Clinical Investigation Plan

Investigation Title: Feasibility, prospective, within-subject, interventional study comparing the performance of a categorical loudness scaling based fitting with a behavioural fitting in adults with a Nucleus cochlear implant in the first 3 months post-activation.

Short Title:	**CALOS4**
CIP Number:	**AI5824**
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**

NCT: NCT05709223
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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]

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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

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
ADRO	Adaptive Dynamic Range Optimisation
AE	Adverse Event
[redacted]	[redacted]
AUSTIN	Adaptive Australian Sentence Test in Noise
BKB-SIN	Bamford-Kowal-Bench Speech In Noise
CBCT	cone-beam computed tomography
C-level	Comfort level, the upper limit of electrical stimulation judged to be comfortable
CI	Cochlear Implant
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
[redacted]	[redacted]
CNC	Consonant-Nucleus-Consonant
CRF	Case Report Form
CRO	Contract Research Organisation
CSS	Custom Sound Suite
CU	Current Units
CVC	Consonant-Vowel-Consonant monosyllabic words test
DD	Device Deficiency
[redacted]	[redacted]
[redacted]	[redacted]
EC	Ethics Committee Synonymous abbreviations/terms include: IRB (Institutional Review Board) IEC (Institutional Ethics Committee or Independent Ethics Committee) HREC (Human Research Ethics Committee)
[redacted]	[redacted]
eCRF	Electronic Case Report Form
[redacted]	[redacted]
EDC	Electronic Data Capture
[redacted]	[redacted]
EU MDR	European Union Medical Device Regulation
[redacted]	[redacted]

Term	Description
FDA	United States' Food & Drug Admistration
GCP	Good Clinical Practices
IB	Investigator's Brochure
ICF	Informed Consent Form
ID	Identification
IDMC	Independent Data Monitoring Committee
IFU	Instructions For Use
IMD	Investigational Medical Device
LT	Loudness Target
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
NAS	Non-Auditory Stimulation
NCA	National Competent Authority
[redacted]	[redacted]
OLSA	Oldenburg sentence test
[redacted]	[redacted]
PI	Principal Investigator
PW	Pulse Width
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SNR	Signal to Noise Ratio
SOP	Standard Operating Procedure
SRT	Speech Reception Threshold
[redacted]	[redacted]
[redacted]	[redacted]
SPL	Sound Pressure Level

Term	Description
[redacted]	[redacted]
T-level	Threshold Level, the least amount of electrical stimulation leading to perceived sound
[redacted]	[redacted]
[redacted]	[redacted]
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VC	Volume Control
WNR	Wind Noise Reduction

2 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	Feasibility, prospective, within-subject, interventional study comparing the performance of a categorical loudness scaling based fitting with a behavioural fitting in adults with a Nucleus cochlear implant in the first 3 months post-activation.
Short title	CALOS4
Investigation number	AI5824
[redacted]	[redacted]
[redacted]	[redacted]
Name and description of comparator device/product(s)	The comparator is the commercially available fitting method (i.e. the streamlined behavioural fitting method) using Custom Sound Suite (CSS 6.3) software.
Estimated recruitment period	18 months
Expected duration per subject	12 weeks
Number of subjects planned	34
Number of investigational sites planned	Up to 6 sites
Inclusion criteria	1. Aged 18 years or older (no upper age limit).

	2. Post-lingually deafened defined as severe or greater sensorineural hearing loss onset after the age of 2 years as reported by the subject. 3. Implanted with the CI600 Series (CI612, CI622, CI632) or CI500 series (CI512, CI522, CI532) cochlear implant. 4. Fluent speaker in the language used to assess speech perception performance, as determined by the investigator. 5. Willingness to participate in and comply with all requirements of the protocol. 6. Willing and able to provide written informed consent.
Exclusion criteria	1. Score below 3 on the screening subset of questions from the Mobile Device Proficiency Questionnaire. 2. Subject who will be programmed with an acoustic component in the implanted ear. 3. Pure tone average (average of unaided thresholds at 0.5, 1, 2 and 4 kHz) less than or equal to 30 dB HL and aided word score of more than 80% in the contralateral ear. 4. Diagnosis of auditory neuropathy. 5. Additional health factors, known to the investigator, that would prevent or restrict participation in the evaluations, including significant visual impairment and/or dexterity issues. 6. Unable or unwilling to comply with the requirements of the clinical investigation as determined by the Investigator. 7. Investigator site personnel directly affiliated with this study and/or their immediate families; immediate family is defined as a spouse, parent, child, or sibling. 8. Cochlear employees or employees of Contract Research Organizations or contractors engaged by Cochlear for the purposes of this investigation. 9. 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).

Objectives and Endpoints	
Primary Objective	**Primary Endpoint**
1. To determine whether the Loudness Target (LT) MAP provides non-inferior speech understanding in quiet compared to the Behavioural (Behav) MAP.	• Percentage correct monosyllabic word scores in quiet (S0) at 50 dB SPL averaged across the sessions at visit 4 and visit 5.
2. To determine whether the Loudness Target (LT) MAP provides non-inferior speech understanding in noise compared to the Behavioural (Behav) MAP.	• Adaptive sentence in noise scores (S0N0 test setup) averaged across the sessions at visit 4 and visit 5.

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

	and type of interactions by recipients
[redacted]	

3 SCHEDULE OF EVENTS

Visit Type	Screening*	[redacted]	[redacted]	[redacted]	Visit 4	Visit 5
Timing of Investigation	**NA**	[redacted]	[redacted]	[redacted]	**Week 8**	**Week 12**
Visit window (±)	**-4 weeks prior to D0**	[redacted]	[redacted]	[redacted]	**± 1 week**	**± 1 week**
Procedures						
Written informed consent	X					
Mobile Device Proficiency Questionnaire	X					
Demographics	X					
Eligibility	X					
Hearing history	X					
Device history	X					
Medical history	X					
[redacted]						
Device activation		X				
[redacted]		[redacted]				
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Loudness Target Tuner			[redacted]	[redacted]	X	X
Behavioural programming		[redacted]		[redacted]	X	X
[redacted]						
[redacted]			[redacted]	[redacted]		[redacted]
Speech perception testing FF – Words in Quiet at 50 dB SPL					X	X
[redacted]			[redacted]	[redacted]		[redacted]
[redacted]						[redacted]
Speech perception testing FF – Sentences in Noise					X	X
[redacted]			[redacted]	[redacted]		
[redacted]						
[redacted]	[redacted]					

Visit Type	Screening*	[redacted]	[redacted]	[redacted]	Visit 4	Visit 5
Timing of Investigation	NA	[redacted]	[redacted]	[redacted]	Week 8	Week 12
Visit window (±)	-4 weeks prior to D0	[redacted]	[redacted]	[redacted]	± 1 week	± 1 week
[redacted]		[redacted]			[redacted]	
[redacted]		[redacted]			[redacted]	
[redacted]			[redacted]			
[redacted]		[redacted]				
[redacted]						
[redacted]	[redacted]					
[redacted]					[redacted]	[redacted]
[redacted]			[redacted]			
[redacted]						[redacted]
[redacted]		[redacted]				
Other						
Concomitant medications/therapies	X	X	X	X	X	X
Adverse Events		X	X	X	X	X
Device Deficiencies		X	X	X	X	X
Device exposure		X	X	X	X	X

Abbreviations: NA=Not Applicable; LSLV=Last subject last visit; CVC=Consonant Vowel Consonant; [redacted] F=Free Field; [redacted].

The test period between the first and last visit is expected to be 12 weeks for each subject. Visits planned outside of this time window are not reported as deviations.

**The screening can be combined with visit 1.*

[redacted]

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

[redacted]

4 BACKGROUND INFORMATION AND RATIONALE

4.1 Introduction

[redacted]The cochlear implant (CI) community generally accepts that an optimal MAP (the set of T and C parameters) is achieved if

(1) T-levels are set such that soft sounds (approximately 25 dB SPL) are audible

(2) C-levels are first set in narrow band mode (only one electrode active) such that the perceived loudness is comfortably loud and balanced across electrode positions

(3) the loudness of broad sound (speech) at conversational level (65 dB SPL) is comfortably loud.

This is called here the "CI fitting target". It has not changed for several decades. Cochlear promotes it in its fitting guidelines. However, we see a large and unexplained variance of levels when analysing field data. Some of it has to do with "fitting for comfort". Some patients find the sound quality of the higher pitch electrodes not pleasant, while they are important for speech understanding. [redacted]

[redacted]

The technologies have already been derisked in prior studies where experienced and recently implanted CI listeners were participating (see section 4.2.2). This study aims to collect data in newly implanted CI-recipients to inform future development of fitting methods to optimally and efficiently program a CI. It is not yet a pivotal trial of a technology ready to be launched commercially. [redacted]

[redacted] This is a study to learn about the potential of this technology in a group of CI listeners, new to electrical hearing. The study results will inform whether further research activities are required, or whether a product development activity can be considered. All software tools are research prototypes, that at best will serve as an inspiration and reference for product development. Cochlear's product development organization will consider these learnings and concepts and make decisions on what components to integrate. New clinical data will have to be collected with a future product implementation.

4.2 Findings of Previous Nonclinical and Clinical Studies

4.2.1 Nonclinical Data

[redacted]

4.2.2 Clinical Data

Electrical Categorical Loudness Scaling (ELS)

Various procedures in setting the T-and C-levels for adults are described in literature. Traditionally, individual T-levels are set using an adaptive bracketing-procedure, such as the modified Hughson-Westlake (1944), the count-the-beep method, psychophysical loudness scaling or threshold estimation (Wolfe et al., 2010). Setting C-levels is a more challenging task in determining exactly where these must be set in order to provide optimal sound quality and speech recognition. C-levels are often set using psychophysical loudness scaling, where stimulation levels (on individual channels or in live mode) are directly related to perceived loudness.

Different gradations or categories (Categorical Loudness Scaling or CLS) are used in practice, going from soft to loud with varying step size. The CLS method in the acoustical domain is well described in literature (Brand & Hohmann, 2002; ISO 16832) and evaluated in CI-recipients in several studies (Theelen - van den Hoek, et al, 2014; Busby and Au, 2017; Theelen - van den Hoek, et al., 2015). Categorical loudness scaling is an alternate approach to measure loudness for electrical stimulation (ELS). As a procedure it is clinically appealing because of its simplicity, the categorical labels have intrinsic meaning, and it requires minimal training (Busby, et al., 2017). Theelen - van den Hoek et al (2014) collected ELS data on four electrodes across the Nucleus array using single-electrode electrical stimuli. Ten adult CI recipients were tested using this methodology over two different sessions. Results showed that test-retest variability of ELS measurements in the electrical domain did not significantly differ between loudness categories or electrode positions and was found to be equivalent to acoustical stimulation in normal-hearing and hearing-impaired listeners. In addition, the correlation between the T- and C-levels as measured in clinical practice and the ELS outcomes (levels corresponding to L5 and L40) was investigated. The correlation between the L40 levels and clinically measured C-levels was strong and significant ($r = 0.85$, $p < 0.01$), but the correlation between the L5 levels and clinically measured T-levels was only moderate and non-significant ($r = 0.41$, $p = 0.13$). The findings by Busby and Au (2017) overall confirmed

the reliability of categorical loudness judgements in a larger group of 30 adults implanted with the Nucleus CI system. These results indicate that ELS is applicable as a reliable measurement tool for CI, especially towards the upper-end of the dynamic range. When conducting or interpreting ELS measurements for fitting purposes, Theelen - van den Hoek, et al. (2015) indicated that it is important to account for spectral loudness summation.

[redacted]

[redacted]

[redacted]

4.3 Study Rationale

[redacted] Therefore, the co-primary objective of this feasibility study is to determine whether the Loudness Target (LT) MAPs, [redacted], provide

non-inferior speech understanding in quiet and in noise compared to the standard behavioural (Behav) MAP, using all degrees of freedom, at 3 months post-activation, using a crossover design at 4 weeks after initial activation. The take-home intervals provided throughout this study will serve to gather real-world experience with both the LT and the Behav MAPs. The Behav reference MAP created on streamlined programming principles is considered standard clinical practice and assumed to approximate optimal performance. The hearing ability of the CI-recipient in daily life with the investigational MAPs will be collected as well for the Behav MAP. As reported by Buchman et al. (2020) and Gajadeera et al. (2017) although further learning is still expected at 3 months post-activation, T- and C-levels of a recipient's MAP tend to stabilize. Fine-tuning of the MAP is likely required but this is out of scope of the investigational fitting method and thus not investigated in this feasibility study.

[redacted]

5 MEDICAL DEVICE INFORMATION

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

[redacted]

[redacted]

This study will compare the MAPs programmed as per the above Nexus fitting workflow with the MAPs programmed as per the standard streamlined behavioural fitting method.

An overview of the IMDs used in the clinical investigation is given in Figure 3. Note that iterations to the research tools can be used during the study. [redacted]

[redacted]

The investigational device and all research tools are manufactured by Cochlear Limited. The investigational device and all research tools are manufactured by Cochlear Limited. Sotware and firmware will be kept current at the direction of the Sponsor. Software and/or firmware updates that directly impact the clinical

investigation – impact study design or outcomes - will first be submitted to the respective Ethics Committee for approval. Updates that are applied for maintenance purposes only (bug fixes, etc.), and changes that do not impact the study design or outcomes, will be considered non-significant and not submitted prior to distribution. Version control will be maintained through Cochlear's compliant software development processes, release process and distribution of software via the Cochlear Software Distribution System.

All investigational devices will be labelled exclusively for use in a clinical investigation (see section 12 for further detail). [redacted] CI recipients/investigators will use the IMD and 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 involved in the fitting will be experienced in programming cochlear implants. As indicated in section 8.2, they 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 tools and will receive ongoing support from the investigator during the execution of the study procedures. The investigational devices are software-only and will not be in contact with body fluid or tissue.

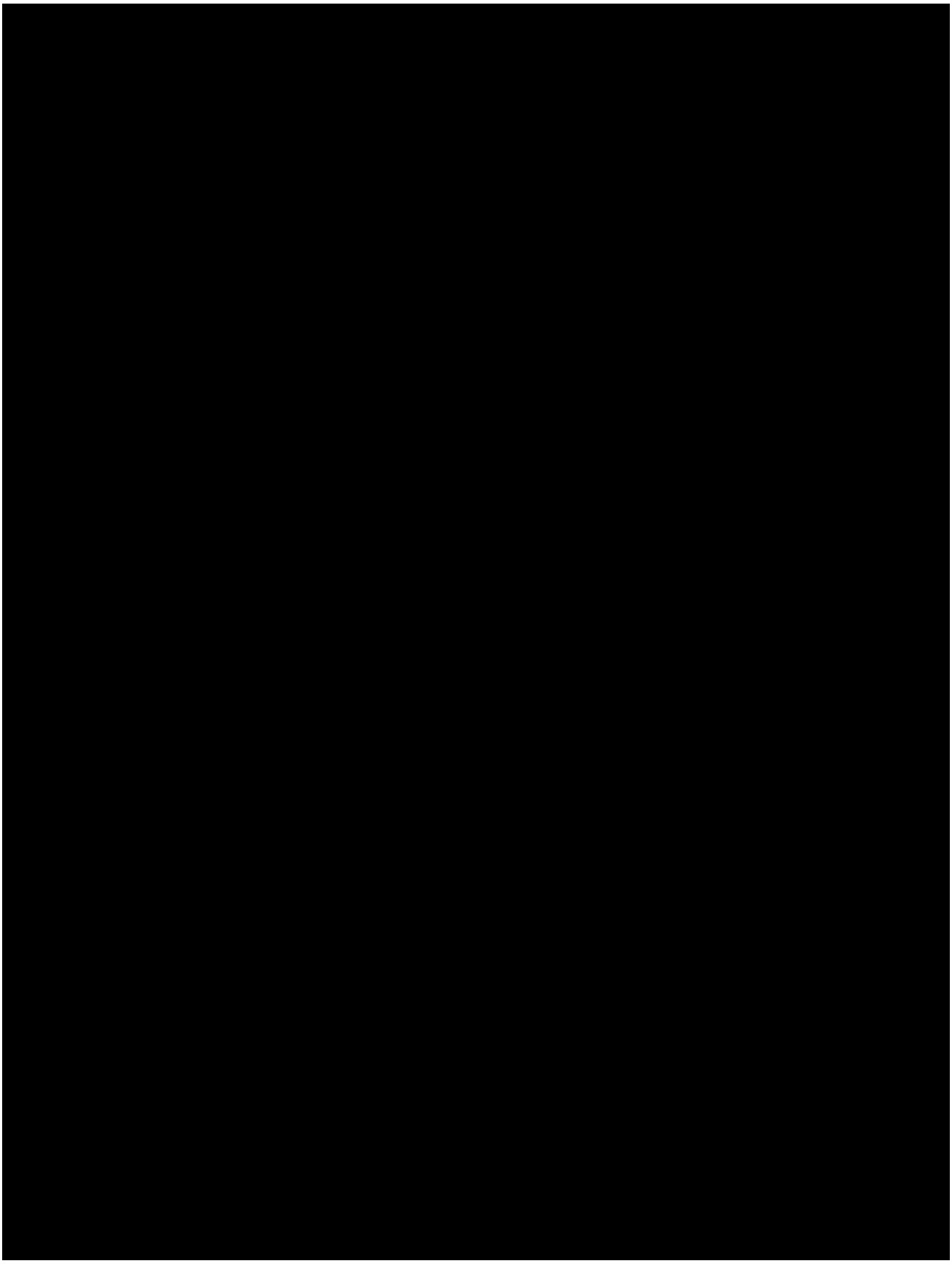
Further details regarding the investigational device and research tools are provided in the Investigator Brochure (IB) and Instructions for Use (IFU).

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

5.1.4 Additional system components – CP1000 or CP1150 sound processor

The CP1000 (Nucleus 7) and CP1150 (Kanso 2) sound processor are approved devices but used in the context of the above. Their intended use in combination with other devices as part of a hearing implant system is to provide hearing sensation. The processing unit/sound processor converts sounds into electrical signals, which it sends (via a coil) to the implant. The processing unit/sound processor also provides power to the implant.

The commercial CP1000 and CP1150 sound processor are part of the system and are programmed with investigational firmware to become compatible with the newly created fitting method by means of research tools.

5.2 Identity and Description of the Comparator

The comparator for this study is the streamlined behavioural fitting method that is widely used in standard of care in CI-clinics worldwide. The clinician uses Custom Sound software (CSS) to program the sound processor so that the cochlear implant system delivers sound that is audible and comfortable to the cochlear implant recipient. The streamlined programming methods in Custom Sound software help the clinician by simplifying the programming procedure and reducing programming time. The streamlined method that will be used in this clinical investigation is based on behavioural responses and is appropriate for adults who can reliably respond to sound. Once the appropriate MAP parameters are chosen in CSS, T-levels are set using the Hughson-Westlake method on 6 channels across the array and interpolation is applied to predict T-levels for the other channels, while C-levels are set using live voice (Plant, et al., 2005). A detailed description of this behavioural fitting method is provided in the procedures manual. Custom Sound Pro version 6.3 (or subsequent later versions available) will be used to create this behavioural MAP. [redacted]

5.3 Accessory Device Requirements

The investigator will use Custom Sound Suite Software to create the standard behavioural MAP, and to verify the operation of the system by means of diagnostics and objective measures. The following approved accessory devices are required to program the subject's CI:

- CP1000 or CP1150 programming cable (depending on subject's Sound Processor)
- Cochlear Wired Programming pod. An additional adaptor cable is required for the CP1150.

Throughout the investigation, subjects will be required to use a loaner CP1000 (Nucleus 7) or CP1150 (Kanso2) sound processor which is further compatible with several optional accessories, including the commercial available Cochlear and GN Resound wireless accessories. They will also require a compatible loaner iOS device ® [redacted]

6 OBJECTIVES

6.1 Primary Objectives

- To determine whether the Loudness Target (LT) MAP provides non-inferior speech understanding in quiet compared to the Behavioural (Behav) MAP.

- To determine whether the Loudness Target (LT) MAP provides non-inferior speech understanding in noise compared to the Behavioural (Behav) MAP.

[redacted]

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 General

The study is an early feasibility, prospective, multi-country, multi-centre, single-blind, repeated-measures, interventional study in adults with a CE labelled cochlear implant. In total, 34 eligible subjects are planned to be recruited in the clinical investigation. The early feasibility categorisation relates to the use of research tools and the purpose of the investigation being to assess the technical feasibility of the proposed fitting methodology. The subjects include adults from the age of 18 years or above who are implanted with a commercially available Nucleus CI600 series (CI612, CI622, CI632) or CI500 series (CI512, CI522, CI532) implant and where initial activation of the cochlear implant didn't take place yet. Subjects will be screened according to the inclusion and exclusion criteria as described in section 7.2 and will attend 5 visits over an expected period of 12 weeks as described in section 2. The time of each visit is estimated to be between 2 and 4 hours. At study visits, subjects will undergo hearing assessments and safety assessments as defined in the CIP

schedule of events in section 3. The study procedures will involve assessment using the commercially available CP1000/CP1150 sound processor acutely and after take-home use. Take-home use will be applied to evaluate the acceptance of the listening programs with newly fitted T- and C-levels in as many listening environments in daily life as possible. Figure 10 shows a schematic overview of the study design with a counterbalanced crossover design at visit 4 and 5. Half of the subjects will take home a Behav MAP for 4 weeks from week 4 to week 8 followed by a LT MAP for 4 weeks from week 8 to week 12. Conversely the other half of the subjects will take home the Behav and LT MAP in the opposite order. At visit 4 (week 8) all subjects will be tested on words in quiet and sentences in noise with both a Behav MAP and a LT MAP. Similarly, at visit 5 (week 12), all subjects will be tested for words in quiet and sentences in noise using each of these two MAPs.

The co-primary objectives of the study are to determine whether the Loudness Target (LT) MAP provides non-inferior speech understanding in quiet and in noise compared to the Behavioural (Behav) MAP at 3 months post-activation. The data for these objectives are the percentage correct monosyllabic word scores in quiet (S0) at 50 dB SPL and the adaptive sentence in noise scores (S0N0) averaged for each subject for the Behav MAPs across visits 4 and 5 and averaged for the LT MAPs across visits 4 and 5. [redacted]

Safety will be assessed by recording and summarizing all Adverse events (AEs)/Adverse Device Effects (ADEs) and Device Deficiencies (DDs). The endpoints are described in Section 9.2. No Independent Data Monitoring Committee (IDMC) will be used for this clinical investigation. Analyses are described in section 9. All subjects will have an end-of-study visit at the time they complete this study.

Evaluations will be conducted at one centre in Germany, two centres in Australia and up to three centres in the United States. At the site in Germany, investigators of the clinic will conduct all study procedures at the

facilities of the clinic. [redacted]. The PI will assume overall responsibility for the conduct of the study in Melbourne, but will delegate the study tasks to the investigators of Cochlear Ltd Melbourne. At both sites in Australia, internal Cochlear investigators will be responsible for initial activation, follow-up device fittings, and postoperative research procedures. Although initial activation will be conducted by internal investigators of the sponsor, the physical location of this first visit will be either at the sponsor's Cochlear research lab or, for convenience of the subjects, at the external clinical site. The sites in the USA will be conducted solely by Cochlear investigators at the Cochlear Americas Denver Research Center and Cochlear Hearing Clinics

7.1.1 Design Rationale

Post-lingually deafened adult CI recipients

Subjects must be capable of providing feedback to the clinician during fitting and of judging the loudness during the loudness scaling tasks. Also, performance measures [redacted] are obtained to answer the primary, [redacted] objectives. The results on these performance tasks [redacted] may be influenced by whether a recipient has unilateral or bilateral Cis. Furthermore, the new fitting method and the newly developed research tools that will be used in this investigation, are currently designed for unilateral CI recipients only who have no acoustical amplification in the ipsilateral ear. Therefore, only adult CI recipients without ipsilateral acoustic component will be enrolled. Bilateral sequentially implanted adults are nevertheless eligible to participate in the study. The most recent implanted ear will be programmed using the newly developed research tools and also the performance tasks will be conducted only on this ear. [redacted] The newly implanted study population will allow for evaluation of the novel fitting method without introducing bias from previous listening experience.

Speech performance at 3 months post-activation as primary endpoint

The investigational fitting method aims to standardize and streamline the fitting process based on agreed fitting targets from activation onwards without impairing the performance of the CI-recipient. Hearing ability and MAPs undergo significant changes in the first three months after activation, as reported by Buchman et al. (2020) and Gajadeera et al. (2017).

Speech recognition is one of the primary outcome measures for cochlear implantation (Messersmith, et al., 2019). Ma et al. (2022) demonstrated that the most critical time period for improvements in speech recognition for words in quiet and sentences in noise occurs in the early post-implantation period (up to three months). Afterwards, scores, on average, might undergo small incremental changes, but are less likely to demonstrate any further significant improvements. Testing open-set speech perception performance at the softer level of 50 dB SPL for monosyllabic words, represents speech spoken at a normal conversational level but at a distance of 3 meters. Successful access to spoken conversation over a range of levels, including soft speech, is essential for everyday communication (Firszt, et al., 2004).

We do not function in a quiet world, however. The world is noisy. Therefore, a standard in-clinic measure is to to assess speech recognition of sentences in noise. Sentence recognition requires the complete integration of auditory information provided by the CI into the recipient's existing linguistic processing capacities. Testing in noise is a complex task for CI-recipients early in their hearing journey but reflects the daily reality (James et al., 2018).

Study design

As outcomes are variable in cochlear implant users, comparing fitting approaches between different patient groups requires high subject numbers. Therefore, the study is set up as a repeated measures within-subject design in which each participant is acting as his/her own control. Take-home use will be applied to evaluate the acceptance of the listening programs with newly fitted T- and C-levels in as many listening environments in daily life as possible. A counterbalanced cross-over design will be used for the take home period of 8 weeks: while one group will use first the Behavioural MAP in daily life followed by the investigational Loudness Target MAP, the other group will use each of these conditions in the opposite order. The percentage correct monosyllabic word scores in quiet (S0) at 50 dB SPL RMS and the adaptive sentence in noise scores are averaged across the sessions at visit 4 and visit 5 and this to minimise bias towards one specific fitting method. To further prevent bias, subjects will be blinded (i.e. information is concealed from the recipient) from knowing the specific listening program (i.e. Behav versus LT MAP) during the take home and testing. A loaner CP1000 or CP1150 processor as well as a loaner iOS device will be provided for the duration of the study. The information collected will be used for the purpose of the current study as well as provide input for related future studies as stated in the Informed Consent Form.

[redacted]

[redacted]

7.2 Subjects

Written, informed consent must be obtained from the subject before any study procedures are initiated. Eligibility of subjects shall be supported by medical, demographics and audiological information as well as their mobile device 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.

- Aged 18 years or older (no upper age limit).
- Post-lingually deafened defined as severe or greater sensorineural hearing loss onset after the age of 2 years as reported by the subject.
- Implanted with the CI600 Series (CI612, CI622, CI632) or CI500 series (CI512, CI522, CI532) cochlear implant.
- Fluent speaker in the language used to assess speech perception performance, as determined by the investigator.
- Willingness to participate in and comply with all requirements of the protocol.
- 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.

- Score below 3 on the screening subset of questions from the Mobile Device Proficiency Questionnaire.
- Subject who will be programmed with an acoustic component in the implanted ear.
- Pure tone average (average of unaided thresholds at 0.5, 1, 2 and 4 kHz) less than or equal to 30 dB HL and aided word score of more than 80% in the contralateral ear.
- Diagnosis of auditory neuropathy.
- 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 Organizations 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).

7.2.3 Number of Subjects Required

A total of thirty-four subjects will be recruited into this feasibility clinical investigation to meet the sample size calculation requirements set out in section 9.4. Cross-regional pooling of data is justified due to the within-subject study design.

7.2.4 Vulnerable Populations

Not applicable for the current clinical investigation.

7.2.5 Recruitment and Study Duration

The following subject status definitions apply:

- Enrolled: A subject that has a signed the Informed Consent form for the study.
- Screen Fail: An Enrolled subject that has been determined to not meet one or more eligibility criteria.
- Participated: Subjects who have met eligibility criteria and have commenced baseline assessment.
- 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 each individual centre is estimated to be 9 months from the time of site initiation, but to allow for any variation in study start at each centre, the recruitment period for the clinical investigation is estimated to be 18 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 approximately 12 weeks from the time of informed consent through the end of study visit 3 months after initial activation.

Clinical Investigation completion is last subject last visit. In the event of an ongoing Serious Adverse Event (SAE)/Serious Adverse Device Effect (SADE) 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.

As part of this clinical investigation, subjects will be withdrawn in case of:

- Inability to be programmed with a fixed pulse width (PW) MAP with a maximum PW of 50 us per channel on the sound processor MAP at activation.
- Inability to be programmed with a MAP with ≥ 20 enabled channels on the sound processor MAP at activation.

Subject withdrawal may be also for any of the following reasons:

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

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

Participating subjects who are withdrawn/discontinued will be replaced.

7.2.7 Randomisation Procedures

This single-arm feasibility study uses a within-subject design. Subjects who meet all eligibility criteria for participation will be randomly assigned to one of two groups for the counterbalanced crossover. Both groups will receive the investigational and comparator MAP, but the randomisation will determine the order of take-home phases from visit 3 onwards, in order to reduce potential order effects (see section 7.1.1). A separate randomization schedule will be maintained which will define the testing order and take-home order for the investigational and comparator MAPs across subjects.

7.2.7.1 Blinding Procedures

This study is a single-blinded investigation. This means that investigators will not share with subjects which program is being used for testing or take-home usage. Subjects will not be able to see the programming software during mapping sessions. The conditions will be referred to as program 1, 2, etc. When conducting testing with more than one program during the same visit, the investigator will usually control switching between programs. If the subject is given control to switch between programs during testing, then the investigator will not inform the subject which MAP is in which program location.

In some cases, subjects may be able to hear differences between the programs. It may be necessary to break the blind at the end of the study to counsel subjects on what they might expect to hear after the last visit in the study. However, the study team will avoid making any explicit references to the types of programs used during the investigation.

7.2.8 Post-investigation Medical Care

Following the investigation, subjects will continue with standard of care treatment. The preferred listening program is written by the investigator to the sound processor of the CI-recipient using the commercial Custom Sound Suite software. The investigator provides the commercial Nucleus Smart App to the CI-recipient. Subjects return the loaner iOS device and the loaner CP1000/CP1150 sound processor to the investigator. No extra medical care needs to be provided after the clinical investigation.

7.3 Evaluations and Procedures

See the Schedule of Events in Section 3 for details on the timing and frequency of each procedure listed in the following sections. This section provides a description of all evaluations and procedures in the clinical investigation including a summary of the procedures to be conducted on the most recent implanted ear at each visit. Further details will be provided in procedural documents.

[redacted]

7.3.1.2 Words in quiet

The purpose of this test is to establish the test subject's word recognition score in quiet. The different conditions will be evaluated in Australia and the United States using the monosyllabic CNC word test (Peterson & Lehiste, 1962) and in Germany using the monosyllabic Freiburg words (Hahlbrock, 1953 and 1960), in quiet at soft presentation level (50 dB SPL RMS) [redacted] with

configuration of speech presented from the front (S0). The CNC word test consists of 30 lists each with 50 words per list, recorded in a female voice. The Freiburg word test consists of 20 lists, each with 1 practice word and 20 test words per list, recorded in male voice. Scores shall be recorded as percentage correct words.

7.3.1.3 Sentences in noise

The purpose of this test is to establish the test subject's ability to recognise speech in the presence of background noise. To measure an adaptive speech reception threshold (SRT), sentence recognition will be measured using the Adaptive Australian Sentence Test in Noise (AuSTIN) (Dawson, et al., 2013) in Australia, the matrix Oldenburg sentence test (OLSA) (Wagener, et al. 1999) in Germany, and the Bamford-Kowal-Bench Speech In Noise test (BKB-SIN) (Etymotic Research, 2005) in the United States. With configuration of speech and noise presented from the front (S0N0). The AuSTIN corpus comprises 80 lists of 20 sentences each, recorded in female voice. Each OLSA sentence consists of five words, following the structure name-verb-numeral-adjective-object. For each of these word classes, the matrix contains ten alternatives, recorded in female/male voice. The BKB-SIN is composed of 36 lists of BKB Sentences (Bench, Kowal, & Bramford, 1979) spoken by a male target talker amidst four-talker babble. The 36 lists are divided into 18 equally difficult pairs of sentence lists. The adaptive sentence test will determine the SRT or signal to noise ratio in dB where 50% of words in the sentence are correctly identified.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.3.5 Device fitting

The anticipated investigational fitting method for creating the Activation and Loudness Target MAPs is described in section 5.1. The behavioural MAP will be created using the streamlined fitting method. In streamlined fitting, a listening program is created by measuring T-levels on a few electrodes and deriving levels for other electrodes by interpolation. C-levels will be set in live-mode to a loud but comfortable loudness level using a loudness rating scale. Levels will be swept and balanced along the array as needed for fine-tuning. Any other modifications will be made as needed for an acceptable take-home MAP.

[redacted]

[redacted]

[redacted]

[redacted]

7.3.8 Postoperative Standard of Care Procedures

Clinical follow-up after initial activation will be conducted according to the standard of care schedule at the external clinical site. Medical treatment and auditory rehabilitation will be provided as clinically appropriate (with the exception of device fittings, which will be conducted as part of the investigational procedures). The procedures at the end of the clinical investigation are described in section 7.2.8.

7.3.9 Study visit procedures

The following procedures are outlined for screening, randomisation and visits 1 to 5 starting at initial activation. Attempts should be made to complete all procedures described per visit on a single day. Where the investigator is unable to complete all visit procedures in a single session, e.g. due to time constraints, the investigator may provide the subject with an option to complete the visit on a separate day within one week of the planned study interval. Some procedures are optional and may be omitted. When crossing over between programs, the new MAP should only be provided for take-home use when all expected procedures have been completed on the previous MAP. Medical management during the study will be in accordance with the clinics' routine follow-up.

7.3.9.1 Screening/eligibility and baseline

Candidates will be consented at the screening visit (approx 2 weeks post CI surgery), prior to their cochlear implant activation. Screening and baseline may be completed in parallel. If retrospective data or standard of care exams are available, they must be completed within the time frames provided.

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 randomisation:

- Written informed consent: must be completed before any study-specific procedures are completed
- Demographics: document age and sex
- Eligibility: confirm subject meets all inclusion criteria and no exclusion criteria. Audiogram and CVC word testing in quiet collected according to the site's standard clinical routine. Source documentation must be available before confirming eligibility
- Hearing History: document history of hearing loss (may be subject reported)
- Device history: document history with hearing aids (may be subject reported)
- Medical History: document medical history
- Mobile Device Proficiency Questionairre: must be completed at screening (see section 7.3.6.1)

[redacted]

7.3.9.2 Randomisation

Randomisation for the prescribed sequence in the crossover may only be conducted once all activities under Screening are completed, subject screening data is entered into the EDC, and eligibility has been confirmed.

7.3.9.3 Visit schedule

The different procedures specific for the clinical investigation are described below. Note that the standard clinical counselling that new cochlear implant recipients routinely receive covering use of the device and accessories, [redacted] are the responsibility of the investigator and may be done in conjunction with a member of the participants clinical care team, if required by site. A member of the clinical care team may also attend the last appointment or request a separate appointment with the investigator and participant to facilitate participant handover to standard of care upon patient completion of study procedures.

Visit 1: Initial Activation (Day 0)

[redacted]

[redacted]

Visit 2: 2 weeks post-activation

[redacted]

Visit 3: 4 weeks post-activation

[redacted]

- Take Home: Program as per the prescribed crossover sequence: 2nd LT MAP or 1st Behav MAP

Visit 4: 8 weeks post-activation

[redacted]

[redacted]

- Monosyllabic words at 50 dB SPL, S0 for 2nd Behav MAP (acutely) and 3rd LT MAP (acutely)
- Sentences in noise, S0N0 for 2nd Behav MAP (acutely) and 3rd LT MAP (acutely)

[redacted]

- Take Home: Program as per the prescribed crossover sequence: 2nd Behav MAP and 3rd LT MAP

Visit 5: 12 weeks post-activation

[redacted]

- Monosyllabic words at 50 dB SPL, S0 for 3rd Behav MAP (acutely) and 4th LT MAP (acutely)

[redacted]

- Sentences in noise, S0N0 for 3rd Behav MAP (acutely) and 4th LT MAP (acutely)

[redacted]

7.3.10 Safety Evaluations and Procedures

The risks and anticipated ADEs for the investigational fitting method, 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.
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 de-identified source documents to review the event.

7.3.10.1 Concomitant Medication and Therapies

Concomitant medications will be recorded in the subject's CRF at the baseline appointment and updated during the clinical investigation when changes to medication and/or therapies occur. Possible interactions with concomitant medications are not anticipated in this clinical investigation. 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 conduct fittings, [redacted] assess hearing performance. Software and firmware should be kept current at the direction of the Sponsor.

[redacted] words in quiet and adaptive speech in noise testing shall be performed using a loudspeaker configuration in a sound insulated room within the clinic. Equipment used for audiological testing should be calibrated in accordance with local procedures before initiation of the investigation. Calibration records must be maintained in site files and copies provided to the Sponsor. As part of the Site Initiation Visit, records should be provided to the Sponsor and confirmed to be up-to-date. Records will be monitored in accordance with the Sponsor's Monitoring Plan.

[redacted]

7.5 Sponsor Role in Conduct of the Clinical Investigation

In Australia and the United States, employees of the Sponsor organisaton (in Sydney,Melbourne and Denver) will act as investigators, conducting all study visits and procedures.

In Sydney, study oversight will be maintained by the site, Cochlear Macquarie. Participants will be recruiting from external clinics, but all study procedures will be conducted by investigators from Cochlear Macquarie. Patient Informed Consent discussions, activation of the device, and handover at study completion will be performed by the investigational team of Cochlear and may take place at the local clinical centre or at the Cochlear Macquarie.

In Melbourne, study oversight will be maintained by the site, [redacted] Study tasks may be delegated to employees of Cochlear Melbourne added to the study team by the PI. Study procedures may be conducted at Cochlear Melbourne facilities or [redacted] clinics.

In the USA, study oversight will be maintained by the site, Cochlear Americas. Participants will be recruited from external clinics, but all study procedures will be conducted by investigators from Cochlear Americas. Patient Informed Consent discussions, activation of the device, and handover at study completion will be performed by the investigational team of Cochlear and will take place at the Cochlear Americas Denver Research Center or Cochlear Hearing Centers.

The Cochlear employees acting as investigators in Sydney,Melbourne and the USA will not be involved in Sponsor procedures.

In Germany, the Sponsor will not be involved in any study data collection or in subject recruitment.

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

8.1 Anticipated Clinical Benefits

The potential benefits associated with participation in the clinical investigation include:

- Closer monitoring of the subject's hearing performance during the first 3 months post-activation.
- The chance to play an active role in their own hearing health and gain a greater understanding of their condition.
- The ability to use multiple MAPs in the early post-operative period and select the MAP with the best hearing performance.

8.2 Anticipated Adverse Device Effects

The subjects of this investigation are already implanted with a CE and FDA approved Nucleus implant device, independent of this study. No medication will be prescribed for the study. There is a remote likelihood of discomfort, pain and non-auditory stimulation in using the investigational [redacted] tools. This risk is higher than with the commercial fitting software, given that several novel programs will be created for the subject and research tools are used. The risk of pain associated with device programming is mitigated by careful clinician training and software warnings. Furthermore, the subject will be reminded by the investigator during programming to remove the coil immediately if they experience an uncomfortably loud sound or sensation, and the investigator will stop the stimulation immediately in the software if the recipient hears an uncomfortably loud sound or experiences non-auditory stimulation. [redacted]

8.3 Risks Associated with Participation in the Clinical Investigation

Potential clinical risks associated with participation in the clinical investigation are shown below.

- The study schedule requires several changes in listening programs over the course of participation. Subjects may experience difficulty adjusting between programs. It may be difficult for a subject to adjust to a different program after they have become comfortable with the previous program. Some programs could have poorer sound quality than others, which may or may not improve with additional listening experience or device adjustments. If required, the Behav MAP can be modified to address sound quality issues within the boundaries as per the procedures manual.

- It is possible that the investigational fitting method results in a decline of hearing outcomes. It is well known that some types of changes to a MAP may lead to an acute minor decline in hearing outcomes. As the CI user adapts to the new sound quality, this decline is often temporary. The investigator will be available to provide hearing care, and address reports of degraded performance. The risk of decline in performance is remote given the previous experience. Also, the study design involves a direct comparison between 2 MAPs, namely the LT and the Behav MAP and therefore any poorer performance related to one of these MAPs will be short-term only. In the case of prolonged observed systematic decrease in performance the particular test setup/condition can be halted.

[redacted]

8.4 Risk Mitigation

The investigational [redacted] to be assessed in this investigation will undergo safety testing according to Cochlear product risk management procedures, in accordance with EN ISO 14971 (Medical devices – Application of risk management to medical devices) standards.

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 [redacted] 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 and programming support. The duration and level of support provided by the Sponsor will be guided by the investigators. Sponsor representatives may attend postoperative sessions also to trouble-shoot any device deficiencies 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.

- Specific risk mitigations to address risks in section 8.3 are described in that section.

8.5 Benefit-to-Risk Rationale

The residual risk levels that may be posed by the [redacted] and investigational fitting method and by participating in this study have been assessed as low or medium and do not alter the conclusion that the risks are acceptable weighed against the intended benefits to the patient and are consistent with current state-of-the-art therapies.

9 STATISTICAL CONSIDERATIONS

9.1 General Considerations

In the statistical analyses for the primary hypotheses, the most complete sets of data will be prioritised when there is missing data. Rule based imputation may be used where appropriate.
Further details on statistical analyses will be provided in the Statistical Analysis Plan.

9.2 Endpoints

9.2.1 Primary Endpoint

- Percentage correct monosyllabic word scores in quiet (S0) at 50 dB SPL averaged across the sessions at visit 4 and visit 5.
- Adaptive sentence in noise scores (S0N0 test setup) averaged across the sessions at visit 4 and visit 5.

[redacted]

[redacted]

9.3 Hypotheses

9.3.1 Primary Hypothesis

The co-primary objective is to compare the performance of the LT MAP with the Behav MAP. A non-inferiority test for word recognition scores and sentences in noise scores with the LT MAP versus the Behav MAP will be performed.

The co-primary objective is represented by two primary hypotheses. The first primary hypothesis is related to the word recognition in quiet scores:

> H_0: The LT MAP will be inferior compared to the Behav MAP for word recognition in quiet at 50 dB SPL:
>
> H_1: LT MAPs will be non-inferior compared to the Behav MAP for word recognition in quiet at 50 dB SPL.

The mathematical statement of this hypothesis test is written as:

> H_0: Behav MAP – LT MAP ≥ 10%
> H_1: Behav MAP – LT MAP < 10%

The non-inferiority margin (NIM) is set to 10% based on previous clinical consensus (see also section 9.4).

The second co-primary objective is related to the sentences in noise scores:

> H_0: The LT MAP will be inferior compared to the Behav MAP for sentence in noise scores.

H_1: LT MAPs will be non-inferior compared to the Behav MAP for sentence in noise scores.

The corresponding mathematical statement is written as:

H_0: LT MAP – Behav MAP ≥ 1.0 dB

H_1: LT MAP – Behav MAP < 1.0 dB

Here, the formula is reversed compared to the first hypotheses since higher SRT scores correspond to a poorer speech outcome. The NIM of 1.0 dB is again based on previous clinical consensus.

Successful rejection of the null hypotheses indicates the LT is non-inferior to the Behav based on the averaged word recognition and sentence score.

[redacted]

9.4 Sample Size Determination

Sample size estimation using SigmaPlot 14.0 will be based on the two co-primary endpoints, using one-tailed paired t-tests that provide the same result as one sample t-tests that use paired difference scores between the LT MAP and the Behav MAP. The non-inferiority test of difference between means in a 2X2 cross-over design (PASS 15.0.11) also yields the same sample size estimation as the paired t-test.

<u>Primary endpoint related to monosyllabic words in quiet:</u>

To reject the null hypothesis of inferior word perception in quiet at 50 dB for the Loudness Target MAP compared to Behavioural MAP the following assumptions have been made:

A non-inferiority margin of 10%; that is, poorer performance of the LT MAP compared to the Behav MAP of up to but not including 10% (Behav MAP minus LS MAP) is deemed tolerable. The NIM is based on clinical consensus. Several regulatory submissions for CI studies have similarly used a NIM of 10%; Hybrid L24 Implant (IDE# G070191), Nucleus 6 for Hybrid L24 Implant supplement (IDE# G070191/S031), Remote Programming (IDE #G150238), and Nucleus 6 for Traditional Cochlear Implants (IDE #G130246). The NIM of 10% is set above the standard error of measurement of the test measures. Freiburg words has a higher test-retest variability than CNC words. Hey et al. (2016) refers to a SD of test-retest difference scores of 12% for Freiburg words (Schmidt 2015 unpublished data) which corresponds to a standard error of measurement of 8.49% (12%/√2).

An expected standard deviation of change of 14% for the SD of difference scores between the LT and Behav MAPs for words in quiet. This is based on the SD of change data for both the CNC and Freiburg word tests. For 26 subjects tested with CNC words in the previous CALOS study (AI5805; VV-TMF-16140) the SD of difference scores between the Loudness Tuner MAP 1 (with T- and C-levels set using group ELS data) and the Behavioural MAP was 9%. Higher variability is assumed for Freiburg words, higher than the SD of test-retest difference scores of 12% (Schmidt 2015 unpublished data) referred to by Hey et al. (2016). A conservative SD of change of 14% has been chosen given that the subjects in the current study will be tested at the more challenging, softer presentation level of 50 dB SPL.

A one tailed significance level $\alpha = 0.025$ (equivalent to a two-tailed alpha of 0.05).

A desired power of 0.8.

Based on these assumptions, a sample size of 18 subjects is required to reject the null hypothesis.

<u>Primary endpoint related to SRT in noise:</u>

To reject the null hypothesis of inferior sentence in noise scores for the LT MAP compared to the Behavioural MAP the following assumptions have been made:

A non-inferiority margin (NIM) of 1.0 dB in adaptive SRT testing. That is, a true mean difference (LT MAP minus Behavioural MAP) of up to but not including 1 dB is acceptable and not deemed clinically meaningful. Note that a higher SRT value is poorer. This NIM is based on clinical consensus and has been used in several regulatory cochlear implant submissions (see above for the words primary endpoint). Furthermore, it is not less than the standard error of the test measures (Dawson et al. 2013; Hey et al. 2014).

An expected standard deviation of change or difference scores of 1.7 dB. This is based on the SD of change for both the AuSTIN and the OLSA speech in noise tests. Relevant data for the AuSTIN test is from the previous CALOS study (AI5805, VV-TMF-16140) with 26 subjects which reported a SD of change of 1.7 dB - the SD of difference scores between the Behavioural MAP and the Loudness Tuner MAP 1 that used group ELS data. Hey et al. 2014 reported a SD of difference (test-retest) of 1.12 dB for the OLSA in a group of 38 experienced adults using the Cochlear Ltd cochlear implant.

A one tailed significance level $\alpha = 0.025$.

A desired power of 0.84, which has been adjusted from 0.8 since study success will be based on the acceptance of both co-primary endpoints. The adjustment is performed to achieve an overall power of 0.8 for the two primary endpoints. A sample size of 28 subjects provides a power of 0.954 for words in quiet, so the combined power of 0.84 multiplied by 0.954 achieves the overall desired 80% power.

Based on these assumptions, a sample size of 28 subjects is required to reject the null hypothesis.

Final Sample Size:

To allow for the inability of some subjects to provide valid adaptive speech in noise data the number of subjects to be recruited has been increased by 10% to 31 subjects. It is estimated from past studies that approximately 10% of CI subjects are unable to provide reliable speech in noise data on the adaptive SRT test due to poorer speech recognition in quiet.

To allow for subject attrition during the course of the study, the sample size has been further increased by 10% to 34 subjects. Equal enrollment across the sites will not be enforced if one region recruits more quickly than the other.

9.5 Analysis Populations

Reporting of endpoints will include the following populations:

- Intent-to-Treat (ITT): all subjects who participate to the study.
- Per-protocol (PP): subjects who complete all endpoint visits in accordance with the assignment.

Results from the ITT and PP population will be reported and analysed for the primary and secondary endpoints. [redacted]

9.6 Endpoint Analyses

9.6.1 Primary Endpoint Analyses

To determine whether the Loudness Target MAP provides non-inferiority of speech understanding in quiet at 50 dB SPL and in noise compared to the Behavioural MAP at 3 months post-activation, paired t-tests will be conducted and the confidence limits of the mean paired differences scores will be examined for both co-primary endpoints:

1. Words in quiet at 50 dB SPL: If the upper 97.50% one-sided confidence bound of the averaged word recognition differences (Behav minus LT MAP) is less than the non-inferiority margin of 10%, statistically significant non-inferiority will be met at the 0.025 (0.05 2-tailed) alpha level.
2. Sentences in noise: If the upper 97.50% one-sided confidence bound of the mean adaptive SRT differences (LT MAP minus Behav MAP) is less than 1.0 dB, statistically significant non-inferiority will be met at the 0.025 (0.05 2-tailed) alpha level.

The non-parametric Wilcoxon signed ranks test will be used in both cases if the data is non-normally distributed.

[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 IMD and/or study procedures when required and to continuously inform the development of the evidence based fitting system.

10 INFORMED CONSENT PROCESS

The Investigator shall obtain written informed consent from the subject using an approved ICF prior to any clinical investigation-related examination or activity. The rationale of the clinical investigation, as well as the

benefits and risks, what participation will involve, and established alternatives to participation will be explained to the subject in native non-technical language, understandable to the subject. Ample time will be provided for the subject to enquire about details of the clinical investigation and to decide whether to participate.

All questions about the clinical investigation shall be answered to the satisfaction of the subject or the subject's legally designated representative. Subjects shall not be coerced or unduly influenced to participate or to continue to participate in a clinical investigation. They shall not waive or appear to waive their legal rights.

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

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

The subject, or the subject's legally designated representative, shall be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the clinical investigation. The communication of this information must be documented as an update to the ICF and re-consent of the subject.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1 Definitions

11.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons whether or not related to the medical device or the procedures required for implant or use, and whether anticipated or unanticipated.

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 the use of 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.

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

11.1.3 Serious Adverse Event

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

1) death,
2) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    - a life-threatening illness or injury, or
    - a permanent impairment of, 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 risk management summary report, hazards analysis, IB, IFUs, CIP, or ICF.

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

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

11.1.6 Adverse Events of Special Interest

AEs that interfere with the use of the research tools such as the Activation, Electrical Loudness Scaling and Loudness Target Tuner module, as well as the Daily Loudness Task on the MRA, such that it is impossible to continue with the session. These Aes may include non-auditory stimulation (NAS) and poor hearing from the CI-recipients that can't be overcome by the IMD.

11.1.7 Device Deficiency

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

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

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

11.1.8 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 the first visit. AE recording will continue for each subject until completion of their End of Study visit. Ongoing SAEs, SADEs and AESI will be followed for 30 days, or until resolution or stabilisation of the event, whichever comes first.

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

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

11.2.1 Assessment of Severity

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

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

11.2.2 Assessment of Causality

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

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

	– the medical device or procedures have an effect on; • the event follows a known response pattern to the medical device (if the response pattern is previously known); • the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible); • other possible causes (for example, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the medical device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

11.2.3 Assessment of Seriousness

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

11.2.4 Assessment of Expectedness

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

For this clinical investigation the listed items in Section 8.2 and 8.3 of this CIP and/or the risk management summary report, hazards analysis, IB, IFU, or ICF 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

Device deficiencies will be captured in the EDC, described in section 14. Clinical and technical support will be provided by Cochlear as required to resolve any device deficiencies that require troubleshooting.

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.

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 and AESI must be reported to the Sponsor in accordance with timeframes required by local regulations, as follows:

Country	Timeframe
Germany	Immediately
Australia	24 hours
USA	10 working days for UADEs

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

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

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

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

11.4.2 Sponsor Notification of Events

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

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:

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

11.5 Independent Data Monitoring Committee

Given the low residual risk associated with this study (such as no changes to the implant, no significant changes to the stimulation pattern, only minor changes to the sound processor firmware, absence of surgical risk, audiological risk comparable to clinical follow-up), an IDMC will not be established for this study.

12 Device Accountability

Supply of investigational medical devices will be recorded using the Sponsor Device Tracking Form (1295388) and Software Tracking Form (1302326). Investigational medical device(s) will be quarantined at the investigational site and clearly labelled to identify exclusively for use in a clinical investigation. Subject level device supply will be tracked using the Individual Subject Device Accountability Log Form (1295295). At the end of the clinical investigation, all investigational medical devices shall be returned to the Sponsor. Also loaner processors and eventual GN Resound/Cochlear Accessories, iOS devices and programming laptops [redacted], will be returned to the sponsor at the end of the clinical investigation, whether used or unused. In cases where a commercially released product is required to facilitate the functionality of the investigational device, the commercial product shall be registered following the standard product registration process.

Contact information regarding the IMD and comparator is provided below.

[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 IMD and/or comparator, or data integrity.

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

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

14 DATA MANAGEMENT

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

14.1 Source Data

Source data will be captured in clinic notes, paper-based source data worksheets, or printed directly from testing software. 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 must 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 will be collected from Custom Sound Suite [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.

[redacted] De-identified electronically generated data will be stored outside of Medidata Rave in a password-protected secure file location.

[redacted]

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, [redacted], 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 and the Health Insurance Portability and Accountability Act of 1996 (HIPAA)].

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 month/year of birth 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 exemption – applicable local regulation of Germany
United States	21 CFR Part 812 – Investigational Device Exemption

** See VV-TMF-18596 for applicable Statement(s)/Declaration(s) of conformity*

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

Should the Sponsor discontinue the clinical investigation, the Sponsor will assist subjects in finding an appropriate cochlear implant clinic for standard of care follow up if one if the subject does not already have one.

In the case of suspension or premature termination of the clinical investigation, the investigator will inform the subject on the blinding for the take-home condition. No special process for this unblinding needs to be put in place.

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 Investigators (and to the relevant regulatory authority(s) by the Sponsor, if applicable).

19 Record Keeping and Retention

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

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

Country	Retention period
Germany	15 years
Australia	15 years
United States	2 years after the latter of the following two dates: the date on which the investigation is terminated or completed, OR the date that the records are no longer required for the purposes of supporting a premarket approval application.

The Sponsor will notify the Principal Investigator when records are no longer needed. The Investigator will not discard any records without notifying the Sponsor. If the Principal Investigator moves from the current investigational site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the investigational site or the new address at which the records will be stored. The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

20 PUBLICATION POLICY

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

A joint publication or presentation will be co-authored by the clinical investigator(s) and Sponsor following study completion. 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 14155:2020 Clinical investigation of medical devices for human subjects – Good Clinical Practice, and any regional or national regulations, as applicable.

22 QUALITY CONTROL AND ASSURANCE

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

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

22.1 Monitoring

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

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

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

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

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

22.2 Audits

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

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

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

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

23 TRADEMARKS AND COPYRIGHT

24 REFERENCES

[redacted]

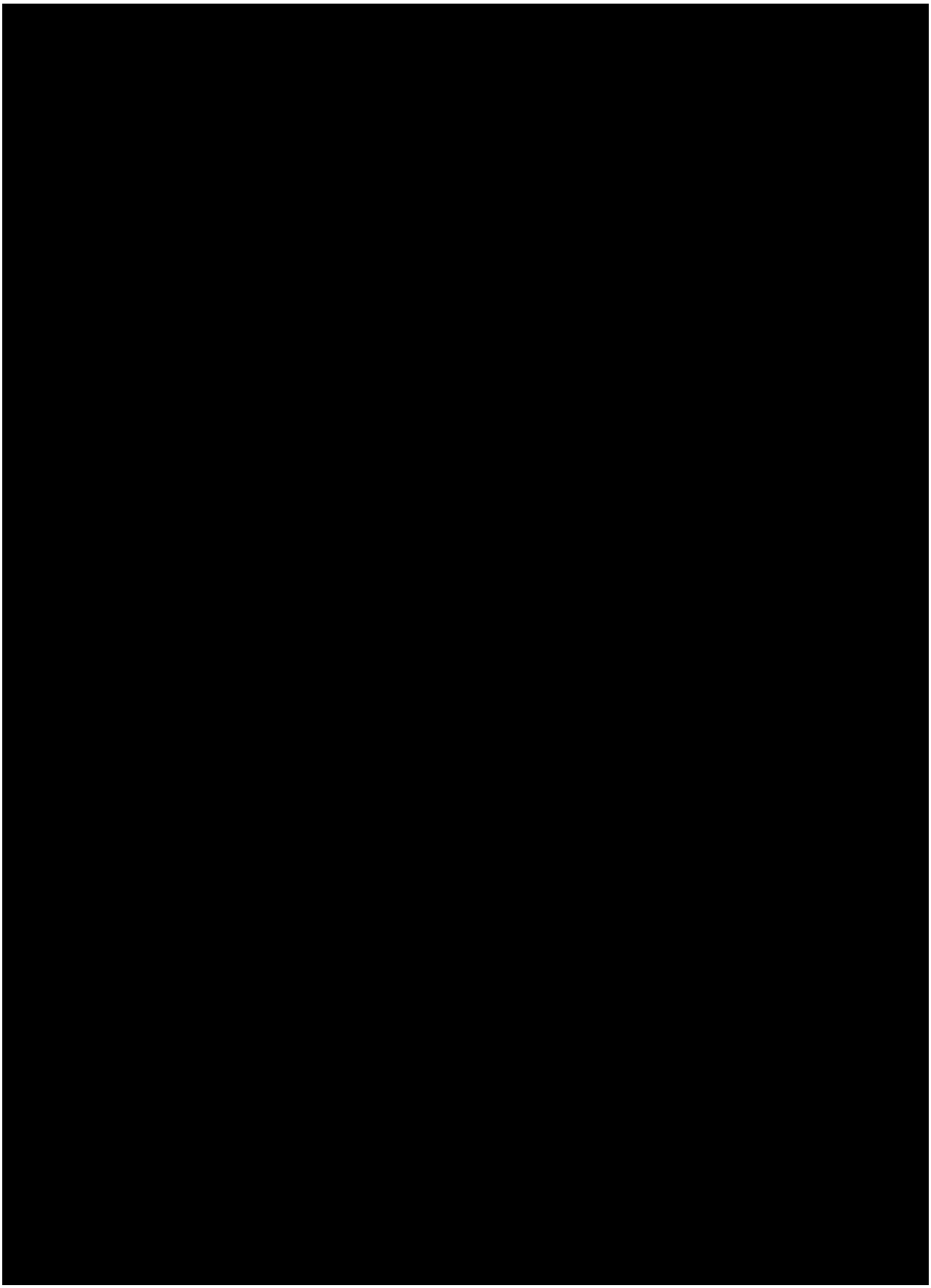
[redacted]

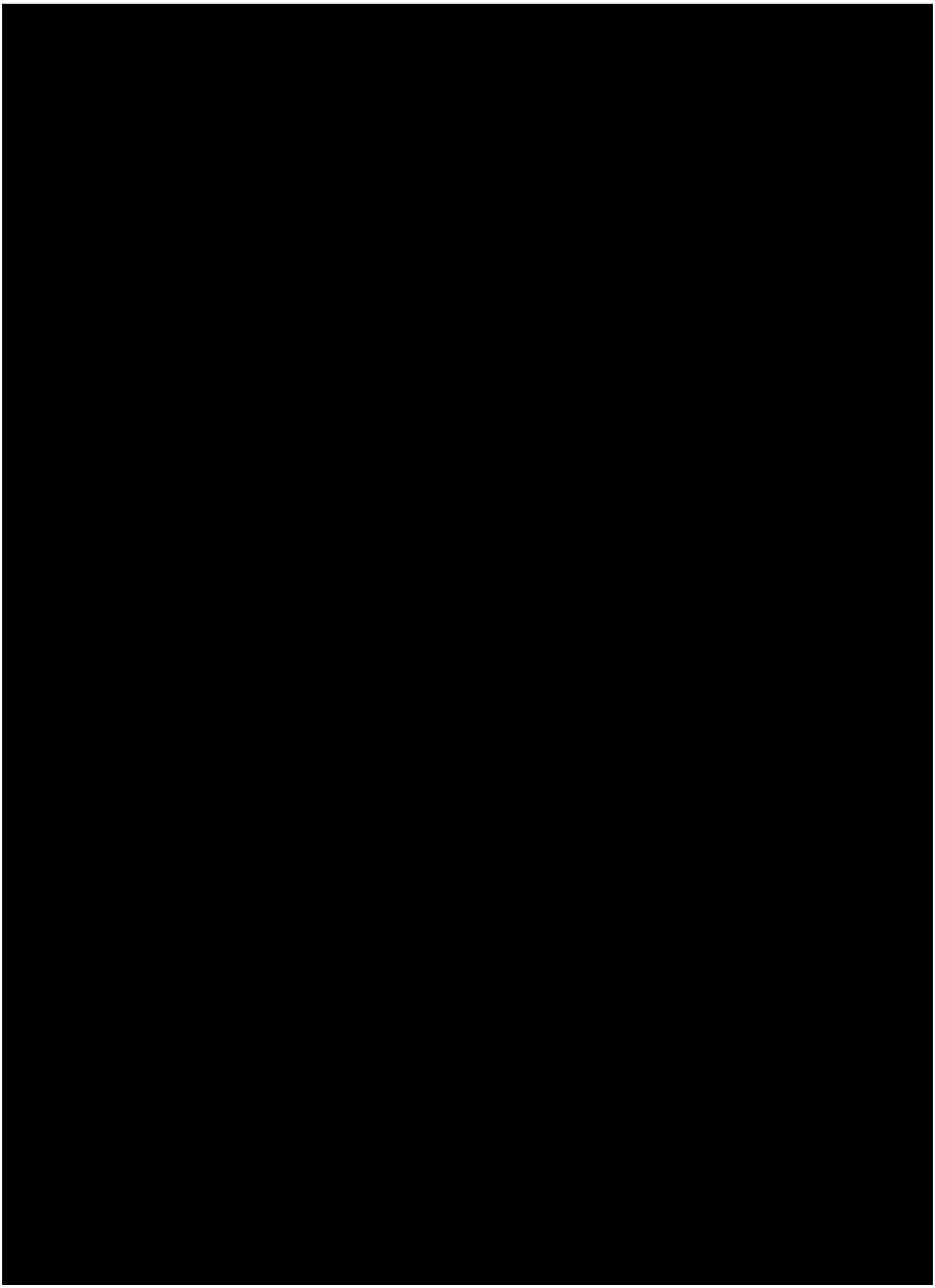
[redacted]

[redacted]

25 CHANGE HISTORY

[redacted]





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Signature Page for VV-TMF-15070 v7.0

Reason for signing: Approved	Name: Filiep Vanpoucke Role: Approver Date of signature: 25-Mar-2024 17:00:31 GMT+0000

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