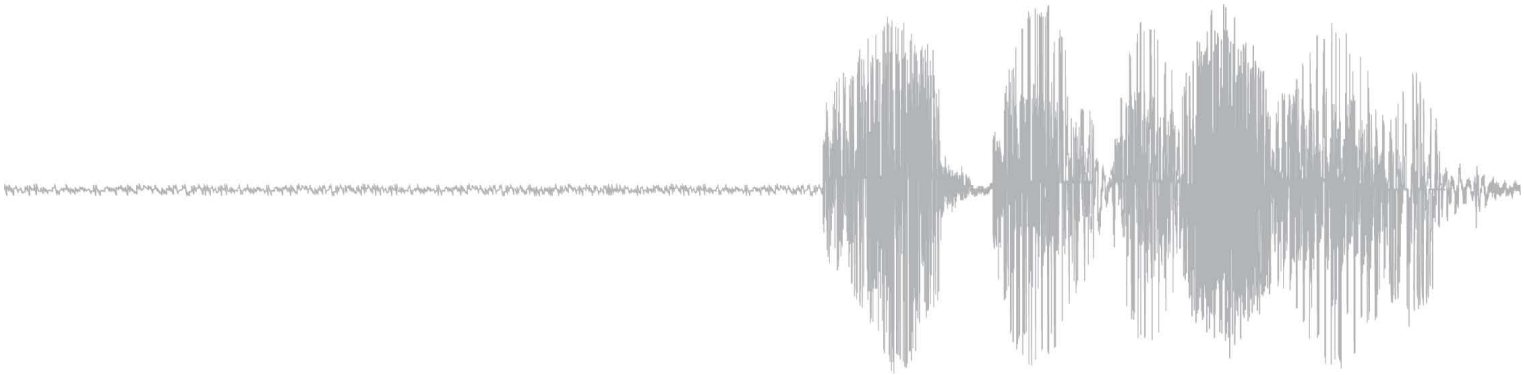

CIP_CAMSEN_AI-5770

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Version: 5
State: Approved (T+B)
Approver: Kerrie Plant (kplant)
Date : 06 Feb 2020

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Clinical Investigation Plan

Investigation Title: A prospective, single-centre evaluation of Carina microphone sensitivity and maximum stable gain in adult recipients

Short Tile:	**CAMSEN**
CIP Number:	**AI-5770**
Version Number:	**5.0**
Date:	**05-Feb-2020**
Sponsor	**Cochlear Limited** **1 University Avenue** **Macquarie University** **NSW 2109** **Australia**

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

Manufacturer	Cochlear Boulder LLC 5445 Airport Boulevard, Boulder, CO 80301, USA *EC Representative:* Cochlear Deutschland GmbH & Co. KG Karl-Wiechert-Allee 76A 30625 Hannover, Germany
Sponsor Organisations	Cochlear Limited 1 University Avenue Macquarie University, NSW 2109 Australia
Principal Investigator	Dr Victor Correia da Silva, Clinical Director, CUF Hospital, Porto
Clinical Research Organisation	Syneos Health Address: Stefan-George-Ring 6, 81929 München, Germany Phone: +49 89 9939130
Contract Services	NA
Safety Contact	CLTD-SafetyMonitor@cochlear.com

INVESTIGATOR AGREEMENT

Principal Investigator Approval and Declaration

By my signature below, I confirm my review and approval of this Clinical Investigational Plan (CIP).

I also confirm that I will strictly adhere to the requirements therein and undertake to ensure that all staff with delegated responsibilities in the conduct of this CIP have 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.

Name	**Title**
Dr. Victor Correia da Silva	Principal Investigator
Signature	**Date**

TABLE OF CONTENTS

1 DEFINITIONS AND ABBREVIATIONS

Term	Description
ADE	Adverse Device Effect
AE	Adverse Event
AMDT	Approved Medical Device on Test
AMEI	Active Middle Ear Implant
CER	Clinical Evaluation Report
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computed tomography
DCF	Data Clarification Form
DD	Device Deficiency
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
HL	Hearing loss
HP	Hearing Preservation
IB	Investigator's Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMD	Investigational Medical Device
NCA	National Competent Authority
PI	Principal Investigator
PIL	Principal Investigator List
PMS	Post-Market Surveillance
RW	Round window
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Term	Description
SNR	Signal-to-noise ratio
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

2 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	A prospective, single-centre evaluation of Carina microphone sensitivity and maximum stable gain in adult recipients
Short title	CAMSEN
Investigation number	AI-5770
Name of Approved Medical Device on Test	Cochlear™ Carina® 2 System MET-7000
Intended use of investigational medical device(s) **AMDTs for adults**	The Carina Fully Implantable Middle Ear Implant System MET-7000 with the MET-7500 actuator is intended to compensate auditory deficits in individuals aged 14 or older with moderate to severe sensorineural hearing loss, and for moderate to severe conductive or mixed hearing loss when used with one of the actuator extensions. The system provides amplification via direct mechanical stimulation of the auditory system.
Name and description of comparator device/product(s)	Not applicable
Expected start date (first subject consented)	January 2020
Expected enrolment period	2 months
Expected duration per subject	1 day
Expected total duration of the clinical investigation	2 months
Number of subjects planned	Up to 20 subjects will be enrolled.
Number of investigational sites planned	Single site
Inclusion criteria	1. Eighteen years of age or older at the time of enrolment in the study 2. Current recipient of a Cochlear Carina System.
Exclusion criteria	1. Unwillingness or inability of the candidate to comply with all investigational requirements as determined by the Investigator

Objectives and Endpoints	
Objectives	**Endpoints**
1. To characterize Carina microphone sensitivity	Acoustic sensitivity of implanted microphone [dB FS for 0.1 Pa], in-situ, for audiometric frequencies 250-6000 Hz, median and percentiles
2. To characterize Carina microphone : accelerometer ratio for acoustic stimulation	Ratio [dB] of response of implanted microphone to response of implanted accelerometer, in-situ, for audiometric frequencies 250-6000 Hz, median and percentiles
3. To characterize Carina microphone impulse response for acoustic and actuator stimulation	Identification of the system's acoustic and vibration transfer functions including non-linear components.
4. To characterize Carina maximum stable gain.	Transfer function from Carina output to actuator [dB FS] to Carina input from implanted microphone [dB FS], for audiometric frequencies 250-6000 Hz, with and without plugged ear canal

3 SCHEDULE OF EVENTS

Visit Type	Screening	Visit
Timing of Investigation		
Visit window (±)		
Procedures		
Written informed consent	X	
Eligibility	X	
Audiogram (bone conduction)		X
Direct thresholds		X
Microphone sensitivity		X
Microphone impulse response		X
Maximum stable gain		X
Adverse Events		X

4 BACKGROUND INFORMATION AND RATIONALE

4.1 Introduction and Study Rationale

The totally implanted Carina System is an active middle ear implant where all components (microphone, signal processing electronics, power source, and middle ear actuator) are implanted under the skin, making the system invisible and compatible with occupations and lifestyles that involve exposure to humidity or dust.

Placing a microphone under the skin affects its acoustic sensitivity and vibration sensitivity. With higher vibration sensitivity of the microphone, it may pick up small vibrations of the skull caused by the actuator coupled to a middle ear ossicles, which may lead to feedback squealing, similar to a conventional hearing where an acoustic feedback pathway from speaker to microphone may led to feedback squealing.

So far, acoustic sensitivity of an implanted microphone has been measured in bench and cadaver studies, and in a very small number of subjects implanted with a percutaneous access to the microphone (Gérard et al., 2017). Now, software is available to enable non-intrusive microphone measurements in existing patients with the Carina device, through a wireless link to the implant.

Detailed knowledge of the acoustic sensitivity of the implanted microphone, and its inter-individual variability, will allow more accurate calculation of overall system performance, and thereby more accurate prediction of clinical outcomes.

Detailed knowledge of the vibration sensitivity and the ratio of acoustic to vibration sensitivity will help to optimize future signal processing strategies intended to reduce the perception of body sounds, and the to reduce feedback.

Clinical studies on device performance typically report speech intelligibility scores and aided thresholds or functional gain, but it cannot be inferred to what extend the observed functional gain is determined by audiological needs, or the subject's preferences, or device limitations. With the research software available now, an objective measurement of the feedback transfer function and thereby of maximum stable gain can be made, which is independent of the audiological profile of the individual study subject, and their listening preferences.

Detailed knowledge of objectively measured maximum stable gain, and its inter-individual variability, will allow more accurate calculation of overall system performance, and thereby more accurate prediction of clinical outcomes.

4.2 Findings of Previous Nonclinical and Clinical Studies

4.2.1 Nonclinical Data

n/a

4.2.2 Clinical Data

The performance with an implanted microphone was compared to a standard external sound processor, in one patient fitted with temporary percutaneous access to the microphone (Jenkins & Uhler, 2012). A similar study on 4 subjects, also fitted with temporary percutaneous access to the microphone, was reported by (Gérard et al., 2017). Neither study investigated the sensitivity of the acceleration sensor. Maximum stable gain could also not be measured, because those were cochlear implant recipients, not recipients of an active middle ear implant.

5 MEDICAL DEVICE INFORMATION

5.1 Identity and Description of the Approved Medical Device on Test (AMDT)

The intended purpose of the Carina System for adults is to compensate auditory deficits in individuals aged 14 or older with moderate to severe sensorineural hearing loss, and for moderate to severe conductive or mixed hearing loss when used with one of the actuator extensions. The system provides amplification via direct mechanical stimulation of the auditory system.

As shown in Figure 1, the Carina System consists of a main implant body, containing the signal processing electronics and rechargeable battery, the pendent with the implantable microphone, and an output actuator intended to be coupled to a middle ear ossicles or the cochlea.

Figure 1: Carina implant, composed of the main implant body with electronics and battery (top), the implantable microphone pendent (middle), and the MicroDrive™ actuator (bottom).

5.2 Identity and Description of the Comparator

There is no comparator in this study.

5.3 Accessory Device Requirements

The AMDT is used in conjunction with the Carina Charging System (composed of the Carina Charger Base AUD-5112, the Carina Charger Body AUD-5111 and the Carina Charging Coil AUD-5120), the Carina Remote Control AUD-5900, and optionally the Carina Button Processor BAP-11x0.

During the measurements, the implant will be controlled using Carina 2 Surgical & Fitting Software (CE marked) via the Carina Interface SUR-2300 and the Carina Interface Coil SUR-2320.

6 OBJECTIVES

6.1 Objectives

Since this study is a pilot investigation without powering to reject specific null hypotheses, objectives and associated endpoints in section 9.2 are listed without differentiation between primary and secondary objectives.

1. To characterize Carina microphone sensitivity, in-situ, and its variability
2. To characterize the ratio of (a) microphone response to sound to (b) accelerometer response to sound, in-situ, and its variability
3. To characterize Carina microphone impulse response for acoustic and actuator stimulation
4. To objectively measure maximum stable gain, i.e. gain before feedback squealing would occur

6.2 Exploratory Objective

There are no exploratory objectives.

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 General

The investigation is a single-centre, prospective, single-arm, post-market, non-interventional, pilot clinical investigation in adults previously implanted with the Carina system.

The subjects will include men and women aged 18 years and over.

Subjects will attend one scheduled study visit to be assessed as described in the CIP Schedule of Events (section 3). At the study visit, several objective acoustic measurements will be performed that do not require active participation from the subject. No data monitoring committee will be used for this clinical investigation.

7.1.1 Design Rationale

The single-subject repeated measures, pilot design will enable an estimation of microphone sensitivity and maximum stable gain.

7.2 Subjects

Written, informed consent must be obtained from subject before initiating any study procedures which are not part of clinical routine.

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

7.2.1 Inclusion Criteria

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

1. Eighteen years of age or older at the time of enrolment in the study
2. Current recipient of a Cochlear Carina System.

7.2.2 Exclusion Criteria

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

1. Unwillingness or inability of the candidate to comply with all investigational requirements as determined by the Investigator.

7.2.3 Number of Subjects Required

Up to 20 subjects will be enrolled, which is the total number of patients implanted at the investigational site at the time of writing of this document.

Since the study is a pilot investigation, sample size calculations have not been conducted.

7.2.4 Vulnerable Populations

Not applicable.

7.2.5 Enrolment & Study Duration

The preoperative assessment will be composed of one evaluation. The ICF must be signed prior to any study related evaluation taking place.

The enrolment period for the clinical investigation is anticipated to be 1 month from the time of first subject consent to enrolment of the last subject.

The expected duration of each subject's participation in the clinical investigation, is 1 month, from the time of informed consent through to the only study visit.

The anticipated total duration of the clinical investigation is therefore 2 months.

Clinical Investigation completion is last subject visit completed. In the event of an ongoing SAEs/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 for Subject Withdrawal

Subjects can decide to withdraw from the investigation at any time. The Investigator shall ask the reason(s), although the subject does not have to give a reason. If a reason for withdrawal is offered, it should be documented in the subject's source files and the case report form (CRF).

The Investigator or Sponsor may also decide to withdraw a subject from the clinical investigation if it is considered to be in their best interests.

Subject withdrawal may be for any of the following reasons:

- Adverse Event (AE)
- Device Deficiency (DD)
- CIP or GCP deviation
- Subject lost to follow-up
- Subject withdrew consent
- Subject death
- Sponsor decision
- Investigator decision
- Other (specify)

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. It must be remembered however that the subject does not need to provide a reason/s. At least 3 separate attempts taken to contact the subject must be documented.

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

7.2.7 Randomisation Procedures

Not applicable

7.2.7.1 Blinding Procedures

Not applicable in this pilot study with no comparator.

7.2.8 Post-investigation Medical Care

Not applicable

7.3 Performance Evaluations and Procedures

7.3.1 Microphone sensitivity and impulse response

Measurement of microphone and accelerometer signal (spectrum and impulse response) in response to an external sound, as defined in D1673818.

7.3.2 Maximum stable gain

Measurement of microphone and accelerometer signal (spectrum and impulse response) in response to a stimulus generated by the implanted actuator, as defined in D1673818.

7.3.3 Audiometric thresholds

Bone conduction thresholds at audiometric frequencies from 250 to 6000 Hz, measured in accordance with clinical practice.

Direct thresholds (using the implant as a test signal generator), at audiometric frequencies from 250 to 6000 Hz, measured in accordance with clinical practice.

7.4 Safety Evaluations and Procedures

There will be a data safety monitor who will review all AEs, ADEs and DDs.

Safety endpoints will be a summary of AEs/ADEs and DDs from the screening to end of the last subject last visit.

7.4.1 Concomitant Medication and Therapies

Not applicable

7.5 Equipment Used for Evaluation of Performance and Safety

The annual calibration certificates of the audiometer, tympanometer and sound treated room for audiometric testing will be kept in the site resources file.

7.6 Sponsor Role in Conduct of the Clinical Investigation

Subject matter experts employed by the sponsor will perform the acoustic measurements on-site.

8 RISKS AND BENEFITS OF THE APPROVED MEDICAL DEVICE ON TEST AND CLINICAL INVESTIGATION

8.1 Anticipated Clinical Benefits

The anticipated clinical benefits of implantation of the AMDT prior to the start of the study are described in the Physician's Guides and not affected by the study.

The anticipated future clinical benefit of the data collection and analysis of the study is to provide optimized clinical guidance for patient selection based on level of hearing loss.

The study endpoints are expected to inform future designs of active middle ear implants with an implantable microphone.

8.2 Anticipated Adverse Device Effects

There are no anticipated adverse device effects related solely to this investigation.

8.3 Risks Associated with Participation in the Clinical Investigation

The clinical trial does not prescribe medical treatments. No interaction with medication that may be given as part of clinical routine is anticipated.

Theoretically, the stimulation of the patient's cochlea with the white noise signal used to measure maximum stable gain could damage residual hearing, if it was dangerously loud. The maximum stimulation level that can be set in the software is 85 dB MET (broadband), which is a -35 dBV drive level to the actuator (Jenkins, Pergola, & Kasic, 2007). Actuator efficiency as measured in temporal bone studies and clinically (Grossöhmichen et al., 2017) is below 120 dB SPLeq @ 1V median, so the -35 dBV corresponds to 85 dB SPLeq loudness perceived by the patient. Even at exceptionally good actuator efficiency of 125 dB SPLeq @ 1V, equivalent loudness will be below (125-35) = 90 dB SPLeq.

A stimulation level of 91 dB SPL is deemed safe for a maximum of 2 hours per day continuous exposure, it is the maximum acceptable loudness dosage for workplace noise hazards (NIOSH, 1998), below which an employer is not even required to offer hearing protection. The planned measurement duration (see below) is 2 conditions x 3 repetitions x 10s = 60s, far below the 2h limit.

8.4 Risk Mitigation

- The risk of acoustic overstimulation will be mitigated by limiting the stimulus level by design, as described above
- 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.

8.5 Risk-to-Benefit Rationale

The software and hardware that will be used is CE marked, ensuring conformity with the relevant Medical Device Directive essential requirements. The clinical safety (risks) and benefit relevant to

the anticipated performance of the Carina system are documented in the respective Physician's Guides for these devices.

The findings from this clinical investigation will be important to providing optimized clinical guidance for patient selection based on level of hearing loss, and it will inform the design of future active middle ear implants with an implantable microphone.

9 STATISTICAL CONSIDERATIONS

9.1 General Considerations

There will be no formal statistical analyses given the absence of statistical null hypotheses in this pilot investigation.

Descriptive statistics will used to summarise the endpoints; such as means, medians, standard deviations, confidence intervals and interquartile ranges.

9.2 Endpoints

1. Acoustic sensitivity of implanted microphone [dB FS for 0.1 Pa], in-situ, for audiometric frequencies 250-6000 Hz, median and percentiles
2. Ratio [dB] of response of implanted microphone to response of implanted accelerometer, in-situ, for audiometric frequencies 250-6000 Hz, median and percentiles
3. Transfer function from Carina output to actuator [dB FS] to Carina input from implanted microphone [dB FS], for audiometric frequencies 250-6000 Hz, with ear canal open and ear canal plugged
4. Identification of the system's acoustic and vibration transfer functions including non-linear components.

9.2.1 Exploratory Endpoints

Not applicable

9.3 Hypotheses

No formal testable hypotheses are applicable in this pilot study.

9.4 Sample Size Determination

No sample size has been calculated given the pilot nature of the investigation (see section 7.23). Up to 20 subjects will be enrolled in this study.

9.5 Analysis Populations

Given that the study is single arm with no formal statistical analyses, there is no clear need to impute missing data. The descriptive statistical analyses will be computed with the per protocol data set.

9.6 Primary Endpoint Analyses

See section 9.1.

9.7 Secondary Endpoint Analyses

See section 9.1.

9.8 Exploratory Endpoint Analyses

Not applicable

9.9 Safety Analyses

The number and percent of patients with adverse events will be reported and tabulated. Adverse events will be summarized by event type, severity, seriousness, as well as relatedness to the device and implant procedure

9.10 Interim Analyses

There will be no planned interim analyses

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 risks and benefits, what participation will involve, and alternatives to participation will be explained 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 this clinical investigation.

Each subject (or their legally authorised representative) and the person who conducted the informed consent discussion, shall sign and date the ICF. Where required, a 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.

The subject, or the subject's legally authorised 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 medical device or the procedures required for implant or use.

NOTE 1: This definition includes events related to the medical device 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 medical devices.

11.1.2 Adverse Device Effect

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

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 medical device.

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

11.1.3 Serious Adverse Event

A serious adverse event (SAE) is any AE that:

a) led to a death,

b) led to a serious deterioration in the health of the subject that either resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of, or damage to, a body structure or a body function, 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, or
- Chronic disease.

c) led to foetal distress, foetal death or a congenital physical or mental abnormality, or birth defect

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 CI500 Series Implant Hazards Analysis (Internal document 389012).

NOTE: An anticipated serious adverse device effect is an effect, which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.

11.1.6 Device Deficiency

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

NOTE: Device Deficiencies include malfunctions, use errors, and inadequate labelling or information supplied by the manufacturer.

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 screening. AE recording will continue for each subject until completion of their End of Study visit. Ongoing SAEs, 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 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 AMDT 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 AMDT will be considered and investigated. The causal relationship to the AMDT 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 (e.g. 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 (e.g., 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 (e.g., 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 risk analysis report, 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 Product Information/IFU 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 (e.g., 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 (e.g., 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 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;

a) suitable action had not been taken,

b) intervention had not been made, or,

c) circumstances had been less fortunate

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

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 immediately.

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.

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, and shall conduct an expedited assessment of all SAEs, unanticipated ADEs, DDs that could have led to an SADE.

The contact for the Safety Monitor for AE/DD assessment and any AE/DD related queries is: CLTD-SafetyMonitor@cochlear.com

11.5 Independent Data Monitoring Committee

Not applicable

12 DEVICE ACCOUNTABILITY

The device used within the clinical investigation is the commercially released CI622/CI522 electrode array. The device shall therefore be registered following the standard product registration process.

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 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 AMDT, 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 subject status according to the following criteria:

- Consented: Signed consent and eligibility evaluations underway
- Screen Fail: Subject determined not to be eligible to proceed for participation
- Enrolled: Completion of screening activities and confirmation of eligibility after the signing of the consent.
- Withdrawn: Enrolled subjects who withdraw or are withdrawn by the Investigator or Sponsor before the expected End of Study visit. Withdrawn subjects may still continue in safety follow up until their scheduled End of Study visit, for reasons described in section.
- Complete: Enrolled subjects who complete the planned follow up schedule and End of Study visit.

Source data will be captured in clinic notes, paper-based source data worksheets, or printed directly from testing software. If electronic medical records do not permit read only access for monitoring purposes, a verified printout must be provided.

Data collection for demographics, medical history, adverse events, device deficiencies, protocol deviations and completion will be performed using Medidata Rave for electronic data capture (EDC) on electronic Case Report Forms (Medidata Safety eCRF), to support safety analysis and reporting. All other data will be collected from the source data for audiometric tests, speech perception tests, surgical and self-reported questionnaires and x-rays and entered into a password controlled managed document on the Windchill database that has restricted access or a restricted access folder on a dedicated server set up by Cochlear Ltd Information Technology employees and located in Hannover. Unamended data files shall be regarded as the source. A privacy assessment was undertaken to ensure a secure, acceptable process for managing the non-safety data.

Site personnel will be trained on the completion of the Medidata Safety eCRF 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.

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

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, 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.

16 ETHICS COMMITTEE AND REGULATORY AUTHORITY APPROVAL

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 Principal 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 Investigator (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 for a period of at least 10 years after completion of the investigation or after the last device was placed on the market, if the AMDT has market authorisation.

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

A joint peer-reviewed publication authored by the clinical investigator(s) and Sponsor will be prepared. In addition, the results of the clinical investigation may also be disseminated as conference presentations (e.g., abstract and poster session). Manuscript 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 in a timely manner. All contributors who do not meet the criteria for authorship will be listed in an acknowledgments section of the publication.

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 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 describing all the activities performed during site qualification, initiation, monitoring, and close out.

22.2 Audits

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.

23 TRADEMARKS AND COPYRIGHT

24 REFERENCES

International Organization for Standardization. ISO 14155:2011 Standard: Clinical investigation of medical devices for human subjects – Good clinical practice. 2011. Available at: https://www.iso.org/obp/ui/#iso:std:iso:14155:ed-2:v1:en

World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. 2013. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

Gérard, J.-M., Demanez, L., Salmon, C., Vanpoucke, F., Walraevens, J., Plasmans, A., … Levébvre, P. (2017). Feasibility of an implanted microphone for cochlear implant listening. *Eur Arch Otorhinolaryngol*, *274*, 1383–1390. https://doi.org/10.1007/s00405-016-4410-x

Grossöhmichen, M., Waldmann, B., Salcher, R., Prenzler, N., Lenarz, T., & Maier, H. (2017). Validation of methods for prediction of clinical output levels of active middle ear implants from measurements in human cadaveric ears. *Nature Scientific Reports*, *7*(1), 1–10. https://doi.org/10.1038/s41598-017-16107-9

Jenkins, H. A., Pergola, N., & Kasic, J. (2007). Intraoperative ossicular loading with the Otologics fully implantable hearing device. *Acta Oto-Laryngologica*, *127*(4), 360–364. https://doi.org/10.1080/00016480601089424

Jenkins, H. A., & Uhler, K. (2012). Speech perception comparisons using an implanted and an external microphone in existing cochlear implant users. *Otology and Neurotology*, *33*(1), 13–19. https://doi.org/10.1097/MAO.0b013e31823c9335

NIOSH. (1998). *Occupational Noise Exposure Revised Criteria 1998* (No. DHHS (NIOSH) Publication No. 98–126). Retrieved from https://www.cdc.gov/niosh/docs/98-126/pdfs/98-126.pdf

25 CHANGE HISTORY

Version	Change	Rationale
V1.0		Introduction of document
V2.0	Study will not prospectively registered at a public clinical trial registry	Prospective registration not required
V3.0	Section 21 added “With the exception of prospective registration on a public clinical trials registry”	Content in Section 21 now matches approved Cochlear template
V4.0	Section 7.1 changed from interventional to non-interventional	Incorrectly defined as an interventional trial.
V5.0	Study to be prospectively registered on a public clinical trial registry	Post-market, non-interventional trial needs prospective registration

26 APPENDICES

26.1 Appendix 1: Certificates of Conformity

Cochlear®

Cochlear Boulder LLC

Declaration of Conformity

Legal Manufacturer:	Cochlear Boulder LLC 5445 Airport Blvd. Boulder, Colorado 80301 USA
EC Representative:	Cochlear Deutschland GmbH & Co. KG Karl-Wiechert-Allee 76A 30625 Hannover Germany
Product:	Implantable Hearing Prosthesis Systems, Models: MET-1000, MET® Middle Ear Implant and Template MET-7000, Carina® Fully Implantable Middle Ear Implant and Template And all accessories as listed in Design Examination Certificate No. I7 083323 0012 Rev. 00 (see Attachment 1)
Classification:	Active Implantable Medical Device

I herewith declare that the above-mentioned product(s) conform(s) to the provisions of:

The Active Implantable Medical Devices Directive 90/385/EEC Annex 1 and the conformity assessment route of Annex 2 including Part 4:

Notified Body: TÜV SÜD Product Service GmbH
Ridlerstraße 65, 80339 München
Germany

Notified Body No: 0123

Design Examination Certificate No.: I7 083323 0012 Rev. 00

I declare that Cochlear Boulder LLC is exclusively responsible for this Declaration of Conformity.

Authorised Signatory:

Scott D. Dickerhoff

Name, Title: Scott D. Dickerhoff, Director of Regulatory Affairs – Acoustic Implants

Place, Date: Boulder, Colorado, USA, 03 April 2019

Benannt durch/Designated by
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
www.zlg.de
ZLG-BS-200.14.03

TÜV SÜD Product Service

EC Certificate

EC Design-Examination Certificate
Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD), Annex 2 (4)
(Other devices than custom made or intended for clinical investigation)

No. I7 083323 0012 Rev. 00

External Components

Carina® Interface Coil	SUR-2320
Carina® Interface	SUR-2300
Carina® Interface Extension Cable	SUR-2330
NoahLink Programming Coil	AUD-6201
Carina® Software Suite	AUD-6300
Carina® Charger Body	AUD-5111
Carina® Charger Base	AUD-5112
Carina® Charging Coil	AUD-5120
Carina® Remote Control	AUD-5900
Button Audio Processor	BAP-XXXX (Suffix dependent on color, configuration & accessory)
Reference Receiver	AUD-1100
MET® Interface Coil	SUR-2230
MET® Interface	SUR-2200

Test Report No.: 713138750

Carina® 2 Software	AUD-6310

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