after cochlear implant surgery may result in better hearing performance for recipients.

There is evidence from clinical studies and animal models, as described in Section 4.2, that dexamethasone given in association with cochlear implant surgery can reduce electrode impedances, inflammation, fibrosis, bone formation and loss of tissue, and result in better preservation of residual hearing. In a previous Cochlear™-sponsored pilot study (CLTD 5495, see section 4.2.2.2), electrode impedances were lower over the 24-month follow-up period in patients who were implanted with an [redacted]

Currently, there is no standard method of administering dexamethasone during cochlear implant surgery (see section 4.2.2.1). Advantages of intracochlear delivery compared with systemic delivery include bypassing of the blood-brain labyrinth barrier, higher local drug concentrations with lower doses and avoidance of the 'first pass' effect of rapid metabolism. Published reports describe various routes of administration of dexamethasone including via application to the middle ear cavity, transtympanic injection and round window injection (Bento et al., 2016, Cho et al., 2016, Kuthubutheen et al., 2017). In some studies, local application of dexamethasone was combined with systemic steroids before or after surgery (Cho et al., 2016, Usami et al., 2011). The use of controlled release dexamethasone to treat cases of decreased speech performance and raised electrode impedances in cochlear implant users was found to be effective and require a smaller total dose of dexamethasone of 0.7 mg (Plontke et al., 2017).

Steroid elution has been employed in cardiac pacemaker electrodes since the 1980s. As is the case for CI632D, the drug is incorporated into a silicone matrix within the pacemaker electrode and although the total amount of dexamethasone in pacemaker electrodes (typically less than 0.5mg) is greater than that incorporated into the CI632D, no systemic side effects have been recorded (Mond et al., 2014). Lower stimulation thresholds were recorded and reduced connective tissue formation was observed around steroid-eluting electrodes than non-eluting electrodes in animal studies (Radovsky et al., 1988). Decreased stimulation thresholds were also recorded for the steroid-eluting electrodes compared with non-eluting electrodes in clinical investigations and these thresholds were stable over the ten year study period (Mond and Stokes, 1996). Increased device longevity was predicted for steroid-eluting devices, suggesting that the incorporation of dexamethasone resulted in decreased battery drain (Crossley et al., 1995, Kutyifa et al., 2013, Mond et al., 2014).

[redacted]

5 MEDICAL DEVICE INFORMATION

5.1 Identity and Description of the Investigational Medical Device (IMD)

[redacted]

5.1.2 Biological compatibility

The materials in direct contact with the body (silicone, titanium, and platinum) are biocompatible, and have a long history of successful use in medical devices. The materials used within the receiver-stimulator have been chosen for long term stability. The receiver-stimulator and magnet are hermetically sealed to prevent the ingress of fluid leading to premature failure.

5.1.3 Receiver-stimulator and receiver coil

Data from the externally worn sound processor, encoded in a radio frequency (RF) stream, are received by the receiver-stimulator via the receiver coil. The incoming data stream is decoded into a sequence of electrical stimulation pulses that are directed to the 22 electrode contacts of the intracochlear electrode array, stimulating neural processes inside the cochlea. The current that is induced in the receiver coil by the RF stream is also used to power the internal implant.

The electronic assembly can measure the voltage on any intra- or extra- cochlear electrode, allowing electrode impedances and neural responses to electrical stimulation to be recorded. All electronic functions are carried out by a non-programmable custom application-specific integrated circuit, the CIC4 chip.

The magnet at the centre of the receiver coil retains the external transmitter coil on the head and ensures that the transmitter and receiver coils are properly aligned for efficient data and power transfer. The CI600 Series magnet cassette comprises a neodymium-iron-boron magnet polarised across the short-axis. The magnet is encased in a titanium cassette and coated in gold. The titanium cassette is marked to indicate the correct orientation of the cassette in the magnet pocket.

The magnet cassette is retained within the magnet pocket, consisting of two poly-ether-ether-ketone (PEEK) plates, embedded in the silicone of the receiver coil. The magnet pocket is designed to enable the recipient to undergo MRI procedures up to 3T without the need to remove the magnet. The plates reduce the risk of magnet dislocation during MRI. The magnet cassette can be removed and replaced if necessary by gripping the white silicon tab moulded into the cassette (Figure 2).

Figure 2: Removal of the magnet cassette from the magnet pocket.

5.1.4 Drug-eluting electrode array

The electrode array used on the CI632D is identical to the EA32 slim modiolar electrode array [redacted]

[redacted]

Dexamethasone, a synthetic glucocorticoid, was chosen because of its potent anti-inflammatory properties and long half-life (36-54 hours) compared to other corticosteroids, and for its history of use to treat diseases of the inner ear. Intracochlear administration with direct dosing in the perilymph and resulting in a lower systemic exposure should result in minimal or absent systemic side effects. The additional advantages of intracochlear delivery compared with systemic delivery include bypassing of the blood-brain labyrinth barrier, higher local drug concentrations with lower doses and avoidance of the 'first pass' effect of rapid metabolism.

[redacted]

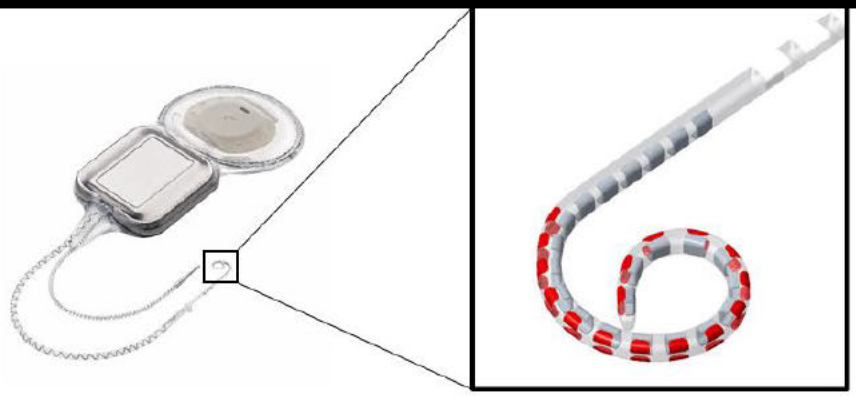

Figure 4: The EA32D drug-eluting electrode. The discrete wells filled with dexamethasone are indicated in red.

5.1.5 Extracochlear (reference) electrodes

The role of the extracochlear electrodes (ECE) is to provide a return path for the stimulation current delivered to the intracochlear electrode contacts. ECE 1, also referred to as MP1, is attached to the receiver-stimulator via a short (60 mm) lead and is typically placed under the temporalis muscle by the surgeon. The lead contains micro-coiled platinum/iridium (90%/10%) electrode wire insulated with Parylene C and is encapsulated in silicone. ECE 2, also referred to as MP2, is located on the top shell of the receiver-stimulator. Both ECE are capacitively coupled to the stimulation circuitry. During programming of the device, the clinician can select the reference electrode to be used in the stimulation protocol.

5.1.6 Surgical procedures

The CI632D can be implanted using surgical procedures identical to those used for the CI632. Please refer to the CI632 Physician's Guide for further details.

5.2 Identity and Description of the Comparator

The comparator device is the CI632, which is identical in design and function to the CI632D except that it incorporates the EA32 electrode array, which does not include dexamethasone-containing wells.

5.3 Accessory Device Requirements

The CI632D must be used together with other system components for normal operation. All CI600 Series cochlear implants are compatible with the CP1000 and the CP900-series Sound Processor System and programming software (Custom Sound® Suite and Nucleus® Fitting Software or the latest Cochlear software platform for advanced objective measurements). In addition, the CI600 Series Cochlear™ Implants are compatible with the CR220 Intraoperative Remote for intraoperative testing and the Integrity Test (IT) System for diagnostic testing.

During the study, subjects will be required to use a Cochlear Nucleus® 8 behind-the-ear (BTE) sound processor (CP1110; figure 5) or a Cochlear Nucleus 7 behind-the-ear (BTE) sound processor (CP1000; figure 6).

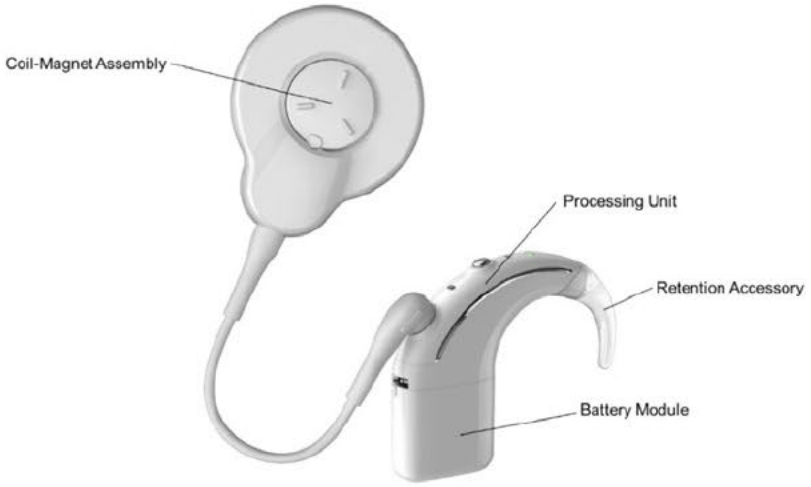

Figure 5: Cochlear Nucleus 8 Sound Processor

Figure 6: Cochlear Nucleus 7 Sound Processor.

The following surgical tools and accessories may be used with the CI632D and CI632.

1) BTE Template (Z33011)
2) CI500/CI600 Series Recess Gauge (Z139274)
3) CI500/CI600 Series Implant Template (Z139273)
4) CI500/CI600 Series Sterile Silicone Implant Template (S211296)
5) CI500/CI600 Series Non-Sterile Silicone Implant Template (Z179609)
6) Spacer for Intraoperative Testing (Z33012)
7) Cochleostomy Sizing Tool (S407840)
8) Non-Magnetic Cassette (P782484)
9) Replacement Magnet Cassette (P782485)

6 OBJECTIVES

6.1 Primary Objective

To show the efficacy of a dexamethasone eluting electrode in an adult population with post-lingual, bilateral, moderate to profound sensorineural hearing loss:

- In the reduction of fibrosis (as measured by impedance) when compared to a conventional, non-dexamethasone eluting electrode.
- In the improvement of speech recognition from preoperative baseline.

6.2 Secondary Objective

- Demonstrate that the safety of a dexamethasone eluting electrode is similar to a standard electrode by comparison of adverse events and speech outcomes in an adult population with post-lingual, bilateral, moderate to profound sensorineural hearing loss.

6.3 Exploratory Objective

[redacted]

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 General

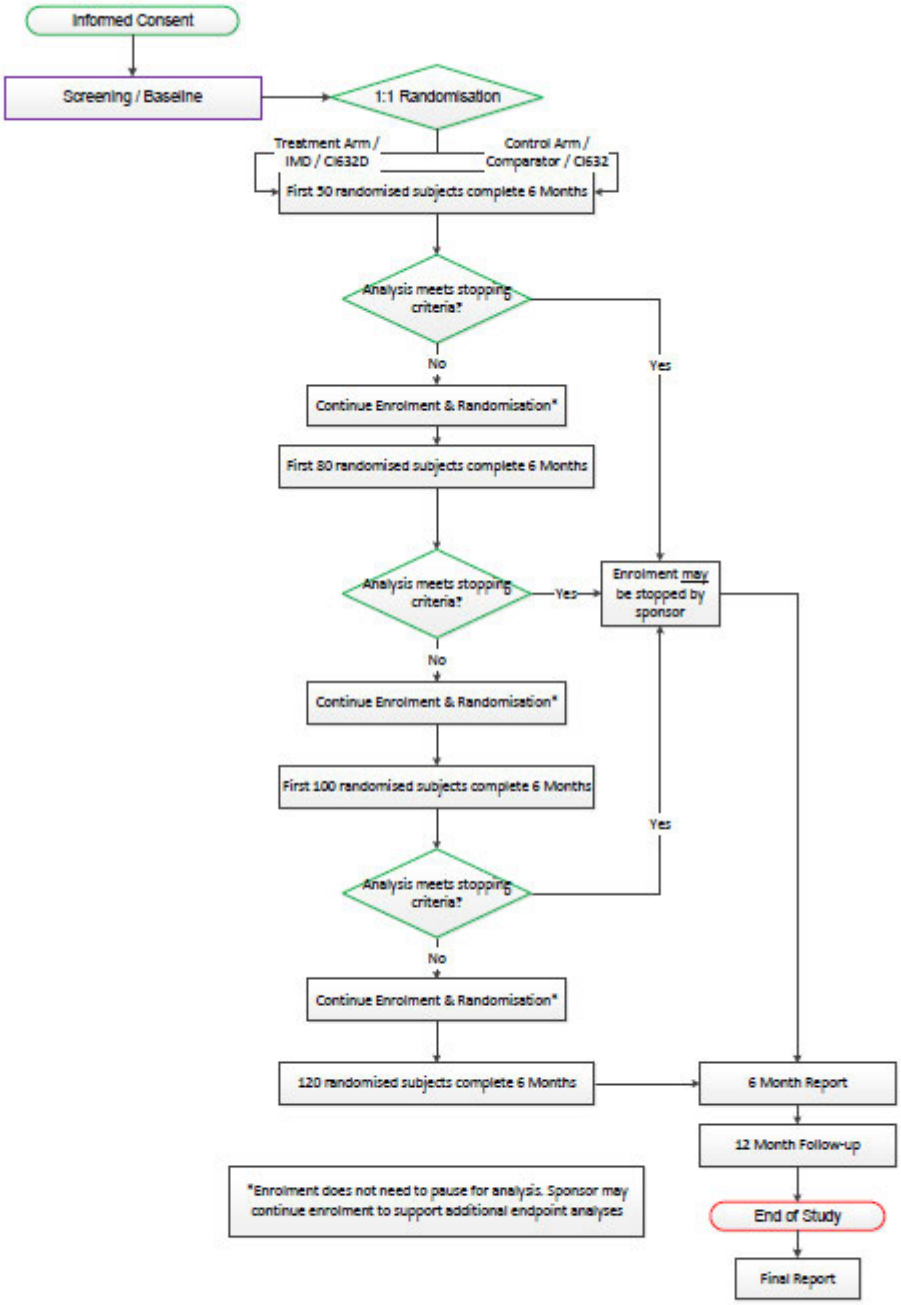

Figure 7: Schematic for study.

The clinical investigation is a pivotal, prospective, multi-centre, randomised, blinded, two-arm, parallel, comparator-controlled trial in an adult population with post-lingual, bilateral, moderate to profound sensorineural hearing loss.

Clinical investigation subjects include adults (age ≥ 18 years old) with post-lingual, bilateral, moderate to profound sensorineural hearing loss at 5-25 clinical investigation sites in Australia, New Zealand, and United States. Eligibility criteria includes assurance subjects are able to participate in either arm of the trial, present with similar profiles to current device indications, and able and willing to complete the clinical investigation. Potential subjects will be formally consented to participate in the clinical investigation and all eligibility criteria confirmed prior to 1:1 randomisation into one of two arms: implantation with CI632D IMD or CI632 comparator device.

Randomised subjects cannot be replaced and will count toward the total trial population. Up to 60 subjects will be randomised into each arm for a combined total of up to 120 randomised subjects. A group sequential analysis will be completed which may impact the final number of subjects.

To limit bias during data collection, the subject and clinicians completing questionnaires and speech perception testing will be blinded to the randomisation assignment, see Section 7.2.7. The implanting surgeon will not be blinded to the randomisation assignment.

The primary endpoints assess the efficacy of the IMD by measure of impedance and speech perception of words in quiet. Secondary endpoints include efficacy assessment via sound processor battery life estimation and safety assessment via adverse event collection and speech perception performance tested in specified listening conditions. Data collection for endpoint assessment and all other clinical investigation measures are listed in the Schedule of Events.

The Sponsor's data monitoring requirements are summarised in Section 22.1 and described in detail in a separate Monitoring Plan. An Independent Data Monitoring Committee (IDMC) will be used for safety and compliance oversight. Activities of the IDMC are documented in the IDMC Charter.

7.1.1 Design Rationale

This clinical investigation will compare the effects of long-term dexamethasone delivery via the CI632D IMD to a standard CI632 comparator device. For the assessment, qualifying subjects will be randomised to either the IMD or comparator. The current clinical investigation has a prospective design, with 1:1 randomisation to the dexamethasone treatment arm (CI632D) or the control arm (CI632).

The CI632 control arm represents the standard of clinical care for an adult population with post-lingual, bilateral, moderate to profound sensorineural hearing loss and who obtains limited benefit from appropriately fitted hearing aids. A randomised controlled trial (RCT) research design is appropriate as it has high internal and external validity, whereby the differences observed between arms are related to the intervention being tested and can be generalized into clinical practice and the general population.

Subjects and delegated study personnel completing the specified assessments will be blinded to the randomisation assignment to ensure that the data are captured without bias. Surgeons will not be blinded to the randomisation assignment because of the differences in the appearance of the IMD and comparator device. Although dexamethasone is commonly used during surgery, its use will be restricted in both arms of the study to avoid confounding effects on the evaluation of extended-release dexamethasone.

The clinical investigation will include subjects who are indicated for a cochlear implant following candidacy evaluation assessments and those that meet additional eligibility criteria (see sections 7.2.1 and 7.2.2). Potential subjects will be given information about the clinical investigation design as part of the informed consent process and will be required to consider their ability to commit to completing the study according to the CIP. Only subjects that can provide consent for themselves and who meet all inclusion and no exclusion criteria will be eligible to participate in the study.

All subjects will complete a 12-month follow-up period with 7 scheduled post-cochlear implant follow-up visits. Data collection requirements are structured to rigorously evaluate the endpoints and correspond to the standard of care for cochlear implant recipients. However, additional study visits and data collection outside the standard of care are expected and will enable the collection of the required data to fulfil primary and secondary endpoints.

Blinding of subjects and study personnel to randomised treatment will be maintained until final database lock to protect the integrity of the data. Database lock will occur when all data have been entered into the electronic data capture (EDC) system. After this time it will not be possible to amend the data, which will then be ready for analysis. Adverse events will be collected and reviewed by a designated blinded investigator throughout the clinical investigation.

The efficacy of dexamethasone will be evaluated by comparing MP1+2 impedance measurements between the IMD and comparator groups at six months post-implantation and also by evaluating the clinical utility of the IMD by comparing change in CNC word in quiet speech perception scores at six months post-cochlear implant and baseline (primary endpoints). The timing of the primary endpoint measurement is based on an evaluation of the impedance data obtained in the feasibility clinical investigation CLTD5495. In this study, MP1+2 impendences for both the IMD and comparator device stabilised by four weeks after activation and there were no significant differences between adjacent time points for the remainder of the 24 month study period. Measurement of MP1+2 impedances, in which the impedance of each intracochlear electrode is measured with reference to both extracochlear electrodes (see section 5.1.5), is the standard measurement of electrode impedances and is used because it most closely reflects the electrode impedances present during normal use of the implant. In addition, four point impedances will be measured as an exploratory endpoint. Four point impedance measurements require the stimulation of two electrodes while recording the impedance of the intervening two electrodes. The advantage of four point impedance is that, since non-stimulating electrodes are used for measurement, the impedance of the surrounding tissue can be measured without the influence of the electrode-tissue interface, which usually has a much greater impedance.

The size of the study population has been powered to determine whether the electrode impedances of CI632D are lower than the comparator device. However, clinical data on the effects of dexamethasone delivery via cochlear implant are limited, and there are no clinical data on dexamethasone delivery via a Slim Modiolar electrode array (the electrode array used in the CI632 and CI632D). Therefore, the clinical investigation will be completed under a group sequential design where a formal interim analysis occurs following the 6 month endpoint of analysis groups of 50, 80, 100 and 120 randomised subjects (see Section 9.10 Interim Analysis). Enrolment does not need to stop for group analysis and the Sponsor may choose to randomise 120 subjects to capture more data for other endpoint analyses.

7.2 Subjects

Written, informed consent must be obtained from the subjects before any study procedures are initiated. If historical exams and assessments meet specified criteria, they do not need to be repeated.

An independent Sponsor representative (employee of Cochlear™) will confirm certain eligibility criteria prior to Randomisation in accordance to inclusion and exclusion criteria. A representative may be either a qualified ENT surgeon, audiologist or qualified subject matter expert. A representative will not participate in any other capacity in the management of the clinical investigation and will be trained on the CIP and Good Clinical Practice (GCP). Following consent of a subject, the site must provide a de-identified audiogram, detailed CT read summary and speech perception results to be reviewed by a representative.

Prior to randomisation of a subject, the representative must have confirmed eligibility, and all screening and baseline assessments must be completed and entered into the EDC in accordance with the Schedule of Events.

Throughout the duration of the clinical investigation, source document records must be maintained to validate subject data.

[redacted]

7.2.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria described below to be eligible for this clinical investigation.

1. Postlingual, bilateral, moderate to profound sensorineural hearing loss, defined by a pure-tone average (PTA):
   a. ≥ 40 dB HL at 250 through 1000 Hz and,
   b. ≥ 65 dB HL at 2000 through 8000 Hz.
2. Preoperative aided word score is 40% correct or less in the ear to be implanted (60% or less in the contralateral ear).
3. 18 years or older at time of consent.
4. Willing to be randomised into either a treatment (CI632D) or control (CI632) arm.
5. Evidence of pneumococcal vaccination (e.g. Pneumovax) according to local guidelines prior to randomisation.
6. Fluent speaker in the local language used to assess clinical performance as judged by the investigator.
7. Willing and able to provide written informed consent.

7.2.2 Exclusion Criteria

Subjects who meet any of the exclusion criteria described below will not be eligible for this clinical investigation.

1. Deafness due to lesions of the acoustic nerve or central auditory pathway.
2. Diagnosed active middle-ear infections or history of middle ear infection within the past six months prior to randomisation. Must not have had surgery, drainage, pain, or need for oral or topical antibiotics within the past six months in the ear to be implanted.
3. Previously reported diagnosis of auditory neuropathy.
4. Previously reported diagnosis of Large Vestibular Aqueduct Syndrome (LVAS), Meniere's disease, or cochlear hydrops.
5. Prior history of surgery in the ear to be implanted (excluding grommets).
6. Current use of grommets or evidence of unhealed tympanic membrane perforation.
7. Ossification, otosclerosis, malformation or any other cochlear anomaly, such as common cavity, that might prevent complete insertion of the electrode array, as confirmed by imaging.
8. Existing cerebrospinal fluid (CSF) shunts or drains, existing perilymph fistula, skull fracture or CSF leaks.
9. History of bacterial meningitis.
10. Known allergic reaction or contraindication to dexamethasone or corticosteroids.
11. Use of ototoxins and/or steroids (does not include topical or inhaled steroids) up to 30 days prior to randomisation.

    Note: Systemic ototoxin and/or steroids therapy must be completed at least 7 days prior to Screening/Baseline audiometric and speech testing
12. Evidence of severe or greater sensorineural hearing loss prior to five years of age, as reported by the subject.
13. Severe to profound sensorineural hearing loss for more than 20 years, as reported by the subject.
14. Existing contralateral cochlear implant.
15. Medical plan to implant a contralateral cochlear implant during the clinical investigation.
16. History of recurrent otitis media or chronic otitis media in the ear to be implanted within the past six months prior to randomisation.
17. Medical or psychological conditions that contraindicate general anaesthesia, surgery or participation in the clinical investigation.
18. Pregnant or breastfeeding women. Women who plan to become pregnant during the course of the investigation.
19. 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.
20. Additional disabilities that may affect the subject's participation or safety during the clinical investigation.

21. Unable or unwilling to comply with all the requirements of the clinical investigation as determined by the Investigator.
22. Investigator site personnel directly affiliated with this study and/or their immediate families; immediate family is defined as spouse, parent, child, or sibling.
23. Cochlear™ employees or employees of Contract Research Organisations or contractors engaged by Cochlear for the purposes of this investigation.
24. Currently participating, or participated within the last 30 days, in another interventional clinical investigation/trial involving an investigational drug or device.

7.2.3 Number of Subjects Required

Up to 120 subjects will be randomised into the clinical investigation. Randomisation is 1:1 to the treatment or control arm. See Section 9.4 for the sample size calculations.

The clinical investigation will be completed under a group sequential design where analysis of the primary endpoints occurs following the 6-month endpoint for the first 50 randomised subjects. If stopping criteria (see Section 9.10) are not met at this first analysis of both primary endpoints, then enrolment will continue, and analysis will be completed again for the first 80 randomised subjects at 6 months post-cochlear implant. If stopping criteria are not met again, then enrolment will continue, and analysis will be completed again for the first 100 randomised subjects at 6-months post-cochlear implant. If stopping criteria is not met again enrolment will continue for a total of 120 subjects. Enrolment does not need to stop for group analysis and the Sponsor may choose to randomise 120 subjects to capture more data for other endpoint analyses.

7.2.4 Vulnerable Populations

The clinical investigation aims to treat individuals with post-lingual, bilateral, moderate to profound hearing loss. There is a risk that subjects will have difficulty completing the informed consent process due to limited hearing and potential cognitive impairments, which may be associated with hearing impairment. Recruitment must include processes to ensure the investigator discusses the informed consent with all subjects and all questions are answered to the subject's satisfaction. Additional measures taken to review the study with potential subjects must be documented in the informed consent process. The Ethics Committee (EC) may have additional requirements which must be followed.

IMD and comparator devices may be provided at no cost to the subject or hospital. This financial model may provide added benefit to potential subjects and clinical investigation sites. Subjects may be compensated for their time in the clinical investigation in alignment with fair market value. The informed consent process must include ensuring subjects are not choosing to participate for the financial benefits, and site personnel must not use the financial model to coerce subjects to participate in the clinical investigation.

Women that are pregnant, breastfeeding or women who plan to become pregnant during the clinical investigation are excluded from participation. Women of childbearing potential will be required to take a pregnancy test prior to randomisation and agree to use appropriate (as deemed by the Investigator) methods to avoid becoming pregnant during their participation in the clinical investigation.

7.2.5 Recruitment and Study Duration

The following subject status definitions apply:

- Enrolled: A subject that has a signed the Informed Consent form for the study.
- Screen Fail: An Enrolled subject that has been determined to not meet one or more eligibility criteria.
- Participated: Consented subjects who have met all eligibility criteria, have qualified for surgery, and have been randomised.
- Implanted: A participating subject who has received the IMD/comparator in accordance to the randomisation assignment
- Treatment Failure: A participating subject who has not been successfully implanted or does not receive the IMD or comparator treatment in accordance with the randomisation assignment
- Discontinued: An Enrolled subject who withdrew consent, was discontinued by the Investigator or Sponsor before the expected End of Study visit or lost to follow-up. Discontinued subjects may still have safety follow up data collection until their scheduled End of Study visit, for reasons described in section 7.2.6.
- Completed: Enrolled subjects who complete the required treatment and visit schedule.

The recruitment period for the clinical investigation is estimated to be 28 months from the time of first subject consent to recruitment of the last subject. If the recruitment numbers increase following the interim analysis, the recruitment period is expected to extend approximately one month for every eight enrolments.

The expected duration of each subject's participation in the clinical investigation, is 14 months. From the time of implant through to the End-of-Study visit is 12 months after implantation.

Therefore, the anticipated total duration of the clinical investigation is 42 months. Clinical Investigation completion is at the last subject's last visit. In the event of ongoing SAEs/SADEs at the time of a subject's last visit, the subject's clinical investigation completion will be extended for a further 30 days, or until resolution or stabilisation of the event, whichever comes first.

7.2.6 Criteria and Procedures for Subject Withdrawal

Subjects can decide to withdraw from the investigation at any time. The Investigator shall ask the reason(s), however subjects have the right to withhold their reason if preferred. The reason for withdrawal should be documented in the subject's source files and the case report form (CRF), if provided.

The Investigator or Sponsor may also decide to withdraw a subject from the clinical investigation or stop the use of the investigational device if it is considered to be in the subject's best interests.

Subject withdrawal may be for any of the following reasons:

- Adverse Event (AE)
- Device Deficiency (DD)
- CIP or GCP deviation
- Subject withdrew consent
- Subject lost to follow-up

- Subject death
- Sponsor decision
- Investigator decision
- Other (specify): Treatment failure

If subject withdrawal is due to problems related to the IMD and/or comparator safety or performance, the Investigator shall ask for the subject's permission to continue in safety follow up (for example, adverse events and device deficiencies) until their scheduled End-of-Study visit.

If a subject is lost to follow-up, every possible effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation. At least 3 separate attempts taken to contact the subject must be documented.

Participating subjects who are withdrawn/discontinued will not be replaced.

7.2.7 Randomisation Procedures

Subjects who meet all eligibility criteria with approval by an independent Sponsor representative, will be randomised to an intervention based on a computer-generated randomisation schedule prepared by a Statistician. Subjects will be randomly assigned to one of two interventions using a ratio of 1:1 within each site. Assignment to intervention groups will be determined by a system defined under a randomization plan. The investigational medical device or comparators will be packaged and labelled for blinded randomization.

7.2.7.1 Blinding Procedures

The clinical investigation is partially blinded, with the subject and delegated site personnel who will administer tests and subject facing questionnaires and program the device being blinded to the treatment assignment. This is to reduce risk of bias during these assessments. Training to blinding and unblinding procedures will be provided prior to site personnel prior to them completing clinical investigation activities. Where required for resourcing reasons, prior approval may be sought from the Sponsor for site personnel to be blinded to the subjects they will test, but not the subjects they will not test.

IMD and comparator packaging will be visually identical with exception of tracking numbers that will not identify the device type.

Investigators performing the cochlear implant surgery will not be blinded to the randomisation assignment. Blinding the surgeon is not possible as there are visually apparent differences between the two devices. Surgeons and other unblinded site personnel will be instructed to not disclose randomisation assignment through discussion, documentation or other means. The surgeon will be instructed to document the “cochlear implant” (or similar) was implanted in medical records. The monitor will need to ensure blinded site personnel do not become unblinded during discussions.

The Data Management Plan includes processes for managing the randomisation process. The Sponsor will not be blinded to the randomisation assignment. The Sponsor’s delegated monitor(s) will be blinded to the randomisation assignment.

Investigators completing adverse event assessments will be blinded to the randomisation assignment. The IDMC will be aware which randomisation group a subject is randomised, but identification of the group (CI632 or CI632D) will not be provided to the IDMC. The Sponsor will only analyse data as outlined in this clinical investigation plan. The Sponsor will provide data to the IDMC as outlined in the IDMC Charter and as requested; the Sponsor will not evaluate this data.

At the end of the clinical investigation, the database will be locked. After this time point, subjects and blinded site-personnel may be unblinded to the randomisation assignment and subjects' medical records may be updated.

If a subject becomes unblinded or an unblinded site personnel completes assessments with subjects they are unblinded to, it must be recorded in the EDC as a protocol deviation. If site personnel become unblinded, efforts should be made to assign an alternative blinded site personnel to complete assessments with the subject. In the event blinding must be broken, the decision should be documented by the Principal Investigator and the Sponsor should be notified.

Designated Sponsor personnel will have access to the randomisation assignments. If unblinding is required, the site may contact the Sponsor to retrieve the subject's randomisation assignment.

7.2.8 Post-investigation Medical Care

Following the investigation, subjects will continue with standard of care treatment.

7.3 Evaluations and Procedures

For each enrolled subject, the clinical investigation will include Screening and Baseline procedures, Randomisation assignment to the IMD or comparator, Surgery to implant the assigned device, and seven post-surgical follow-up visits.

7.3.1 Screening/eligibility

Screening and Baseline may be completed in parallel. If historical exams are available, they must be within the timeframes indicated below. The following must be completed prior to Randomisation:

- Written informed consent: must be completed before any study specific procedures are completed.
- Demographics: document age and sex.
- Eligibility: confirm subject meets all inclusion criteria and no exclusion criteria (see section 7.2.1 and 7.2.2). Source documentation must be available before confirming eligibility.
- Hearing History: document history of hearing loss (may be subject reported)
- Device history: document history with hearing aids and cochlear implant (contralateral ear) (may be subject reported)
- Medical History: document medical history.

- Audiogram: must be completed less than 90 days prior to randomisation and document bilateral, moderate to profound hearing loss. (see section 7.3.2.2)
- Speech Perception testing: must be completed less than 90 days prior to randomisation. Subject's own or loaner hearing aid must be optimally fitted using National Acoustics Laboratories' hearing aid fitting formula to confirm eligibility for clinical investigation. (see section 7.3.2.3)
- High Resolution CT imaging: must be completed within 2 years prior to randomisation and show entire cochlea per the imaging protocol. (see section 7.3.1.6)
- Health Survey (HS): must be completed within 90 days prior to randomisation. (see section 7.3.2.1)
- Hearing-Impaired Montreal Cognitive Assessment (HI-MoCA): must be completed within 90 days prior to randomisation. (see section 7.3.2.1)
- Health Utilisation Index III (HUI3): must be completed within 90 days prior to randomisation. (see section 7.3.2.1)
- Dizziness/Tinnitus Questionnaire (DTQ): must be completed within 90 days prior to randomisation. (see section 7.3.2.1)
- Dizziness Handicap Inventory (DHI): must be completed within 90 days prior to randomisation as required by DTQ. (see section 7.3.2.1)
- Tinnitus Handicap Inventory (THI): must be completed within 90 days prior to randomisation as required by DTQ. (see section 7.3.2.1)

7.3.2. Performance/Effectiveness

7.3.2.1. Description of Questionnaires

The following subject facing questionnaires will be completed during the clinical investigation at specified Visits:

- Hearing-Impaired Montreal Cognitive Assessment (HI-MoCA): clinician guided questionnaire that assists in the detection of cognitive impairment. The questionnaire was developed by V. Lin and Sunnybrook Health Sciences Centre (Toronto, Canada).
- Health Survey (HS): clinician guided questionnaire to review for potential inflammatory conditions. The questionnaire was developed by the Sponsor.

The Health Survey (HS) is a clinician guided questionnaire that was developed by the Sponsor to collect health-related data that may be linked to inflammatory conditions that could affect impedance measurements. These include:

- Body temperature
- Blood pressure
- Menstrual cycle phase (if appropriate)
- Relevant medical history, including arthritis, allergies, frequent headaches, other chronic inflammatory conditions [information is captured in the Medical History form]

- Use of antibiotic or anti-inflammatory medication [information captured in the Concomitant Medications Form]

- Other applicable informationHealth Utilities Index III (HUI3): a self-administered questionnaire that includes a rating scale used to measure general health status and health-related quality of life (HRQoL). The questionnaire was developed by Health Utilities Inc.
- Dizziness/Tinnitus Questionnaire (DTQ): clinician guided questionnaire to review dizziness and tinnitus characteristics. The questionnaire was developed by the Sponsor.
- Dizziness Handicap Inventory (DHI): self-administered questionnaire that includes a scale to identify difficulties that you may be experiencing because of dizziness. The questionnaire was developed by Dr. G.P. Jacobson and Dr. C.W. Newman.
- Tinnitus Handicap Inventory (THI): self-administered questionnaire that identifies difficulties that you may be experiencing because of tinnitus. The questionnaire was developed by Dr. C.W. Newman, Dr. G.P. Jacobson, and Dr. J.B. Spitzer.
- Blinding Questionnaire (BQ): self-administered questionnaire to assess subject's understanding of randomisation assignment. The questionnaire was developed by the Sponsor.

7.3.2.2. Description of Audiometric Testing

7.3.2.2.1. Unaided thresholds

Unaided audiometric thresholds will be obtained for each ear independently, 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. Preoperatively, unaided audiometric thresholds will be obtained in both ears. Post-operatively unaided audiometric thresholds will be obtained in the implanted ear to assess the impact of cochlear implantation.

- Air Conduction: 250, 500, 750, 1000, 1500 2000, 3000, 4000, 6000 & 8000 Hz

  Hearing thresholds that exceed the air conduction limits of the audiometer, where the participant reports feeling the acoustic stimuli, shall be recorded as vibrotactile (VT). Appropriate masking will be employed where required.

- Bone conduction: 250, 500, 750, 1000, 1500, 2000, 3000 & 4000 Hz

  Where the participant reports feeling rather than hearing the acoustic stimuli, the response shall be recorded as vibrotactile (VT). Appropriate masking will be employed where required.

7.3.2.2.2. Aided thresholds: 250, 500, 1000, 2000 & 4000 Hz

Aided audiometric thresholds will be obtained for both ears preoperatively and the implanted ear post-operatively using warble tones. The contralateral ear will be plugged for all tests.

7.3.2.3. Description of Speech Perception Testing

The following speech perception testing will be completed during the clinical investigation:

1. Two lists of CNC words at 60 dBA in quiet delivered from a speaker located directly in front of the listener (S0):

- Screening/Baseline testing scenarios:
    i. Each ear in the aided condition, with the contralateral ear plugged.
    ii. Both ears together in the aided condition.
- Post-operative:
    i. Unilateral: Cochlear implant[p] with the contralateral ear plugged.
    ii. Bimodal: Cochlear implant[p] with a hearing aid in contralateral ear.

2. One list of AzBio sentences at 60 dBA in quiet delivered from a speaker located directly in front of the listener (S0):
    - Screening/Baseline testing scenarios:
        i. Each ear in the aided condition, with the contralateral ear plugged.
        ii. Both ears together in the aided condition.
    - Post-operative:
        i. Unilateral: Cochlear implant[p] with the contralateral ear plugged.
        ii. Bimodal: Cochlear implant[p] with a hearing aid in contralateral ear.

The American AzBio sentences are recorded in Australian and New Zealand accents for use at Australian and New Zealand sites.

In the United States, contralateral hearing aids may be provided to subjects should their own hearing aid not provide optimal therapy.

7.3.2.4. Description of Battery Life Estimation Test

Measuring projected sound processor battery life will be completed during the clinical investigation on the ear with CI632/CI632D. [redacted]

- [redacted]
- [redacted]

7.3.2.5. Impedance Measurements

Four point impedance measurements are measured using Custom Sound® EP software or the latest Cochlear software platform for advanced objective measurements. The four point impedance measurement is an investigational measurement and therefore requires a research key in order to activate this measurement in

[p] Some individuals will make use of the ipsilateral acoustic component to augment the cochlear implant and as a result allow access to Hybrid stimulation. In these cases, "Cochlear implant" would correspond to Hybrid (i.e., cochlear implant + hearing aid in the same ear).

Custom Sound EP. FDA reviewed the four point impedance measurement during the IDE review of G200098. The Sponsor may provide a laptop to use this software during the cochlear implant operation and at study visits. A CP910/CP920 sound processor will be used when testing with Custom Sound EP at all study visits.

7.3.2.6. CT Core Lab

Anatomy and cochlear implant electrode placement will be reviewed using high resolution CT of preoperative and post-operative CT scans. Independent review analysis of CT imaging will be completed by a CT corelab.

7.3.2.7. Schedule of Events

A table with a schematic overview of the events is provided in section 3. Please refer to section 3 for details regarding the timing and frequency of the events. In this section more information about the separate events is given.

7.3.2.7.1. Screening and Baseline

Screening and Baseline is described in section 7.3.1

7.3.2.7.2. Randomisation

Randomisation may only be completed once all activities under Screening and Baseline are completed, subject screening/baseline data is entered into the EDC, and eligibility has been confirmed by an independent Sponsor representative.

The ear to be implanted will need to be determined prior to randomization and must be compliant with the inclusion and exclusion criteria. The decision will be made between the investigator, audiologist and subject, and the justification for ear selection must be documented.

7.3.2.7.3. Surgery (day 0)

Data collection from time of Surgery through discharge from hospital includes:

- High Resolution CT: Post insertion to assess electrode placement. Cone beam CT and flat panel CT are examples.

  OR

- X-Ray or fluoroscopy (C-arm): required intraoperatively to assess placement of electrode using Modified Stenver's View. X-ray or fluorscopy will be repeated if electrode is repositioned/replaced.
    - If final placement of cochlear implant is not positioned correctly (tip foldover or translocation), the subject will remain in the clinical investigation and complete all assessments. Outcome will be documented in the CRF.
- Electrode Electrical Testing: must be completed intraoperatively after final placement of electrode. If electrode position is altered or second device is used, testing must be repeated. Complete tests in the following order:
    1. Impedances (MP1+2 and Four point).
    2. AutoNRT® (standard 9 electrodes).
- Surgical Questionnaire: surgeon's review of surgical implant.
- Discharge Summary: subject's stay in hospital.

The following requirements are to be followed for the Surgery:

- At the surgeon's discretion, dexamethasone may be utilised in anaesthesia, IV and take-home pack, which will be documented in the CRF.
- Dexamethasone may not be used to treat (e.g. topically) the cochlear implant electrode.
- Dexamethasone may not be used within or near the ear/cochlea.
- Cochlear implant electrode may not be dipped in saline, hyaluronic acid (healon), or other treatment prior to insertion.
- The implant procedure must follow Instructions for Use (IFU). A back up CI632D or CI632 may be required if preparation/insertion is not possible according to IFU.
- Following impedance and/or NRT testing, if the electrode is re-inserted or replaced with a new device, the testing must be repeated

If the IMD or comparator is inserted but not implanted (eg implanted with commercial device), the subject should remain in the clinical investigation for 30 Days or until all AEs are resolved (whichever is longer).

If the IMD or comparator is implanted and then explanted during Surgery or at a later date, the subject should remain in the clinical investigation for 30 Days or until all AEs are resolved (whichever is longer).

7.3.2.7.4. Visit 1: 0-10 days post-Surgery

Data collection 10 days or less post-insertion and after-effects of anaesthesia have worn off:

- Health Survey (HS): complete prior to impedance measurements.
- Impedance (MP1+2 and Four point).
- High Resolution CT: Post-operative imaging within 3 months (before end of Visit 4 window) to assess electrode placement. Cone beam CT and flat panel CT are examples. Not applicable if completed intraoperatively.

7.3.2.7.5. Visit 2: 15 Days post-Surgery / Activation (±7 days)

- Health Survey (HS): complete prior to impedance measurements.
- Blinding Questionnaire.
- Impedance (MP1+2 and Four point): measured two times:
    - Before activation.
    - After activation and mapping is complete.
- Cochlear Implant Activation with selected sound processor.
- CI optimisation / Mapping.
- High Resolution CT: Post-operative imaging within 3 months (before end of Visit 4 window) to assess electrode placement. Cone beam CT and flat panel CT are examples. Not applicable if completed intraoperatively.

7.3.2.7.6. Visit 3: 30 days after Visit 2 (±5 days)

Thirty days after the IMD/comparator is activated, the following should be completed:

- Audiogram
- Health Utilisation Index III
- Dizziness/Tinnitus Questionnaire (DTQ)
- Dizziness Handicap Inventory (DHI)
- Tinnitus Handicap Inventory (THI)
- Health Survey: complete before impedance measurements
- Impedance (MP1+2 and Four point) (complete before CI optimisation / Mapping)
- CI optimisation / Mapping
- Battery Life Estimation Test with 900Hz/channel and 8 max. (as required) (complete after CI optimisation / Mapping)
- High Resolution CT: Post-operative imaging within 3 months (before end of Visit 4 window) to assess electrode placement. Cone beam CT and flat panel CT are examples. Not applicable if completed intraoperatively.

7.3.2.7.7. Visit 4: 3 Months post-Surgery (90 days, ±14 days)

- Audiogram
- Health Utilisation Index III
- Dizziness/Tinnitus Questionnaire (DTQ)
- Dizziness Handicap Inventory (DHI)
- Tinnitus Handicap Inventory (THI)
- Health Survey: complete before impedance measurements
- Speech Perception Testing
- Impedance (MP1+2 and Four point) (complete before CI optimisation / Mapping)
- CI optimisation / Mapping
- Battery Life Estimation Test with 900Hz/channel and 8 maxima. (as required) (complete after CI optimisation / Mapping)
- High Resolution CT: Post-operative imaging within 3 months (before end of Visit 4 window) to assess electrode placement. Cone beam CT and flat panel CT are examples. Not applicable if completed intraoperatively.

7.3.2.7.8. Visit 5: 6 Months post-Surgery (180 days, +14 days)

- Audiogram
- Health Utilisation Index III

- Dizziness/Tinnitus Questionnaire (DTQ)
- Dizziness Handicap Inventory (DHI)
- Tinnitus Handicap Inventory (THI)
- Health Survey: complete before impedance measurements.
- Blinding Questionnaire
- Speech Perception Testing
- Impedance (MP1+2 and Four point) (complete before CI optimisation / Mapping)
- CI optimisation / Mapping
- Battery Life Estimation Test with 900Hz/channel and 8 max. (as required) (complete after CI optimisation / Mapping)

7.3.2.7.9. Visit 6: 9 Month post-Surgery (270 days, ±30 days)

- Audiogram
- Dizziness/Tinnitus Questionnaire (DTQ)
- Dizziness Handicap Inventory: Should be completed in accordance with DTQ.
- Tinnitus Handicap Inventory: Should be completed in accordance with DTQ.
- Health Survey: complete before impedance measurements.
- Impedance (MP1+2 and Four point) (complete before CI optimisation / Mapping)
- CI optimisation / Mapping
- Battery Life Estimation Test with 900Hz/channel and 8 max. (as required) (complete after CI optimisation / Mapping).

7.3.2.7.10. Visit 7: 12 Month post-Surgery (365 days, +30 days)

- Audiogram
- Health Utilisation Index III
- Dizziness/Tinnitus Questionnaire (DTQ)
- Dizziness Handicap Inventory (DHI)
- Tinnitus Handicap Inventory (THI)
- Health Survey: complete before impedance measurements.
- Speech Perception Testing
- Impedance (MP1+2 and Four point) (complete before CI optimisation / Mapping)
- CI optimisation / Mapping
- Battery Life Estimation Test with 900Hz/channel and 8 max. (as required) (complete after CI optimisation / Mapping).

7.3.2.7.11. End-of-Study

Document reason for Subject's study completion. Ensure device deficiencies, device exposure, adverse events, concomitant medication and deviations are reviewed, and end dates recorded where appropriate.

7.3.2.8. Collected from point of Consent

- Concomitant Medication: includes all prescription medications, routine over-the counter medications, and any use of steroids. Concomitant medications should be reviewed at each visit.
- Protocol Deviations: approved and unapproved deviations

7.3.2.9. Collected from point of Randomisation

- Adverse Events and review of ongoing adverse events. Adverse events should be reviewed at each visit.

7.3.2.10. Collected from point of Surgery

- Device Exposure
- Device Deficiency

7.3.2.11. Remote Programming

Cochlear™'s Remote Programming tool may be used as an alternative data collection option, should a subject not be able to return to clinic due to the impact of the COVID-19 pandemic at Visit 3, Visit 4, Visit 5, Visit 6 and Visit 7. Equipment (which may include laptop, pod, virtual machine, sound processor cables and N6 Sound Processor) will be mailed to subject by the clinic to complete the impedance testing. The subjects own N7 Sound Processor may be used as well. After testing is completed, the subject mails the equipment back to the clinic.

The following assessments may be completed with Remote Programming:

- Impedance (MP1+2 and four point) (complete before CI optimisation / Mapping)
- CI optimisation / Mapping
- Battery Life Estimation Test with 900Hz/channel and 8 max. (as required) (complete after CI optimisation / testing)

Use of Remote Programming will be recorded in the eCRF. Protocol deviations are required to be entered if the subject cannot attend the clinic for other assessments.

7.3.2.12. Electrical Testing

Electrocochleography (ECochG) is permitted outside of the clinical investigation. ECochG and other cochlear implant electrical testing not specified within this clinical investigation plan must be completed after clinical investigation required electrical testing (e.g. impedance or NRT).

7.3.3 Safety Evaluations and Procedures

The risks and anticipated ADEs for the CI632D and CI632, as identified in Sections 8.2 and 8.3 of the CIP, will be assessed in the clinical investigation via reporting of all AEs/ADEs from the time of first subject randomisation until last subject last visit. Individual collection of adverse events will end when the subject exits the clinical investigation. Safety data review will be conducted by the Sponsor's Safety Officer in accordance with the Sponsor's standard operating procedures.

Safety data review will be conducted by an Independent Data Monitoring Committee (IDMC) in accordance with the defined Charter for operations.

Upon review of data available in the CRF, the Sponsor or IDMC may query data or request de-identified source documents to review the event.

7.3.3.1. Concomitant Medication and Therapies

Concomitant Medications recorded in the CRF includes all prescription medications, routine over-the counter medications, and any use of steroids. Dexamethasone cannot be delivered into the ear or used to treat the electrode (Section 7.3.1.). There are no further prohibited medications under this clinical investigation. Medications taken for anaesthesia purposes during surgery will not be recorded unless their use deviates from normal clinical practice.

7.4. Equipment Used for Evaluations and Procedures

The clinical investigation includes use of equipment to complete assessments. Equipment including software, firmware, sound equipment (e.g. speakers) are used to assess impedance measurements and speech perception performance. Software and firmware should be kept current at the direction of the Sponsor. Versions of applicable software and firmware used for each subject assessment should be documented. For equipment used in this clinical investigation, records of equipment calibration requirements and the calibration records must be maintained in site files and copies provided to the Sponsor. As part of the Site Initiation Visit, requirements and records should be provided to the Sponsor and records to be confirmed to be up-to-date. Records will be monitored at interim monitoring visits, in accordance with the Sponsor's Monitoring Plan.

Custom Sound® and Custom Sound® EP software or the latest Cochlear software platform for advanced objective measurements, will be used to measure MP1+2 impedances, four point impedances and other collected data points. Four point impedances will be measured during stimulation of two intracochlear electrodes while measuring impedances on two separate intracochlear electrodes. Measurement of four point impedances with Custom Sound EP software allows assessment of tissue impedance without measuring the impedance of the interface and aims to provide information about fibrous tissue growth around the electrode array. Upload of all Custom Sound data to Sponsor database for analysis is required, which may be done automatically or manual file sharing.

The Sponsor may provide equipment to utilise Remote Programming should the COVID-19 pandemic impact a subject's ability to visit the clinic. Equipment (may include laptop, pod, virtual machine, sound processor cables and N6 Sound Processor) will be mailed to subject by the clinic to complete the impedance testing and

returned after the visit. The use of equipment will be logged and reviewed as per the Sponsor's Monitoring Plan.

Speech perception performance in quiet for monosyllabic word and sentence lists will be assessed using a loudspeaker configuration with the signal from the front, zero Azimuth (S_0) at head height and 1 metre distance. The Sponsor may provide equipment (such as laptop, software, microphone and speaker) if the clinical site does not have it available.

7.5. Sponsor Role in Conduct of the Clinical Investigation

The Sponsor may support certain activities at the clinical investigation site. Sponsor representatives may be present in the operating room with the surgical team and subject. The representative will not provide medical assistance and will not discuss the trial with the subject. During the surgery or during study visits, the sponsor representative may assist in completing the electrical testing of the cochlear implant.

The Sponsor may pay for third party clinical trial support ("coordinator") at clinical investigation sites should there be resource constraints, which may support subject recruitment, data entry and reporting under the authority of the Principal Investigator. The coordinator will be required to comply with hospital policy and will be trained on the CIP and GCP. The coordinator will not complete any activities on behalf of the Sponsor.

An independent Sponsor representative will review evidence of subject eligibility before the subject is accepted for randomisation. This representative will not work in any other capacity of the clinical investigation and will be trained on the CIP and GCP.

8. BENEFITS AND RISKS OF THE INVESTIGATIONAL MEDICAL DEVICE AND CLINICAL INVESTIGATION

8.1 Anticipated Clinical Benefits

The anticipated clinical benefits include the benefits associated with the CI632, as described in the Physician's Guide. Benefits may include:

- detection of medium to loud environmental sounds at comfortable listening levels.
- detection of conversational speech at comfortable listening levels.
- limited improvement in the recognition of environmental sounds.
- limited ability to use the telephone.
- improvement in speech recognition in a quiet environment in the implanted ear.
- improvement in speech recognition in a noisy environment.
- improvement in overall sound quality.

- reduced tinnitus.
- reduced fatigue when listening.

The additional potential clinical benefits of the CI632D relate to release of therapeutic dose of dexamethasone into the cochlea over a period of 30 days. This is anticipated to aid in minimising the inflammatory response to electrode insertion. Possible benefits could include:

- Reduced formation of fibrosis within the cochlea, as measured by decreased electrical impedance.
- Reduced electrode electrical impedance, possibly resulting in improved sound processor battery life.

The clinical investigation may require more appointments than standard of care. Study subjects may receive benefit from extra medical attention.

8.2 Anticipated Adverse Device Effects

Prospective recipients should be advised of the following possible effects of receiving a cochlear implant, as described in the CI632 Physicians Guide:

Adverse effects

- Normal risks associated with surgery and general anaesthesia.
- Increased surgical and anaesthetic risks for certain populations.
- Complications most frequently associated with this surgical procedure—stimulation of the facial nerve, taste disturbance and tinnitus.
- Complications that may require additional medical treatment, surgery and/or removal of the device, such as:
  - Acute Otitis Media (AOM)
  - facial nerve injury leading to temporary facial nerve weakness
  - perilymph fistula
  - Concurrent Cerebrospinal Fluid (CSF) leakage
  - vestibular dysfunction
  - subdural injury
  - subcutaneous haematoma
  - irritation, inflammation or breakdown of the skin flap; infection; and in some cases, extrusion of the device caused by the presence of a foreign body under the skin
  - decreased hearing ability caused by the electrode array migrating partially or completely out of the cochlea
  - perforation of external ear structures, such as the tympanic membrane or canal wall, by the electrode lead

- perception of non-auditory sensations and poorer performance than expected from misplacement of the electrode array
- Electrical stimulation may result in increased tinnitus, temporary facial nerve stimulation, temporary dizziness, or temporary pain
- The long-term effects of electrode insertion trauma or 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, intermittent sound, 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.

Meningitis

- Before implantation, candidates should consult their primary care physician and implanting surgeon regarding vaccination status against micro-organisms that cause meningitis.
- Meningitis is a known risk of inner ear surgery and candidates should be appropriately counselled of this risk. Certain preoperative conditions may increase the risk of meningitis with or without an implant. These conditions include:
  - Mondini's syndrome and other congenital cochlear malformations.
  - CSF shunts or drains.
  - recurrent episodes of bacterial meningitis before implantation.
  - perilymph fistulas and skull fracture/defect with CSF communication.

Loss of residual hearing

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

8.3 Risks Associated with Participation in the Clinical Investigation

The surgical procedure may result in adverse effects, as described in the Investigators Brochure for CI632D. The risks for undergoing the cochlear implant surgery are the same as the risks if not participating in the clinical investigation. If the subject is randomised to the IMD arm, there may be risks associated with the dexamethasone delivered via the cochlear implant. The likelihood of experiencing these risks is minimal given the small amount of dexamethasone that will be eluted.

The clinical investigation may include some inconveniences to the subject as the number of follow-up visits may be more than if the subject was not participating. Follow-up visits may be longer in duration than a routine cochlear implant follow-up. Some of the required assessments and exams may result in discomfort for the subject. Subjects may feel discomfort during the process of identifying the most appropriate program settings.

8.3.1 Risks specifically associated with the CI632D

The additional risks associated with the use of the investigational dexamethasone-eluting electrode array have been assessed. One residual risk has been identified as a "High" risk and relates to the possibility that introduction of the therapeutic substance may adversely affect local immunity, leading to an increased risk of infection.

However, the hazards analysis indicates that the residual likelihood of infection is not expected to be any higher than the residual likelihood of meningitis and other central nervous system infections for the CI632 and therefore a residual likelihood of 'remote' has been assigned. Together with the severity of "catastrophic', this results in a residual risk that is rated "High".

Other residual risks related to the presence of dexamethasone, including the risks related to long-term presence of the implant in the body, variation in drug release, instability or interactions with other drugs have been assigned residual likelihoods of "remote" or "improbable", with a risk level of "medium".

8.4 Risk Mitigation

- All surgeons will receive surgical training in the use and handling of the CI632 and CI632D as part of study initiation. In addition, the Sponsor's surgical support may be present during surgeries performed by the investigational site(s). There is no difference to the implant technique or device handling between CI632 and CI632D.
- All reported AEs, ADEs and DDs will be regularly reviewed by the Sponsor's Clinical review Board for the duration of the study to facilitate early detection and appropriate intervention if events are unanticipated with respect to incidence, severity, or outcome.
- An Independent Data Monitoring Committee (IDMC) will review all SADEs and infection-related AEs for the duration of the study to facilitate early detection and appropriate intervention if events are unanticipated with respect to incidence, severity, or outcome.
- Inclusion in the study requires evidence of pneumococcal vaccination prior to randomisation.
- Defined eligibility criteria to address preoperative conditions that may increase risk of meningitis.

8.5 Benefit-to Risk Rationale

Benefits of a cochlear implant to the recipient may include improved detection and recognition of environmental sounds, improved detection and recognition of conversational speech, limited ability to use the telephone and overall improvement in sound quality. The clinical safety (risks) and benefit relevant to the anticipated performance of CI600-series devices, including CI632, were evaluated in the CI600 series Clinical Evaluation Report (CER) and it was concluded that the device is effective and has a favourable safety profile. The CI600 series cochlear implants are commercially available in multiple countries. Cochlear™-sponsored clinical investigations and a systematic literature review, coupled with the design verification/validation and post-market surveillance data, established that the benefits of the CI600-series devices outweigh the risks.

The anticipated additional benefits of dexamethasone, compared with a conventional CI electrode, that will be investigated in this study are reduced fibrosis in the cochlea as measured by electrode impedances, and

improved battery life due to reduced power consumption for stimulation. The additional risks that may be posed by the dexamethasone-eluting electrode incorporated into the CI632D have been assessed and do not alter the conclusion that the potential benefits outweigh the risks for the investigational device.

It is anticipated speech outcomes for CI632D will be non-inferior to CI632.

Delivery of dexamethasone to the middle and inner ear via intratympanic or transtympanic injection, or application to the round window is widely used and accepted in cochlear implant surgery (see Section 4.2.2.1) and delivery of dexamethasone via the round window is included in the FDA-approved recommended hearing preservation surgery technique for Med-El cochlear implants (https://www.accessdata.fda.gov/cdrh_docs/pdf/P000025S084c.pdf). Intratympanic delivery of dexamethasone has been shown to result in highly localized delivery of a relatively small quantity of drug with much lower systemic concentrations than intravenous delivery (Bird et al., 2011). Consequently, the risks of systemic side-effects are reduced. The total quantity of dexamethasone incorporated into the CI632D is approximately 15 to 110-fold smaller than the quantities used for local application in the studies referred to in Section 4.2.2.1, further reducing the risk of adverse effects.

9. STATISTICAL CONSIDERATIONS

9.1. General Considerations

A detailed summary of statistical analysis is documented in the Statistical Analysis Plan (SAP).

9.2. Endpoints

9.2.1. Primary Endpoints

1. Difference between CI632D and CI632 mean MP1+2 impedance measurements of the available electrodes at 6 months post-cochlear implantation.
2. Difference between CI632D mean speech perception performance for open-set monosyllabic word recognition in quiet in the unilateral listening condition at six months post-implant compared to preoperative baseline.

9.2.2. Secondary Endpoints

1. Comparison of CI632D and CI632 procedural and device related adverse events at 6 Months and 12 Months post-cochlear implant.
2. Difference between CI632D and CI632 mean speech perception performance for an open-set monosyllabic word recognition in quiet in the unilateral listening condition at six months post-cochlear implant.
3. Difference between CI632D and CI632 mean speech perception performance for sentence recognition in quiet in the unilateral listening condition at six months post-cochlear implant.
4. Comparison of CI632D and CI632 Custom Sound® estimated remaining battery life of the sound processor at all data collection time points.

[redacted]

9.3. Hypotheses

9.3.1. Primary Hypothesis

9.3.1.1. Primary Endpoint #1

Mean MP1+2 impedance will be significantly lower with the CI632D ("treatment" arm) than the standard CI632 ("control" arm) 6 months post-implant.

H0: $MP1+2_{treatment} \geq MP1+2_{control}$

H1: $MP1+2_{treatment} < MP1+2_{control}$

9.3.1.2. Primary Endpoint #2

Mean CNC word score in quiet will show at least 10% improvement with the CI632D ("treatment" arm) at 6 months post-implant compared to "treatment" arm's preoperative Baseline, is as follows:

H0: CI632D CNC $word_{6\ Month}$ < CI632D CNC $word_{Baseline}$ + 10%

H1: CI632D CNC $word_{6\ Month}$ ≥ CI632D CNC $word_{Baseline}$ +10%

9.3.2. Secondary Hypothesis

Three secondary endpoints are planned; one related to adverse events and two related to mean change in speech perception performance.

Analyses of secondary endpoints, as well as other assessments, will be performed but there are no plans for formal prespecified hypothesis tests for these analyses with type I error control. It is recognized that this may limit the ability for such analyses to support labelling claims with inferential quantities.

9.3.3. Exploratory Hypothesis

There are no exploratory hypotheses.

9.4. Sample Size Determination

The following evidence was used to support the sample size calculation of the first primary endpoint:

Cochlear™'s feasibility clinical investigation CLTD5495 comparing outcomes of the dexamethasone eluting CI400 Combined Investigational Device (CI4CID) and standard CI24RE(CA) device. At 6 months post-activation MP1+2 impedance data showed a decrease of 3.8 kOhms for the CI4CID compared to the CI24RE(CA). The CI4CID standard deviation from its mean was 1.0 while the CI24RE(CA) standard deviation was 1.7. The electrode array used in this clinical investigation is the Contour Advance electrode.

CI632 predicate device is the Cochlear™ Nucleus® CI532 cochlear implant with Slim Modiolar electrode (CI532). Six month mean MP1+2 impedance data for 43 subjects under the clinical investigation CLTD5446 provides similar results to the CI24RE(CA) control group of the CLTD5495 clinical investigation, with mean MP1+2 impedance measuring at 7.9 kOhms with a standard deviation of 1.7.

Considering results from CLTD5495 and CLTD5446, the following assumptions have been made regarding this clinical investigation:

Using an independent t-test (SigmaPlot 13.0) the sample size has been calculated to have reasonable power to detect a 1.5 kOhm decrease difference in MP1+2 impedance at 6 months post-cochlear implant for those implanted with the CI632D IMD compared to those implanted with the CI632 comparator device.

This change of 1.5 kOhms to be detected is based on clinical consensus and has taken into consideration the significant mean impedance reduction (3.8 kOhms) observed in the CI4CID feasibility clinical investigation CLTD5495. Due to the nature behind the design of CI632, it is likely there will be less insertion trauma as it is a precurved electrode designed to stay closer to the medial wall of the cochlea.

An expected standard deviation (SD) of the change is 2.0 kOhms. This SD of the change to be detected is based on the SD of the mean impedance of 1.7 observed in separate clinical investigations for CI24RE(CA) and CI532. The expected standard deviation of the mean in the current study has been chosen to be more conservative, allowing for increased impedance variability between the two arms.

A significance level $\alpha = 0.025$ (one-tailed).

A desired power of 0.9

The sample size for a 1:1 allocation has been calculated to have reasonable power to detect a decrease in mean (SD) MP1+2 impedance of 1.5 kOhm (1.5) for the CI632D IMD compared to the CI632 comparator device at 6 months post-implantation.

A 1.5 kOhms drop in impedance is expected to result in a mean increase in battery life of 1.79 hours for recipients with high powered maps, demonstrating a meaningful clinical benefit. This calculation is based on prior investigation using the DEE battery model (D1672865).

In the absence of literature to support a clinically meaningful change in impedance values for cochlear implants, the Sponsor positions 1.5kOhms effect size as clinically meaningful as shown by the battery life model increasing battery life by a mean of 1.79 hours. An improvement of 1.79 hours in battery life clearly equates to a meaningful duration of time for a cochlear implant recipient, such as a round trip commute to work, multiple meetings at work, a child's soccer game, meal out with friends, etc. The clinical investigation is powered to capture the 1.5kOhm effect size.

Based on these assumptions, a minimum sample size of 39 subjects in both arms is required to reject the null hypothesis of equivalent or higher MP1+2 impedance for the CI632D IMD compared to the CI632 comparator device at 6 months post-implantation with a power > 0.9. An increased sample size of 100 subjects (approximately 50 subjects in each arm) will be included, which will allow for the possibility of non-normally distributed data (approximately 15%) and subject attrition (approximately 10%). In addition, the population is extended to 120 randomised subjects to account for uncertainty in the estimates used in the power calculation, with approximately 60 subjects in each arm.

The following evidence and assumpters were used to support the same size calculation of the second primary endpoint:

CI632 predicate device is the Cochlear™ Nucleus® CI532 cochlear implant with Slim Modiolar electrode (CI532). Six month mean CNC word in quiet data 96 subjects under the clinical investigation CLTD5685 provided a mean change of 46 ± 22.6 (SD) word improvement from baseline

A significance $\alpha = 0.025$ (one-tailed).

A desired power of 0.9

A 10% improvement at 6 Months post-cochlear implant is required to reject the null hypothesis. Based on these assumptions, a minimum sample size of 10 subjects is required to reject the null hypothesis of equivalent or lower CNC words in quiet for the CI632D at six month post-cochlear implant compared to baseline with a power > 0.9. To account for non-normally distributed data (approximately 15%) and subject attrition (approximately 10%), not less than 13 subjects need to be randomised to CI632D ("treatment"

group) and successfully implanted. More than 13 subjects will be randomised to the treatment to meet sample size requirements for the first primary endpoint.

As the CI632D is a novel medical device, a group sequential analysis strategy is planned. The first analysis will occur with the first 50 randomised subjects completing the 6 month endpoint. If stopping criteria are not met, the analysis will be repeated at 80 subjects, 100 subjects and 120 subjects.

9.5. Analysis Populations

Analyses of endpoints will include the following populations:

- Intent-to-Treat (ITT): all subjects that are randomised. Analysis will be based on randomisation assignment.
- As-Treated (AT): subjects that receive a CI632 or CI632D. Analysis will be based on treatment received (rather than randomisation assignment).
- Per-protocol (PP): subjects that receive a CI632 or CI632D in accordance with randomisation assignment and do not have a translocated electrode as confirmed by imaging.

In addition to these populations, there may be subgroup analysis which could include geography, sex, age or race. The complete analysis strategy will be outlined in the Statistical Analysis Plan (SAP).

9.6. Endpoint Analyses

9.6.1. Primary Endpoint Analyses

There are two primary endpoints.

Primary analysis of MP1+2 impedances will include the ITT population evaluating mean differences at 6 months post-cochlear implantation based on a t-test at the one-sided 0.025 alpha level. If there is evidence of non-normality (based on a Shapiro-Wilks test at the 0.05 alpha level), a non-parametric alternative will be employed for the primary endpoint.

Primary analysis of speech perception performance will include the cohort of subjects randomised to CI632D and for whom CI632D is their first cochlear implant in the ITT population, evaluating the difference at 6 months post-cochlear implantation compared to baseline via a one-sample sample t-test at the one-sided 0.025 alpha level. If there is evidence of non-normality (based on a Shapiro-Wilks test at the 0.05 alpha level), a non-parametric alternative will be employed for the primary endpoint.

For both endpoints, analysis may include description of population differences in the final analysis. Additional analysis may include both the AS and PP analyses groups. Missing data will be analysed under a multiple imputation strategy that will be outlined in the Statistical Analysis Plan (SAP).

9.6.2. Secondary Endpoint Analyses

See Section 9.7 for Safety Analysis under the secondary endpoint. There are two speech perception endpoints at six months post-implantation. There are no formal statistical hypothesis planned for these endpoints; analyses will be based on descriptive statistics and nominal 95% confidence limits, with results reported separately by randomized group. The ITT population will be used for primary analysis for each endpoint. A secondary analysis will include the Per Protocol group. Missing data will be analysed under a multiple imputation strategy that will be outlined in the Statistical Analysis Plan (SAP). Analysis of estimated remaining battery life of CI632D and CI632 Custom Sound® will be conducted.

9.6.3. Exploratory Endpoint Analyses

All exploratory endpoints will be included in the final analysis for each time point. Further detail of analysis, including management of missing data, can be found in the SAP. Formal hypothesis testing is not planned for exploratory endpoints.

9.7. Safety Analyses

Safety analysis will be completed with the AT population at both 6 months and 12 months post-cochlear implantation. The rate of AE type will be compared between treatment and control arm.

For AE/ADEs and DDs, data will be tabled to present event type, severity, device/procedural relationship, count and percentage, and subjects with event will be summarised by randomisation group. Any subjects who died, who discontinued an intervention due to an AE/ADEs, or who experienced a severe or an SAE/SADEs will be summarised separately. In addition to Secondary Endpoint Analyses, AE/ADE and DD frequency data will be provided to the IDMC in accordance to the IDMC Charter.

9.8. Interim Analyses

Group sequential analysis based on an O'Brien-Fleming like alpha spending function, will be completed for the primary endpoints following the collection of 6 Month data for subjects at the following intervals: the first 50 randomised subjects, first 80 randomised subjects, first 100 randomised subjects, and first 120 randomised subjects. If the null hypothesis cannot be rejected for both primary endpoints following analysis at each interval (stopping criteria), then further analysis will take place at the subsequent interval until the final analysis of the 120 randomised subjects.

The first primary endpoint will be analysed first. The second primary endpoint will be analysed if the null hypothesis is rejected. Analysis of secondary or exploratory endpoints will not occur until both the primary endpoint null hypotheses are rejected, or 120 randomised subjects are analysed.

Prior to final analysis at study completion, group sequential analysis may be used as part of Premarket Approval (PMA) if both primary endpoint null hypotheses are rejected.

9.9. Sub-Group Analyses

Sub-group analyses may be completed as an additional analysis to any endpoint. Sub-groups may include analysis of specific clinical investigation sites, sex, age, race or specific procedural/device outcome (such as translocation). Detail of sub-group analysis can be found in the SAP.

10. INFORMED CONSENT PROCESS

The Investigator shall obtain written informed consent from the subject using an approved ICF prior to any clinical investigation-related examination or activity. The rationale of the clinical investigation, as well as the benefits and risks, what participation will involve, and established alternatives to participation will be explained to the subject in native non-technical language, understandable to the subject. Ample time will be provided for the subject to enquire 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. They shall not waive or appear to waive their legal rights.

Each subject (or their legally designated representative) and the person who conducted the informed consent discussion, shall sign and personally date the Informed Consent Form (ICF). Where required, an independent and impartial witness shall sign and personally date the ICF. A copy of the signed ICF shall be given to the subject. The original signed ICF shall be archived in the Investigator's Site File or subject file at the investigational site.

This process shall be documented in the subject's source documents.

The subject, or the subject's legally designated 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 must be documented as an update to the ICF and re-consent of the subject.

11. ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1. Definitions

11.1.1. Adverse Event

An adverse event (AE) is 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 and whether anticipated or unanticipated.

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 the use of investigational medical devices or comparators.

11.1.2. Adverse Device Effect

An adverse device effect (ADE) is an AE related to the use of an investigational medical device.

NOTE 1: This includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or 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.

NOTE 3: This includes 'comparator' if the comparator is a medical device.

11.1.3. Serious Adverse Event

A serious adverse event (SAE) is any AE that led to any of the following:

1) death,
2) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function including chronic diseases, or
- in-patient or prolonged hospitalisation, or
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

3) foetal distress, foetal death or a congenital abnormality, or birth defect including physical or mental impairment.

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

11.1.4. Serious Adverse Device Effect

A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a SAE.

11.1.5. Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (USADE) is a SADE, which by its nature, incidence, severity, or outcome has not been identified in the current version of the Investigator's Brochure.

USADE are also known as a UADE (Unanticipated Adverse Device Effect) for the purposes of US FDA reporting.

NOTE: An anticipated serious adverse device effect is an effect, which by its nature, incidence, severity, or outcome has been identified in the Investigator's Brochure.

11.1.6. Device Deficiency

A Device Deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance.

NOTE 1: Device Deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

NOTE 2: This definition includes device deficiencies related to the IMD or the comparator.

11.1.7. Serious Health Threat

A signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

NOTE: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

11.2. Recording and Handling of Adverse Events

Subjects shall be carefully monitored during the clinical investigation and the investigator should enquire about AEs at investigation visits.

All AEs will be recorded from the time of treatment assignment (randomisation). AE recording will continue for each subject until completion of their End of Study visit. Ongoing SAEs will be followed for 30 days, or until resolution or stabilisation of the event, whichever comes first.

Source notes should indicate the evaluation for AEs, even if there was none to report. All required AEs will be reported if observed, even if anticipated and/or acknowledged as a risk factor in the consent.

All AEs will have the following information documented: start and stop dates, action taken, outcome, severity and investigators opinion on the potential relationship to the IMD and/or comparator and study procedures. If an AE changes in severity, the most severe (highest) grade will be captured for that event on the Adverse Events CRF.

11.2.1. Assessment of Severity

The Principal Investigator (or qualified delegate) will make an assessment of severity for each event based on clinical judgement. The intensity of each event recorded in the CRF should be assigned to one of the following categories:

Mild	An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate	An event that is sufficiently discomforting to interfere with normal activities
Severe	An event which is incapacitating and prevents normal everyday activities

11.2.2. Assessment of Causality

The Investigator will assess the potential causal relationship of each event, using clinical judgement. Alternative causes, such as natural history of underlying diseases, other risk factors and the temporal relationship of the event to the IMD and/or comparator product will be considered and investigated. The causal relationship to the IMD and/or comparator is to be assessed by the Investigator (or medically qualified delegate) and should be assessed using the following classifications:

Not related	Relationship to the medical device or procedures can be excluded when: • the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has no temporal relationship with the use of the device or the procedures; • the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event;

	• the event involves a body-site or an organ not expected to be affected by the device or procedure; • the event can be attributed to another cause (for example, an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the investigational medical device used for diagnosis, when applicable; • harms to the subject are not clearly due to use error; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely related	The relationship with the use of the medical device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly related	The relationship with the use of the medical device is weak but cannot be ruled out completely. Alternative causes are also possible (for example, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possibly related.
Probably related	The relationship with the use of the medical device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Definitely related	The event is associated with the medical device or with procedures beyond reasonable doubt when: • the event is a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has a temporal relationship with the medical device use/application or procedures; • the event involves a body-site or organ that – the medical device or procedures are applied to – the medical device or procedures have an effect on; • the event follows a known response pattern to the medical device (if the response pattern is previously known); • the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible); • other possible causes (for example, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the medical device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

11.2.3. Assessment of Seriousness

The Investigator will assess the seriousness of each event according to clinical judgement and the definition provided in section 11.1.3.

11.2.4. Assessment of Expectedness

An event should be considered unanticipated if the nature, severity, or frequency of that event is not consistent with the applicable safety reference information, such as the hazards analysis, IB, or Product Information/IFU if the product is approved for marketing.

For this clinical investigation the listed items in section 8.2 and 8.3 of this CIP and/or the Investigator's Brochure are anticipated ADEs.

Anticipated	An adverse device effect (ADE) which by its nature, incidence, severity, or outcome is consistent with the applicable safety reference information (for example, IB, IFU).
Unanticipated	An adverse device effect (ADE) which by its nature, incidence, severity, or outcome is not consistent with, or has not been identified in the applicable safety reference information (for example, IB, IFU).

11.3. Recording and Handling of Device Deficiencies

Subjects shall be carefully monitored during the clinical investigation and routinely questioned about DDs at investigation visits. Source notes should indicate the evaluation for DDs, even if there are none to report.

The Investigator shall assess if the DD led to an AE or could have led to a serious medical occurrence (serious adverse device effect) if;

1) suitable action had not been taken,
2) intervention had not been made, or,
3) circumstances had been less fortunate

All DDs will be documented in the source notes and the DD page of the CRF.

All non-implanted IMDs that are found to have a DD and all explanted IMDs must be returned to the Sponsor for analysis. The study team should be contacted to arrange for return of device.

11.4. Reporting Responsibilities

The Investigator is responsible for reporting all AEs and DDs in the CRF.

11.4.1. Investigator Reporting of Serious Adverse Events

All AEs meeting the criteria for an SAE, or DD that could have led to an SADE, must be reported to the Sponsor in accordance with timeframes required by local regulations, as follows:

Country	Timeframe
Australia	24 hours
New Zealand	24 hours
United States	24 hours

Reporting is achieved through completion of the events details in the Adverse Event page of the eCRF.

The Investigator shall always provide an assessment of causality at the time of the initial report, as described in section 11.2.2 'Assessment of Causality'. If data obtained after reporting indicates that the assessment of causality is incorrect, then the SAE form may be appropriately amended, signed, dated, and resubmitted to the Sponsor.

If the Investigator does not have all other information regarding an SAE, he/she will not wait to receive additional information before reporting the event. The reporting forms shall be updated when additional information is received.

The Investigator is responsible for reporting of safety events to their local EC using the applicable report form, in accordance with local regulations.

11.4.2. Sponsor Notification of Events

The Sponsor is responsible for reviewing all safety data to evaluate potential causality and anticipation of all ADEs, and shall conduct an expedited assessment of all SAEs, unanticipated ADEs, DDs that could have led to an SADE, including serious health threat.

The Sponsor is also responsible for reporting all reportable events according to the requirements and timelines of the regulatory authorities relevant to this clinical investigation. Country specific sponsor reporting responsibilities are outlined in the Sponsor's Safety Data Handling Plan.

The Safety Monitor for AE/DD assessment and any AE/DD related queries is:

Name Sponsor Safety Monitor:	[redacted]
Country:	[redacted]
Phone number:	[redacted]
E-mail:	[redacted]

11.5. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to provide independent review of safety and compliance outcomes. The IDMC will review trial data and provide recommendations to the Sponsor regarding the course of the clinical investigation. The scope of the IDMC and its procedures are outlined in the IDMC Charter.

12. Device Accountability

Supply of investigational medical devices and approved medical devices will be recorded [redacted] Investigational medical device(s) will be quarantined at the investigational site and clearly labelled to identify exclusively for use in a clinical investigation.

Subject level device supply will be tracked using the Sponsor's Individual Subject Accountability Log Form (1295295) for serialised devices.

Contact information regarding the IMD and/or comparator is provided below.

Name of contact person of the Sponsor:	[redacted]
Country and time zone:	[redacted]
Phone number:	[redacted]
Email:	[redacted]

13. Deviations from the Clinical Investigation Plan

The Investigator(s) must not deviate from the CIP, except in case of an emergency to protect the safety and well-being of the subject(s). Such deviations will be documented by the site personnel in the source documentation for the subject and reported to the relevant EC as per institutional requirements and to the Sponsor as soon as possible, but not later than 48 hours from the date of the emergency.

If there is a deviation from CIP-defined assessments or parts thereof are omitted or completed incorrectly, the deviation will also be documented by the site personnel in the source documentation for the subject. Depending on the type or severity of the deviation the Investigator may be required to notify the EC,

particularly if the deviation potentially impacts subject safety, performance of IMD and/or comparator, or data integrity.

All CIP deviations will be documented in the eCRF to enable analysis and reporting by the Sponsor in the Clinical Investigation Report (CIR), or to the relevant regulatory authority(s), if applicable.

Gross misconduct on behalf of an Investigator, such as intentional non-compliance with CIP or GCP requirements or fraud, will result in disqualification of the Principal Investigator and/or Investigational Site from participation in the investigation. Data provided by the Principal Investigator or Investigational Site will be excluded from the per-protocol analysis group.

14. DATA MANAGEMENT

The CRF will capture the datapoints necessary to determine the subject status according to the criteria described in section 7.2.5.

14.1. Source Data

Source data will be captured in clinic notes, paper-based source data worksheets, or printed directly from testing software. No data will be entered directly into EDC. If electronic medical records do not permit read only access for monitoring purposes, a certified printout must be provided, indicated by a dated signature by a member of the site team or generated through a validated process.

An Origin of Source Data Form will be used to capture the location of source data kept at each site, outlining the individual site's process for certification.

14.2. Methods for Data Entry and Collection

Data collection will be performed using Medidata Rave for electronic data capture (EDC) on electronic Case Report Forms (eCRFs). Site staff will be trained on the completion of the eCRFs prior to obtaining access to the system and will have their own Login/Password. Access to clinical study information will be based on an individual's role and responsibilities.

Medidata Rave uses role-based user permissions for data entry, viewing, and reporting options. All communications between users and the EDC server are encrypted. Web servers are protected by a managed firewall. This application is designed to be in compliance with applicable regulations including 21 CFR Part 11.

The application will include programmed data consistency checks and supports manual generation of data clarifications/queries, including documentation of site responses. The application maintains a comprehensive audit trail for all data entered, including updates and queries, and documents the time that each entry occurred and who made the entry.

Principal Investigators will affirm that the data for each subject at their site is accurate and complete by way of an electronic signature.

In addition, de-identified electronically generated data will be collected from clinical fitting software, x-ray imaging, CT imaging, questionnaires and other methods. The unamended data file shall be regarded as the source.

14.3. Database Lock

A Data Quality Review Meeting (DQRM) will be conducted every month and will also review the locking.

Prior to database lock the Principal Investigator at the site shall electronically sign to verify the accuracy and completeness of the data. Where this responsibility is delegated to a suitably qualified Investigator it will be documented on the site signature and delegation log.

In final analyses, all dataset shall be frozen and locked before analyses.

Following database lock, raw datasets will be generated to enable analysis. The analysis are outlined in the Statistical Analysis Plan (SAP).

15. CONFIDENTIALITY

The investigator and site staff will collect and process personal data of the subjects in accordance with governing data privacy regulations.

Data will be reported to the Sponsor on CRFs or related documents (for example, questionnaires). Subjects will be identified on CRFs and other related documents only by a unique subject identification code and shall not include the subject's name or other personal identifiable information. Completed CRFs or related documents are confidential and will only be available to the Investigator and site staff, the Sponsor and their representatives, and if requested to the Ethics Committee and national regulatory authorities. Publications or submission to a regulatory authority shall not disclose the identity of any subject.

All cochlear implants and sound processors are registered to Cochlear™ using the recipient's name and other identifying information. Cochlear will follow the same procedures and policies to protect confidentiality for recipients with a commercial or investigational cochlear implant.

16. ETHICS COMMITTEE AND REGULATORY AUTHORITY APPROVAL

This clinical investigation will be conducted under the following regulatory pathways:

Country	**Pathway**
Australia	CTN
US	Investigational Device Exemption (IDE)
NZ	Not applicable

The clinical investigation will not commence prior to the written favourable opinion or approval from the EC and or regulatory authority (if appropriate) is obtained.

The final Sponsor-approved version of the CIP, Informed Consent Form, and other necessary documents shall be submitted to the EC. A copy of the EC opinion/approval shall be provided to the Sponsor.

The Investigator shall forward to the Sponsor, for review and approval, any amendment made to the approved ICF and any other written information to be provided to the subject prior to submission to the EC.

The Sponsor and Principal Investigator will continue communications with the EC, as required by national regulations, the clinical investigational plan, or the responsible regulatory authority.

Any additional requirements imposed by the EC or regulatory authority will be implemented by the Sponsor.

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

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

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

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

17. SUSPENSION OR PREMATURE TERMINATION

The Sponsor will discontinue the clinical investigation site if:

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

An ongoing clinical investigation may be discontinued in case of:

1. device failure
2. serious or intolerable ADE, leading to the explant or discontinued use of the device
3. subject's death

18. AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

No changes in the CIP or investigation procedures shall be made without mutual agreement of the Coordinating Investigator and the Sponsor. This agreement will be documented as a CIP amendment. Amendments will require notification to the Ethics Committees (ECs) by the Principal Investigators (and to the relevant regulatory authority(s) by the Sponsor, if applicable).

19. RECORD KEEPING AND RETENTION

Data generated from the clinical investigation will 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 maintained by the Investigator. This information will be treated with strict adherence to professional standards of confidentiality.

The investigator must retain study-related records in accordance with the period required by local regulation, as follows:

Country	Retention period
Australia	15 years after completion of the clinical investigation
New Zealand	10 years after completion of the clinical investigation
United States	2 years after the latter of the following two dates: The date on which the investigation is terminated or completed or the date that the records are no longer required for purposes of supporting a premarket approval application

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.

20. PUBLICATION POLICY

This clinical investigation will be prospectively registered at a public clinical trial registry ClinicalTrials.gov.

One or more joint peer-reviewed publications, co-authored by the clinical investigator(s) and Sponsor, will be prepared to enable timely communication of the research outcomes. In addition, the results of the clinical investigation may also be disseminated as conference presentations (for example, abstract and poster session). Manuscript content, authorship and responsibilities will be discussed and agreed upon prior to investigation start and in accordance with guidelines and recommendations provided by the International Committee of Medical Journal Editors (ICMJE) to enable communication within 12 months of the Clinical Investigation Report (CIR) approval. All contributors who do not meet the criteria for authorship will be listed in an acknowledgments section of the publication.

Investigators will be able to publish and/or present the data generated from the clinical investigation after mutual agreement between the Coordinating Investigator, the Principal Investigators, and the Sponsor prior to investigation start. Manuscript authorship and responsibilities will be in accordance with guidelines and recommendations provided by the International Committee of Medical Journal Editors (ICMJE) for authorship and acknowledgement. to enable communication within 12 months of the CIR approval. All contributors who do not meet the criteria for authorship will be listed in an acknowledgments section of the publication.

Individual publications will not be completed until the main objectives are publicly available through publication or regulatory approval.

21. STATEMENTS OF COMPLIANCE

This clinical investigation shall be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, International Standard ISO 14155:2020 Clinical investigation of medical devices for human subjects - Good Clinical Practice, and any regional or national regulations, as applicable.

22. QUALITY CONTROL AND ASSURANCE

In accordance with Cochlear™'s Quality Management System, all clinical investigations shall be conducted according to internationally recognised ethical principles for the purposes of obtaining clinical safety and performance data about medical devices.

The Sponsor employees (or designee) shall use standard operating procedures (SOP) to ensure that clinical study procedures and documentation are consistently conducted and compliant with the ISO 14155 Standard, Good Clinical Practice (GCP), and applicable local regulations.

22.1. Monitoring

The Sponsor will perform on-site and remote monitoring visits as frequently as necessary to oversee conduct, data collection and record keeping by sites. The clinical investigation monitoring plan is a separate document for the sponsor to follow, describing all the activities performed during site qualification, initiation, monitoring, and close out.

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the CIP, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved CIP
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

22.2. Audits

To ensure compliance with GCP, the CIP, study procedures and applicable regulatory and EC requirements, an independent audit of the study may be conducted. The investigator/institution will be informed of the outcome for audits involving their site.

In addition, inspections by regulatory health authority representatives and EC(s) are possible. An Investigator must, in reasonable time, upon request from a relevant health authority or regulatory agency, permit access to requested records and reports, and copy and verify any records or reports made by the Investigator. Upon notification of a visit by a regulatory authority, the Investigator will contact the Sponsor immediately.

The Investigator will grant the Sponsor representatives the same access privileges offered to relevant health authority or regulatory agents, officers, and employees, for the purposes of a Sponsor audit of the site, or in preparation for an inspection.

Audits and inspections may occur at any time during or after completion of the study.

23. TRADEMARKS AND COPYRIGHT

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25. CHANGE HISTORY

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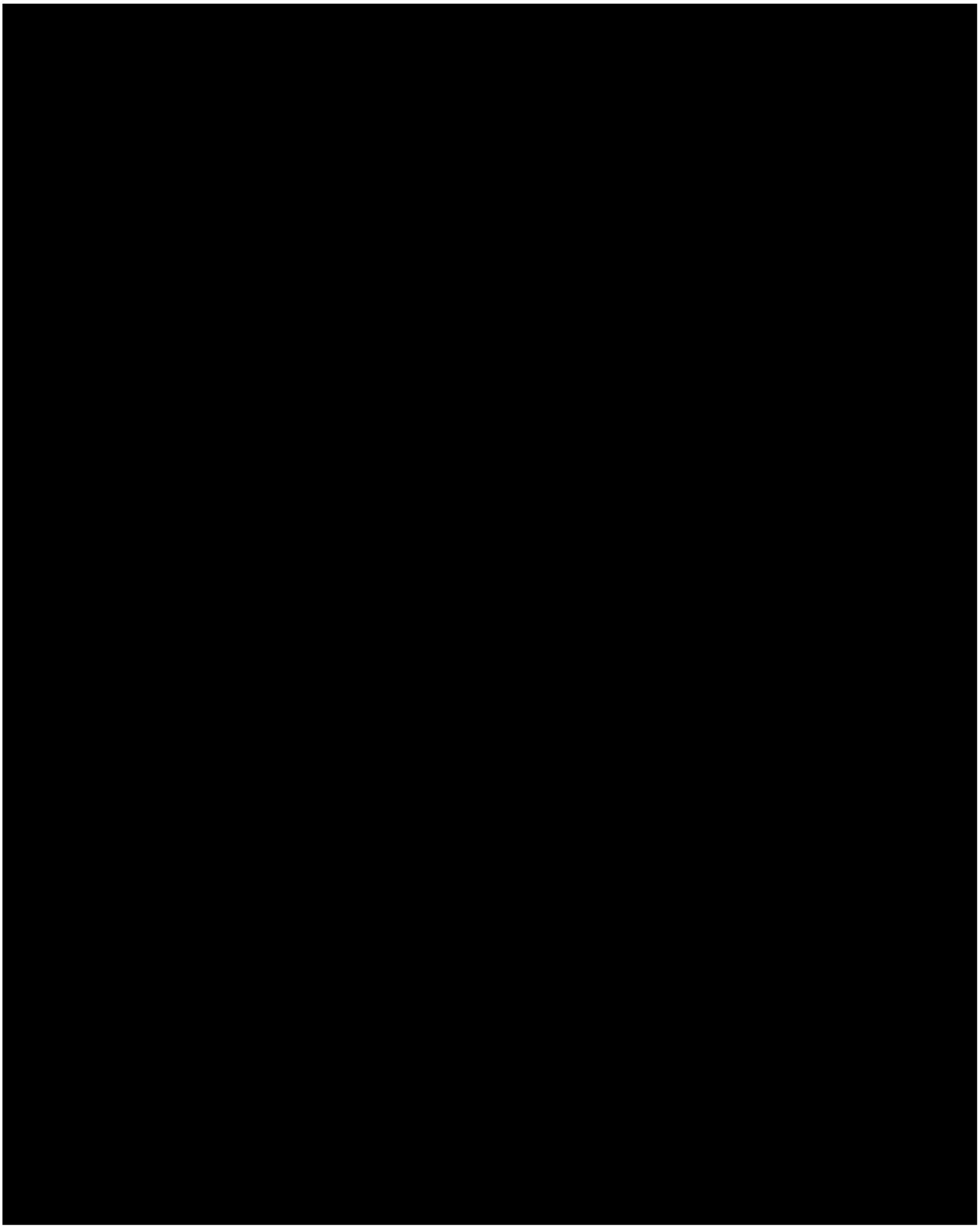

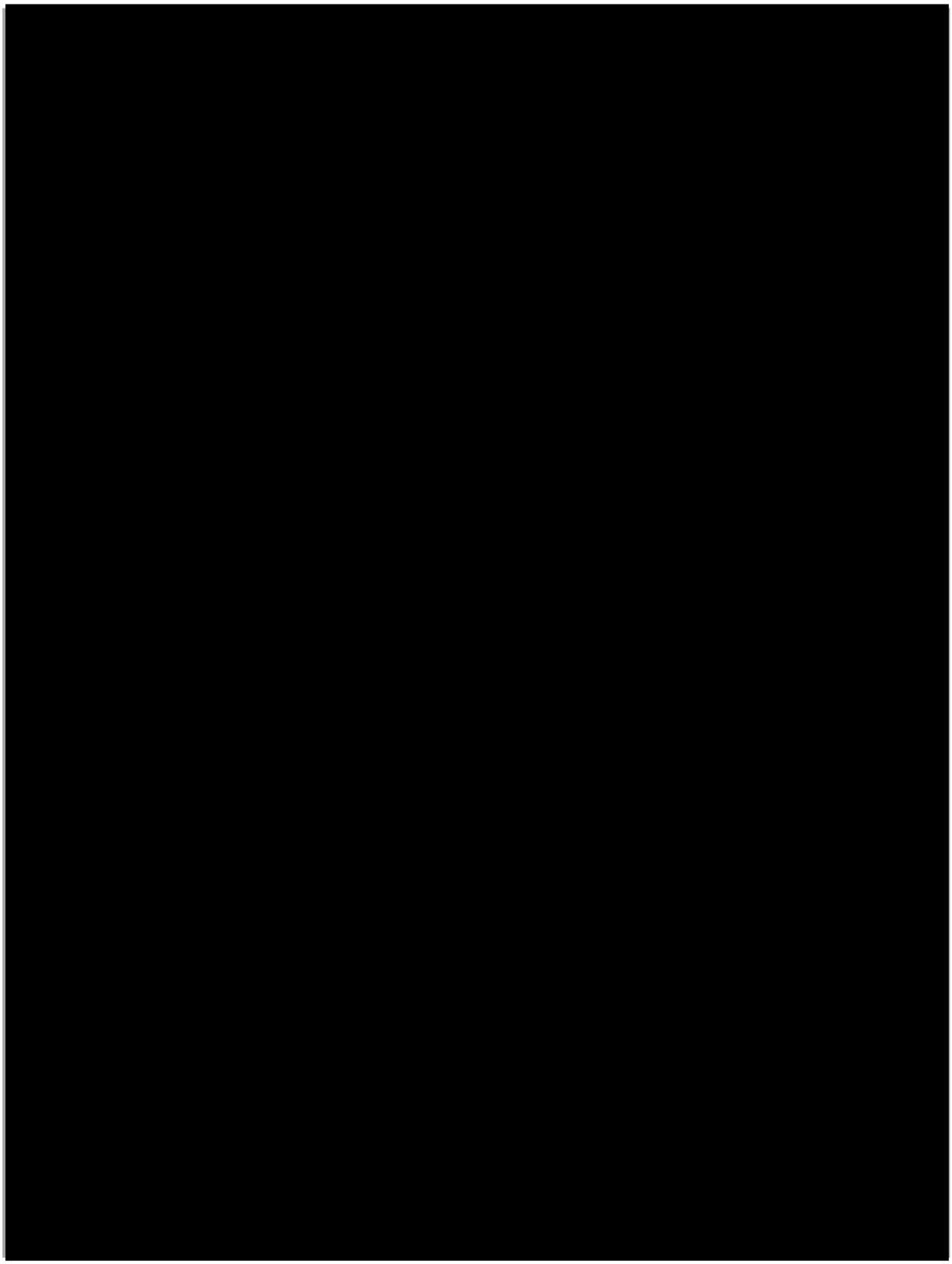

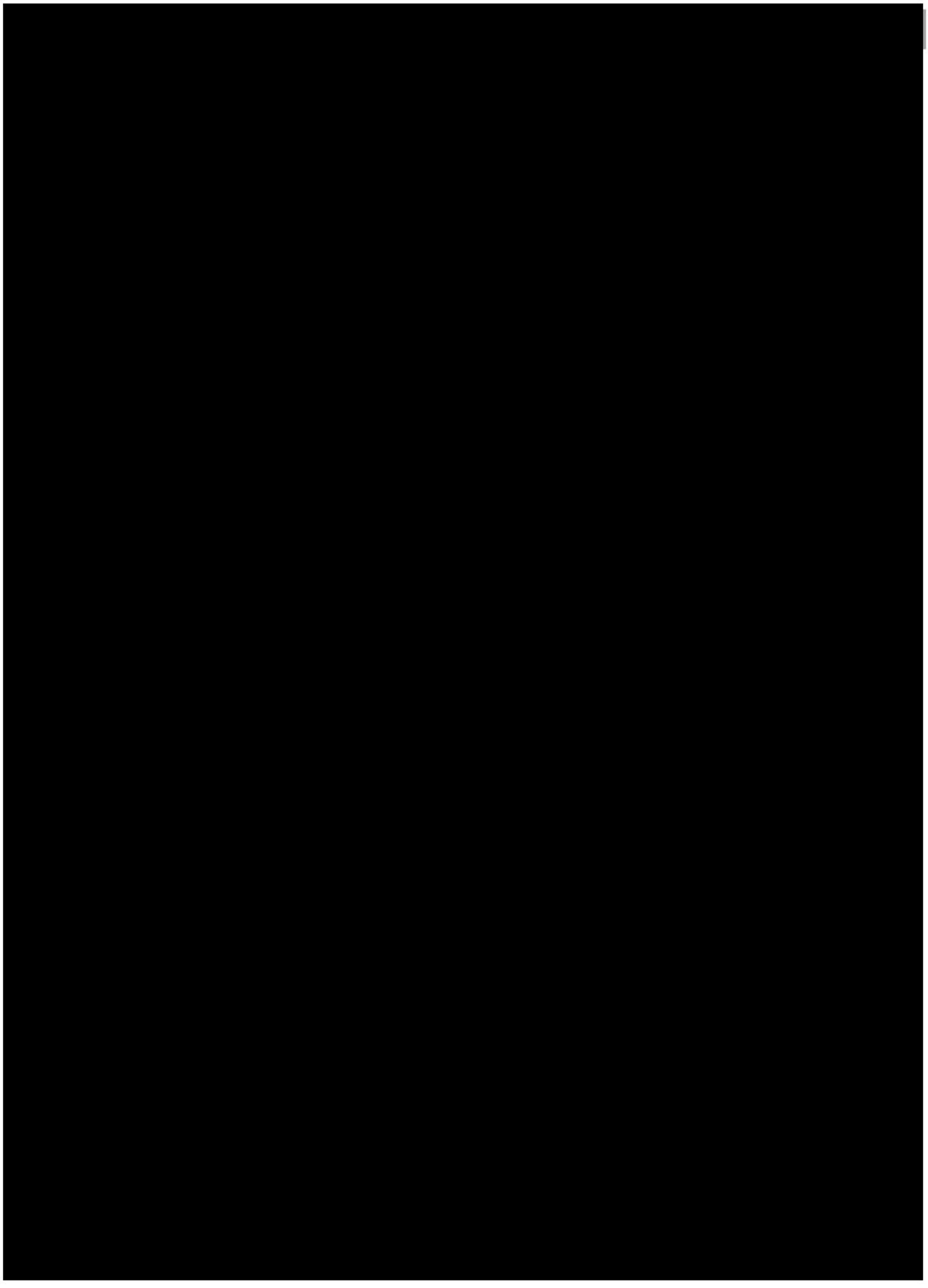

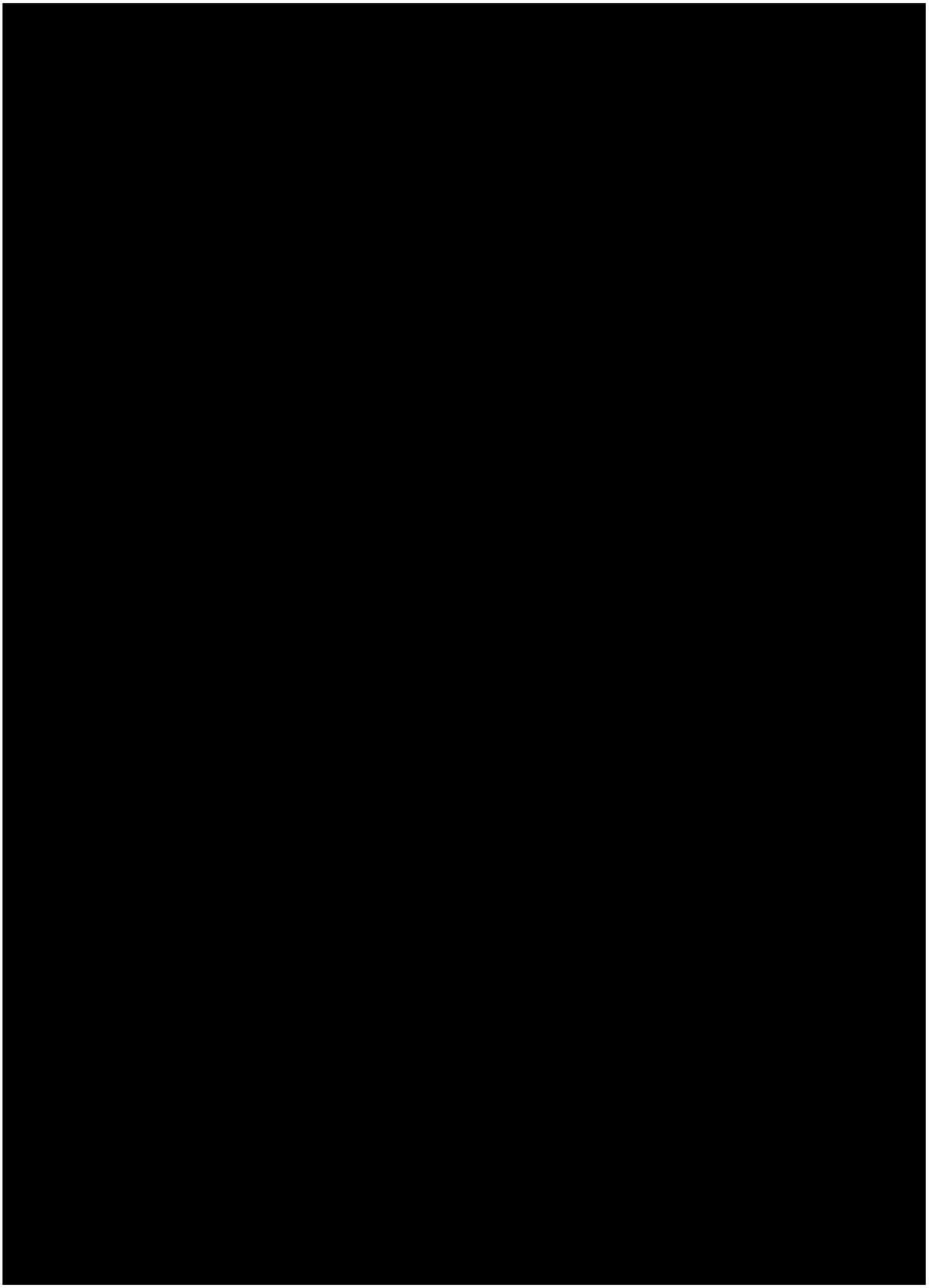

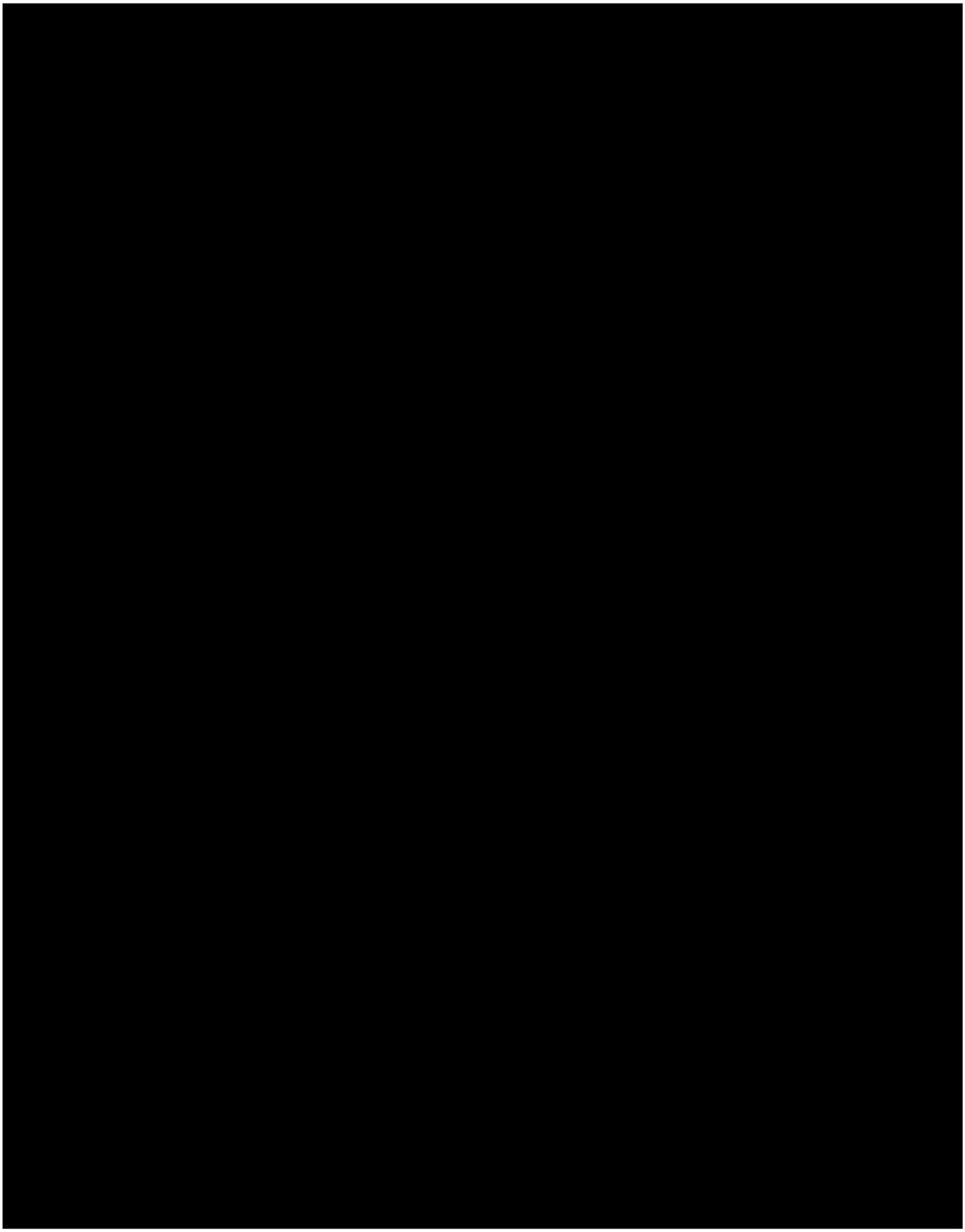

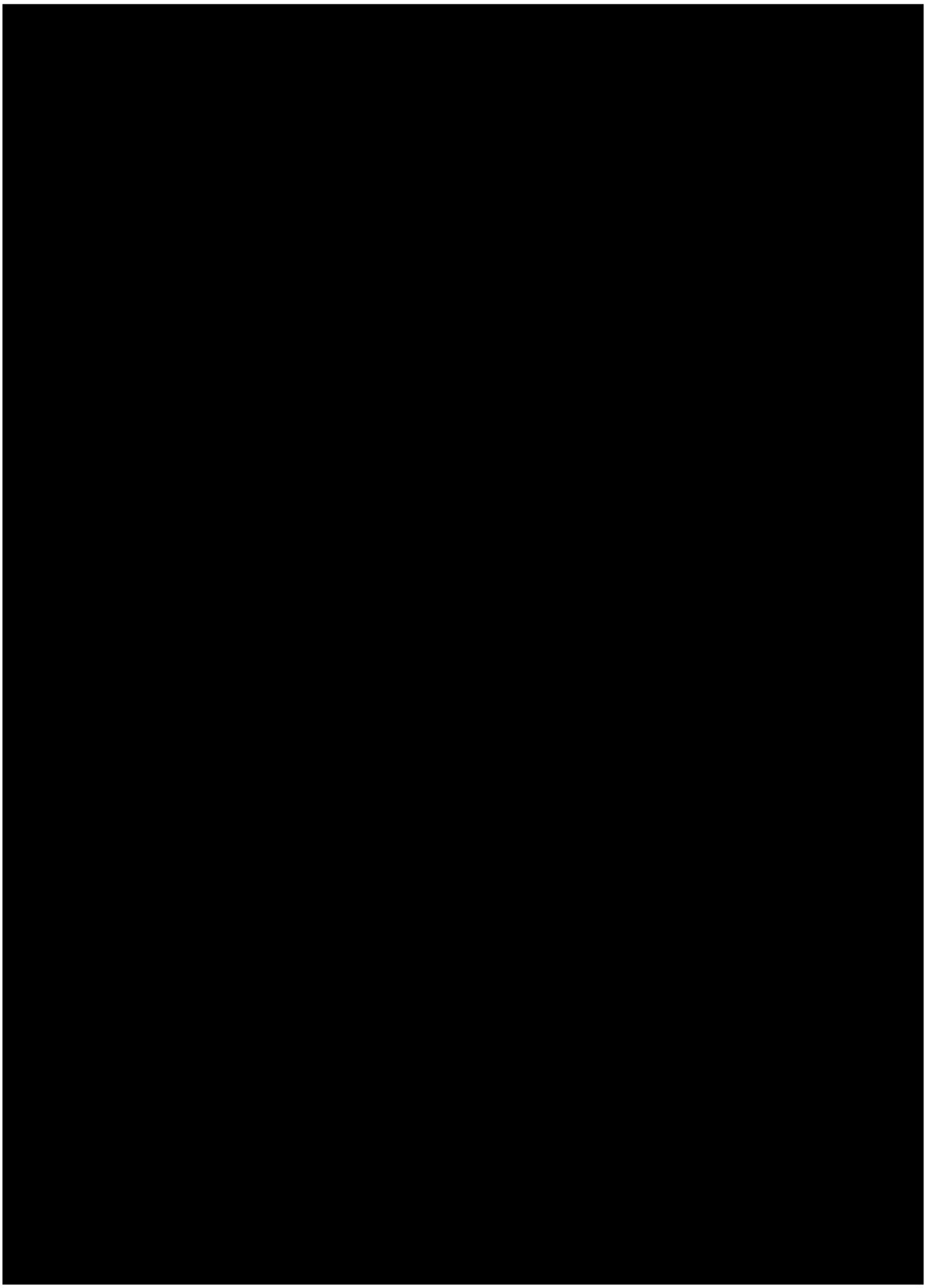

APPENDICES

APPENDIX 1: STATEMENT/DECLARATION OF DEVICE CONFORMITY

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Cochlear

QMS Document

STATEMENT OF CONFORMITY FOR UNAPPROVED DEVICE

Clinical Investigation Details:

Clinical Investigation ID:	CLTD5759
Sponsor of Investigation:	Cochlear Limited, 1 University Avenue, Macquarie University, NSW 2109, Australia

Device and Manufacturer Details:

Device Manufacturer:	Cochlear Limited, 1 University Avenue, Macquarie University, NSW 2109, Australia
Investigational Device:	Dexamethasone eluting slim modiolar electrode (CI632D)

We, Cochlear Limited, declare that where appropriate technical and biological and pre-clinical evaluations have been conducted, and as a result the investigational device(s) conforms to the applicable general safety and performance requirements, and every precaution has been taken to protect the health and safety of the subjects, the users and third persons.

The Device incorporates no materials of animal or human origin.

All supporting documentation is retained under the premises of the manufacturer.

Name:	[redacted]
Position:	[redacted]
Signature:	[redacted]
Date:	13 Apr 2022

Template 1419103 Version 1.0 1 of 1

Signature Page for VV-TMF-01100 v13.0

Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 07-Nov-2022 03:43:53 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 07-Nov-2022 04:07:46 GMT+0000

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