Clinical Investigation Plan

Investigation Title: Prospective investigation to explore the impact of electrical stimulation parameter changes within the ACE strategy: A sub-study to umbrella investigation AI5763.

Short Title:	**IPACHA**
CIP Number:	**AI5822**
Date:	**Refer to e-signature date**
Sponsor	**Cochlear Limited** **1 University Avenue** **Macquarie University NSW 2109** **Australia** **Phone: +61 294 28 65 55**

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

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Sponsor Organisation	Cochlear Limited 1 University Avenue Macquarie University NSW 2109 Australia Phone: +61 294 28 65 55
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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

Coordinating Investigator Approval and Declaration

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

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

Name	**Title**
[redacted]	Coordinating Investigator
Signature	**Date**

Principal Investigator Declaration

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

Name	**Title**
	Principal Investigator
Site Name	**Site Address**
Signature	**Date**

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1 DEFINITIONS AND ABBREVIATIONS

Term	Description
4TB	Four Talker Babble
ACE	Advanced Combination Encoder
ADE	Adverse Device Effect
AE	Adverse Event
AuSTIN	Adaptive Australian Sentence Test in Noise
CDI	Cochlear's research Device Interface
CI	Cochlear Implant
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CL	Current Level
C-level	Comfortable level
CNC	Consonant Nucleus Consonant
CRF	Case Report Form
CSS	Custom Sound Suite
CTC	Cochlear Technology Centre
DD	Device Deficiency
eCRF	Electronic Case Report Form
ICF	Informed Consent Form
IMD	Investigational Medical Device
LIST	Leuven Intelligibility Sentences Test
NVA	Nederlandse Vereniging Audiologie
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SD	Standard Deviation
SNR	Signal to Noise Ratio
SRT	Speech Reception Threshold
T-level	Threshold Level

2 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	Prospective investigation to explore the impact of electrical stimulation parameter changes within the investigational ACE strategy: A sub-study to umbrella investigation AI5763
Short title	IPACHA
Investigation number	AI5822
Name of investigational medical device(s)	CP1000 sound processor with investigational ACE MAPs incorporating changes in electrical stimulation parameters (stimulation rate, pulse width and inter phase gap) as programmed by the investigational software Cochlear Device Interface Tool (CDI Tool).
Intended use of investigational medical device(s)	The investigational device is intended to be used in this investigation for individuals 18 years or older who are implanted with a commercially approved Nucleus cochlear implant. This clinical investigation utilizes repeated measures single-subject evaluation of changes in electrical stimulation parameters. All stimulation parameters are programmed to the CP1000 sound processor via CDI tool.
Name and description of comparator device/product(s)	The commercially available ACE strategy
Estimated recruitment period	7 months
Expected duration per subject	3 visits over an approximate 3-week period. This period can be extended/ shortened depending on subjects' availability without impact to the study outcomes. Up to 2 additional visits can be planned if required.
Number of subjects planned	20
Number of investigational sites planned	3
Inclusion criteria	1) User of a commercially approved CI24RE/CI422/CI500/CI600 series of Nucleus cochlear implants. 2) At least three months of experience with the cochlear implant. 3) Older than 18 years when entering the study. 4) User of ACE (Advanced Combination Encoder) strategy. 5) Open set speech understanding sufficient to complete the study protocol as judged by the investigator. 6) Subject is fluent speaker in the language used for assessments. 7) Willing and able to provide written informed consent.
Exclusion criteria	1) Unable or unwilling to comply with the requirements of the clinical investigation as determined by the investigator.

	2) Additional health factors, known to the investigator, that would prevent or restrict participation in the audiological evaluations. 3) Investigator site personnel directly affiliated with this study and/or their immediate families; immediate family is defined as a spouse, parent, child or sibling. 4) Cochlear employees or employees of Contract Research Organizations or contractors engaged by Cochlear for the purposes of the investigation. 5) Currently participating, or participated within the last 30 days, in another interventional clinical investigation/trial involving an investigational drug or device.

Objectives and Endpoints	
Primary Objectives	**Primary Endpoint**
1. To evaluate the effect of varying pulse width on speech perception in quiet.	1. Monosyllabic (NVA/CNC) word scores in quiet at 50 dB SPL.
Secondary Objective	**Secondary Endpoint**
1. To evaluate the effect of varying pulse width on speech perception in noise. 2. To assess the impact of reducing maxima or reducing stimulation rate for complex MAPping cases that require use of wide pulse widths. 3. To establish the T- & C-levels & T-NRT offsets for a range of MAPs of varying parameters to inform clinical workflows when parameters will be varied.	Secondary objective 1 1. Adaptive sentence in noise scores (4-talker babble, S0N0 test setup). Secondary objective 2 1. Monosyllabic (NVA/CNC) word scores in quiet at 50 dB SPL. 2. Adaptive sentence in noise scores (4-talker babble, S0N0 test setup). Secondary objective 3 1. AutoNRT thresholds, MAP T- and MAP C-levels.
Exploratory Objective	**Exploratory Endpoint**
1. To examine whether the T- & C-levels can be predicted reliably with widening of the pulse width.	1. Difference between predicted and measured T-levels 2. Difference between predicted and measured C-levels

3 SCHEDULE OF EVENTS

Visit Type	Screening & Visit 1	Visit 2	Visit 3	2 optional visits
Timing of Investigation	**Day 0**	**NA**	**NA**	**NA**
Visit window (□)	NA	NA	NA	NA
Procedures				
Written informed consent	X			
Demographics	X			
Eligibility	X			
Hearing history	X			
Device history	X			
Medical history	X			
Program conditions	X	(X)	X	X
Loudness balancing of MAPs	X	(X)	X	X
Speech perception testing in noise (LIST/AuSTIN sentences)	(X)	X	X	X
Speech perception testing in quiet (NVA/CNC)	(X)	X	X	X
Neural Response Telemetry (NRT) measures	(X)	X	X	X
Concomitant medications/therapies	X	X	X	X
Adverse Events	X	X	X	X
Device Deficiencies	X	X	X	X
Device exposure	X	X	X	X

The above table is a guide. For subjects, who do not complete the study visit requirements within the given sessions, up to two additional visits will be scheduled. Note that the timing of specific visits has not been pre-specified since this is not of consequence to the study conduct nor outcomes. Note that, if deemed to be necessary (e.g., pandemic restrictions due to the current ongoing pandemic), speech perception tests, NRT measures and sound processor programming can be performed remotely. If the visits are performed remotely, it is

envisaged that the testing for each of the visits could occur in a number of smaller remote appointments and will not be reported as deviations. (X) = measurement can be performed at this session if time permits or could not be completed at the planned visit due to time constraint.

4 BACKGROUND INFORMATION AND RATIONALE

4.1 Introduction

During a CI programming session, appropriate current levels for individual electrodes are determined by obtaining psychophysical threshold levels (T-levels) and maximum comfort levels (C-levels) on each CI electrode. When programming a CI recipient, a clinician chooses a number of electrical stimulation parameters such as stimulation rate, number of maxima, and pulse width. These parameters impact the current levels required to achieve the T- and C-levels. The maximum current delivered on each electrode should not exceed the voltage compliance limit of the device. There is benefit in use of a wide pulse width to lower the electrical T- and C-levels where this does not impact negatively on power consumption. The primary objective of the current study is to explore the effect of varying pulse width for the ACE MAP with a moderate per channel stimulation rate of 500 Hz. This stimulation rate is of interest given it enables the pulse width to be increased more than if using a stimulation rate per channel of 900 Hz.

Table 1 Stimulation parameters for commercially approved CI24RE/CI422/CI500/CI600 series of Nucleus cochlear implants)

Stimulation Parameter	CIC4 Implants
Per channel stimulation rates	Clinician-selectable, various between 250 and 3500 Hz
Default rate (per channel)	900 Hz
Pulse width values	Clinician-selectable, various between 9.6 µs and 400 µs
Default pulse width	25 or 37 depending on implant type
Maximum number of maxima	Clinician-selectable, varies between 1 and 20
Interphase gap (IPG)	Non-selectable, various between 4.8 µs and 9 µs

In the fitting software Custom Sound Pro (CSPro) the parameter set in the case of a wide pulse width of 200 µs maintains the stimulation rate (currently at 900 Hz per channel) and reduces the number of maxima. The current study will compare this approach to an alternative approach of reducing the stimulation rate and maintaining the number of maxima as close as possible to the default of 8 for this wider pulse width scenario. One of the secondary objectives of the current study is to compare the speech perception performance with pulse width-maxima adjustment vs pulse width-rate adjustment for cases that require use of the wider pulse width. This will inform clinical recommendations for managing complex cases.

The study will also investigate the impact varying pulse width on 'T-NRT offsets' (or the difference between the threshold of the ECAP response (obtained during Neural Response Telemetry measures) and the T- and C-levels measured behaviourally.

The pulse width used is 25 µs for NRT measurements. This study will establish the T- & C-levels and T-NRT offsets for a range of MAPs of varying pulse widths and parameter combinations.

This investigation will be conducted at Cochlear Ltd. Melbourne premises by the investigator of HEARnet (in collaboration with Royal Victorian Eye and Ear Hospital, East Melbourne) and Cochlear Ltd. and at Cochlear Technology Centre Belgium (CTC) premises by the investigator of CTC. Subjects from respectively HEARnet (in collaboration with Royal Victorian Eye and Ear Hospital, East Melbourne), GZA Sint-Augustinus Antwerp and AZ Sint-Jan Brugge-Oostende AV will be included in this sub-study.

This investigation is a sub-study falling under the umbrella study "A feasibility, prospective, repeated-measures investigation to investigate innovations in clinical care in adult and paediatric recipients implanted with CE approved Nucleus cochlear implants: an umbrella investigation" (AI5763). All sections from the Clinical Investigation Plan (CIP) of umbrella study AI5763, apply to this sub-study. More detailed information specific for this sub-study is described in this document. As mentioned in the CIP of umbrella study AI5763, this sub-study comes with a sub-study specific CIP and an Informed Consent Form (ICF).

4.2 Findings of Previous Nonclinical and Clinical Studies

4.2.1 Nonclinical Data

Not applicable

4.2.2 Clinical Data

The primary task of the CI MAPping is to set the T- and C-levels for each electrode using electrical pulse trains, so that variations in the acoustic input level produce auditory precepts ranging from "very soft" to "loud but comfortable". Along with the electrical current level (CL), other stimulation parameters also have influence on the perceived loudness of electrical pulses. Increase in stimulation rates, pulse widths and interphase gap increase the perceived loudness of electrical pulses (Shannon, 1985; McKay and McDermott,1999; Macherey et al., 2006).

The current default stimulation rate and pulse widths provide sufficient loudness for a majority of the CI users. In some cases, however, the maximum available current may not be sufficient. In these cases, clinicians tend to increase the pulse width, which lowers the stimulation currents and provides higher compliance limits. The current study will explore the effect of widening pulse width for a moderate stimulation rate (500 Hz) ACE MAP, as the pulse width can be increased to a greater extent than if a higher rate was used. Studies on the effect of stimulation rates have shown comparable performance for the 500 and 900 Hz rates. For example, studies by Arora et al. (2009, 2011) showed that there was no significant difference between the 500 and 900 Hz rates for listening in quiet or in noise. Group mean results for sentence perception in noise showed improved performance for 500 and 900 Hz stimulation rates compared to the lower rates of 250 and 350 Hz. The 500 Hz was perceived to be at least comparable to 900 Hz by CI users. In one of the few larger studies, Balkany et al (2007) reported preference for lower rates for the ACE strategy (500 to 1200 Hz) for 37 of the 55 subjects, compared to higher rates (1800 to 3500 Hz), based on a questionnaire which required subjects to choose the preferred rate of three provided in each of the groupings. Results from a Cochlear internal study- CRC5607, showed that the 500 Hz stimulation rate program was non-inferior to the 900 Hz program for all clinical measures. Fifty-three percent of the subjects reported no overall difference in preference between the two programs, despite the majority having a

longer period of 900 Hz per channel use prior to enrolment. For the subjects who reported a preference for 900 Hz, the degree of difference was reported to be only slight. Finding from these studies suggest that a moderate rate of 500 Hz for the ACE strategy is expected to provide similar performance to the 900 Hz stimulation rate program.

An important clinical question relates to the optimal parameters to be selected to support complex cases. There are two options for example when widening the pulse width to 200 us, as is required in rare cases. To ensure there is sufficient time to deliver the stimulation, it is required to either reduce the number of maxima presented during each analysis period, or to reduce the stimulation rate. It is of interest to examine this to provide enhanced guidance regarding the recommended approach.

4.3 Study Rationale

The purpose of this study is to develop clinical guidance relating to the new parameter sets compared to the current defaults on CI recipients' performance.

The study, will specifically evaluate following:

1) Comparison of speech perception (in quiet and noise) for a 500 Hz MAP with a new parameter set relative to the current default as used in commercially approved CI24RE/CI422/CI500/CI600 series of Nucleus cochlear implants.
2) Explore the optimal parameter set (incorporating stimulation rate, maxima and pulse width), for complex MAPping cases that require use of wide pulse width.

Currently, in Custom Sound software, if a compliance limit is reached, an option to adjust pulse width is offered, wherein pulse width is increased and T- and C-levels are globally reduced by a certain amount of current depending on the pulse width. However, at pulse widths ≥200 µs, the number of maxima is reduced significantly (≤2), which may affect CI recipients' speech perception in noise. A study by Plant et al. (2002) suggests that the number of maxima should be higher than six for optimal listening in situations with background noise. The current study will investigate the effect of reducing stimulation rate vs reducing maxima on speech perception performance.

3) Establish T-NRT offset data for the wider pulse widths.

The NRT thresholds are currently measured with a probe pulse width of 25 µs, which matches the default pulse width used in current clinical defaults. Varying the stimulation parameters will impact the offset between T-NRT and T/C levels. Understanding where the T-NRT is expected to fall within the electrical dynamic range for the different parameter configurations is of interest.

5 MEDICAL DEVICE INFORMATION

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

The IMD is the CP1000 sound processor with investigational ACE MAPs incorporating changes in electrical stimulation parameters (stimulation rate, pulse width and inter phase gap) as programmed by the investigational software Cochlear Device Interface Tool (CDI Tool). Table 2 shows the parameter details of the investigational MAPs to be tested in the current study.

Table 2 parameter details of the investigational MAPs to be tested in the current study

		Parameters set using the CDI tool				
Investigational MAPs*	Related objectives	Stim. rate (Hz)	Pulse width (µs)	ISG (µs)	IPG (µs)	Maxima
Investigational MAP 1 (INV1)	Primary objective Secondary objective 1 Exploratory objective	500	100	10	28	8
Investigational MAP 2 (INV2)	Secondary objectives 2 Exploratory objective	250	200	10	45	8
Investigational MAP 3 (INV3)	Secondary objective 3 Exploratory objective	500	150	10	36	5

*All MAPS will use Advanced Combination Encoders (ACE) strategy

CDITool is a cochlear research platform that allows fitting of a CI recipient with the investigational sound coding strategies that are not available in the commercial Custom Sound clinical software. It downloads the firmware to the CP1000 sound processor and determines the patient specific parameters, e.g., stimulation levels, as well as the IMDs pulse width, stimulation rate and interphase gap parameters. This investigational software/firmware is used for the purpose of the clinical investigation only. A screenshot of the CDITool software is shown in figure 1.

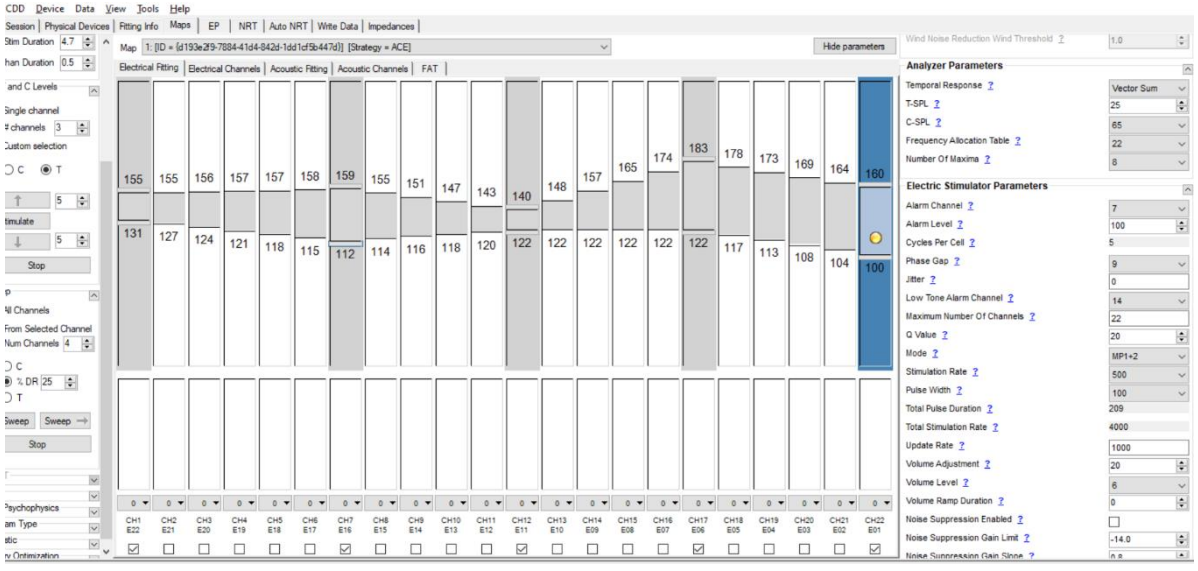

Figure 1 Screenshot of Cochlear Device Interface Tool (CDITool).

The clinical hardware used in this study consists of a computer with the research CDITool Software. The computer is connected to a commercially available programming pod which is connected to a commercially available Nucleus 7 sound processor (CP1000).

The development of investigational devices, including investigational software/firmware releases, follows a design control process which is part of Cochlear's ISO13485 compliant quality management system. All investigational devices are verified for safety and technical correctness prior to use in a human trial. The research software and firmware underwent safety and performance 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 overall residual risks associated with the investigational devices are acceptable. All risk reduction measures as shown in the essential requirements document have been implemented into the final design and verified to be effective.

Subjects will use the IMD for the duration of the sub-study only. The PC with the IMD will be clearly labelled to identify it as exclusively for use in a clinical investigation. Subjects will use the IMD for the duration of the sub-study only. Traceability of the build number will be documented in the tracking forms such as the Software Tracking Form (1302326), as mentioned in section 12 of the CIP of umbrella study AI5763. The investigator will be trained on using the investigational device. This training will be logged on a training log. The investigational devices will not be in contact with body fluid or tissue.

5.2 Identity and Description of the Comparator

The comparator shall be the commercially available ACE coding strategy on the CP1000 sound processor. All active channels for these MAPs will be set by the investigator using Custom Sound Suite (CSS). The MAPs will be written on the commercially available Nucleus 7 sound processor (CP1000). Table 3 displays the parameter information of the comparator MAPs.

Table 3 Stimulation parameter details of the comparator MAPs.

Comparator MAPs*	Related objectives	Stimulation rate (Hz)	Pulse width (µs)	Inter stimulus Gap (µs)	Interphase gap (µs)	Maxima
Comparator MAP 1 (COM1)	Primary objective Secondary objective 1 Exploratory objective	500	25	10	9	8
Comparator MAP 2 (COM2)	Secondary objectives 2 Exploratory objective	900	200	10	9	2
Comparator MAP 3 (COM3)	Secondary objective 3 Exploratory objective	500	50	10	9	8

*All MAPS will use Advanced Combination Encoders (ACE) strategy

5.3 Accessory Device Requirements

Not applicable.

6 OBJECTIVES

6.1 Primary Objective

1. To evaluate the effect of varying pulse width on speech perception in quiet.

6.2 Secondary Objectives

1. To evaluate the effect of varying pulse width on speech perception in noise.
2. To assess the impact of reducing maxima or reducing stimulation rate for complex MAPping cases that require use of wide pulse widths.
3. To establish the T- & C-levels & T-NRT offsets for a range of MAPs of varying parameters to inform clinical workflows when parameters will be varied.

6.3 Exploratory Objective

1. To examine whether the T- & C-levels can be predicted reliably with widening of the pulse width.

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 General

This is a prospective with sequential enrolment, single-subject repeated-measures clinical investigation in adults with a CE labelled cochlear implant. Evaluations will be conducted at one centre in Belgium and at one centre in Australia with subjects recruited from two sites in Belgium and from one site in Australia.

The subjects include adults from the age of 18 years or older who are implanted with a commercially approved CI24RE/CI422/CI500/CI600 series of Nucleus cochlear implants. Subjects will be screened according to the inclusion and exclusion criteria, and 20 eligible subjects will be recruited in the clinical investigation.

Subjects will attend 3 visits over an approximate 3-week period. This period can be extended/ shortened depending on subjects' availability without impact on the study outcomes. For subjects, who do not complete the study visit requirements within the given sessions, up to two additional visits will be scheduled. Note that the timing of specific visits is not of consequence to the study conduct nor outcomes.

The time for each visit is estimated to be three hours and up to 4 hours. At study visits, subjects will undergo assessments as defined in the procedures manual of this sub-study.

If deemed to be necessary (e.g., restrictions due to the current ongoing pandemic), programming, speech perception testing and NRT measures can be obtained remotely like in the home situation, with mutual agreement of all involved parties, i.e., investigator, sponsor, subject and Ethics Committee.

The study procedures will involve assessment using the commercially available Nucleus CP1000 sound processor. The Nucleus CP900 sound processor will be used for AutoNRT measurements.

Section 7.3 describes the procedure and measurement methods applied in this sub-study. A detailed description of the randomization, specific method for assessing, recording variables, the equipment used will be described in the sub-study procedures manual.

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 will be continuously during this sub-study. All subjects will have an End-of-Study visit at the time they complete this sub-study.

7.1.1 Design Rationale

The goal of this sub-study is to compare speech perception (in quiet and noise) for a 500 Hz stimulation rate ACE strategy program using an alternative parameter set to that currently used when this stimulation rate is selected in Custom Sound Suite.

The sub-study is set up as a repeated measures single-subject design in which each participant is acting as his/her own control to accommodate the heterogeneity in the implant population. The commercially available ACE strategy program will be compared to one or more of the investigational conditions.

In Australia, this investigation will be conducted at Cochlear Ltd. Melbourne premises by the investigators of HEARnet (in collaboration with Royal Victorian Eye and Ear Hospital, East Melbourne) and Cochlear Ltd.. In Belgium, this investigation will be conducted at CTC by the investigator of CTC. If necessary (e.g., restrictions due to the current ongoing pandemic), certain measurements can be obtained remotely like in the home situation.

Twenty subjects will be enrolled. However, new subjects may be recruited to maintain subject numbers in case subjects withdraw from the study. In Australia, subjects from HEARnet (in collaboration with Royal Victorian Eye and Ear Hospital, East Melbourne) will be included in this sub-study, while in Belgium, subjects will come from GZA Sint-Augustinus Antwerp and AZ Sint-Jan Brugge-Oostende AV.

CI recipients from the age of 18 or older can participate in the study, as long as they meet the in- and exclusion criteria as described in section 7.2. This sub-study will be single-blinded (i.e., information is concealed from the recipient) and randomized (i.e., the order of testing). The information collected will be used for the purpose of the current sub-study as well as provide input for related future studies.

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, demographic and audiological information that confirm the subject inclusion as stated in section 7.2.1.

Twenty subjects will be enrolled into the sub-study.

7.2.1 Inclusion Criteria

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

1) User of a commercially approved CI24RE/CI422/CI500/CI600 series of Nucleus cochlear implants.
2) At least three months of experience with the cochlear implant.
3) Older than 18 years when entering the study.
4) User of ACE (Advanced Combination Encoder) strategy.
5) Open set speech understanding sufficient to complete the study protocol as judged by the investigator
6) Subject is fluent speaker in the language used for assessments.
7) Willing and able to provide written informed consent.

7.2.2 Exclusion Criteria

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

1) Unable or unwilling to comply with the requirements of the clinical investigation as determined by the investigator.
2) Additional health factors, known to the investigator, that would prevent or restrict participation in the audiological evaluations.
3) Investigator site personnel directly affiliated with this study and/or their immediate families; immediate family is defined as a spouse, parent, child or sibling.
4) Cochlear employees or employees of Contract Research Organizations or contractors engaged by Cochlear for the purposes of the investigation.
5) Currently participating, or participated within the last 30 days, in another interventional clinical investigation/trial involving an investigational drug or device.

7.2.3 Number of Subjects Required

Twenty subjects will be recruited. Any subjects that withdraw from the study will be replaced to maintain this number.

7.2.4 Vulnerable Populations

Not applicable for this sub-study.

7.2.5 Recruitment and Study Duration

The subject status definitions are described in the Clinical Investigation Plan of Umbrella AI5763.The enrolment period for the clinical investigation is anticipated to be 7 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 3 visits over approximately 3 weeks. This period can be extended/ shortened depending on subjects' availability

without impact on the study outcomes. For subjects, who do not complete the study visit requirements within the given sessions, up to two additional visits will be scheduled. Note that the timing of specific visits is not of consequence to the study conduct nor outcomes.

Clinical Investigation completion is last subject last visit. In the event of an ongoing Serious Adverse Events (SAEs)/Serious Adverse Device Effects (SADEs) at the time of this last visit, the clinical investigation completion will be extended for a further 30 days, or until resolution or stabilization of the event, whichever comes first.

7.2.6 Criteria for Subject Withdrawal

The criteria for withdrawal are described in the Clinical Investigation Plan of Umbrella AI5763.

Enrolled subjects who are withdrawn/discontinued will be replaced to meet the number of included subjects.

7.2.7 Randomisation Procedures

The word and sentence lists used for testing speech performance in quiet and noise will be randomized between subjects as well as the order of testing the different conditions. This is described in the Procedures Manual of the sub-study.

7.2.7.1 Blinding Procedures

This sub-study is a single blinded investigation. This means that subjects will be blinded to the conditions they are tested. The conditions will be referred to as program 1, 2, etc.

The investigational programs will be provided to the subject on a loaner CP1000 processor. The subject will have at all time access to his/her own processor and thus no separate procedure for un-blinding the subject is required in case of emergency.

7.2.8 Post-investigation Medical Care

No extra medical care needs to be provided after the clinical investigation.

7.3 Performance Evaluations and Procedures

The principal investigators of HEARnet (in collaboration with Royal Victorian Eye and Ear Hospital, East Melbourne), GZA Sint-Augustinus Antwerp and AZ Sint-Jan Brugge-Oostende AV are responsible for subject recruitment, obtaining Informed Consent, assessment of inclusion- and exclusion criteria and assessment of hearing and medical history related to the umbrella CIP of AI5763.

For the sub-study, subjects will be evaluated in Australia by HEARnet and Cochlear Ltd. at the facilities of Cochlear Ltd. Melbourne and in Belgium by investigators of CTC at the facilities of CTC.

Detailed procedures will be described in the procedures manual of this sub-study. Details of the timing and frequency of evaluations is also provided in Section 3.

During the initial visit, the following study MAPs will be created:

Table 4 Study MAPs to be created at visit 1

MAP	Stimulation rate (Hz)	Pulse width (µs)	Inter stimulus Gap (µs)	Interphase gap (µs)	Maxima
COM1	500	25	10	9	8
INV1	500	100	10	28	8
COM2	900	200	10	9	2
INV2	250	200	10	45	8

These MAPs will be compared with the COM1 MAP for equal loudness. A categorical loudness scale will be used to ensure balanced loudness and C-level adjustments made to ensure loudness match as much as possible. Note that further (re)programming can be done at the subsequent visits, including the additional visits if required. If deemed to be necessary, the (re)programming can be done remotely.

During visit 2, the first two MAPs (COM 1 and INV 1) in Table 4will be compared using tests of speech perception (in quiet and noise). Subjects will be provided practice with both MAPs for at least 10 minutes prior to the testing. If the subject wears a contralateral hearing aid or cochlear implant, the contralateral ear will be blocked and/or the contralateral sound processor will be removed. The effectiveness of blocking the contralateral ear shall be checked by presenting audio with the CI coil off; if the subject still hears the audio then masking noise shall be applied. AutoNRT using Custom Sound will also be performed during this visit for these two MAPs.

During visit 3, the COM2 and INV2 MAPs will be evaluated for speech perception (in quiet and noise) and AutoNRT. Subjects will be provided practice with both MAPs for at least 10 minutes prior to the testing.

In addition to that, MAPping for the following Maps (Table 5) will be performed. The MAPs will be loudness balanced with the COM1 MAP. Categorical loudness scale will be used to ensure balanced loudness. These MAPs will be tested for AutoNRT measures.

Table 5 Study MAPs to be created at visit 3

MAP	Stimulation rate (Hz)	Pulse width (µs)	Inter stimulus Gap (µs)	Interphase gap (µs)	Maxima
INV3	500	150	10	36	5
COM3	500	50	10	9	8

The alternative INV3 MAP, which uses a pulse width of 150 µs, will be evaluated as this MAP would be expected to be selected by clinicians in some cases where compliance limits are reached and so ascertaining the offsets is of interest to facilitate clinicians' ease of fitting within Custom Sound fitting software. COM3 MAP will be tested for T- and C- levels and AutoNRT to compare them against those for the COM1 MAP which uses a pulse width of 25 µs. The goal of this testing is to determine how total charge varies as a function of pulse width.

Two additional visits might be added in case the measurements for all conditions are not collected in the session (e.g., because of such issues as time constraints of the recipient and/or investigator, or technical difficulties, or further (re)programming required).

The order in which the MAPs are evaluated during the study sessions will be counterbalanced across the group.

The test levels, speaker configurations and test conditions will be outlined in detail in the study procedures manual.

The time for a clinical visit is estimated to be three hours and will be limited to a maximum of 4 hours. The following sections summarize the different tests that will be used in this sub-study.

Figure 2 provides the procedures overview.

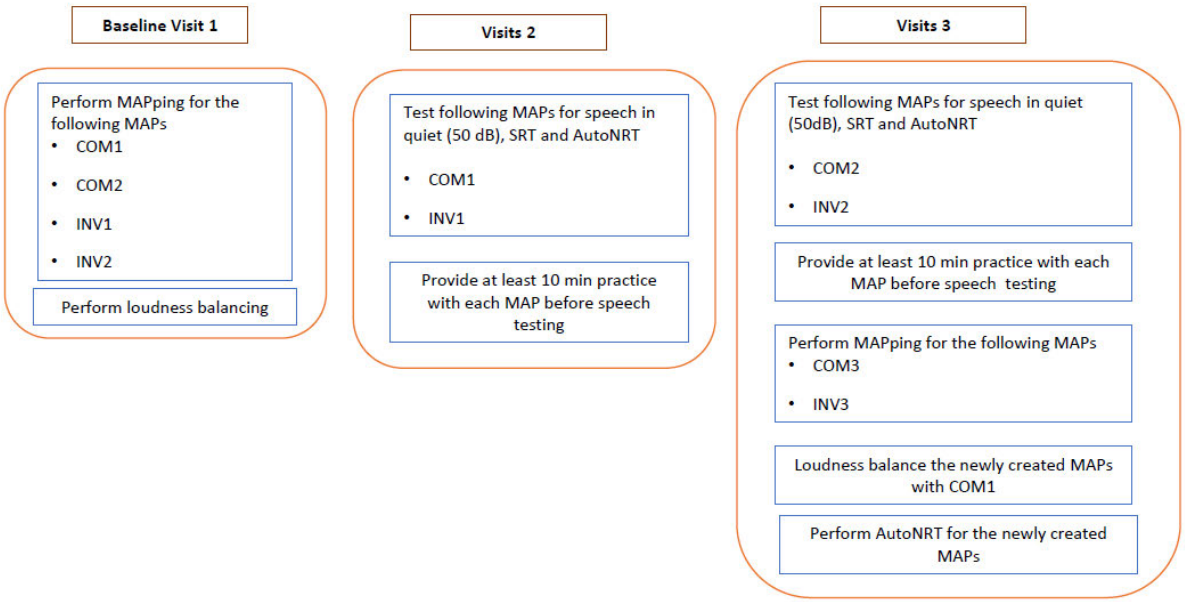

Figure 2 Procedures overview

7.3.1 Sentences in noise

Test conditions will be evaluated using the Adaptive Australian Sentence Test in Noise (AuSTIN) (Dawson et al., 2013) in Australia and the Leuven Intelligibility Sentences Test (LIST) in Belgium 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 (Dawson, Hersbach, & Swanson, 2013). The LIST corpus comprises 35 lists of 10 sentences each, recorded in female and 38 lists of 10 sentences each, recorded in male voice (van Wieringen et al., 2008 and Jansen et al., 2014). The goal of the adaptive SIN is to obtain the Speech Reception Threshold (SRT). We define the Speech Reception Threshold (SRT) as the Signal to Noise Ratio (SNR) in decibels at which a patient can understand 50% of the keywords in the sentences. A similar method has been used in previous studies (e.g., Dawson, Hersbach, & Swanson, 2013).

The presentation order of the lists and sentences will be randomized as well as the order of conditions.

If deemed to be necessary, this test can be obtained remotely.

7.3.2 Words in quiet

Test conditions will be evaluated in Australia using the Consonant Nucleus Consonant (CNC) word test (Peterson & Lehiste, 1962) and in Belgium using the Nederlandse Vereniging Audiologie (NVA) words (Flemish version: Wouters et al, 1994) in quiet at soft presentation level (50 dBSPL) 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 female voice. The NVA word test consists of 15 lists, each with 1 practice word and 11 test words per list, recorded in male voice.

The presentation order of the lists will be randomized as well as the order of conditions.

If deemed to be necessary, this test can be obtained remotely.

7.3.3 AutoNRT

An AutoNRT measurement will be obtained on 9 electrodes using the commercially available CSS software. Electrodes flagged in the MAP will be excluded if necessary. No protocol deviation will be created in case AutoNRT measurement can't be obtained on certain electrodes. This measurement can be obtained at any visit. If deemed to be necessary, this test can be obtained remotely.

7.4 Safety Evaluations and Procedures

The risks and anticipated ADEs for the investigational device, as identified in Sections 8.2 and 8.3 of the CIP, will be assessed in the clinical investigation via reporting of all AEs/ADEs from the time of first subject first visit until last subject last visit for this sub-study.

Safety data adjudication may be conducted by the Sponsor's Medical Officer in accordance with the Sponsor's standard operating procedures.

7.4.1 Concomitant Medication and Therapies

In case of concomitant medication, this is administered as part of the safety CRF.

7.5 Equipment Used for Evaluation of Performance and Safety

The study will be conducted in Australia at the facilities of Cochlear Ltd. Melbourne and in Belgium at the facilities at CTC. The sound booth equipment is maintained and calibrated according to the clinical sound room characterization and calibration work instruction.

7.6 Sponsor Role in Conduct of the Clinical Investigation

The procedures performed by the sponsor investigator are described in section 7.3 and are specified in more detail in the Procedures Manual.

There is no mitigation for potential bias to the data integrity.

8 Risks and Benefits of the Investigational Medical Device and Clinical Investigation

8.1 Anticipated Clinical Benefits

There is no anticipated clinical benefit for subjects. The investigational program and research tools will be used within the study period only.

The indirect benefit could be that through this clinical investigation Cochlear will bring product improvements to the market that may result, in future, in an increased efficiency of time for clinicians and/or provide a more consistent and improved outcome for CI recipients.

8.2 Anticipated Adverse Device Effects

Anticipated ADEs, such as risk of sub-optimal performance, are described in the CIP of umbrella AI5763.

8.3 Risks Associated with Participation in the Clinical Investigation

Risks associated with participation in the clinical investigation are described in the Clinical Investigation Plan of Umbrella AI5763.

8.4 Risk Mitigation

Risk mitigation is described in the Clinical Investigation Plan of Umbrella AI5763.

8.5 Risk-to-Benefit Rationale

The risk-to-benefit rationale is described in the Clinical Investigation Plan of Umbrella AI5763.

9 STATISTICAL CONSIDERATIONS

9.1 General Considerations

A total of twenty subjects will be recruited, coming in Australia from HEARnet (in collaboration with Royal Victorian Eye and Ear Hospital, East Melbourne), and in Belgium from the centres Sint-Augustinus Antwerp and AZ Sint-Jan Brugge-Oostende AV.

Data will be analysed continuously in order to make rapid changes to the IMD and/or study procedure when required.

Analysis of the data of this sub-study will take place at Cochlear. A sub-study Clinical Investigation Report (CIR) will be written when the endpoints as described in section 9.2 are reached.

9.2 Endpoints

The endpoints are listed below.

9.2.1 Primary Endpoint

1. Monosyllabic (NVA/CNC) word scores in quiet at 50 dB SPL

9.2.2 Secondary Endpoint

Secondary objective 1

1. Adaptive sentence in noise scores (4 talker babble, S0N0 test setup).

Secondary objective 2

1. Monosyllabic (NVA/CNC) word scores in quiet at 50 dB SPL
2. Adaptive sentence in noise scores (4 talker babble, S0N0 test setup).

Secondary objective 3

1. AutoNRT thresholds, MAP T- and MAP C-levels

9.2.3 Exploratory Endpoint

1. Difference between predicted and measured T-levels.
2. Difference between predicted and measured C-levels

9.3 Hypotheses

9.3.1 Primary Hypotheses

H0: There will be no significant difference in monosyllabic word scores in quiet at 50 dB SPL for the COM1 MAP and INV1 MAP.

H1: There will be a significant difference in monosyllabic word scores in quiet at 50 dB SPL for the COM1 MAP and INV1 MAP.

9.3.2 Secondary Hypotheses

H0: There will be no significant difference in adaptive sentence test in noise scores for the COM1 MAP and INV1 MAP.

H1: There will be a significant difference in adaptive sentence test in noise scores for the COM1 MAP and INV1 MAP.

H0: There will be no significant difference in monosyllabic word scores in quiet at 50 dB SPL

for the COM2 MAP and INV2 MAP.

H1: There will be a significant difference in monosyllabic word scores in quiet at 50 dB SPL for the COM2 MAP and INV2 MAP.

H0: There will be no significant difference in adaptive sentence test in noise scores for the COM2 MAP and INV2 MAP.

H1: There will be a significant difference in adaptive sentence test in noise scores for the COM2 MAP and INV2 MAP.

The objective to establish the T- & C-levels & T-NRT offsets for a range of MAPs of varying parameters is exploratory in nature. Hence, no formal hypotheses is formulated. Descriptive statistics, such as means, standard deviations (SD), confidence intervals etc, will be used to summarise the endpoints.

9.4 Sample Size Determination

Sample size estimation has been based on the primary endpoint, using a paired t-test.

Primary endpoint related to monosyllabic words in quiet:

To reject the null hypothesis of no difference in word perception scores in quiet at 50 dB for the wide pulse width MAP (INV1) compared to the narrow pulse width MAP (COM1), the following assumptions have been made:

A non-inferiority margin (NIM) of 5%; that is, poorer performance of the COM1 MAP compared to the INV1 MAP of up to 5% (INV1 MAP minus COM1 MAP) is deemed tolerable. The NIM is based on clinical consensus.

An expected standard deviation of difference scores of 6% for CNC words in quiet. This SD is based on the mean standard deviation of difference score data collected in completed clinical studies involving 1-3 clinical centres (the 43 channel gain, IIDR, Hi ACE versus ACE, and Freedom for N24).

A significance level $\alpha = 0.05$ (two-tailed).

A desired power of 0.8.

Based on these assumptions, a sample size of 14 subjects is required to reject the null hypothesis (using Minitab 20.0).

I think what is trying to be said here is:

An increased sample size of 20 subjects will be enrolled so as to determine the impact of varying pulse width on speech perception in noise (one of the secondary objectives), thus the larger dataset required.

9.5 Analysis Populations

Analyses will be conducted per-protocol only.

9.6 Endpoint Analysis

9.6.1 Primary Endpoint Analysis

To determine whether there is a significant difference between the wide and narrow pulse width MAPs (COM1 and INV1) for speech perception in quiet, percent correct word scores at 50 dB SPL for the NVA/CNC words in quiet at 50 dB SPL will be analysed using paired t-tests.

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

9.6.2 Secondary Endpoint Analyses

To determine whether there is a significant difference between the wide and narrow pulse width MAPs (COM1 and INV1) for adaptive sentences test in noise scores, speech reception threshold (SRT) for the LIST/AusTIN sentences in 4TB will be analysed using paired t-tests.

Differences in speech perception scores (quiet and noise) for the COM 2 and INV2 MAPs will be evaluated using repeated measures paired t-test.

The non-parametric Wilcoxon signed rank test will be used if the data is non-normally distributed.

Means, standard deviations and confidence intervals of the means will be used for the objective to establish the T- & C-levels & T-NRT offsets for a range of MAPs of varying parameters.

9.6.3 Exploratory Endpoint Analyses

Means, standard deviations and confidence intervals of the means will be used to compare predicted and measured T- and C-levels for COM1 and COM3 MAPs.

9.7 Safety Analyses

Adverse events will be listed by verbatim term, according to severity, seriousness and relationship to the investigational device and investigation procedures. Also, device deficiencies will be listed by verbatim term. No separate statistical analysis will be done. All reported AEs and ADEs with onset during the intervention will be included in the report.

9.8 Interim Analyses

No formal interim analysis will be conducted.

10 INFORMED CONSENT PROCESS

The informed consent process is described in the CIP of umbrella AI5763.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1 Definitions

The definitions of an Adverse Event, Adverse Device Effect, Serious Adverse Event, Serious Adverse Device Effect, Unanticipated Serious Adverse Device Effect and Device Deficiency are described in the CIP of umbrella AI5763.

11.2 Recording and Handling of Adverse Events

The recording and handling of Adverse Events is described in the CIP of umbrella AI5763.

11.3 Recording and Handling of Device Deficiencies

The recording and handling of Device Deficiencies is described in the CIP of umbrella AI5763.

11.4 Reporting Responsibilities

The reporting responsibilities is described in the CIP of umbrella AI5763.

11.5 Independent Data Monitoring Committee

The independent data monitoring committee is described in the CIP of umbrella AI5763.

12 DEVICE ACCOUNTABILITY

Device accountability is described in the CIP of umbrella AI5763.

13 DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

The procedures for recording, reporting and analysing CIP deviations are described in the CIP of umbrella AI5763.

14 DATA MANAGEMENT

Data management is described in the CIP of umbrella AI5763.

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

Data collection will be performed using Medidata Rave for electronic data capture (EDC) on electronic Case Report Forms (eCRFs).

In addition, de-identified electronically generated data will be collected from Custom Sound Suite. The unamended data file shall be regarded as the source.

15 CONFIDENTIALITY

Confidentiality is described in the CIP of umbrella AI5763.

16 ETHICS COMMITTEE AND REGULATORY AUTHORITY APPROVAL

Ethics committee and regulatory authority approval is described in the CIP of umbrella AI5763.

17 SUSPENSION OR PREMATURE TERMINATION

The suspension or premature termination is described in the CIP of umbrella AI5763.

18 AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

The procedure for amendments to the clinical investigation plan is described in the CIP of umbrella AI5763.

19 RECORD KEEPING AND RETENTION

Record keeping and retention is described in the CIP of umbrella AI5763.

20 PUBLICATION POLICY

The publication policy is described in the CIP of umbrella AI5763.

21 STATEMENTS OF COMPLIANCE

The statements of compliance are described in the CIP of umbrella AI5763.

22 QUALITY CONTROL AND ASSURANCE

Quality control and assurance is described in the CIP of umbrella AI5763.

23 TRADEMARKS AND COPYRIGHT

24 REFERENCES

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25 CHANGE HISTORY

Version	Change	Rationale
1.0	Introduction document	NA
2.0	Addition of sites- HEARnet, Melbourne and Cochlear Ltd., Melbourne. Updated sample size. Deletion of speech testing in quiet at medium presentation level (60 dB SPL). Adaptation of primary and secondary objectives, hypothesis, endpoints and sample size. Updated section 14- data management	Additions/changes made to add HEARnet Melbourne and Cochlear Ltd. Melbourne as participating sites. Deletion of speech testing in quiet at medium presentation level (60 dB SPL) to be consistent with the defined endpoints. Adaptations made to align with primary objectives as per umbrella AI5763 CIP. A full eCRF option will be utilised instead of safety only eCRF

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