Clinical Investigation Plan

Redacted Version

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Investigation Title: Feasibility, prospective, multicentric, cross-sectional investigation to characterize daily impedance fluctuations and satisfaction in challenging listening environments in experienced adult CI recipients using the Mobile Research App (MRA)

Short Title:	**DICE**
CIP Number:	**AI5846**
CIV-ID	**CIV-23-08-043857**
Version and Date:	**Refer to system version control**
Sponsor:	**Cochlear Limited** **1 University Avenue** **Macquarie University NSW 2109** **Australia** **Phone: +61 294 28 65 55**

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.

[redacted]

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	Sponsoring Organisation
Legal Representative in the EU	Cochlear France SAS 135 Route de Saint Simon CS43574 31035 Toulouse France
Coordinating Investigator	Not applicable
Clinical Research Organisation	Belgium: Support submission QbD Clinical NV Groenenborgerlaan 16 2610 Wilrijk Belgium
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A complete list of participating Principal Investigators' names, titles and addresses, and the names and addresses of participating institutions (sites) will be maintained by the Sponsor and will be 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
CI	Cochlear Implant
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRF	Case Report Form
CRO	Contract Research Organisation
CSEP	Custom Sound EP
CVC	Consonant-Vowel-Consonant
CSS	Custom Sound Suite
DD	Device Deficiency
DTT	Digit Triplet Test
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
EFP	Extensible Fitting platform
EMA	Ecological momentary assessment
EOS	End of Study
FAMHP	Federal Agency for Medicines and Health Products (Competent Authority Belgium)
FF	Free Field
GCP	Good Clinical Practices
Home environment	The subjects personal every-day environment. This scan be any situation or location outside of the clinic or research facility.
IB	Investigator's Brochure
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors

Term	Description
IDMC	Independent Data Monitoring Committee
IFU	Instructions for Use
MDPQ	Mobile Device Proficiency Questionnaire
MPA	Medical Product Agency (Competent Authority Sweden)
MRA	Mobile Research App
MRA-C	MRA cloud component backend infrastructure
MRA-M	MRA iOS-compatible mobile application
MRA-W	MRA web application
NH	Normal Hearing
NR	No Response
PI	Principal Investigator
PIL	Principal Investigator List
QNR	Questionnaire
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SD	Standard deviation
Sensitive personal information	Personal information relating to racial or ethnic origin, political opinions, religious or philosophical beliefs, trade union partnership, genetic or biometric data, the physical or mental health or sex life or sexual orientation of an individual, or the commission or alleged commission of any offence and any related proceedings and outcome thereof.
SNR50	Signal-to-noise ration required for 50% word understanding
SOP	Standard Operating Procedure
SPIN	Speech in Noise
SRT	Speech Reception Threshold
SSQ12	Speech Spatial and Qualities of Hearing Scale
TIM	Trans Impedance Matrix
TRL	Technology Readiness Level
USADE	Unanticipated Serious Adverse Device Effect
VT	Vibrotactile

2 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	Feasibility, prospective, multicentric, cross-sectional investigation to characterize daily impedance fluctuations and satisfaction in challenging listening environments in experienced adult CI recipients using the Mobile Research App (MRA).
Short title	DICE
Investigation number	AI5846
Name of research tool	[redacted]
Intended use of research tool	[redacted]
Name and description of comparator device/product(s)	Not applicable
Estimated recruitment period	8 months
Expected duration per subject	2 months
Number of subjects planned	50
Number of investigational sites planned	3
Inclusion criteria	• Aged 18 years or older (no upper age limit). • Implanted with CIC4-based implant with a Contour Advance, Slim Straight or Slim Modiolar electrode array with at least 6 months experience. • Candidate is a fluent speaker in the language used to assess speech perception performance, as determined by the investigator. • Willing and able to provide written informed consent.
Exclusion criteria	• Score below 3 on the screening subset of questions from the Mobile Device Proficiency Questionnaire (digital literacy check). • A failed ECE1 or ECE2 (i.e. flagged, open circuit or short circuit) • Additional health factors, known to the investigator, that would prevent or restrict participation in the evaluations, including significant visual impairment and/or dexterity issues. • Unable or unwilling to comply with the requirements of the clinical investigation as determined by the Investigator. • Investigator site personnel directly affiliated with this study and/or their immediate families; immediate family is defined as a spouse, parent, child, or sibling. • Cochlear employees or employees of Contract Research Organisations or contractors engaged by Cochlear for the purposes of this investigation. • Current participation, or participation in another interventional clinical study/trial in the past 30 days, involving an investigational drug or device

	(unless the other investigation was/is a Cochlear sponsored investigation and determined by the investigator or Sponsor to not impact this investigation) • Pregnant or breastfeeding

Objectives and Endpoints	
Primary Objective	**Primary Endpoint**
To collect and describe time series data for complex impedances (access resistance & polarization) collected between clinic visits.	Descriptive summaries of the complex impedance measurements on all enabled electrode-contacts collected via the MRA (multiple times per day, every day, long period) between clinic visits.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3 SCHEDULE OF EVENTS

Visit Type	Screening[1]	Visit 1	Take-home	Unscheduled visit if needed	EOS
Timing of Investigation	**NA**	**Day 0**	**NA**	**NA**	**Week 8**
Visit window (±)	NA	**NA**	**NA**	**NA**	**± 14 days**
Procedures					
Written informed consent	X				
Mobile Device Proficiency Questionnaire	X				
Demographics	X				
Eligibility	X				
Hearing history	X				
Device history	X				
Medical history	X				
Device activation		X		X	
T-levels		X		X	X
Performance measurements					
Speech perception testing – Words in Quiet (free-field)				X	X[2]

Visit Type	**Screening[1]**	**Visit 1**	**Take-home**	**Unscheduled visit if needed**	**EOS**
Timing of Investigation	**NA**	**Day 0**	**NA**	**NA**	**Week 8**
Visit window (±)	NA	**NA**	**NA**	**NA**	**± 14 days**
Speech perception testing – Digit Triplet Test in noise (MRA)			X[4]	X	
Speech perception testing – Sentences in noise (free-field)				X	X[2]
Unaided Pure-Tone Audiogram (headphones)		X		X	X[3]
	Objective measurements				
Complex impedance/TIM (CSS)		X		X	X
Complex impedance/TIM (MRA)		X	X[4]	X	X
Data collected with iOSsmartwatch (Temperature, stress level, activity)			X[4]		
	Questionnaires and audio recording				
Wellbeing questionnaire (MRA)			X[4]		
SSQ12 questionnaire (MRA)		X		X	
EMA (incl. audio recording) (MRA)			X[4]		
	Other				
Concomitant medications/therapies	X	X			X

Visit Type	Screening[1]	Visit 1	Take-home	Unscheduled visit if needed	EOS
Timing of Investigation	**NA**	**Day 0**	**NA**	**NA**	**Week 8**
Visit window (±)	NA	**NA**	**NA**	**NA**	**± 14 days**
Adverse Events	X	X	X		X
Device Deficiencies		X	X		X
Device exposure		X	X		X
Map settings/Programs from sound processor		X			X
Datalogs from sound processor			X[4]		

Abbreviations: FF: Free field; MRA: Mobile Research App; CSS, Custom Sound Suite; TIM: Trans-impedance Matrix test; SSQ12: Speech Spatial and Qualities of Hearing Scale; EOS: End of Study

The above table is a guide. The test period between the first and last visit is expected to be 8 weeks (+-14 days) for each subject. Visits planned outside of this time window are not reported as deviations. All visit measurements may be obtained remotely, like in the home situation, if preferred by the investigator or subject.

[1]The screening can be combined with visit 1.

[2]These measurements can also be completed at visit 1 if preferred by investigator or subject.

[3]This measurement on visit 2 is conditional. It is only measured in case of residual hearing with the average of pure tone audiogram thresholds on 250 and 500 Hz lower than 70 dB HL.

[4]No protocol deviations will be created for these measurements in case no data/limited data are collected.

4 BACKGROUND INFORMATION AND RATIONALE

4.1 Introduction

[redacted]

Health of the cochlea can be monitored e.g. through checking the stability of impedances. Currently this information is obtained only during clinical visits in consultation with clinician. However, impedance-based biomarkers have been proposed for fibrous tissue growth along the CI electrode and for inner ear pathology (Shaul et al., 2019), which could possibly predict future residual hearing loss (Choi et al., 2017). Currently we know very little about the normal daily variability of impedances. At-home monitoring would allow for enough data to establish what daily fluctuations are normal or abnormal for a patient and thus flag issues with the health of the inner ear, e.g. to reduce the risk of loss of residual hearing.

[redacted]

[redacted]

4.2 Findings of Previous Nonclinical and Clinical Studies

4.2.1 Nonclinical Data

Most animal studies investigating impedance fluctuations focus on the period between surgery and a few months postop (Clark et al., 1995; Huang et al., 2007; Needham et al., 2020; Tykocinski et al., 2001; Wilk et al., 2016; Xu et al., 1997). This period is characterized by strong changes due to (1) fibrous tissue formation along the electrode array and (2) passivation and reactivation of the electrode contacts before and after device switch-on, respectively. The latter phenomenon may be the result of Pt-oxidation due to the inactivity of the electrode in this period but might be attributed as well to inflammatory reactions following electrode insertion at implantation. Some studies sample the impedance with an interval of a couple of days. The most intense measurement schedules in literature record the impedance twice a day. Most of the latter studies measure it before and after device switch-on, focusing on the impedance change after overnight inactivity (Needham et al., 2020). Other studies measure the impedance at two unspecified instances (Tykocinski et al., 2001; Xu et al., 1997). As such, these studies do not provide information on impedance changes in a period of a few months post-op.

Only one study was found that investigated impedance changes in four implanted cats during a 4-weeks period six months after implantation. During this period, strong implantation-related modifications of the intracochlear environment are assumed to have settled and normal daily impedance fluctuations may be distinguished more easily. This work by Newbold et al. (2014) recorded the impedance in the morning before device switch-on and several times within four hours after device switch-on. As such, it addresses specifically the effect of overnight inactivity of the cochlear implant and subsequent device switch-on. The study reported a reduction of the impedance with 20% within 15 min after the onset of stimulation. The effect was stronger

for animals exhibiting higher impedances at the implanted electrodes. This study did, however, not provide more insight in impedance changes within a day.

4.2.2 Clinical Data

Studies of impedance fluctuations on humans typically have in common that the sampling interval of the measurements follows that of the routine clinical visits of the subjects. This means a measurement interval of at least one week during the postoperative period up to three months. Thereafter, the interval is at least a couple of months or more (Brkic et al., 2020; Busby et al., 2002; Choi et al., 2017; Jia et al., 2011; Leblans et al., 2022; Molisz et al., 2015; Paasche et al., 2006; Sanderson et al., 2019; Shaul et al., 2019; Tykocinski et al., 2005; Zarowski et al., 2020). Several of them investigate the strong variations directly induced by CI-implantation, either due to electrode passivation/reactivation, tissue formation around the electrode, the influence of medication or surgical procedure on those phenomena, or due to adverse issues related to the electrode (Busby et al., 2002; Leblans et al., 2022; Molisz et al., 2015; Paasche et al., 2006; Tykocinski et al., 2005; von Mitzlaff et al., 2021). Two of the exceptions are (Choi et al., 2017; Shaul et al., 2019). They investigated in the postoperative period of 3 months up to 3 years the relation between impedance changes and episodes of hearing loss, vertigo or tinnitus, using an impedance sampling period of at least a few months. Their work illustrates very well the limitations when monitoring these medical events, which are often transient in nature, by means of in-clinic impedance measurements. They try to correlate substantial impedance increases, which had disappeared in 50% of the cases at the subsequent visit, to medical events that occurred in the period four weeks before and after the observed increase. This raises two questions: (1) How many relevant impedance changes/medical events have been missed? (2) What is the reliability of relating the impedance increase and the medical event in the case of such a broad time interval?

An exception is the work of (Newbold et al., 2014), investigating the effect of overnight inactivity of the cochlear implant and subsequent device switch-on in experienced human CI-users (1.5 – 5.5y postop), which is similar to their animal study. Three CI-users are followed only for three subsequent days, while electrode impedances were recorded three times a day: before device activation in the morning, half an hour later and just before device switch-off at the end of the day. An average impedance reduction of 5% after device switch-on was reported. This study, however, focussed on overnight activity and not on impedance variation throughout the day. Furthermore, the number of datapoints in this study was limited.

The following work also measured impedances multiple times per day in humans, but during 1-month post-op. Parreño et al. (2020) recorded impedances twice a day (with a 12h difference) over the first 30 days after implantation, using a self-developed system for at-home monitoring. Because the data are acquired before initial stimulation, the data are dominated by huge impedances mostly attributable to the passivation of the electrode contact, building up during the first 2 weeks. Ausili et al. (2022) used the same setup to record complex impedances daily (once per day) over the first 30 days after implantation. The dynamics of total impedance changes between days were Similar to the findings by Parreno et al. In addition, it was found that the main contributor to changes are the capacitive components of the impedance. The dynamics of impedances during a day (before and after stimulation) have not been analyzed. Overall, published studies lack information on impedance variation during a day and as day-to-day variation, especially during a period of at least six months post-implantation.

[redacted]

[redacted]

4.3 Study Rationale

The possibility to continuously monitor the health of the implanted cochlea, with associated algorithms to detect events such as inflammations and scar tissue formation (fibrosis) will address a major challenge in our field, namely long-term preservation of residual hearing. A candidate biomarker for cochlear health may be found through the measurement of the different components of the complex electrode contact impedances. A prerequisite to develop detection algorithms for abnormal events, is the collection of normative data. However, as mentioned in section 4.2, data on impedance variation during a day and as day-to-day variation, especially during a period of at least six months post-implantation is not currently available. Past studies

analysed clinical impedance measurements retrospectively or data prospectively in-clinic at scheduled visits of the subjects. Consequently, the availability of data is limited to irregular and rather coarse time intervals of week(s) or months, while the phenomena contributing to the impedance often fluctuate on a faster time scale. Therefore, when measuring the impedance in-clinic, it is impossible to control the appropriate sampling times in case of several potential origins of the impedance fluctuations, such as infections of the upper respiratory pathways (Zarowski et al., 2020), (over-night) inactivity of the cochlear implant prior to the measurement, the intensity of implant use, the use of medication, and clinical events such as vertigo, Ménière-like symptoms, tinnitus, and loss of residual hearing (McNeill and Eykamp, 2016; Parreño et al., 2020; Shaul et al., 2019). This motivates the primary objective of this investigation, which is to collect and describe time series data for complex impedances collected at home. [redacted]

5 RESEARCH TOOL INFORMATION

5.1 Identity and Description of the research tool

The primary interest of this investigation is the impedance measurement collected in the home environment of the participant. To collect this data a research system is used consisting of Mobile Research App (MRA) (participant facing app) V3.0 and above. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

All research tools are manufactured by Cochlear Limited. The iOS device® with the MRA installed will labelled exclusively for use in a clinical investigation. The study data will result in learnings that will be useful towards the design of a future daily impedance feature in the commercial software. CI recipients/investigators will use the research tools for the duration of the study only. Traceability of the build number will be documented in the tracking forms such as the Software Tracking Form (1302326). The investigators will receive comprehensive, specific training in the use of the research tools and in ongoing support during the execution of the study procedures as needed. This training will be logged on a training log. The CI-recipients will receive specific training in the use of the research tool and will receive ongoing support from the investigator during the execution of the study procedures. The research tools are software-only and will not be in contact with body fluid or tissue. Further details regarding the research tools are provided in the IB and Instructions for Use (IFU).

[redacted]

[redacted]

[redacted]

6 OBJECTIVES

6.1 Primary Objective

To collect and describe time series data for complex impedances (access resistance & polarization) collected between clinic visits.

[redacted]

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 General

This is a feasibility, prospective, multi-country, multi-centre, cross-sectional interventional clinical investigation in adults with a CE labelled cochlear implant.

The early feasibility categorisation relates to the use of research tools and the purpose of the investigation being to collect pilot data on impedance measurements in real-world environments, reflecting any situation the subjects encounter during their normal life outside of the clinic.

In total, 50 eligible subjects are planned to be recruited in the clinical investigation. The subjects include adults from the age of 18 years or above who are currently using a commercial available Nucleus CIC4-based implant with a Contour Advance, Slim Straight or Slim Modiolar electrode array with a minimum of 6 months experience. Subjects will be screened according to the inclusion and exclusion criteria as described in section 7.2. No Randomisation nor blinding to avoid bias is applicable in this study since there is no comparator.

Subjects will attend two scheduled study visits over a two-month study period as described in the Clinical Investigation Plan (CIP) Schedule of Events (Section 3). At and in between study visits, subjects will undergo hearing assessments and safety monitoring. The time of each visit is estimated to be less than 2 hours. During the first two weeks of the take-home the subjects will start to perform daily impedance test tasks and complete a questionnaire five times a day and a speech test once per day with the MRA application in order to obtain the first primary endpoint, i.e. characterization of Daily Impedance Fluctuations. For the rest of the two months study two daily impedance tests with questionnaire and one speech test will be measured per day. In case of any of symptoms or impacted hearing (sound quality) reported by the participant in the

questionnaire, one additional week of daily impedance tests with questionnaire for five times a day will be done.

[redacted]

[redacted]

[redacted]

[redacted]

Safety will be assessed by recording and summarising all adverse events (AEs)/advice device effects (ADEs) and device deficiencies (DDs). The investigator will be able to view and monitor results during take-home, however this is not required for the study. Given the feasibility nature of this study, characterisation as primary endpoint and monitoring of results by the investigator, the data can be analysed continuously. The purpose is acquiring knowledge at this stage. No data monitoring committee will be used for this clinical investigation. All subjects will attend an End-of-Study visit at the time they complete the study.

The principal Investigator List will specify where evaluations will be conducted and who will be responsible. The principal investigator may determine to do study visit measurements remotely where possible, like in the home situation.

7.1.1 Design Rationale

This is one of the first exploratory studies investigating daily impedance fluctuations at the CI-electrode contacts with a high sampling frequency over a longer period in a population of CI users who are expected to have reached a stable state of impedances. Because there is no clear evidence yet which underlying factors may be expressed most prominently that explain impedance fluctuations, the inclusion criteria are chosen broad with respect to implant type and medical/hearing background of the subjects. Also, medical, hearing, medication and device usage parameters are collected to find possible correlations with impedance

fluctuations, which may be the subject of future investigations with well-founded hypothesis. Because the subjects have their own specific conditions and because the study also addresses events that may occur in an uncontrolled way, it has a single-subject repeated measures design, in which each participant is acting as his/her own control.

The study will investigate both impedance fluctuations within a single day and over a total period of 2 months. The sample frequency of the impedance, the monitoring period and the number of subjects is chosen to be superior to available data, to detect subtle changes that may not be apparent with less frequent data collection and to allow for a realistic chance on recording impedances and related measures during uncontrolled medical/hearing events. The measurement schedule aims to result in a high subject compliance, resulting in a consistent data set.

[redacted]

7.2 Subjects

Written, informed consent must be obtained from the subject before any study procedures are initiated.

Eligibility of subjects must be supported by medical, demographics and audiological information as well as their mobile proficiency that confirm the subject inclusion as stated in Section 7.2.

7.2.1 Inclusion Criteria

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

1) Aged 18 years or older (no upper age limit).
2) Implanted with CIC4-based implant with a Contour Advance, Slim Straight or Slim Modiolar electrode array with at least 6 months experience.
3) Candidate is a fluent speaker in the language used to assess speech perception performance, as determined by the investigator.
4) 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) Score below 3 on the screening subset of questions from the Mobile Device Proficiency Questionnaire (digital literacy check).
2) A failed ECE1 or ECE2 (i.e. flagged, open circuit or short circuit)
3) Additional health factors, known to the investigator, that would prevent or restrict participation in the evaluations, including significant visual impairment and/or dexterity issues.
4) Unable or unwilling to comply with the requirements of the clinical investigation as determined by the Investigator.
5) Investigator site personnel directly affiliated with this study and/or their immediate families; immediate family is defined as a spouse, parent, child, or sibling.
6) Cochlear employees or employees of Contract Research Organisations or contractors engaged by Cochlear for the purposes of this investigation.
7) Current participation, or participation in another interventional clinical study/trial in the past 30 days, involving an investigational drug or device (unless the other investigation was/is a Cochlear sponsored investigation and determined by the investigator or Sponsor to not impact this investigation).
8) Pregnant or breastfeeding

7.2.3 Number of Subjects Required

As the current study is a feasibility study, no sample size calculation using power analysis can be done. [redacted] Overall, a sample size of 50 subjects of which 10 subjects are expected to show fluctuating impedances is considered appropriate for this feasibility study. Cross-regional pooling of data is justified due to the within-subject study design.

7.2.4 Vulnerable Populations

Pregnant or breastfeeding woman will be excluded in this clinical investigation as this study will not give direct benefit to this vulnerable population group.

7.2.5 Recruitment and Study Duration

The following subject status definitions apply:

- Enrolled: A subject that has 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: Subjects who have met eligibility criteria and have commenced baseline assessments.
- 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 8 months from the time of first subject consent to recruitment of the last subject.

The expected duration of each subject's participation in the clinical investigation is 2 months, from the time of informed consent through to the End of Study visit.

Clinical Investigation completion is last subject last visit. In the event of an ongoing Serious AEs (SAEs)/Serious ADEs (SADEs) at the time of this last visit, the 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

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.

In case more than 10 % of the participating subjects are withdrawn/discontinued, the subjects will be replaced to ensure 45 subjects adhere to both conditions:

- During the initial 'intense' 2 weeks, the participant performed a minimum of 20% of the target complex impedance and TIM measurements.
- After the initial 'intense' 2 weeks, the participant performed a minimum of 10% of the target complex impedance and TIM measurements.

7.2.7 Randomisation Procedures

Not applicable

7.2.7.1 Blinding Procedures

This is a pilot study with the aim to collect data on impedances in the home environment to be potentially used to inform larger data collection initiatives for characterisation and/or diagnostic purposes. The subjects will not see the impedance data collected. Blinding is not applicable in this study.

7.2.8 Post-investigation Medical Care

Following the investigation, subjects will continue with standard of care treatment. [redacted] No extra medical care needs to be provided after the clinical investigation.

[redacted]

7.3.1 Screening/eligibility

Screening will only be conducted after the participant has consented into the study. Eligibility will be confirmed according to the eligibility criteria in section 7.2. The following must be completed prior to any study procedures not related to screening:

- Written informed consent: must be completed before any study-specific procedures are completed
- Demographics: document month and year of birth and sex
- Eligibility: confirm subject meets all inclusion criteria and no exclusion criteria. Source documentation must be available before confirming eligibility. For pregnancy or breastfeeding subject reporting is sufficient.
- Hearing History: document history of hearing loss (may be subject reported)
- Device history: document history with hearing aids and hearing implants (may be subject reported)
- Medical History: document medical history (may be subject reported)
- Mobile Device Proficiency Questionnaire: must be completed at screening (see below)

7.3.1.1 Mobile Device Proficiency Questionnaire (MDPQ)

The purpose of this questionnaire is to screen subjects on their proficiency with a mobile device.

Eligible subjects must be able to perform basic tasks with a (smart) mobile device for them to successfully complete tasks associated with the MRA app. Proficiency with a mobile device will be screened using the Mobile Device Proficiency Questionnaire (Roque & Boot, 2018). The MDPQ is a validated questionnaire which measures the ability of older adults (over 65 years old) to perform certain tasks with a mobile device, specifically smartphones. The questionnaire is comprised of 46 statements, split into eight (8) sections:

1. Mobile Device Basics
2. Communication
3. Data and File Storage
4. Internet
5. Calendar
6. Entertainment
7. Privacy
8. Troubleshooting and Software Manager

Each statement is prefaced with "Using a mobile device I can:" and scored on a 5-point Likert scale, where 1 corresponds to "Never tried" and 5 corresponds to "Very easily". All subjects will be asked to complete the full questionnaire, however, only a subset of the tasks are directly relevant to the ability to use the MRA app. Therefore, only scores from a subset of the statements in sections 1 (Mobile Device Basics) and 8 (Troubleshooting and File Storage) will be used to determine eligibility for the study. Subjects will need to score an average of 3 (suggesting at least some level of ability to perform the tasks) or higher to proceed in the study. Scores from the following questions will be used to determine eligibility:

Section 1 – Device Basics

Using a mobile device I can:

a. Turn the device on and off
b. Charge the device when the battery is low
c. Navigate onscreen menus using the touchscreen
d. Use the onscreen keyboard to type
e. Copy and paste text using the touchscreen (*Will not be used for eligibility)*
f. Adjust the volume of the device

g. Adjust the screen brightness

h. Adjust text size (*Will not be used for eligibility)*

i. Connect to a Wi-Fi network

Section 8 – Troubleshooting & Software Management

Using a mobile device I can:

a. Restart the device when it is frozen or not working right

b. Update games and other applications

c. Close games and other applications

d. Delete games and other applications *(Will not be used for eligibility)*

e. Upgrade device software

In case of a score of less than 3 to the MDPQ, the subject will not be enrolled into the study and routine ongoing management and care will be scheduled with the clinic.

7.3.2 Performance/Effectiveness

7.3.2.1 Data collection at site visit

[redacted]

[redacted]

7.3.2.1.3 Objective measures: Standard impedances and Trans-Impedance Matrix test (TIM)

Standard clinical impedances will be collected using the CSS Software. The TIM is an electrophysiological method based on electric field imaging that can provide images of electrode position and electrode folding. In TIM, the CI stimulates one contact and records the electrical potential decay along the cochlea on all contacts. In general, the decay constants may depend on the electrode type and location, the cochlear anatomy and tissue properties (Ramos, et al., 2022). TIM measurements will be obtained on all enabled electrodes post-operatively, using the commercially available CSS software. Electrodes flagged in the MAP will be excluded if necessary. No protocol deviation will be created in case TIM measurement cannot be obtained on all enabled electrodes.

[redacted]

[redacted]

7.3.2.2 Data collection during take-home with MRA

[redacted]

7.3.2.2.1 Complex impedance

The complex impedance measurement is an objective measurement of the characteristics of the electrode-tissue interface (section 4.1) and requires no feedback or interaction by the user. It can be started by the user with a single button press. The measurement data is stored automatically by the system and uploaded to the web portal for off-line analysis. The measurements are expected to be inaudible or at least only perceived as soft sounds.

7.3.2.2.2 Trans-Impedance Matrix test

As described above, the TIM measurement is implemented on the MRA to measure on a daily basis. The measurement is equivalent to the TIM measurement in CSS. Like the complex impedance measurements, it does not need feedback or interaction by the user. It can be started by the user with a single button press. The measurement data is stored automatically by the system and uploaded to the web portal for off-line analysis. The measurements are expected to be perceived as soft sounds.

[redacted]

[redacted]

[redacted]

[redacted]

7.3.3 Safety Evaluations and Procedures

The risks and anticipated ADEs for the investigational device, 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 first visit until last subject last visit. The stimulation characteristics of the electrode sweep are standard charge-balanced bi-phasic pulses presented sub-threshold, with an associated medium-risk anticipated device effect possible. The subject is requested to complete a well-being questionnaire each day to provide information relating to the association between impedance fluctuations and clinical symptoms, and to capture adverse events. The investigator is required to capture any adverse event or any new information in the CRF on each study visit.

Safety data adjudication will be conducted by the Sponsor in accordance with the Sponsor's standard operating procedures. Upon review of data available in the CRF, the Sponsor may query data or request deidentified source documents to review the event.

7.3.3.1 Concomitant Medication and Therapies

Concomitant medications will be recorded in the subject's CRF at the screening visit and updated during the clinical investigation when changes to medication and/or therapies occur. The subject can report any change in these conditions through self-reporting by means of the wellbeing questionnaire on the Mobile Research App. As long as the subject is capable of performing the self-test and self-reporting, concomitant medication and therapies do not obstruct the validity of the study data. To the contrary, identifying the potential effects of concomitant medication and therapies on the impedance measured at the CI-electrode contacts is a secondary objective of the study. There are no prohibited medications under this clinical investigation.

7.4 Equipment Used for Evaluations and Procedures

Tools including software, firmware, and sound equipment (e.g., speakers or audio streaming accessories) will be used to write the investigational firmware to the loaner sound processor, measure TIM responses, collect subject's self-reporting during take-home, collect audio recordings, collect datalogs and assess hearing performance. Software and firmware should be kept current at the direction of the Sponsor.

The investigational firmware will be written to the loaner CP1000 or CP1150 sound processor using an application on a standard personal computer.

[redacted]

Impedances, [redacted] will be administered to subjects via the MRA on a compatible iOS device. Subjects will be instructed to complete the Impedances, [redacted] in a quiet room in the home environment with low ambient noise, free from distractions.

7.5 Sponsor Role in Conduct of the Clinical Investigation

Employees of the Sponsor organisation may act as investigators, conducting all study visits and procedures.

In case Cochlear employees acting as investigators will be involved in Sponsor procedures, this will be clearly documented in the study documentation.

A Sponsor representative may provide support during study procedures performed by the investigational sites. They may also attend study visits to trouble-shoot issue that may arise during the investigation. The duration and level of support provided by the Sponsor will be guided by the investigators.

8 BENEFITS AND RISKS OF THE RESEARCH TOOL AND CLINICAL INVESTIGATION

8.1 Anticipated Clinical Benefits

Participation in this clinical investigation is not expected to provide individual clinical benefit to the subjects.

8.2 Anticipated Adverse Device Effects

Residual risks have been assessed in accordance with Cochlear's Product Risk Management Procedure. Only the following residual risk is relevant for this study and is classified as medium risk:

- During the execution of measurements, some of the stimulation pulses may be perceived as uncomfortable or result in pain or non-auditory stimulation for a short period of time. The users will be informed that they have the option to use a stop button in the app or take off the coil from their head.

Risk mitigations have been identified and will be implemented to ensure the residual risk associated with the use of this tool is acceptable. The likelihood of these risks is estimated low enough to judge them acceptable in the scope of the intended use cases.

8.3 Risks Associated with Participation in the Clinical Investigation

There are limitations associated with using the Research system as listed below.

- The sound processor can't be controlled using Nucleus Smart App, nor the Remote Check app . However, the sound processor can be controlled via the research tool with the following available features: volume control, program slot selection and Forward Focus selection. NSA will be made available again at the end of the study according to local availability.

[redacted]

[redacted]

- The subject will not be able to hear during the impedance measurements.

8.4 Risk Mitigation

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

- All investigators will receive training in the use and handling of investigational Research tools and in the procedures specific for the study. A detailed procedures manual will be provided to the investigator. In addition, a Sponsor representative is available to provide support during study procedures performed by the investigational sites until such time as the investigational site team are confident and competent to complete the study requirements. As mentioned before, the sponsor representatives may also attend sessions to trouble-shoot any issue that may arise during the investigation.

- All reported 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.

- In addition, the clinical investigator will regularly review reported ADEs for the duration of the study to facilitate early detection and appropriate intervention if events are unanticipated with respect to incidence, severity, or outcome.

- The users will be informed that they have the option to use a stop button in the app or take off the coil from their head. This information will be provided by the MRA manual and will also be shown right before actively starting the measurement.

8.5 Benefit-to Risk Rationale

The residual risks associated with the MRA system have been reduced to the lowest possible level. Verification activities show that the hazards have been effectively mitigated by design.
It is concluded that the risks related to MRA system and its associated measurements, when used as intended by the intended user groups, are acceptable when weighed against the intended benefits to the subject and are consistent with current state-of-the-art therapies. Therefore, it is concluded that the benefit-risk ratio is favourable for the MRA system. This benefit-risk analysis will continue to be reviewed throughout the use of the system as new clinical data becomes available from clinical investigations. Any new risks identified during the investigations will be managed according to Cochlear's Product Risk Management Procedure.

9 STATISTICAL CONSIDERATIONS

9.1 General Considerations

This clinical investigation plan outlines the statistical considerations for a feasibility multicentre study involving 50 subjects. As this is a feasibility study with no formal hypothesis, the primary objective is to generate preliminary data and identify trends or associations that may warrant further investigation in future studies.

Descriptive statistics will be used to summarize subjects demographics, clinical characteristics, and outcomes. Continuous variables will be presented as means and standard deviations or medians and interquartile ranges, depending on the distribution of the data. Categorical variables will be presented as frequencies and percentages.

Given the exploratory nature of the study, inferential statistics will be used cautiously, and any findings should be interpreted as hypothesis-generating rather than confirmatory. Potential associations between variables of interest may be explored using correlation analyses, time series analysis, or logistic regression models, as appropriate.

9.2 Endpoints

9.2.1 Primary Endpoint

Descriptive summaries of the complex impedance measurements on all enabled electrode-contacts collected via the MRA (multiple times per day, every day, long period) between clinic visits.

[redacted]

- [redacted]

[redacted]

9.3 Hypotheses

9.3.1 Primary Hypothesis

Given the exploratory nature of the objectives, there are no formal hypotheses formulated. Descriptive statistics, such as means, standard deviations (SD), confidence intervals will be used to summarise the endpoints.

[redacted]

9.4 Sample Size Determination

A total of 50 subjects will be included in this feasibility study. This sample size is not based on formal power calculations, as there is no specific hypothesis being tested. Instead, the sample size is chosen to provide a reasonable amount of data for preliminary analyses and to identify potential trends or associations that may be of interest for future studies.

9.5 Analysis Populations

Analyses will be conducted on the complete dataset.

The data of the subjects who do not satisfy both of the following conditions will be excluded:

- During the initial 'intense' 2 weeks, the participant performed a minimum of 20% of the target complex impedance and TIM measurements.
- After the initial 'intense' 2 weeks, the participant performed a minimum of 10% of the target complex impedance and TIM measurements.

[redacted]

9.6 Endpoint Analyses

9.6.1 Primary Endpoint Analyses

The primary objectives will be assessed by using descriptive statistics such as means, SD, confidence intervals.

[redacted]

9.7 Safety Analyses

There is no formal statistical hypothesis. Adverse events will be tabulated according to the study interval, the

number of procedure-related events, and the number of device-related events. Procedure- and device-related adverse events will be summarized as rates, where the numerator for each rate will be the number of subjects with at least one procedure- or device-related event, and the denominator will be the total number of subjects. Adverse events will be reported by type, frequency, and severity. No formal statistical comparisons will be conducted.

9.8 Interim Analyses

No formal interim analysis will be conducted. However, given the feasibility nature of the study, it is planned to monitor findings continuously to inform modifications to the research tool and/or study procedures when required and to continuously inform the development of the research tool.

10 INFORMED CONSENT PROCESS

The Investigator shall obtain written informed consent from the subject using an approved Informed Consent Form (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. 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 and the person who conducted the informed consent discussion, shall sign and personally date the 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 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 research tool or the procedures required for implant or use, and whether anticipated or unanticipated.

NOTE 1: This definition includes events related to the research tool or the comparator device.

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 research tools.

11.1.2 Adverse Device Effect

An adverse device effect (ADE) is an AE related to the use of a research tool.

NOTE 1: This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the research tool.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the research tool.

NOTE 3: This includes 'comparator' if the comparator is a research tool.

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, or damage to, a body structure or a body function including chronic diseases, or
    - in-patient hospitalisation or prolonged hospitalisation, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment or damage to a body structure or a body function,
3) foetal distress, foetal death or a congenital physical or mental 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 hazard analysis, IB, IFU, CIP or ICF.

NOTE: An anticipated serious adverse device effect is an effect, which by its nature, incidence, severity, or outcome has been identified in the hazard analysis, IB, IFUs, CIP or ICF.

11.1.6 Adverse Events of Special Interest

Not applicable

11.1.7 Device Deficiency

A Device Deficiency (DD) is an inadequacy of a research tool 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 research tool or the comparator.

11.1.8 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 contact with the research tool. AE recording will continue for each subject until completion of their End of Study visit. Ongoing SAEs and SADEs 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 research tool 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 research tool product will be considered and investigated. The causal relationship to the research tool 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.

Due to the different causality reporting requirements in participating regions, the Sponsor will request causality assessments from investigators using the five categories described in the preceding table. Cochlear will report causality to competent authorities and ethics committees based on local regional requirements as described in Section 11.4.2.

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 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).

11.2.5 Non-reportable Adverse Events

As determined by risk assessment by the Sponsor, this study is deemed as a low risk study. AEs that occur as a result of a planned procedure that is not related to hearing or to the study procedure e.g. in-patient hospital stay for hip replacement, will not be reported.

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.

Clinical and technical support will be provided by Cochlear as required to resolve any device deficiencies that require troubleshooting.

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
Belgium	24 hours
Sweden	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. In Belgium/Sweden, reporting to the local EC is coincident with that to the Competent Authority.

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 a 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:

Sponsor Safety Monitor:	Clinical Review Board Email: Cltd-safetymonitor@cochlear.com

11.5 Independent Data Monitoring Committee

Given the low residual risk described in Section 8.5 of the CIP an Independent Data Monitoring Committee (IDMC) will not be established for this study.

12 Device Accountability

Supply of research tools will be recorded using the Sponsor Device Tracking Form (1295388) and Software Tracking Form (1302326). Research tool(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 Individual Subject Device Accountability Log Form (1295295).

At the end of the clinical investigation, all research tools shall be returned to the Sponsor. [redacted]

Contact information regarding the research tool is provided below.

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[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 72 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 research tool, 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 Good Clinical Practice (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. Data collected for specific tests as documented in the Origin of Source Data Form will be entered directly into the eCRF which shall be considered source data for these items. If electronic medical records do not permit read only access for monitoring purposes, a certified printout will be provided, indicated by a dated signature by a member of the site team or generated through a validated process.

In addition, de-identified electronically generated data collected from the software tools used during the study visits will comprise measures such as impedance data, TIM data and map settings. [redacted] The unamended data files shall be regarded as the source.

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 collected from the software tools used during the study visits will be stored outside of Medidata Rave in a password protected secure sharefile location. Also, de-identified electronic collected data from the CI recipient for the [redacted] complex impedances [redacted] will be collected and stored by the sponsor password protected in the electronic trial master folder with limited access. Site staff and CI recipients will be trained in conducting and completing the tasks in the MRA prior to obtaining access to the system. Site staff will have their own Login/Password.

Access to clinical study information will be based on an individual's role and responsibilities. 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 maintains a comprehensive log for all data entered and documents the time that each entry occurred.

14.3 Database Lock

The Sponsor shall confirm that no further subject visits will be conducted, all required forms have been completed and required data have been entered into the EDC including resolution of ongoing Adverse Events in accordance with CIP requirements, study has been closed in MRA, all electronic data collected for specific tests by means of the MRA have been closed and stored on a password-protected secure file location, all electronically generated data collected from clinical fitting software, electrophysiology applications and the research MRA tools have been stored on a password-protected secure file location, all required monitoring has been performed according to the Monitoring Plan, all data queries have been closed, all completed CRFs have been signed off by the PI or delegate. The Sponsor shall lock clinical investigation database and generate raw datasets to enable analysis. Sites will be sent PDF representations of the data captured in Medidata Rave, including audit trail, to enable the site to archive the data for their subjects. Additionally, the study data of those subjects who consented may be used for other medical scientific research purposes in the field of hearing loss.

15 CONFIDENTIALITY

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

Data will be reported to the Sponsor on CRFs or related documents (for example questionnaire). 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.

16 ETHICS COMMITTEE AND REGULATORY AUTHORITY APPROVAL

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

Country	**Pathway**
Australia	CTN
European Union*	EU MDR Article 82

*See Veeva VV-TMF-27244 for applicable Statement/Declaration of conformity

The clinical investigation will not commence prior to the written favourable opinion or approval from the Ethics Committee (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/CA. A copy of the EC/CA 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/CA.

The Sponsor and Principal Investigator will continue communications with the EC/CA, 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/sponsor shall submit the appropriate documentation if any extension or renewal of the EC/CA 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/CA.

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

Upon completion of the clinical investigation, the Investigator shall provide the EC/CA with a brief report of the outcome of the clinical investigation, as per local EC/CA requirements. Local requirements are listed below.

Australia:

If a clinical investigation is prematurely terminated or suspended, the sponsor should promptly inform the investigator(s), institution(s), the EC, and the regulatory authorities. The sponsor should provide the reason(s) for the termination or suspension.

European Union:

Upon end of a clinical investigation, the sponsor shall notify the EC and regulatory authority within 15 days. In the case the clinical investigation is temporarily halted or terminated early, notification of this shall be made to the EC and regulatory authority within 15 days. Justification for the halt or termination shall be included. If either situation is on safety grounds, then the reporting timeframe is 24 hours.

The clinical investigation report and summary needs to be submitted within one year of the end of the clinical investigation or within three months of the early termination or temporary halt to the EC and regulatory authorities.

For Sweden, an approval from the Swedish regulatory authority is required to restart the clinical investigation if the temporary halt was due to safety reasons.

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 Principal Investigator and the Sponsor. This agreement will be documented as a CIP amendment. Amendments will require notification to the Ethics Committees by the Principal Investigators (and to the relevant regulatory authority(s) by the Sponsor, if applicable). In Belgium and Sweden, the reporting of substantial modifications to the Ethics Committee is coincident with the reporting to the FAMHP/MPA. Only one submission is required through the national contact point (FAMHP/MPA). Substantial changes to the Clinical Investigation Plan may not be implemented until they have been notified and assessed in accordance with MDR Article 75.

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: At least 15 years after completion of the investigation, or, in the event that the device is subsequently placed on the market, at least 15 years after the last device has been placed on the market.

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.

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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 research tools.

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, 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 or its designee 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

24 REFERENCES

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